Splenic Inflammatory Myofibroblastic Tumor (Inflammatory Pseudotumor)

A Clinicopathologic and Immunophenotypic Study of 12 Cases

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• ***Context.*—Inflammatory pseudotumor is an uncommon and enigmatic lesion. The spindle cells found in this tumor have features of myofibroblasts. Because of the indefinite relationship of these lesions with inflammatory fibrosarcoma and their indefinite biologic behavior, inflammatory pseudotumor is currently classified as inflammatory myofibroblastic tumor (IMT). To date, only case reports or small series have been published on these tumors, which are primary in the spleen.**

***Design.*—In this study, we describe the clinical, morphologic, and immunophenotypic findings of 12 cases of splenic IMT and examine their relationship to Epstein-Barr virus (EBV).**

***Results.*—The patients included 8 women and 3 men, ranging from 19 to 77 years of age (mean, 53 years; median, 60 years). Demographic data were unavailable for 1 patient. Patients generally presented with abdominal pain (n = 5) and fever (n = 4). Associated lesions included renal cell carcinoma (n = 2), colonic adenocarcinoma (n = 1), and cholecystitis (n = 1). All tumors were composed of a bland spindle cell proliferation in association with a variable mixed inflammatory component. There were 2 growth patterns, namely, a cellular spindle cell pattern and a hypocellular fibrous pattern. An immunohistochemical panel confirmed the myofibroblastic nature of the spindle cells. The spindle cells of 2 cases were immunoreactive for EBV latent membrane protein 1, whereas 6 of 10 cases were positive for EBV-encoded RNA using in situ hybridization. Follow-up was available for 8 patients; 6 were alive with no evidence of recurrence and 2 were dead of other causes.**

***Conclusion.*—Splenic IMTs are uncommon lesions that can be distinguished from other conditions using a combination of clinical, histologic, and immunophenotypic findings. Epstein-Barr virus may play a role in the pathogenesis of splenic IMT, and there may be an association of splenic IMT with concomitant disease or malignancy. Most splenic IMTs have an excellent long-term prognosis.**

(*Arch Pathol Lab Med.* 2001;125:379–385)

Inflammatory pseudotumor tumor (IPT) is a lesion of unknown etiology that has been reported in numerous anatomic sites, including the spleen.[1] By definition, the tumor is composed of a dominant spindle cell proliferation with a variable inflammatory component.[2–9] Recent studies have demonstrated the spindle cells are myofibroblasts, prompting the currently preferred designation of *inflammatory myofibroblastic tumor* (IMT).[6,9,10] Long considered a benign reactive proliferation, investigators have demonstrated the presence of chromosomal abnormalities and documented cases showing aggressive behavior,[10,11] supporting the theory that IMTs are true neoplasms.

Since the original description of 2 cases involving the spleen,[1] there have only been sporadic reports and small series reports of splenic IMT.[2–5,7–9,11–23] We attempted to further expand the understanding of these tumors by examining the clinical, morphologic, and immunophenotypic findings of 12 cases. Because of the recent association of IMT with Epstein-Barr virus (EBV),[4,24,25] we performed studies for EBV latent membrane protein 1 (LMP-1) and EBV-encoded RNA (EBER) by immunohistochemistry and in situ hybridization, respectively. The reported similarities between follicular dendritic cell (FDC) tumors and IMT also prompted us to perform CD21 and factor XIIIa (FXIIIa) studies by immunohistochemistry.[24–27]

MATERIALS AND METHODS

Twelve cases of primary splenic IMT were selected from the Hematopathology Registry at the Armed Forces Institute of Pathology, Washington, DC, between 1970 and 1998. The 12 cases represented approximately 3.2% (12/376) of all benign or malignant primary splenic tumors seen in consultation during this period. Ten cases were obtained from civilian sources and 2 cases from military hospitals.

Hematoxylin-eosin–stained slides were reviewed in all cases.

Accepted for publication September 25, 2000.

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The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Air Force, Department of the Army, or the Department of Defense.

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Table 1. Immunohistochemical Antibodies

Antibody (Clone)	Primary Antibody	Supplier	Dilution	Antigen Enhancement*
ALK-1	Mouse	Dako Corporation, Carpinteria, Calif	1:100	Microwave
CD3	Rabbit	Dako	1:500	Enzyme
CD8 (C8/144B)	Mouse	Dako	1:100	Microwave
CD20 (L26)	Mouse	Dako	1:400	N/A
CD21 (1F8)	Mouse	Dako	1:100	Enzyme
CD30 (Ber-H2)	Mouse	Dako	1:150	Enzyme
CD34 (Q BEND)	Mouse	Immunotech, Westbrook, Me	1:100	N/A
CD68 (KP1)	Mouse	Dako	1:500	Enzyme
Cytokeratins (AE1/AE3, CK1)	Mouse	Boehringer Mannheim, Indianapolis, Ind	1:400	N/A
Desmin (D33)	Rabbit	Dako	1:100	Enzyme
EBV LMP-1 (CS1–4)	Mouse	Dako	1:100	Enzyme
Factor XIIIa	Rabbit	Calbiochem, La Jolla, Calif	1:800	Enzyme
HMB-45 (HMB-45)	Mouse	Enzo Diagnostics, Farmingdale, NY	1:2000	N/A
κ Light chain	Rabbit	Dako	1:50 000	Enzyme
λ Light chain	Rabbit	Dako	1:50 000	Enzyme
Muscle-specific actin (HHF35)	Mouse	Dako	1:100	N/A
S100	Rabbit	Sigma Chemical Co, St Louis, Mo	1:2000	N/A
Smooth muscle actin (1A4)	Mouse	Sigma	1:1200	N/A
Vimentin (V9)	Mouse	Dako	1:80	N/A

* EBV LMP-1 indicates Epstein-Barr virus latent membrane protein; N/A; not applicable.

All cases met the established light microscopic histopathologic criteria for IMT.[28] Three basic histologic growth patterns were observed in the literature[1]: the myxoid/vascular pattern reminiscent of granulation tissue[2]; the compact spindle cell pattern similar to the cellular zones of nodular fasciitis or myofibromatosis, characterized by loose storiform or short fascicular growth patterns[3]; and the heavily collagenized hypocellular fibrous pattern, similar to scar.[29] In addition to growth pattern, the cases were assessed for presence or absence of necrosis, hemorrhage, hemosiderin, calcification, thrombosis, Russell bodies, a pseudocapsule, eosinophils, neutrophils, granulomas, extramedullary hematopoiesis, and germinal centers.

Formalin-fixed, paraffin-embedded sections were available in 11 of the 12 cases. Periodic acid–Schiff stains (with and without diastase digestion) were performed in all cases. Additional studies for microorganisms were performed for 1 case, which included Grocott methenamine silver, Brown-Brenn Gram, Brown-Hopps Gram, Ziehl-Neelsen, Warthin-Starry, and Fite stains.

Immunohistochemistry was performed according to the standardized avidin-biotin method of Hsu et al[30] using 4-μm-thick, formalin-fixed, paraffin-embedded sections (Table 1). When required, tissue sections were treated for 3 minutes with 0.05% protease VIII (Sigma Chemical Co, St Louis, Mo) in a 0.1 mol/L phosphate buffer at a pH of 7.8 at 37°C[31] or were heated in a microwave oven in 1 mmol/L EDTA buffer solution at pH 8.0 for 10 minutes. Standard positive and negative controls were used throughout.

In situ hybridization for the presence of EBER was performed on sections of formalin-fixed, paraffin-embedded tissue using an EBER in situ kit (DA160SS; BioGenex, San Ramon, Calif). The manufacturer's instructions were used with no modifications, and appropriate positive and negative controls were used.

Materials within the files of the Armed Forces Institute of Pathology were supplemented by a review of the patient demographics, signs and symptoms at presentation, duration of symptoms prior to presentation, medical history, radiographic studies, laboratory test results, surgical pathology and operative reports, and by written questionnaires or oral communication with the treating physician(s). Follow-up included information regarding the specific type(s) and length of treatment modalities and the current status of the disease and patient. This clinical investigation was conducted in accordance and compliance with all statutes, directives, and guidelines of the Code of Federal Regulations, Title 45, Part 46, and the Department of Defense Directive 3216.2 relating to human subjects in research.

RESULTS

Clinical Features

The patients included 8 women and 3 men, aged 19 to 77 years, with a mean age of 53.0 years at initial presentation (median, 60 years) (Table 2). Demographic data were unavailable for 1 patient. The mean age at presentation was slightly older for men than for women (59.7 years and 50.5 years, respectively). The most common presentations were abdominal pain (n = 5) and fever (n = 4), followed in decreasing order by weight loss (n = 3), headache with exertional dyspnea (n = 1), chills (n = 1), and arthralgias (n = 1) (Table 2). Physical examination revealed no significant findings in 7 of 12 patients (Table 3). Four patients had concurrent diseases, namely, renal cell carcinoma (n = 2), colonic adenocarcinoma (n = 1), and cholecystitis (n = 1).

Laboratory Findings

Laboratory data were available for 9 cases. Results were reported as 'normal' or 'unremarkable' in 6 cases (66.7%). One patient had a Coombs-positive hemolytic anemia with a total bilirubin level of 76 μmol/L, while another patient had an increased serum amylase level. Infection or sarcoidosis was not identified in any patients at presentation.

Radiographic Findings

Radiographic results were available in 7 patients, with computed tomography being the most frequently used modality (n = 6). Additional studies performed included ultrasonography (n = 3), magnetic resonance imaging (n = 1), and angiography (n = 1). The most common finding was a discrete splenic mass (n = 5), followed by splenic enlargement (n = 2). Hepatomegaly (n = 1), aortic lymphadenopathy (n = 1), and a discrete liver mass (n = 1) were also found.

Treatment and Patient Outcome

All patients were treated by splenectomy only. Follow-up information was available for 8 of the 12 patients (Table

Table 2. Clinical Presentation and Disease Course of Splenic Inflammatory Myofibroblastic Tumors

Case No.	Age, y/Sex	Presenting Symptoms, Duration	Concomitant Disease	Therapy	Status and Follow-up
1	19/F	Headache with exertional dyspnea, fever, 9 mo	None	Splenectomy	A, NED, 19 y
2	77/F	Melena, fever, weight loss, 30 mo	3-y history of colon carcinoma	Splenectomy	D, NED, 1 y
3	N/A	Abdominal pain following blunt trauma, 2 y prior	N/A	Splenectomy	N/A
4	24/F	Fever, 18 mo	IMT in lymph nodes and spleen	Splenectomy and LND	A, NED, 10 y
5	72/M	Epigastric pain, 2 mo	N/A	Splenectomy	N/A
6	73/F	Weight loss, abdominal pain	IMT in liver and spleen	Splenectomy, liver biopsy	N/A
7	36/M	Fever, chills, arthralgias, 120 mo	N/A	Splenectomy, steroids	A, NED, 10 y
8	61/F	Fever, 3 mo	N/A	Splenectomy	N/A
9	71/M	Hematuria, 4 mo	Renal carcinoma	Splenectomy, nephrectomy	D, NED, 1 mo
10	56/F	Hematuria, 3 mo	Renal carcinoma	Splenectomy, nephrectomy	A, NED, 1 y
11	34/F	Abdominal pain, 5 mo	None	Splenectomy	A, NED, 1 mo
12	60/F	Discovered incidentally	Cholecystitis	Splenectomy	A, NED, 1 mo

* N/A indicates not available; IMT, inflammatory myofibroblastic tumor; LND, lymph node dissection; A, alive; NED, no evidence of disease; and D, dead.

Table 3. Macroscopic Features of Splenic Inflammatory Myofibroblastic Tumors

Case No.	Physical Findings	Spleen Weight, g	Splenic Cut Surface	Dominant Lesion	Size, cm
1	None	184	Multiple, punctate, gray-white nodules	No	0.3
2	HSM	1030	Well-circumscribed, yellow, necrotic tumor	Yes	15.0
3	SM	N/A	Single tumor in lower pole	Yes	18.0
4	SM	310	Focal yellow-red hemorrhagic areas	No	0.7
5	None	140	Single well-delineated tumor	Yes	6.0
6	HSM	N/A	Dominant tumor	N/A	N/A
7	SM	N/A	Dominant tumor	N/A	N/A
8	None	225	Well-delineated, soft, white mass	Yes	6.5
9	None	274	Well-defined mass with foci of necrosis	Yes	5.5
10	None	282	Two small separate lesions	No	0.7
11	None	260	Well-delineated bulging mass	Yes	7.0
12	None	270	Well-defined bulging yellow mass	Yes	4.0

* HSM indicates hepatosplenomegaly; SM, splenomegaly; and N/A, not available.

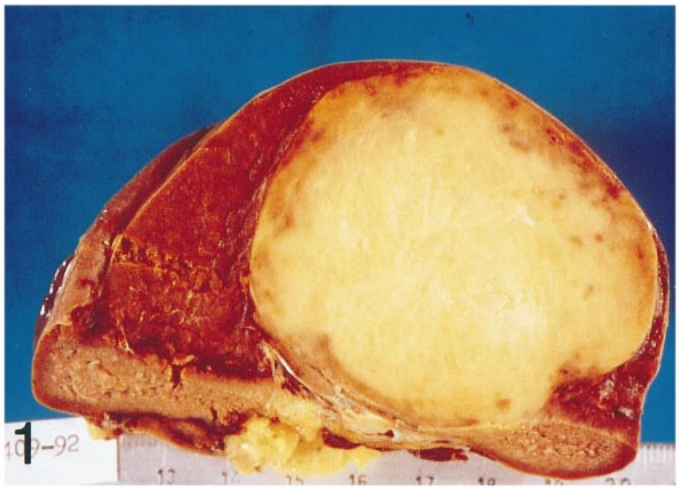
2). A lymphadenectomy was performed on the patient with aortic lymphadenopathy, and a liver biopsy was obtained from the patient with a liver mass. Results of these procedures revealed IMT in these locations, as well as in the spleen. One patient with recurrent fevers and arthralgias had received ''steroids'' for 10 years. Two patients had undergone nephrectomy for renal cell carcinoma, and 1 patient had a partial colectomy for colonic adenocarcinoma. Six were alive at last follow-up, which ranged from 1 month to 19 years (mean, 6.7 years) following initial diagnosis. Two patients had died, each as a complication of their epithelial malignancy (renal cell carcinoma and colonic adenocarcinoma).

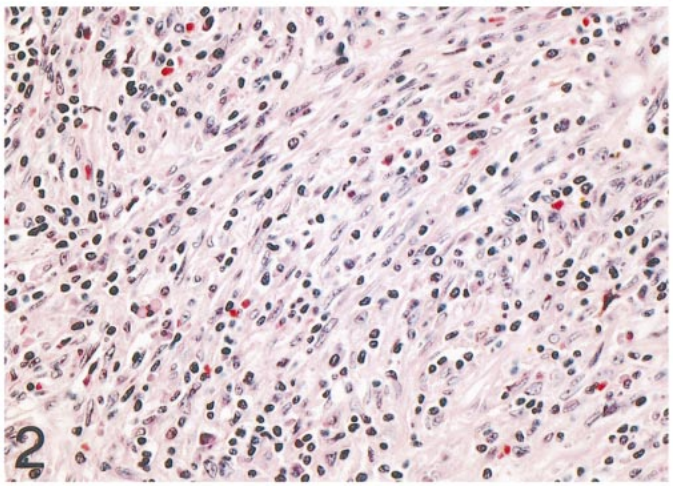
Pathology

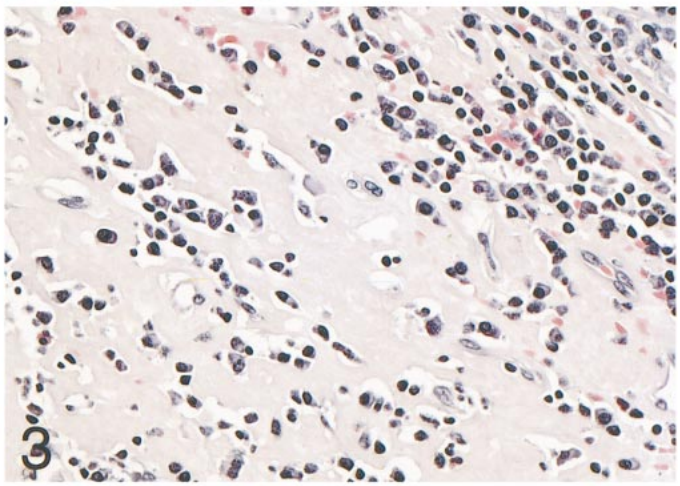
Macroscopic Features.—The splenic weight ranged from 140 to 1030 g, with a mean of 331 g. Splenomegaly, defined as a weight greater than 250 g,[32] was found in 5 patients. One case qualified as massive splenomegaly, arbitrarily defined as splenic weight greater than or equal to 1000 g. Concomitant hepatomegaly was found in 2 patients. The splenic capsule was universally described as smooth, without evidence of splenic rupture. A dominant, well-delineated lesion was described in 7 of 10 cases and ranged in size from 4.0 to 19.0 cm (mean 8.9 cm) (Figure 1). Three cases were described as multinodular lesions, one with yellow-red hemorrhagic areas.

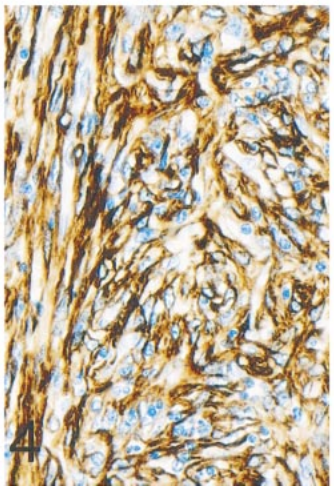
Histologic Features.—All cases were composed of spindle cells, a variable fibrocollagenous stroma, and an inflammatory cell component made up of plasma cells, lymphocytes, and histiocytes. The proportion of each of these elements varied between cases, as well as within cases. The lymphoid cells were predominantly small and mature with isolated immunoblasts and cytologically unremarkable plasma cells.

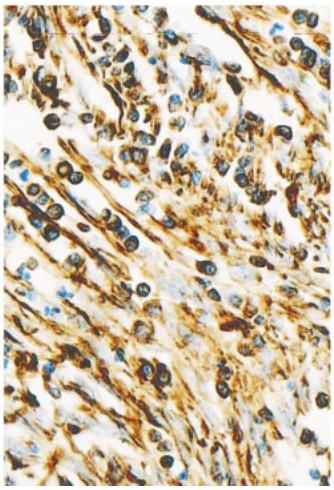
The basic patterns of IMT were present and blended with one another, except for the myxoid/vascular pattern, which was not identified. The compact spindle cell pattern (Figure 2) was the dominant finding in 11 of the 12 cases and was focally storiform (n = 3). Collagenous stroma was identified in 9 cases and was dominant in 1 case (Figure 3). The collagenous stroma resembled amyloid in 2 cases, but Congo red stains were negative. There was no cellular atypia. Mitotic figures were occasionally identified, but no atypical mitotic figures were present. In addition to the spindle cell proliferation and lymphoplasmacytic infiltrate, foci of necrosis (n = 7) associated with neutrophils (n = 6), hemorrhage (n = 6), hemosiderin deposition (n = 4), lymphoid follicles with reactive germinal centers (n = 5), Russell bodies in association with aggregates of plasma











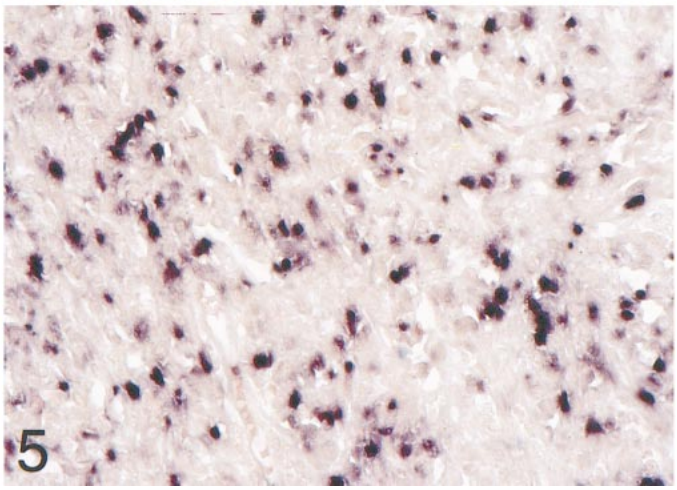


Figure 1. *A dominant, well-circumscribed, inflammatory myofibroblastic tumor within the spleen.*

Figure 2. *Tumor composed of spindle cells, plasma cells, lymphocytes, and histiocytes. Occasional Russell bodies identified within plasma cells. The compact spindle cell pattern dominates in the majority of cases (hematoxylin-eosin, original magnification ×300).*

Figure 3. *Collagenous stroma with individual or clusters of spindle cells, lymphocytes, and plasma cells observed in many cases (hematoxylin-eosin, original magnification ×360).*

Figure 4. *Spindle cells characteristically immunoreactive for smooth muscle actin (left, original magnification ×350) and vimentin (right, original magnification ×350).*

Figure 5. *Six of 10 cases showed strong positivity for Epstein-Barr virus–encoded RNA by in situ hybridization (original magnification ×400).*

Table 4. Immunohistochemical Phenotype of Splenic Inflammatory Myofibroblastic Tumors

Antigen	No. Positive/Total
Smooth muscle actin	10/11
Vimentin	7/10
CD68	6/10
Muscle-specific actin	3/11
Factor XIIIa	2/10
CD21	2/10
EBV LMP-1	2/10
S100	2/10
CD30	1/11
CD34	0/10
Desmin	0/10
CD8	0/8
Cytokeratin	0/11

* EBV LMP-1 indicates Epstein-Barr virus latent membrane protein.

cells (n = 6), and a pseudocapsule (n = 5) were detected. Two cases contained scattered adipocytes. One case each contained fibrin thrombi, foci of extramedullary hematopoiesis, calcification, and noncaseating epithelioid granulomas. Microorganisms were not found in any case.

Immunohistochemical Profile.—The spindle cells were most frequently immunoreactive for smooth muscle actin (10/11 cases) and vimentin (7/10 cases) (Table 4; Figure 4). At least focal immunoreactivity for CD68 (n = 5) and S100 protein (n = 2) was noted in the spindle cells, without HMB-45 immunoreactivity. Two cases each were positive for factor XIIIa (FXIIIa), CD21, and the latent membrane protein of EBV (LMP-1). CD3-positive T cells predominated in 6 cases, whereas CD20-positive B cells were prominent in 4 cases. Light chain restriction was not detected in the 10 cases studied. Ten of 10 cases studied were negative for the ALK-1 protein. This is in contrast to the findings of Coffin et al,[33] who reported 12 of 45 cases of extrasplenic IMT that expressed this protein. Although the number of intralesional CD8-positive T cells varied between cases, the spindle cells were negative in all 8 cases tested.

In Situ Hybridization.—Six of the 10 cases studied showed positivity for EBER (Figure 5).

COMMENT

Our findings are similar to those reported previously by other authors.[1–3,5,7–9,11–13,18–23] Inflammatory myofibroblastic tumor is predominant in women, who often present with fever of unknown origin or other vague, nonspecific symptoms. Splenomegaly is a frequent finding.

The etiology of IMT remains unsettled, although a number of theories have been proposed, including infectious agents, tumor-associated factors, and cytokines. Infectious agents, such as *Legionella,* EBV, and those associated with scarlet fever and urinary tract infections, have all been associated with IMT (IPT).[7,14,25,29,34] The frequent clinical findings of fever, anorexia, and lymphadenopathy in concert with the histologic findings of a fibroinflammatory infiltrate, necrosis, and epithelioid granulomas may lend support to this hypothesis. We demonstrated an association with EBV by immunohistochemical studies in 2 of 12 cases and by in situ hybridization in 6 of 10 cases. These findings corroborate those of Arber et al,[4] who found an association of IMT with EBV in 4 of 6 splenic tumors and 1 of 2 liver tumors.

Investigators have reported an association of IMT (IPT) with synchronous tumors, including small cell carcinoma and Hodgkin disease,[1] colonic adenocarcinoma,[35] cholecystitis,[13] and adrenocortical adenoma.[36] Our series identified 2 patients with renal cell carcinoma, 1 patient with colonic adenocarcinoma, and 1 patient with cholecystitis. Because patients with IMT (IPT) frequently manifest systemic symptoms, such as fever, fatigue, and cachexia, an association with overexpression of cytokines, specifically interleukin (IL)-1β and IL-6,[37] has been considered.[6,22] In a previous report, when the tumor was removed, the levels of IL-1β and IL-6 normalized, resulting in amelioration of the symptoms.[37]

Many researchers have reported that IL-6 promotes the proliferation of fibroblasts, and that both IL-1 and IL-6 promote differentiation of B cells.[38,39] The major cellular sources of IL-1 and IL-6 are monocytes and macrophages (among others), which are constant constituents of IMT (IPT).[40] It is possible, therefore, that IMT (IPT) may be related to the overproduction of these cytokines, whether produced by the host cells, tumor cells, or both. This postulate may be supported by the associated presence of synchronous tumors and inflammatory diseases in our patients, since these processes are associated with increased cytokines. Before reaching this conclusion, however, additional studies with a larger cohort of cases are necessary.

It has been suggested that IMT (IPT) and FDC tumors may be related, sharing a common myofibroblastic lineage. A number of case reports lend credence to this hypothesis.[25,27] The spindle cells in FDC tumors are immunoreactive for CD21, CD35, CD45, actin, FXIIIa, and the LMP of EBV (confirmed by Southern blot analysis and detection of EBERs by in situ hybridization), and they typically demonstrate large, pleomorphic, atypical cells and few plasma cells. Two of our cases were focally immunoreactive for CD21 and FXIIIa, as well as LMP-1 of EBV. Six of 10 cases were positive for EBERs.

However, FXIIIa has been found in multiple cell types, including populations of dendritic cells, histiocytes, fibroblasts, placenta, and megakaryocytes.[26,27,41–46] Although some of our cases showed a combination of spindled morphology, focal necrosis, and some immunophenotypic features described in association with FDC tumors, the presence of numerous plasma cells, bland appearance of the spindled cells, and benign clinical course supported the diagnosis of IMT. If IMT (IPT) and FDC tumors are related, it is possible that occasional cases with features of IMT may represent a less aggressive subset of FDC, with a graded myofibroblastic differentiation.[1–3,5–7,14–23,25]

The finding of fat within 2 of these splenic lesions is remarkable. Because normal spleen does not usually contain adipocytes, the presence of adipose tissue within the myofibroblastic lesions may indicate fatty differentiation from primitive mesenchymal cells. Fat has been seen in association with hamartomas or benign soft tissue lesions,[47–49] and its presence may further distinguish IMT from FDCs or other tumors in some cases.

The differential diagnosis of IMT can be quite broad, including spindle cell tumors, infection, sarcoidosis, and splenic hamartoma. However, it is most frequently confused with malignant non-Hodgkin lymphoma.[3,5,15,19,21] Similar to IMT, many malignant lymphomas (Hodgkin disease or non-Hodgkin type) present as a large mass or masses within the spleen. Unlike IMT, they are either composed microscopically of sheets or aggregates of malignant lymphoid cells, or with diagnostic Reed-Sternberg

cells and/or their variants. Immunophenotypic and/or cytogenetic studies in concert with morphologic findings are helpful in confirming the nature of the malignant lymphoma in most cases.

The sinus or cordlike spaces characteristically observed in splenic hamartoma are not observed in IMT. However, marked sclerosis is occasionally a dominant feature in splenic hamartoma, rendering a similar appearance to sclerotic IMTs.[5] In these cases, the finding of immunoreactivity for CD8 might favor the former.[50,51] None of the cases tested in our study were positive for this marker. Infectious processes can be excluded with appropriate histochemical stains and cultures. Sarcoidosis has characteristic systemic manifestations that are different from IMT. Our single case with epithelioid granulomas was negative for organisms, and there was no history of sarcoidosis or infection.

In conclusion, IMT (IPT) is usually a benign tumor that may rarely be found in the spleen. It most frequently presents as a single lesion, but multifocal disease has also been seen. The tumor is composed of a proliferation of spindle cells with variable numbers of lymphocytes, plasma cells, and histiocytes. Although the dense hypercellular pattern is usually dominant, multiple patterns can be seen in individual cases.

The etiology of IMT (IPT) remains unresolved; however, EBV may be involved in its pathogenesis. There also may be a relationship with synchronous neoplasms and disease and cytokine production. While some IMTs can be confused with or share histologic and immunophenotypic characteristics with FDC tumors, the absence of cellular pleomorphism in IMT helps differentiate between the 2 disease processes. Surgical excision is usually curative. However, the aggressive clinical course of occasional cases of IMT warrants close clinical follow-up.

The authors thank Robin-Anne Ferris, MFA, for her photographic expertise.

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