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Information for Authors:

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Only original, unpublished materials will be considered for publication. Submissions should be made electronically by e-mail to Terry Bennett (tll2e@hscmail.mcc.virginia.edu). When submitting a manuscript, authors should provide full disclosure of any duplicate publication of any content of the paper in a cover letter to the Editor. Funding sources and any potential conflicts of interest reported in the cover letter should also be included in the manuscript text file.

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- All submissions should Include a title page, text, references, and as appropriate, figure legends, tables, and figures. For preparation of accepted manuscripts, a manuscript text file in Word must be submitted. Figure images should be submitted in separate files, with labels. Legends for all figures should be included at the end of the manuscript text file. Tables must be submitted as text, not images, and included in the manuscript text file.

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- The manuscripts must be free of any identifying patient information in order to respect confidentiality.

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  UVA faculty and students:
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  2. Edgar Poe, MD, MPH, Assistant Professor of Medicine, Division of General Medicine

  Non-UVA authors:
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A structured abstract of no more than 300 words for reports of original data. Structured abstracts should include the following sections: Background, explaining the clinical (or other) importance of the study and stating the objective or question addressed. Methods, describing the basic design of the study, patient or participant characteristics, and interventions. Results, reporting and quantifying the main outcomes of the study. Conclusions, providing conclusions of the study supported by the results, along with implications for clinical practice.

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References

- All information not considered statements of common knowledge must be supported by citation of published articles in the medical scientific literature.

- Literature sources must be cited according to AMA guidelines. List all authors and/or editors up to 6; if more than 6, list the first 3 followed by "et al." Number references in the order they appear in the text; do not alphabetize. In text, tables, and legends, identify references with superscript Arabic numerals. Abbreviate names of journals according to PubMed guidelines.

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1. Crusher BC, McCoy LH, Bashir JS, et al. Extraterrestrial transfusion methods. *J Interplanetary Med.* 2800;13:53-65.

Book:

2. West H. *Reanimation in Theory and Practice.* Providence, RI: Miskatonic Universtiy Press; 1923.

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i. Originality of case presentation
ii. Clarity of teaching points
iii. Balanced and evidence-based representation of recommendations
iv. Quality of the writing

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- Clinical vignettes describe patients with classic presentations of rare diseases or common diseases with unusual or interesting aspects. Authors are encouraged to present a brief review of pertinent literature and discuss salient parts of the patient diagnosis. Clinical Vignettes are coauthored by the resident or fellow and the attending physician who supervised the care of the patient and focus on one or two teaching points related to diagnosis, management, or treatment.

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- A review article written by an attending physician who recently presented during Medical Grand Rounds at the University of Virginia. Specifically, this article should provide readers a thorough overview of recent scientific and technologic advances, discussed during the Grand Rounds and developed at the University of Virginia, which have contributed to the overall understanding and management of specific conditions.

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- The Clinical Commentary offers attending or resident physicians an opportunity to provide a unique clinical perspective on a component of patient care, education, or medical advancements. The scope of this submission is quite broad and may incorporate discussion of controversial issues in the practice of medicine, topics related to or examples of patient care that have affected the author's personal or professional outlook, and/or commentaries about health care policy or public health.

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- Presentation of original data from clinical research conducted wholly or in part at the University of Virginia. Research accepted for publication must be current, well-executed, and applicable to patient care.

Falls And Gait Instability as the Presenting Symptoms of an Extramedullary Cervical Spinal Meningioma

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Central nervous system neoplasms are categorized on the basis of their location, either within the nervous tissue (intramedullary) or external to the tissue (extramedullary). Extramedullary tumors are predominately nerve sheath tumors and meningiomas and tend to produce symptoms by exerting a mass effect that compresses the brain or spinal cord.

Meningiomas usually have a broad dural attachment and typically grow slowly and insidiously, often producing a vague clinical picture that can be confused with musculoskeletal disorders or other lesions within the central and peripheral nervous systems.[1] We present an elderly patient with a multifaceted neurologic history and a chief complaint of falls, whose previously known spinal pathology could explain a clinical picture of gait instability and radiculopathy. However, his rapid progression of symptoms and key physical diagnosis findings suggested an additional possibility.

CASE DESCRIPTION

A 90-year-old gentleman with a history of degenerative disk disease and gait instability presented to his primary care physician with increasing episodes of falling. Until recently, the patient had described his occasional falls as mechanical, resulting from being tripped up on his walker. However, over the last 4 weeks he experienced several episodes of sudden upper and lower extremity weakness resulting in ground level falls, after which he was able to regain most of his strength. The patient did not experience any visual changes, dizziness, or lightheadedness prior to his falls.

The patient also complained of worsening urinary incontinence, but attributed this to ambulatory difficulties and his inability to get to the bathroom in time. He also complained of worsening occipital headaches and the onset of deep right shoulder pain unrelated to movement or activity, with radiation into the upper chest.

His medical history was significant for multilevel degenerative disk disease, including severe c-spine facet arthropathy and L4-L5 radiculopathy and recurrent episodes of isolated upper extremity myoclonus, as well as suspected systemic amyloidosis as evidenced by previous frontal lobe hemorrhages, abnormal spinal fluid proteins, urinary kappa and lamda light chains and left anterior hemifascicular block, and complete right bundle branch block on electrocardiogram. He had declined biopsy or other diagnostic studies to confirm the diagnosis.

His family history was significant for a sister with systemic amyloidosis. Social history and review of systems were noncontributory.

Physical examination revealed an elderly gentleman in no apparent distress, who walked into the clinic with an antalgic gait, using a cane. His blood pressure was 200/82 mm Hg, pulse 62 beats per minute and regular; respirations were 16 per minute and unlabored and oxygen saturation was 99% on room air.

A significant finding was a 2/6 blowing holosystolic murmur most consistent with mitral regurgitation. His range of motion in all 4 extremities was full, and was not limited by shoulder pain. There was no tenderness to palpation of the spine or right scapula. He had significant dextroscoliosis, as well as an antalgic, wide-based gait. Neurological examination showed normal cranial nerves. Strength was 5/5 in all 4 extremities, with spasticity in the upper extremities, without atrophy or fasciculations. A very fine postural tremor was noted in his upper extremities that persisted with point-to-point testing. Upper extremities were hyperreflexic, and lower extremities were normoreflexic. Jaw-jerk reflex was within normal limits. Further testing revealed a hyperreflexic right pectoralis muscle. There was a mild stocking-glove distribution of diminished primary sensory modalities in the upper and lower extremities, as well as pain to palpation in his lower extremities. Romberg testing results were normal.

NEUROIMAGING

Because of the clinical findings of peripheral hyperreflexia with a normal jaw jerk, the patient was scheduled for neuroimaging of his head and cervical spine. A small subarachnoid hemorrhage was identified, and the patient was subsequently hospitalized. Magnetic resonance imaging (MRI) of the cervical spine revealed a homogeneously enhancing, dural-based extramedullary mass at T1-T2 that was causing a severe mass effect on the cord (Figure 1). The lesion filled the canal at the level of the right neural foramen, causing a severe mass effect on the exiting T1 nerve root. Cervical imaging revealed marked facet arthropathy at C3-C4 and central canal stenosis with marked cord deformity and abnormal signal (Figure 2).

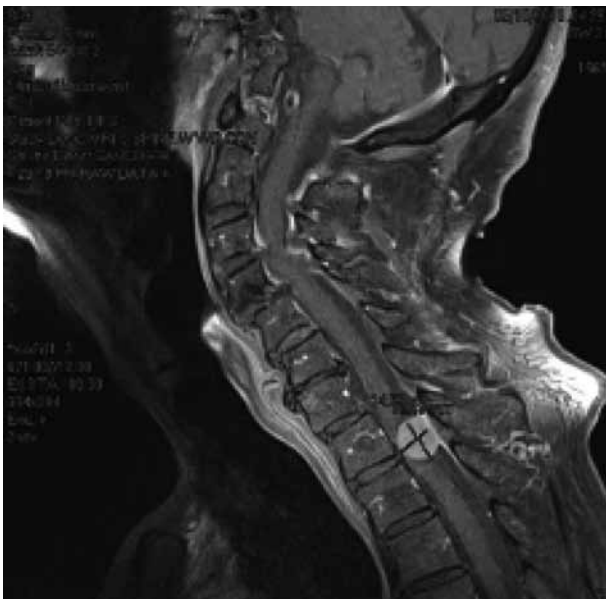

Figure 1. Sagittal T2-weighted image showing an extramedullary mass at T_1-T_2 with spinal cord compression in addition to marked cervical spine degeneration and marked stenosis.

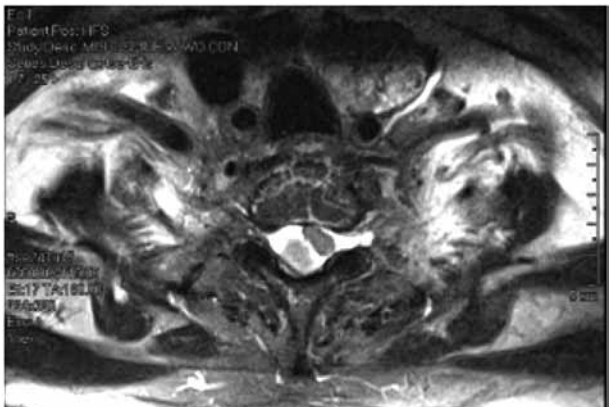

Figure 2. Transverse T2-weighted image at T_1-T_2 showing right posterolateral tumor with mass effect and cord compression.

Further neurologic examination during the patient's hospitalization revealed bilateral hyperactive reflexes in the upper extremities and weakness in both upper and lower extremities, as well as a very active right-sided pectoralis reflex. The patient was started on steroids and underwent a C3, C4, and partial C5 laminectomy, as well as a T1 and partial T2 laminectomy with removal of the intradural extramedullary lesion. Pathological analysis of the lesion revealed that it was a meningioma, World Health Organization grade 1.

The patient's postoperative course was uneventful, and he was discharged home for rehabilitation. On follow-up evaluation in the outpatient clinic he was walking normally, using a cane for confidence, and his urinary incontinence was improved.

DISCUSSION

Meningiomas are most often intradural and extramedullary, and account for approximately 25% of all primary spinal cord tumors.[2] They are believed to arise from arachnoid cluster cells, and therefore are often at the nerve root junction with the spinal cord where the laterally positioned spinal arteries penetrate the cord.[1] For this reason, lateral meningiomas predominate over ventral or dorsal meningiomas. These lesions are confined within the collagen-rich dural tissue and grow slowly and insidiously within the spinal canal. As they grow, the adjacent medullary tissue is compressed and displaced, creating a widened subarachnoid space both superior and inferior to the lesion.[3]

Although schwannomas also tend to arise from nerve root sheaths and can produce radiculopathy, meningiomas can be differentiated by their extramedullary origin and myelopathic clinical picture. This presentation is often slow and gradual, and can be obscured by other primary neurologic deficits, making the diagnosis elusive. As the tumor enlarges, symptoms frequently begin with regional paraspinal pain, most often at night. This is often followed by sensorimotor changes, not infrequently of the Brown-Sequard type, including a constellation of symptoms such as contralateral pain and temperature deficits, as well as ipsilateral paralysis and decreased sensation to tactile and deep touch. As would be expected by their lateral position, sensory and motor deficits are seen equally. As the tumor continues to grow, sphincter dysfunction can be seen as well.[4]

Before the advent of MRI, spinal meningiomas were confused with herniated disks, syringomyelia, pernicious anemia, and multiple sclerosis, leading to delay in diagnosis or even misdiagnosis, often complicated by inappropriate exploratory surgeries.[3] MRI has proven to be the best imaging technique, revealing signals isointense to the normal spinal tissue on T1- and T2-weighted images, with a high degree of signal enhancement with gadolinium injection.[5] This modality can clearly delineate the spinal cord and the tumor, and is useful in planning surgical interventions.

Because the majority of these tumors are benign and slow growing, there is often an indolent clinical course that leads to delay in diagnosis. In this patient, the unusual finding of peripheral hyperreflexia with a normal jaw jerk (mediated through the trigeminal nerve) suggested possible compression of the cervical spine. Despite his multiple comorbidities, a careful physical examination enabled diagnostic modalities to be aimed toward a specific site, leading to the correct diagnosis and successful surgical intervention.

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MEDICAL SCHOOL

Glucarpidase: A Novel Therapy for Methotrexate Toxicity

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Methotrexate (MTX) is commonly used in the treatment of multiple malignancies, including acute lymphoblastic leukemia, Burkitt lymphoma, primary central nervous system lymphoma, and osteosarcoma. MTX acts as a dihydrofolate reductase inhibitor and has preferential activity during the synthesis (S) phase of the cell cycle, during which DNA replication occurs in preparation for mitosis. High-dose MTX (HDMTX) therapy can cause severe systemic toxicity, including neurotoxicity (transverse myelopathy, acute/subacute encephalopathy, leukoencephalopathy), nephrotoxicity (including acute renal failure), myelosuppression, mucositis, and hepatotoxicity. In patients who are receiving HDMTX, leucovorin rescue is the standard of care because leucovorin provides a reduced form of folic acid for DNA/RNA synthesis in nonmalignant cells and thus "rescues" them. The combination of HDMTX and leucovorin is extremely effective in treating malignancy and protecting nonmalignant cells from toxicity. Along with leucovorin rescue, urine alkalinization and aggressive hydration are used to enhance MTX excretion. Despite these measures, however, systemic toxicity can still occur. Glucarpidase (also known as carboxypeptidase-G2) rapidly hydrolyzes MTX into inactive metabolites (glutamate and 2,4-diamino-N10-methylpetroic acid) with increased water solubility. We describe a case of HDMTX-induced renal failure in a patient with Burkitt lymphoma and the use of glucarpidase in an attempt to prevent further MTX toxicity.

CASE PRESENTATION

A 31-year-old woman with Burkitt lymphoma presented to the inpatient hematology/oncology service for scheduled admission to receive cycle 5 of chemotherapy with CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, mesna, etoposide, and cytarabine). Her Burkitt lymphoma had been diagnosed 3 months earlier on the basis of findings of monotypic CD-10^{+} B lymphocytes of medium to large size in her bone marrow and a right axillary lymph node. The patient had received 4 previous treatments of CODOX-M/IVAC chemotherapy and had tolerated this regimen without any major toxicities or life-threatening side effects. However, she had recently been hospitalized for neutropenic fever and *Clostridium difficile* colitis and had been discharged 2 weeks before this admission. She had completed a 14-day course of metronidazole and had no diarrhea, abdominal pain, fever, chills, nausea, or vomiting. Her leukopenia had resolved. In addition to Burkitt lymphoma, the patient's medical history was notable only for migraine headaches, gastroesophageal reflux, and a ganglion cyst removal. She was a high school teacher without a history of alcohol or tobacco use. On admission the patient's vital signs were normal with a temperature of 36.3°C, blood pressure of 122/62 mm HG, pulse of 76 beats per minute, and a respiratory rate of 18 beats per minute. Findings of her admission physical exam, which included a nonfocal neurologic exam, were normal.

Results of the admission basic metabolic panel were within normal limits. The patient's renal function was preserved, with a blood urea nitrogen of 4 mg/dL and a creatinine of 0.7 mg/dL. Results of a complete blood count indicated the presence of resolving pancytopenia from previous chemotherapy, with a hemoglobin of 8.1 g/dL, hematocrit of 24.5%, white blood cell count of 4200 x 10^3/μL, and platelet count of 95,000/μL. Results of her liver function tests and coagulation studies were all normal. On admission, the patient was hydrated with 1/2 normal saline plus 75 meq/L bicarbonate to achieve a urine pH >7.0 and urine output >125 mL/h. After these parameters were met, she was started on HDMTX therapy consisting of a planned 24-hour infusion of approximately 6.5 grams/m^2 on the evening of admission. The next morning, the patient's laboratory data showed a significant increase in her creatinine to 1.2 mg/dL. This measurement was repeated 2 hours later, and her creatinine continued to increase to 1.4 mg/dL. The HDMTX infusion was immediately stopped and leucovorin rescue was initiated with an initial dose of 200 mg/m^2 intravenously (IV) and continued at 100 mg/m^2 IV every 3 hours. Aggressive hydration with alkalinzed IV fluids was continued to increase MTX solubility and excretion. In total the patient received HDMTX for approximately 16 hours. The patient received approximately 5 g/m^2 of the planned total dose. Despite a rising creatinine level,

the patient was asymptomatic and was producing >100 mL/h of urine.

The patient's serum creatinine continued to rise. The nephrology service was consulted for assistance with fluid management and for the potential need for dialysis. The patient's serum creatinine peaked at 3.3 mg/dL until 8 days after initiation of MTX; however, she never underwent dialysis. A renal ultrasound was performed that showed no evidence of obstruction or hydronephrosis. It was concluded that she had sustained acute tubular necrosis from HDMTX therapy. The patient soon began to experience systemic toxicities from HDMTX, including grade 4 thrombocytopenia requiring platelet transfusion, grade 4 anemia requiring red blood cell transfusion, neutropenia with fever, hyperbilirubinemia, nausea, and vomiting. Despite antiemetics, she was unable to maintain oral intake because of mucositis. In addition, the aggressive IV fluid hydration led to significant fluid overload, anasarca, shortness of breath, and hypoxia requiring up to 6 L per minute supplemental oxygen by nasal cannula. Glucarpidase, a novel enzyme that metabolizes MTX, was initiated on the basis of MTX levels obtained at 24 and 42 hours after the initiation of HDMTX.

Glucarpidase is not currently approved by the FDA for use in the United States and can be obtained only through an open-label clinical trial. Criteria to receive glucarpidase include evidence that the patient has acute kidney injury as well as a MTX level >10 μmol/L at the 42-hour time point after initiation of HDMTX. Both criteria were present in our patient, with her MTX level of 24 μmol/L at 42 hours along with a serum creatinine of 2.5 mg/dL. Glucarpidase was administered on hospital day 4, approximately 90 hours after the HDMTX infusion was started. A total of 50 mg of glucarpidase was infused IV over 5 minutes, bringing the serum MTX level of 2.6 μmol/L down to 0.81 μmol/L within 3 hours.

Despite the administration of glucarpidase, which decreased the free serum MTX level without evidence of rebound, the patient continued to experience MTX-induced toxicity. Specifically, she experienced 2 tonic-clonic seizures, as well as continued nausea, vomiting, diarrhea, flushing, fevers, myelosuppression, and mucositis. MTX levels after glucarpidase administration continued to slowly but steadily decrease until the day of discharge, when the MTX level was 0.10 μmol/L. Fortunately, HDMTX-induced side effects abated and the patient was discharged to home on hospital day 14 with resolution of her symptoms and recovering blood counts. The patient was discharged with 8 additional doses of oral leucovorin. Her renal function began to improve, and her serum creatinine was 2.1 mg/dL at discharge.

An investigation into the underlying cause(s) for the patient's delayed MTX metabolism were inconclusive. She had tolerated CODOX-M/IVAC as expected to date including no unexpected toxicity from her prior single treatment with high dose methotrexate. When this case was reviewed, no deviations from nursing or infusion protocols were identified. Fortunately, the patient was able to recover completely to her baseline within a few weeks and was able to receive the originally planned treatment, which did not include high-dose MTX. At the time of this report she had completed her therapy and was in remission with normal renal function. It is highly likely that her clinical course would have been more severe without glucarpidase administration, because her renal function would have likely continued to decline. Decline in her renal function would have further impaired MTX excretion and could have led to potentially irreversible systemic toxicity.

DISCUSSION

The development of renal dysfunction during HDMTX therapy is a medical emergency because it can markedly enhance MTX toxicity. Mainstays of therapy are continued alkalinized hydration and high-dose leucovorin rescue. Other options include dialysis or administration of glucarpidase. Glucarpidase was granted orphan drug status in the United States in 2003, and according to the manufacturer's website, FDA approval is expected as early as 2011.[1] For now, this recombinant enzyme must be obtained through an open-label treatment protocol. Practical considerations regarding glucarpidase administration include its clearance of leucovorin's active metabolite, 5-methyltetrahydrofolate, a compound that is necessary for leucovorin rescue to occur in nonmalignant cells. Therefore, glucarpidase should be given at least 2 hours after leucovorin administration. Similarly, leucovorin should be readministered 1 to 2 hours after the glucarpidase infusion is complete. In addition, glucarpidase clears only extracellular MTX and will continue to leave intracellular MTX levels unaffected, potentially resulting in rebound levels of serum

MTX. Therefore, hydration, alkalinization, and high-dose leucovorin should be continued even after the completion of the glucarpidase infusion.

In September 2010, a nonrandomized prospective clinical trial performed to evaluate glucarpidase's utility in the treatment of HDMTX toxicity was published in the *Journal of Clinical Oncology*.[2] In this study, 100 patients with HDMTX-induced nephrotoxicity received 1 to 3 doses of IV glucarpidase. Plasma MTX levels, leucovorin, and 5-methyltetrahydrofolate (leucovorin's active metabolite) concentrations were measured before and after glucarpidase administration. Toxicities were monitored and logistic regression was used to monitor severe toxicity and/or death. Glucarpidase was administered at a median of 96 hours in a subset of 44 patients and at 66 hours in the other subset of 56 patients. Inclusion criteria in this study were MTX concentrations >10 μmol/L at 42 hours after infusion, serum creatinine>1.5 times the upper limit of the reference interval, and plasma MTX levels >2 standard deviations above the mean at >12 hours after MTX administration. Results demonstrated that MTX concentrations were decreased by 98.7% at 15 minutes after glucarpidase infusion, and 5-methyltetrahydrofolate concentrations by 98%, indicating that leucovorin administration must be continued after glucarpidase administration has been stopped. Of the 12 deaths in the study, 6 were directly attributed to irreversible MTX toxicity, and the other 6 were attributed to rapid cancer progression. The presence of grade 4 toxicity before glucarpidase administration, inadequate leucovorin dosing, and administration of glucarpidase more than 96 hours after MTX infusion were associated with grade 4 or 5 toxicity. In addition, the question of whether multiple doses of glucarpidase were associated with a statistically significant decrease in serum MTX levels after the first dose was evaluated by random assignment of groups to receive either a single dose of glucarpidase, 2 doses separated by 24 hours, or three 50-U/kg doses of glucarpidase every 4 hours. The trial did not demonstrate statistically significant changes in MTX levels or toxicities when multiple-dose therapy of glucarpidase was compared with single-dose therapy. Although limited data have been reported regarding the adverse-effect profile of glucarpidase, it appears to be generally well tolerated, but flushing, allergic skin reactions, fever, and rigors are reported adverse effects.

Because no randomized studies have been performed, it is not absolutely clear if systemic toxicity or irreversible renal dysfunction occur at a higher rate without the rapid MTX clearance provided by glucarpidase. However, an area of future research could focus on the optimal interval between MTX and glucarpidase administration, which in previous studies has occurred at a median of 52 to 96 hours. As in the above study, data demonstrating that administration of glucarpidase after 96 hours from the start of the HDMTX infusion are associated with a statistically significant increase of grade 4 to 5 toxicity, which suggests that there is less benefit from this therapy after 96 hours.

Another important area of investigation is the comparative efficacy of glucarpidase versus dialysis, because dialysis can be used to decrease serum MTX levels. In a literature review published in 2004, the reviewers attempted to compare glucarpidase with dialysis in regard to MTX clearance. Thirty publications were reviewed, and reported results of dialysis-based methods of MTX removal were published for 49 patients.[3] The most frequently used single methods were hemodialysis (10 patients), high-flux hemodialysis (9 patients), and charcoal hemoperfusion or charcoal hemofiltration (7 patients). Sixteen patients were treated with multiple modalities. Results demonstrated that attempted MTX removal by dialysis resulted in a median decrease in plasma MTX concentrations of 52% (range, 26%–82%). Dialysis-based methods were used for up to 14 days. The use of high-flux hemodialysis resulted in the greatest decrease in plasma MTX concentrations (median, 75.7%; range, 42%–94%). Only a total of 3 patients had a decrease of >90% in MTX concentrations with the use of a single-method dialysis session. Increases in plasma MTX concentrations after the completion of dialysis were reported and quantified in 7 reports. Significant rebound increases in postdialysis plasma MTX concentrations were common, and increases of 10% to 221% of the postprocedure MTX levels and of 90% to 100% of the preprocedure MTX levels were reported. The authors concluded that the level of reduction, degree of rebound, and complexity of the procedure were all significant drawbacks to dialysis-based therapy of HDMTX toxicity compared to glucarpidase.

In conclusion, in patients receiving HDMTX, it is critical to recognize renal dysfunction early, and its discovery warrants urgent intervention, the most critical of which is appropriate leucovorin rescue. Although not currently approved by the FDA, glucarpidase administration should also be considered early. Data support the use of

glucarpidase single-dose administration within 96 hours of the initiation of the HDMTX infusion, in addition to continuation of high-dose leucovorin, alkalinization, and hydration to decrease the probability of severe and potentially irreversible or fatal MTX toxicity.

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Extranodal Diffuse Large B-Cell Lymphoma Presenting with Involvement of the Myocardium and Large Intestine

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CLINICAL HISTORY

A 68-year-old white woman presented to the University of Virginia Health System with left lower-quadrant pain of approximately 4 weeks duration. She reported worsening shortness of breath with dyspnea on exertion for 4 days preceding admission. At a visit with her primary care physician she was found to have a hematocrit of 29% and lower-extremity edema, which were new findings. She was started on furosemide and oral iron replacement and sent home. Subsequently, she developed hematochezia and presented to an outside hospital with a hematocrit of 27%, an elevated brain natriuretic peptide concentration of 595 pg/mL, and an elevated serum calcium of 11 mg/dL. She underwent transthoracic echocardiography, which demonstrated increased right atrial pressure. Because of the possibility that the patient might have a pulmonary embolism, a computed tomographic (CT) pulmonary angiogram was performed. The angiogram did not show any evidence of pulmonary embolism, but it did show a 3- to 4-cm right atrial mass. The patient was subsequently admitted for management and further work-up of this mass. A CT scan of the chest, abdomen, and pelvis was obtained and revealed a lobular, heterogeneously enhancing mass centered within the right atrium myometrium with slight extension into the right ventricle myometrium, measuring approximately 7.5 x 7.4 x 5.9 cm. In addition, the CT scan also showed extensive mesenteric adenopathy and a prominent preaortic lymph node measuring approximately 8 cm. Further work-up included cardiac magnetic resonance imaging, which revealed a heterogeneously enhancing mass in the right atrial myometrium with extension into the right ventricular myocardium (Figure 1A, B). Furthermore, CT of the pelvis demonstrated that the uterus was enlarged, lobular, and ill-defined, with areas of heterogeneous enhancement peripherally.

The patient underwent ultrasound-guided core needle biopsy of the pelvic mass. Pathologic review of the biopsy showed cells in diffuse sheets in a background of small lymphocytes, with features most consistent with diffuse large B-cell lymphoma (DLBCL). Results of a positron emission chromatographic (PET) scan demonstrated a hypermetabolic mass in the pelvis consistent with a malignant neoplasm, a hypermetabolic left adrenal nodule consistent with a metastatic implant, hypermetabolic aortocaval and mesenteric lymph nodes, a hypermetabolic cardiac mass invading the right atrium consistent with a metastatic implant,

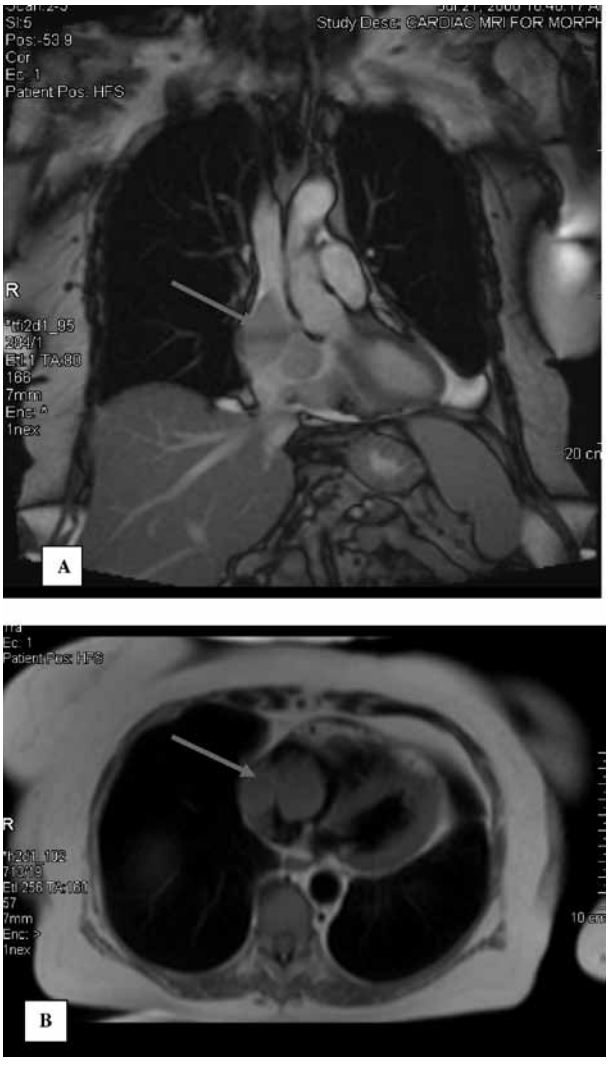

Figure 1. Cardiac MRI demonstrating (A) intracardiac involvement of diffuse large B-cell lymphoma (arrow) originating from right atrium and (B) involvement of right ventricular myocardium (arrow).

and multisegmental bowel wall thickening with increased fluorodeoxyglucose (FDG) uptake likely related to neoplastic infiltration of the bowel. As a result, it was determined she had stage IV-E DLBCL.

TREATMENT COURSE

The patient proceeded with her first round of an R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy cycle as an inpatient on the oncology service. She was started on intravenous fluids for management of hypercalcemia, and her serum calcium decreased appropriately. She received a transfusion of 2 units of packed red blood cells for her anemia, which was due to gastrointestinal bleeding. Her hospitalization was further complicated by an acute gastrointestinal bleed requiring angioembolization of the pelvic mass, as well as a symptomatic third-degree heart block secondary to invasion by the atrial mass, for which she underwent placement of a cardiac pacemaker.

A follow-up, repeat CT scan showed a decrease in the size of her intracardiac tumor from 2.4 x 3 cm to 2.3 x 1.9 cm after only 1 cycle of R-CHOP.

Table 1. Patient Laboratory Values at Hospital Admission

Laboratory Test	Result
White blood cell count	11.08 x $10^3/\mu L$
Neutrophils	69.0%
Lymphocytes	12.0%
Monocytes	12.0%
Eosinophils	3.7%
Basophils	0.0%
Blasts	0.9%
Metamyelocytes	1.9%
Hematocrit	33.8%
Platelets	214 ´ $10^3/\mu L$
Calcium	11.0 mg/dL
Lactate dehydrogenase	536 U/L
Haptoglobin	203 mg/dL
Parathyroid hormone	<3.0 pg/mL
Creatinine	0.9 mg/dL
Phosphorus	3.7 mg/dL
Potassium	3.9 mmol/L

After 4 cycles, she was noted to have a depressed ejection fraction of 30% to 35%, and thus the anthracycline portion of the R-CHOP regimen was discontinued. Fifteen months after her sixth cycle of chemotherapy, a PET scan revealed interval decrease in the size of the right adnexal mass without abnormal FDG uptake and no abnormal FDG uptake of the right atrial mass. The repeat PET scan, however, was notable for circumferential mural thickening involving the colon and rectum, with elevated FDG uptake indicating either resolving colitis or lymphomatous involvement of the colon.

PATHOLOGY

Immunohistochemical stains showed that the cells were strongly positive for CD20 and CD10, and negative for CD3, CD5, and CD43. According to the pathological analysis, the morphologic and immunohistochemical features were most consistent with DLBCL.

DISCUSSION

The heart and pericardium are not uncommonly involved in patients with metastatic neoplasms, with an incidence of 1.23% reported for 1 autopsy series.[1] This involvement is frequently asymptomatic. Primary tumors of the heart are less common; however, they are often symptomatic. The majority (75%) are benign, with myxomas being the most common benign tumor, whereas angiosarcomas are the most common primary malignant cardiac neoplasm.[1-3] Non-Hodgkin lymphoma (NHL) may involve the heart primarily or as a site of disseminated disease.

DLBCL accounts for approximately one third of NHL in adults, and the most common NHL involving the heart is DLBCL. Approximately 20% to 40% of these cases of DLBCL are classified as extranodal in involvement.[4-6] Although the term extranodal lymphoma is not specific, it is most commonly used to refer to lymphomas with either isolated or predominant involvement of any organ other than the spleen, thymus, and Waldeyer's ring, which are organs predominantly composed of lymphoid tissue. Bone marrow is considered as extranodal, and cases in which there is both extensive nodal and extranodal involvement are usually referred to as nodal.

When all stages of disease were included, Moller et al found no difference in 2-, 5-, and 10-year overall survival (OS) in 1075 patients treated with

combination chemotherapy.[4] These investigators did, however, demonstrate a statistically significant improvement in survival for nodal stage I and IV disease. In the second largest study to date, which included 382 patients with DLBCL, the patients with neoplasms arising from the gastrointestinal tract appeared to have improved complete response (CR) rates (80% versus 57%) and 5-year OS (68% versus 45%) compared with patients with nodal disease; however, there were no significant differences in CR and OS when patients with disease arising from other extranodal sites were compared with patients with nodal disease.[7] Historically, the finding of more than 1 extranodal site of disease at presentation has been considered an adverse prognostic indicator; however, it is unclear whether the higher adverse outcomes reflect the biology of extranodal DLBCL or that extranodal disease is simply a marker of more aggressive disease.

Gene expression profiles have been examined in nodal versus extra nodal DLBCL. As noted above, many studies have revealed clinical differences between nodal and extranodal NHL, including differences in outcome and genetic variation.[7-9] It has been reported that over the last 20 years the incidence of extranodal lymphomas has increased more rapidly than the incidence of nodal lymphomas. This observation suggests that different pathogenetic mechanisms may underlie these 2 types of neoplasms.[10,11] Differences between the 2 types of DLBCL at the molecular level have already been reported, such as *Bcl6* expression, *Fas* mutations, and *REL* gene amplifications.[12,13] Jeehan et al[14] found variations in gene expression between nodal and extranodal DLBCL in more than 200 genes involved in different cellular pathways. They also found differences in the regulation of *CCL19* and *CCL2*, genes involved in lymphocyte homing to lymph nodes. It has been postulated that loss of homing factors may ultimately cause extranodal locations of lymphoma. These investigators also found that *CCL2* and *CCL19* were highly expressed in nodal DLBCL, which could explain why the lymphoma remains within lymphoid tissue. It remains to be seen whether attempts to better define the molecular distinction between nodal and extranodal DLBCL will help to identify important clinical factors and guide therapeutic management.

The patient we describe here had DLBCL presenting with extensive extranodal disease and involvement of the myocardium. Although her clinical course was complicated and required omission of anthracycline secondary to cardiomyopathy, she remained in complete remission 18 months after therapy.

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A Case of Relapsing Sarcoidosis with Myopathy

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Sarcoidosis is a systemic disease of unknown etiology. Its essential features are a compatible clinical picture along with the presence of noncaseating epitheliod cells in several affected tissues and organs. These granulomas either resolve or become featureless hyaline connective tissue.[1] Although sarcoidosis can affect every organ of the body, the lung is most commonly affected. Other organs commonly affected are the liver, skin, and eye.[2,3] Patients tend to be between the ages of 20 and 40 years, and the disease has a high prevalence in blacks and women. We report an unusual case of relapsing sarcoidosis presenting as granulomatous myositis (GM).

CASE DESCRIPTION

A 75-year-old man with a history of sarcoidosis, coronary artery disease, chronic kidney disease, cerebrovascular accident, diabetes mellitus, hypertension, and bilateral total knee arthroplasties was admitted to the Hospital of the University of Pennsylvania by his rheumatologist because of gradually worsening weakness of both of his lower extremities. Medications at the time of admission included allopurinol, aspirin/extended-release dipyridamole (Aggrenox), nifedipine, folate, a statin drug, and insulin. Pulmonary sarcoidosis had been diagnosed in this patient 25 years before this admission. The disease responded to oral corticosteroid therapy (CST), and the patient was followed by a pulmonologist. He was initially treated for 9 months, and because he showed symptomatic and radiographic improvement, steroid treatment was tapered off completely. In the available records for this patient, however, it was unclear whether he had spontaneous remission or a response to CST. After 6 to 7 years the patient had a relapse of pulmonary symptoms and worsening disease revealed by chest x-ray, and he was treated again with oral CST for 3 months. Since then he had been treated with oral CST 3 times, for a maximum of 4 months for each course of treatment. At the time of this admission the patient had not had a relapse for 6 years and had remained off steroids during this period. His diabetes was well controlled on insulin therapy, and his most recent hemoglobin A1C was 6.9 %.

About a year prior to this admission, the patient began to experience generalized body weakness. He noted diffuse body aches, difficulty standing for long periods of time, and a decrease in his ability to walk long distances. He was seen by a rheumatologist, who initially attributed the problem to statin-induced myopathy. Discontinuation of the statin for 6 weeks did not result in any improvement, however, and statin treatment was resumed. Two injections of vitamin B12 were administered subsequently, but no benefit was observed. The patient had progressive worsening of symptoms to the point that he was unable to get out of a chair without assistance. This condition prompted hospitalization for further examination. An extensive review of systems, including regarding pulmonary symptoms, did not provide any relevant information. Physical examination revealed profound lower-extremity weakness. Results of laboratory studies performed within the year before and at the time of this admission included a thyroid-stimulating hormone concentration within the reference interval, negative serological test for autoimmune disease and hepatitis B and C, creatinine of 2.0 mg/dL, creatinine kinase of 2900 to 3900 U/L, sedimentation rate of 85 mm/hour, and mean corpuscular volume of 112 fL. The differential diagnosis included inflammatory or metabolic myopathy and fungal disease.

Further workup during the admission included magnetic resonance imaging scan of the patient's thighs, which revealed bilateral diffuse edema in the anterior compartment muscles, which was worse on the right. These findings were consistent with an inflammatory process. Subsequently, the patient underwent an electromyography and a test of nerve conduction velocity. These tests revealed mild sensory-motor axonal polyneuropathy, and a skeletal muscle biopsy of the right thigh was performed for further assessment.

Surgical pathological analysis of the thigh biopsy specimen revealed well-oriented skeletal muscle that showed marked variation in fiber size. The frozen sections used for enzyme histochemical analysis showed only rare intact muscle fibers; the majority of the frozen specimen showed fat

and collagen replacing the muscle. The paraffin-embedded sections showed ample portions of muscle. There was a marked increase in endomysial collagen deposition, a profound inflammatory infiltrate throughout the muscle, and areas where the inflammation formed round, granulomatous accumulations. The inflammatory infiltrate was mixed, with predominantly lymphocytes and macrophages. Grocott and acid-fast bacilli (AFB) stains showed no evidence of fungal or acid-fast organisms, respectively. Steiner stain showed no evidence of organisms. Trichrome stain highlighted the collagen deposition, but showed no evidence of ragged red fibers or inclusions. Congo red stain showed no evidence of amyloid deposition. Periodic acid-Schiff stain showed no evidence of carbohydrate deposition. The acid phosphatase stain highlighted clusters of degenerating fibers. NADH (nicotinamide adenine dinucleotide tetrazolium reductase) and succinate dehydrogenase stains showed preservation of the normal internal architecture in the few remaining intact muscle fibers. The muscle tissue pathology was interpreted to indicate GM, possibly secondary to sarcoid.

Sarcoid myopathy is a chronic form of sarcoidosis that classically presents in middle age or later.[4] Although asymptomatic sarcoid involvement of skeletal muscle is common, symptomatic involvement is rare and scantly reported. Muscle pain and tenderness occur in acute myositis, but in chronic myopathy, bilateral weakness and wasting of the proximal muscles of the extremities and of the trunk and neck occurs. Our patient`s symptoms of diffuse achiness at the onset may have been due to acute myositis, which gradually progressed to chronic myopathy. A thorough workup excluded medication-induced myopathy and metabolic causes. The biopsy results suggested granulomatous disease with negative fungal and AFB stains, and in this patient with longstanding and relapsing pulmonary sarcoidosis, the likely cause for myopathy was extrapulmonary sarcoid presenting as sarcoid myopathy.

The patient was subsequently started on oral prednisone 20 mg twice a day, and after 2 weeks of treatment he reported that he felt slight improvement in his weakness. However, therapy was halted because of a gastrointestinal bleed.

DISCUSSION

GM is a rare condition with a prevalence of only 0.5% on all skeletal muscle biopsies[5] and is histologically characterized by the development of endomyseal and/or perimyseal granulomas.[6] Clinical hallmarks are generalized muscle weakness, myalgias, and bulbar symptoms. An association of GM with sarcoidosis has been demonstrated in several case studies.[5,7,8] Myalgias and arthralgias are a common complaint among a large percentage of patients with sarcoidosis. Granulomatous bone and muscle involvement as documented by x-ray, magnetic resonance imaging, gallium scan, or biopsy can be seen in 50% to 80% of patients with sarcoidosis.[4] GM is often asymptomatic, however, and becomes symptomatic in only 1.4% to 2.3% of patients.[6] Muscle lesions can occur in the course of systemic sarcoidosis long before a myopathic picture develops and patients become symptomatic. The clinical spectrum of sarcoid myopathy includes a palpable nodular type, which is infrequent; an acute myositis type, which is also rare and is seen more commonly in early sarcoidosis; and a chronic myopathic type, which is more common, is slower in onset, and occurs later in life.

Other differential diagnoses for GM include infectious diseases (mycobacterium, sporothrix, *Pneumocystis carinii*), inflammatory bowel disease, foreign-body giant-cell reaction, malignancy (lymphoma), thymoma, graft-versus-host disease,[9] and myasthenia gravis, all of which are seen less commonly in association with GM. GM may also be mistaken for a slowly progressive motor neuron disease.[10] The etiology of GM can be difficult to determine. If no specific cause can be attributed, some clinicians diagnose isolated GM. Commonly used tests are electromyography and muscle biopsy. Other tests used to rule out possible causes include AFB staining of tissue, measurement of serum angiotensinogen-converting enzyme, determination of nerve conduction velocity, and chest imaging by computed tomography.

Evidence-based information pertaining to the long-term course and treatment of chronic sarcoid myopathy does not exist. Consensus opinion suggests that sarcoid myopathy is often poorly responsive or unpredictably responsive to CST. Excellent results have been suggested in some, but not all, case reports, and in some case studies patient steroid dependence has occurred. For patients who failed to respond to oral CST, other drugs such as cyclophosphamide, cyclosporine, azathioprine, and methotrexate have been used, with mixed results.[11] Alternatives to corticosteroids are often introduced because of steroid intolerance or in an attempt to reduce steroid dose and side effects.[2]

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Invoking Occam's Razor: A Case Report of Cardiac Sarcoidosis

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Cardiac involvement in patients with systemic sarcoidosis is underdiagnosed and is associated with a poor prognosis. Cardiac sarcoidosis may present as symptomatic left ventricular dysfunction, congestive heart failure, atrioventricular block, arrhythmia, and sudden death. To date, cardiac sarcoidosis has been extremely difficult to diagnose and optimal management has not been well defined. We describe a 32-year-old woman with a history of nonischemic cardiomyopathy in whom cardiac sarcoidosis was diagnosed.

CASE DESCRIPTION

A 32-year-old black woman with a history of nonischemic cardiomyopathy diagnosed 7 months prior to admission, asthma, and a recent ventral hernia repair presented to the emergency department after 2 days of progressive bilateral lower-extremity edema, fatigue, and worsening dyspnea on exertion. In addition, the patient reported significant shortness of breath at rest, which increased in the recumbent position. She denied symptoms suggestive of paroxysmal nocturnal dyspnea. She denied having experienced fevers, nausea, vomiting, chest pain, or leg pain.

Physical examination revealed morbid obesity, which limited the abdominal examination, but otherwise the findings were unremarkable for hepatomegaly or splenomegaly, 1+ pitting edema of her lower extremities, tachycardia, and prominent S3. Computed tomography–pulmonary angiogram was performed and showed a pulmonary embolism in the right main pulmonary artery extending into the segmental branches supplying the right middle and upper lobes, with bilateral axillary, mediastinal, and inguinal lymphadenopathy. The patient was admitted and started on anticoagulation therapy with dalteparin.

An electrocardiogram performed on admission demonstrated sinus tachycardia with poor R-wave progression, no ST-T wave changes, and right atrial enlargement (Figure 1). To evaluate for right heart strain, a transthoracic echocardiogram was performed, which demonstrated right ventricular

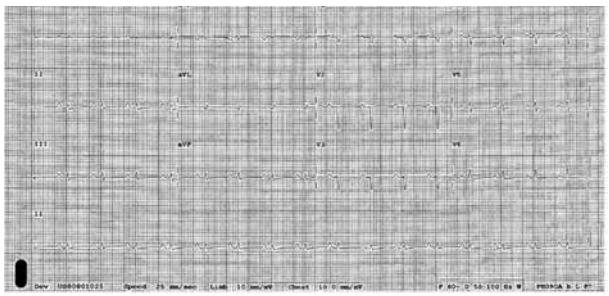
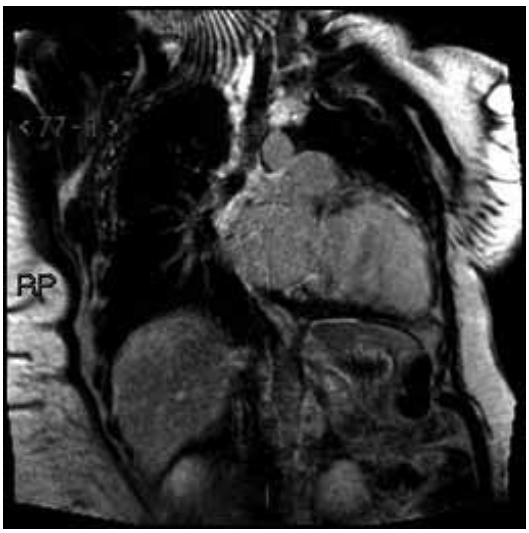


Figure 1. Patient electrocardiogram on admission

global systolic dysfunction and an estimated ejection fraction (EF) of 10% to 15%. Her previous workup, including cardiac catheterization demonstrating normal coronary arteries, had been unrevealing and no underlying cause of her cardiomyopathy had been identified at the time of admission. Previous radiologic studies demonstrated persistent mediastinal and axillary adenopathy and therefore a diagnosis of sarcoidosis was made. The patient subsequently underwent core needle biopsy of a right-sided axillary node. The pathology demonstrated noncaseating granuloma consistent with sarcoidosis. Cardiac magnetic resonance imaging (MRI) demonstrated a markedly dilated left ventricle with severe systolic dysfunction, a markedly dilated right ventricle with severe systolic dysfunction, and patchy late gadolinium enhancement with a noncoronary distribution consistent with the diagnosis of myocardial sarcoidosis (Figure 2). The patient was discharged on anticoagulation therapy and scheduled for close follow-up with cardiology and pulmonary medicine.

DISCUSSION

Sarcoidosis was first described in 1899 by Norwegian dermatologist Caesar Boeck as a foci of "epitheloid cells with large pale nuclei and also a few giant cells." The etiology of sarcoidosis remains a mystery. It affects people of all races and ethnic groups and occurs at all stages of life. It is more common in females than males, regardless of race or ethnicity. Northern Europe has the highest annual incidence of sarcoidosis, with 5 to 40 cases per 100,000 people being diagnosed annually; however, black Americans have a 3-fold higher incidence of sarcoidosis



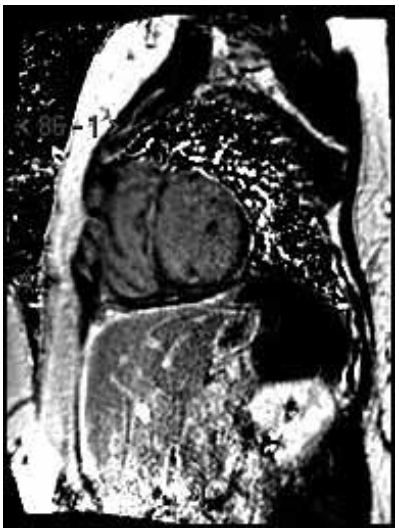


Figure 2. Cardiac MRI late gadolinium-enhanced phase-sensitive inversion recovery gradient echo images from the patient. Normal myocardium is demarcated by dark black, and in contrast scarring of the myocardium is bright white.

compared with white Americans (35.5 cases per 100,000 compared with 10.9 per 100,000).[1]

Although the etiology is elusive, several hypotheses have been proposed. Associations have been made to environmental exposures, such as wood-burning stoves, tree pollen, insecticides, and mold. More recently, an increase in the incidence of sarcoidosis was observed in New York City Fire Department rescue workers following the World Trade Center attacks in 2001.[2] Furthermore, mycobacteria and propionibacteria with concominant serum antibodies to mycobacterial antigens have been implicated. Genetic factors are also believed to contribute to the pathogenesis of sarcoidosis. Two specific gene products have been implicated in predisposition to sarcoidosis. Both class I HLA-B8 antigens and HLA class II antigens encoded by HLA-DRB1 and DQB1 have been associated with the development of sarcoidosis.

CLINICAL MANIFESTATION

Patients with cardiac sarcoidosis may present with a variety of signs and symptoms ranging from asymptomatic electrographic abnormalities to sudden cardiac death. Conduction abnormalities tend to be the most common presentation of cardiac sarcoidosis. Patients can present with a variety of conduction abnormalities based on the location of the granulomatous disease within the conduction system. Atrioventricular block is the most common finding on electrocardiogram, with 26% to 64% of patients with cardiac sarcoid demonstrating some degree of atrioventricular block. Complete heart block is the most common presenting conduction abnormality, and usually presents with syncope.[3] In addition, patients may demonstrate bundle branch blocks, supraventricular arrhythmias, and sinus node arrests. Patients may also present with ventricular arrhythmias, the second most common presentation of cardiac sarcoidosis. These arrhythmias are thought to be due to granulomatous infiltration of the myocardium, causing both sustained and nonsustained ventricular tachycardia (VT). Sudden cardiac death as a result of either complete heart block or ventricular arrhythmias is responsible for 24% to 62% of all deaths secondary to cardiac sarcoidosis.[3]

Congestive heart failure is a relatively common consequence of cardiac disease, representing 10% to 30% of cardiac findings.[3] Patients may display systolic or diastolic dysfunction, as well as a combination of the 2 disorders, secondary to granulomatous infiltration of the myocardium. Patients may present with the typical clinical symptoms of heart failure, such as dsypnea, orthopnea, peripheral edema, or paroxysmal nocturnal dsypnea. Patients are also at risk for developing ventricular aneurysms secondary to the granulomatous infiltration and pathological thinning of the ventricular wall. Valvular disease, with mitral regurgitation being the most common valvular complication, has also been demonstrated.[3] Mitral regurgitation is secondary to papillary muscle dysfunction; however, direct granulomatous involvement of the valve leaflets has been described in all 4 valves, although this condition is rare. Patients also may demonstrate evidence of right heart failure as a result of sarcoid-induced pulmonary hypertension secondary to fibrotic pulmonary changes.

DIAGNOSIS

Cardiac involvement is diagnosed clinically in only about 5% of patients with sarcoid, yet it is present in the myocardium at autopsy in approximately 20% to 30% of patients.[4] Patients with myocardial sarcoid usually have minimal or no clinical evidence of extracardiac organ involvement, a situation that generally leads to delayed recognition of sarcoidosis as an etiology of cardiac symptoms. In addition, approximately 60% of patients present initially with sudden cardiac death. In 1993, the Japanese Ministry of Health and Welfare (JMH) published guidelines for diagnosing cardiac sarcoidosis (Table 1). However, the role of these guidelines in the diagnosis of cardiac sarcoidosis has not been validated.

Considerable evolution has occurred in the diagnosis of cardiac sarcoid with the advent of cardiac MRI. Cardiac MRI enables clinicians to visualize the myocardium directly and assess its regional structure and function from the subendocardial to subepicardial level, as well as to simultaneously assess regional and global ventricular function via both static and functional imaging techniques.[4] One recent study evaluated the utility of delayed-enhancement cardiovascular MRI (DE-CMR) compared with the current standard consensus criteria for the diagnosis of cardiac sarcoidosis developed by the JMH.[5] In this study 81 patients with biopsy-proven extracardiac sarcoidosis were prospectively recruited for a parallel and masked comparison of cardiac involvement between DE-CMR and JMH guidelines. Cardiac MRI identified 21 patients (26%) with hyperenhancement consistent with myocardial damage, whereas JMH criteria identified cardiac involvement in 10 patients (12%), of which 8 were also positive by DE-CMR. On pathological confirmation of 15 of these patients, cardiac sarcoid was identified in 4 patients, and all 4 of the sarcoids in these patients were detected by DE-CMR, whereas only 2 patients were identified by JMH criteria. Moreover, in 2 patients with autopsy-confirmed diagnosis of cardiac sarcoid, gross examination of the heart demonstrated 1 to 1 concordance between the location, shape, and extent of the myocardial lesions and in vivo hyperenhancement. Furthermore, those patients with evidence of myocardial damage on DE-CMR had a 9-fold higher rate of adverse events and an 11.5-fold higher rate of cardiac death than those without damage. This evidence further supports the hypothesis that relatively small regions of myocardial damage in the absence of systolic dysfunction can provide the substrate for ventricular arrhythmias and conduction disturbances. Cardiac sarcoidosis typically appears as patchy subepicardial delayed enhancement with right-to-left ventricular involvement.

TREATMENT

The management of cardiac sarcoid is based on the clinical manifestations and activity of the disease. Therapeutic strategies include limiting disease progression, treating the active phase of the disease, preventing complications associated with cardiac involvement, and improving cardiac function despite preexisting cardiac damage.

Corticosteroids are the focus of active disease suppression and have been associated with improved survival. A study of 95 patients with cardiac sarcoid demonstrated a substantially higher 5-year survival in patients treated with corticosteroids (75%) compared with control patients in whom cardiac sarcoidosis was proven at biopsy (10%).[6] In this study, the outcome was optimal when the left ventricular EF (LVEF) was >50%, with an 89% 5-year survival, suggesting that early initiation of corticosteroid therapy has a significant impact on overall survival. Although the optimal dose and duration of therapy

Table 1. Japanese Ministry of Health and Welfare Guidelines for Cardiac Sarcoid

Histological Diagnosis Group

1. Cardiac sarcoidosis is confirmed when histological analysis of operative

or

2. Endomyocardial biopsy specimens shows epithelioid granuloma without caseating granuloma

Clinical Diagnosis Group

In patients with a histological diagnosis of extracardiac sarcoidosis, cardiac sarcoidosis is suspected when item (a) and one or more of items (b) through (e) are present:

(a) Complete right bundle branch block, left axis deviation, atrioventricular block, ventricular tachycardia, premature ventricular contraction (Lown 2) or abnormal Q or ST-T change on the electrocardiogram or ambulatory electrocardiogram
(b) Abnormal wall motion, regional wall thinning, or dilatation of the left ventricle
(c) Perfusion defect by thallium-201 myocardial scintigraphy or abnormal accumulation by gallium-67 or technetium-99m myocardial scintigraphy
(d) Abnormal intracardiac pressure, low cardiac output or abnormal wall motion or depressed ejection fraction of the left ventricle
(e) Interstitial fibrosis or cellular infiltration over moderate grade even if the findings are nonspecific

have yet to be established, the current Japanese protocols recommend 30 mg/day or 60 mg every 2 days of prednisone for 8 to 12 weeks, with a gradual tapering of the dose to 10 to 20 mg every other day over a period of 6 to 12 months to establish the minimum effective dose.[2] Once the disease has remained stable, further tapering and eventual discontinuation of therapy can be achieved.

Common cardiac complications of sarcoidosis include complete heart block, sustained VT, left ventricular (LV) dysfunction, and reduced systolic function. These complications can all be managed by the implantation of various cardiac devices. The timing of device placement must be orchestrated with the initiation of corticosteroid therapy, given the risk of poor wound healing and increased risk for device infections in patients on chronic immunosuppressive corticosteroid therapy. If a device is required, it should be placed prior to the initiation of steroids, and complete wound healing should be achieved prior to treating with steroids.

Treatment of advanced heart block involves placement of a dual-chamber pacemaker. In patients with reduced LV systolic function (EF <35%) both implantable cardiac defibrillator (ICD) and cardiac resynchronization therapy (CRT) devices should be considered. Although data are limited regarding the efficacy of CRT in sarcoidosis, patients who would benefit the most from a CRT device are those with class III or IV heart failure, complete left bundle branch block pattern, and reduced systolic function, with an EF <35%.[7]

Treatment of reduced cardiac function (EF <50%) is similar to treatment of other cardiomyopathies and etiologies of heart failure, with the addition of corticosteroids. All patients should be treated with angiotensin-converting enzyme inhibitors and beta-blockers. Patients with severely reduced cardiac function (EF <35%) should undergo an electrophysiology study with programmed ventricular stimulation to determine the utility of ICD implantation. In one study of 32 patients, on the basis of the ability of the electrophysiology study to induce sustained ventricular arrhythmias, programmed ventricular stimulation predicted subsequent life-threatening arrhythmias in patients presenting without spontaneous sustained ventricular arrhythmias.[7] Sustained inducible ventricular arrhythmias were associated with an increased incidence of appropriate ICD therapy or sudden death (relative hazard 4.47%). In addition, spontaneous sustained ventricular arrhythmias predicted appropriate ICD therapy or sudden death (relative hazard 6.30). The combined sensitivity of spontaneous or inducible sustained ventricular arrhythmias to predict appropriate ICD therapy or sudden death was 0.82, and the specificity was 0.86. Patients who received appropriate ICD therapy had an increased mean survival time of 80 months, and ICDs reliably terminated life-threatening arrhythmias in this high-risk patient population, demonstrating that patients who are treated with ICD therapy may derive a prolonged survival with preserved quality of life. In addition to ICD placement, catheter ablation is emerging as a treatment for VT. It has been demonstrated that most VT is reentrant[8] and particularly inducible at the active inflammatory sites. Results of one study demonstrated that 50% of patients who underwent ablation for VT were free of recurrent VT at long-term follow-up.[9]

CONCLUSIONS

Cardiac sarcoid is a manifestation of sarcoidosis that is relatively underdiagnosed given the difficulty in determining the presence of cardiac involvement by conventional methods. Cardiac MRI is emerging as a noninvasive means for early identification of cardiac involvement in sarcoid. Although optimal treatment has yet to be clearly established, studies have demonstrated that early diagnosis leads to improved treatment outcomes.

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Minoxidil-Associated Pericardial Effusion

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We report a case of recurrent pericardial effusions in a 64-year-old woman. After an initial evaluation in which she underwent multiple pericardiocenteses and the more common causes of pericardial effusion were excluded, the antihypertensive medication minoxidil was identified as a possible source of this patient's pericardial effusion. After discontinuation of this medication the patient had no reaccumulation of pericardial fluid. Pericardial effusion is a known complication of the use of minoxidil, and it is important for clinicians to consider this medication as a potential cause of pericardial effusion because the best treatment is discontinuation of the offending agent.

BACKGROUND

Idiopathic pericardial effusion presents a significant diagnostic challenge and is an important clinical entity because of the possibility of progression to tamponade. It is not uncommon for clinicians to encounter a patient with a pericardial effusion for which the etiology remains unclear after laboratory analyses have been performed. Common etiologies of pericardial effusions include malignancy, infection, autoimmune disease, iatrogenic cardiac wall injury, hypothyroidism, aortic dissection, and adverse drug effects.[1,2] Acute pericarditis often drives the accumulation of pericardial fluid in patients with autoimmune disease, infection (most commonly by coxsackie virus, echovirus, Epstein-Barr virus, or tuberculosis, which is more common in patients from developing countries), or malignancy. Adverse drug effects are an uncommon but important cause of pericardial fluid accumulation. We report a case of the antihypertensive drug minoxidil as the etiological agent in persistent pericardial effusion.

CASE DESCRIPTION

Our patient was a 64-year-old black woman who had initially presented 3 months previously with weakness and failure to thrive. Transthoracic echocardiography done at that time revealed a large pericardial effusion, and she underwent pericardiocentesis with aspiration of 800 mL of straw-colored fluid. Two and one-half months later the large effusion recurred and a second pericardiocentesis was done, with removal of 1200 mL fluid. On her third admission for pericardial effusion the patient presented with pulsus paradoxus, suggesting the development of pericardial tamponade. All 3 presentations occurred within a 3-month period.

The patient had a history of T1c N0 invasive ductal carcinoma of the breast, diagnosed 5 years previously, which was treated with lumpectomy and sentinel lymph node dissection. Because of the predicted low risk of recurrence the patient did not receive treatment with either radiotherapy or systemic chemotherapy. Three months prior to this admission she had undergone restaging with brain magnetic imaging and positron-emission tomography–computed tomography, which showed no evidence of metastatic disease. In addition, serial yearly mammograms had shown only a stable postlumpectomy scar. The patient also had a history of hypertension, a significant stroke with persistent aphasia, seizures, coronary artery disease, diabetes mellitus, chronic kidney disease, and hypercholesterolemia. She had no history of systemic lupus erythematosus or rheumatoid arthritis.

On the day of admission the patient's physical exam revealed a blood pressure of 127/63 mmHg and pulse of 72 beats/min. Pulsus paradoxus was documented with a pressure drop of 48 mmHg with respiratory variation. The cardiovascular examination revealed distant heart sounds and regular rate and rhythm without murmur, rub, or gallop. There was no jugular venous distension, and Kussmal's sign was not present. The patient did have trace lower extremity edema. Her pulmonary examination revealed bibasilar rales.

The results of pertinent laboratory and diagnostic studies are reported in Table 1. The Manitoux purified protein derivative test was nonreactive. The patient's medications at admission included aspirin, labetalol, amlodipine, simvastatin, anastrozole, phenytoin, levetiracetam, glargine, regular insulin, doxazosin, minoxidil, omeprazole, paroxetine, and albuterol. There had been no significant

medication changes in the preceding months, and she had started treatment with minoxidil 5 mg daily approximately 3 years prior to this admission. Her electrocardiogram showed no evidence of electrical alternans. Her transthoracic echocardiogram revealed a large circumferential pericardial effusion (Figure 1). There was evidence of increased pericardial pressure, including diastolic collapse of the right ventricle and exaggerated respiratory variation of early mitral inflow velocity on pulse-wave Doppler.

With immunological studies pending for possible drug-induced lupus, minoxidil and phenytoin were identified as 2 possible causes of the patient's recurrent pericardial effusion, and both medications were discontinued. Results of her antihistone antibody test were negative, and subsequently the effusion was considered most likely to be secondary to minoxidil. A follow-up echocardiogram done 3 weeks after discontinuation of minoxidil showed no reaccumulation of fluid. In the 6 months after discharge the patient showed no clinical signs of pericardial tamponade or fluid reaccumulation.

DISCUSSION

Drug-associated pericardial effusions are relatively rare and occur through various mechanisms. One mechanism for the development of pericardial effusion is drug-induced lupus erythematosus. Although there are no standard diagnostic criteria,

Table 1. Laboratory Evaluation Results

Test	Result	Reference Range
Thyroid stimulating hormone	2.93 IU/mL	0.45-4.50 IU/mL
Free T4	0.6 ng/mL	0.7-1.5 ng/mL
Sedimentation rate		
Admission	25 mm/h	0-20 mm/h
3 mo before admission	9 mm/h	0-20 mm/h
C-reactive protein	1.2 mg/dL	<0.8 mg/dL
Antinuclear Antibodies	Negative	Negative
Antihistone antibody	0.1	<1.0
Anti–double-stranded DNA antibody	<1 IU/mL	<5 IU/mL
Rheumatoid factor	<20 IU/mL	<30 IU/mL
Manitoux test (PPD)	0 mm	<15 mm
Serum creatinine	1.4 to 1.8	0.6-1.1 mg/dL

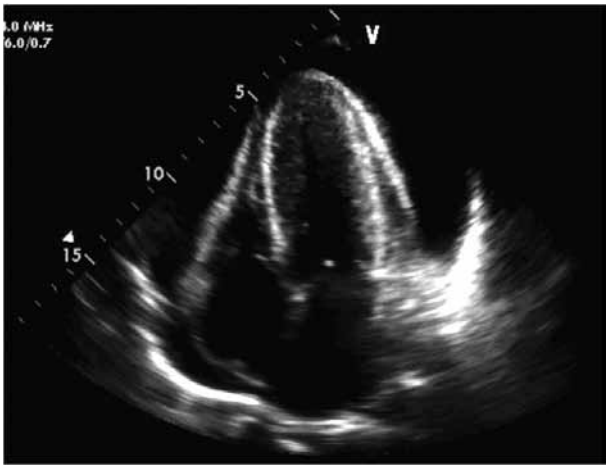

Figure 1. Echocardiogram obtained at the time of admission

up to 95% of cases of drug-induced lupus are associated with antihistone antibodies,[3] whereas anti–double-stranded DNA antibodies are typically not detected.[4] Patients with drug-induced lupus often complain of generalized arthritis and myalgias, although the typical malar rash is less common.[3] These patients may also exhibit photosensitivity or erythema nodosum.[3] Procainamide, hydralazine, and quinidine are the drugs most commonly associated with drug-induced lupus.[3,4] In regard to this case, the patient's recurrent pericardial effusions did not seem to be secondary to drug-induced lupus given the negative results for the antihistone antibody test along with a lack of clinical evidence of systemic lupus. She had no apparent increased joint pain/swelling, typical skin manifestations of lupus, or electrocardiogram changes to indicate acute pericarditis.

Minoxidil is an antihypertensive medication that is associated with pericardial effusions usually unrelated to drug-induced lupus.[5-9] Minoxidil is a potent arterial vasodilator that targets adenosine triphosphate–sensitive potassium channels in smooth muscle cells.[10] Minoxidil was initially used in the early 1970s as an antihypertensive medication in patients with resistant hypertension.[9,11-14] Minoxidil is typically used in combination with a beta blocker and a loop diuretic to counteract its common adverse effects of fluid retention and tachycardia.[9] Minoxidil has been shown to effectively control blood pressure in patients with resistant hypertension.[11,14,15]

The most common adverse effects of minoxidil include fluid retention, tachycardia, and hypertrichosis.[15] Fluid retention is associated with potassium-channel activation in the glomerulus, leading

to increased Na/Cl/K cotransporter activity and increased sodium retention.[10] Minoxidil-associated tachycardia is attributed to its induction of arterial dilation, leading to carotid and aortic baroreceptor activation and subsequent sympathetic nervous system activation.[10,14] Orthostatic symptoms are limited with this antihypertensive owing to the lack of venous dilation,[9] although there are concerns about an increased risk of myocardial ischemia in the presence of increased oxygen demand. Cardiac output has been shown to increase with minoxidil use because of tachycardia and increased stroke volume.[12]

The etiology of minoxidil-associated pericardial effusion remains unclear. It is possible that the effusion is a variant of the fluid retention that is a common adverse effect of minoxidil.[9] In one series 4 of 6 patients with pericardial effusion in the setting of minoxidil use without other associated risk factors for pericardial disease were found to have at least 10 pounds of weight gain during the study.[13] Another possible mechanism is increased myocardial blood flow that is induced by minoxidil and leads to transudative flow from increased hydrostatic force.[12] Current evidence suggests that minoxidil-induced pericardial effusion resolves with cessation of the medication.[5-7,9]

The diagnostic evaluation of the pericardial effusion in this patient was challenging because of her multiple medical problems. A timeline of events leading to our evaluation and treatment is shown in Figure 2. Because of the patient's history of breast cancer, this disease was initially thought to be the most likely etiology, but we excluded this possibility on the basis of the negative results of cytological anaylsis of 3 separate samples as well as a negative positon-emission tomography–computed tomography scan. The patient's chronic kidney disease was a risk factor for the development of minoxidil-associated pericardial effusion. In one series, 8 of 37 patients treated with minoxidil developed pericardial disease (7 patients had effusion and 1 patient had isolated pericarditis), and all 8 of these patients had a baseline serum creatinine of >2.5 mg/dL.[5] In a limited number of case reports minoxidil has been implicated as the source of pericardial effusion in patients with normal renal function.[7] The association of chronic kidney disease with cardiac effusion in patients taking minoxidil may be spurious, however, because typically the only patients considered for minoxidil

Table 2. Pericardial Fluid Analysis

Test	Result
White blood cells	184 10^3/μL
Segmented neutrophils	4%
Lymphocytes	17%
Monocytes/macrophages	79%
Eosinophils	0%
Basophils	0%
Hematocrit	No visible blood present
pH	7.6
Total Protein	4.4 g/dL
Lactate dehydrogenase	171 U/L
Gram stain	Few mononuclear cells, no red blood cells, no bacteria seen, no acid fast bacilli
Culture, acid fast bacilli	No acid fast bacilli isolated after 8 wk
Culture, aerobic and anaerobic	No growth
Cytology	Chronic inflammation, no malignancy
	Chronic inflammation, no malignancy
	Chronic inflammation, no malignancy

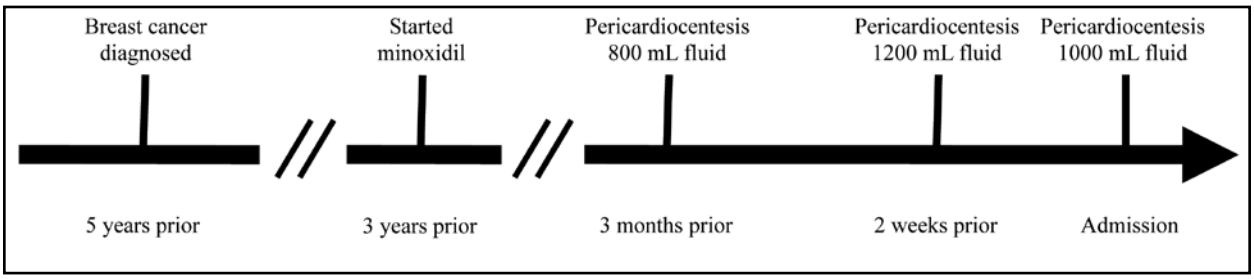

Figure 2. Timeline of clinical events for this patient.

therapy are those with resistant hypertension, which often occurs concomitantly with advanced chronic kidney disease.

The time course of minoxidil-associated pericardial effusion is quite variable; in reported cases it ranged from 2 months to 10 years, with resolution noted only upon medication cessation.[6,8] The average time of onset in another case series with 10 documented cases of associated pericardial disease (9 effusions, 1 pericarditis) was 13.7 months after medication initiation.[11] Two of these 9 cases of pericardial effusion were clinically significant and resolved with medication cessation. In an even larger study of 1869 patients treated with minoxidil who were followed for 8 years, pericardial disease was found in 91 patients (4.8% of the population).[13] Although this study remains the largest to date in which pericardial effusions were investigated in patients undergoing chronic minoxidil treatment, this finding of 4.8% was likely falsely inflated because the investigators failed to rule out the typical causes of pericarditis such as infection, malignancy, and autoimmune disease.

Minoxidil has been demonstrated to be effective in the control of resistant hypertension. Typical causes of recurrent pericardial effusion include neoplasm, systemic autoimmune disease, infection, hypothyroidism, trauma, heart failure, and renal disease. Drug-associated effusions should also be considered as a potential cause. In patients with pericardial effusion who are on minoxidil therapy, cessation of this medication should be considered and was an effective intervention for resolving the pericardial effusion in this patient.

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Hypertensive Emergency after Mannitol Administration for Ciguatera Fish Poisoning

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Ciguatera fish poisoning is a clinical syndrome that may develop after ingestion of ciguatoxin-containing fish. We describe a 67-year-old woman with acute onset of symptoms after consumption of a grouper fish while on vacation in the Bahamas. After ingestion, the patient developed diarrhea, abdominal pain, perioral paresthesias, lower extremity weakness, and cold allodynia, which is a classic clinical finding in ciguatera fish poisoning. As part of her treatment the patient was administered mannitol and subsequently developed a hypertensive emergency. The patient had no lasting significant improvement in neurological symptoms after administration of mannitol, although her symptoms did resolve with time. Mannitol is generally considered a safe treatment for the neurological sequelae of ciguatera fish poisoning. This patient's apparent adverse reaction to mannitol, however, and the limited data supporting its use in ciguatera fish poisoning highlight the importance of future research to better characterize the benefits and risks of this regimen.

CASE DESCRIPTION

A 67-year-old woman with a history of hypertension presented to the emergency department at the University of Virginia Health System with complaints of lower extremity weakness. The patient reported that she had recently visited the Bahamas, where she had developed diarrhea and abdominal pain hours after eating a locally caught grouper fish, and severe substernal chest pain the following day. She sought medical attention and per her report after receiving sublingual nitroglycerin in a local hospital she was discharged with the diagnosis of indigestion. The patient later developed perioral tingling, which progressed over the next few hours into complete paresthesia of the tongue and all extremities. The patient said that her oral symptoms were so pronounced that when drinking cold water she felt like she was "drinking gasoline." In addition, the lower extremity weakness progressed to the sensation that her legs would "give way" with ambulation. The patient returned to the United States 7 days after the onset of symptoms and sought medical care at the University of Virginia Health System.

On admission the patient's blood pressure was elevated at 186/86 mm Hg, her pulse was 90 beats per minute, respirations were 16 per minute, and she was afebrile at 36.5°C. Results of a physical examination were remarkable only for weakness of the lower extremities. She was otherwise neurologically intact without motor or sensory deficit. The patient reported cold allodynia, a classical finding in ciguatera poisoning. When her hand was submerged in cold water she experienced dysasthesia, which she described as tingling that quickly progressed to a burning sensation in the hand. Results of routine laboratory evaluation did not reveal a cause of her weakness. The patient had normal renal and liver function. All electrolytes were within the reference range. The patient's medications prior to presentation included domperidone, esomeprazole, valsartan, and hydrochlorathiazide.

Because the patient's history was consistent with the clinical diagnosis of ciguatera poisoning, she was administered mannitol 1 g/kg (60 g total) intravenously. After receiving mannitol the patient reported a moderate lessening of her symptoms. In particular she stated that it became more comfortable to drink cold water. However, approximately 1 hour after mannitol administration the patient developed substernal chest pain and her blood pressure increased to 220/106. At this point the patient was considered to have a hypertensive emergency and she was admitted to the hospital for further observation in the intensive care unit. The patient received intravenous labetalol and hydralazine for acute blood pressure control. When she was stabilized she was restarted on her home blood pressure medications. Her chest pain resolved completely. At discharge her blood pressure was 116/54. Results of electrocardiogram and laboratory evaluation of cardiac enzymes revealed no evidence of myocardial infarction.

By the time she was discharged the patient's neurologic symptoms had returned to their preadmission baseline. These symptoms continued for the next 4 months and then spontaneously resolved.

DISCUSSION

Ciguatera poisoning is a clinical syndrome that develops after consumption of ciguatoxin-contaminated fish. Ciguatoxins are produced by the dinoflagellate Gambierdiscus species, which are common in warm water coral reefs between the latitudes of 35 degrees north and south.[1-3,4] The toxin bioaccumulates through the food chain. It is initially ingested by herbivorous fish, like the surgeonfish and parrotfish, which are subsequently consumed by carnivorous fish that are eaten by humans. Species commonly associated with ciguatera poisoning in humans are predatory fish such as barracuda, grouper, amberjack, sea bass, and Spanish mackerel.[3,5]

In the continental United States, the National Poison Data Center reported only 168 single-exposure cases during 2008.[6] However, 20,000 to 40,000 cases occur in Puerto Rico and the United States Virgin Islands every year, and the true incidence is considered significantly underreported.[7,8] Oceania and the tropical Atlantic and Caribbean area are considered ciguatera-endemic regions and cases in the continental United States can often be linked to exposure from fish in these regions.[9]

Ciguatoxins are heat-stable molecules. Although the exact mechanisms for toxicity are under investigation, ciguatoxins are known to open voltage-sensitive sodium ion channels, which can cause neuronal depolarization and axonal swelling.[9,10] Gastrointestinal symptoms of ciguatera fish poisoning include nausea, vomiting, abdominal pain, and diarrhea, which commonly occur within 3 to 30 hours of ingestion of ciguatoxin-containing fish.[4,11,12] Neurological symptoms include circumoral and extremity parasthesias, weakness, arthralgias, and myalgias.[13] The classically described neurological finding in ciguatera poisoning is the reversal of the sensations of hot and cold. Some descriptions state that gross hot/cold sensation remains intact while exaggerated nerve depolarization leads to an intense sensation perceived on contact with cold.[14] Therefore this finding is best described as cold allodynia.

Cardiovascular effects of ciguatera poisoning include hypotension and bradycardia or tachycardia, all mediated by ciguatoxin effects on myocardial ion channels.[4] Typical duration of illness includes gastrointestinal symptoms that last 1 to 2 days, cardiovascular symptoms for 2 to 5 days, and neurological symptoms for 2 to 3 weeks. In severe cases, however, all symptoms have been reported to last for months.[15]

The treatment of ciguatera poisoning is largely supportive with the exception of administration of mannitol. Case series and anecdotal reports of treatment with intravenous mannitol describe significant resolution of symptoms in treated patients. The mechanism of action of mannitol in ciguatera poisoning is unclear. One possibility is that mannitol, through osmotic diuretic action, may result in reduced edema in Schwann cells and reduced nodal swelling.[16] Another possible mechanism of action is direct inhibition of ciguatoxin-induced neural membrane sodium-channel opening.[17] Mannitol also may act by directly causing dissociation of ciguatoxin from its binding site.[17]

Reports of the effectiveness of mannitol have led to the clinical recommendation that when ciguatera toxicity is diagnosed mannitol should be given within 48 to 72 hours of symptom onset. Many practitioners also administer treatment beyond 72 hours of ingestion.[8,12,18-20] However, the only double-blind randomized controlled trial performed to evaluate the use of mannitol showed no difference in outcomes in patients with ciguatera poisoning treated with saline compared with patients treated with mannitol.[21]

There have been no reported adverse reactions to mannitol when used for treatment of ciguatera fish poisoning in case series or controlled trials.[8] Mannitol is thus considered safe provided volume depletion and electrolyte abnormalities are addressed before administration.[10] However, in that mannitol is a hypertonic solution, infusion causes a transient expansion of the extracellular volume.[22] Although hypertension has not been reported previously as an adverse reaction to mannitol infusion, in this patient with significantly elevated blood pressure at presentation the infusion of mannitol and subsequent extracellular volume expansion likely precipitated a hypertensive crisis. Mannitol administration has been linked to other complications, including electrolyte abnormalities, acute kidney injury, and complications of transient hypervolemia and diuretic effect–induced hypovolemia.[23,24]

CONCLUSIONS

This case is important because it highlights the classical and unique features of this clinical syndrome. This case is also interesting in that this patient presented in Charlottesville, Virginia, which is a landlocked city far from ciguatera-endemic regions. As physicians in Central Virginia we often view illness in the returning traveler as an opportunity to evaluate patients for infections with foreign etiologies. This case reminds us to also consider toxicities of foreign origin in the ill returning traveler.

This patient's adverse reaction after administration of mannitol highlights the need for clarification of the role of this commonly used medication in ciguatera fish poisoning. With a well-established low incidence of serious adverse reactions, mannitol is appropriately viewed as a safe and typically benign intervention. Much of the support for administration of mannitol in ciguatera toxicity comes from anecdotal testimony and case reports. The symptomatic benefit from mannitol has been measured only by patient description, which is subjective and prone to significant interpatient reporting variability. The benefits of mannitol described in case reports and case series are also subject to recall and reporting bias. The only randomized controlled double-blind trial of mannitol use for ciguatera fish poisoning did not show mannitol administration to be beneficial.

The effects of ciguatera poisoning can be debilitating and even fatal. Because no alternative treatment options are available other than supportive care, mannitol remains a common therapy despite limited evidence supporting its use. However, considering how little, if any, clinical benefit has been scientifically documented from mannitol administration in ciguatera poisoning, it is important to carefully weigh the risks of even the minor and infrequent adverse effects against the potential benefits. This case is significant because it demonstrates a potential complication associated with routine treatment and clearly indicates that further research is needed to better elucidate the benefits and risks of mannitol for the treatment of ciguatera fish poisoning.

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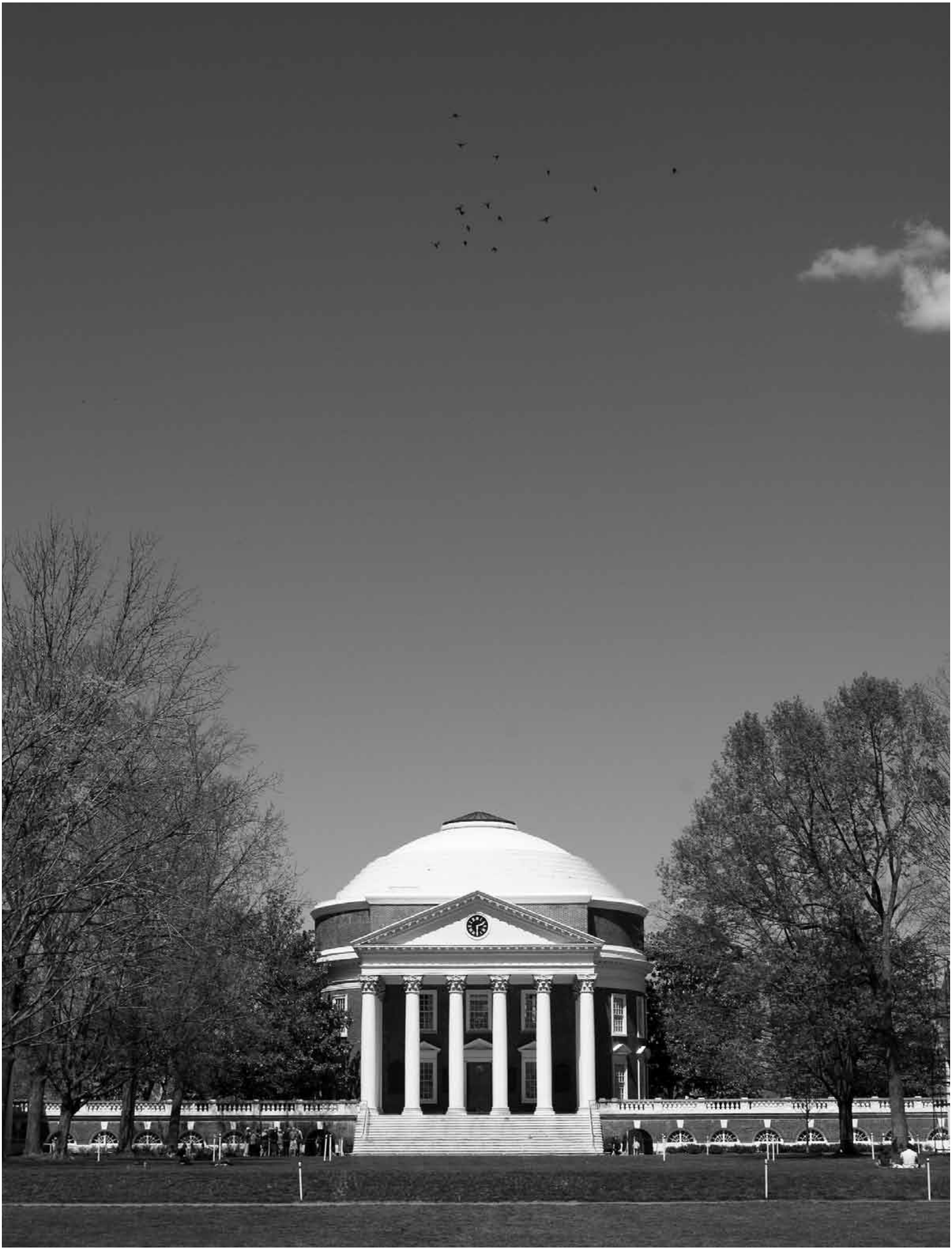

An Unusual Presentation of Multiple Myeloma

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Multiple myeloma is a malignant proliferation of plasma cells that produce a monoclonal paraprotein. It can present in a variety of ways, including bone pain from pathologic fractures, fatigue from anemia, and asymptomatic disease found on laboratory review with renal failure or hypercalcemia[1] In this case, the patient presented with spinal cord compression and lung lesions.

CASE DESCRIPTION

A 47-year-old white man with a 15 pack-year smoking history presented to our emergency department with an 8-month history of bilateral lower extremity and back pain and a 2- to 3-month history of lower extremity weakness, which ultimately led to his being confined to a wheelchair. Physical examination revealed weakness and sensory neuropathy. Magnetic resonance imaging (MRI) was performed, which demonstrated a large epidural soft-tissue mass along the posterior bodies of L3-S1 with marked narrowing of the spinal canal on T2 imaging (Figure 1). A chest radiograph (Figure 2) showed multiple round soft-tissue densities, appearing pleural based, growing from ribs in bilateral hemithoraces. Laboratory studies

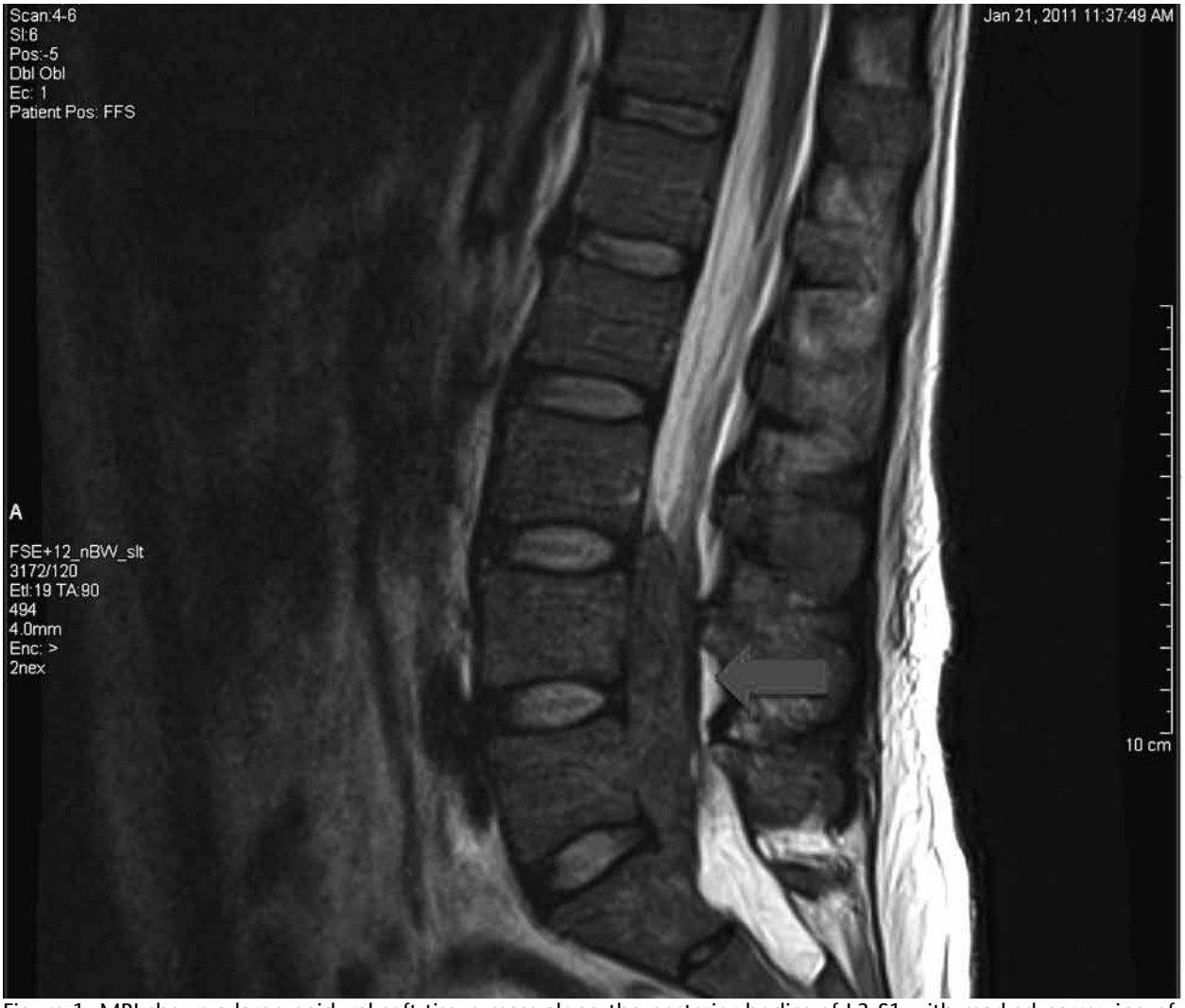

Figure 1. MRI shows a large epidural soft tissue mass along the posterior bodies of L3-S1 with marked narrowing of the spinal canal on T2.

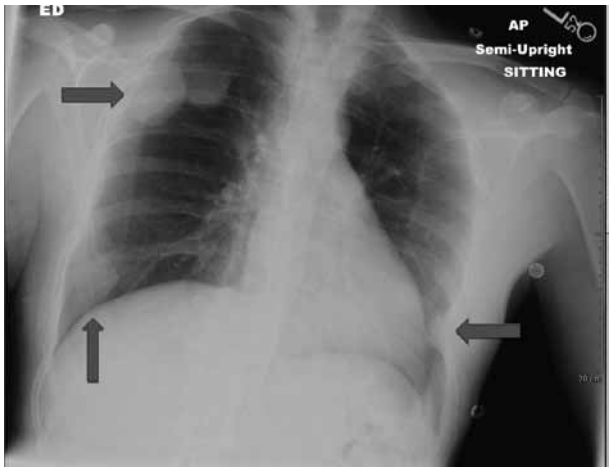

Figure 2. Chest radiograph shows multiple round soft-tissue densities, which appear to be pleural based, growing from the ribs in bilateral hemithoraces.

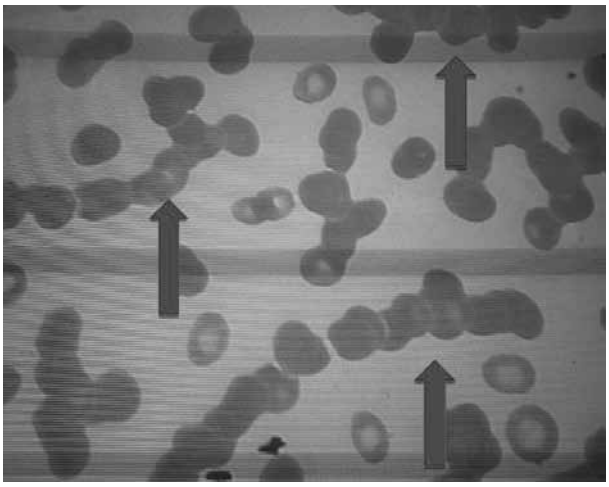

Figure 3. A peripheral smear in which rouleaux are apparent.

revealed thrombocytopenia, anemia, and an elevated total protein. Results of a white blood cell count with differential and liver function tests were within normal limits, and lactate dehydrogenase, haptoglobin, calcium, and creatinine concentrations were within reference intervals. A peripheral smear was performed, and rouleaux were apparent (Figure 3). The patient had a mass on the chest that was amenable to biopsy, and plasma cells were found in the biopsy sample. Serum protein electrophoresis demonstrated a restricted band. Immunofixation was performed, and the band was identified as an IgA kappa monoclonal protein. A skeletal survey showed multiple lytic lesions, and a bone marrow biopsy specimen showed >90% cellularity with atypical plasma cells.

With these findings, the diagnosis of multiple myeloma was made, with the spinal cord lesion and pleural lesions presumed to be plasmacytomas.

TREATMENT

Given the patient's spinal cord compression, treatment with dexamethasone was immediately initiated. Neurosurgery and radiation oncology consultations were obtained. but with multiple myeloma in the differential of diagnoses and the ability to perform a prompt chest wall biopsy, the patient was spared neurosurgical intervention. He underwent radiation therapy to the spinal cord, and with steroid treatment and physical therapy had marked improvement of his strength. He was seen in the hematology oncology clinic for follow-up after the completion of his radiation therapy, with plans to initiate revlimid and decadron on 28-day cycles.

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Aggressive Potassium Repletion Leading to Iatrogenic Pill Esophagitis

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Hypokalemia in hospitalized patients is seen regularly by internists. Reflexive treatment with oral potassium supplementation is commonly done without pause. However, we present a case of iatrogenic pill esophagitis in a patient with a previously undiagnosed radiation-induced esophageal stricture.

CASE DESCRIPTION

An 81-year-old man with a medical history of unresectable stage III non–small-cell lung cancer treated with chemoradiation therapy presented with multifocal aspiration pneumonia. He was malnourished. The patient responded well to antibiotics, but required continued electrolyte replacement. The patient received a 10-milliequivalent potassium chloride tablet and complained of a "sticking sensation" in his throat. A barium swallow revealed an undiagnosed esophageal stricture with the retained potassium chloride pill present in the proximal esophagus (Figure 1). Diagnostic and therapeutic endoscopic balloon dilatation advanced the pill into the stomach and revealed signs of pill esophagitis.

DIAGNOSIS

Esophageal stricture secondary to radiation therapy with retained pill causing pill esophagitis.

DISCUSSION

Esophageal stricture is a known complication of radiation treatment for head and neck cancers (HNCA). Outside of peptic esophagitis (occurring in 63% of patients), stricture is the second most frequent esophageal complication in the treatment of HNCA, occurring in 23% of patients.[1] Similarly to our case, esophageal stricture was noted in 2 of 16 study participants in a recent trial of combined radiation and chemotherapy treatment of non–small-cell lung cancer.[2] It is important to consider esophageal pathology in patients receiving any thoracic radiation, not just HNCA patients. Given this fact, the American Academy of Otolaryngology recommends routine esophageal screening in patients receiving radiation treatment.[1]

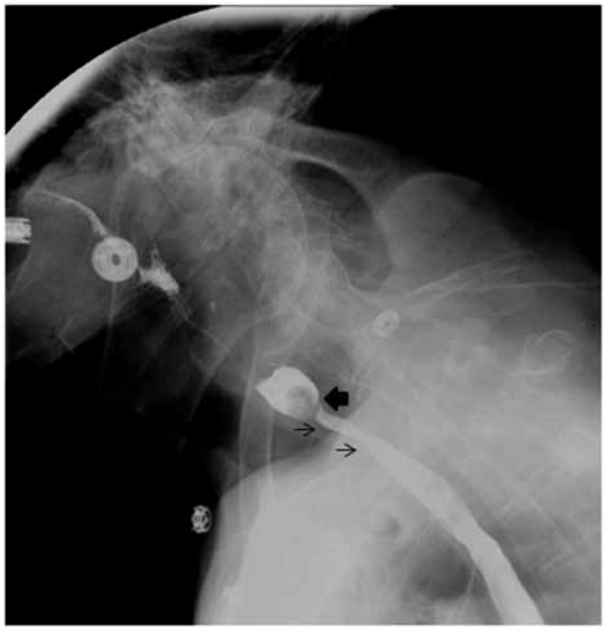

Figure 1. Esophagogram with rapid-sequence fluoroscopic imaging demonstrating a filling defect at the junction of the cervical and thoracic esophagus representing a retained pill (large black arrow). There is an upper thoracic esophageal stricture approximately 5 cm in length (thin arrows) distal to the filling defect.

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Identification of Massive Free Air on Supine Roentgenogram of the Abdomen

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CASE DESCRIPTION

A 59-year-old man was admitted to the medical intensive care unit with the diagnosis of a bleeding gastric ulcer. The patient initially presented with hematemesis and hematochezia and underwent an emergency esophagogastroduodenoscopy. This procedure revealed a 1.5-cm ulcer in the cardia of the stomach with a pulsatile bleeding vessel at the ulcer margin. The bleeding was controlled with hemoclip placement. Two days after the initial endoscopy the patient developed cardiac arrest with pulseless electrical activity and was successfully resuscitated. Physical examination performed after resuscitation revealed that the patient's abdomen was rigid and board-like.

DIAGNOSIS

Given the concerning physical exam finding of a rigid abdomen, the patient underwent a supine abdominal roentgenogram, which clearly showed an intraabdominal free air collection (Figure 1). The oval pattern evident on the roentgenogram was identified as an early "football sign." This radiographic sign, which appears in the shape of the American football, is more commonly found in children and classically outlines the entire abdomen.[1,2] Although present in only 2% of cases of pneumoperitoneum in adults,[3] this radiographic sign of abdominal free air is important for all physicians to recognize because it heralds the need for urgent surgical intervention.

MANAGEMENT

After review of the patient's roentgenogram, he was taken to the operating room for an exploratory laparotomy, during which a perforated gastric ulcer was found and treated with a partial gastrectomy.

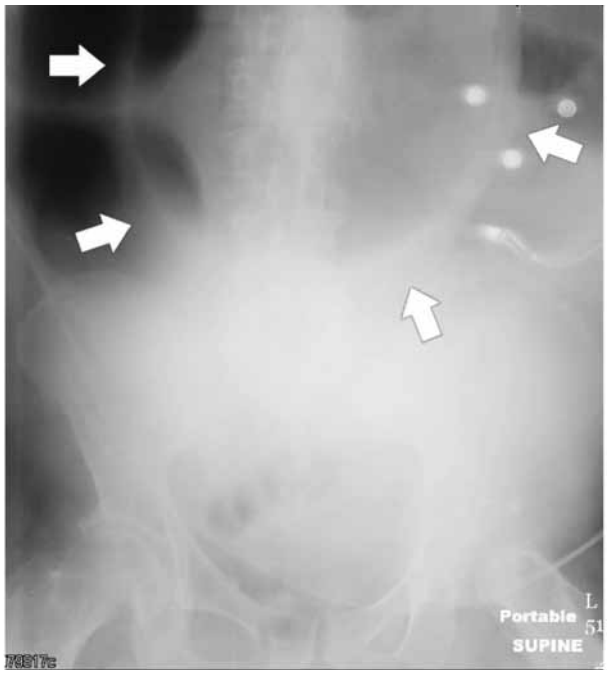

Figure 1. Supine roentgenogram performed after the patient was resuscitated. White arrows demarcate the boundaries of the intraabdominal air collection.

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Swyer-James-MacLeod Syndrome

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Swyer-James-MacLeod Syndrome (SJMS) is an acquired hypoplastic lung disease and is an uncommon manifestation of postinfectious obliterative bronchiolitis, typically following severe respiratory infections in the developing lung. This presentation of a case of SJMS in a young woman highlights several features of SJMS.

CASE DESCRIPTION

A 20-year-old woman with a history of recurrent and severe childhood pneumonia presented to the clinic with upper respiratory infection symptoms. In general, the patient appeared well, her vital signs were normal, and the results of her physical examination were unremarkable. Chest plain-films were ordered and disclosed tracheal deviation with a mediastinal shift to the left and obscuration of the left heart border (Figure 1). She was referred to the emergency department for further work-up and computed tomography (CT) of the chest with contrast was ordered. The CT showed a small, hypoplastic left lung with diminished pulmonary vasculature, peripheral cystic changes, scattered bronchiectasis, and juxtapleural scarring (Figure 2).

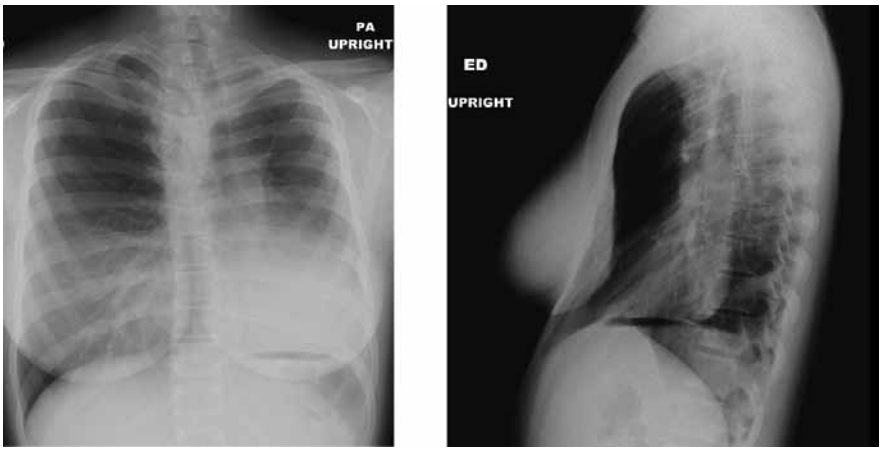

Figure 1. Posterior-anterior inspiratory chest radiograph demonstrated significant tracheal deviation with mediastinal shift to the left and inability to perceive the left heart border.

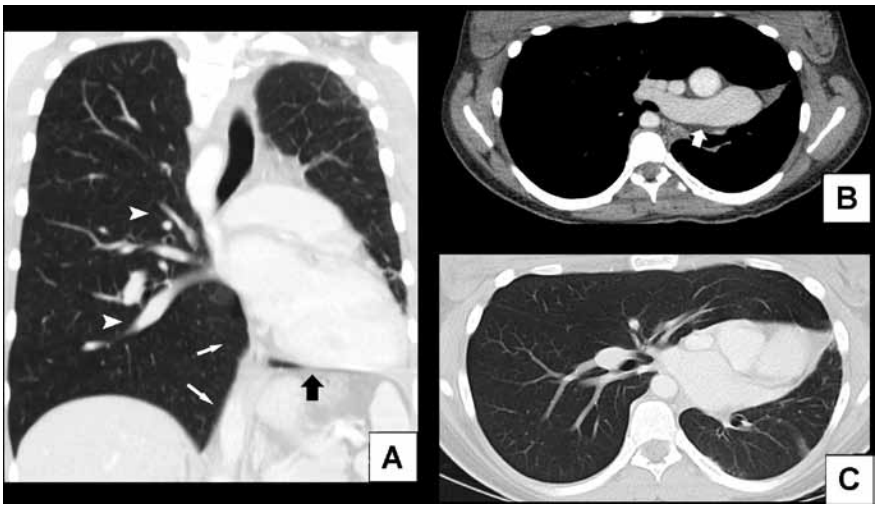

Figure 2. A. CT of the chest with contrast viewed in the coronal plane demonstrates a mediastinal shift to the left, a diffusely hypoplastic left lung with diminished vascularity compared to the contralateral side (arrowheads), elevation of the left hemi-diaphragm (black arrow), and hyperexpansion of the contralateral lung (white arrows). Relative hyperlucency in the diseased lung is not readily apparent, as classically seen in SJMS. B. Axial view reveals absence of the left pulmonary artery (arrow). C, Axial view further illustrating the findings in a lung parenchyma window.

DISCUSSION

The constellation of findings in this patient, given her history of significant childhood pneumonia, is consistent with SJMS, a consequence of postinfectious obliterative bronchiolitis that typically follows lower respiratory tract infections in infancy or childhood.[1] SJMS is characterized by a small, hyperlucent lung with decreased radiographic density due to decreased vascularity and destruction of alveolar structures in the affected lung. The syndrome is sometimes referred to as "unilateral bronchiolitis obliterans with hyperinflation" or "unilateral emphysema" to describe classical morphologic findings,[2] which are best observed on expiratory films. CT imaging is the modality of choice in diagnosing SJMS,[3,4] and may or may not demonstrate bronchiectasis. Typically, there is diminutive vascularity of the affected lung, and tapering or even absence of a pulmonary artery may be seen. A chief differential diagnosis is unilateral pulmonary artery agenesis, a rare congenital anomaly often misdiagnosed in adulthood.[5] Important distinguishing features of SJMS include evidence of air trapping on expiratory imaging as well as reduction in both ventilation and perfusion (matched defects in SJMS),[3] whereas in congenital pulmonary artery agenesis lung scans demonstrate ventilation with no perfusion.[6] Scintigraphy therefore aids in the diagnosis of SJMS.

Clinically, patients usually present with cough, shortness of breath, or dyspnea on exertion, although there is a varied spectrum of symptoms ranging from asymptomatic to recurrent pulmonary infections.[3,7] Management of SJMS includes regular influenza and pneumococcal vaccinations as well as early treatment of lung infections,[7] with pneumonectomy reserved for severe cases.[2] In our case, the patient was diagnosed incidentally and her symptoms were self-limited, improving shortly after the chest CT revealed her condition. Her work-up demonstrated unilateral bronchiolitis obliterans, but hyperlucency was not easily observable. To further support a diagnosis in patients with SJMS, expiratory images and perfusion-ventilation scans should be obtained.

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ABSTRACTS SELECTED FOR PRESENTATION AT

ASSOCIATES' DAY

VIRGINIA CHAPTER

AMERICAN COLLEGE OF PHYSICIANS

JANUARY 8, 2011

VARICELLA ZOSTER VIRUS ENCEPHALITIS IN A PATIENT WITH AIDS AND SEIZURES

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Varicella Zoster virus (VZV) infection occurs mainly in children 1 to 9 years old and usually presents as an acute viral exanthem. Seroprevalence in adults is >95%. After primary infection, the virus establishes latency in dorsal root ganglia, and reactivation results in herpes zoster, neuropathy, myelitis, or rarely encephalitis. Prompt diagnosis and treatment of VZV encephalitis is critical to minimize morbidity and mortality.

A 31-year-old homeless woman with HIV infection (non-adherent to HAART or follow-up) presented to the hospital in August after being found on a park bench shivering, disoriented, covered in urine and feces, and complaining of headache. A month earlier the CD4 was 376 cells/uL with a viral load (VL) of 829 copies/ml. She was arousable, but slow to respond to questions. Blood pressure was 109/68, pulse 48, temperature 33 °C, and respirations 38. The general and neurological examinations were otherwise unremarkable. The serum sodium was 125 mmol/L and a brain CT showed moderate atrophy, ventriculomegaly and nonspecific periventricular white matter changes. The CSF was xanthochromic with RBC 383/mm3, WBC 165/mm3 with 41% lymphocytes and 23% neutrophils, glucose 76 mg/dL and protein 1140mg/dL. Acyclovir was administered. The next day she developed refractory status epilepticus, required intubation, and was treated with fosphenytoin, phenobarbital and propofol. Vancomycin, ceftriaxone, ampicillin and fluconazole were added. The EEG continued to show periodic left hemisphere seizure activity. The brain MRI showed generalized leptomeningeal enhancement on post-contrast T1W sequences and FLAIR/T2W hyperintensities in the midbrain and pons. HIV VL was 327,894 copies/ml with CD4 132 cells/uL. Initial CSF PCR was negative for HSV, EBV, CMV, WNV and M. tuberculosis. Also negative were CSF cultures, VDRL, cryptococcal antigen, cytology, microscopy for ameba, comprehensive meningoencephalitis panel, and tests for rabies (serum, CSF, skin). Acyclovir and antibiotics were discontinued when the above studies returned negative. Repeat lumbar puncture on day 4 showed persistent lymphocytic pleocytosis. CSF VZV PCR was sent and returned positive 3 days later (>2,000,000 copies/ml). Acyclovir and HAART were restarted. There was minimal improvement in her encephalopathy, but she later declined and died on day 25.

VZV encephalitis may occur during primary infection or more commonly after viral reactivation in immunocompromised patients. Imaging findings are variable, but MRI may reveal cortical and subcortical infarcts with leptomeningeal enhancement. VZV serologic tests on serum and CSF lack sensitivity and specificity. CSF PCR for VZV DNA is the most sensitive and specific test and should be ordered early in immunocompromised patient with aseptic meningoencephalitis. In this setting, continued administration of empiric acyclovir is recommended until the result of VZV PCR is known.

AN UNFORESEEN BENEFIT TO GASTRIC BYPASS SURGERY

Kristen Peichert, M.D., University of Virginia

A twenty-seven year old female presented to her new primary care physician for follow up after a Roux-en-Y gastric bypass as she logistically could no longer see her surgeon. She underwent the procedure two and a half years prior, experiencing weight loss of over one hundred pounds. Her medications included a multivitamin with iron and B complex. She had previously taken a prenatal vitamin, switching to the multivitamin secondary to cost. During the visit she complained of lethargy and fatigue. Her physical exam was unremarkable except for class II obesity with a BMI of 35. In accordance with the guidelines, she underwent laboratory evaluation including: CBC, comprehensive metabolic panel, iron studies, vitamin B12, lipid panel, parathyroid hormone, thiamine and folate. Numerous abnormalities were noted: Vitamin B12 209 (normal 251-911), iron level 225 (normal 40-145), Transferrin 192 (normal 200-340), and percent saturation 82 (normal 16-48), with normal ferritin and CBC . Given her elevated total iron and percent saturation, she was instructed to stop taking her multivitamin with iron, take vitamin B12 supplementation, and return to clinic in 3 months time. At follow up, her results showed improved, though still elevated iron and percent saturation.

Given these results, continued menstruation, and having undergone a surgery typically associated with iron deficiency secondary to intestinal malabsorption, she was tested for hemochromatosis. She was found to be homozygous for the most common genetic mutation for this disease, C282Y, and negative for the H63D and S65C mutations in the HFE gene. She was then referred to gastroenterology with the diagnosis of hemochromatosis. The pathology read of the liver biopsy, done intraoperatively during the original Roux-en-Y procedure, was obtained showing mild parenchymal iron deposition and no fibrosis. While her ferritin levels were not at the ideal level of less than fifty, given her relatively benign biopsy, the fact that she is a menstruating female status post gastric bypass, plans were made for her to have annual gastroenterology follow up, deferring phelbotomy and repeat liver biopsy. Of note, her mother and father underwent genetic testing and found to both have the same homozygous C282Y mutation.

Hereditary homochromatosis, an autosomal recessive disorder was thought to be rare, with the classic manifestation of “bronze diabetes”, but is now known to be more common, affecting 0.2-1 % of Caucasions. It is now often diagnosed secondary to routine blood draws and the testing of relatives of those known to have the disease. In this patient’s case, her history of bariatric surgery and the recommended routine post operative laboratory follow-up led to the fortuitous discovery of iron overload and an earlier diagnosis of hemochromatosis than would otherwise be expected. Her early diagnosis could potentially delay the sequelae related to hemochromatosis.

ISOLATED DIPLOPIA: AN ATYPICAL PRESENTATION OF TEMPORAL ARTERITIS

Mayur Patel M.D., Virginia Tech Carilion School of Medicine

A 76 yr old female with a past medical history significant only for hypertension and osteoarthritis, presented to her PCP's office with a chief complaint of double vision. She had experienced two episodes over the previous three days, each lasting under a minute. Neither episode was associated with visual field loss, headache, lightheadedness, chest pain, vertigo, focal weakness, dysphagia or dysarthria. She denied myalgias or proximal muscle weakness and there was no history of jaw claudication. Her ophthalmologist found a normal eye exam after the first day of her illness. On examination, extra-ocular movements were found to be intact initially. After 3 minutes of persistent testing, she experienced another episode of diplopia with evidence of right lateral rectus and left superior rectus weakness. There was no other cranial nerve abnormality nor limb weakness during this episode and she denied any sensory symptoms. The remainder of her physical examination was unremarkable. Her basic metabolic panel, thyroid studies and complete blood count were normal. Antinuclear antibodies and acetylcholine antibody testing were negative but her c-reactive protein and sedimentation rate were elevated at 19.30 and 113 respectively. She was immediately started on high dose prednisone and bilateral temporal artery biopsy was performed 72 hours later. Biopsy specimens confirmed the presence of temporal arteritis. The differential diagnoses for new-onset diplopia include myasthenia gravis, thyroid opthalmopathy, cerebrovascular accidents, intracranial aneurysm, Guillian Barre (Miller Fisher variant) and migraine. In the absence of headache, the diagnosis of temporal arteritis may not be considered. Diplopia occurs in 6-21% of patients with temporal arteritis but is rarely the sole complaint as was seen in our patient. The pathophysiology involves ischemia of the oculomotor nerves or extra-ocular muscles from inflammation of the supplying small vessels. The authors wish to use this case as a reminder that isolated diplopia may be the only presenting symptom for this potentially devastating disease.

A HOT DOG MEAL THAT STARTED IT ALL

Robert Cajes, M.D., Eastern Virginia Medical School

Introduction: Chronic solid food impaction is rare among young adults and is secondary to a wide range of pathologies involving the esophagus. Over the last decade, eosinophilic esophagitis has rapidly become a recognized entity causing relapsing dysphagia in this population. Case Presentation: This is a 24-year-old male who complained from recurrent solid food impaction over the past nine months. This was described as recurrent foreign body sensation specifically after solid food intake that often requires repetitive swallowing or occasional self-induced emesis for relief. He had no asthma, allergic rhinitis, or atopic dermatitis. He denied HIV risk factors and had no symptoms of an autoimmune disorder. Physical examination of the oral cavity, neck, chest, and abdomen were normal. He denied heartburn, cough, weight loss, or odynophagia. On the time of presentation, he complained from sudden onset dysphagia after a hotdog meal. A food bolus obstruction was suspected although it was unclear if it had fully cleared. Esophagogastric duodenoscopy EGD) was performed which demonstrated multiple esophageal concentric rings and 'trachealization' with no residual foreign body. The endoscope could not be passed into the stomach due to luminal narrowing with most narrowed ring estimated at 7mm. A graduated esophageal dilation was performed using a 10-12mm balloon. Tissue biopsy revealed >15 intraepithelial eosinophils/high power field consistent with eosinophilic esophagitis. The patient was placed on a twice daily PPI and counseled extensively regarding a dysphagia diet. Significant clinical improvement was subsequently noted. Discussion: Eosinophilic esophagitis is a newly established cause of dysphagia in young adults especially men. There is either a family or personal history of atopy in most patients but can also be familial in up to 10%.The classical symptoms are chronic, intermittent solid-food dysphagia and food impaction, with no weight loss or history of reflux disease. Endoscopic features include multiple rings and linear furrows which can be subtle and the mucosa may be macroscopically normal. The presence of >15 eosinophils/high power field (HPF) in the esophageal mucosa is hallmark of the disease. Therapeutic options include avoidance of dietary allergens, topical or systemic steroids, and endoscopic dilation for strictures. As this is a lifelong disease, dysphagia diet instructions are critical with specific recommendations for cutting food into small pieces. Specific diet counseling includes avoidance of provocative foods like tough meats, doughy bread products or pasta, uncooked vegetables or fruits and foods with skins. Despite the chronic dysphagia, patients have no other alarming symptoms thus diagnosis is delayed. As a rapidly emerging disease, increased awareness is necessary since early diagnosis means early appropriate treatment and counseling.

UNKNOWN PREGNANCY PRESENTING AS SEVERE PREECLAMPSIA

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Case Presentation: A 21 year-old female presented with shortness of breath for 3 weeks when she developed a dry cough and lower extremity edema. Patient also endorsed a three day history of orthopnea. Patient woke on morning of admission with acute worsening of shortness of breath. Patient denied chest pain, fevers, chills, sputum, hemoptysis, weight change, urinary changes. Medical history was significant for acute lymphocytic leukemia at age 13 treated with doxorubicin. Vital signs were significant for pulse of 18, respiratory rate of 18, pulse oximetry of 95% on room air, blood pressure of 169/117. Physical exam revealed morbid obesity (BMI 63), mild respiratory distress, normal cardiac exam without extra heart sounds, bibasilar rhales in lungs, lower extremities with 3+ pitting edema and diffuse red papules

on lower extremities. Laboratory work was significant for pH 7.47, albumin 2.2, moderate proteinuria, BNP 842, D-dimer 2.33, WBC13.9. Chest radiograph demonstrated pulmonary edema and opacity in bilateral lung bases, more prominent on the right. EKG showed sinus tachycardia, possible left atrial enlargement. Patient started on a heparin drip for suspected pulmonary embolism. Hypertension was initially treated with lisinopril, however it was difficult to control. Furosemide and fluid restriction were started for suspected fluid overload. The patient started on vancomycin and ceftriaxone for lower extremity cellulitis and suspected pneumonia. PE-CT was performed and was negative for a PE. Heparin was discontinued. Transthoracic echo revealed poor windows, however the LVEF was markedly reduced, and diuresis was continued with improvement in the patient's dyspnea. The patient's creatinine continued to rise, renal ultrasound was unremarkable, transjugular renal biopsy was scheduled. Urine pregnancy test ordered on second day of admission was positive. Transvaginal ultrasound confirmed 34 week intrauterine twin pregnancy. Obstetrics was consulted and an emergent cesarean section performed given the diagnosis of severe preeclampsia. After delivery, the patient's renal failure resolved, she diuresed without additional lasix, and her blood pressure became manageable.

Discussion: Preeclampsia is defined as new onset of hypertension and proteinuria after 20 weeks of gestational age. The condition is further delineated into mild or severe. The latter includes CNS dysfunction, liver capsule distention, severe hypertension, thrombocytopenia, oliguria, severe proteinuria, severe intrauterine growth retardation, or cerebrovascular accident. This patient was classified as severe given her BP greater than 160/110 and pulmonary edema. Her risk factors included nulliparity and obesity. Acute renal failure has been noted to occur in some cases. Patient's heart failure may be a result of chemotherapy (can occur as late as 7-8 years after initial administration of daunorubicin), peripartum cardiomyopathy, or as a response to the increased afterload. This patient presented with classic symptoms for preeclampsia and demonstrates the importance of including the disorder in the differential diagnosis when a woman of child bearing age presents with new onset hypertension and proteinuria.

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS AFTER A PREMATURE DELIVERY FOR HELLP SYNDROME

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Idiopathic type I membranoproliferative glomerulonephritis (MPGN) is a rare disease process by which immune complexes and mesangial matrix are interposed between the glomerular endothelial cells and the glomerular basement membrane. The subsequent complement cascade and inflammation is responsible for the ensuing renal damage.

We present the case of a 22-year-old G1P1 postpartum female with no past medical history who was diagnosed with HELLP syndrome at 34 weeks EGA, resulting in urgent premature delivery via Caesarian section. At delivery she had normal blood pressure, normal kidney function, and no proteinuria. Two weeks postpartum she presented with hypertension, pulmonary edema and peripheral edema. She was treated for presumed preeclampsia and discharged on anti-hypertensive medications. Her hypertension was difficult to control and at six weeks postpartum she also developed acute kidney injury (AKI), nephrotic-proteinuria, hematuria, a hemolytic anemia with rare schistocytes and a mild thrombocytopenia concerning for persistent HELLP syndrome, hemolytic-uremic syndrome, or a rapidly progressive glomerulonephritis. She was empirically started on high-dose steroids and underwent a renal biopsy.

Renal biopsy revealed type I MPGN with a single crescent. She was tested for concurrent autoimmune diseases, viral infections, bacterial infections, and monoclonal gammopathies to rule out secondary MPGN. All testing was within normal limits and she received the final diagnosis of idiopathic type I MPGN. Aspirin and dipyridamole were added to her initial high-dose steroid course as well as an ACE-inhibitor, HMG-CoA reductase inhibitor, and diuretics to manage her hypertension, dyslipidemia, and edema. She responded very well to therapy and her anemia and AKI quickly resolved; her proteinuria remitted six months into her steroid taper.

This is the first reported case (in the MEDLINE literature) of a postpartum diagnosis of idiopathic type I MPGN. A prior case report documented MPGN in a patient who prematurely delivered at 28 weeks EGA and required hemodialysis, high-dose steroids and six months of cyclophosphamide therapy before proceeding on to a complete remission. Another case report documented an MPGN lesion in a patient who developed HELLP syndrome at 33 weeks EGA, complicated by anuric AKI that also recovered completely after delivery of a stillborn and a brief course of hemodialysis. Idiopathic type I MPGN is a rare disease that most commonly occurs in childhood and usually requires treatment with prolonged or indefinite steroid therapy. Given the excellent clinical recoveries of our postpartum patient and prior cases of peripartum MPGN with associated HELLP syndrome, adult idiopathic type I MPGN in the pregnancy setting may represent a different disease process that responds well to early aggressive medical therapy.

"STINK BUGS" AND PERMETHRIN INHALATION: A STIMULUS FOR APICAL BALLOONING CARDIOMYOPATHY

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A 91 year old female presented to emergency department (ED) with acute onset of dyspnea and dysphonia. She had accidentally inhaled a pyrethrin containing bug fogger when she was spraying it manually for control of Halyomorpha halys (stink bugs.) In the ED her physical exam revealed bilateral crackles on auscultation of lungs, ECG showed non-specific ST-changes and cardiac enzymes were significantly elevated with troponin 7.84 ng/ml (normal <0.08 ng/ml).

Acute coronary syndrome (ACS) protocol with aspirin and heparin was initiated and an echocardiogram obtained. This demonstrated typical features of Takotsubo cardiomyopathy with marked anteroapical, apical, and anterolateral hypokinesis with preserved basal left ventricular (LV) contraction. Overall ejection fraction was 20%. These changes were new compared with echocardiogram done two years earlier. Coronary angiogram revealed normal coronary arteries. She was treated with beta blocker and ACE inhibitor therapy and remained symptom free during hospitalization. Follow-up echocardiogram was arranged in 4 weeks.

Apical ballooning cardiomyopathy (ABC) also known as Tako-tsubo cardiomyopathy or stress-induced cardiomyopathy, is an acute and reversible cardiomyopathy provoked by stress. It is relatively uncommon with highest prevalence in postmenopausal women under emotional or physical stress. It occurs in approximately 1-2% patients presenting with suspicion of ACS and is recognized only after coronary angiography excludes significant coronary artery disease. Pathogenesis of ABC is unknown; however it is postulated to be related to increased catecholamine release and direct myocardial toxicity or microvascular coronary vasospasm. Given the transient nature of ABC, management is supportive. Most experts recommend treatment for systolic heart failure with beta blockers and ACE inhibitors. LV dysfunction is generally transient and cardiac function recovers over one to four weeks.

Pyrethrin found in the insecticide is known to cause bronchospasm and allergic reactions however it has not been implicated in cardiotoxicity. Pyrethrins prolong sodium depolarization in the axon causing paralysis in insects. In mammals, it is rapidly metabolized and toxicity related to inhalation exposures is rare. It is possible that sudden dyspnea in our patient resulted in enough stress to induce cardiomyopathy although toxin induced pathogenesis cannot be completely excluded. To our knowledge this is first such case reported after accidental inhalation of pyrethrin.

BILATERAL ANKLE ARTHRITIS

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A 39yo African-American female with past medical history significant for sarcoidosis with ocular involvement presented to outpatient clinic with a chief complaint of bilateral ankle swelling. Two weeks prior to presentation, redness started on her anterior shin and spread to her right ankle. This was followed by right ankle joint pain and swelling. One week prior to presentation, the patient was seen by an urgent care clinic. Laboratory analysis revealed normal complete blood count and basic metabolic panel. The patient was given a prescription for oral bactrim and keflex. A few days later, the same symptoms developed on the left side. On interview, the patient noted that her ankle swelling had not improved with oral antibiotics. The patient denied fever and chills. The past medical history included sarcoidosis with ocular involvement and no known pulmonary involvement. Outpatient medications were, keflex, bactrim, and oral prednisone 1mg daily. The patient denied history of smoking, alcohol, or illegal drug use. On physical examination, vital signs were normal. Lower extremity exam was significant for erythematous tender nodules present bilaterally on the anterior shin. The nodules were extremely tender to palpation. Bilateral ankle joints were significant for warmth, swelling, decreased range of motion, and tenderness to palpation. There was no peripheral edema and neurological exam was normal. Isolated joint swelling and warmth is commonly caused by gout or septic arthritis. Bilateral symmetric arthritis often is caused by an autoimmune disease. The skin findings on this patient were typical for a diagnosis of erythema nodosum. This condition is characterized by red and tender subcutaneous nodules. The etiology of erythema nodosum includes sarcoidosis, streptococcal infection, inflammatory bowel disease, idiopathic, medication induced, and tuberculosis. The diagnosis is clinical, and skin biopsy is only recommended if tuberculosis is suspected. The management depends on treatment of the underlying disease process. Acute arthritis in sarcoidosis may present independently or as part of Lofgren's syndrome. The most common joint involved is the ankle and it is commonly mistaken for reactive arthritis. Lofgren's syndrome includes bilateral hilar adenopathy, acute arthritis, and erythema nodosum. Approximately one third of patients with the diagnosis of sarcoidosis will have arthritis as a complication. Due to the absence of bilateral hilar lymphadenpathy on previous CXR, the patient was not diagnosed with Lofgren's syndrome. Bilateral ankle arthritis and erythema nodosum are associated with a favorable prognosis. The skin findings and joint swelling typically resolve within a few months of diagnosis. Bilateral ankle arthritis is not a routine complaint in a primary care setting and it is important to remember that it could be secondary to a systemic disease.

SUPERIOR MESENTERIC VENOUS THROMBOSIS IN SETTING OF DIVERTICULITIS

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Introduction: Mesenteric venous thrombosis is a rare cause of abdominal pain and clinicians must have a high index of suspicion in order to effectively diagnose and treat the condition to avoid possible mesenteric ischemia.

A 59 year old African American male with no relevant past medical history presented with four days of severe abdominal pain. On exam the patient was visibly distressed, shaking, and had tenderness limited to the right lower quadrant without peritoneal signs. CT abdomen/pelvis at outside hospital revealed thrombus in the superior mesenteric vein as well as possible right -sided diverticular disease.

Hospital course was complicated by cyclical pyrexia, rigors and chills. Blood cultures showed polymicrobial growth,

including E coli, Clostridium paraputrificum and Pseudomonas and the patient was started on doripenem. Repeat CT abdomen/pelvis was performed showing perforated cecal diverticulum with extensive cellulitis in the right retroperitoneum with persistence of the initial thrombus and gas within the embolus. The patient remained remarkably stable without peritoneal signs; he clinically improved and was treated conservatively with antibiotics and anticoagulation. Repeat CT abdomen/pelvis showed resolution of both the perforation and the thrombus. The polymicrobial nature of the bacteremia in conjunction with the CT findings suggested inflammation associated with cecal diverticulitis as the initial nidus for thrombus and subsequent perforation of diverticulum as cause of bacteremia and pyrexia. Additionally, work up for malignancy, cirrhosis, and hypercoaguable state was negative before diagnosis was made.

Discussion: This case highlights a rare cause of mesenteric venous thrombosis. The majority of patients have underlying cirrhosis; the prevalence seems to coincide with the severity of the underlying liver disease and possibly related to retrograde flow through the portal vein. Other causes include hypercoaguable states such as polycythemia vera and protein C and S deficiencies, visceral infection, perforated viscous, malignancy, previous abdominal surgery, and in patient who smoke. Malignancy may cause thrombosis via induced hypercoaguable state or direct extension of the tumor.

The major risk of mesenteric venous thrombosis is mesenteric ischemia. Thrombus results in influx of fluid into the bowel wall and lumen and subsequent bowel wall edema. This in conjunction with impedance of venous outflow from thrombus leads to limited arterial influx, resulting in bowel ischemia. Early heparinization has been shown to improve outcome.

Physicians should consider the possibility of mesenteric venous thrombosis in a patient with abdominal pain out of proportion to physical exam in patients who do not have a common etiology for their pain. Additionally, there are a wide range of causes of mesenteric venous thrombosis, and work-up should include that for cirrhosis and portal hypertension, hypercoaguable state, malignancy, and intra-abdominal infection.

ASYMPTOMATIC NEUROSYPHILIS IN A NEWLY DIAGNOSED HIV POSITIVE PATIENT

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Syphilis is a sexually transmitted disease caused by the spirochete Treponema pallidum. Humans are the only host. Dissemination, with potential invasion into the central nervous system, occurs during the secondary stage of syphilis. In the HIV co-infected patient, the primary chancre and secondary septicemic phase often overlap, thus manifestations of neurosyphilis can occur during any stage of the disease. Symptomatic neurosyphilis has a variety of presentations. Acute syphilitic meningitis occurs within the first two years of infection, and is accompanied by cranial nerve deficits in up to one third of patients. Meningovascular syphilis, or endarteritis obliterans, affects the small vessels of the brain and meninges, eventually leading to multiple small areas of infarction. General paresis and tabes dorsalis are parenchymatous forms of neurosyphilis that occur 10 to 30 years after primary infection. Up to 40% of patients with secondary syphilis have asymptomatic central nervous system involvement. We report a case of neurosyphilis associated with HIV infection in a 23 year-old African American male. During his initial evaluation after a positive HIV screening test, he was found to have a CD4 count of 465 cells/mcL, and a rapid plasma reagin (RPR) titer of 1:128. The patient denied any history of genital lesions or rash, and no prior RPR was available to establish duration of infection. No neurological or general manifestations of syphilis were present on exam, and the patient denied any symptoms consistent with neurosyphilis. Due to his high RPR titer, a lumbar puncture was performed to evaluate for neurosyphilis. Cerebrospinal fluid (CSF) analysis was significant for a white blood count of 6 cells/mcL, protein of 27 mg/dl, and a Venereal Disease Research Laboratory (VDRL) titer of 1:1. A diagnosis of asymptomatic neurosyphilis was given based on the weakly positive VDRL titer. The patient was treated with aqueous crystalline penicillin G (4 million units intravenously every four hours for ten days) with appropriate fall in RPR titer to 1:4 noted at follow-up. Treponema pallidum neurologic infection occurs more frequently in the HIV positive population, but neurosyphilis is curable with adequate therapy. Standard benzathine penicillin does not reliably produce cidal levels of penicillin in the CSF, necessitating use of aqueous penicillin G or other alternatives. In the absence of neurologic symptoms, many experts recommend evaluation for neurosyphilis when the RPR titer is greater than 1:32 or when the CD4 count is less than 350 cells/mcL in the HIV positive patient. CSF evidence of neurosyphilis is manifested by pleocytosis (>20 cells/mcL in an HIV positive patient), elevated protein level, or VDRL reactivity. This case highlights the importance of CSF evaluation of syphilis in the HIV co-infected patient.

A PARTICULARLY AGGRESSIVE COURSE OF ACUTE MYELOMONOCYTIC LEUKEMIA LEADING TO SPONTANEOUS SPLENIC RUPTURE AND CARDIAC ARREST

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Acute Myeloid Leukemia of the myelomonocytic phenotype represents 15 to 25% of the cases of AML with a variety of atypical symptoms at presentation and proclivity for organ infiltration. In this case, a 47 year old male with no significant past medical history presented to his primary care physician complaining of several days of nausea, dyspnea, and fever. He denied any history of weight changes, easy bleeding or bruising, melena, gingival hyperplasia, or petechial rashes. Lab work revealved an elevated white blood cell count of 21 K/UL with a large population of blasts and monocytes

along with mild anemia, neutropenia, and thrombocytopenia. He was admitted to a community hospital for presumed acute myelogenous leukemia. His dyspnea rapidly progressed and a CT pulmonary angiogram was performed showing pulmonary vascular congestion with interstitial edema and no evidence of pulmonary emboli. He was febrile to 103°F, so broad specrum antibiotics were initiated and he was transferred to the University of Virginia for further management. Upon arrival, the patient became significantly more tachycardic and tachypneic with complaints of worsening dyspnea and epigastric fullness. Within 12 hours, his WBC count rapidly increased to 58 K/ul (76% monocytes, 12.4% blasts), along with anemia (hgb 12.3) and thrombocytopenia (14K/UL). He also had evidence of acute renal failure with a creatinine of 1.5 (eGFR 53). Other labs were remarkable for a transaminititis (AST 72, ALT 98 , Alk phos 220 , Tbili 2.9) in the setting of a normal abdominal ultrasound and a troponin of 0.33 with an ECG showing no evidence of ischemia. Leukapheresis and hydroxyurea were promptly initiated to treat the complications of hyperviscocity syndrome. Unfortunately, the patient did not have a sustained response to this initial therapy as his WBC increased to 134(1% Blasts, 90% monocytes). He then developed acute onset abdominal pain followed suddenly by hypotension and PEA arrest with an unsuccessful resuscitation, less than 24 hours after admission. Immunophenotypic analysis confirmed acute myelomonocytic leukemia, FAB subtype M4. An autopsy was performed showing extensive multiorgan infiltration by leukocytes, including overwhelming involvement of the spleen. This led to massive splenomegaly and capsular rupture with resultant hemoperitoneum. The immediate cause of death was felt to be exsanguination due to the spontaneous splenic rupture. This case is notable for a rare, but well described complication of leukemia. There have been less than 17 cases of splenic rupture associated with AML described in the literature. Early recognition of this complication is critical as the mortality rate approaches 100% without definitive surgical management.

SO YOU THINK A RIGHT BUNDLE BRANCH BLOCK IS HARMLESS?

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Case Presentation: A 73 year-old male, with a history of poorly controlled type II diabetes mellitus, was admitted for diabetic ketoacidosis. The patient responded well to routine interventions and treatment and was to be discharged on hospital day four. Just prior to discharge, the patient experienced acute onset dyspnea, and anterior chest pressure. On evaluation, the blood pressure was 104/75 mmHg, heart rate 103 bpm, respiratory rate 18 bpm, oxygen saturation 96% on room air. The patient appeared diaphoretic. JVD was noted to the angle of the mandible. No rales or peripheral edema was appreciated. An electrocardiogram did not reveal any acute ischemic changes, however, the patient was empirically treated with aspirin as part of an ACS protocol and continuous cardiac monitoring was initiated. Review of serial electrocardiograms revealed a new and transient right bundle branch block pattern, raising concern for right heart strain. Further evaluation with spiral CT confirmed the presence of a large "saddle" pulmonary embolism; a bedside echocardiogram revealed septal bowing. The patient was treated acutely with heparin and thrombolytic therapy and was discharged home several days later without sequelae.

Case Discussion: Approximately 10% of elderly patients are documented to have right bundle branch block (RBBB) patterns on electrocardiogram, and most are regarded as a benign finding. This case highlights a transient RBBB as subtle evidence of an underlying massive pulmonary embolism. It serves as a potent reminder that RBBBs are not always benign findings, and in acute settings, should be regarded as evidence of right heart strain similar to the more classical pattern of S1Q3T3. This patient was receiving enoxaparin for DVT prophylaxis since admission, reminding the learner that prophylaxis decreases the risk of clot formation by approximately 50%, but does not completely eliminate the risk. We use this case to emphasize these teaching points, as well as to review the indications for use of thrombolytic therapy in the management of acute pulmonary embolism.

ANTI-RETROVIRAL AGENT TURNED ANTI-TUBULE AGENT: TENOFOVIR-INDUCED FANCONI'S SYNDROME

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With over one million HIV+ individuals in the U.S, ART management is no longer reserved for infectious disease specialists. However, are medicine practitioners equipped to deal with these double agents? A 57-year-old HIV+ male (CD4 391, undetectable viral load) on ART presented with a three week history of weakness and falls. He denied numbness, polyuria, or polydypsia. On examination, the patient was malnourished with psychomotor retardation. He had mild, symmetric proximal muscle weakness. Labs were significant for hypokalemia (3.2mmol/L), hypophosphatemia (0.8mg/dL), nongap metabolic acidosis (bicarbonate 16mmol/L), hypouricemia (1.3mg/dL) and acute renal failure (creatinine 1.8mg/dL, GFR 37mL/min). Calcium was normal. Urinalysis revealed glucose greater than 1000mg/dL, in the setting of a normal serum glucose, and proteinuria. Of note, the patient was started on his current ART regimen (raltegravir, norvir, darunavir, and tenofovir/emtricitabine) in 2008. At that time, his creatinine was 0.9mg/dL.

His clinical picture was consistent with acquired Fanconi's syndrome, characterized by profound electrolyte abnormalities, and associated renal failure. Tenofovir was identified as the likely causative agent and was stopped. With repletion, his electrolytes normalized and renal function improved.

Acquired Fanconi's syndrome is a defect in transport at the proximal tubule, resulting in renal wasting of glucose, calcium, phosphate, uric acid, bicarbonate and amino acids. Cardinal features include glucosuria, aminoaciduria

and phosphaturia. Other manifestations include hyperchloremic metabolic acidosis/RTA type 2, hypokalemia and hypouricemia. Several drugs are associated with this phenomenon. However, antiretrovirals, including tenofovir, are rarely associated with this disorder.1.

Tenofovir, introduced in 2001, was embraced for its once-daily dosing and safety after two randomized trials demonstrated that tenofovir had a "safety profile similar to placebo". Currently, it is a component of all four CDC-preferred treatment regimens. However, recently it has been discovered that tenofovir may be associated with more nephrotoxicity and proximal tubule dysfunction than previously recognized. From July 2001 to June 2006, the FDA Adverse Events Reporting System identified 164 patients with tenofovir-associated Fanconi's, half of which required hospitalization. Furthermore, a study in 2010 demonstrated that patients on tenofovir had a greater decline in renal function and a higher risk of proximal tubular dysfunction, as compared to tenofovir-sparing regimens.

As the number of patients exposed to tenofovir exponentially increases with the use of popular combination therapies, such as Truvada and Atripla, this complication will become more prevalent. Physicians must be on guard with these double agents and closely monitor electrolytes for signs of tubular abnormalities. These manifestations precede renal insufficiency, signaling renal toxicity, and are an indication for discontinuation of tenofovir 1. A recent study demonstrated the effectiveness of probenecid in preventing recurrent Fanconi's with continued tenofovir use. However, further studies are desperately needed to identify methods of preventing this potentially irreversible complication of an otherwise well-tolerated drug.

NAFCILLIN INDUCED HYPOKALEMIA SECONDARY TO ELECTROLYTE REDISTRIBUTION AND KALIURESIS

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Hypokalemia is a common, clinically important electrolyte imbalance, with potential complications such as muscle weakness, ileus and cardiac dysrhythmias. Penicillins such as nafcillin and oxacillin are established causes of hypokalemia; however, the mechanism whereby hypokalemia is induced by these agents remains poorly elucidated. We report the case of a patient with staphylococcal cervical osteomyelitis in whom treatment with nafcillin sodium resulted in refractory hypokalemia.

A 65-year-old-man with coronary artery disease, hypertension and hyperlipidemia presented with neck pain and limb weakness. Outpatient medications included furosemide 40 mg daily and potassium chloride 10 mEq daily. The blood pressure was 126/75 mm Hg, pulse 74, and BMI 28. Serum sodium was 138 mEq/L, potassium 3.5 mEq/L, chloride 103 mEq/L, bicarbonate 25 mEq/L, urea nitrogen 31 mg/dL, and creatinine 1.2 mg/dL. An MRI suggested C5-C6 osteomyelitis prompting drainage and fusion. On day # 3,wound cultures grew nafcillin-sensitive Staphylococcus aureus, and he was treated with 2 g of this agent every four hours.

On day #10, the serum potassium was 2.9 mEq/L, magnesium 2.0 mg/dL, BUN 5 mg/dl, and creatinine 0.92 mg/dL. He received 480 mEq of Potassium supplementation orally and intravenously over next 48 hrs, but he remained hypokalemic.

Urine studies on day #12 showed K 61.5 mEq/L, Na 73 mEq/L, Cl 127 mEq/L, 496 mOsm/L. The calculated urine anion gap was 8. The BUN became immeasurably low by day #12. The transtubular potassium gradient was 12, suggesting urinary K wasting. Nafcillin was discontinued one day later and the serum potassium promptly normalized from 2.9 to 4.0 mEq/L within 10hrs.

There are three proposed mechanisms of Nafcillin-induced hypokalemia: (1) nafcillin's impermeant anion effect on the distal tubule, (2) the increased sodium load of the antibiotic preparation on the distal tubule leading to potassium wasting, and (3) an antibiotic-associated cellular redistribution effect. Our patient had urinary potassium losses, supporting the sodium load and impermeant ion effect mechanisms. The immeasurably low BUN, which corrected after antibiotic discontinuation, also supports the increased tubular flow theory. However, the absent urine anion gap and the normal urine Cl do not support the presence of urinary nafcillin; and the immediate correction of serum potassium after nafcillin discontinuation supports the cellular redistribution theory.

We suggest that hypokalemia remains an important, poorly understood and overlooked complication associated with nafcillin therapy, and the etiology may be multifactorial, with a combination of potassium redistribution and urinary potassium losses. The most effective treatment, as in this case, is antibiotic discontinuation.

FATAL LEFT CORONARY ARTERY ANEURYSM INFECTION

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Coronary artery aneurysms are found incidentally in 0.5%-4.9% cardiac catheterizations. Atherosclerosis is the most common underlying etiology. Superimposed infection in a previously documented left main coronary artery aneurysm has not been previously reported.

A 69 year old female with past medical history significant for obesity, hypertension, diabetes mellitus II and hyperlipidemia presented to the ER with atypical chest pain and urinary tract infection. Coronary angiography revealed diffuse non-obstructing atherosclerotic coronary artery disease and a 5mm non-obstructing, saccular aneurysm at the junction of the left main coronary artery(LMCA) and circumflex artery. This was treated with antiplatelet agents with discharge to home on a short course of antibiotics for the UTI. One week later, she presented again with high grade fevers, Non ST-Elevation MI and decompensated heart failure. Treatment with broad spectrum antibiotics and ACS protocol was initiated in an ICU setting. A transthoracic echocardiogram revealed moderate mitral regurgitation (MR) with preserved EF. E.Coli bacteremia was confirmed on blood cultures on day 3. Marked clinical improvement occurred over the next 2 weeks and she was transferred to regular floor pending discharge. However, the following morning, she developed severe crushing chest pain. An emergent Transesophageal Echocardiogram revealed severe MR with possible aneurismal dilatation. Cardiac CT confirmed significant aneurismal expansion with burrowing into the left ventricular outflow tract through the anterior LV wall and compression of the distal LMCA. The patient expired after a complex cardiothoracic surgical repair which comprised of aneurismal resection, distal coronary artery bypass grafting(CABG), Mitral valve repair and Aortic valve and root replacement. Histo-pathological analysis of the aneurysm later revealed atherosclerosis with inflammatory infilteration, mycotic degeneration and E.Coli infection.

Coronary artery aneurysms are found in 1% to 4% cardiac catheterizations.(1) 50-70% occur secondary to atherosclerosis. Other etiologies include Kawasaki disease, coronary artery revascularization procedures, polyarteritis nodosa, Marfan's syndrome, HIV, Syphilis and endocarditis.(2,3,4)There are no previously reported cases of mycotic conversion of atherosclerotic aneurysms. The disconnect between clinical symptoms and underlying disease can be significant. Prompt evaluation for this complication should be done in the presence of concomitant fever, ischemia and new heart failure.

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REFRACTORY HYPOGLYCEMIA DUE TO PROSTATE CANCER-RELATED NICTH

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Non–islet cell tumor–induced hypoglycemia (NICTH) is a rare phenomenon caused by the production of insulin-like growth factor-II (IGF-II). First described in 1929 in a patient with hepatocellular carcinoma, it has since been reported in association with a number of mesenchymal, epithelial or hematopoietic malignancies with a large tumor burden. We present a case of refractory hypoglycemia associated with prostate cancer.

An 86-year-old man was transferred to our facility for symptomatic refractory hypoglycemia. He had a history of hormone-refractory, Gleason 9 adenocarcinoma of the prostate metastatic to the spine, atrial fibrillation and valvular heart disease. His medications were leuprolide, bicalutamide, finasteride, amiodarone, diltiazem, ramipril and furosemide. He was admitted elsewhere for delirium due to a urinary infection and hypoglycemia. He was treated with ceftriaxone and infusions of dextrose. He developed volume overload with respiratory failure, was intubated, and transferred on day 9. Refractory hypoglycemia continued with frequent glucoses <20 mg/dL. Glucagon, dexamethasone and a continuous infusion of octreotide were added. The serum hypoglycemic agent screen was negative. Abdominopelvic CT was unremarkable except for osseous metastases. In the setting of a glucose <40, levels of insulin, C-peptide and IGF binding protein-3 were undetectable. The IGF-II level was elevated at 846 ng/mL (mean for adults 512); IGF-I 28 ng/mL (47-195), TSH normal and random cortisol 16 mcg/dL. Despite interventions above, a continuous infusion of 70% dextrose, with intermittent boluses with 50% dextrose, was required. The patient was extubated on day 2 and renal replacement therapy was started on day 4 in an attempt to remove IGF-II and treat volume overload. We were subsequently able to stop the octreotide and decrease the dextrose infusion to 45%. In the ensuing days the patient developed delirium, hypotension and respiratory insufficiency. Prostate cancer rescue therapy with samarium-153 was considered, but declined, and the patient expired on day 8.

NICTH should be considered in hypoglycemic patients with known or suspected malignancy. Tumors cause hypoglycemia through pancreatic or ectopic insulin production, infiltrative destruction of the liver or adrenals, or the production of substances that alter glucose metabolism (IGF-II, cytokines, catecholamines, receptor antibodies). IGF-I and IGF-II are structurally and functionally similar to insulin. They are largely produced by the liver, although other tissues can also

synthesize these peptides. Hypoinsulinemic hypoglycemia supports the diagnosis of NICTH, which is usually due to oversecretion of IGF-II or incompletely processed high-molecular weight IGF-II precursors ("big" IGF-II). In the event of the latter, commercial IGF-II assays will be normal or low. Pending resection or reduction of the tumor burden, supportive treatment consists of dextrose, glucocorticoids, octreotide and/or growth hormone.

UNCONTROLLED HYPERTENSION AND ELEVATED ALKALINE PHOSPHATASE: PRESENTING SYMPTOMS OF LOW GRADE METASTATIC NEUROENDOCRINE CARCINOMA

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Case presentation: A 68 year old African American female presented to our facility in the ambulatory setting for difficulty controlling her blood pressure. Her past medical history was notable for stage III chronic kidney disease and gastroesophageal reflux. Her medications included metoprolol XL 100mg daily, hydrochlorothiazide 25mg daily, amlodipine 10mg, valsartan 320mg, and clonidine 0.1mg TID. Vitals illustrated a blood pressure of 180/77 and heart rate of 73. She denied any symptoms including chest pain, shortness of breath, headache, change in vision, flushing and diarrhea. Physical exam was unremarkable for any rashes, abdominal masses. Routine labs were remarkable for a creatinine of 1.5 mg/dL and Alkaline phosphatase of 12 IU/L. Secondary causes of hypertension were investigated. Serum TSH, renin and aldosterone levels were normal, as well as 24 hour urine metanephrines and normetanephrine. Doppler renal ultrasound did not show any evidence of renal artery stenosis, however two incidentally noted isoechoic, vascularized hepatic masses were noted. A follow up CT abdomen/pelvis showed multiple liver and pancreatic lesions with two masses in the mesentery measuring 7.7 cm and 1.2cm respectively, and normal adrenal size. Ultrasound guided biopsy of the liver lesion revealed metastatic low-grade neuroendocrine carcinoma. Immunohistochemical stains performed on the cell block showed that tumor cells were stained positive for markers consistent with carcinoid tumor. A transthoracic echo showed thickening of tricuspid valve, with severe regurgitation which is consistent with carcinoid heart disease. Chromogranin A levels were 291 nmol/L (normal 0-5nmol/L). Patient was started on octreotide and blood pressure improved.

Discussion: Carcinoid tumors are well-differentiated neuroendocrine tumors that are characterized by an indolent disease course. They represent between 29 – 40 % of primary small intestine malignancies, and the highest incidence is reported between 50 and 60 years of age. Carcinoid syndrome occurs in only 7.7 percent of all carcinoids tumors, with small intestinal carcinoids accounting for the 35 percent. Additionally, 90 percent of patients with the carcinoid syndrome have metastatic disease, typically to the liver. These tumors are characterized by the production of biologically active amines and secretion of products including dopamine, noradrenaline, histamine and other metabolites accounting for the diverse symptoms at presentation including hypertension. However, carcinoid syndrome classically presents with diarrhea and episodic flushing which is seen in 85% of the patients with carcinoid syndrome, which was not observed in our patient. This case illustrates the need to entertain the diagnosis of carcinoid syndrome in a patient with resistant hypertension.

MASSIVE HEMATEMESIS DUE TO A HEPATIC ARTERY PSEUDOANEURYSM COMPLICATING PANCREATITIS

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Background: Hepatic artery psuedoaneurysms (HPA) are a rare cause of life-threatening upper gastrointestinal (UGI) hemorrhage that can be difficult to treat. Predisposing conditions include blunt or penetrating abdominal trauma, pancreaticoduodenal or hepatic surgery, vasculitis, and periarterial inflammation due to pancreatitis or cholecystitis. Prompt diagnosis and intervention is critical to decrease the susbstantial mortality associated with HPA-associated bleeding into the stomach, duodenum or biliary tract.

Case: A 71-year-old woman with diabetes, hypertension and GERD presented with massive hematemesis and syncope. She was a former smoker who drank alcoholic occasionally. Seven months earlier she had mild pancreatitis without gallstones (edema marginating the pancreas and the second portion of duodenum without vascular abnormalities and lipase 165 U/L [114-286 U/L]). Her medicines included metformin, glipizide, telmisartan, pravastatin and omeprazole. She was pale, diaphoretic and had an initial blood pressure of 37/29 mm Hg with a pulse of 84. She was resuscitated and treated with crystalloids, blood, plasma, platelets, pantoprazole and octreotide. She required tracheal intubation for upper endoscopy, which revealed a 2 cm submucosal ulcerated lesion in the second portion of the duodenum with pulsatile oozing of blood. Therapeutic intervention was not thought to be safe or feasible, nor was she hemodynamically stable for emergency surgery. Liver and pancreatic enzymes were normal. Abdominopelvic computed tomographic angiography revealed a 3.4 cm pseudoaneurysm arising from the right hepatic artery, prominent reactive wall thickening of the duodenum, a 4.4 cm abdominal aortic aneurysm, and perigastric varices suspicious for portal hypertension. Transcatheter arterial embolization (TAE) of the right hepatic and distal common hepatic arteries was accomplished with a variety of coils and plugs with excellent results. Her course was complicated by a large NSTEMI (troponin 60 ng/mL) and bilateral leg DVT with pulmonary embolism requiring an IVC filter. She was discharged to inpatient rehabilitation on day 13.

Discussion: This case highlights the rare complication of HPA with massive UGI hemorrhage due to preceding pancreatitis. TAE is the preferred initial intervention to manage unstable patients with life-threatening UGI hemorrhage

due to hepatic and other visceral arterial aneurysms and pseudoaneurysms. Conventional surgery can be undertaken later, if required. TAE of the liver is usually well-tolerated due to the dual portal and systemic arterial blood supply. However, because of the underlying conditions associated with HPA, a number of these patients do not have patent portal veins. These individuals have a higher risk of hepatic ischemia, necrosis and abscess formation with TAE. In these patients one should strongly consider the placement of percutaneous endovascular balloon-expandable coronary stent-grafts in order to preserve the arterial blood supply to the liver.

NEPHROTIC SYNDROME AND UNRECOGNIZED PLASMODIUM MALARIAE INFECTION IN A U.S. NAVY SAILOR FOURTEEN YEARS AFTER DEPARTING NIGERIA

Richard U.D. Hedelius, M.D., Naval Medical Center Portsmouth

Nephrotic syndrome, a non-specific kidney disorder, may present as lower extremity edema, anasarca, hypertension, hyperlipidemia and frothy urine signifying proteinuria (greater than 3.5grams/day). Malaria commonly presents with fevers and non-specific systemic illness. With the exception of severe P. falciparum malaria complicated by acute tubular necrosis, malaria rarely presents with renal involvement.

We report a case of Plasmodium malariae-associated nephrotic syndrome in a 34- year-old Nigerian active duty US Navy sailor whose last exposure to malaria was at least 14 years prior to immigrating to the United States. The patient presented to his ship's medical doctor with a four month history of bilateral lower extremity pitting edema, swelling of his face upon awakening and frothy urine. He was diagnosed with hypertension and hyperlipidemia and medically managed at sea with hydrochlorothiazide and simvastatin, but did not respond to treatment. Upon referral to Internal Medicine, the patient had a spot protein/creatinine ratio of 22.61 grams per day, consistent with nephrotic syndrome. Renal biopsy confirmed membranous glomerulonephritis, but initial investigations for secondary causes including malaria were unrevealing. Because chronic P. malariae infection was suspected, the Giemsa-stained blood smears were referred to a malariologist and a blood blot sample sent to the U.S. Naval Medical Research Unit #2 (NAMRU-2) in Indonesia for species specific, small subunit ribosomal ribonucleic acid polymerase chain reaction (ssrRNA PCR) amplification. The assay was negative for P. falciparum and P. vivax but positive for P. malariae. Review of the blood smears also confirmed P. malariae. The patient's malaria was curatively treated with atovaquone/proguanil. However, as with most cases of P. malariae associated nephrotic syndrome reported primarily in children, his overall renal function did not improve.

This case highlights the importance of obtaining even remote travel histories from ill immigrants and considering occult quartan malaria in patients from endemic locations with nephrotic syndrome. Unlike other plasmodia, P. malariae can remain quiescent for decades in the reticuloendothelial system and recrudesce more than 40 years after initial infection. The association between P. malariae and nephrotic syndrome and the pathophysiology of this condition will be reviewed. This case is particularly relevant to Navy Medicine because it illustrates the significance of the practice of recruiting immigrants into US military forces from developing countries with regard to evaluation of illnesses among immigrant sailors; specifically, in the context of the known geographical distribution, epidemiology, incubation period and chronicity of infectious agents. Also, it raises awareness of the wide variety of advanced technological resources available through the U.S. Navy's CONUS and overseas research laboratories to aid in the diagnosis of infectious diseases not commonly seen in the United States but of significant importance to forward deployed force protection.

MIGRATORY POLYARTHRALGIA IN A RENAL TRANSPLANT PATIENT

Jean Fiedler, M.D., Virginia Commonwealth University

A 61 year old male who was status post living donor renal transplant with a history of diabetic neuropathy presented to transplant clinic complaining of multiple joint pains that started 2 months ago. He stated prior to onset of arthralgias, he had an upper respiratory illness which was treated with azithromycin. The pain, described as throbbing and constant, started in his left wrist and hand with associated swelling. It then migrated to his left elbow and 2-3 days later, subsequently to his right ankle and foot. He noted some improvement of pain with Percocet and gabapentin, but symptoms did not completely resolve. He then experienced swelling and pain in his right hand and wrist, right elbow, left foot, and ankle. He was bedridden and unable to ambulate for 1-2 weeks due to the arthralgias. He also reported fevers, chills, and fatigue, but denied rash, new medications, dysuria, urethral discharge, headache, or visual changes. He also denied any change in his baseline lower extremity paresthesias. His immunosuppression included mycophenolate, tacrolimus, and prednisone. The vital signs on presentation included a temperature of 37.3 C, blood pressure 145/77, heart rate 72, respiratory rate of 18, and 98% oxygen saturation on room air. On exam, he was in mild distress and was holding his right arm due to pain. He had tenderness, warmth, and swelling in left elbow, right second MCP with total hand swelling, second and fifth MTP, and bilateral ankle. His laboratory findings were significant for ESR 110mm, CRP 28.9mg/dL, rheumatoid factor 103IU/mL, WBC of 9,800 cells/mL, uric acid 11.9mg/dL, and urinalysis significant for trace protein. Patient was negative for Gonorrhea and Chlamydia via urine sample. He subsequently underwent right elbow aspiration which showed needle shaped negatively birefringent crystals, and a diagnosis of acute gout was made based on these findings. Increase prednisone dose was used to manage his gout, leading to substantial clinical improvement, as manifest by increased pain-free mobility in his right elbow.

Even though gout usually presents as an acute monoarticular tenosynovial inflammation, it can be polyarticular in severe cases. It is important for physicians to be aware of prevalence and assortment of musculoskeletal disorders in transplant population and should include gout in their differential. Not only does renal insufficiency predispose patients to hyperuricemia and gout, but there has also been association of hyperuricemia and gout with immunosuppressants cyclosporine and less commonly tacrolimus.

THERE IS A FUNGUS AMONG US

Margaret Williams, M.D., Eastern Virginia Medical School

A 71-year-old male presented to the ER with multiple new skin lesions located on his penile shaft, elbows, and hands. The patient reported chills, night sweats, nausea, vomiting, and weight loss of 60 lbs. over the past six months.

As an outpatient, the skin lesions were treated with Levaquin for ten days, without improvement. Subsequently he received treatment with Bactrim for possible MRSA skin infection. One-month prior, the patient underwent a transurethral resection of the prostate. He then received radiation to the lip for squamous cell carcinoma (SCC). Other past medical history included lymphoma in remission, depression, resection of SCC in the lung, chronic obstructive lung disease, and benign prostatic hypertrophy. Significant social history includes his occupation as a horticulturist in Kentucky. He denies recent sexual activity and denies any history of sexually transmitted diseases.

Physical exam revealed an afebrile patient with non-tender cervical lymphadenopathy. His lung sounds were clear bilaterally. On the penile shaft was a 3x3 cm ulcer with a serpentine raised well-demarcated border. The drainage was creamy sero-sanguineous fluid. There was also the presence of a 1x1 cm raised lesion on his cheek, a 1x1 cm erythematous tender abrasion on his elbow, two 0.5 cm erythematous closed round papular lesions present on his left 5th digit laterally, and 1st digit on the right hand.

A biopsy was performed on the penile lesion. An empiric antibiotic course was initiated. A computed tomography (CT) of the head, chest, abdomen, and pelvis was performed to look for metastasis of lymphoma. The CT of his head revealed two enhancing foci in his left cerebral hemisphere with possible representation of metastasis. The patient's penile biopsy revealed blastomycosis. The follow-up Magnetic Resonance Imaging (MRI) revealed sub-centimeter-enhancing nodules in the cerebrum and cerebellum, including the nodules subtly visible on CT. Lumbar puncture was performed and revealed high blastomycosis titer.

The patient was treated with Lipoid Amphotericin B for the central nervous system infection with blastomycosis. A follow-up MRI revealed decreased lesion size. The patient's skin lesions improved.

Teaching point: Blastomycosis infection can present as a multi-organ disease most commonly with pulmonary involvement, however this patient had no pulmonary involvement. While skin involvement is present in 18% of cases, only 2% present with genitourinary and 1 % present with CNS blastomycosis. The patient's weakened immune system most likely contributed to the indolent course. It is unknown whether the initial SCC of the lip was indeed SCC or blastomycosis since there was no biopsy performed at that time.

A CASE OF INTRAMUSCULAR MONOSODIUM URATE CRYSTAL "ABSCESSES"

Leia Ince-Mercer, M.D, Virginia Tech-Carilion School of Medicine

This is the case of a 38 year old caucasian male admitted with acute on chronic renal insufficiency, complaints of abdominal discomfort and intractable left anterior tibial pain. The patient denied any recent history of trauma. On physical examination, the patient was afebrile and hemodynamically stable. Non-pitting edema, warmth and exquisite pain on palpation were noted in the left leg. There were no palpable subcutaneous nodularities. The remainder of the physical exam was unremarkable. Laboratory values obtained noted a white blood cell (WBC) count of 11.8 K/uL, creatinine of 1.58 mg/dL, sedimentation rate (ESR) of 97 mm/HR, and uric acid of 14.4 mg/dL. Ultrasonography of the lower extremity was completed and reported no deep vein thrombosis, but noted an incidental finding of multiple cysts to the left leg musculature, questionable for abscesses.

To follow further, since the patient was already scheduled to complete a computed tomography (CT) scan of the abdomen to further investigate his abdominal complaints, a CT scan with contrast of the lower extremity was also completed, and noted: multifocal abscesses within multiple muscles of the thigh and upper leg and what may have represented an infected popliteal cyst. At this point surgery was consulted, and an incision and drainage procedure collected "caseaous" specimens. The specimens were sent for multiple analyses. Cultures were negative for bacteria, tuberculosis, and fungus; but ultimately were significant for monosodium urate crystals. The final diagnosis was intramuscular gout. Accordingly, the patient was started on steroids (with planned taper) as well as colchicine. His extremity complaints slowly resolved with this therapy, and he was eventually discharged on allopurinol for maintenance therapy.

Non-traumatic acute gout of the peripheral muscle is very rare, with only one other reported case in the literature (1). Chaoui et. al. described intramuscular gout in the forearm of an immunosuppressed heart transplant patient, but who had previous history of a traumatic wound to that area (2). Similar to our case, these caseous urate crystal laden deposits – or "urate milk" (3) – of the muscle will radiographically mimic pyomyositis with abscess formation; although secondary infection would be a rare complication of intramuscular gout (4).

Acute intramuscular gout is a rare presentation. In this case, the intramuscular "urate milk" deposits were surgically collected for definitive diagnosis. With the treatment regimen described, WBC, ESR, and uric acid levels significantly improved, and the patient's subjective lower extremity complaints resolved, with no reported recurrences at 2-weeks and at 3-months reassessments.

SILENT HERALD: A UNIQUE CASE OF IDIOPATHIC MEMBRANOUS GLOMERULONEPHRITIS PRESENTING AS PULMONARY EMBOLISM

Mary Caroniti, M.D., Naval Medical Center Portsmouth

Nephrotic syndrome is defined as renal injury resulting in hyperlipidemia, edema, nephrotic range proteinuria (3.5 grams per 24 hours in adults), and hypoalbuminemia. It is associated with hypertension, hypercoagulability, and acute kidney injury. Hypercoagulability is thought to be secondary to increased liver synthesis of clotting factors while there is a concurrent urinary loss of inhibitors of coagulation. The net effect is an increased tendency for both arterial and venous thrombosis. There are many specific causes of the syndrome.

We present the case of a 42 year-old active duty USN male without significant past medical history who presented for evaluation of left-sided rib pain. After a CT scan was performed, but before it was resulted, he developed abdominal pain. Urinalysis was performed for the evaluation of abdominal pain. His CT scan subsequently demonstrated bilateral pulmonary emboli. The patient had not endorsed any risk factors for pulmonary emboli or deep venous thrombosis. His urinalysis was consistent with 7grams per 24 hours of proteinuria. Subsequent lower extremity duplex demonstrated no apparent clots. He demonstrated neither edema nor hypertension. His serum creatinine was normal. Due to the proteinuria, he was referred to the Nephrology service. Laboratory evaluation demonstrated previously unrecognized hyperlipidemia and hypoalbuminemia. Renal biopsy demonstrated membranous glomerulonephritis, a known cause of nephrotic syndrome. After further evaluation, the membranous glomerulonephritis was judged idiopathic.

In reviewing the literature, we could find no example of idiopathic membranous glomerulonephritis presenting as pulmonary emboli without deep venous thrombosis. This case highlights the importance of screening for proteinuria in patients with unexplained pulmonary emboli. Identification of proteinuria may provide valuable diagnostic insight into the cause and save unnecessary testing for other clotting disorders. Further, prompt identification of intrinsic renal disease may provide better outcomes due to earlier initiation of treatment. As demonstrated by this case, proteinuria may exist without any of the other classic findings of nephrotic syndrome.

A TRIPLE-SECRETING CHALLENGE

Faizah Siddique, M.D., Virginia Commonwealth University

Adrenocortical carcinomas (ACC) are rare, affecting 1-2 people in every 1.5 million, with rare reports of ACC secreting glucocorticoids, mineralocorticoids, or both. Treatment of non-resectable ACC can be challenging for physicians.

48 year-old Caucasian man with hypertension presented with complaints of abdominal swelling associated with progressive fatigue, dyspnea and weight gain over 6 weeks. He denied cough, fevers, pain or change in urinary or bowel habits. On admission, BP 103/68, HR 98, temperature 98.4 degrees Fahrenheit, respiratory rate 20 with oxygen saturation 91% on room air. He was diaphoretic, without jaundice, and had distended abdomen without shifting dullness, scars, tenderness, or palpable organomegaly. Heart and lungs were normal, but he did have bilateral lower extremity edema. Lab work was significant for potassium 2.4 mmol/L, chloride 97 mmol/L, bicarbonate 38 mmol/L, BUN 34 mg/dL, creatinine 1.07 mg/dL, WBC 13.2x109/L with 86.9% neutrophils, Hb 14.1 g/dL, platelets 358 x 109/L, AST 225 units/L, ALT 119 units/L. CT angiogram was negative for embolus. CT of the abdomen showed a 15.6 cm x 8.4 cm retroperitoneal mass surrounding the left renal artery, pancreas, and displacing the spleen with minimal ascites. There were numerous, well-circumscribed heterogeneous and predominantly low attenuation masses throughout the liver as well as enlarged abdominal lymph nodes. Further analysis showed elevated cortisol 44.9 ug/dL, androstenedione 741 ng/dL, estrone 44.9 ug/dL, and aldosterone 31.3 ng/dL levels. Plasma metanephrines were normal. Biopsy of the mass was consistent with adrenocortical carcinoma (stage IV). The patient was not a surgical candidate due to the degree of metastases and size of primary tumor. He received mitotane 1500 mg/day following chemoembolization with doxorubacin, etoposide, and carboplatin. Six days post-procedure, the patient developed hypotension secondary to relative hypocortisolism (cortisol 30.3 ug/dL). The mitotane dose was then decreased to 1000 mg/day, with stabilization of his blood pressure. Thirteen days post-chemoembolization, repeat abdominal CT showed no changes in size of the mass, but did show multiple new nodules in the peritoneum, indicating new metastases. The patient was eventually discharged to home hospice.

This case demonstrates the rare presentation and challenges of treatment of a non-resectable ACC. Medical management includes cytotoxic agents: etoposide, doxorubicin, cisplatin (FIRM-ACT trial) or streptozotocin; and reversal of hormone imbalances. Hypercortisolism is further treated with ketoconazole (assuming no liver impairment), metyrapone, or etomidate. Adjuvent therapies include long-term mitotane and radiotherapy, especially for bone and/or brain metastases. Mitotane is used to suppress cortisol release, and although monitoring mitotane drug levels is advised, measuring hormone levels can indicate relative changes leading to symptoms (i.e. hypotension from relative adrenal insufficiency). This will undoubtedly increase quality of life for patients with this devastating illness.

MASSIVE PULMONARY EMBOLISM DIAGNOSED BY BEDSIDE ULTRASOUND

Alisha Young, M.D., Eastern Virginia Medical School

Introduction: With the arrival of inexpensive and portable ultrasound devices, ultrasonography can be incorporated into bedside assessment to supplement physical exam and provide real-time diagnostic information vital in managing hemodynamically unstable patients.

Case: A 54-year-old female with hypertension, diabetes, recurrent right jaw amelobloastoma who recently underwent surgical resection and closure with anterolateral thigh flap, presented with subjective fever and chills, persistent dry heaving, vomiting, and general malaise since her discharge.

On initial evaluation, patient was afebrile with tachycardia and hypotension that improved after normal saline bolus in the ED. Patient denied cough, dyspnea, chest pain, abdominal pain, lower GI symptoms, dysuria, and peripheral edema. Physical exam was significant for tachycardia, clear breath sound, mildly tender facial flap with peripheral facial palsy and right eye chemosis, and post-operative buccal mucosal change. Laboratory studies were significant for WBC 9.2, glucose 317, lactic acid 2.5, negative cardiac enzymes x 2, and ABG pH 7.43, PaCO2 28.9, PaO2 83.0, HCO3 18.7, oxygen saturation at 97% on 2 liter oxygen. Chest X-ray was unremarkable. Soft tissue neck CT revealed multiple fluid collections with air worrisome for abscesses. Patient was started on IV fluid resuscitation and antibiotic for systemic inflammatory syndrome (SIRS) with pending blood cultures.

Over the next 18 hours, patient developed progressive dyspnea, tachypnea, new onset of abdominal pain, labile blood pressure, and decreasing urine output after six liters of IV fluid. A bedside ultrasound by the resident to assess volume status and fluid responsiveness revealed a non-compressible inferior vena cava, dilated and rigid right ventricle and severely under-filled left ventricle, consistent with acute cor pulmonale. This prompted a stat chest CT angiography and confirmed the diagnosis of massive acute pulmonary emboli with a large saddle embolus crossing bilateral main pulmonary arteries extending to nearly all segmental levels. Patient was started on heparin drip and underwent emergent mechanical thrombectomy, thrombolysis with locally adminstered tPA, and IVC filter placement. PVL of bilateral lower extremities at a later time showed asymptomatic acute deep venous thrombosis in bilateral popliteal, peroneal and right posterior tibial veins. Patient was started on warfarin and discharged home in stable conditions eight days later.

Discussion: The atypical presentations of this patient's PE and DVT highlight the challenges in diagnosing thromboembolism. A high index of suspicion and the incorporation of additional diagnostic tools, such as bedside ultrasound, led to the diagnosis and timely intervention for this patient when she was acutely unstable. Through dedicated electives or serial workshops, residents and medical students can learn to supplement their bedside assessment with ultrasonography and gain real-time diagnostic information invaluable in managing hemodynamically unstable patients.

A CASE OF GRAVE'S DISEASE PRESENTING AS VASOSPASM-INDUCED MYOCARDIAL INFARCTION

Christopher Arnold, M.D., University of Virginia

Thyrotoxicosis frequently affects the cardiovascular system in many ways. However, coronary artery spasm is an uncommon manifestation of thyrotoxicosis. A 41 year old female with no significant past medical history presented with a 3 month history of angina that had progressed to unstable angina over a week. The electrocardiogram revealed diffuse ST segment depression. She was transferred to the University of Virginia to undergo emergent cardiac catheterization. A review of systems revealed a several month history of dyspnea on exertion, palpitations, tremors, 10 pound weight loss, as well as a lump on her anterior neck that had been enlarging over the past month and was causing increasing difficulty with swallowing. She took no medications and endorsed a 70 pack year smoking history. There was no strong family history of cardiac disease.

Physical examination revealed a blood pressure of 110/76 mmHg with a pulse rate of 105 bpm. She was thin, weighing 41.3 kg and had fine hair. There was mild proptosis of the left eye. The left thyroid lobe was diffusely enlarged, smooth, and non-tender and the right lobe had a 1 cm nodule in the upper pole. The remainder of her examination was unremarkable.

Laboratory evaluation revealed an elevated troponin at 0.53 ng/mL which eventually peaked at 0.86 ng/mL. Thyroid studies showed a TSH of <0.01 uIU/mL, total T4 18.2 µg/dL with a free T4 3.9 ng/dL, and T3 279 ng/dL. Thyroid antimicrosomal antibody was elevated at 207 IU/mL and thyroglobulin antibody was also elevated at 2656 IU/mL.

She was started on esmolol and nitroglycerin infusions, and received 60 mg of IV solumedrol prior to cardiac catheterization. Cardiac catheterization revealed stenoses of 60% RCA ostium, 80% left main ostium, 60% left main coronary, and 60% proximal LAD. Nitroglycerin was infused during the catheterization with some improvement in the right coronary stenosis consistent with vasospasm. After catheterization, further evaluation of the coronary system was performed with a CT scan, demonstrating mild narrowing of the left main artery but no evidence of focal or osteal stenosis.

Given these findings, it was felt that the patient's cardiac ischemia was likely secondary to vasospasm as opposed to true underlying coronary artery disease. As such, the patient was continued on esmolol and nitroglycerin infusions and treated with methimazole and dexamethasone. Her symptoms improved with no recurrence of chest pain. She was discharged on a beta-blocker, statin, aspirin, long acting nitrate, methimazole, and a steroid taper.

This case illustrates a rare instance of Grave's Disease presenting as vasospasm-mediated non-ST elevation myocardial infarction. Failure to recognize this interesting pathophysiology could have resulted in unnecessary percutaneous intervention or even thoracic surgery. Its diagnosis allowed for correct treatment of a complex disease process and a positive patient outcome.

ACUTE CHEST SYNDROME: I-N-O SPELLS RELIEF

Marcus Carden, M.D., Virginia Commonwealth University

Clinical Presentation: A 21 year-old woman presented to the hospital two days after an elective abortion with acute onset abdominal pain, shortness of breath, and subjective fevers. Past medical history was significant for hemoglobin SS disease without previous pulmonary hypertension (PH) and a baseline hemoglobin of 8.5 g/dL. Vital signs were significant for a blood pressure of 120/80 mmHg, heart rate of 140 bpm, respiratory rate of 35 bpm with an oxygen saturation of 92% on 8 lpm by nasal cannula, and temperature of 39.1 degrees Celsius. Physical exam revealed scleral icterus, increased work of breathing and poor inspiratory effort, bibasilar crackles, an RV heave, and a 3/6 holosystolic murmur with S3 gallop. EKG showed sinus tachycardia. A bedside echocardiogram revealed a dilated right ventricular cavity of 5.2 cm with moderately reduced function, moderate tricuspid regurgitation, and pulmonary hypertension with a pulmonary artery systolic pressure (PASP) of 40 mmHg. Labs revealed WBC of 21,700/mL, hemoglobin 6.1 g/dL, total bilirubin 31.8 mg/dL, and BNP 247 pg/mL. Blood smear revealed a markedly increased number of sickled erythrocytes. Chest radiograph was concerning for a new pulmonary infiltrate. Chest CT showed several foci of consolidation and enlargement of the right heart. The patient was emergently started on broad spectrum antibiotics and inhaled nitric oxide (iNO) at 20 ppm by high flow nasal cannula. Twenty four hours after initiation of iNO and prior to exchange transfusion, repeat bedside echocardiogram revealed a reduced RV size of 3.9 cm with normal function, trivial tricuspid regurgitation, and a PASP of 30 mmHg. Serum BNP was 92 pg/ml. On day 4, the iNO was discontinued and the patient was discharged from the intensive care unit on supplemental oxygen at 3 lpm by nasal cannula.

Discussion: This case suggests that iNO delivered by high-flow nasal cannula is a novel therapy that rapidly reduces right ventricular strain and pulmonary hypertension during the acute chest syndrome in patients with sickle cell disease. The patient in this case had a rapid improvement in pulmonary hypertension and RV size. While the results of this case report need to be further evaluated in larger clinical trials to estimate true mortality and morbidity benefit when using iNO, the impressive resolution of RV strain and PH in the absence of other interventions is intriguing. Improved PH and RV strain in acute chest syndrome could improve clinical outcomes and lead to better treatment of patients with sickle cell anemia.

AGGRESSIVE REFRACTORY CERVICAL, VAGINAL AND VULVAR CARCINOMA IN-SITU AS A MANIFESTATION OF IDIOPATHIC CD4 LYMPHOCYTOPENIA

Sean Cowley, M.D., Naval Medical Center Portsmouth

Introduction: Idiopathic CD4 lymphocytopenia (ICL) is a rare acquired adult immunodeficiency disorder that is not caused by HIV infection or any other transmissible virus. This syndrome's pathogenesis is not completely understood. Most patients will be diagnosed after having an opportunistic infection such as disseminated viral, cryptococcal or mycobacterial infection and have no evidence of known immunodeficiencies. We present a case of a young female with refractory vulvar and cervical intraepithelial neoplasia as a manifestation of ICL.

Case Presentation: The patient is a 23 year old female with essentially unremarkable history until an abnormal pap smear was positive for Human Papilloma Virus (HPV). Colposcopy and biopsies confirmed CINIII (cervical intraepithelial neoplasia, grade 3), VAIN III (vaginal intraepithelial neoplasia, grade 3), and VIN III (vulvar intraepithelial neoplasia, grade 3). Of note, previous annual pap smears were negative for 4 years as well as her HIV tests. She was referred

to Gynecologic Oncology who treated her with a LEEP (loop electrosurgical excision procedure), laser therapy, and 5-flurouracil, and ultimately with a wide local excision. She was referred to the Allergy and Immunology clinic by her Gynecologic Oncologist for consultation of possible immunodeficiency. History revealed that she was also being treated by Dermatology with cryotherapy for recurrent flat warts on her hands and arms at that time. Review of systems was relevant only for new onset of fatigue, requiring daily naps after work over the past year. Laboratory evaluation revealed low absolute lymphocyte count of 300 with a CD4 count of 32. Additional pertinent tests include: negative anergy panel showing poor T cell function, normal quantitative immunoglobulins, and negative HIV-1 RNA, HTLV, HHV6, CMV, EBV PCRs. Due to her very low CD4 count, the patient was started on prophylaxis for opportunistic infections. She was then referred to the National Institutes of Health with the diagnosis of ICL.

Discussion: Our patient met the Centers for Disease Control and Prevention (CDC) criteria for ICL with "a documented absolute CD4 T lymphocyte count of less than 300 cells per cubic millimeter on more than one occasion, no evidence of infection on HIV testing, and the absence of any defined immunodeficiency or therapy associated with depressed levels of CD4 T cells." Previous functional investigations suggest that there may be defects on CD4 T lymphocyte chemokine receptors resulting in apoptosis, however, etiology is yet unknown and there are no treatments available for this condition. Current experimental protocols are using interleukin-2 and interleukin-7 to increase CD4 T-lymphocyte counts and improve overall patient outcomes. Although this is a rare condition, ICL and immune evaluation should be considered in HIV negative patients who develop opportunistic infections or have recurrent viral associated cancers.

"BROKEN HEART SYNDROME": A CRITICAL, REVERSIBLE COMPLICATION OF STATUS EPILEPTICUS

Om Samantray, M.D., Virginia Tech Carilion School of Medicine

This is a case of a 57 year old caucasian female with a past medical history significant for chronic pancreatitis and seizure disorder for which she takes oral phenytoin. She presented to our hospital with convulsive status epileticus. The patient had been having episodes of nausea and vomiting secondary to her pancreatitis for the past week and had been unable to keep her phenytoin down. Prior to this hospital presentation, she had no reports of chest pain, cough, fever, or chills. On admission, she received intravenous fluids, ativan, levetiracetam, and midazolam. With her seizures refractory to this initial regimen, she was eventually placed on a midazolam infusion that controlled the seizures. She was intubated for airway protection. On physical examination the patient had a blood pressure of 70/48 mmHg, a regular but tachycardic pulse of 114 beats per minute, and marked jugular venous distension. The remainder of her physical exam was unremarkable. The admission electrocardiogram was significant for tachycardia and S-T segment elevation in leads V4 to V6 that progressively developed Q-waves. Laboratory values obtained showed an undetectable phenytoin level, Troponin I of 0.02 ng/mL and CK-MB of 2.2 ng/mL.

A transthoracic echocardiogram revealed a cardiomyopathy with severely reduced left ventricular systolic function with an ejection fraction of 20-25%, with preserved contractility only at the level of the basilar segments. The rest of the left ventricle was severely hypokinetic to akinetic, and the right ventricle was enlarged and hypokinetic globally. Cardiac catherization showed no obstructive coronary lesions. Ultimately, a preemptive diagnosis of Takotsubo cardiomyopathy was given, and the patient was treated accordingly.

The pathophysiology of Takotsubo cardiomyopathy ("Broken Heart Syndrome") is thought in part to come from myocardial stunning secondary to the massive release of catecholamines (1). This level of release has been shown to occur during status epilepticus (2). One study reviewed the cardiac pathology of patients who died during status epilepticus and showed that catecholamine release caused contraction banding, resulting in apical hypokinesis of the myocardium (3). A later report by Legriel et. al. in 2008 further supported this potentially fatal, but fully reversible cardiac complication in patients with status epilepticus (4).

Takotsubo cardiomyopathy is a potentially critical complication of status epilepticus that Internists must seriously consider. Fortunately, this can be an entirely reversible complication. With appropriate supportive treatment in the acute phase of her presentation, serial transthoracic echocardiograms showed progressive improvement in our patient's cardiac function: such that approximately 5 months after her acute presentation, her left ventricular systolic function normalized, with an ejection fraction of 60%.

CHIARI 1 MALFORMATION PRESENTING AS UNILATERAL FACIAL AND ABDUCENS NERVE PALSIES

Tamika Khan, M.D., Virginia Tech Carilion School of Medicine

Introduction: Chiari 1 malformation has a prevalence of approximately 0.5% with the majority of cases being asymptomatic. Most cases are diagnosed in adulthood or late adolescence. Symptoms tend to occur with increased intracranial pressure, which is caused by interruption of normal flow of cerebrospinal fluid due to compression of the cervicomedullary junction by the ectopic cerebellar tonsils. Therapeutic strategies are mainly surgical with posterior fossa decompression via shunting being the standard of care. We present an novel management strategy of a symptomatic Chiari 1 malformation complicated by increased intracranial pressure and consequent cranial nerve paresis successfully treated with acetozolamide therapy.

Case Presentation: A 32-year-old woman was admitted to evaluate a 10-day history of diplopia, right-sided facial weakness, and headaches. Her medical history included hypertension, hypothyroidism and hepatitis C, and her medications were hydrochlorothiazide, verapamil, thyroxine, ribavarin and pegylated interferon. Her vital signs were normal. Fundoscopy revealed bilateral grade 4 disc edema, axoplasmic stasis, and multiple flame hemorrhages. There was a right abducens nerve palsy, an enlarged blind spot, and a right lower motor neuron facial nerve palsy. Brain MRI demonstrated bilateral cerebellar tonsillar ectopia with the tonsils extending 1 cm below the foramen magnum, consistent with a Chiari 1 malformation. Subsequent brain MRA was unremarkable. Routine CSF studies and cytology were normal, but the opening pressure was 48cm H2O. Acetazolamide was started to reduce the intracerebral pressure. Upon discharge there was complete resolution of her papilledema, facial and abducens nerve pareses.

Discussion: Although numerous case reports exist describing Chiari 1 malformations in adults, there is a paucity of information documenting cranial nerve paresis as a complication. Unilateral facial and abducens nerve palsy is indeed an uncommon presentation. Headaches, diplopia and vertigo are more commonly described. Symptoms typically result with cerebellar tonsillar herniation greater than 5mm through a narrowed foramen magnum. Recommended care ranges from observation and symptomatic management to posterior fossa decompression and shunting of any detected syrinx noted on spinal cord imaging. Medical treatment generally consists of simple analgesics, muscle relaxants and/or a soft cervical collar. Though not described as a standard of care, a trial of acetazolamide should be considered in the management of symptomatic Chiari 1 malformations.

ENHANCED INTERLEUKIN-1 ACTIVITY IN PLASMA OF PATIENTS WITH ACUTE DECOMPENSATED HEART FAILURE

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BACKGROUND: Interleukin -1β(IL-1) is an inflammatory cytokine that suppresses cardiac contractility in cellular and animal models, referred to as circulating myocardial suppressant factor in sepsis. We hypothesize that the plasma in patients with acute decompensated heart failure (ADHF) may have increased plasma IL-1 activity which may contribute to impaired cardiac function.

METHODS: Adult mice (N=5 per group) underwent baseline echocardiography to measure left ventricular ejection fraction (LVEF) and then at 4 hours after receiving either plasma derived from healthy controls (0.2 ml), recombinant murine IL-1β(0.3 μg/Kg), or plasma from patients admitted with ADHF (0.2 ml, without and with pre-treatment with anakinra, recombinant human IL-1 receptor antagonist [10 mg/Kg]).

RESULTS: Mice given recombinant IL-1 βor plasma from patients with ADHF had significantly depressed LV systolic function at 4 hours after injection (LVFS reduction of 27% +/- 4%, and 25% +/- 4%, respectively, $p < 0.05$ vs. baseline) when compared to mice receiving plasma from healthy controls. Pretreatment with anakinra prevented the systolic dysfunction (LVFS reduction of 2%, $p < 0.05$ vs. IL-1 B, ADHF) seen in mice given the plasma from patients with ADHF, suggesting that the plasma of ADHF had sufficient IL-1 activity to induce systolic dysfunction.

CONCLUSIONS: Patients with ADHF have enhanced plasma IL-1 activity which may contribute to impaired cardiac function. IL-1 blockade may represent a novel approach for the prevention or treatment of ADHF.

DEGREE OF PERIPHERAL INFLAMMATION IS ASSOCIATED WITH POOR OUTCOMES IN HOSPITALIZED PATIENTS WITH C. DIFFICILE INFECTION

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Background: C. difficile infection (CDI) can induce both an intense intestinal inflammation (pseudomembranous colitis) and peripheral inflammation (leukemoid reaction) both of which are associated with increased morbidity. However, it is unclear if the degree of inflammation correlates with the severity of disease. Patients with invasive infectious diarrhea have been shown to have positive fecal lactoferrin, yet it is not clear if the level of intestinal inflammation correlates with more severe CDI and poor outcome. Purpose: To evaluate whether the degree of peripheral inflammation (maximum serum WBC within 24 hours of CDI diagnosis) and intestinal inflammation (quantitative fecal lactoferrin) can predict poor clinical outcomes in hospitalized patients with CDI. Methods: IRB approval was obtained (HSR-IRB# 13630) for a prospective cohort study of hospitalized patients with CDI at University of Virginia. Once consent was obtained, patients who had been diagnosed with CDI clinically, via toxin assay or PCR, were followed while hospitalized and then at one and three months. Peripheral inflammation was defined by maximum serum white blood cell count (WBC) in cells per cubic millimeter (cmm) within 24 hours of CDI diagnosis. Intestinal inflammation was measured via quantitative fecal lactoferrin (IBD-SCAN, TechLab, Inc.) per manufacturer's instructions. Poor outcome was defined as Intensive Care Unit (ICU) stay, colectomy, death from all causes, and death from C. difficile. Data was analyzed using SPSS for t-test and linear regression. Results: Forty-two participants were enrolled. Subjects with who died from any cause in three months (n=6) had higher mean WBC than those alive (n=18) (15.66 cmm vs. 10.63 cmm, p=0.032) Subjects who died from CDI by 1 month (n=2) also had significantly higher WBC, than those alive (n=33, 28.14 cmm vs. 12.66 cmm, p=0.001). WBC >15,000 cmm was associated with an increased rate of ICU stay (p=0.004). All subjects with WBC> 20,000 cmm (n=6) had ICU stay, higher all-cause mortality at 3 months (p=0.024), and a trend toward

a higher incidence of death from CDI at 3 months (p=0.083). Although age and WBC were not highly correlated (R2=0.02), age and intestinal inflammation were highly correlated (R2=0.201). Subjects ≥ 65 years with WBC >15,000 had higher mean fecal lactoferrin (1728.657 vs. 307.552 µg/mL, p=0.028), although we were not able to show worse outcome. Conclusion: Subjects with increased peripheral WBC at CDI diagnosis had worse clinical outcomes, including ICU stay and death. Although elderly subjects had a higher degree of intestinal inflammation, we were not able to show an association with worse outcome in this small study. These findings suggest that patients with elevated WBC may need closer monitoring or more aggressive therapy at time of initial CDI diagnosis. Further larger studies are needed to validate these results.

THE PRESENCE OF THE KPC GENE IN KLUVYVERA INTERMEDIA: AN ENVIRONMENTAL BYSTANDER

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There have been recent outbreaks of carbapenemase-mediated carbepenem resistance in the northeastern United States. The carbepenemase has been traced to a plasmid first isolated from Klebsiella pneumoniae, and thus has been named Klebsiella pneumoniae carbapenemase (KPC). The KPC gene has appeared in several other members of the Enterobacteriaceae. Recent studies suggest that the spread of resistance is mediated through a transposon. In this report we are investigating a small outbreak of Kluyvera Intermedia colonization in our hospital. Kluyvera is part of the family Enterobacteriaceae that is a rare cause of infection in humans. It is normally found in the environment as a free living organism in water, soil, sewage, and food products of animal origin. In humans, it is normally isolated from sputum, urine and stool samples. It is a normal inhabitant of the digestive tract, although it is found in low numbers. Perirectal swabs were collected in our study that were part of a hospital wide screening for KPC. This screening had been initiated in our hospital secondary to an institutional outbreak of KPC in our Surgical Intensive Care Unit, and the subsequent demise of two liver transplant patients. Most KPC carrying isolates were identified as Klebsiella, however a few samples were identified as Kluyvera species, which prompted our investigation. In our study, we found that the Kluyvera species was in fact a carrier of the KPC transposon, as demonstrated by PCR. Experiments that are in progress include: sequencing isolates, pulse field electrophoresis, and conjugation experiments. The presence of the KPC gene is a novel finding for Kluyvera Intermedia. The presence of the KPC gene in an environmental bystander such a Kluyvera is a humbling prospect, since they can serve as stepping stones or "carriers" of the resistance gene to be passed on to other human pathogens.

CIRCULATING CARDIODEPRESSANT FACTORS IN PATIENTS WITH SEPSIS

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BACKGROUND: Cardiac dysfunction is a common feature in sepsis associated with a very high mortality. The presence of soluble cardiodepressant factors in patients with sepsis has been postulated based on in vitro studies in cultured myocytes. In the present study, we investigated the presence of these cardiodepressant factors in patients with sepsis according to the ability of these factors to suppress cardiac function in the healthy mouse.

METHODS: Adult mice (N=6 per group) underwent baseline echocardiography using the VEVO770 system dedicated to rodents in order to measure baseline left ventricular ejection fraction (LVEF) and then LVEF at 4 hours after receiving either plasma derived from healthy controls (0.2ml) or plasma from patients admitted with sepsis (0.2ml).

RESULTS: Mice given plasma from patients with sepsis had significantly depressed LV systolic function at 4 hours after injection when compared to mice receiving plasma from healthy controls $p<0.05$).

CONCLUSIONS: Patients with sepsis have circulating cardiodepressant factors capable of inducing systolic dysfunction in the healthy mouse. Characterization of this model of septic cardiomyopathy may allow identification of these cardiodepressant factors ex vivo and may lead to a better understanding and potentially to new treatments for cardiac dysfunction in sepsis.

DEHYDRATION PREVALENCE AMONG ELDERLY PATIENTS ADMITTED TO A TERTIARY CARE HOSPITAL USING ICD-9 CODING VERSUS LABORATORY DATA

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Purpose: To compare the prevalence of dehydration in elderly patients admitted to the hospital using ICD-9 coding versus laboratory data.

Methods: Retrospective review of all patients aged 65 years old and older admitted to University of Virginia Hospital from January 2005 through June 2006. ICD-9 coding was examined in addition to lab results on admission to determine incidence of dehydration by each method. ICD-9 codes considered dehydration equivalents included dehydration, azotemia, hypernatremia, and hyperosmolarity. Subsequent lab values associated with dehydration included BUN:Creatinine ratio >20:1, Na >145, a measured serum osmolarity >295, or a calculated serum osmolarity >295 (serum osmolarity = (2(Na + K))+ Glucose/18).

Results: 12,757 patients fit the inclusion criteria from January 2005 –June 2006. Of these, patients 677 or 5.3% had an ICD-9 code associated with a diagnosis of dehydration. In comparison, 6135 patients, or 48.1%, met laboratory criteria for dehydration, a difference of 42.8%. Furthermore, out of the total sample of patients, 33.6% met criteria using BUN:creatinine ratio > 20:1, 1.6% met criteria using serum sodium levels >145, and 24.2% met criteria using serum osmolarity ≥295 (both measured and calculated). Of note, not all patients had comprehensive laboratory data on admission. In fact, of the 12,757 original patients, 11655 patients had a BUN:Cr ratio measured, 11660 patients had serum sodium levels measured, and 11660 patients had serum osmolarity measured or calculated.

Conclusion: Dehydration is a common, yet often under diagnosed condition in elderly patients. Geriatric patients often have decreased thirst response, decreased appetite, increased illness, and increased disability resulting in an overall increased risk for dehydration. Presumably, geriatric patients admitted to the hospital are more likely than the general population of geriatric patients to be dehydrated. Surprisingly, the above data shows a wide discrepancy between health care provider documentation of dehydration on admission (5.3%) and laboratory data suggestive of dehydration (48.1%), a difference of 33.6%. Additionally, the vast majority of patients with dehydration in the retrospective analysis met laboratory criteria using BUN:Cr ratio >20:1, 33.6%, followed by serum osmolarity >295 at 24.1%. Fewer patients met criteria using serum sodium suggesting that hypernatremic dehydration represents a very small portion of dehydrated patients. The most concerning potential conclusion from this analysis is that dehydration in this vulnerable patient population could be under diagnosed and therefore under treated. Dehydration can be a difficult diagnosis in the elderly since they often do not present with classic signs such as decreased skin turgor or orthostatic hypotension and utilizing various indicators could increase physician recognition and treatment. Future studies regarding dehydration are challenging since the most accurate indicator of dehydration is unclear and diagnostic discrepancy is large.

A PILOT PHASE II TRIAL OF MAGNESIUM SUPPLEMENTS TO REDUCE MENOPAUSAL HOT FLASHES IN BREAST CANCER PATIENTS

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Not published at request of author.

EVALUATION OF POSSIBLE ASSOCIATION BETWEEN STATINS AND ABNORMAL ESOPHAGEAL MOTILITY

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BACKGROUND AND AIMS: Statin therapy has a well established safety profile however, many patients develop complaints of muscle pain or weakness. Myasthenia gravis is an autoimmune disease that affects neuromuscular transmission leading to dysphagia in up to 15% of affected patients. There is also a case series of 4 patients that supports an association between statin use and myasthenia gravis. The reported rate of muscle toxicity with statin use is 0.1%. It is plausible that the use of statins leads to a mild form of muscle inflammation that presents with esophageal dysmotility which clinically presents as dysphagia. The goal of our study was to evaluate motility and pH impedance studies performed at our hospital for a possible association between statin use and esophageal dysmotility.

METHODS: We evaluated all 179 patients with completed motility studies and pH impedance studies from January 2007 through January 2009. Data collected included: age, sex, indication of esophageal motility study, proton pump inhibitor use, Johnston DeMeester Score, statin use, BMI, EGD results, proximal esophageal amplitude, motility results, lower esophageal sphincter pressure. Data evaluated with a Chi-squared test. Patients excluded were those over 80 years old and less than 18 years old, patients with a prior history or esophageal or gastric surgery, and patients with known connective tissue disease. RESULTS: No associations were noted for either motility abnormalities or sphincter pressures in statin group verse non-statin group with the exception of age having statistically higher rates of use in older patients. CONCLUSIONS: In patients referred for dysphagia or reflux symptoms it is unlikely that the use of statin medications leads to increasing incidence of dysmotility.

EVALUATION OF CLINICAL AND ANGIOGRAPHIC FACTORS ASSOCIATED WITH THE PRESENCE OF CORONARY COLLATERALS IN PATIENTS WITH CORONARY ARTERY DISEASE

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Background: Coronary collateral recruitment is an important protective mechanism to maintain myocardial perfusion following arterial occlusion. The purpose of this study was to identify clinical and angiographic factors associated with the presence of coronary collaterals.

Methods: The study design was a closed cohort study. Patients were eligible if they were 21 years of age or older with obstructive coronary artery disease found at elective coronary angiography. Obstructive coronary artery disease was defined as ≥ 70% occlusion of at least one epicardial artery. Information regarding medical co-morbidities, past medical history and medications were abstracted from the patient medical record.

Results: A total of 553 patients had a coronary artery lesion of ≥70% on angiography. In this group of 553 patients with a mean age of 62.2 years, 251 (45.4%) had evidence of coronary collaterals. The majority of patients had hypertension and hyperlipidemia [454 (82.1%) and 481 (87%), respectively]. A total of 217 (39.2%) had diabetes mellitus, and 149 (26.9%) were current smokers. A history of angina was present in 287 (51.9%), while 63 (11.4%) had a history of congestive heart failure, and 115 (20.8%) had a history of peripheral vascular disease. The majority of patients (84.5%) were on HMG-COA reductase inhibitor therapy. On multivariate regression analysis the number of coronary arteries with obstructive disease ($p<0.001$; OR 2.304, 95% CI 1.832 to 2.897) and a history of heart failure ($p=0.019$; OR 2.097, 95% CI 1.119 to 3.582) were significantly associated with the presence of coronary collaterals. Other associated factors which did not reach statistical significance but were included in the model were diabetes mellitus ($p=0.053$; OR 0.684), current smoking ($p=0.073$; OR 1.457); prior angina ($p=0.067$; OR 0.710), and peripheral vascular disease ($p=0.098$; OR 1.460).

Conclusions: In a large cohort of patients undergoing coronary angiography we found that both clinical and angiographic factors play a potential role in the recruitment of coronary collaterals in patients with obstructive coronary artery disease. The presence of multivessel coronary artery disease and a history of congestive heart failure were predictive of the presence of collaterals.

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