WHAT TO EXPECT WHEN YOU'RE *UN*EXPECTING

University of the Philippines – Philippine General Hospital Interhospital Case Presentation

INTRODUCTION

The diagnosis of a tumor – or any disease for that matter concurrent with pregnancy is one of the most extreme scenarios in medicine: the creation of new life possibly coinciding with the mother's death. This situation can put immense stress firstly on the patient, their families, and on us doctors and medical staff as well[1].

OBJECTIVES

The aim is to discuss a case of an anterior mediastinal mass, specifically to describe its clinical presentation and course, the approach to its diagnosis; to discuss the management, present the prognosis and outcome and to identify ethical issues both in terms of diagnosis and management - all these occurring in the setting of a patient who became pregnant during the course of her disease.

CASE DISCUSSION

History of Present Illness

Patient is V.B. 32 year old female, single with live – in partner from Quezon City who sought consult due to chest pain. She is non-hypertensive, non-diabetic, non-asthmatic; with no known history of pulmonary tuberculosis. She was able to do activities of daily living independently without dyspnea or easy fatigability.

The history of present illness started two years prior to consult when patient experienced recurrent chest pain associated with exertion. It was described as pricking and at times squeezing in character with a VAS score of 8/10, initially localized over the left anterior chest wall at the 2nd to 3rd intercostal spaces, occasionally radiating to the left shoulder, lasting for a few minutes to 1 hour at times. The pain was relieved with as needed intake of Ibuprofen + Paracetamol tablet. The chest pain was occasionally accompanied by undocumented fever and non-productive cough. During this time, she was working as a domestic helper in Saudi Arabia and attributed the chest pain to her load of work. There was no orthopnea, paroxysmal nocturnal dyspnea, edema, no hemoptysis. No consult was done at this time.

A year later, due to the persistence of the mentioned symptoms, patient consulted a private physician and was allegedly treated as bronchial asthma and pneumonia. No records of any of the diagnostics done were available for review. She was given unrecalled medications for the pneumonia and the pain reliever was continued. Allegedly, the patient became asymptomatic for about 2 to 3 months. However, symptoms recurred and became more frequent during which the patient would take pain relievers which afforded temporary relief. Patient eventually came home to the Philippines as her contract with her employer ended.

Two months prior to consult, the chest pain worsened, associated with persistent cough of more than three weeks. At this time patient experienced easy fatigability, generalized body malaise and undocumented weight loss. Patient self-medicated with amoxicillin 500mg/tab, 1 tab thrice a day for seven days. She consulted a private physician and a chest radiograph done allegedly revealed mediastinal mass versus left pulmonary mass. Patient was then advised that a chest computed tomography and biopsy of the mass be done. Patient then decided to consult at the Philippine General Hospital for second opinion.

Family History

There was no hypertension, diabetes, nor bronchial asthma in the family. There was no family history of pulmonary tuberculosis. However, there was history of breast cancer.

Personal and Social History

She previously smoked about 1 to 2 sticks per day for 2 years from 2000 – 2002. She was an occasional alcoholic beverage drinker but denies history of any illicit drug intake. Patient finished her first year in college and worked as a domestic helper in Saudi Arabia from 2009 – 2011. She did not recall any exposure to fumes, biomass fuel, and chemicals

Review of Systems

GENERAL: (-) chills, (-) anorexia
EENT: (-) blurring of vision, (-) diplopia, (-) ptosis, (-) dysphagia, (-) hoarseness
CARDIOVASCULAR: (-) palpitations
GASTROINTESTINAL: (-) abdominal pain, (-) nausea vomiting, (-) change in bowel habits, (-) change in appetite
GENITOURINARY: (-) dysuria, (-) abnormal vaginal bleeding, (-) pelvic pain
MUSCULOSKELETAL: (-) musculoskeletal pain / weakness, (-) joint pain / swelling, (-) back pains
DERMATOLOGICAL: (-) skin lesions
NEUROLOGIC: (-) weakness of extremities, (-) difficulty in ambulation/ unstable gait, (-) slurring of speech

The patient was first seen at our institution's General Medicine Clinic on January 2012, advised to have her chest radiograph plates retrieved and reviewed. She was unfortunately lost to follow up for 5 months. When she finally came back, she was immediately referred to the Pulmonary Medicine Outpatient clinic.

Physical examination on consultation was as follows:
GENERAL: Awake, coherent, ambulatory, not in cardiorespiratory distress
VITAL SIGNS: BP: 110/80 HR: 108 RR: 22 T: 36◦
HEENT: Anicteric sclerae, pink palpebral conjunctiva, no palpable cervical lymphadenopathy, no anterior neck mass noted
CHEST AND LUNGS: No gross deformity, chest lag on the left, equal vocal and tactile fremitus, decreased breath sounds on the left, dullness on percussion left, no crackles/wheezes, clear breath sounds right
CARDIOVASCULAR: adynamic precordium, tachycardic, regular rhythm, distinct heart sounds, apex beat noted at the 4th ICS left mid-clavicular line, no murmurs/heaves/thrills, no pulsus paradoxus,
ABDOMEN: Flat abdomen, normoactive bowel sounds, soft, non-tender, no mass palpated
EXTREMITIES: Full equal pulses, pink nail beds, no cyanosis, no clubbing, no edema
NEUROLOGIC EXAMINATION: unremarkable

Given these physical examination findings, the patient's history and the PA view of the patient's chest radiograph dated January 2012 which showed a homogenous opacity with indistinct

borders, occupying most of the left hemithorax, obscuring both the left heart border and the left hemidiaphragm. There is no noted tracheal deviation and no other significant infiltrates seen. Unfortunately, no lateral view was provided. A chest CT scan at this point was imperative to confirm whether the mass is located in the mediastinum or in the lung parenchyma.

A step-wise approach was applied for the diagnosis in our case. We have gone through the clinical history and physical examination and subsequently, for the radiologic localization, a chest CT scan was done[2]. The CT scan of the patient dated April 2012 showed a large, heterogenous mass with areas of hypodensities located in the anterior mediastinum measuring 9.0 x 11.5 x 11.0 cm. It extends to and occupies more than 75% of the left hemithorax, occluding the left mainstem bronchus, with consequent collapse of the left lung. The mass also compresses the left pulmonary veins and artery; also encases the thoracic aorta. There was no note of any enlarged lymph nodes. The liver is unremarkable.

At this point, we have localized the lesion in the anterior mediastinum. In the systematic approach to diagnosis of mediastinal tumors, we first take into consideration the location of the mass, the patient's age and symptoms and the radiologic appearance[2]. (Figure 1)

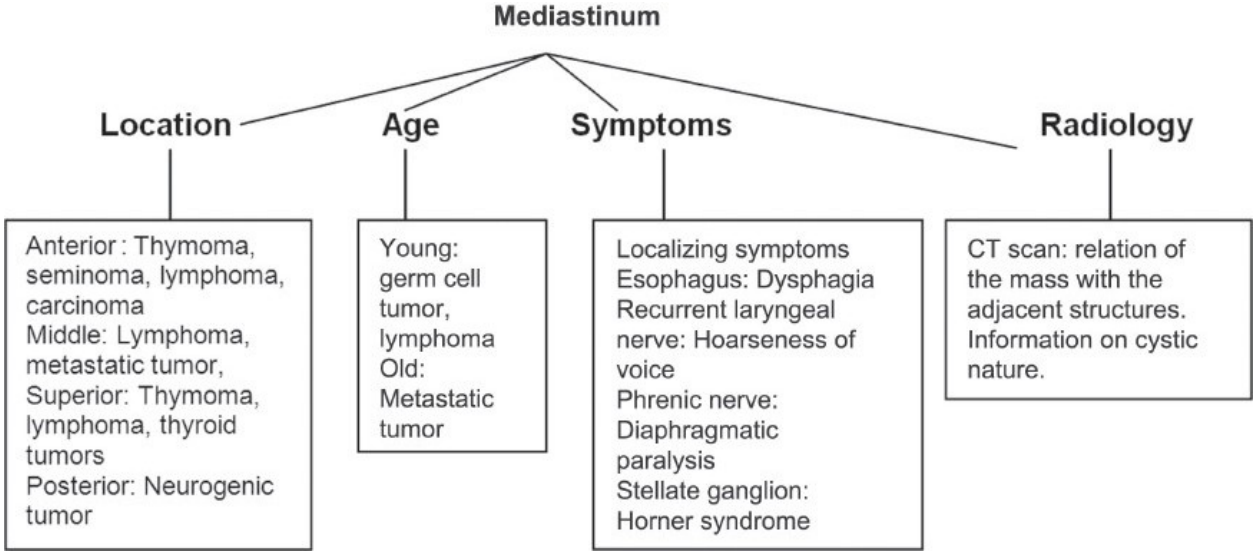

Figure 1. History and other relevant information for diagnosis of mediastinal tumors. Adapted from Indian J Pathol Microbiol 2010;53:395-402

A CT allows for the characterization of the tumor as well as assessment of the possibility of invasion into surrounding structures. Contrast study is preferred to assess vascular invasion and cystic components. Magnetic resonance imaging can potentially improve staging and differential diagnosis determination. The positron emission tomography may also be utilized for tumor detection and differentiation between invasive ad non-invasive thymoma with mixed results[3]. It has the advantage of assessing the biological and functional aspects of different tumors which may help shed light in the differentiation of benign vs malignant tumors[4].

The localization of the mass, coupled with the history and physical examination have led us to narrow down our differential diagnoses to: thyroid tumors, lymphoma, teratoma/germ cell tumors and thymoma[2]. Thyroid gland/tumors originate in the neck, extending downward into the mediastinum through the thoracic inlet. We may see displacement or narrowing of the trachea on imaging. High attenuation value of the thyroid tissue than the adjacent muscles is also evident. All these however were not seen in our case. Lymphoma often extends beyond the anterior mediastinal compartment usually involving multiple lymph node chains. The CT scan appearance may be similar to thymoma or germ cell tumor. However, our tumor was confined in the anterior mediastinum, and

there was no appreciated involvement of any of the lymph node chains. In addition, there were no cervical lymphadenopathies appreciated and the serum LDH was within normal limits. Teratoma and other germ cell tumors are found in patients of all ages but are most common in adolescents and young adult. These masses usually produce a well-defined, rounded, lobulated mass in the anterior mediastinum with calcifications, ossifications, teeth or fat. The CT scan may show cystic components. Unequivocal fat within the mass confirms the diagnosis of teratoma, but its absence does not exclude such. Tumor markers such as: ß HcG, AFP, TRA-1-60 and CD 30 also aid in the diagnosis of teratoma and other germ cell tumors. For our patient, we were only able to get B HCG which was elevated: over 770 (0 – 5.0) mIU/ml. Lastly, thymoma is the most common tumor of the anterior mediastinum, accounting for approximately 50% of all tumors in adults. It usually occurs during the 4th to 5th decade of life, arising in the upper anterior mediastinum, anterior to the ascending aorta above the right ventricular outflow tract and main pulmonary artery, the mass can extend into the adjacent middle or posterior mediastinum, and they can occur or extend into the lower 3rd of the mediastinum as low as the cardiophrenic angles. It has no gender predilection. Half of the patients are asymptomatic and are detected incidentally; while the other half will present with symptoms associated with paraneoplastic syndrome, or with symptoms attributable to the local mass effect – most common of which are cough, vague chest pain, dyspnea and symptoms attributable to superior vena cava syndrome. Punctate, curvilinear, or ring-like calcification is common in both benign and malignant thymoma. On a CT scan, thymomas are usually of homogenous attenuation and show uniform enhancement, but rarely can they appear cystic with discreet nodular components. Malignant behavior is based on observed invasion either macroscopically into surrounding organs and structures or microscopically through the thymic capsule[5].

Patient was also worked up for pulmonary tuberculosis – which was all negative. Pulmonary function test was requested however patient was not able to comply. Ideally, patients with thymoma should also be worked up and monitored for the co-existence of myasthenia gravis[1,5] however; this was no longer pursued since the history and physical examination showed otherwise.

To come up with the diagnosis, we have gone through the clinical history and physical examination and subsequently, for the radiologic localization, a chest CT scan was done in our patient. In addition, serum tumor markers as mentioned can be done while awaiting the histopath results. To finally confirm the diagnosis, we pushed through with the biopsy of the mass. According to Reidel and Burfeind, routine biopsy of encapsulated lesion is not recommended; instead, complete surgical resection should be performed. However, if a more advanced disease is being considered or an alternative diagnosis other than thymoma is likely, biopsy is recommended to confirm diagnosis[3].

The initial biopsy result of our patient showed presence of malignant epithelial cells with an associated admixture of non-malignant lymphocytes (Figure 2). Epithelial cells maybe elongated, spindle-shaped cells or ovoid and polygonal in appearance. This was signed out as: Malignant Lesion, Considerations: Germ Cell Tumor probably Yolk Sac Tumor vs Thymoma.

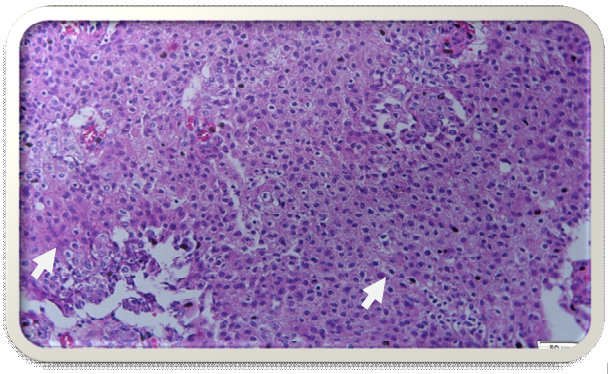

Figure 2. H and E stained biopsy of anterior mediastinal mass

With this biopsy result on hand, it is worthy to note the difference between malignant thymoma and thymic carcinoma. Malignant epithelial cells lack features typically characteristic of malignancy; thymomas generally have bland cytologic features. Malignant behavior is based on observed invasion either macroscopically into surrounding organs and structures or microscopically through the thymic capsule. Approximately 30 – 40% of thymomas are invasive[1]. (Table 1)

Malignant Thymoma	Thymic Carcinoma
Arise from or exhibit differentiation towards thymic epithelial cells	Malignant epithelial tumors lacking organotypic features
4TH to 5TH decade of life	
Smooth contours and round shape	Usually irregular borders Evident mediastinal invasion
Bland cytologic appearance	Aggressive cytologic features: cellular atypia, increased proliferative capacity, anaplastic features
Associated with paraneoplastic syndromes (MG)	Not associated with paraneoplastic MG Polymyositis

Table1. Difference between Malignant Thymoma and Thymic Carcinoma[1]

Table 2 on the other hand summarizes the differentiation of thymoma vs germ cell tumor[2]. Of note is the importance of ancillary tests to further confirm the diagnosis.

FEATURES	THYMOMA	GERM CELL TUMOR
Mediastinal Location	Anterior, Superior	Anterior
Cell Arrangement	Cohesive	Non-Cohesive
Tumor Cells	Epithelial cells with mild to moderate cytoplasm	Cells with large nuclei and prominent nucleoli
Lymphoid Cells	Mature looking, small	Mature looking, small
Background	Lymphoglandular bodies from lymphoid cells	Trigroid
Ancillary tests	CK+, EMA, vimentin, CD5	PLAP+, α-fetoprotein, ß-HCG

Table 2. Differentiation between Thymoma and Germ Cell Tumor. Adapted from Indian J Pathol Microbiol 2010;53:395-402

Immunohistochemical staining was done to further confirm the diagnosis (Figure 3 – 5). The 34 BE 12 or high molecular weight cytokeratin stained POSITIVE with strong diffuse cytoplasmic expression in the epithelial cells (Figure 3). 34 BE 12 also known as CK 903 or the High Molecular Weight Cytokeratin is a marker for epithelial cells. It is positive in Type B2, B3 thymomas. It is a useful marker for thymomas with high grade malignancy and is correlated with vascular and capsular invasion[6]. The CD5 was NEGATIVE in epithelial cells, POSITIVE cytoplasmic expression in scattered lymphocytes (Figure 4). CD 5 is recognized on subsets of lymphocytes. It is detected in THYMIC CARCINOMA. Vimentin stained NEGATIVE in epithelial cells with strong POSITIVE cytoplasmic expression among endothelial cells lining the blood vessels (Figure 5). Vimentin is an intermediate filament for mesenchymal tissue. It confirms mesenchymal origin of tumors. Absence of staining may confirm fat like structures or other spaces actually lack a cellular lining[1]. The pathologists concluded that the immunomorphologic features are compatible with thymoma, type B3. At this point, the diagnosis of malignant thymoma is confirmed.

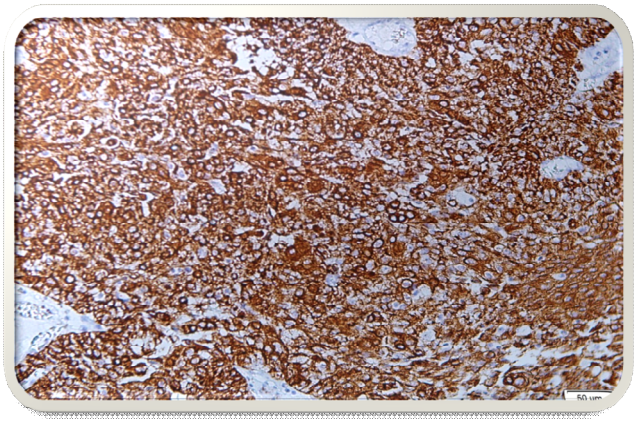

Figure 3. 34BE12 or High Molecular Weight Cytokeratin stain

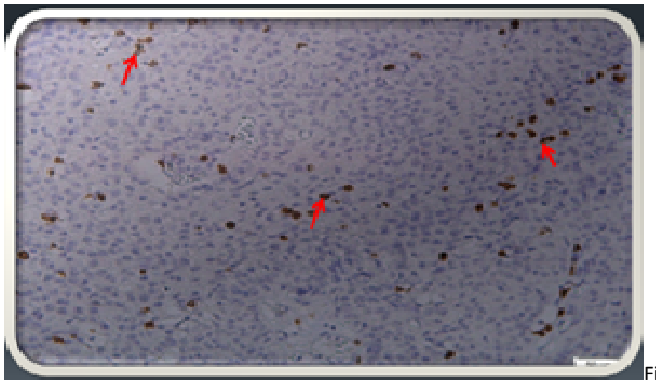

Figure 4. CD 5 Stain

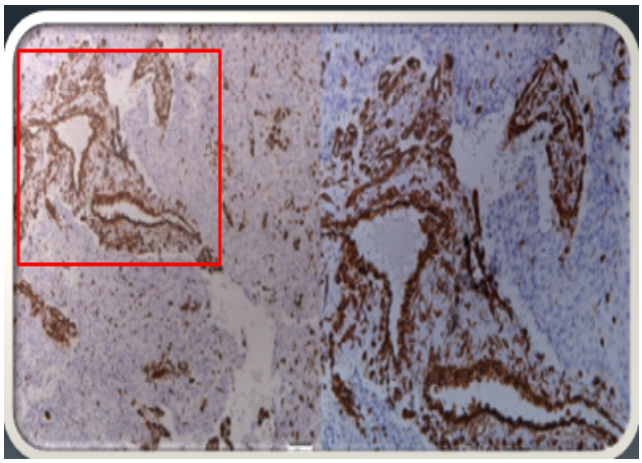

Figure 5. Vimentin Stain

Through time, the classification of thymoma has evolved. It was Bernatz et al in 1961 who first classified thymoma according to the dominant cell type, however it did not have any clinical significance[8]. The classification by Levine and Rosai in 1978 that used both the clinical stage and cellular atypia followed that of Bernatz[9].Then in 1985, Marino and Muller developed a classification system which reflects both anatomic and functional aspects[10]. At present, we follow the World Health Organization Classification System for Thymic Tumors[1]. (Table 3) The two major classification of thymoma are: spindle-shaped and epitheloid. Our patient is type B3.

WHO CLASSIFICATION	DESCRIPTION
A	Medullary; Spindle – cell thymoma
AB	Mixed Thymoma
B1	Predominantly cortical; lymphocyte-rich; lymphocytic, organoid thymoma
B2	Cortical
B3	Epithelial; Squamous; atypical thymoma; well – differentiated thymic carcinoma
C	Thymic Carcinoma

Table 3. World Health Organization (WHO) Classification System for Thymic Tumors.

The Masaoka Clinical Staging System for Thymoma is the most commonly used staging system (Table 4). Unlike the TNM staging system, this is based on the degree of invasiveness[11]. The tumor exhibited invasion of the great vessels.

Stage	Diagnostic Criteria
I	Macro- and microscopically completely encapsulated (tumor invading into but not through the capsule is included)
II	A. Microscopic transcapsular invasion
	B. Macroscopic invasion into surrounding fatty tissue or grossly adherent to but not through mediastinal pleura or pericardium
III	Macroscopic invasion into neighboring organs (i.e., pericardium, great vessels, or lung)
	A. Without invasion of great vessels
	B. With invasion of great vessels
IV	A. Pleural or pericardial dissemination
	B. Lymphogenous or hematogenous metastases

Table 4. Masaoka Clinical Staging of Thymoma

Our diagnosis of Malignant Thymoma Type B3 Masaoka Stage IIIB is confirmed. At this point, we have started discussing the treatment options until it dawned on the patient that she has been amenorrheic for two months. Pregnancy test revealed positive. Patient was then immediately referred to Obstetrics and perinatology service and was confirmed pregnant of 11 1/7 weeks. On re-history, our patient was a G3P1 (1011). First pregnancy in 2005 had spontaneous abortion at 2 months age of gestation; second pregnancy in 2006 was delivered full term, via spontaneous vaginal delivery; pregnancy and delivery was unremarkable; no feto-maternal complications were reported. She is currently on her 3rd pregnancy; menarche was at 18 years old, regular menses occurred monthly of 7 days duration. There was no dysmenorrhea or abnormal vaginal bleeding.

The situation at hand led us to backtrack on the possible situations that may have caused danger both to the fetus. Fortunately, the chest radiograph and CT scans were done prior to her conception. However, it is worth mentioning that among women of reproductive age, the possibility that the patient is pregnant should always be sought and the diagnostic work up safety should always be employed; bearing in mind that abdominal ultrasound, chest radiographs and CT scans are indicated as staging procedures[12]. In general, the doses involved in diagnostic radiology are much lower than the threshold dose for deterministic effects and present no substantial risk causing fetal death, malformation, or impairment of mental development (Table 5).

EXAM	DOSE	
	mSv (mrem)	Gray
Chest AP	0.02 (2)	0.00002
Chest Lateral	0.04 (4)	0.00004
Chest CT Scan	8 (800)	0.008

Table 5. Radiation Doses in Diagnostic Radiology. Data Adapted from Health Physics Society

Will the patient's pregnancy affect her clinical course, response to treatment and prognosis? Most common cancers are those seen during the reproductive age of the woman (breast cancer, cervical cancer, hodgkin's disease, malignant melanoma and leukemias).[13] However apart from case reports, our literature review have not led us to large scale studies specifically identifying thymoma

co-existing with pregnancy However apart from a few case reports, our literature review has not led us to large scale studies specifically identifying thymoma co-existing with pregnancy.

According the Thomas and colleagues, the co-existence of thymoma and pregnancy is extremely rare – occurring at eight described cases[14]. Engels in his epidemiologic study in 2010 identified the potential risk factors for thymoma[15]. (Table 6)

RISK FACTORS	EVIDENCE REGARDING RELEVANCE IN THYMOMA
Tobacco/Alcohol	Absence of increased risk of tobacco and alcohol-related cancers
Ionizing radiation	No increased risk after radiation for benign, enlarged thymus or other cancers
Occupation	No Data
Environmental Contaminants	No Data
Diet and Nutrition	No Data
Genetic variants	No family clustering. However, increased risk among Asians/Pacific Islanders, and association with sarcomas are suggestive
Immunosuppression	No increase risk in HIV-infected people or transplant recipient
Infections	Unconfirmed reports of associations with viral infections

Table 6. Potential Risk Factors for Thymoma. Adapted from Engel's Study

According to Argubright and colleagues, the natural history of slow, localized progression usually seen with thymomas seems to be transformed by pregnancy into one of rapid growth and distant metastatic spread. Five of the six previously reported cases died within 6 months postpartum. One previous long-term survivor died of treatment-induced complications[16]. With this information, the following questions come to mind: What is the risk of recurrence in the patient who has no residual disease at the time of conception? What is the risk to the patient who is first diagnosed while pregnant? Approximately 50 per cent of female patients can anticipate having complete resection of their thymoma, and their recurrence risk is about 2 per cent. Potentially, there are many patients who have conceived and delivered after surgical therapy. Documentation of these case histories is needed for an accurate prediction of the true risk. Whether there is a cause and effect relationship between pregnancy and recurrences is unknown[16].

Goldman discussed two cases of malignant thymoma and pregnancy[17]. The cases presented suggest that continuation of the pregnancy may have exerted an adverse influence on the course of the disease. The first case is a 22-year-old woman, with unresectable malignant thymoma. First pregnancy was terminated at 20 weeks AOG, patient underwent radiotherapy and serial CXR showed complete tumor regression. She had two more successful pregnancies, the last of which was delivered via caesarian section, unfortunately patient died less than an hour after operation due to cardiac arrest. Autopsy showed no thymoma cells. Coronary atheroma and post-irradiation pericardial fibrosis were considered the causes of death. The second case was a 27-year-old patient who was 22 weeks pregnant. Exploratory thoracotomy showed an unresectable large thymoma infiltrating the surrounding structures. The pregnancy was continued while radiotherapy was given. There was symptomatic relief and a decrease in the size of the tumor. Patient delivered two months

after treatment. Two months postpartum, widespread metastatic tumors were found, all histologically identical with the primary thymic tumor. The patient died 8 months and 2 weeks after beginning radiotherapy. Autopsy showed widespread large thymic tumor deposits but only small nodules at the original tumor site.

Other reported cases occurring during pregnancy have shown rapid downhill course with early death from metastases. In one of the cases reported, the outcome was more favorable when pregnancy was terminated. Therefore, in such a situation termination of pregnancy seems indicated[17]. McLaughlin on the other hand reported a case of uncomplicated pregnancy and delivery AFTER treatment/management of thymoma metastatic to the brain. Close oncologic follow up throughout pregnancy. No evidence of cancer recurrence 17 months after delivery[18]. Lo et al, stated that the rapid disease progression, the limited therapies and the sparse evidenced-based-medicine practices in pregnancy all contribute to poor outcomes[19]. According to Lee and Roberts et al, hormones and growth factors required for successful implantation and pregnancy may accelerate tumor growth[20].

The management of malignant thymoma involves a multidisciplinary approach. Table 7 summarizes the treatment strategies for thymoma[21].

MASAOKA STAGE	TREATMENT RECOMMENDATION
I	Complete resection; with out adjuvant or neo-adjuvant therapy
II	Complete resection with consideration of adjuvant radiation for high risk tumors
III	A: surgery either initially or after neo-adjuvant therapy or surgery followed by adjuvant therapy B: combination therapy: chemotherapy, radiation, and/or surgery; or if technically possible, surgery in combination with chemoRT
IV	A: as per stage III, with surgery only if metastases can be resected B: case to case basis

Table 7. Summary of Treatment Recommendations based on Clinical Stage. Adapted from Falkson et al.

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For stage 1 and 2 malignant thymoma, surgery is the mainstay of treatment with the goal of complete surgical resection being the main determinant of survival. Patients should be explored through a complete median sternotomy with en bloc removal on the entire thymus and mediastinal fat from phrenic nerve to phrenic nerve and from diaphragm to brachiocephalic vein. Table 8 summarizes the survival rates depending on the stage. Radiotherapy is not warranted in stage I disease, assuming complete resection is achieved. Role in completely resected stage II disease is debated since published literature is largely retrospective, limited in sample size and conflicting results[3]. For invasive stage 3 and stage 4 tumors as well, en bloc resection of the pericardium, brachiocephalic vein, SVC, lung and up to one of the phrenic nerves can be performed. If pleura and lung metastases are discovered, these should also be resected. The role of subtotal resection is still debated. According to the study of Riedel and Burfeind, 10 – year survival rates for patients achieving a complete surgical resection averaged 75%, while 10 – year survival rates in partially resected patients is 39%, approaching the 33% observed in biopsy alone[3].

	SURVIVAL RATES	
	5 YRS	10 YRS
STAGE 1	100%	95%
STAGE 2	91%	81%
STAGE 3	74%	46%
STAGE 4	<25%	-

Table 8. Survival Rates of Malignant Thymoma according to Stage

For patients deemed initially inoperable, induction strategies have been investigated – the goal of which is attempted surgical resection post therapy. Induction chemotherapy followed by surgical resection, postoperative radiation and consolidation chemotherapy can be done. Riedel also reported complete response in 3 out of 22 patients, partial response in 14 out of 22 patients, complete surgical resection in 16 out of 22 patients and incomplete resection in 5 out of 22 patients. Survival rates are as follows 95% at 5 years 79% at 7 years[3]. Our case being a Stage IIIB was initially referred to thoracic and cardiovascular surgery, however, with the knowledge of the tumor's invasiveness and unresectability, and after discussion with the patient, the plan was for her to undergo chemotherapy and hence was referred to medical oncology[22].

Thymoma exhibits sensitivity to a number of single agents including the following and for the purpose of our discussion, we will focus on these three. Cisplatin is an alkylating agent most active in the resting phase of the cell. Doxorubicin is an antimitotic and a cytotoxic agent that intercalates between DNS base pairs. It inhibits topoisomerase II and induces DNA strand breakage. Cyclophosphamide adds an alkyl group to DNA causing DNA damage and cell death. Table 9 shows the various studies reporting the response rates of stage 3 and 4 malignant thymoma to chemotherapy; of note, the highest complete response rate is only 23%. The regimen used is the PAC – cisplatin, doxorubicin and cyclophosphamide. The study of Kim et al, included Prednisone in the regimen[3, 21, 23].

	Shine et al	Kim et al	Loehrer et al
Regimen	PAC	PACPr	PAC
Setting	Stage III – IV B (induction)	Stage III – IV B (induction)	Metastatic/ recurrent
# of Patients	13	22	30 (1 thymic carcinoma)
Over all response rate (%)	92	77	50
Complete Response Rate (%)	23	14	10
Median Response (mos)	-	-	11.8

Table 9. Response rates of Stage III and IV to Chemotherapy

When a patient with advanced inoperable cancer becomes pregnant and the treatment cannot be delayed until delivery, there are concerns as to whether radiotherapy can be safely given. Curran and Kornstein et al, reported mediastinal relapse rate to be higher for those patients subjected to surgery alone[24]. The results of Strobel's study similarly showed that the recurrence rate is higher among patients who did not receive adjuvant therapy[22].

Surgery remains a mainstay of treatment for thymoma, even for recurrent disease. Radiation therapy is also applied if not used previously[23].

Studies on other treatment options are currently ongoing - these include: 1. Octreotide in combination with prednisone; 2. umbilical cord transplantation; 3. Gefitinib; and 4. Sunitinib[3]. Octreotide is a somatostatin analog. Thymomas highly express somatostatin receptor on their surface. Radiolabeled octreotide exhibits high specificity for thymoma compared with thymic hyperplasia and other benign thymic disorders. Octreotide 0.5 mg subcutaenously three times daily and Prednisone 0.6mg/kg four times daily per orem was given to patients who are octreotide positive on examination. Octreotide alone has modest activity among octreotide positive patients on examination. Prednisone improves overall response but associated with increased toxicity[25]. The clinical trial for umbilical cord transplantation is currently ongoing recruitment of subjects[3]. In the study done by Kurup and Burns et al., 26 patients with metastatic or recurrent thymic malignancies were given Gefitinib 250mg daily for a total of 6 cycles if no evidence of disease progression for 2 months. Only one partial response was noted[26]. Sunitinib is multi-targeted tyrosine kinase inhibitor that has shown benefit in various other cancers and Strobel and colleagues are investigating its role in malignant thymoma[27]. In summary, the management of thymoma is relatively straightforward - surgical resection remains the primary mode of therapy. However, some literature contains contradictory points, like the place of video - assissted thoracoscopic surgery in the treatment of thymoma. According to Kohman, demonstrating the equivalence of minimally invasive thoracoscopic approaches to standard thymectomy will take many years of investigation[23].

The final decision for therapeutic abortion is not always easy; it becomes more important when the diagnosis of cancer is made during the first trimester of pregnancy[12]. However, since 1930, abortion has been a crime under the Philippine Law. The 1987 Philippine constitution further emphasizes this as it underlines the statement that the state “shall equally protect the life of the mother and the life of the unborn from conception”.

Any treatment option is not without any risks – which in our case needs more attention than the usual malignant thymoma cases, considering that we are subjecting NOT just one but two individuals to treatment. All chemotherapeutic drugs are potent teratogens and hence are category D for pregnant women. Detrimental effects to mother include spontaneous abortion and sterility[12, 28].

All chemotherapeutic drugs are capable of crossing the placenta, fetal toxicity is dependent on the time of treatment. As a general rule, chemotherapy should be avoided during the first trimester as the risk for malformation is increased. However, exposure during the 2nd and 3rd trimester has been associated with greater risk for premature birth, low birth weight, and a temporary reduction in some of the hematopoietic cells[1, 28]. The usual rate of malformations in the general population is around 1 – 3%. With Cyclophosphamide use, the risk of malformation is about 1:6[3]. Table 10 summarizes the effect of the three chemotherapeutic drugs most frequently used in malignant thymoma[1]. Antineoplastic agents administered systemically might reach clinically significant levels in breastmilk, so breastfeeding is contraindicated[28].

	SIDE EFFECTS
Cisplatin	Ototoxicity
Doxorubicin	Imperforate anus, rectovaginal fistula, brachycephaly, hypoplasia of the anterior cranial base and face, synostoses of cranial sutures, hypoplastic digits, fetal maceration & fetal death
Cyclophosphamide	Facial and palate defects, absent fingers and toes, absence of some coronary arteries, imperforate ani, hernias, growth retardation, multiple eye defects, microcephaly, hypotonia, and pancytopenia

Table 10. Summary of Fetal Effects of Chemotherapeutic Drugs Used in Malignant Thymoma

Expected radiation effects are lethality, malformations, mental retardation, & cancer induction as listed in Table 11. It is therefore recommended that babies whose mothers received chemotherapy and/or underwent radiotherapy be monitored for growth during pregnancy and after delivery. Reduction of fetal dose through shielding should therefore always be done[29].

Time after conception (weeks)	Effect	Risk per 0·01 Gy	Spontaneous frequency
0–2	Prenatal death*	0·01–0·001	0·3–0·6
3–8	Malformation*	0·005†	0·06
8–15	Mental retardation IQ decrease‡	0·004	0·005
16–25	Mental retardation IQ decrease§	0·001	0·005
0–38	Leukaemia, solid tumours in childhood	0·003–0·004	0·002–0·003

*Based on experimental data.[32] †Above threshold dose of 0·1–0·2 Gy.[32] ‡Reduction of 21 IQ points per 1 Gy above threshold of about 0·05 Gy;[13,14] threshold dose for mental retardation about 0·06 Gy;[15] §Reduction of 13 IQ points per 0·1 Gy above threshold dose of about 0·05 Gy;[13,14] threshold dose for mental retardation about 0·25 Gy.[15]

Table 11. Summary of Radiation Effects to Fetus

Taking all these into consideration, a potential conflict exists between the mother and the fetus, since the mother is the major beneficiary whereas the fetus could be at substantial risk. The clinician has to achieve an ethical balance in terms of responsibility to the fetus and to the mother. Decision of giving any treatment should be taken by the patient after adequate information.

After presenting and thoroughly discussing all the therapeutic options, our patient decided to undergo chemotherapy. From September to December 2012, she completed 4 cycles chemotherapy with Cisplatin, Doxorubicin, Cyclophosphamide given every 21 days. This regimen is category 1 according to the National Comprehensive Cancer Network Guidelines for Thymic Malignancies[30].

Since August to December 2012, our patient is on regular follow up with the obstetrics and perinatology service. In SEPTEMBER 2012, Targeted Imaging for Fetal Anomalies (TIFFA) and Congenital Anomaly Scan was done which revealed no gross structural abnormality. In OCTOBER 2012, biometry done revealed single live intrauterine pregnancy with good cardiac and somatic

activities and an estimated fetal weight appropriate for gestational age. In DECEMBER 2012, repeat biometry, biophysical profile, doppler studies revealed single live intrauterine pregnancy with an estimated fetal weight appropriate for gestational age. There was normal fetoplacental and maternal blood flow.

The timing of obstetric delivery is a controversial issue in the management of cancer in pregnancy. Deliberate delay in treatment is not associated with poor survival for pregnant women with early stage cancer. Early elective delivery is carefully considered to ensure best outcomes for both mother and neonate. The timing however may also depend on the cancer type[20].

OUTCOME

Patient delivered live baby girl via spontaneous vaginal delivery at 38 2/7 weeks age of gestation by last menstrual period with an APGAR score of 9,9; fetus was appropriate for gestational age. The course of delivery was unremarkable. The newborn screening was normal.

Patient was seen at the out-patient clinic two weeks after the delivery. She claimed to be more dyspneic, now even at rest. At this time, there were visible veins on the anterior chest wall - compatible with a possible superior vena cava syndrome.

A repeat chest radiograph and chest CT Scan done postpartum, 9 months from the initial CT scan and after 4 cycles of chemotherapy showed an interval increase in size of the previously seen large heterogenous mass in the anterior mediastinum. It now has approximate largest dimensions of 16.8x19.5x13.0cm from 9x11.5x11cm previously. The mass still contains irregular areas of hypodensities. It occupies the left hemithorax, occluding the left mainstem bronchus and displacing the rest of the mediastinal structures to the right. The left lung is subsequently collapsed. The mass also compresses the left pulmonary veins and artery. It encases the thoracic aorta with obliteration of the intervening fat plane. Superiorly on the left, the mass compresses the left brachiocephalic vein; on the right, it extends across the midline to abut the middle lobe. The superior vena cava is narrowed by the mass but remain patent. The visualized liver showed heterogenous enhancement.
Whole abdominal ultrasound revealed normal ultrasound of liver, spleen, pancreas and gall bladder. With these findings it is evident that there was tumor progression despite chemotherapy. AS of this writing, the patient has completed radiotherapy for the superior vena cava syndrome. Further plans for the patient include administration of second line chemotherapy and the option of tumor debulking.

Despite the absence of strict guidelines in management of pregnancy complicating cancers, the following gold standards should be followed: 1) Try to benefit the mother's life; 2) Try to treat curable malignant disease of pregnant women; 3) Try to protect the fetus and newborn from harmful effects of cancer treatment; 4) Try to retain the mother's reproductive system intact for future gestations[12].

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