

Case Report

## Splenic Inflammatory Pseudotumor (Inflammatory Myofibroblastic Tumor)

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We report a case of a splenic inflammatory pseudotumor (myofibroblastic tumor) in a 43-year-old man with a 5-year history of chronic bronchitis and sleep apnea syndrome. The patient was hospitalized because of a screen-detected splenic mass lesion. His sputum cultures revealed *Mycobacterium avium* complexes on only one occasion. Imaging studies revealed a 7 cm solitary tumorous lesion, and differential diagnoses of splenic hamartoma, hemangioma, lymphoma, and angiosarcoma were obtained from the radiologist. A splenectomy followed by pathological investigations was performed. By histology, the lesion contained fibroblastic or myofibroblastic spindle cell proliferations, accompanied by variable degrees of inflammatory cell infiltration. Ziehl-Neelsen staining did not reveal acid-fast bacteria. Immunohistochemically, the fibroblastic or myofibroblastic spindle cells were positive for vimentin, human smooth muscle actin, and muscle actin, but negative for desmin, CD8, CD21, CD23, CD35, p80, Epstein-Barr virus LMP, and human herpesvirus type 8. The infiltrating lymphoid cells demonstrated a nonneoplastic pattern. The results of *in situ* hybridization for Epstein-Barr virus encoded RNA were negative. The postoperative course was uneventful and he has had no recurrence in 22 months. His sleep apnea syndrome and chronic bronchitis have resolved spontaneously since the splenectomy. [*J Clin Exp Hematopathol* 47(2) : 83-88, 2007]

**Keywords:** splenic tumor, inflammatory myofibroblastic tumor, p80 (NPM-ALK) protein, Epstein-Barr virus encoded RNA, *Mycobacterium avium*

### INTRODUCTION

Splenic inflammatory pseudotumor, also known as inflammatory myofibroblastic tumor, is a rare mass-forming lesion characterized by fibroblastic or myofibroblastic spindle cell proliferations with varying degrees of inflammatory cell infiltration. The disease was first described in 1984 but the disease etiology remains unknown.<sup>1</sup> In this report, we present a case of primary splenic inflammatory pseudotumor in order to further elucidate the clinicopathological features of this disease.

### CASE REPORT

#### Clinical Summary

A 43-year-old man with a 5-year history of chronic bronchitis and sleep apnea syndrome was admitted to our hospital after detection of a splenic tumorous lesion. He had been internally administered dextromethorphan and fudosteine to treat chronic bronchitis during the previous 12 months. There were no distinguishing family or occupational histories. He was a nonsmoker and a social drinker. The results of our complete blood cell count and biochemical analyses were normal except for a slightly elevated erythrocyte sedimentation rate (15 mm/h) and high C-reactive protein levels (1.8 mg/dl). A sputum culture revealed *Mycobacterium avium* complexes on one occasion, and *Haemophilus influenzae* (1+) and *Staphylococcus epidermidis* (1+) were detected several times during the follow up period. His human immunodeficiency virus antibody test was negative. A chest computed tomography examination did not demonstrate any abnormalities; therefore, antimycobacterial drugs were not administered.

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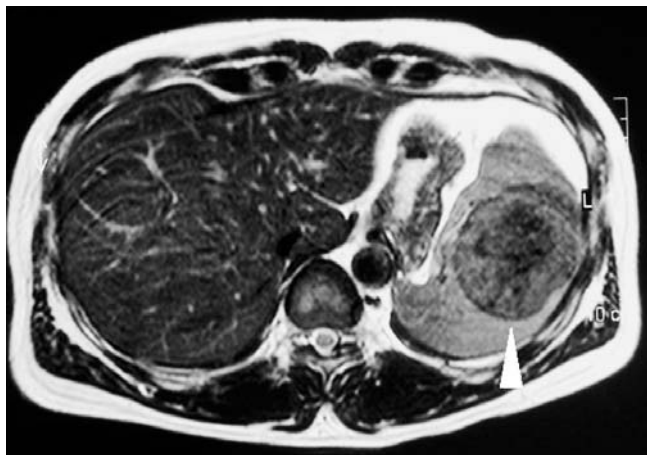
### Imaging Studies

We performed preoperative diagnostic imaging using abdominal computed tomography and detected a well-demarcated, low-density mass splenic lesion of about 7 cm that was not enhanced by contrast medium. Magnetic resonance imaging further demonstrated a splenic tumorous lesion showing an isosignal intensity on the T1-weighted image and a slightly lower signal intensity on the T2-weighted image, which was not enhanced after gadolinium administration (Fig. 1). Spotty or linear areas of no signal were found predominantly in the central portion, suggesting hemosiderosis. By ultrasonography, we detected a well demarcated, peripherally low echoic, and centrally isoechoic or slightly hyperechoic splenic tumor. Doppler ultrasonography and angiography showed hypovascularity of this splenic tumor and positron emission tomography did not show fluorine-18 fluorodeoxyglucose uptake. We reviewed the computed tomography analysis performed two years previously on this patient and also detected a splenic mass lesion 2 cm in diameter. The radiologist gave a differential diagnosis of splenic hamartoma, hemangioma, malignant lymphoma, and angiosarcoma.

Because of the possibility of rapid lesion growth, lesion rupture, and malignant neoplasm, we performed a splenectomy by laparotomy. The postoperative course for this individual was uneventful. The patient has had no recurrence in 22 mon and his sleep apnea syndrome and chronic bronchitis have resolved spontaneously.

### MATERIALS AND METHODS

Informed consent was obtained from the patient. The removed spleen was fixed in 10% neutral-buffered formalin and embedded in paraffin. Formalin-fixed and paraffin-embedded tissue samples were then subjected to hematoxylin



**Fig. 1.** Abdominal magnetic resonance imaging (T2WI) of the splenic tumorous lesion (arrowhead).

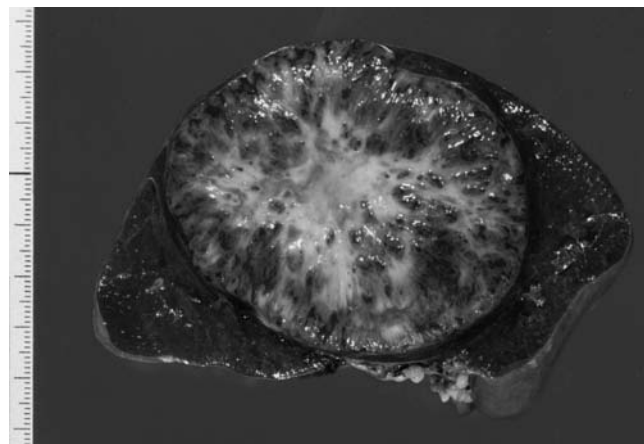
and eosin staining, Grocott staining, periodic acid-Schiff staining, immunohistochemistry, *in situ* hybridization, and polymerase chain reaction (PCR).

Immunohistochemistry was performed using monoclonal antibodies against vimentin (V9; Dako; Copenhagen, Denmark), human smooth muscle actin (1A4; Dako), muscle actin (HHF35; Enzo; New York, NY), desmin (DE-R-11; Novocastra; Newcastle upon Tyne, UK), CD3 (PS1; Nichirei; Tokyo, Japan), CD8 (C8/144B; Dako), CD20 (L26; Dako), CD21 (1F8; Dako), CD23 (MHM 6; Dako), CD30 (Ber-H2; Dako), CD34 (QBEnd-10; Immunotech; Marseille, France), CD35 (Ber-MAC-DRC; Dako), CD68 (PG-M1; Dako), kappa light chain (R10-21-F3; Dako), lambda light chain (N10/2; Dako), p80 (anaplastic lymphoma kinase: ALK) (5A4; Novocastra), Epstein-Barr virus LMP (CS. 1-4; Dako), and human herpesvirus type 8 (latent nuclear antigen) (13B10; Novocastra). Immunohistochemical staining using a rabbit polyclonal antibody against S-100 (Nichirei) was also performed.

*In situ* hybridization analysis for Epstein-Barr virus encoded RNA was performed using the EBER PNA probe and PNA *in situ* hybridization Detection Kit (Dako), according to the manufacturer's instructions. Immunoglobulin heavy chain gene rearrangements were examined by semi-nested PCR as described previously.<sup>2,3</sup>

### RESULTS

The removed spleen weighed 328 g and measured 12 × 12 × 8 cm. A well-circumscribed, solid, grayish-white or brownish-red tumorous lesion was identified in the spleen, measuring 8 × 8 × 6 cm and containing a central scar (Fig. 2). Histologically, the lesion contained fibroblastic or myofibroblastic spindle cell proliferations with a background of collagen fibers and granulation tissue-like components (Figs. 3A



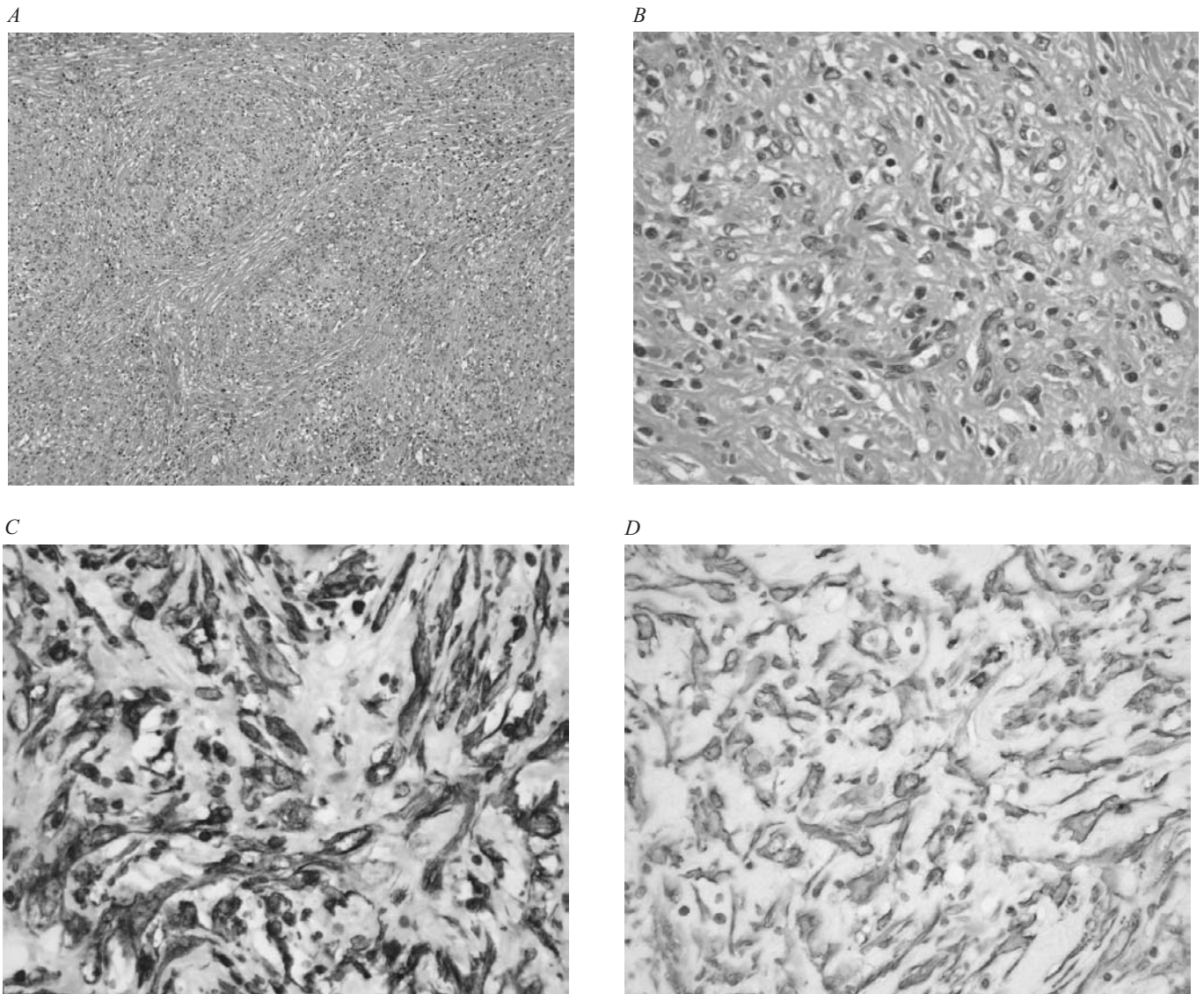
**Fig. 2.** Section of the splenic lesion revealing a well-circumscribed, solid, and tumefacient mass with a central scar.

and 3B). This lesion also contained varying degrees of inflammatory cell infiltrations, predominantly plasma cells, lymphocytes, and macrophages with occasional eosinophils and neutrophils. An epithelioid granuloma was not detectable. Gandy-Gamma nodules were sparse but neither calcification nor bone metaplasia was found. Fibrosis and hemosiderosis were conspicuous in the central portion of this tumorous lesion. Ziehl-Neelsen staining, Gram staining, and Grocott staining did not reveal any microorganisms.

Immunohistochemically, the fibroblastic or myofibroblastic spindle cells were positive for vimentin (Fig. 3C), human smooth muscle actin (Fig. 3D), and muscle actin, but

were negative for desmin, CD8, CD21, CD23, CD30, CD34, CD35, p80, Epstein-Barr virus LMP, human herpesvirus type 8, and S-100 protein. These spindle cells were focally and weakly CD68 positive. The infiltration of lymphoid cells demonstrated a non-neoplastic pattern at the immunohistochemical level, and B-cell polyclonality was confirmed by PCR. The results of our *in situ* hybridization analysis for Epstein-Barr virus encoded RNA were negative.

These findings were consistent with the features of a splenic inflammatory pseudotumor (inflammatory myofibroblastic tumor).



**Fig. 3.** Photomicrographs of the splenic lesion. (A) Spindle cell proliferation (hematoxylin and eosin stain, objective  $\times 10$ ). (B) Myofibroblastic cells (hematoxylin and eosin stain, objective  $\times 40$ ). (C) Myofibroblastic cells positive for vimentin (immunohistochemical stain, objective  $\times 40$ ). (D) Myofibroblastic cells positive for smooth muscle actin (immunohistochemical stain, objective  $\times 40$ ).

## DISCUSSION

A splenic inflammatory pseudotumor was first described in 1984 by Cotelingam and Jaffe, who categorized the lesion as a spectrum of nonneoplastic, inflammatory and reparative changes.<sup>1</sup> Although more than 50 instances of splenic inflammatory pseudotumor have been reported since, most cases contain miscellaneous entities. According to the World Health Organization classification of soft tissue and bone tumors, inflammatory pseudotumor is synonymous with inflammatory myofibroblastic tumor, inflammatory myofibroblastic proliferation, plasma cell granuloma, plasma cell pseudotumor, and inflammatory fibrosarcoma.<sup>4</sup> Originally identified in the lung, inflammatory pseudotumors are generally designated as inflammatory myofibroblastic tumors and have been encountered in a multitude of extrapulmonary sites. Histologically, the lesion is composed of myofibroblastic spindle cells, accompanied by plasma cells, lymphocytes, and eosinophils. Immunohistochemically, the myofibroblastic spindle cells can be positive for vimentin (99%), smooth muscle actin (92%), muscle-specific actin (92%), desmin (69%), cytokeratin (36%), CD68 (KP-1) (24%), and CD30 (Ki-1) (6%).<sup>5</sup> Cytoplasmic reactivity for ALK has also been demonstrated in approximately 50% of these lesions.<sup>4</sup> Ultrastructurally, the myofibroblastic cells display poorly developed Golgi, abundant rough endoplasmic reticulum, extracellular collagen, and intracytoplasmic thin filaments and dense bodies.<sup>5,6</sup> Genetic rearrangements involving 2p23, to which the *ALK receptor tyrosine kinase* gene has been mapped, are also often demonstrated.<sup>4</sup>

The biological behavior of inflammatory myofibroblastic tumors is somewhat controversial. Meis and Enzinger<sup>6</sup> performed a study of 38 extrapulmonary cases of this lesion and documented the locally aggressive and recurrent nature of these neoplasms, as well as the occurrence of metastases (11%) and tumor deaths, indicating that they are potentially malignant neoplasms. Meanwhile, Coffin, *et al.*<sup>5</sup> examined 84 extrapulmonary cases and described the lesion as a benign, nonmetastasizing proliferation of myofibroblasts with potential recurrence and persistent local growth, similar to fibromatosis. In contrast to these two reports, the World Health Organization classification places inflammatory myofibroblastic tumors in an intermediate category (rarely metastasizing, <5%) between benign and malignant.<sup>4</sup>

The main differential diagnoses of splenic inflammatory pseudotumor (inflammatory myofibroblastic tumor) include hamartoma, vascular neoplasm, follicular dendritic cell tumor, malignant lymphoma, and low-grade inflammatory myofibroblastic sarcoma. Hamartoma can be eliminated by the absence of CD8-positive endothelial cells. Hemangioma and hemangiosarcoma can also be excluded in our current case study due to the lack of proliferation of endothelial cells positive for CD31 and CD34. Follicular dendritic cell tumors

are characterized by dendritic cell proliferation and are associated with Epstein-Barr virus infection,<sup>7</sup> but our case did not demonstrate such characteristics. Polyclonal immunoglobulin gene rearrangement and the lack of Hodgkin/Reed-Sternberg cells in the present case study reduce the possibility that this lesion is a malignant lymphoma. Low-grade myofibroblastic sarcomas can present a diffusely infiltrative growth pattern of atypical myofibroblastic cells with enlarged, hyperchromatic and irregular nuclei without prominent inflammatory cell infiltration. However, the myofibroblastic spindle cells in our case showed vesicular rather than hyperchromatic nuclei, small to large nucleoli, eosinophilic to amphophilic cytoplasm, and interspersed growth, accompanied by varying degrees of inflammatory cell infiltration.

Although it is difficult to review the current literature with certainty from an etiological point of view, splenic inflammatory pseudotumors have been detected almost exclusively in adults (4 - 87 years, median 49), with a slight female predominance (56.5%).<sup>8</sup> However, this gender predilection might be due to inflammatory pseudotumor-like follicular dendritic cell tumors of the spleen that are characterized by a striking female predominance. A substantial proportion of the inflammatory pseudotumors of the spleen are discovered incidentally upon screening<sup>8</sup> and symptoms roughly correlate with the lesion size. Symptomatic patients with splenic inflammatory pseudotumors most often manifest left upper quadrant pain, fever of unknown origin, weight loss, malaise,<sup>8</sup> and occasionally idiopathic thrombocytopenic purpura.<sup>9,10</sup> Laboratory findings are also non-specific in splenic inflammatory pseudotumors and include leukocytosis, anemia, thrombocytopenia, hypergammaglobulinemia, an elevated erythrocyte sedimentation rate, hypercalcemia, and/or elevated serum levels of soluble interleukin (IL)-2 receptor.<sup>11</sup> A variety of imaging techniques have also been used for detection. The splenic mass is most often described as low density via computed tomography, hypoechoic by ultrasound, and either hypovascular or avascular following angiography. The most common preoperative diagnosis is lymphoma.<sup>12</sup> Splenectomy is both diagnostic and curative, and results in an excellent prognosis.<sup>8</sup>

In splenic inflammatory pseudotumors, the respiratory symptoms of chronic bronchitis and sleep apnea syndrome seen in our case have not been reported previously; only one case with complications of interstitial pneumonia was reported.<sup>13</sup> Some investigators demonstrated that cytokines such as IL-1 $\beta$ , IL-6, IL-8, and monocyte chemoattractant protein-1 were overexpressed in inflammatory pseudotumors.<sup>14-17</sup> These cytokines are not only associated with the histogenesis of inflammatory pseudotumors but also contribute to clinical manifestations of inflammatory disorders of the lung and sleep-related breathing disorders.<sup>18-21</sup> Because sleep apnea syndrome and chronic bronchitis in our case resolved after splenectomy, we conjecture that these symptoms could be

pathophysiologically related to the splenic inflammatory pseudotumor.

Recent genetic analyses have enabled the detection of certain neoplastic features in many of the so-called inflammatory pseudotumors. Inflammatory pseudotumors in children and young adults often contain clonal cytogenetic rearrangements. These include *ALK* fusions involving *tropomyosin-3*, *tropomyosin-4*, *clathrin heavy chain*, *cysteinyl-tRNA synthetase* and *Ran-binding protein 2* genes as fusion partners.<sup>22-25</sup> However, for many splenic tumors, detecting these genetic abnormalities has been unsuccessful. Inflammatory pseudotumors of the spleen generally undergo non-aggressive clinical courses without local recurrences or metastases if the lesions are removed completely. These findings prompted Kutok, *et al.* to speculate that a splenic inflammatory pseudotumor is biologically separate from inflammatory myofibroblastic tumors arising in other sites.<sup>26</sup> However, it has also been noted that *ALK* expression levels in inflammatory myofibroblastic tumors do not appear to be associated with clinical manifestations, histological appearances, or prognoses.<sup>27-29</sup> More studies are necessary to resolve these controversies.

In summary, 'inflammatory pseudotumor of the spleen' is a descriptive term that may encompass several different entities. The term 'inflammatory myofibroblastic tumor of the spleen' is a more acceptable designation if myofibroblastic proliferation of the lesion is histopathologically evident. Detailed investigations are indispensable for elucidating the pathogenesis.

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