Sclerosing extramedullary hematopoietic tumor of the colon: A case report and literature review

ZHIBO ZUO[1*], QI ZHANG[2*], WANXIN WU[1], XIN LI[1], LIN ZHANG[1], JINGYU WANG[1], ZHIQIN GUO[1], SHAOQING HU[1] and HONGYAN LIU[2]

[1]Department of Pathology, First Hospital of Jiaxing, Jiaxing, Zhejiang 314000; [2]Graduate School of Nursing, Huzhou University, Huzhou, Zhejiang 313000, P.R. China

Received September 29, 2022; Accepted January 26, 2023

DOI: 10.3892/etm.2023.11831

Abstract. Sclerosing extramedullary hematopoietic tumor (SEMHT) is a rare tumor that can occur in association with some chronic myeloproliferative neoplasms, particularly myelofibrosis. The morphology of SEMHT can mimic that of a wide variety of other lesions, both macroscopically and microscopically. SEMHT originating from the colon is extremely rare. The present study reports a case of SEMHT in the colon with involvement of the peri-intestinal lymph nodes. On the basis of the clinical symptoms and endoscopic results, a malignant tumor of colon was suspected. Pathological examination revealed the deposition of collagen and hematopoietic components in the fibrous mucus background. Immunohistochemical staining for CD61 confirmed the presence of atypical megakaryocytes, while immunohistochemical staining for myeloperoxidase and glycophorin A highlighted the existence of granulocyte and erythrocyte precursors, respectively. These findings combined with a clinical history of myelofibrosis led to the final diagnosis of SEMHT. The presence of atypical megakaryocytes with immature hematopoietic cell morphology and a good understanding of the clinical history of the patient are essential to prevent misdiagnosis. The present case emphasizes the necessity of reviewing previous hematological history and considering clinical findings together with the associated pathological results.

Correspondence to: Dr Wanxin Wu or Dr Zhibo Zuo, Department of Pathology, First Hospital of Jiaxing, 1882 Central South Road, Nanhu, Jiaxing, Zhejiang 314000, P.R. China
E-mail: wanxinwu@outlook.com
E-mail: zhibozuo@163.com

*Contributed equally

Key words: sclerosing extramedullary hematopoietic tumor, colon, myelofibrosis, megakaryocyte

Introduction

Sclerosing extramedullary hematopoietic tumor (SEMHT) is a rare lesion, previously known as fibrous hematopoietic tumor or myelosclerosis. Lesions of this type are associated with chronic myeloproliferative neoplasms, particularly chronic idiopathic myelofibrosis, in older adults (1). When chronic myeloproliferative neoplasms lead to insufficiency in the hematopoietic function of the bone marrow, hematopoietic tissues in locations other than the bone marrow develop abnormally to compensate. These deposits of extramedullary hematopoietic tissue have the propensity to form a tumor, known as an SEMHT (2). The clinical, radiological and morphological features of SEMHT may complicate its differentiation from lymphoma, carcinoma and sarcoma. In some cases, it is challenging to distinguish SEMHT from extramedullary hematopoiesis (EMH) (3). SEMHTs are characterized by the presentation of myelofibrosis-like components with atypical megakaryocytes and different proportions of granulocyte and erythrocyte precursors in a significantly sclerotic background, with thick collagen deposition (4). Although the pathogenesis of SEMHT has not yet been fully elucidated, it is known to involve the inappropriate production of cytokines by megakaryocytes, which stimulate the proliferation of fibroblasts and the production of extracellular matrix (2). SEMHT typically presents as a retroperitoneal mass (5), but may occur in other organs, although rarely. The present study describes a case of SEMHT originating in the colon that involved the peri-intestinal lymph nodes.

Case report

A 59-year-old female patient presented to the First Hospital of Jiaxing (Jiaxing, China) with abdominal pain in March 2022. The patient had a 1-month history of abdominal pain, diarrhea and mucinous bloody stools. Her medical history was pertinent for myelofibrosis 6 years ago, and she was maintained on 15 mg lucotinib twice daily. Abdominal contrast-enhanced computed tomography (CT) revealed cecal thickening with intestinal obstruction, and no contrast enhancement was observed (Fig. 1A and B). Colonoscopy revealed a large necrotic mass in the cecum, which blocked the intestinal cavity (Fig. 1C). Bone scintigraphy revealed a superscan appearance, with a high

ratio of tracer accumulation in the bone compared with soft tissue, which was consistent with diffuse lesions in the bone marrow hematopoietic system (Fig. 1D). The laboratory test results were as follows: Hemoglobin level, 145 g/l; erythrocyte count, $5.01x10^{12}$/l; white blood cell count, $44.17x10^{9}$/l; and platelet count, $147x10^{9}$/l (Table I). Due to the secondary infection caused by intestinal obstruction, the white blood cell count was increased. A bone marrow biopsy was not performed due to the previous failure to obtain bone marrow owing to dry tap bone marrow aspiration. Due to the huge tumor blocking the intestinal cavity, the patient subsequently underwent surgical resection of the colon.

On macro-examination, the cecal mass was found to measure 6x5x5 cm. The tumor extended from the mucosa to the serosa, with evident necrosis. Microscopically, extensive hemorrhage, necrosis and thrombosis were observed in the intestinal wall (Fig. 2). The serous layer of the colon exhibited obvious interstitial fibrous hyperplasia and myxoid degeneration. In the fibromyxoid background, scattered atypical megakaryocytes and a small number of erythrocytes and granulocyte precursors were observed. Atypical megakaryocytes were also noted in several peri-intestinal lymph nodes. Immunohistochemical staining for CD61 revealed the presence of atypical megakaryocytes (Fig. 3A). Myeloperoxidase (MPO) and glycophorin A immunohistochemical staining differentiated granulocyte and erythrocyte precursors, respectively (Fig. 3B and C), while CD117 staining was observed in a small number of cells (Fig. 3D). Immunohistochemical staining for cytokeratin, smooth muscle actin and desmin yielded negative results. Based on these findings and the history of myelofibrosis, the patient was diagnosed with SEMHT. After surgery, the patient continued to take 15 mg lucotinib twice daily for myelofibrosis treatment. Four months after the surgery, the patient developed abdominal pain and underwent abdominal CT examination, which indicated intestinal edema and ascites. Subsequently, enteral nutrition and antibiotic treatment were administered to the patient in the hospital. After half a month of treatment, the symptoms experienced by the patient were ameliorated.

IHC staining was performed on a BenchMark XT (Roche Diagnostics), an automatic IHC staining device. All procedures were performed as per the manufacturer's protocols. The endogenous peroxides and protein were blocked using the Endogenous Biotin Blocking kit (cat. no. ab64212; Abcam) at 37˚C for 4 min. The following primary antibodies were used: Anti-CD61 (cat. no. ab179473; 1:800 dilution), anti-MPO (cat. no. ab208670; 1:1,000 dilution), anti-glycophorin A (cat. no. ab129024; 1:2,500 dilution), anti-CD117 (cat. no. ab32363; 1:400 dilution), anti-CK (cat. no. ab215838; 1:100 dilution), anti-SMA (cat. no. ab5694; 1:100 dilution) and anti-desmin (cat. no. ab32362; 1:2,000 dilution) (all Abcam). Primary antibodies were added and incubated for 16 min at 37˚C. A light microscope was used for observation.

Table I. Blood analysis determined at admission.

Blood parameter	Value	Laboratory range
Hemoglobin level, g/l	145	115-150
Erythrocyte count, $x10^{12}$/l	5.01	3.80-5.10
White blood cell count, $x10^{9}$/l	44.17	3.50-9.50
Platelet count, $x10^{9}$/l	147	125-350

Discussion

SEMHT is a rare condition associated with chronic myeloproliferative neoplasms. This tumor is mainly detected in individuals in their 50s or 60s (6). SEMHT may occur at various sites, including the thyroid gland, lung, lymph nodes, gastrointestinal tract, kidney, skin and breast (7). The clinical symptoms depend on the location of the SEMHT and mainly include abdominal pain, headache, appearance of a skin mass and lacrimal gland swelling (2,8-10). At present, few cases of SEMHT have been reported, and the majority of SEMHT cases have a history of myelofibrosis. Few cases are associated with essential thrombocytosis, acute B-cell lymphoblastic leukemia or myelodysplastic syndrome, and the patients without myelofibrosis who develop SEMHT are young individuals (6,7). SEMHT presents with single or multiple tumor foci that vary in size and can be as large as 16 cm in diameter. In terms of gross pathology, SEMHT appears rubbery, pink, white or yellowish-brown with clear boundaries. SEMHT can be sometimes lobulated and has the ability to infiltrate the surrounding tissues (8).

Histopathologically, SEMHT is characterized by atypical megakaryocytes, erythrocytes and granulocyte precursors distributed in the sclerotic or fibromyxoid stroma (2). SEMHT can also include adipose tissue trapped within the tumor (8). Usually, the fibrous stroma is dominant; therefore, it is challenging to identify the hematopoietic components in conventional hematoxylin and eosin-stained sections. Due to the marked fibrotic background, the observed hematopoietic components may only be giant atypical megakaryocytes (11). In this context, megakaryocytes are scattered throughout the matrix and may appear alone or in clusters (12). Atypical megakaryocytes are characterized by hyperchromatic, multilobulated, giant, ink-blot-like nuclei with a slightly eosinophilic cytoplasm (8). In addition to the enlarged atypical megakaryocytes, loose aggregates of immature granulocyte precursors and scattered erythroid precursor cells are present, which are most apparent near to blood vessels (9).

It may be a challenging to recognize the presence of hematopoietic cells in SEMHT only through morphological examination as these cells lack specificity. Immunohistochemistry can help to highlight the hematopoietic components of SEMHT and guide diagnosis when similar malignant lesions are suspected. Atypical megakaryocytes stain positively for CD61, CD41, CD31 and factor VIII. Granulocytes stain positively for MPO, and erythrocyte precursors stain positively for glycoprotein A and hemoglobin (8). CD163 staining reveals the accompanying histiocytes rather than the expanded megakaryocyte forms. However, the immunohistochemical staining of vimentin in SEMHT should be avoided because it highlights a large number of accompanying fibroblasts that have been shown to be polyclonal (9).

The genetic analysis of patients with SEMHT has revealed the presence of the JAK2 V617F point mutation (6). As cytoplasmic tyrosine kinases, proteins of the JAK family participate

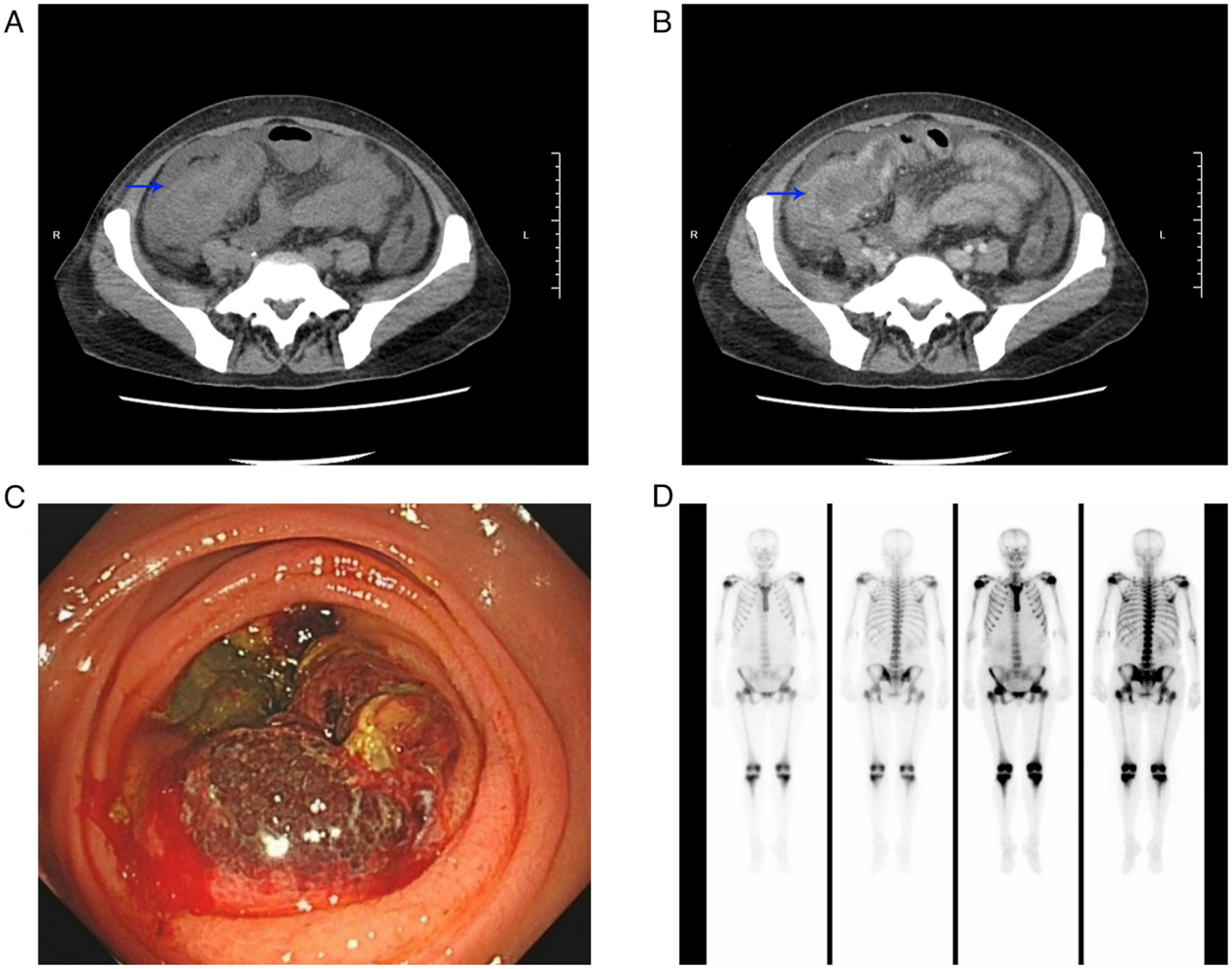

Figure 1. Preoperative examination of the patient with a sclerosing extramedullary hematopoietic tumor. (A) Thickened cecal wall and turbid surrounding mesentery shown by abdominal computed tomography (blue arrow indicates the tumor). (B) No abnormal enhancement was observed after enhancement (blue arrow indicates the tumor). (C) A huge necrotic mass was visible in the cecum, blocking the intestinal cavity during colonoscopic examination. (D) The nuclear medical examination comprising a whole-body bone scan revealed a superscan appearance, in which the contrast in radioisotope uptake between axial bone and soft tissue was markedly enhanced.

in cytokine receptor superfamily signaling. The activation of JAK signaling and downstream gene transcription is a cytokine-mediated signal transduction pathway. JAK is essential for normal hematopoiesis, and its activation mainly involves the response of JAK2 to type 1 cytokine ligands, including thrombopoietin, granulocyte-macrophage stimulating factor and erythropoietin (4). V617F is the most common mutation in the JAK2 gene in chronic myeloproliferative neoplasms, with the exception of chronic myeloid leukemia, and is a sign of clonal proliferation (4). A significant difference in complications between JAK2 V617F negative and positive cases has been reported in patients with chronic myeloproliferative neoplasms. Specifically, the incidence of fibrosis, bleeding, thrombosis and associated complications is significantly higher in patients with JAK2 point mutations that in those with wild-type JAK2 (4). Chromosomal aberrations can lead to disease progression to the secondary myelofibrosis or accelerated phase, and leukemic transformation in some patients with chronic myeloproliferative neoplasms. Aberrations of chromosomes 1q and 9p have been found to be positively associated with disease progression to the accelerated phase (13). In addition, the acquisition of one or more aberrations involving chromosome 5, 7 or 17p has been indicated to be associated specifically with progression to acute myeloid leukemia, and to significantly affect overall survival (14). Unfortunately, data on the chromosome mutation status of the present patient are not available.

As previously mentioned, SEMHT rarely occurs in the colon. A previous study reported considerable thickening of the serosa, which almost completely surrounded the small and large bowels and was accompanied by diffuse mesenteric sclerotic fibrosis and scattered large, atypical megakaryocytes (15). However, in the present case, the SEMHT was mainly located in the serosal layer of the intestinal tube. Another distinctive feature of the present case is that extensive bleeding, necrosis and thrombosis of the bowel were additionally observed. These pathological changes may explain the mucinous bloody stools with which the patient presented. In addition, atypical megakaryocytes were found in the peri-intestinal lymph nodes, suggesting that the lymph nodes were also involved. This phenomenon is consistent with a previous study, which observed atypical megakaryocytes in dilated lymph node sinuses (16).

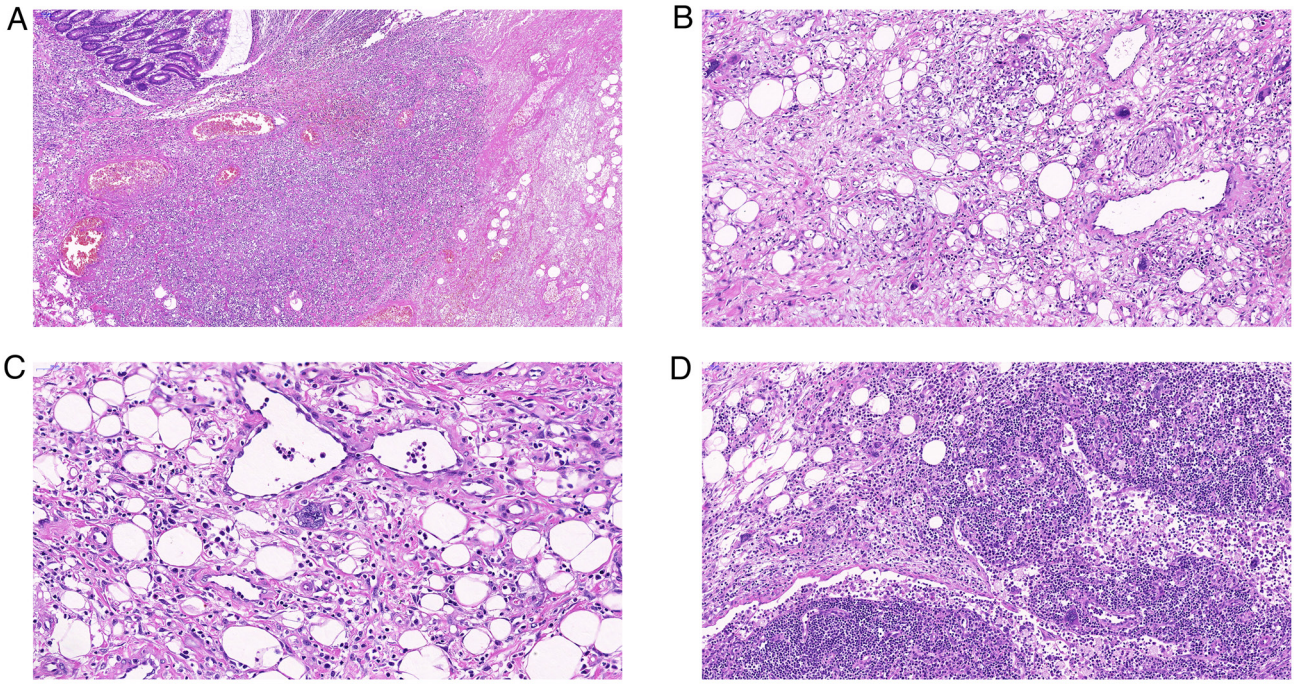

Figure 2. Microscopic images of hematoxylin and eosin staining. (A) Extensive hemorrhage, necrosis and thrombosis are visible in the intestinal wall (magnification, x100). (B) Scattered atypical megakaryocytes can be observed in the fibromyxoid matrix (magnification, x200). (C) The nuclei of atypical megakaryocytes are huge and multilobulated. Chromatin is abnormally concentrated within these cells. The megakaryocytes are surrounded by scattered granulocytes and erythrocyte precursors (magnification, x400). (D) Atypical megakaryocytes are discernable in the lymph sinuses of the peri-intestinal lymph nodes (magnification, x200).

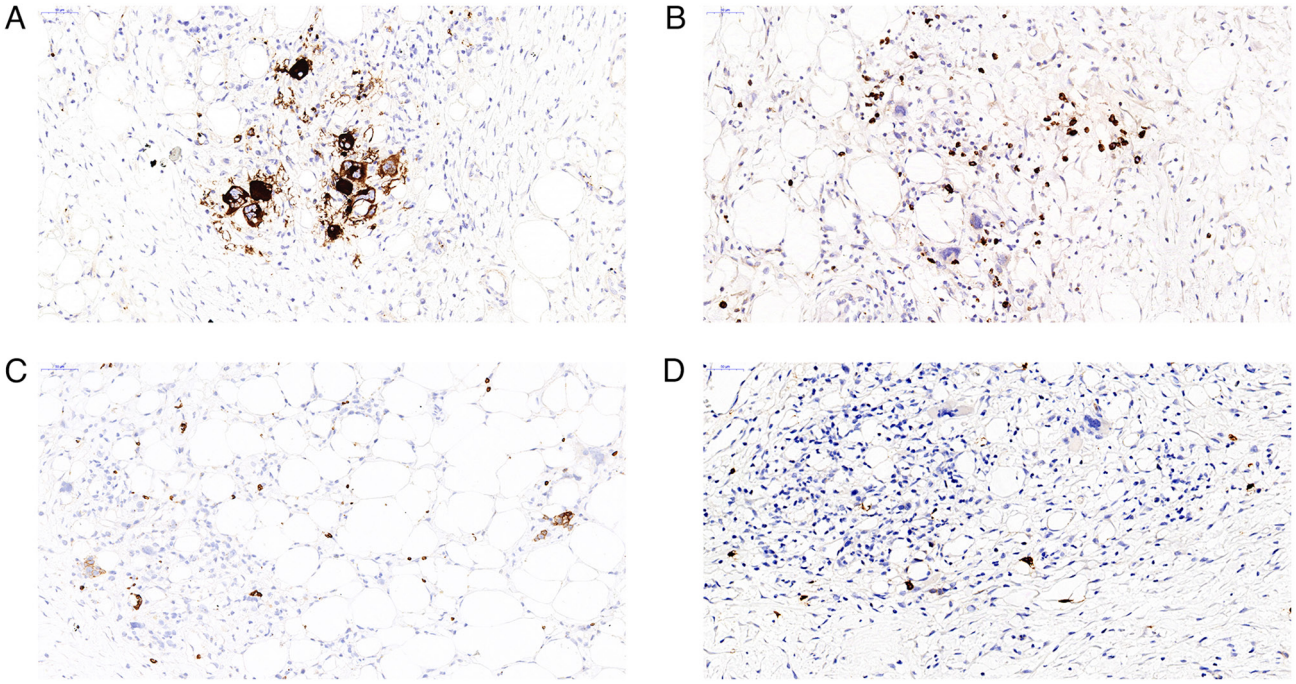

Figure 3. Microscopic images of immunohistochemical staining. (A) Megakaryocytes show positive staining for CD61, (B) granulocyte precursors show positive staining for myeloperoxidase, (C) erythroid precursors show positive staining for glycophorin A and (D) scattered cells are positively stained for CD117 (all magnification, x400).

The development of extramedullary hematopoietic tissue is known as EMH and is usually accompanied by chronic myeloproliferative neoplasms. When the hematopoietic function of the bone marrow is insufficient, EMH acts as a compensatory response (2). In this context, since SEMHT and EMH have similar clinical features, clinicians may find it challenging to differentiate between these two conditions (3). EMH occurs not only in chronic myeloproliferative

neoplasms, but also in other diseases, including hereditary spherocytosis, hemoglobinopathies, thalassemia and sickle cell anemia (7). EMH commonly affects the spleen, liver and lymph nodes, where it is accompanied by hepatosplenomegaly or lymphadenopathy (8). Moreover, EMH may produce one or more normal blood components in parts of the body other than in the bone marrow, similar to SEMHT. The difference is that SEMHT is an extramedullary dissemination of the neoplastic bone marrow proliferation. These lesions resemble their tumor counterparts in the bone marrow rather than the normal myeloid tissue that undergoes trilineage hematopoiesis and maturation (9). The presence of atypical megakaryocytes in SEMHT is a diagnostic hallmark for distinguishing between the two entities, as is not found in EMH (7). Additionally, SEMHT forms a hard gray mass and exhibits prominent fibrous stroma, similar to myelofibrosis (17). Furthermore, compared with EMH, SEMHT usually has less cellular, more atypical megakaryocytes, and a more mucoid matrix (2,7).

The specific details of the pathogenesis of SEMHT are currently unclear. However, research has shown that myelofibrosis can lead to an increase in the number of circulating stem cells in the peripheral blood. The adhesion of integrin molecules may lead to the deposition of these stem cells in peripheral organs, which can lead to the emergence of ectopic hematopoietic foci (12). Previous studies have shown that an inappropriate cytokine response is associated with the myelofibrosis observed in chronic myeloproliferative neoplasms (4,11). Clonal populations of megakaryocytes release calmodulin, epidermal growth factor, transforming growth factor and platelet-derived growth factor, which stimulate the proliferation of nonclonal fibroblasts and promote the production of extracellular matrix, and the occurrence of myelofibrosis may be caused by this inappropriate cytokine expression (11). The mechanism of SEMHT formation may be similar that of myelofibrosis, and involve the induction of fibroblast proliferation and matrix production by megakaryocytes. The fibrous matrix produced by the fibroblasts causes collagen deposition, which can lead to sclerotic changes in tumors (1,18). In terms of the hypothetical mechanism, the progression of SEMHT may resemble that of the transfer process (primary tumor to metastasis). The cytogenetic or clonal analysis of megakaryocytes may be used to verify this mechanism (18), as there is evidence to suggest that the extramedullary proliferation of hematopoietic cells in primary myelofibrosis indicates the spread of tumor clones rather than compensatory EMH (9). At present, to the best of our knowledge, there is no literature on the association between drugs and SEMHT. In some cases, patients have been treated with ruxolitinib for myelofibrosis and SEMHT subsequently occurred during the treatment (15,16). The occurrence of extramedullary complications may reflect differences in drug distribution, cell trafficking or metabolism in extramedullary regions. With prolonged survival times, the increased duration of aggressive disease and the associated hypercytokinemia may also lead to the development and progression of these rare end-stage complications (15).

The prognosis of patients with SEMHT is variable and usually depends on the underlying disease. In some cases, the survival period is short, which may be associated with advanced disease; however, the disease can also remain stable for a long time without aggressive local therapy (8). Notably, chronic myeloproliferative neoplasms present with extramedullary neoplasms, which serve as a marker of the acute phase. SEMHT itself may be regarded as an advanced manifestation of myelofibrosis. Adverse prognostic factors for SEMHT include skin involvement, thrombocytopenia, leukocytosis, anemia and old age. An abnormal karyotype in the nucleus, which is associated with acute transformation, has been recognized as an independent risk factor for poor prognosis (8). SEMHT may respond to hydroxyurea and low-dose radiation therapy; however, research on the topic has found that the effectiveness of the response is short-lived (17).

In conclusion, the present study describes a novel case of SEMHT. The identification of these rare lesions is important when diagnosing tumors with anaplastic morphology in order to guide appropriate treatment. In addition, it is important to have a complete medical history for the patient, because when the medical history is insufficient, the pathological and radiological data may be challenging to evaluate. The present case thus highlights the requirement for physicians to consider SEMHT as a differential diagnosis for gastrointestinal masses, particularly when a history of previous hematological disease is present.

Acknowledgements

Not applicable.

Funding

The study was financially supported by a grant from the Jiaxing Municipal Science and Technology Project (grant no. 2021AD30160).

Availability of data and materials

All data used and/or analyzed during this study are included in this published article.

Authors' contributions

ZZ and QZ obtained and analyzed the patient's information and wrote the manuscript. XL and LZ collected and analyzed the patient data. JW and ZG contributed to data extraction and quality assessment. SH and HL analyzed and interpreted the imaging findings. ZZ and WW designed the study and reviewed the manuscript. All authors contributed to the manuscript and all authors read and approved the final manuscript. ZZ and QZ confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The study was approved by the Medical Ethics Committee of the First Hospital of Jiaxing (Jiaxing, China; approval no. 2022-LY-243).

Patient consent for publication

The patient provided written informed consent for the publication of this case report and all the accompanying images.

Authors' information

Dr Zhibo Zuo; ORCID: 0000-0002-3222-4530 (https://orcid.org/0000-0002-3222-4530).

Competing interests

The authors declare that they have no competing interests.

References

1. Deniz K, Kahriman G, Koçyiğit İ, Ökten T and Ünal A: Sclerosing extramedullary hematopoietic tumor. Turk J Haematol 35: 209-210, 2018.
2. Woodward Z, Robertson T, Sim S and Tollesson G: Intracranial sclerosing extramedullary haematopoietic tumour mimicking meningioma in a patient with myelofibrosis: Case report. J Clin Neurosci 88: 268-270, 2021.
3. Karaarslan S, Nese N, Oncel G, Ozsan N, Akalin T, Kaplan H, Buyukkececi F and Hekimgil M: Sclerosing extramedullary hematopoietic tumor mimicking intra-abdominal sarcoma. J Pathol Transl Med 49: 335-338, 2015.
4. Gualco G, Ojopi EB, Chioato L, Cordeiro DL, Negretti F and Bacchi CE: Postsplenectomy sclerosing extramedullary hematopoietic tumor with unexpected good clinical evolution: Morphologic, immunohistochemical, and molecular analysis of one case and review of the literature. Appl Immunohistochem Mol Morphol 18: 291-295, 2010.
5. Gu MJ: Sclerosing extramedullary hematopoietic tumor presenting as an inguinal mass in a patient with primary myelofibrosis: A diagnostic pitfall. Int J Clin Exp Pathol 8: 3381-3383, 2015.
6. Sezgin GC, Deniz K, Karahan Öİ and Gürsoy Ş: Hepatobiliary and pancreatic: Sclerosing extramedullary hematopoietic tumor involving hepatic hilum. J Gastroenterol Hepatol 34: 817, 2019.
7. Wang D, Castro E, Rao A and McPhaul CM: Sclerosing extramedullary hematopoietic tumor: A case report. J Investig Med High Impact Case Rep: Sep 10, 2020 (Epub ahead of print).
8. Dema S, Lazar F, Barna R, Dobrescu A, Dema ALC, Popa O, Ionita I and Taban SM: Sclerosing extramedullary hematopoietic tumor (SEHT) mimicking a malignant bile duct tumor-case report and literature review. Medicina (Kaunas) 57: 824, 2021.
9. LeBlanc RE, Lester L, Kwong B and Rieger KE: JAK2-positive cutaneous myelofibrosis presenting as sclerosing extramedullary hematopoietic tumors on the scalp: Case presentation and review of the literature. J Cutan Pathol 42: 858-862, 2015.
10. Ghazi NG, Bowman AM and Shields MD: Bilateral lacrimal system involvement by sclerosing extramedullary hematopoietic tumor. Ophthalmic Plast Reconstr Surg 22: 296-298, 2006.
11. Sukov WR, Remstein ED, Nascimento AG, Sethi S and Lewin M: Sclerosing extramedullary hematopoietic tumor: Emphasis on diagnosis by renal biopsy. Ann Diagn Pathol 13: 127-131, 2009.
12. Yuen HK, Mahesh L, Tse RK, Yau KC, Chan N and Lam DS: Orbital sclerosing extramedullary hematopoietic tumor. Arch Ophthalmol 123: 689-691, 2005.
13. Klampfl T, Harutyunyan A, Berg T, Gisslinger B, Schalling M, Bagienski K, Olcaydu D, Passamonti F, Rumi E, Pietra D, *et al*: Genome integrity of myeloproliferative neoplasms in chronic phase and during disease progression. Blood 118: 167-176, 2011.
14. Rumi E, Harutyunyan A, Elena C, Pietra D, Klampfl T, Bagienski K, Berg T, Casetti I, Pascutto C, Passamonti F, *et al*: Identification of genomic aberrations associated with disease transformation by means of high-resolution SNP array analysis in patients with myeloproliferative neoplasm. Am J Hematol 86: 974-979, 2011.
15. Babushok DV, Nelson EJ, Morrissette JJD, Joshi S, Palmer MB, Frank D, Cambor CL and Hexner EO: Myelofibrosis patients can develop extramedullary complications including renal amyloidosis and sclerosing hematopoietic tumor while otherwise meeting traditional measures of Ruxolitinib response. Leuk Lymphoma 60: 852-855, 2019.
16. Barouqa M and McPhail ED: Sclerosing extramedullary hematopoietic tumor in chronic myeloproliferative neoplasms. Blood 139: 3345, 2022.
17. Kwon Y, Yu E, Huh J, Lee SK and Ro JY: Sclerosing extramedullary hematopoietic tumor involving lesser omentum and ligamentumteres in liver explant. Ann Diagn Pathol 8: 227-232, 2004.
18. Yang X, Bhuiya T and Esposito M: Sclerosing extramedullary hematopoietic tumor. Ann Diagn Pathol 6: 183-187, 2002.