Inflammatory Pseudotumor of the Spleen in a Patient with Idiopathic Thrombocytopenic Purpura

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Abstract: Inflammatory pseudotumor tumors (IPTs) of the spleen are uncommon lesions of uncertain pathogenesis. A definitive clinical diagnosis is challenging because radiological, as well as gross pathologic features may suggest a lymphoma, an inflammatory myofibroblastic tumor (IMT), or an IPT-like follicular dendritic cell tumor (IPT-FDC).

Herein, we report a case of an IPT of the spleen in a 48-year-old woman who presented with idiopathic thrombocytopenic purpura (ITP) symptoms. The results of abdominal ultrasonography revealed the presence of a splenic mass that continued to enlarge after the recovery from ITP, leading to the suspicion of lymphoma. A splenectomy was performed for diagnostic and curative purposes. The lesion was a non-encapsulated yellowish mass (largest diameter: 4,4 cm). The presence of spindle cells expressing smooth muscle actin, vimentin, and focal CD68 admixed with polymorphous lymphoid infiltrate supported the IPT diagnosis. The negative expression of CD21, CD23, CD35, and ALK excluded inflammatory myofibroblastic and follicular dendritic cell tumors. Any evidence of the recurrence of either ITP or IPTs was not noted 60 months after the operation.

The present case and the review revealed that splenic IPT tends to occur in middle-aged females and diagnosis is challenging due to the absence of specific symptoms or the characteristic hematological or radiological findings. Surgery is the most frequently performed treatment. Although multiple factors have been suggested in the etiology and pathogenesis, previous bleeding may also play a role in the presence of IPTs in patients with ITP. The rare occurrence of splenic IPT and the lack of diagnostic clinical signs and symptoms do not exclude their consideration in the differential diagnosis of spleen tumors, especially in patients with imaging features that cannot rule out malignancy.

Keywords: Splenic tumor, Benign splenic lesion, Splenectomy, Follicular dendritic cell tumor, Inflammatory myofibroblastic tumor, Mycobacterial spindle cell tumors.

INTRODUCTION

Inflammatory pseudotumors (IPTs) are defined as benign localized mass-like lesions with the histological features of bland spindle cells and a polymorphic inflammatory cell infiltrate, with variable fibrosis, necrosis, and granulomatous reaction [1-4]. IPTs are primarily detected and most commonly encountered in the lung [1]. However, they can present in nearly any part of the body [2-4]. Inflammatory pseudotumors (IPTs) of the spleen represent exceedingly rare lesions that can mimic many malignancies, especially lymphomas, and benign conditions, such as hemangiomas, both clinically and radiologically [5-8]. Therefore, it constitutes a critical diagnostic challenge in practice, and clinical diagnosis of these lesions is not always straightforward [8-10].

Although the etiology of IPTs of the spleen is unknown, an inflammatory and autoimmune etiology has been suggested according to its association with concomitant diseases in some cases [5, 6, 9, 11, 12-16]. Here, we present a case of an IPT of the spleen,accompanied with idiopathic thrombocytopenic purpura (ITP), with a review of the literature focusing on differential diagnosis. We aim to contribute to the awareness of the existence of these rare lesions.

CASE PRESENTATION

Our case is a 48-year-old female patient who was admitted to our hematology clinic with a bleeding tendency in her skin. At her first admission, she was not anemic, and a physical examination revealed no abnormal findings other than petechiae on the forearms. Her medical history was unremarkable except for an appendectomy. She did not use any drugs other than antacids for occasional dyspepsia. The laboratory tests were as follows: platelet count: 8000/mm3, WBC: 12000, Hb: 13.2 g/dL, Htc: 42.08%, MCH: 28.79 pg, and MCHC: 34.18 g/dL. The patient was serologically negative for human immunodeficiency virus (HIV), Epstein–Barr virus (EBV), and other infectious markers. Abdominal ultrasonography revealed a small (1 cm) hypoechoic lesion in the anterior region of the spleen. The patient was diagnosed with ITP and received oral prednisolone (1.2mg/kg) for three months. The petechiae

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disappeared, and the platelet count returned to normal. Therefore, prednisolone therapy was ceased. However, during the follow-up of the nodular heterogeneous, hypoechoic lesion in the spleen, continued to enlarge and reached a 4cm diameter over six months. Although any other intraabdominal mass or lymphadenopathy was not detected, lymphoma was considered in the differential diagnosis. A splenectomy was performed for diagnostic and therapeutic purposes.

The removed spleen weighed 200 gr. A nodular, well-circumscribed but not encapsulated yellowish white lesion with small foci of hemorrhage and necrosis, measuring 4,4 x 4 X 3.8 cm was observed in serial sections (Figure **1a**). The adjacent spleen was otherwise normal.

Histologically, the splenic lesion was composed of spindle cells that did not show a fascicular or storiform configuration (Figure **1b**, **1c**, and **1d**). In the immunohistochemical evaluation, they expressed vimentin and SMA (Figure **1e** and **1f**). However, the follicular dendritic cell markers (CD21, CD35, and CD23), CD15, CD30, ALK-1, HHV-type 8, S-100, CMV, and LMP-1 were all negative. These spindle cells were accompanied by inflammatory cells, such as histiocytes, plasma cells, lymphocytes, eosinophils, and PMNL, that formed the background of the lesion. The CD68-decorated histiocytes together with a few spindle cells and immunohistochemistry revealed that CD3-positive lymphocytes predominated the lymphocyte population, followed by CD20-positive B cells (Figure **1g**). These cells, together with plasma cells, were polyclonal (both expressing the kappa and lambda immunoglobulin light chain). Multinuclear giant cells were also found. Special stains for acid-fast bacilli and fungi were negative. In-situ hybridization for Epstein-Barr virus encoded-small RNA's (EBER) and HHV8 were also negative. Because these findings were consistent with the features of an IPT, the lesion was diagnosed as a splenic IPT. The postoperative course of the patient was uneventful, and she remained relapse-free of both ITP and IPT 60 months after the splenectomy.

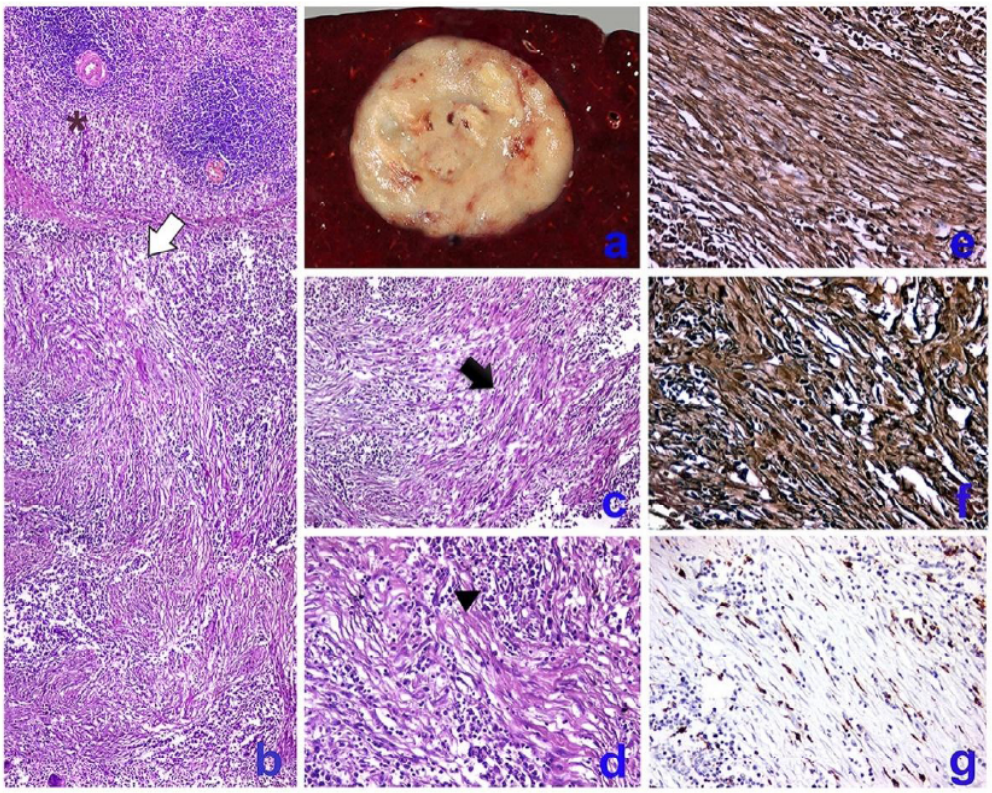

Figure 1: a: Cut surface of the spleen demonstrates a well-circumscribed bulgingyellowish mass withsmall foci of hemorrhage and necrosis. b: Inflammatory pseudotumor (white arrow) in the neighborhood of spleen parenchyma (asterisk) composed of red and white pulp (Hematoxylin and eosin stain,x100).**c:**Spindle cells (black arrow)mixed with inflammatory cells (Hematoxylin and eosin stain,x200) **d:** Spindle cells in a background of lymphocytes, plasma cells and histiocytes (arrowhead) (Hematoxylin and eosin stain,x 400). **e:**Intracytoplasmicexpression of vimentin by spindle cells (Vimentin, monoclonal ab, counterstain Mayer's hematoxylin, x400). **f:** Strong SMA staining of spindle cells (Smooth muscle actin monoclonal ab,counterstain Mayer's hematoxylin, x400). **g:** CD68 expression in a small number of spindle cells (CD68 monoclonal ab, counterstain Mayer's hematoxylin, x200).

DISCUSSION

IPTs of the spleen are rare lesions, and up to 120 cases have been reported since Cotelingam and Jaffe first described them in 1984 [2, 10, 16-20]. Similar to the case presented here, accumulated evidence indicates that IPTs usually affect middle-aged adults, with only a few cases reported in children [21, 22]. Although there is controversy over the association between IPTs and gender, recent studies have demonstrated that women are more frequently affected, with a 5:3 female predominance [6, 9, 10].

IPTs often pose diagnostic difficulties, since they lack characteristic clinical manifestations. They have a broad clinical spectrum ranging from abdominal pain to findings suggestive of malignancy, as well as being incidental in individuals investigated for other diseases [6-8, 11, 12]. Indeed, most reported cases of splenic IPTs were found incidentally during routine physical check-ups or abdominal imaging studies [6, 23, 24]. In symptomatic cases, upper abdominal pain or discomfort was more frequent, followed by fever and splenomegaly in some reports [6, 23, 25]. Our patient presented with a bleeding tendency, supporting the diverse manifestations of IPTs.

Although hypercalcemia, monoclonal peaks in the proteinogram, and polyclonal hypergammaglobulinemia have been described in some cases, the laboratory findings are frequently in normal ranges [7, 11, 12, 19]. A primary splenic tumor usually necessitates the consideration of lymphoma in the differential diagnosis, especially in a rapidly enlarging lesion, as in the present patient. Unfortunately, splenic IPTs do not show specific radiological findings; thus, imaging alone is of limited value in differentiating IPT from other splenic lesions, including benign inflammatory lesions, angiosarcoma, lymphoma, and metastatic disease [5, 6, 8, 11, 12]. Therefore, the correct diagnosis relies on histopathological examination of the resection specimens [6, 12]. Recently, fine-needle aspiration and core biopsy have been reported in a few studies. However, these techniques are not recommended due to the risk of bleeding and tumor seeding in cases of malignancy [6, 12, 23]. Consistent with all these findings, in our case, the imaging findings failed to exclude malignancy and splenectomy, with a preliminary diagnosis of lymphoma required for a definitive diagnosis. These data suggest that although an IPT is an extremely rare lesion, it should be taken into consideration in the differential diagnosis in patients with a splenic mass, especially in middle-aged women, and splenectomy is still the most appropriate treatment option in cases where malignancy cannot be ruled out.

The precise etiology of IPT has not been fully clarified and is still a topic of discussion. It has been suggested that factors such as bacterial infection, EBV and herpes infections, the granulomatous inflammatory process, vascular causes, autoimmune disorders, and bleeding may be involved in the development of this lesion [3, 5, 11, 12, 14, 24-28]. In our case, infections were excluded by either serological tests or a pathological assessment. Furthermore, any sign of vascular disease was not detected during the clinicopathological evaluation. However, our case was diagnosed as ITP, a disease with a severe bleeding tendency. According to the data obtained from the literature, six such cases have been reported [13-16]. In the past, there is some view that ITP complicates IPT [15, 16]. However, since IPT and ITP are concomitant in these patients, the opinion that IPT causes ITP is controversial. In our patient, while the oral prednisolone treated the ITP, the splenic lesion continued to enlarge, a finding that contradicts the autoimmune nature of IPTs [26]. This observation was also noted in recently reported cases, and it is suggested that immunosuppressive therapy may trigger the progression of a splenic lesion similar to a specific disease, such as EBV-related post-transplant lymphoproliferative disorder [27, 28]. Although EBV is involved in the etiology of splenic IPT, we did not observe EBV in the case presented here, similar to the case presented by Hatsuse *et al.* [15]. On the other hand, it is stated that intraparenchymal hemorrhage might occasionally be the initial event in the development of IPT [1, 6]. Accordingly, in our case, the ITP may have been predisposed to parenchymal hemorrhage [29]. However, the number of reported cases is too small to draw a conclusion. Nevertheless, the case presented here supports that IPTS should be considered in the differential diagnosis in patients presenting with ITP and that bleeding may also play a role in the etiology of these lesions.

All IPTs share certain pathological features independent from their anatomical localization. They are solitary, well-defined masses that contain variable numbers of spindle cells admixed with a polymorphous inflammatory infiltrate comprising lymphocytes, plasma cells, eosinophils, and histiocytes [5, 11, 24, 30, 31]. The following differential diagnosis should be considered: mycobacterial spindle cell tumors (MSCTs), inflammatory myofibroblastic tumors (IMTs), and follicular dendritic cell tumors (FDCTs) [3, 25, 31-

33]. MSCTs are usually associated with Mycobacterium avium intercellulare infections and diagnosed with the demonstration of acid-fast bacilli in spindle cells [32]. While spindle cells predominate in IMTs, they are overshadowed by the inflammatory infiltrate in IPTs [32, 33]. The stroma of IMTs contains amyloid-like collagen and calcification in contrast to the fibrous stroma of IPTs [33].

Moreover, the spindle cells in either IMTs or FDCTs display the syncytial, fascicular, or storiform arrangement, sometimes with nuclear atypia or mitotic activity. IMTs also differ from IPTs with their positive ALK expression and negative CD68 staining [31, 33, 34]. It is important that a proportion of IMTs are ALK-negative [34]. Consequently, this finding does not entirely rule out IMTs, and the diagnosis should be based on other histopathological and immunohistochemical features. Finally, in FDCTs, spindle cells are positive for FDC markers such as CD 21, CD 23, and CD 35 [3, 25, 31-33]. These cells do not express CD68. The spindle cells of IPT similar to our case are usually reactive for smooth SMA, vimentin, and CD68, suggesting that they are probably monocyte-derived [31-34].

According to the previously published cases, the prognosis of IPTs has generally been considered favorable following splenectomy, and there have been no reports of metastatic disease, local invasion, or recurrence [6, 10, 11]. Parallel with this observation, we did not observe any recurrence or metastasis during the five-year follow-up of our patient.

In conclusion, splenic IPTs are very rare. The case presented here supports their presence in this localization in middle-aged female patients who present with ITP. Moreover, the present case and recent reports show that the rare occurrence of splenic IPTs and the lack of diagnostic clinical signs and symptoms do not exclude their consideration in the differential diagnosis of splenic tumors, especially in patients with imaging features that cannot rule out malignancy. Splenectomy and histopathological evaluation are the gold standard for a definitive diagnosis and the treatment of splenic IPT in which the prognosis has generally been considered favorable following surgery.

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