Multiple disciplinary team management in rare primary splenic malignancy: Two case reports

Luo H et al. MDT treatment for rare malignant splenic tumor

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Abstract

BACKGROUND
Splenic malignant tumors are rare but fatal, presenting an arduous challenge for diagnosis and management involving hematology, oncology, and general surgery. By contrast, diagnosing and treating other regular malignant tumors (such as lung and gastrointestinal cancer) offers multiple strategies for chemotherapy, radiotherapy, targeted therapy, and immunotherapy with the prospect of a cure. With various specialists involved in clinical multiple disciplinary team (MDT) discussion, personal bias can be minimized. It can also ignite important sparkles to benefit not only a single patient.

CASE SUMMARY
Here, we report on the MDT diagnosis and management for splenic malignant tumors of littoral cell angiocarcinoma and histiocytic sarcoma. Although only two cases of rare primary splenic malignancy are presented, MDT is a novel means of rare disease treatment.

CONCLUSION
To benefit a patient, imaging analysis, safe operation, precise pathology examination, and individualized therapeutic treatment strategies are required. The involvement of various specialists in a clinical MDT discussion minimizes personal bias and can create important ideas to benefit all patients.

Key Words: Multiple disciplinary team, Splenic malignancy, Littoral cell angiosarcoma, Histiocytic sarcoma, Case report

Core Tip: Splenic malignant tumors are rare but fatal, presenting an arduous challenge for diagnosis and management. With various specialists involved in clinical multiple disciplinary team discussion, personal bias can be minimized. It can also ignite important sparkles to benefit not only a single patient. In this case report, we report on the multiple disciplinary team (MDT) diagnosis and management for splenic malignant tumors of littoral cell angiocarcinoma and histiocytic sarcoma. Although only two cases of rare primary splenic malignancy are presented, MDT is a novel means of rare disease treatment.

INTRODUCTION
Splenic masses include benign and malignant tumors. While the most common benign splenic tumor is angioma, the spleen is not a preferred organ for primary malignant tumors[1]. Due to the absence of typical clinical characteristics or imaging methods, it is extremely difficult to distinguish between malignant and benign splenic tumors before surgery[2]. Diagnosing and managing splenic tumors involves hematology, oncology, and general surgery, making multiple disciplinary team (MDT) management necessary. In this case series, we report on applying MDTs to the diagnosis and management of rare splenic malignant tumors. With various specialists involved in clinical MDT discussion, personal bias can be minimized. It can also ignite important sparkles to benefit not only a single patient.

CASE PRESENTATION

Chief complaints

Case 1: A 77-year-old female presented to the emergency room with sudden onset of dizziness that had lasted 10 h and being prone to falling for 8 h.

Case 2: A 60-year-old female was referred to our hospital with an accidental detection of splenic mass by ultrasonic scan with thrombocytopenia.
History of present illness

Case 1: A 77-year-old female presented to the emergency room with sudden onset of dizziness that had lasted 10 h and being prone to falling for 8 h.

Case 2: She presented no other symptoms (such as fever, weight loss, dizziness, or night sweats).

History of past illness

Case 1: There is no other illness before.

Case 2: Her most recent imaging scan and lab examination was traced back to 2009. Upon hospital admission for an elbow fracture, an abdominal ultrasonic scan showed no positive results on the spleen and testing indicated a slightly reduced platelet count of $115 \times 10^9/L$.

Personal and family history

Case 1: No similar situation happens to her family members.

Case 2: No similar situation happens to her family members.

Physical examination

Case 1: Her heart rate was 120 with blood pressure of 106/60 and a respiratory rate of 26. Upon physical examination, the left costal margin exhibited tenderness without muscle intensive or rebound tenderness.

Case 2: Upon physical examination, the spleen was found to be slightly enlarged and palpable 2 cm below the left costal margin. There were no purpuras on the body but some vascular nevus about 1 mm around were noted.
**Laboratory examinations**

**Case 1:** A complete blood count indicated anemia and thrombocytopenia. Her peripheral hemoglobin was 85 g/L (normal range, 115-150 g/L) with a red blood cell count of \(2.65 \times 10^{12}/L\) (normal range, 3.80-5.10 \(\times\) \(10^{12}/L\)) and a platelet count of \(35 \times 10^9/L\) (normal range, 125-350 \(\times\) \(10^9/L\)). Coagulation examination indicated hypocoagulability with a prolonged prothrombin time (PT; 15.10 s, normal range from 9.00-13.00 s) and internal normalized ratio (INR; 1.32, normal range from 0.8-1.20), with a D-dimer over 70 mg/L (normal range, 0-0.55 mg/L).

**Case 2:** A complete blood count showed slight anemia (111 g/L) and thrombocytopenia (34 \(\times\) \(10^9/L\)) with a normal leukocyte count (4.83 \(\times\) \(10^9/L\)). Coagulation, hepatic marker, and tumor marker tests were negative. Bone marrow aspiration showed a subnormal proliferation of bone marrow without atypical cells and myelofibrosis.

**Imaging examinations**

**Case 1:** Emergency ultrasonic examination indicated the spleen was oversized, with non-uniform echoes accompanied by abdominal fluid collection. A subsequent diagnostic puncture contained uncoagulated blood, proving abdominal bleeding. The patient was diagnosed with blunt abdominal trauma and a splenic rupture.

**Case 2:** An abdominal Computed Tomography (CT) angiograph scan revealed splenomegaly and a tumor (6.0 cm \(\times\) 5.7 cm in size), with a CT value of 48Hu and showing gradual enhancement (Figure 1, the arrow indicated the mass in spleen). A general lymph node ultrasonic scan identified no enlarged superficial or abdominal lymph nodes. The patient refused the PET/CT examination.

**MULTIDISCIPLINARY EXPERT CONSULTATION**

**Case 1**

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A post-operation MDT conference was arranged before her discharge. The oncologist remarked on controversial biological features of littoral cell angiomia (LCA). Initially, the LCA was considered a benign splenic tumor, but subsequent evidence confirmed malignancy via distinguishing intermediate features. Given its low grade, the oncologist advised there was no need for further administration.

**Case 2**

A preoperative MDT conference was convened, including an imaging physician, general surgeon, hematologist, and oncologist. Radiologically, the CT value of the mass was similar to that of the normal spleen, but the enhancing mode represented a quick infusion and slow dispersion. This was consistent with the imaging features of splenic angioma. Surgically speaking, Kasabach-Merritt syndrome (KMS) was highly suspected because of the imaging characteristics combined with thrombocytopenia and the vascular nevus around her back. To diagnose, cure KMS, and ameliorate thrombocytopenia, splenectomy can be a better choice. However, the other surgeon reminded us of preceding Case 1 [whose postoperative pathologic diagnosis indicated littoral cell angiosarcoma (LCAS)] so splenic malignancy could not be fully eliminated despite there being no splenic mass according to the patient’s 2009 history. The hematologist stated that negative bone marrow aspiration and lymph node ultrasonic scan results could partially rule out lymphoma. After the MDT discussion, possible diagnoses were splenic KMS, splenic malignancy, lymphoma, or other hematology disease.

**FINAL DIAGNOSIS**

**Case 1**

The patient accepted an emergency splenectomy. Accidentially, the immunohistochemical pathology demonstrated the tumor cell was CD34+/ERG+/CD31+/CD8+/CD68+/Lysozyme+/F8+, sox-10+/S-100+, P53loc+ and Ki-67(4%, 5-10%) (Table 1). Based on the positivity of both endothelial (CD34, ERG, and Cd31)
and histiocytic markers (CD68, CD8, Lysozyme, and F8), she was ultimately diagnosed with a ruptured LCAS (Figure 2).

**Case 2:** After the pre-operative MDT conference, all physicians and the patient agreed to laparoscopic splenectomy to treat the KMS and ameliorate thrombocytopenia. During the surgery, the peritoneal cavity was carefully explored and there were no indications of enlarged lymph nodes or suspicious lesions. The postoperative pathology diagnosis confirmed splenic sarcoma. According to immunohistochemical markers (Table 1), a diagnosis of angiosarcoma or histiocytic sarcoma (HS) confused pathologists. In the postoperative MDT conference, the pathologist revealed that the tumor contained multiple large cells with abundant blue cytoplasm, in which the binucleated and trinucleated cells could also be observed (Figure 3). The CD4+/CD68+/Lysozyme+/CD45+/CD31+ tumor cells coincided with typical HS marker expression[7]. However, there was marker overlap, with Lysozyme, CD31, CD68, and F8 covering HS, angiosarcoma, and other malignancy[7,8]. A regular hematoxylin-eosin stain found no typical epithelial or dilated vessels, so the pathology diagnosis was prone to HS (Figure 3).

**TREATMENT**

**Case 1**

Given its low grade, the oncologist advised there was no need for further administration.

**Case 2**

The oncologist indicated that neither HS nor angiosarcoma was sensitive to chemotherapy, which is consistent with limited patients obtaining benefit from chemotherapy[9,10]. The hematologist advised that trametinib[11,12] and/or imatinib[13] could benefit this specific patient. Meanwhile, it has been reported that chronic myeloid leukemia, other kinds of leukemia and HS present similar medical features[10,14]. These
features might be therapeutic targets for imatinib. Finally, this patient give consent to imatinib treatment (400 mg, po, qd).

OUTCOME AND FOLLOW-UP

Case 1
This patient lost following-up after surgery.

Case 2
Latest follow-up showed it has been tumor-free for more than 15 mo.

DISCUSSION
Primary splenic malignancy is rare but fatal. It does not present typical clinical symptoms, so it is difficult to diagnose pre-operatively. The most common symptoms are hemophagocytosis-related symptoms (e.g., anemia accompanied by dizziness, anergy, loss of appetite) or thrombocytopenia-related symptoms (e.g., purpura or bleeding of mucosa)[15]. However, it is difficult to differentiate these symptoms from those of lymphoma or other benign spleen tumors, such as angioma. For treatment, splenic malignancy tumor is so rare that few guidelines and limited data exist. Therefore, to make an accurate decision for these patients, a general surgeon, an oncologist, a hematologist, a pathologist, and an imaging physician is necessary. While the MDT meeting is a regularly scheduled discussion of patients, comprising professionals from different specialties, such as surgeons, medical and radiation oncologists, radiologists, pathologists and nurse specialists[16]. MDT was first appeared in 1970’s in America known as tumor boards to discuss cases by a group of specialists[17]. MDT meetings were set up to give specialists the opportunity to update new developments in disease diagnosis and give the patient most suitable treatment[18]. MDT management has been broadly applied in cancer management and recommended as best practice by professional guidelines[19]. MDT meeting can be involved in every stage of clinics, and associated with precise diagnosis, initial management plans, higher
rates of treatment, shorter time to treatment after diagnosis, and better survival. Basically, for some rare disease diagnosis is the most challenging problem. With the help of MDT meetings, for case 1, we surgeons and emergency physicians believed that spleen rupture was secondary to blunt trauma. During the MDT discussion, our pathologist pointed out that spontaneous splenic rupture of LCA is not uncommon, reaching as high as 32%\textsuperscript{[20]}. Although we made the right choice to perform emergency surgery, an emergency physician or general surgeon might misdiagnose such a patient. The pathologist from the MDT gave us some clues, and a careful review of medical history illustrated another probable process. Spontaneous splenic LCA rupture can result in dizziness followed by being prone to falling. In case 2, the other unfortunate misdiagnosis was identified, with the patient’s initial diagnosis of KMS making surgery appear unavoidable. However, the recent occurrence of Case 1 reminded us of the possibility of splenic malignant tumor. Although it is difficult to differentiate primary splenic malignancy from lymphoma or other benign tumors, pre-operation MDT members agreed to the surgery unanimously, helping determine the most suitable clinical strategies. For the patient, MDT meeting can benefit patients suffering from rare disease, when the diagnosis is not easy to make like case 2. Meanwhile, MDT management can reduce the time from diagnosis to treatment. For physicians present several advantages that it can improve communication between MDT members, give doctors opportunity for education and to keep up to date with new developments, and improve the job satisfactions as well\textsuperscript{[21]}.

What is more, MDT discussion is necessary for treatment. The postoperative MDT conference for Case 2 saw a debate regarding the diagnosis. One idea considered the tumor as angiosarcoma, and the other regarded it as HS. Historically, HS has been classified together with histiocytic lymphoma, and the 2016 revision of the WHO classification put HS into macrophage-dendritic cell lineage along with other histiocytoses as well as myeloid-derived and stromal-derived dendritic cell tumors\textsuperscript{[22]}. Its diagnosis relies on immunohistochemistry, specifically positive expressions of mature histiocytic markers (such as CD4, CD68, CD163, and lysozyme) and negative
expressions of Langerhans and dendritic cellular markers (e.g., CD1a, Langerin, CD21, and CD35)[7].

However, HS represents an extremely heterogeneous feature with complicated markers. For example, both HS and angiosarcoma positively express CD68, CD31, and Lysozyme[7,8], which were positive in Case 1. As such, some pathologists diagnosed Case 2 as splenic angiosarcoma. After an in-depth MDT discussion and literature review, the HS diagnosis was confirmed.

Following therapy is another focus. Few guidelines and limited data can be referred to for HS treatment, and most HS have limited response to chemotherapy[10,23]. HS is very aggressive with poor prognosis of a median survival of several months, not extending 1 year[11,24-27]. The latterly following-up of our HS patient treated by imatinib has been tumor-free for more than 15 mo. Therefore, an experimental treatment of imatinib was recommended, and the targeted tyrosine kinase inhibitor may be a direction for HS management.

CONCLUSION
Although some physicians indicated that MDT will not demonstrate a beneficial effect on outcomes such as survival rates in regular malignant tumors (such as lung cancer, gastrointestinal cancer, and leukemia), however, it helps a lot for those who are suffering diseases which are difficult to get a clear diagnosis. Diagnosing and treating regular malignant tumors poses little challenge due to multiple available technology and treatment strategies (e.g., chemotherapy, radiotherapy, targeted therapy, immunotherapy, and MDT treatment) that offer the possibility of a cure. However, to definitively diagnose and treat a rare splenic lesion is tough and arduous. While this study only describes two rare cases of primary splenic malignancy, MDT offers a novel attempt to treat rare disease. To benefit a patient, imaging analysis, safe operation, precise pathology examination, and individualized therapeutic treatment strategies are required. With various specialists involved in clinical MDT discussion, personal bias
can be minimized. It can also ignite important sparkles to benefit not only a single patient.

REFERENCES


Footnotes

Informed consent statement: Both patients involved in this study had signed informed written consent.

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Figure Legends

Figure 1 Abdominal computed tomography angiograph scan of case 2. A: (arterial phase) and B (venous phase): In transverse section, pre-operational computed tomography (CT) scan revealed splenomegaly, and a tumor (size 6.0 cm × 5.7 cm) with CT value 48Hu showing gradually enhanced; C (arterial phase) and D (venous phase): The spleen with the tumor was shown in coronal phase. White arrow indicates the tumor.
Figure 2 HE and immunohistochemical characteristics of case 1. For littoral cell angiosarcoma, the tumor contains perivascular sinus-like heterocysts with dark nucleus and multiple mitotic phase in HE staining. As for immunohistochemical phenotype analysis, the tumor cells are CD31 positive, while CD68 is focal positive. Furthermore, it is found that typical endothelial markers CD34 and ERG are positive and perivascular expressed in littoral cell angiosarcoma. However, these two markers positively express only in normal vascular endothelial cell (black arrow) rather than perivascular cells. The Ki-67 index is 5%-10%.

Figure 3 HE and immunohistochemical characteristics of case 2. The tumor of case 2 contained plenty of large cells with abundant blue cytoplasm with binucleated and trinucleated cell, which is coincidence with the characteristic of histiocytic sarcoma. As for immunohistochemical phenotype analysis, tumor cells are CD31 positive, while CD68 is general positive in case 2. The Ki-67 index is 15%-20%.
Table 1 The immunohistochemical markers of angiosarcoma, histiocytic sarcoma, and reported cases

<table>
<thead>
<tr>
<th>Immunohistochemical markers</th>
<th>AS</th>
<th>HS</th>
<th>Case 1</th>
<th>Case 2</th>
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<tr>
<td>CD4</td>
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<td>Lysozyme</td>
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<td>CD45</td>
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<td>ERG</td>
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<td>CD34</td>
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<td>CD68</td>
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<td>Focal positive</td>
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<td>CD163</td>
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<td>CD8</td>
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<td>CK</td>
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<td>F8</td>
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<td>SMA</td>
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<td>Sox-10</td>
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<tr>
<td>Ki-67</td>
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<td>P53</td>
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AS: Angiosarcoma; SMA: Smooth muscle actin; ERG: Erythroblast transformation specific related gene; HS: Histiocytic sarcoma.
