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Treatment with sorafenib plus camrelizumab after splenectomy for primary splenic angiosarcoma with liver metastasis: A case report and literature review

Pan D *et al*. Treatment to PSA with liver metastasis

Abstract

BACKGROUND

Primary splenic angiosarcoma (PSA) is an extremely rare and aggressive mesenchymal malignancy with high metastatic potential and poor prognosis. There are no established treatment guidelines for PSA, even for adjuvant therapy. This rare case may provide a reliable therapeutic regime for a better prognosis.

CASE SUMMARY

A 49-year-old female who complained about right-upper quadrant abdominal pain was diagnosed as having PSA with splenic rupture and liver metastasis. After splenectomy and liver tumor resection, she received sorafenib and camrelizumab therapy. After 15 mo of follow-up, she is in good condition, without recurrence or any identified metastasis.

CONCLUSION

Immunotherapy combined with targeted therapy could be a potential option for the adjuvant therapy of PSA.

Key Words: Primary splenic angiosarcoma; Immunotherapy; Targeted therapy; Prognosis; Case report

Pan D, Li TP, Xiong JH, Wang SB, Chen YX, Li JF, Xiao Q. Treatment with sorafenib plus camrelizumab after splenectomy for primary splenic angiosarcoma with liver metastasis: A case report and literature review. *World J Clin Cases* 2022; In press

Core Tip: Splenectomy is the preferred treatment for primary splenic angiosarcoma (PSA); however, PSA patients may experience a good or poor prognosis after splenectomy. Although the prognosis in patients with liver metastases or rupture of the spleen is extremely poor, no case had attempted immunotherapy or targeted therapy

after surgery. This case is the first report of a PSA patient with liver metastasis and splenic rupture, receiving sorafenib plus camrelizumab as adjuvant therapy. After 15 mo of follow-up, the patient is in good condition without recurrence or identified metastasis. Apart from chemotherapy and radiotherapy, targeted therapies and immunotherapy may also be an option for adjuvant therapy.

INTRODUCTION

Primary splenic angiosarcoma (PSA), as a subtype of soft tissue sarcoma (STS) with an annual incidence of 0.14-0.25 per million[1], is an extremely rare and aggressive mesenchymal malignancy with high metastatic potential and poor prognosis. Upon histopathological examination, abnormal, pleomorphic, malignant patterns of endothelial cells, which can be rounded, polygonal, or fusiform (the hallmark of angiosarcoma or mitotic bodies), are commonly observed[2]. The typically expressed endothelial markers include von Willebrand factor, CD34, CD31, Ulex europaeus agglutinin-1, and vascular endothelial growth factor (VEGF)[2].

PSA patients with liver metastasis have a poor prognosis, especially when the spleen ruptures. Although immunotherapy and targeted therapy are widely used in other tumors, they are rarely considered in the treatment of PSA. In several cases, immunotherapy or targeted therapy is very effective in patients with angiosarcoma[3-5]. We believe that this form of therapy may have great potential in the treatment of PSA.

CASE PRESENTATION

Chief complaints

Pain in the right upper quadrant of the abdomen for one month, which exacerbated within a day, along with significant weight loss (Figure 1).

History of present illness

On 16 February 2020, a 49-year-old female with the complaint described above was brought to our emergency department. The patient did not report any abdominal

trauma but complained of significant weight loss. According to the computed tomography (CT) scan on 16 February 2020 and other examinations (Figure 2), the diagnosis was non-traumatic splenic rupture and hemorrhage, with the suspected presence of liver cancer. Splenic artery embolization was suggested, which was refused by the patient and her family. Two days later, her abnormal pain got worse, after which, she and her family finally agreed to undergo splenic artery embolization (Figure 3). The patient recovered uneventfully and was discharged nine days later. One month later, she was admitted to our hospital again for abdominal pain. According to the contrast-enhanced CT performed on 6 April 2020, the preliminary diagnosis was made as splenic angiosarcoma with peripheral and intrahepatic metastasis (Figure 4).

History of past illness

Surgical history included total thyroidectomy two years ago, followed by an I131 therapy, hysteromyomectomy performed ten years ago, and pancreatic stone removal. The patient did not present a history of hepatitis or diabetes mellitus.

Personal and family history

There was no notable family medical history, such as cancer.

Physical examination

The patient's temperature was 36.6 °C, and blood pressure was 92/62 mmHg. Her heart rate was 101 bpm, and her respiratory rate was 20 breaths per minute. Physical examination revealed a tender abdominal mass in the left upper abdomen and distension of the abdomen. Deep palpation showed diffuse pain, although without clinical signs of peritonitis.

Laboratory examinations

Liver function tests, hematology parameters, as well as tumor markers such as α-fetoprotein (AFP), carbohydrate antigen 199, carcinoembryonic antigen, and

chromogranin A, were all normal, except for a white blood cell count of 13.54 × 10^9/L [normal range: (4.0-10.0) × 10^9/L] and hemoglobin concentration of 177 g/L (normal range: 120-160 g/L), which were beyond normal range. The D-dimer level of 35.65 mg/L (normal range: 0.0-0.55 mg/L) indicated high coagulation function, while the remaining parameters were normal. Electrolyte levels, electrocardiogram, and chest X-ray were normal.

Imaging examinations

Multiple masses were observed in the liver and spleen by abdominal CT and magnetic resonance imaging on 16 February 2020 (Figure 2). Contrast-enhanced CT on 6 April 2020 revealed multiple round shadows of low-density in the spleen and liver (Figure 4).

FINAL DIAGNOSIS

The patient was diagnosed as having PSA with a liver tumor.

TREATMENT

Splenectomy and liver tumor resection were performed not only to perform radical excision of the tumor but also for the histopathological diagnosis. Intraoperatively, we observed a large scleroid tumor mass of 4 cm × 6 cm in size in the upper pole of the spleen. A cross-section of the specimen revealed a demarcated yellowish-white lesion accompanied by hemorrhage and necrosis (Figure 5). The intraoperative observation of neoplasms was in line with the imaging findings. The histopathological biopsy and next-generation sequencing (NGS) were carried out (733 gene panel genetic testing provided by 3D Medicines Inc.). The histopathology revealed that the tumor cells were arranged in sheets, fissures, or papillae, with the cytoplasm in fusiform, oval, or irregular nuclei, and mitosis was easily seen. Immunohistochemical examination revealed that the tumor cells were positive for CD31, S-100 and Ki-67 (positive rate of 60%), and negative for CD34 (Figure 6). The final pathological diagnosis was hepatic angiosarcoma and splenic angiosarcoma. We could see from imaging that splenic

tumors were larger and numerous, while liver tumors were relatively small and uniform in size, which was consistent with the characteristics of metastatic liver cancer. In addition, our patient had no history of hepatitis, preoperative AFP was normal, CT examination showed no obvious characteristics of primary liver cancer, and blood from spleen returned to liver is the way of tumor to metastasize, which further supported the diagnosis of spleen tumor metastasized to the liver. Although the primary site was indistinguishable pathologically, the diagnosis of primary splenic malignancy with hepatic metastasis was suggested based on the characteristics of imaging and blood metastasis. The NGS revealed somatic mutations in the PDGFRA (gene amplification), KIT (gene amplification), KDR (VEGFR2) (gene amplification), and TP53(c.376-4_380del, Mutation abundance: 65.31%), while immunohistochemistry (IHC) showed the expression of programmed death ligand-1 (PD-L1) (Figure 7).

One month after the operation, the patient was given an intravenous infusion of sorafenib (400 mg) twice daily and camrelizumab (200 mg) in a 21-d cycle. After three weeks of combination therapy, she developed hand-foot syndrome and was unable to walk, following which, sorafenib was reduced to 600 mg daily.

OUTCOME AND FOLLOW-UP

Three and a half months after the operation, no metastasis was observed in the single-photon emission tomography-CT (Figure 8). After 15 mo of frequent follow-up, we happily report that the patient is in good condition without any recurrence or metastasis. Also, the side effects of sorafenib and camrelizumab were tolerable. The patient believed that the treatment had little impact on her quality of life.

DISCUSSION

Since the first case that was reported by Theodor Langhans in 1879, only about 200 cases had been reported in literature worldwide[1]. We summarized the characteristics of PSA from case reports in the last ten years (Table 1). Unlike hepatic angiosarcoma, we observed no correlation between splenic angiosarcoma and risk factors such as

thorium dioxide, vinyl chloride, or arsenic[6]. The symptoms of PSA are nonspecific, and although it may occur at any age, it is commonly observed in females aged over 60-years-old[6].

Due to its low incidence, there are no standardized treatments, guidelines, or even consensus to be recommended. Splenectomy is the preferred treatment for splenic angiosarcoma[2]. According to a retrospective analysis by Li *et al*[7], the mean overall survival (OS) for PSA patients was less than 8.1 mo after diagnosis. Despite the long survival of some patients, the prognosis for patients with liver metastases or splenic rupture after splenectomy was generally poor (Table 1).

Almost 30% of the patients experienced splenic rupture associated with hemoperitoneum[6]. When the spleen ruptures, the prognosis for the PSA patients is poor. Kornmann *et al*[8] reported that a 69-year-old PSA male who had splenic rupture associated with hemoperitoneum died within one month after surgery (Table 1). Abbott *et al*[9] reported that the mean OS among patients who had splenectomy after spontaneous splenic rupture was 4.4 mo. If splenectomy was performed before rupture, the mean OS increased to 14.4 mo.

PSA is also a highly aggressive tumor, which can not only spread *via* direct invasion but also metastasize *via* the hematal and lymphatic system[2,7]. The most common site involved is the liver, followed by the lung, bone, lymph nodes, and ovaries[7]. Metastasis in the liver, peritoneum, bone, and lung may occur in PSA patients, and approximately half of such patients died within one year after diagnosis (Table 1). The prognosis of PSA is abysmal, particularly in patients with metastases[6]. Splenic rupture and liver metastases may serve as high-risk factors for PSA. So, the patients with either may need more measures for prolonged survival. Adjuvant therapy may be a potential treatment strategy after surgery to reduce the likelihood of recurrence or spread to other sites.

Postoperative radiotherapy and adjuvant chemotherapy provide a promising choice for sarcomas of the extremities, although the efficacy for PSA was questionable as only a few patients had been enrolled in clinical trials[10,11]. For unresectable angiosarcoma,

treatment with single-agent doxorubicin or paclitaxel is recommended based on the available evidence. However, there is no precise evidence for adjuvant chemotherapy[12]. Given its extensive use in other tumors, targeted therapy and immunotherapy may provide new options for adjuvant therapy against PSA.

Immunotherapy has become a significant option for the treatment of advanced cancer[13]. A retrospective analysis reported that a cohort of patients with unresectable sarcomas, who were treated with nivolumab combined with pazopanib, presented clinical benefit in 50% of the patients after at least four cycles[14]. This may be due to increased lymphocytic infiltration and PD-L1 expression in patients with sarcomas[15,16]. Hence, it is reasonable to perform immunotherapy. Studies have demonstrated that the activity of anti-PD-1 therapy in all types of STS is consistent[17]. Targeted therapies such as bevacizumab, sorafenib, and pazopanib have shown great efficacy in the treatment of advanced STS[13]. A retrospective analysis reported that sorafenib had activity against angiosarcoma[4]. In a phase-III trial for metastatic STS, 372 patients with advanced STS whose disease had progressed despite at least one line of chemotherapy were randomly assigned to either a pazopanib arm or a placebo arm. The difference in progression-free survival (PFS) between the two arms was statistically significant, with a median PFS of 4.6 mo for pazopanib, compared to just 1.6 mo for placebo[18]. Pazopanib has received approval for the treatment of certain STSs in 2012[14]. In an open-label, multicenter, phase-II study, bevacizumab showed great potential in the treatment of angiosarcoma in 30 patients, whose disease was deemed surgically unresectable, with a mean tristetraprolin of 26 wk. Four patients showed partial response, and half of the patients had stable disease[3]. Notably, all the reported targeted drugs were anti-angiogenic agents, possibly because angiogenesis or VEGF plays an important role in carcinosarcoma[4]. Moreover, a previous study suggested that combining immunotherapy and targeted therapies may have complementary roles in cancer treatment and that combinatorial therapy might be synergistic[5]. That study gave us great inspiration and confidence.

In the present case, the patient was treated with sorafenib combined with camrelizumab as adjuvant therapy, instead of chemotherapy, because we found that the prognoses of patients on chemotherapy were stratified, that is, chemotherapy worked well in some patients and presented unsatisfactory clinical outcomes in others[19-22]. Therefore, we performed NGS and IHC for PD-L1. The patient might be sensitive to sorafenib (targets BRAF, CRAF, KIT, FLT3, RET, VEGFR-1/-2/-3, and PDGFRα/β) and PD-L1 inhibitor, as deduced from the mechanism of these drugs and thus received periodic treatment. This was a meaningful attempt of off label use. Now, after 15 mo of follow-up, there is no progress or recurrence of the disease, and the prognosis is good compared to most PSA patients of rupture of spleen or liver metastases without adjuvant therapy among cases published in the last 10 years (Table1).

CONCLUSION

Our data provide excellent evidence that adjuvant targeted therapy and immunotherapy may improve the prognosis in patients with PSA. Meanwhile, more evidence-based medical data and the specific cycle of targeted immunotherapy need to be further explored. NGS can be considered for patients suffering from angiosarcoma, which may suggest possible clinical treatment.

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