A rare splenic and pancreatic inflammatory myofibroblastic tumour with left-sided portal hypertension and gastric varices: A case report

ELENI ZOGRAFOS[1], ALKISTIS PAPATHEODORIDI[1], MARIA KAPARELOU[1], IOANNA TATOULI[1], ANDREAS MPOZIKAS[1], MARGARITA PAPATHEODORIDI[2], ANGELIKI ANDRIKOPOULOU[1], CONSTANTINOS G. ZOGRAFOS[3], GEORGIA KAFIRI[4], EFSTATHIOS MANIOS[1], MELETIOS-ATHANASIOS DIMOPOULOS[1] and FLORA ZAGOURI[1]

[1]Department of Clinical Therapeutics, Alexandra General Hospital, Medical School of the National and Kapodistrian University of Athens, 11528 Athens, Greece; [2]Academic Department of Gastroenterology, Medical School of National and Kapodistrian University of Athens, Laiko General Hospital, 11527 Athens, Greece; [3]Second Department of Surgery, 'Aretaieio' Hospital, 11528 Athens, Greece; [4]Department of Pathology, 'Hippocrateio' General Hospital of Athens, 11527 Athens, Greece

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Abstract. Left-sided portal hypertension or segmental portal hypertension is a rare cause of upper gastrointestinal bleeding. The present study reports a case of isolated gastric variceal haemorrhage and hypersplenism, due to left-sided portal hypertension induced by inflammatory myofibroblastic tumour (IMT)-associated splenic vein compression. IMT is an rare mesenchymal neoplasm of intermediate malignant potential that can develop in any location, frequently remaining entirely asymptomatic until it reaches a size that leads to complications. To the best of our knowledge, this is the first case reported of an IMT involving both the spleen and the pancreas. In this patient, splenectomy and partial pancreatectomy were both diagnostic and curative for IMT, and no adjuvant therapy was followed. This case report, along with a short review of the current knowledge on IMT features, contributes towards the understanding and diagnosis of this rare entity with diverse clinical presentations.

Introduction

Inflammatory myofibroblastic tumours (IMT) are distinctive intermediate-grade soft-tissue neoplasms belonging to the group of inflammatory spindle cell lesions (1). The worldwide incidence of these tumours is low at 0.04-0.7% (2) and clinical data has shown that even though the local recurrence rate after surgical excision is 25%, they fortunately rarely metastasize (3). IMTs can occur in any location, predominantly in the mesentery, retroperitoneum, and pelvis, frequently remaining entirely asymptomatic until they attain a size that leads to complications (4). IMTs involving the spleen, or the pancreas can exert pressure on the surrounding anatomic forms; splenic vein compression is a dire manifestation since it can lead to a localized type of portal hypertension known as 'left-sided.' In this condition, collateral venous blood flow develops, resulting in localized dilation of the submucosal venous reticulum of the gastric fundus, which connects the short and posterior gastric veins to the coronary veins, potentially leading to the development of gastric varices, splenomegaly, and hypersplenism (5). These varices may lead to life-threatening upper gastrointestinal bleeding presenting with hematemesis and/or melena. Although IMTs have been described in various sites, including the spleen (6-8) and the pancreas (9,10), a synchronous occurrence in both organs is exceptionally rare. Herein, we report the first case, to our knowledge, of a patient with upper GI bleeding from isolated gastric varices (IGV) and hypersplenism due to left-sided portal hypertension caused by an IMT involving both the spleen and the pancreas.

Correspondence to: Dr Eleni Zografos, Department of Clinical Therapeutics, Alexandra General Hospital, Medical School of the National and Kapodistrian University of Athens, 80 Vasilissis Sofias Avenue, 11528 Athens, Greece
E-mail: el_zogra@hotmail.com

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Case report

A 33-year-old male of urban origin, presented to the emergency department following multiple episodes of melena. The patient described abdominal cramping and urgency of defecation, followed by the passage of black tarry stool. He denied any associated concerning symptoms in the months prior to the current presentation, including fatigue, weight loss, abdominal or joint pain.

This patient reports a previous admission in a different hospital (within the past six months) for gastrointestinal

bleeding and associated haemoglobin drop requiring blood transfusions. During this prior hospitalization he underwent multiple upper endoscopies that revealed isolated gastric varices (IGV) type 1 located in the fundus that were actively bleeding. Variceal bleeding was treated with endoscopic obturation using tissue adhesive. The patient's melena ceased after the endoscopic intervention and his haemoglobin remained within the normal range. He was discharged with a referral to a specialized gastroenterology centre if symptoms recurred. During the same admission, an abdominal ultrasound examination revealed a 16.5 cm long splenomegaly and a large intrasplenic cyst (6 cm). Based on previous abdominal imaging, this was a known asymptomatic splenic pseudocyst secondary to a car accident injury five years ago. Notably, the patient was a non-smoker and reported alcohol consumption of less than 15 units per week. He was not undergoing any pharmacological treatment and had no significant medical history, including systemic diseases or a relevant family history.

On initial presentation at our hospital, the patient was hemodynamically stable. The physical examination found splenomegaly, with a spleen palpable 3 cm below the left costal margin. His abdomen was soft and non-tender, but the digital rectal exam confirmed black stool. Laboratory data on admission revealed pancytopenia, with white blood cell count 1.8 k/mcl, haemoglobin 7.5 g/dl, mean corpuscular volume (MCV) 69 fl, and platelets 105 k/mcl. Prothrombin time and biochemistry profile, including liver function tests, as well as bilirubin and albumin levels showed no abnormalities. He was admitted to our clinic for monitoring and further investigation.

After the patient was stabilized with intravenous fluid resuscitation and blood transfusion, an immediate endoscopy was performed on this patient, who was rushed to our hospital for upper gastrointestinal bleeding with normal liver function and splenomegaly. Endoscopy revealed the presence of varices localized in the gastric fundus. At that time, no active bleeding was found and thus no intervention was required, with bleeding resolving on its own. Transabdominal ultrasonography (US) with Doppler excluded the presence of systemic portal hypertension and showed no indications of liver cirrhosis. Abdominal computed tomography (CT) confirmed the known splenomegaly (cephalocaudal diameter 16.5 cm) and the 6 cm intrasplenic cyst, which remained unchanged in comparison to previous imaging. Interestingly, a subcapsular hypodense splenic mass of 7x2 cm was described, extending from the portal of the spleen to its inferior pole, with a peripheral localization, showing no contrast enhancement (Fig. 1). Of note, the mass compressed externally the splenic vein, but neither portal, nor splenic vein thrombosis were found. The above-mentioned radiological description did not make it possible to evoke a conclusive diagnosis about the nature of the mass. Therefore, a Positron Emission Tomography (PET) scan was performed, in order to better differentiate this splenic mass as benign or malignant. According to the PET/CT the lesion of interest in the lower medial margin of the spleen displayed moderate 18F-FDG uptake (SUVmax=4.3). These findings were inconclusive for diagnosis.

Concurrently, our management focused on identifying other causative conditions of cytopenias. Characteristically, low ferritin levels were identified due to recent blood loss, whereas no B12 or folic acid deficiency was detected. Iron was repleted with intravenous ferric carboxymaltose. The peripheral blood smear revealed no morphological abnormalities. Bone marrow biopsy and myelogram were performed to investigate the emerging pancytopenia, revealing a cellular bone marrow without evidence of infiltration/replacement or failure. In order to eliminate autoimmune destruction, screening tests for autoantibodies, including antinuclear Ab, anti-Ro/SS-A Ab, anti-La/SS-B Ab, anti-cardiolipin Ab, myeloperoxidase-anti-neutrophil-cytoplasmic Ab (MPO-ANCA) and proteiase-3-ANCA, were carried out, which gave negative results. We also excluded preceding infections such as those of brucellosis, tuberculosis, Epstein-Barr virus, cytomegalovirus, parvovirus, human immunodeficiency virus, varicella zoster virus, hepatitis B and C viruses. Next, chronic myeloproliferative disorders were excluded, with negative BCR-ABL, JAK2 V617F, CARL and MPL W515 mutations. Finally, thrombophilia screening test results, including lupus anticoagulant, aPl, aCL and anti-β2-GPI IgM/IgG isotypes, Protein C and S, along with Factor V Leiden mutation and prothrombin G20210A mutation, were all negative. Since all the aforementioned conditions were ruled out, the diagnosis of pancytopenia attributed to hypersplenism due to left-sided portal hypertension, possibly as a result of the mass compressing and causing partial occlusion of the splenic vein, was taken into consideration.

Our patient was stable until his condition deteriorated with sudden onset haematochezia and subsequent development of hypovolemic shock. He received three units of packed red blood cells (pRBC), tranexamic acid, and was started on intravenous infusion of omeprazole and crystalloids. An emergency upper GI endoscopy was performed, but due to the large amount of bleeding and poor endoscopic field of vision, haemostasis was not achieved. The patient was considered too unstable to proceed with additional imaging evaluation. Consequently, he underwent an urgent laparotomy, where a 6cm mass was found on the inferior pole of the spleen, infiltrating and exceeding the splenic capsule. Unexpectedly, a similar 7.5 cm scleroelastic solid mass was discovered, originating from the pancreatic tail. Given the involvement of both the spleen and pancreas, a splenectomy and distal pancreatectomy were performed. The splenic artery and vein were carefully isolated, ligated, and divided to minimize blood loss. The spleen was then mobilized by dissecting the short gastric vessels and separating adhesions from the surrounding structures. The organ, along with the infiltrating mass, was excised en bloc. For the pancreatic resection, the tail of the pancreas was mobilized by incising the peritoneal attachments along the splenic hilum. The lesion was sharply dissected, and a partial distal pancreatectomy was performed, ensuring a negative resection margin. A closed-suction drain was placed near the pancreatic stump to monitor postoperative fluid collection. Both resected specimens were immediately sent for histopathological examination. The abdominal cavity was irrigated with warm saline, and the incision was closed in layers. The procedure was completed without intraoperative complications.

The diagnosis was consistent with inflammatory myofibroblastic tumour, which is a rare mesenchymal tumour of intermediate malignant potential. The microscopic examination revealed the proliferation of spindle-shaped

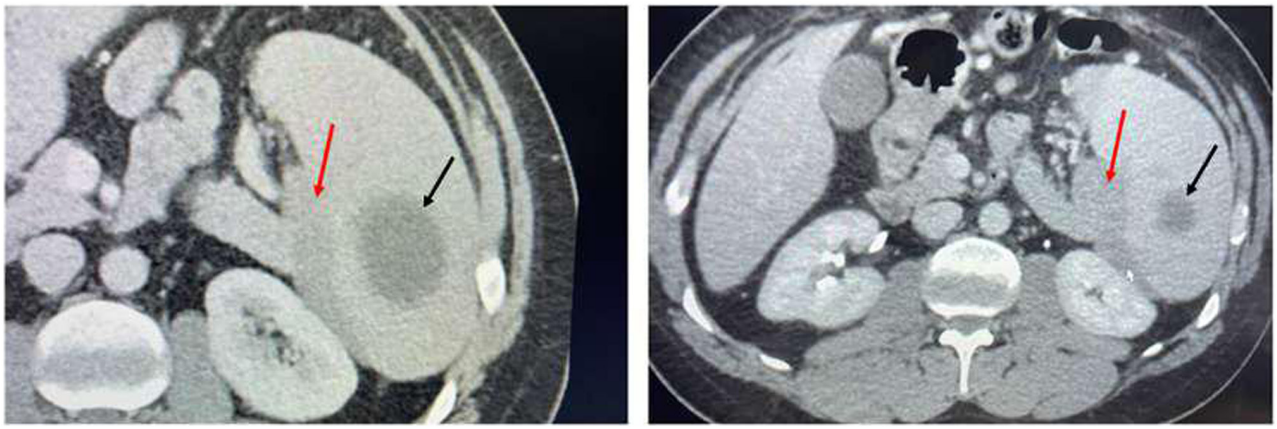

Figure 1. Axial contrast-enhanced abdominal computed tomography imaging findings, shows an intrasplenic cyst (black arrow) and a large low-attenuation mass in the enlarged spleen (red arrow), extending from the portal of the spleen to its inferior pole and involving the splenic vein.

myofibroblasts, showing swirling and fusiform growth patterns and inflammatory lymphocytic infiltration (Fig. 2). The immunohistochemical analysis was performed by manual immunostaining procedures as per Ventana's protocol. According to the histologic description, neither overt cytologic atypia nor mitotic activity were observed, with a low Ki67 marker for proliferation of <1%. Immunohistological staining was positive for vimentin (1:300 dilution with PBS; Dako, Carpinteria, CA, USA) and smooth muscle actin (SMA) (1:150 dilution with PBS; Cell Marque Corp, Rocklin, CA, USA), displayed weaker expression of Desmin (1:100 dilution with PBS; Zeta Corp., Sierra Madre, CA, USA) and CD34 (1/100 dilution with PBS; Deer Park, IL, USA), whereas stains were negative for S100, AE1/3, CK8/18, CD99, ALK and C-KIT. Complete resection with R0 margins was achieved.

Over the following days, the patient did not experience episodes of melena, his haemoglobin remained stable, and stool colour returned to normal. Notably, a gastroscopy was performed two months post-operatively that confirmed the resolution of the gastric varices, and follow-up blood tests showed that pancytopenia had also resolved. The patient was assessed by medical oncology; close follow-up was recommended, and no adjuvant therapy was suggested since complete surgical resection was achieved. Written informed consent for publication was obtained from the patient, ensuring ethical compliance and patient acknowledgment of case reporting.

Discussion

IMTs are tumours of myofibroblast origin which, despite the presence of an inflammatory immunohistochemical background and an apparently benign morphological pattern, have shown malignant potential (11). IMTs are exceptionally rare, affecting only 150-200 people annually in the United States (12). They have been described in patients of all ages, although occurrence is more frequent in children and young adults (13). Concerning the site and clinical presentation, IMTs can be found in a variety of body sites and organs, including the lung, mediastinum, head and neck, liver, retroperitoneum, and abdominopelvic region, causing a wide array of manifestations (1,4,14). They are known for their resistance to standard chemotherapy and radiation. As a result, surgical removal, when possible, remains the primary treatment approach.

Our patient presented to the emergency department with ongoing melena; there have been other cases where patients harbouring IMTs presented with upper gastrointestinal bleeding, but their tumours were located in different anatomical locations, such as the oesophagus (15), the stomach (16), the duodenum (17), or even the liver via the formation of oesophageal varices (18). There have also been IMTs in adults originating in the pancreas, the majority of them in the head of the organ, causing obstructive jaundice (19,20), or even stenosis of the descending duodenum (21). Occurrence in the pancreatic tail, as observed in our case, is rather unusual, as shown in a recent review reporting a total of 26 adult cases of pancreatic IMT in the literature (22). In this series, none of the patients presented had a synchronous splenic tumour, making our case the first one. Usually, splenic IMTs in adults are incidental findings (23-25), although they may present with pain in the left upper abdomen (6,7,26,27), left-sided abdominal distension (28), weight loss, malaise, and fever (7,27). Another finding is splenomegaly, and some patients can present with anaemia and signs of hypersplenism (29), as witnessed in our patient.

Particularly in our case, the tumour originating from the pancreas and the spleen apparently obstructed the splenic vein, leading to left gastric vein dilation and localized splenoportal hypertension, also known as left-sided portal hypertension. This occlusion causes the venous drainage of the spleen to occur via low-pressure collaterals that include the short and posterior gastric veins to the coronary veins, and the gastroepiploic veins to the superior mesenteric vein (5). This leads to the formation of isolated gastric varices (IGV) located in the fundus of the stomach, commonly termed as type 1 (IGV1) (30). IGVs type 1 are usually attributed to splenic or pancreatic disease that blocks the splenic venous flow either by thrombus formation or by neighbouring mass effect, with splenomegaly and gastrointestinal bleeding being two common clinical features (31). In our case, the external compression of the splenic vein by the inflammatory myofibroblastic tutor demonstrates how even a partial splenic vein occlusion can alter venous drainage patterns, despite normal

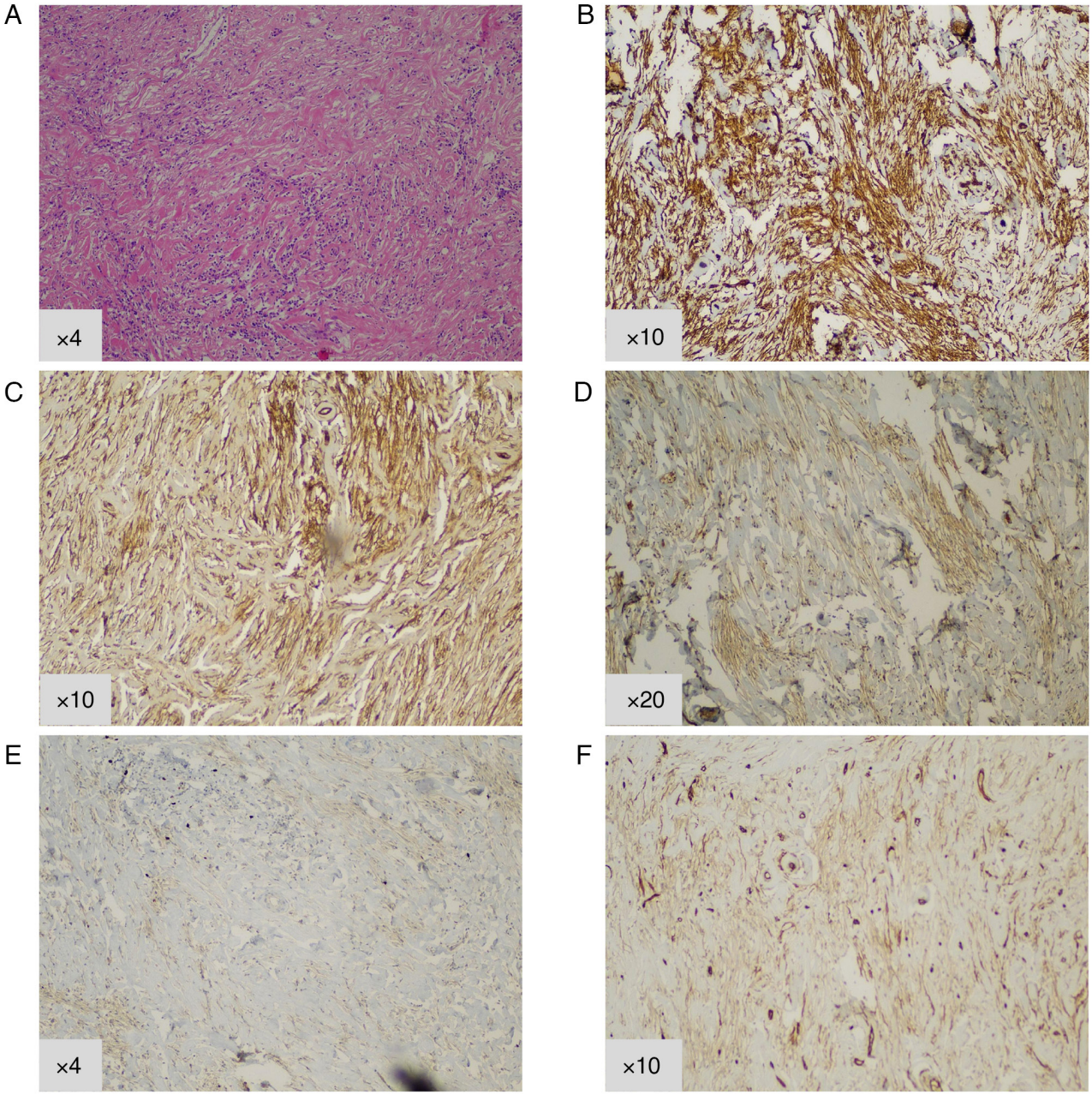

Figure 2. Immunohistological images of the inflammatory myofibroblastic tumour for (A) haematoxylin and eosin (magnification, x4), showing positive staining for (B) vimentin (magnification, x10) and (C) smooth muscle actin (magnification, x10). Immunohistochemical analysis also displayed weaker expression of (D) desmin (magnification, x20) and (E) CD34 (magnification, x4), as well as (F) low Ki67 expression of <1% (magnification, x10), which is a widely used marker for cell proliferation.

Doppler ultrasound findings. This obstruction can contribute to variceal formation in the short gastric and left gastroepiploic veins, with anatomical variations in the portal system and collateral vessel branching potentially influencing this diversity. The precise cause of our patient's splenomegaly remains unclear, but it may stem from increased congestion in the splenic veins and heightened arterial inflow through the splenic arteries (31). The precise cause of splenomegaly remains unclear, but it might be associated with heightened congestion in the splenic veins and increased blood flow and pressure through the splenic arteries (31). Although splenectomy is the preferred approach for managing cases with variceal bleeding complications, there is a lack of agreement in the literature regarding the treatment of asymptomatic patients.

Due to the tumour-related complications, complete surgical resection is also the recommended treatment for localized IMTs, since it ensures a favourable prognosis for most patients (3). Diagnostic splenic biopsies are not routinely recommended due to potentially high risk of haemorrhage and poor specificity (32). Therefore, the final diagnosis of this intricate entity characterized by myofibroblastic differentiation is usually based on pathologic findings obtained after surgery, due to its nonspecific symptoms and imaging findings. Characteristically, radiological tests, including ultrasound and CT imaging,

are not considered pathognomonic for IMTs, but can help narrow down the differential diagnosis (33). Even PET/CT findings cannot provide a definitive diagnosis, besides indicating the biological behaviour of the tumour cells or detecting distant metastases. In fact, IMTs have shown high variability of FDG uptake in PET-CTs, with the SUVmax ranging from 3.3 to 20.8, depending on tumour composition and the level of inflammatory activity (33). In our patient, low Ki67 expression of <1% and lack of mitotic activity could correlate with the failure of the PET-CT to detect the pancreatic mass and the low FDG-uptake of the splenic tumour, possibly suggesting a benign and non-inflammatory tendency.

The immunohistochemical profile of the present case revealed the presence of a myofibroblastic cell type, scattered among inflammatory cells, mostly lymphocytes. Our patient's tumour exhibited positive expression of SMA, desmin and cytokeratin after staining, as do the majority of IMT cases (21,34). Concerning the molecular changes in IMT, anaplastic lymphoma kinase (ALK) gene rearrangements leading to uncontrolled cell proliferation via constitutive tyrosine kinase activation are extremely common (4,34,35). Immunohistochemical ALK positivity reliably correlates with ALK rearrangement, being present in 50 to 60% of IMT cases (36). The *ALK* gene fuses with various partner genes, such as *TPM3, TPM4, CLTC*, and others, through chromosomal translocations, resulting in the formation of fusion proteins (1). These ALK fusion proteins possess constitutive kinase activity, driving tumorigenesis by activating downstream signalling pathways that promote cell proliferation and survival (1). However, in patients over the age of 25, ALK positivity is less frequent (26). This was the case with our 33-year-old patient, in whom the tumour was immunohistochemically negative for ALK expression. The absence of this oncogenic driver alteration could be a possible indication of the low potential for malignant transformation (4). Still, it is difficult to extract safe conclusions since a clear connection between the histological characteristics of IMT and its clinical behaviour has not been established (3). Notably, molecular cytogenetic analysis or next generation sequencing was not performed in our patient's tumour sample to definitively exclude ALK gene rearrangements in the inflammatory myofibroblastic tumour cells (1). Identification of distinct molecular changes is crucial in cases of recurrent, metastatic, or unresectable IMT, as revisiting molecular testing upon disease progression can help determine eligibility for targeted therapies, which may influence treatment decisions and prognosis for patients with ALK mutated IMTs. Specifically, tyrosine kinase inhibitors that disrupt mutant signalling pathways, such as crizotinib, have demonstrated efficacy in locally advanced or metastatic ALK-positive IMTs, exhibiting high overall response rates in case reports and Phase 1b/2 studies (37-39). Based on data from two multicentre, single-arm, open-label studies-including 14 paediatric cases from clinical trial NCT00939770 (40) and seven adult cases from trial NCT01121588 (38)-crizotinib was approved in July 2022 for the treatment of adult and paediatric patients with unresectable, recurrent, or refractory ALK-positive IMT. Overall, long-term follow-up is essential due to the uncertain and unpredictable course of some cases harbouring this rare soft-tissue tumour.

In conclusion, mesenchymal neoplasms represent a diagnostic challenge with diverse clinical presentations. The current case was a rare incidence of IGV1 bleeding and hypersplenism, induced by IMT-associated splenic vein stenosis. Our patient responded well to surgical resection; however, his rapid deterioration that required urgent surgery highlights the importance of early recognition of this rare tumour. In this context, thorough recording of symptoms and presentation of case reports will eventually contribute towards the refinement of diagnostic criteria and, consequently, of therapeutic options for IMT.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

EZ, AP and MK drafted the manuscript and made substantial contributions to the conception of the case report, as well as to the collection of patient data. IT, AM, MP, AA and CGZ significantly contributed to data analysis and interpretation, offering domain-specific expertise. GK was responsible for the immunohistochemical analysis and pathological evaluation of tissue samples. EM, MAD and FZ supervised the progress of the study, contributed to its design, and critically reviewed the manuscript. FZ and EM confirm the authenticity of all the raw data. All authors participated in drafting or critically revising the manuscript for important intellectual content, approved the final version for publication, and agreed to be accountable for all aspects of the work, ensuring the accuracy and integrity of the study are appropriately addressed. All authors have read and approved the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent for publication was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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