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Hepatoid esophagogastric adenocarcinoma and tumoral heterogeneity: a case report

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Abstract: Hepatoid adenocarcinoma of the stomach is an uncommon subtype of gastric cancer remarkably similar to hepatocellular carcinoma in histopathological analysis. It is also commonly associated with high serum alfa-fetoprotein and a poorer prognosis, despite the emergence of new therapeutic options. In recent years, next generation sequencing (NGS) technology has made it possible to identify and describe the genes and molecular alterations common to gastric cancer thereby contributing to the advancement of targeted therapies. A 62-year-old patient, with no prior risk factor for hepatocellular carcinoma (HCC), presented to the emergency room with dysphagia for solids, abdominal pain and weight loss of about 3 kilograms over 3 months. Histopathological analysis presented with disparities regarding HER2 and programmed death-ligand 1 (PD-L1) status in the primary and metastatic sites. We describe a case of a *de novo* metastatic, human epidermal growth factor receptor 2 (HER2) positive esophagogastric junction hepatoid adenocarcinoma. Although this is a rare subgroup of gastric cancer, treatment strategies were based in recent studies in immunotherapy and guided therapy, taking into consideration the molecular findings from the patient's tumor NGS analysis. Data about HER2 and PDL1 heterogeneity were also reviewed. Despite the aggressiveness and rarity of this histology, the patient had a good response to treatment.

Keywords: Case report; hepatoid adenocarcinoma; esophagogastric junction; heterogeneity; human epidermal growth factor receptor 2 (HER2)

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Introduction

After the first description of alfa-fetoprotein (AFP) secreting gastrointestinal malignancies by McIntire *et al*. in 1975, Ishikura *et al.* described in 1985 seven gastric adenocarcinoma patients who presented high serum AFP and the first case of an hepatoid adenocarcinoma of the stomach (HAS). This uncommon subtype of gastric cancer is remarkably similar to hepatocellular carcinoma (HCC) in histopathological analysis and is frequently associated with poorer prognosis (1-4). Despite many theories about the origin of this histology, the exact mechanism is still not defined (5-7).

Besides the increased potential for liver metastasis, HAS is also associated with the production of AFP in the majority of cases, which is usually correlated with HCC (8). This protein is described as part of the immunohistochemical diagnostic of hepatoid adenocarcinoma, with other markers being glypican-3 (GPC-3), Sal-like protein 4 (SALL4) and

less frequently Hepatocyte Paraffin 1 (Hep-Par 1) (9).

Despite the emergence of new therapeutic options for patients with esophagogastric cancer, the prognosis for metastatic and inoperable disease remains poor. Median overall survival (mOS) is approximately 1 year (10,11). Performing next generation sequencing (NGS) and searching for targetable mutations in patients with metastatic esophagogastric cancer is thus crucial to identify predictive biomarkers of response (12). However, disparities regarding human epidermal growth factor receptor 2 (HER2) and programmed death-ligand 1 (PD-L1) status between the primary tumor and metastatic lesion have been described making, showing the heterogeneity of this markers in the systemic disease and making this scenario challenging (13).

Herein we describe a case of a patient presenting with a *de novo* metastatic hepatoid esophagogastric junction (EGJ) adenocarcinoma whose lesions displayed disparities in biomarkers analysis between the primary tumor in the stomach and metastatic site at the liver.

We present the following article in accordance with the CARE reporting checklist (available at https://dx.doi.org/10.21037/jgo-21-287).

Case presentation

A 62-year-old patient presented to the Emergency room with dysphagia for solids, abdominal pain and weight loss of about 3 kilograms over 3 months. He had a medical history of coronary disease and diabetes mellitus. Family oncologic history was significant for a father with gastric cancer at 55-year-old, a brother with lung cancer at 48-years-old and a mother with non-melanoma cutaneous cancer at 85-year-old. No risk factors for HCC like history of alcohol use, known liver disease, or viral hepatitis were reported. A radiologic image screening of the abdomen was performed and showed evidence of diffuse tumor infiltration of the hepatic parenchyma. A liver tumor biopsy was obtained and showed invasive adenocarcinoma with tubular and hepatoid components, suggestive of a primary liver malignancy, including hepatocellular carcinoma (HCC). HER2 was positive (3+) and PD-L1 combined positive score (CPS) was 2 (*Figure 1*).

Staging was performed with whole body computed tomography (CT) that showed multiple confluent hepatic lesions with arterial phase enhancement and rapid wash out, accompanied by enlarged lymph nodes in left gastric, porta hepatis and portocaval chains (*Figure 2*). Despite this the rapid wash out being suggestive of HCC, this could note exclude hepatoid adenocarcinoma. Upper gastrointestinal endoscopy demonstrated a vegetative lesion surrounded by Barret epithelium in the distal esophagus (between 35 to 38 cm from the upper dental arcade). The histopathological analysis of this lesion described poorly cohesive cell carcinoma, HER2 negative and CPS of 12. Despite the presence of signet ring cells in this biopsy, a small part of the lesion was suggestive of HCC, corroborating the idea that this was the primary lesion with liver metastasis (*Figure 3*), as both biopsies showed areas of similar pathological findings (tubular hepatoid areas) and the patient had no HCC risk factors. The serum AFP at this moment was 20 ng/mL.

Patient was already started on first line chemotherapy with docetaxel, oxaliplatin, leucovorin and 5-fluorouracil (FLOT) in another service. Therapy was discontinued though secondary to Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 (14) grade three serum glutamic oxaloacetic transaminase elevation, grade three serum glutamic pyruvic transaminase elevation, grade two international normalized ratio (INR) elevation, grade one bilirubin elevation and grade four neutropenic colitis. At the resolution of these adverse effects and now the result of HER2 is reported, patient therapy was changed to 5-fluorouracil, oxaliplatin and leucovorin (FOLFOX) plus trastuzumab in September 2019. Clinical response and decrease in AFP (from 19.568 to 48 ng/mL) were noted after 3 cycles of therapy. By the fourth cycle of therapy, a radiologic RECIST 1.1 (15) partial response was noted (*Figure 4*). By the eleventh cycle of therapy, patient was switched to maintenance trastuzumab therapy (*Figure 5*).

Two months later, evident progression of disease and elevated AFP were noted. Therapy was changed to paclitaxel plus ramucirumab. Within three cycles of therapy, partial response was noted and was characterized by a decrease in the abdominal lymph nodes and hepatic metastasis size. This was followed by stable disease. However, due to peripheral neuropathy and colitis, paclitaxel was discontinued, and patient stayed on single agent ramucirumab with good tolerance. At this time, a NGS comprehensive panel from liver biopsy was performed and showed a low tumor mutational burden (TMB)—2.52 mutations per megabase, along with *CDK4 amplification*, *PIK3CA equivocal amplification*, *ERBB3 amplification*, *ETV6 deletion*, *SMAD4 splice site 1309-2A>G*, *TP53 Q192**, *RNF43 splice site 953-276_998>AC*. Microsatellite status (MS) was stable and there were no FGFR alterations.

All procedures performed in studies involving human

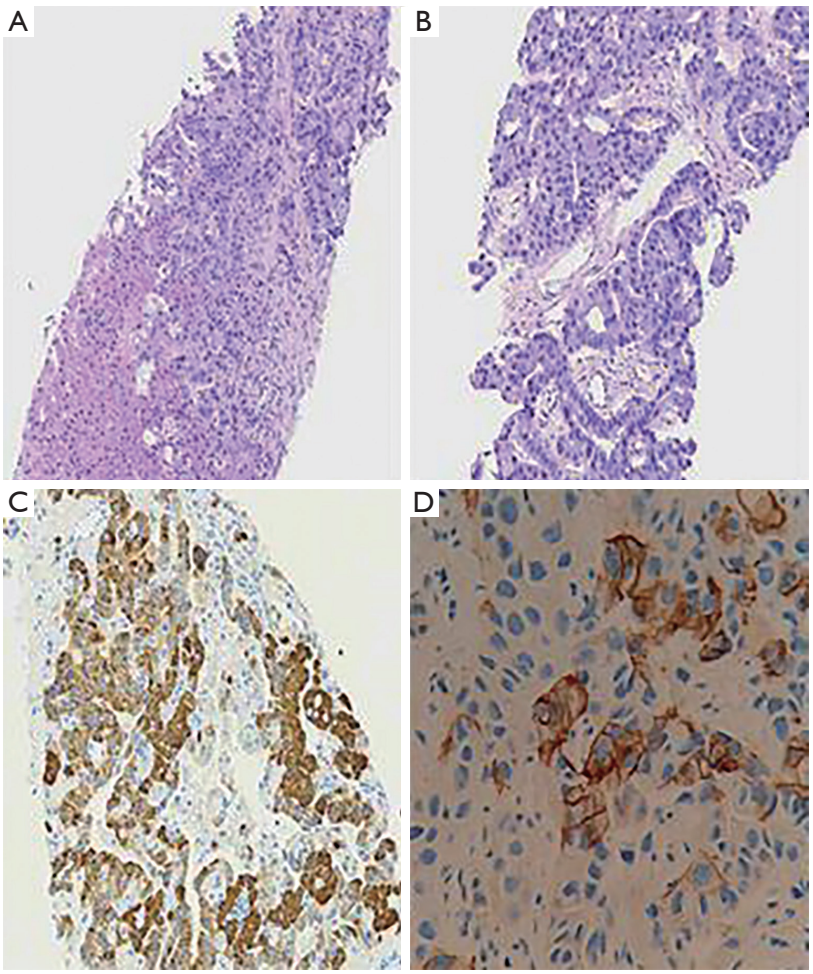

Figure 1 Pathology high magnification views. Histopathological tissue analysis from liver biopsy revealed a tubular and hepatoid adenocarcinoma (A,B; ×100). Immunohistochemistry stained positive for Hepatocyte (C; ×100) and HER2 3+ (D; ×400).

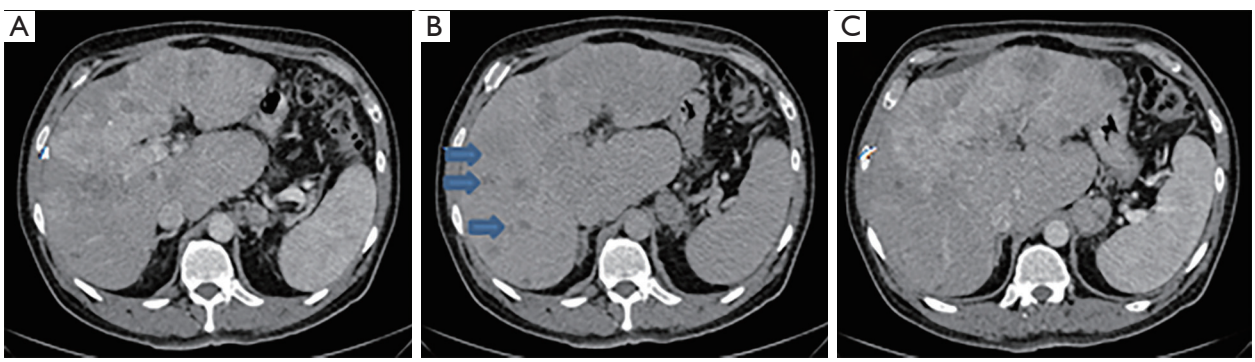

Figure 2 CT scan liver views. Chronic liver disease (liver enlargement and splenomegaly). Several liver lesions with early arterial phase enhancement (A) and rapid washout (B, blue arrows), suspicious for hepatocellular carcinoma. Enlarged gastrohepatic node (C).

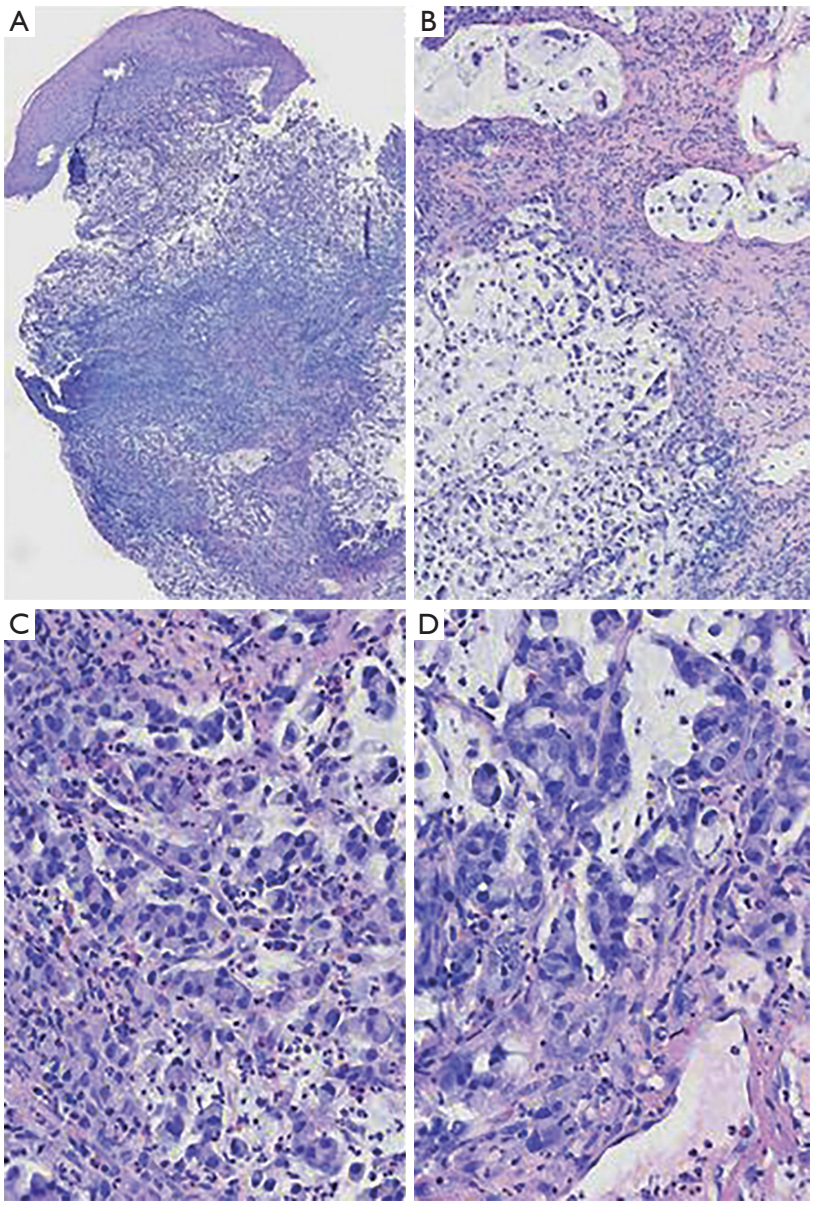

Figure 3 Pathology high and low magnification. Histopathological tissue analysis from esophagogastric junction biopsy revealed a poorly cohesive adenocarcinoma, signet-ring type (A,B; ×100). There was also a focal tubular and hepatoid features (C,D; ×400).

participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Informed consent was obtained from the patient.

Discussion

The incorporation of NGS technology in recent studies has allowed the development of comprehensive datasets that made possible the description of many genetic characteristics of gastric cancer (16-18). Notably, the TCGA Research network defined four major genomic subtypes of gastric cancer based on genetic profile (16). However, due to the rarity and the erratic geographic distribution, genetic alterations in HAS could not be found in a retrospective analysis of this database (19).

Wang *et al.* performed an NGS panel of 483 cancer-related genes on a population of 23 HAS and 18 clinical

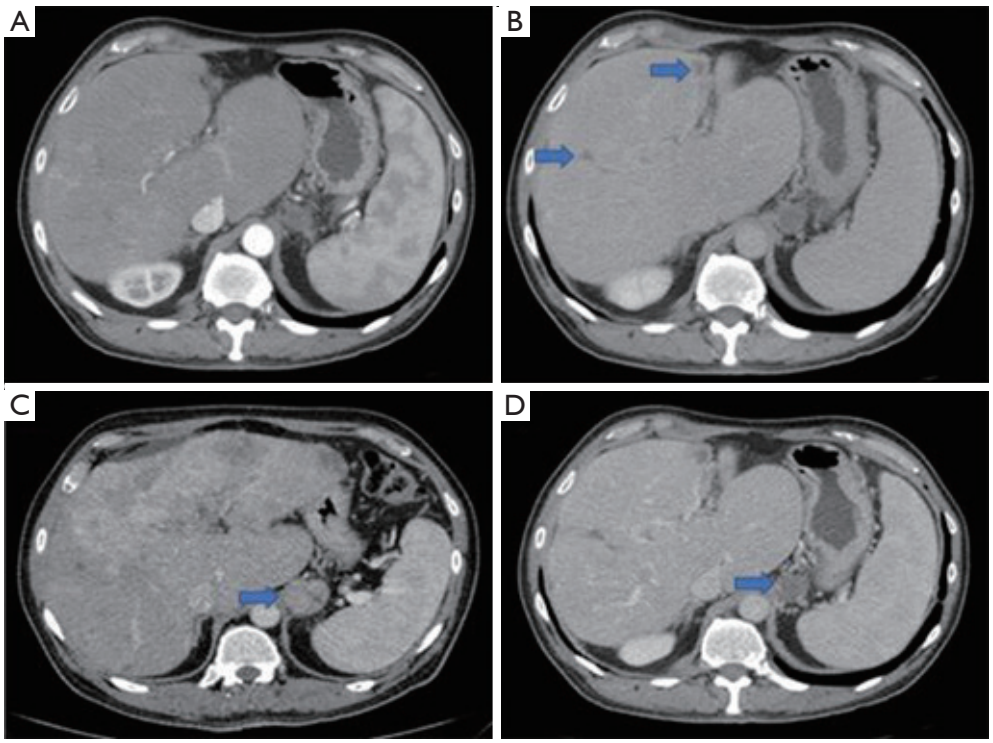

Figure 4 Liver lesion and lymph node regression after first line chemotherapy with FOLFOX and trastuzumab. Nearly homogeneous enhancement of the liver with disappearance of hypervascular areas of enhancement on arterial phase (A) and just a few residual areas of washout on the portal venous phase (B). Previously enlarged gastrohepatic node (C, blue arrow) has decreased in size and attenuation (D, blue arrow).

parameter-matched common gastric cancer (CGC) (20). They found that the most frequent mutated gene was TP53, consistent with previous reports and the TCGA database. However, they found a higher frequency of mutations in CEBPA, RPTOR, WISP3, MARK1 and CD3EAP (10–20%) (16,20,21). Copy number variant (CNV), usually correlated with the overexpression of cancer-promoting driver genes (22), was also analyzed and tended to occur more commonly in HAS than CGC, especially in the genes TOP1 (50%), STK4 (45.5%), CDKN1B (40.9%), H3F3A (36.4%), MYC (22.7%), CCNE1 (22.7%), NFKBIA (22.7%), VEGFA (18.2%), CCND3 (13.6%) and E2F1 (13.6%). Besides that, and based on the analysis of mutations and copy number gains (CNGs), the authors also found that several pathways were significantly enriched in both HAS and CGC (ErbB, PI3K-Akt and the p53 signaling pathway). HIF-1 signaling pathway and the signaling pathway regulating the pluripotency of stem cells thought were especially enriched in HAS. These findings could guide novel personalized therapies going forward (20).

In the first-line setting, taking into consideration the HER2 positivity on the liver metastasis and the results from the TOGA trial (absolute benefit of approximately 4 months in overall survival (OS) for advanced HER2 positive gastric and EGJ cancers) (23), it was decided to initiate trastuzumab plus chemotherapy followed by maintenance trastuzumab. Many studies have proven that the frequency of overexpression of HER2 is slightly higher for EGJ in comparison to the stomach (23-25). Also, when compared to breast cancer, the heterogeneity of this analysis is higher in gastroesophageal adenocarcinoma, with differences in immunostaining requirements between these two neoplasms (26-28).

Nevertheless, the clinical impact of HER2 heterogeneity has already been described not only in breast cancer but also in gastric cancer (29,30). In a trial with twenty-eight HER2 positive gastric cancer treated with gastrectomy and trastuzumab-based chemotherapy, Wakatsuki *et al.* suggested that intratumoral HER2 heterogeneity may have a robust impact on trastuzumab efficacy in this population.

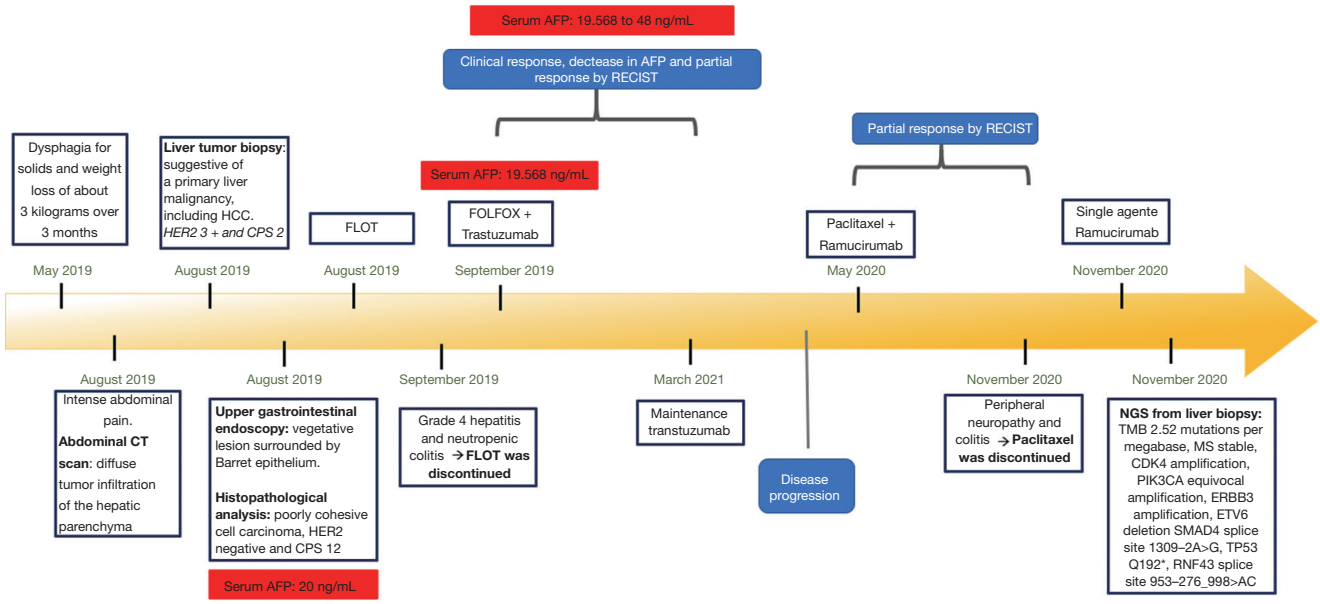

Figure 5 Timeline of the case report. AFP, alfa-fetoprotein; CT, computed tomography; FLOT, docetaxel, oxaliplatin, leucovorin and 5-fluoracil; FOLFOX, 5-fluoruracil, oxaliplatin and leucovorin; RECIST, Response Evaluation Criteria in Solid Tumours.

Patients defined as homo HER2-positive group had significantly longer progression-free survival (PFS) than the hetero HER2-positive group (20 *vs.* 6 months, HR 0.11, P<0.001), with an additional benefit for OS (not reached *vs.* 14 months, HR 0.18, P=0.003, respectively) (30). More recently, Butter *et al.* concluded that predicted HER2 assessment based on biopsies of these neoplasms can lead to false-negative results, with the possibility of HER2 positive tumors being denied of neoadjuvant HER2 therapy. These findings were based on the analysis of 378 adenocarcinomas of the esophagus or stomach paired biopsies and resection specimens (31).

Also, discordant HER2 analysis between primary and metastatic tumors is already described but is a rare event. A meta-analysis conducted by Peng *et al.* focused on this scenario (spatial HER2 heterogeneity) in gastric cancers and found that only 7% of cases (95% CI: 5–10%) had HER2 discordance (32).

Besides the results in first-line, the anti-HER2 blockade in subsequent lines historically did not present relevant benefit, with lack of improvement in OS in the TyTAN (lapatinib plus paclitaxel) and GATSBY (trastuzumab emtansine) trials (33,34). Even so, more recently the DESTINY Gastric01 trial proved that trastuzumab deruxtecan led to significant improvement in OS and overall response rate in patients that progressed on two or more prior regimens, presenting as a new option in the future for patients in advanced line settings (35).

Our patient also presented with discordant *HER2* status in immunohistochemistry (IHC) and NGS. Janjigian *et al.* reported a strong correlation between *ERBB2* copy number as determined by sequencing (pretreatment) and *HER2* IHC/FISH in esophagogastric cancer, with a concordance rate of 93.7% (36). Similarly to our patient, their 4 discordant cases presented with significantly shorter PFS on first-line trastuzumab (median PFS 5.8 *vs.* 14 months). The authors concluded that the intrinsic and acquired resistance to anti-*HER2* therapy was also related to molecular alterations such as lack of *ERBB2* amplification in NGS, deletion of *ERBB2* exon 16, and commutations in the receptor tyrosine kinase, RAS, and PI3K pathways, with this last one also amplified in our case.

Ramucirumab, a monoclonal antibody against vascular endothelial growth factor receptor 2 (VEGFR-2), is widely approved for second-line treatment in adults with advanced gastric or GEJ adenocarcinoma, as monotherapy or combined with paclitaxel, based on two phase III trials (REGARD and RAINBOW) (37-39). However, there are limited data on potential biomarkers of response to ramucirumab and others antiangiogenic agents in gastric cancer and GEJ scenario, especially in second-line (40). The decision of initiating ramucirumab plus paclitaxel was supported on the similarity

already described between HAS and HCC, alongside the results from REACH and REACH 2 trials (41,42). In a subgroup analysis of the REACH trial, which evaluated ramucirumab versus placebo in the second-line treatment in patients with advanced HCC, improvement in overall survival was noted in the population with a baseline concentration of alfa-fetoprotein of 400 ng/mL or greater (41). Based on this information, REACH 2 selected only patients with advanced HCC and increased alfa-fetoprotein of 400 ng/mL or greater and treated them with ramucirumab or placebo in the second line after sorafenib. The primary endpoint of OS was reached (mOS 8.5 *vs.* 7.3 months, HR 0.710, P=0.0199). While these results are suggestive of alfa fetoprotein as a biomarker for response with Ramucirumab in the HCC population, this claim remains debatable (42,43).

In recent years, immunotherapy is a growing option for the treatment of gastric and EGJ, especially in the metastatic and advanced scenario. The first results from CHECKMATE 649 demonstrated that nivolumab was the first anti-Programmed Cell Death Protein (PD1) inhibitor with benefit in OS and PFS when combined with chemotherapy (versus chemotherapy alone), in previously untreated advanced and metastatic HER2 negative esophageal, GC and EGJ adenocarcinoma. Besides the OS benefit being significant in Combined Positive Score (CPS) ≥1, the primary endpoint was achieved in tumors that expressed PD-L1 CPS ≥5 (OS, HR 0.71, P<0.0001) (44).

In KEYNOTE 062, pembrolizumab alone or combined with chemotherapy was not superior to chemotherapy alone for the PFS and OS endpoints (45). There is no clear answer to this discrepancy, however, there have been many discussions about tumor spatial and temporal heterogeneity of PD-L1 and TMB when obtaining tumor samples for molecular testing. This phenomenon was exemplified by Zhou *et al.* in gastroesophageal adenocarcinoma when they compared these two biomarkers at baseline diagnosis and after chemotherapy (46). It was concluded that both exhibited marked spatial and temporal heterogeneity, characteristic that should be considered when deciding the best immunotherapy treatment.

Based on the knowledge that adding trastuzumab in the first line of HER2-positive metastatic gastric cancer improved overall survival, the combination of trastuzumab, pembrolizumab and chemotherapy was tested in HER2-positive GC, esophageal and EGJ adenocarcinoma in a phase II trial. The primary endpoint was achieved and 70% of 37 patients were progression-free at 6 months, with a safety profile of adverse events and a promising activity of the combination to be confirmed in phase III studies (47).

Conclusions

We report a case of a *de novo* metastatic hepatoid adenocarcinoma of esophagogastric junction whose lesions displayed disparities between primary tumor and metastatic site regarding predictive biomarkers. The patient was treated with trastuzumab plus chemotherapy in the first line and paclitaxel and ramucirumab in the second line. Tumor heterogeneity is a well-described phenomenon that interferes in biomarkers of treatment response, but despite the aggressiveness and rarity of this histology, the patient had a good response to treatment. Novel and composite treatment protocols, as well as reliable biomarkers of response, are needed to improve the survival of these patients.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and images referring to it. A copy of the written consent is available for review by the editorial office of this journal.

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