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Case Report Open Access

A Rare Case OF HER 2 Amplified and MET Mutated Metastatic Gastric Cancer with Clinical Benefit to MET Inhibition: A Case Report

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Abstract

The treatment of metastatic stomach cancer has evolved over the last few years. Presently, the most common chemotherapy regimen comprises of Fluorouracil and platinum-based combinations. In the case of HER 2 positive disease, the treatment involves a combination of chemotherapy with trastuzumab. However, there have been cases of resistance to the above combination. Multiple underlying molecular mechanisms have been postulated for the resistance. One of the commonest pathways is CMET mutation. However, the presence of C MET and HER 2 is very rare. Here, we present such a rare case of metastatic stomach cancer who had abnormalities in both the pathways leading to resistance to Trastuzumab.

Keywords: Treatment; Stomach cancer; Mutation; Chemotherapy; Endoscopy

Case Report

A 58-year-old Indian male, who is a diabetic, controlled with oral antidiabetic agents, and hypertensive on amlodipine, presented to our hospital in November 2017 with the chief complaints of pain in the upper abdomen and abdominal distension. He was investigated outside and was found to have a stomach mass in upper GI endoscopy, and hence was referred to our center for further management. On clinical examination, he had pallor and ascites. His performance status was 1 (ECOG). He did not have any lymphadenopathy or organomegaly. There was no palpable lump in the abdomen, but a clinically evident free fluid. Baseline complete blood count revealed hemoglobin of 9 g/dl with a microcytic hypochromic picture. Rest of the complete blood picture was normal. Iron studies revealed low iron stores with transferrin saturation of less than 20%. His routine liver function test and renal function tests were within normal limits. Upper GI endoscopy revealed an ulceroproliferative mass involving the antrum. Endoscopic biopsy revealed moderately differentiated adenocarcinoma. A baseline staging workup was done with a contrast-enhanced CT scan of the thorax and a whole abdomen (CECT T/WA) and bone scan [1-4]. The CT scan revealed the presence of antral gastric mass along with multiple extensive metastases to the liver, lung and retroperitoneal lymph nodes (Figure 1). His histopathology revealed positivity for HER 2 by Immunohistochemistry (score 2+). Hence, Fluorescent In Situ Hybridization (FISH) was done, which showed positive for amplification with a ratio of 20. After a detailed discussion about the prognosis, he was started on systemic chemotherapy with Capecitabine 1000 mg/m^2 and oxaliplatin 130 mg/m^2 q 21 days along with Trastuzumab at 8 mg/kg loading dose followed by 6 mg/kg from the second cycle onwards. After three cycles, he was admitted to the hospital with grade IV cytopenia and sepsis, from which he recovered. His response evaluation was done with a repeat CECT T/WA and a bone scan in February 2018. Response evaluation revealed the significant progression of the disease with an increase in ascites, which was cytology proven to be malignant. In view of the disease progression, we discussed the option of next-generation sequencing and microsatellite instability PCR (Figure 2). As a second line treatment, he was started on weekly paclitaxel 80 mg/m^2 every week and Ramucirumab 8 mg/kg every two weeks. After the initial one doses of paclitaxel, he was admitted with febrile neutropenia grade 3 and grade 4 thrombocytopenia. He had a prolonged hospital stay followed by a significant deterioration of his performance status. So, further chemotherapy was omitted and he was continued only on single agent Ramucirumab from February 2018 to August 2018. Response evaluation after four months revealed progressive disease. By this time, we had the report of next-generation sequencing, and it showed a heterozygous missed mutation in exon 2 of MET gene c.1124A>G;p.Asn375Ser. As no clinical trial was available in our center at that point in time, we started the patient on Cabozantinib at 60 mg once daily from August 2018. He tolerated the drug well except grade 2 hand-foot syndrome and fatigue, for which dose modification was done to 40 mg per day from second month onwards. Response evaluation done in November 2018 revealed stable disease. At this point, the patient had significant

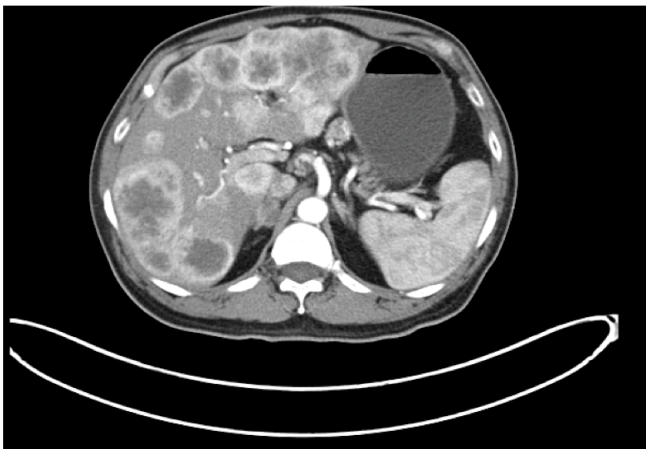

Figure 1: The CT scan revealed the presence of antral gastric mass along with multiple extensive metastases to the liver, lung and retroperitoneal lymph nodes.

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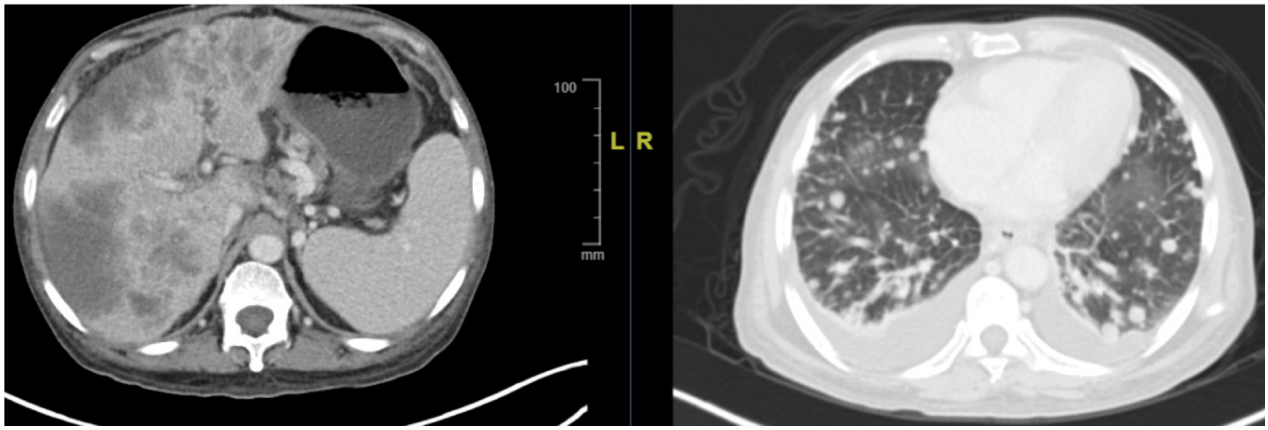

Figure 2: Repeated imaging to rule of obstructive jaundice, it showed extensive lesions with solid and necrotic components, along with a widespread increase in lung nodules and appearance of bilateral pleural effusion, which was malignant in cytology.

clinical improvement with the resolution of ascites and improvement in appetite and general well-being. He was continued till January 2019 and response CT scan was again repeated. This time it showed progressive disease. We started him on crizotinib at 250 milligrams twice daily as a second line MET inhibitor. However, he has poor tolerance with severe fatigue and elevated liver enzymes grade 3. Imaging was repeated to rule of obstructive jaundice, and it showed extensive lesions with solid and necrotic components, along with a widespread increase in lung nodules and appearance of bilateral pleural effusion, which was malignant in cytology. Due to poor performance status and significant liver dysfunction, no further therapy was possible, and he was shifted to home-based palliative care. He died of progressive disease in March 2019 [5,6].

Conclusion

The standard treatment of HER2 positive metastatic stomach cancer is a combination of Trastuzumab with chemotherapy. The median overall survival was 13.8 months. Our patient survived for 15 months. The above case shows how the presence of C MET mutation leads to short duration response (3 months) to Trastuzumab-based chemotherapy regimen. MET mutated patients are more resistant to therapy. It also underlines the fact that there may be a role of looking at MET amplification in a patient who is having HER2 positivity, and not having an expected response to anti HER2 therapy. The use of MET inhibition has not been successful in randomized trials. After the initial progression of first-line Trastuzumab based chemotherapy and Ramucirumab, he would have been considered for best supportive care if we didn't have the option of MET inhibitors. Cabozantinib and Crizotinib both have been shown to inhibit MET. We believe that the use of subsequent oral multikinase inhibitors has improved survival in our patient. Further investigation is warranted in MET mutated/HER2 amplified patients.

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