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A primary splenic angiosarcoma hepatic metastasis after splenectomy and its genomic alteration profile

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Abstract

Rationale: Primary splenic angiosarcoma (PSA) is a rare mesenchymal malignancy of the splenic vascular origin often with a dismal prognosis. Genomic profile may provide evidence for the solution of therapy.

Patient concerns: We reported a case of a 51-year-old woman with splenectomy 4 years ago and the postoperative histopathology diagnosis revealed "splenic hemangioma" with spontaneous rupture. Two years after the operation, the patient's rechecked abdominal computed tomography (CT) showed multiple hepatic occupations.

Diagnoses: Pathological test suggested PSA hepatic metastasis.

Interventions: The patient was treated with trans-catheter arterial chemoembolization (TACE) and a pathological diagnosis of PSA was highly suspected in the hepatic biopsy. Four somatic alterations, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), Fos proto-oncogene, AP-1 transcription factor subunit (FOS), MCL1 apoptosis regulator (MCL1), and phosphoinositide-3-kinase regulatory subunit 1 (PIK3R1) were detected in the tumor tissue using a Next generation sequencing (NGS) technology. The results prompted that the patient may get clinical benefit from using some agents for targeted therapy, Everolimus, Temsirolimus, or Copanlisib.

Outcomes: The patient refused targeted therapy. As a result, the patient passed away within 51 months after splenectomy.

Lessons: PSA is an aggressive disease that often presented with a high propensity for metastasis and rupture hemorrhage. Some of these mutations were first discovered in PSA and these findings added new contents to the genomic mutation profile of PSA.

Abbreviations: NGS = next generation sequencing, PSA = primary splenic angiosarcoma, TACE = trans-catheter arterial chemoembolization.

Keywords: angiosarcoma, genetic profile, hepatic metastasis, next generation sequencing, targeted therapy

1. Introduction

Primary splenic angiosarcoma (PSA) is an extremely rare mesenchymal malignancy of the splenic vascular origin with high metastatic potential. It is often life-threatening if combined with spontaneous rupture or distant metastasis.[1] The incidence of this disease is of 0.14 to 0.23 cases per million, with a rate of tumor metastasis between 69% and 100% which mainly appear lymph node, liver, lung, bone, and thyroid metastasis. In all reported cases, about 93% of patients died of tumor metastasis. However, the PSA liver metastasis after splenectomy is quite rare.

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LC and JH have contributed equally to this work.

The work was approved by the ethical committee of the First Affiliated Hospital, Zhejiang University School of Medicine (Hangzhou, China). The ethical approval number: 2017 scientific research quick review NO.714.

The patient provided written informed consent for the publication of their data and associated images.

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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The authors declare that they have no competing interests.

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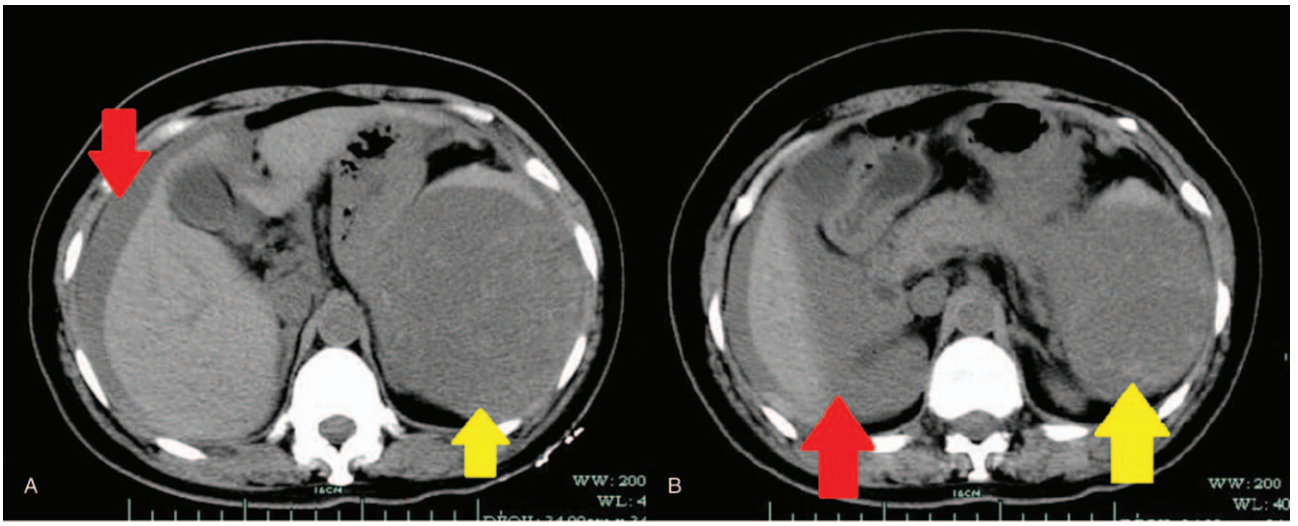

Figure 1. CT images of the splenic hemangioma with spontaneous rupture. CT scan demonstrating splenic mass (yellow arrow) with rupture hemorrhage and hydrops around liver (red arrow). CT = computed tomography.

Here, we reported a case of a 51-year-old woman with PSA liver metastasis after splenectomy because of splenic hemangioma and rupture 3 years later. In addition, genomic profile was tested to offer more evidences for further possible targeted therapy.

2. Case presentation

The patient was 51 years old, female, with no history of smoking or family history of cancer. Four years ago, the patient underwent splenectomy for "splenic hemangioma" with spontaneous rupture (Fig. 1). Now, in a routine reviewed test, abdominal enhancement computed tomography (CT) revealed multiple hepatic occupations with annular enhancement; the enhancement gradually extended to the center of occupations at the portal vein stage and the balance stage, and hepatic metastatic malignant tumor consideration (Fig. 2). Positron emission tomography-CT examination hinted intrahepatic multiple low metabolic malignancy with extensive bone metastases (Fig. 3). The patient was treated with trans-catheter arterial chemoembolization (TACE) and a pathological diagnosis of PSA was highly suspected in the hepatic biopsy (Fig. 4). Subsequently, another TACE was performed. The re-examination of abdominal enhancement CT showed intrahepatic nodules significantly enhanced and active focus still existed around the treatment area (Fig. 5) and revealed the effect of TACE was not satisfactory. So we decided to take the hepatic specimen for further genomic profile to adjust the treatment strategy to achieve good curative effect.

Fresh tumor tissue sections and matched blood from the patient were collected and DNA was extracted from the sample. All coding exons of 450 cancer-related genes and selected introns of 39 common genes rearranged in solid tumors were captured and sequenced with a mean coverage of 1000 times for tumor tissue and 350 times for blood on Illumina NextSeq platform. Genomic alterations including base substitution,

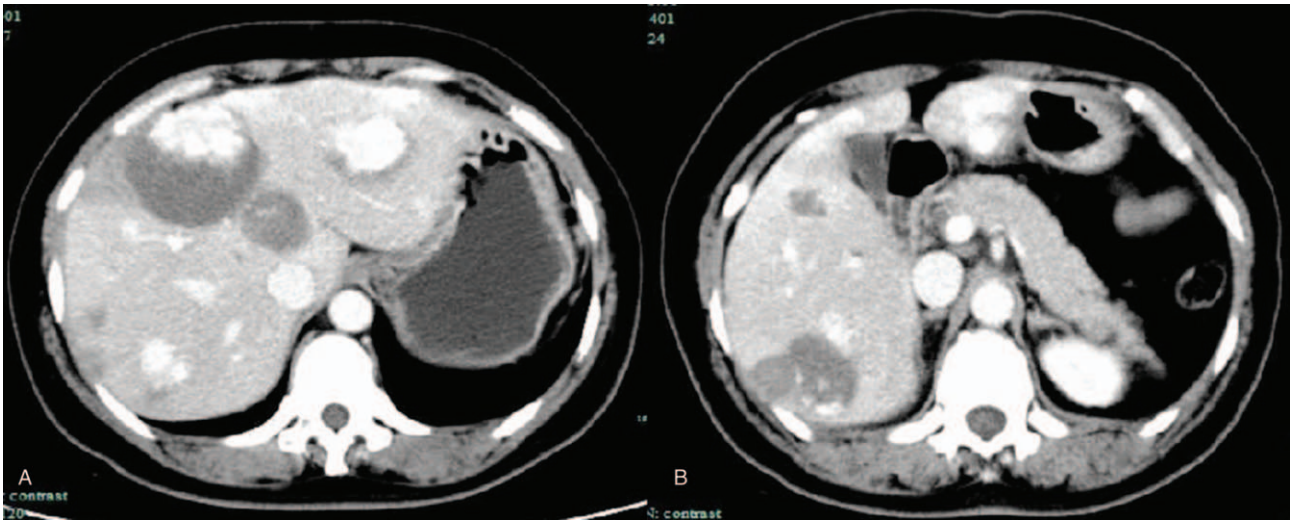

Figure 2. CT scan demonstrating for multiple hepatic mass after 3 years of splenectomy. CT = computed tomography.

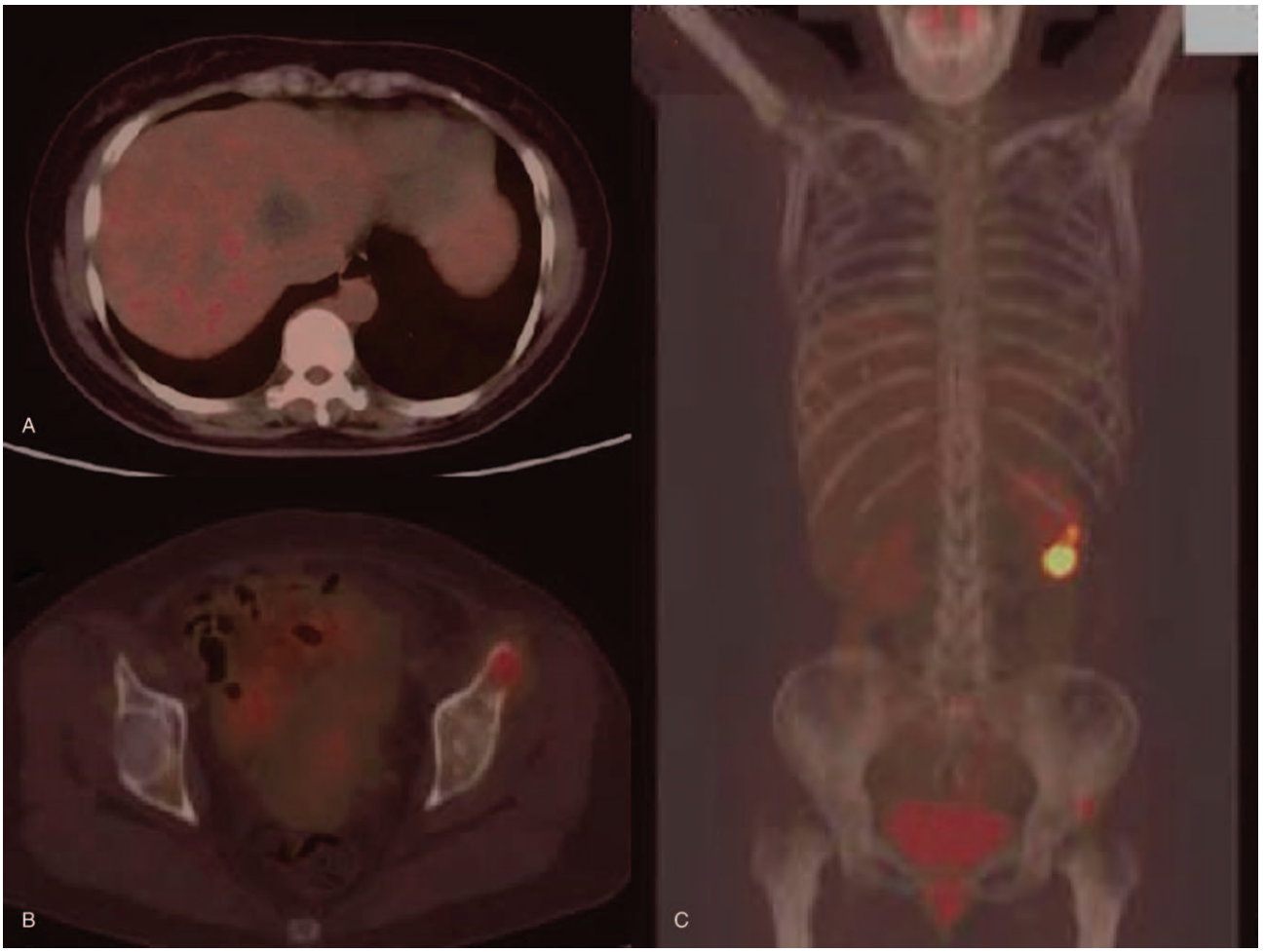

Figure 3. PET-CT demonstrating hepatic and skeletal metastases, (A): CT scan for intrahepatic multiple FDG hypermetabolism metastases; (B): CT scan for FDG hypermetabolism metastases of the left ilium; (C): abdominal orthostatic plain film for hypermetabolism metastases. CT = computed tomography, FDG = fluorodeoxyglucose, PET = positron emission tomography.

short and long insertions/deletions, copy number variations, and gene rearrangement were assessed. Somatic alterations were obtained by comparison with matched blood control samples.

The genomic profile results indicated phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) N1044K and H1047R mutation, Fos proto-oncogene, AP-1 transcription factor subunit (FOS) amplification, MCL1 apopto-

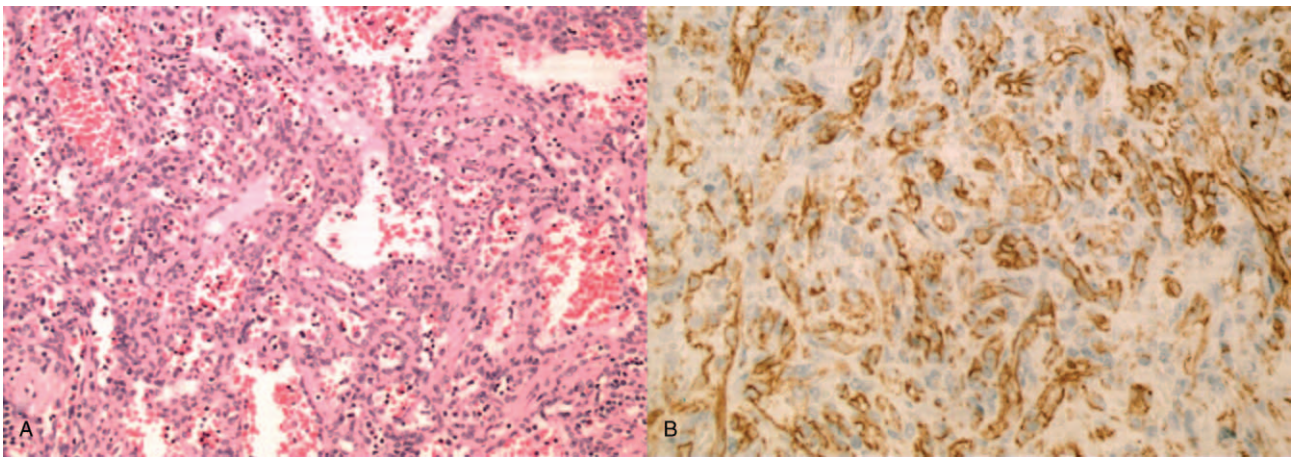

Figure 4. Histological examination results. (A): Vascular channels lined by endothelial cells (×200). (B): Tumor cells showing positive immunohistochemistry staining for CD31 (×400).

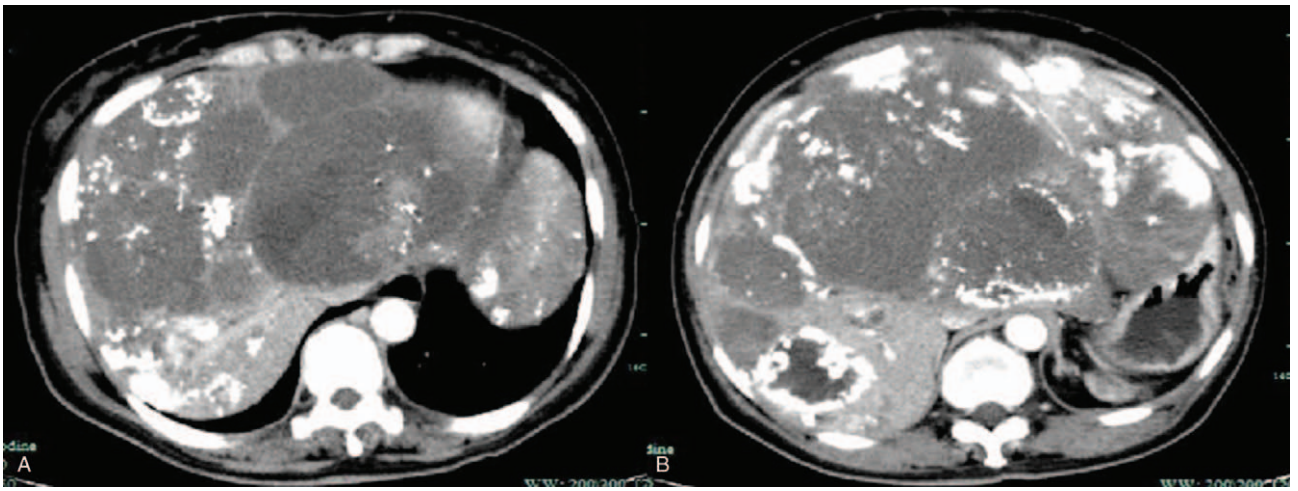

Figure 5. CT scan demonstrating intrahepatic nodules significantly enhanced after twice TACE treatment.

sis regulator (MCL1) amplification, and phosphoinositide-3-kinase regulatory subunit 1 (PIK3R1) c.1746–8_1770del (Figs. 6 and 7). PIK3CA mutation revealed that the patient may get clinical benefit by using Everolimus, Temsirolimus, or Copanlisib. Thus, we recommend the patient to accept targeted therapy according to the genomic profile results, but patient refused to cooperate. As a result, the patient passed away within 51 months after splenectomy.

3. Discussion

The spleen tumors are rare and the primary spleen malignancy are more rare. PSA is a very rare but aggressive malignancy with high metastatic potential. Since Langhans reports the first case of PSA in 1879, there are only approximately 200 cases reported worldwide.[1] The common age of onset was between 50 and 79 years,[2] and about 86% of the patients appeared hepatic metastases.[2] The average survival time was between 4.4 and 14 months, and only about 20% of patients can survive longer than 6 months. PSA needed systemic therapy including splenectomy and chemotherapy.[3] Hsu et al[4] reported that patient with PSA had a maximum survival of 14.8 years after splenectomy.

PSA originated from the vessel endothelial cells of the spleen, while the pathogenesis is not clear yet. It may be caused by exposure to carcinogens and chemo-radio therapy for malignant tumors.[2] It has been reported that the angiosarcoma requires the existence of a benign pathology such as hemangioma or hemangioendothelioma; however, the patients did not have a history of those diseases in many cases.[5] For the present case, the patient had a splenic hemangioma and spontaneous rupture before and it might act as a precursor to angiosarcoma.

The clinical manifestations of PSA vary greatly. Left upper abdominal pain is the most common presentation (about 80%),[6] and other complaints include upper abdominal mass, fatigue, anorexia, weight loss, and dyspnea. Spontaneous rupture hemorrhage is the most serious symptom. There are also reports of unexplained fever and anemia in patient with PSA.[7] Mild to moderate anemia is the major finding of blood routine examination in PSA (about 70%–80%, hemoglobin <100 g/L),[8] and other major abnormities include thrombocytopenia (more than half, thrombocyte count $<100\times10^9$/L),[9] leukopenia (about 20%, leukocyte count $<4\times10^9$/L), erythrocyte sedimentation rate enhancement (15%).[10]

PSA needed to be differential diagnosis with lymphoma, splenic metastatic tumor, splenic vascular benign tumor, splenic abscess, and other splenic diseases.[11] Imaging examination (ultrasound, CT, and magnetic resonance imaging [MRI]) is the main diagnostic and differential diagnostic method for PSA. However, due to lack of typical performance, imaging examination is inaccurate sometimes.[5] CT is the most commonly used method for PSA, which is of high value in the evaluation of general characteristics and complications of PSA. On CT scan imaging, splenic heterogeneous mass can be observed in 60% of cases.[12,13] The abdomen enhanced CT scan shows significant differences between the enhanced region and non-enhanced region of the spleen immediately after the injection of contrast medium. The non-enhanced region is mostly poor blood supply or avascular necrosis focus, which begins to intensify after 10 to 50 minutes, and that is referred as PSA delayed enhancement sign. This can be identified with lymphoma and splenic metastasis which don't have such sign.[11,14] Active bleeding signs can be seen in PSA patients. On MRI scan, both T1-weighted and T2-weighted images reveal nodular lesions with decreased or increased signal intensity which is related to necrosis, hemorrhage or fibrosis within the tumor,[6] and most patients can have a T2 high density image.[13]

Pathological examination and immunohistochemistry are generally considered to be the golden standard for PSA diagnosis.[2] PSA has the typical characteristics of angiogenic malignancy, including vascular structures, highly atypical cell morphology, hyperchromatic and prominent nucleoli, and typical mitotic sign can be seen in some specimens. However, spleen puncture biopsy is considered as a relative contraindication because it may cause splenic rupture. Therefore, histological examination is performed only after splenectomy in such cases. Recently, fine-needle aspiration cytology which used a 22-gauge or smaller needle is identified as safe as postoperative biopsy,[15,16] but hemorrhage occurs after biopsy in few cases. PSA presents 2-way feature of positive vascular endothelial markers and histiocytic markers in immunohistochemistry. Previous studies reveal that at least 2 endothelial markers (CD34, CD31, FVIIIRAg, or VEGFR3, etc.) and 1 histiocytic

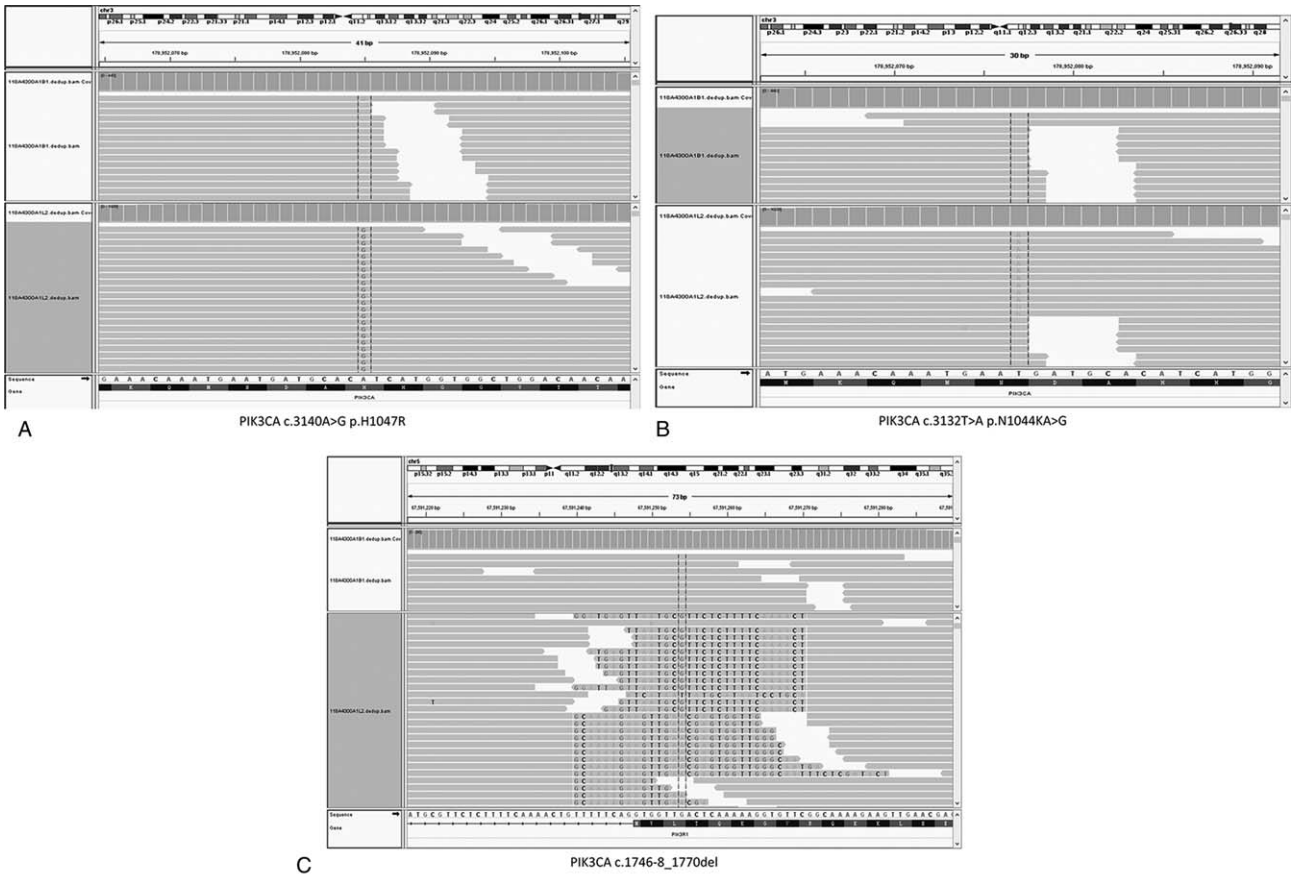

Figure 6. The mutation of PIK3CA and PIK3R1, (A): the 1047th histidine codon mutating into arginine codon; (B): the 1044th asparagine codon mutating into lysine codon; (C): the deficiency of bp in 3′ terminal 8th to 1770th of PIK3R1 13th intron. PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha, PIK3R1 = phosphoinositide-3-kinase regulatory subunit 1.

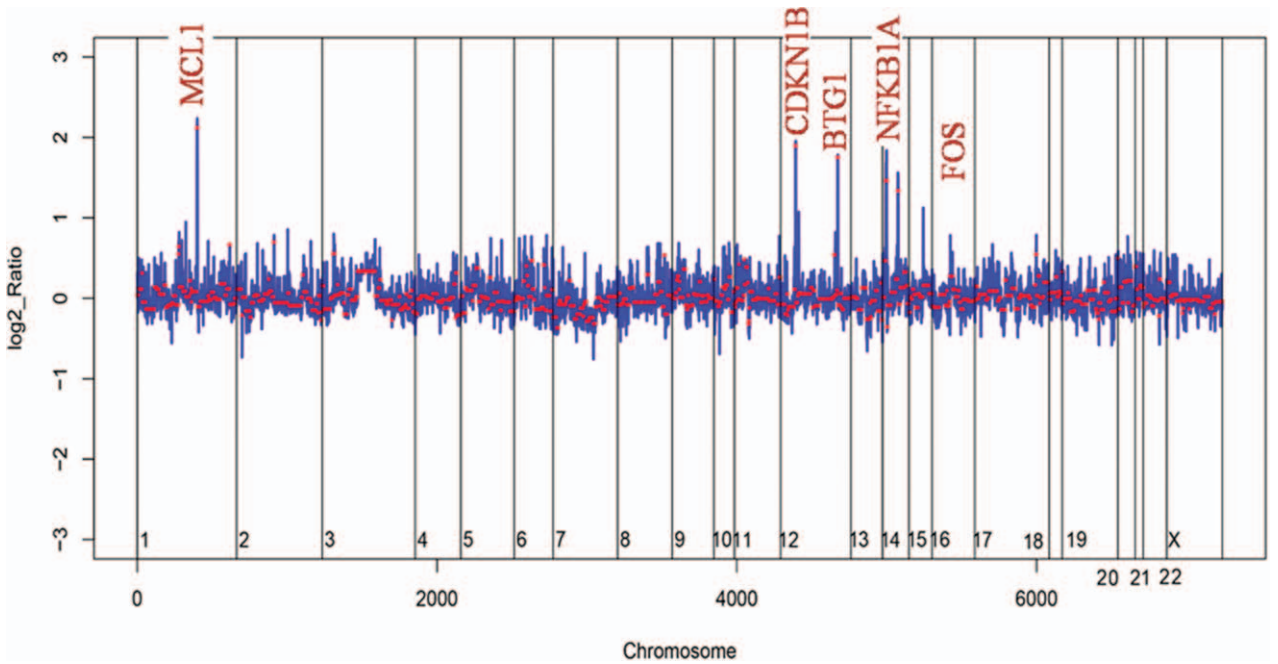

Figure 7. The amplification of FOS and MCL1. FOS = Fos proto-oncogene, AP-1 transcription factor subunit, MCL1 = MCL1 apoptosis regulator.

marker (CD68 or lysozyme, etc.) will be positive.[17] Most patients are positive for both CD31 and CD34. CD31 is a marker of vascular endothelial differentiation, and the sensitivity and specificity of CD31 in PSA diagnosis are >90%. CD34 also suggests vascular endothelial origin. In this case, immunohistochemistry examination was not very helpful for the diagnosis, all the cell markers above were negative except CD31 (Fig. 4).

Genomic profile is a technique for detecting cellular DNA by collecting fresh tissue sections from the patient. The PSA can appear multiple cytogenetic changes represented by the mutations of chromosomal copies,[18] as well as the mutant gene including K-ras, p53, PIK3CA, TP53, PTEN, PLCG1, Hras, etc.[19] In our case, the patient's genomic profile showed PIK3CA, FOS, MCL1, and PIK3R1 mutation and were not the same as the previous reports. The mutation of PIK3CA gene, where the 1044 asparagine codon mutating into lysine codon and the 1047 histidine codon mutating into arginine codon (Fig. 6), increase the catalytic activity of PIK3CA, thereby enhancing the downstream signal conduction, tumor malignant transformation, and tumor cell migration.[20,21] Everolimus, Temsirolimus (mTOR inhibitor of the PI3K/Akt/mTOR signaling path), and Copanlisib (PI3K inhibitor) can be used as a targeted treatment. The gene amplification of FOS and MCL1 (Fig. 7) might affect their mRNA and protein expression levels, however, there is a lack of anti-tumor drugs targeting FOS and MCL1 clinically now.[22,23] The deficiency of basic groups in 3′ terminal 8 to 1770 of PIK3R1 13 intron is frequently reported in tumor case report[24] which cause the abnormality of mRNA splicing in PIK3R1 transcription and protein dysfunction. Also there is a lack of anti-tumor drugs targeting PIK3R1 clinically now. But, Everolimus, Temsirolimus, and Copanlisib for PI3K signal path may still produce some relief effect for patient with PIK3R1 mutation.[25]

Radical surgical treatment is the major treatment for patients with PSA. Splenectomy before splenic spontaneous rupture can significantly prolong the survival of patients better than after. But for the majority of patients with PSA, distant metastasis had already occurred at the time of diagnosis, so splenectomy was seen as an approach more for diagnostic purpose rather than curative purpose. In addition, PSA had the high risk of distant metastasis and local recurrence after splenectomy.[2] Postoperative metastasis was the most significant factor affecting the prognosis of patients. The postoperative radiotherapy or chemotherapy is still a controversial treatment option because there is no evidence statistical data to this disease.[26] Neuhauser et al[27] reported some patients received adjuvant chemotherapy after splenectomy and 1 patient survived with the disease for 8 years, another was disease-free for 10 years. Paclitaxel was considered as an adjuvant and neoadjuvant therapy by Vakkalanka and Milhem,[28] suggesting that chemotherapy may decrease local recurrence and improve overall survival. de Azevedo et al[29] also reported a patient remained disease free for 1 year and 2 months after paclitaxel adjuvant chemotherapy. Hara et al[30] presented a patient who received autologous peripheral blood stem cell transplantation combined with high-dose chemotherapy after splenectomy. The treatment brought 6-year-long complete remission. Recently, Kohutek et al[31] presented a patient who underwent radical splenectomy for primary angiosarcoma of the spleen. Palliative radiotherapy, bisphosphonates, doxorubicin, and paclitaxel chemotherapy can significantly prolonged periods of disease stabilization. They think durable benefit can be achieved in some patients with multimodality management. As for the targeting therapy, there were few experiences. Our patient received twice transcatheter arterial chemoembolization (TACE, using palonosetron + pingyangmycin + iodipin the first time and palonosetron + pharmorubicin + iodipin the second time) 3 years after splenectomy, but the results were unsatisfactory. Genomic profile revealed that 4 somatic mutations, including PIK3CA, FOS, MCL1, PIK3R1. So we suggested her trying chemotherapy combined with Everolimus, but refused.

4. Conclusion

PSA is an aggressive disease that often presented with a high propensity for metastasis and rupture hemorrhage. The diagnosis mainly depends on histological examination and immunohistochemistry. The diagnosis of primary splenic angiosarcoma hepatic metastasis was confirmed by pathological examinations twice. Although the case has made some reports, it occurred after splenectomy is quite rare. For patients with poor response for conventional treatment, relative targeted therapy after genetic profile detection might achieve certain efficacy. Unfortunately, due to the patient refusing the target therapy, we cannot understand the therapeutic effect of targeted therapy in PSA. This is the main limitation and regret of this study.

Author contributions

Conceptualization: Jian Wu, Shusen Zheng.
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Validation: Ruobing Ma.
Writing – original draft: Jiawei Hong.
Writing – review & editing: Jian Wu, Shusen Zheng.

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