Coexisting Sclerosing Angiomatoid Nodular Transformation of the Spleen with Multiple Calcifying Fibrous Pseudotumors in a Patient

Jen-Chieh Lee,1 Huang-Chun Lien,1 Cheng-Hsiang Hsiao1,2 *

Primary tumor or tumor-like lesions of the spleen are rare. Among them, vascular lesions are the most common. Vascular tumor of the spleen is different from the usual hemangioma of soft tissue because the vascular structure of the spleen is unique. Sclerosing angiomatoid nodular transformation (SANT) is a recently described vascular lesion of the spleen. Grossly, it is a multinodular, well-circumscribed tumor containing a hypervascular core. Microscopically, it comprises three types of vessels, and each type recapitulates the immunohistochemical characteristics of the normal vascular elements of the splenic red pulp, i.e., capillaries, sinusoids, and small veins, respectively. Because of the rarity of this entity, its actual pathogenesis is still unknown. In this study, we report a case of SANT occurring in a 43-year-old woman, in whom there were also multiple calcifying fibrous pseudotumors (CFPTs) in the abdominal cavity. Both SANT and CFPT are thought to be variants of inflammatory pseudotumor. Coexistence of these two rare entities in a patient has never been reported, and this fact suggests that there might be a common mechanism contributing to the formation of these two types of lesions. [J Formos Med Assoc 2007;106(3):234–239]

Key Words: calcifying fibrous pseudotumor, sclerosing angiomatoid nodular transformation, splenic hamartoma

Anatomically, the spleen is made up of two parts, the white pulp and red pulp. The white pulp is made up of lymphocytes, and the red pulp of a complex network of venous sinuses and the cords of Billroth. The sinuses are lined by specific endothelial cells, presenting with both endothelial and histiocytic markers, also known as littoral cells. The cords comprise splenic macrophages. Because the vascular structure of the spleen is complex and distinct from the vessels of other organs, there are some vascular neoplasms that are unique to the spleen such as littoral cell hemangioma, splenic hamartoma, etc. Recently, a novel splenic vascular tumor was described by Rosai1 and Martel et al.2 Grossly, the tumor usually presents as a multinodular, well-circumscribed mass containing a hypervascular core. Therefore, it has been designated as sclerosing angiomatoid nodular transformation (SANT). Although the tumor was identified only 3 years ago, about 50 probable cases have been reported in the literature.1–8 Patients with SANT have a relatively high prevalence (20%) of concurrent diseases at other sites, and most are cases of malignancy such as leukemia, lung cancer, colonic carcinoma, gastric carcinoma, and renal cell carcinoma etc.2 Herein, we report a patient with SANT and multiple calcifying fibrous pseudotumors (CFPTs) of the mesentery. No such combination of these two unusual tumors have previously been reported. We performed extensive immunohistochemical staining and reviewed the clinicopathologic characteristics of these two
tumors to determine the possible association between them.

Case Report

A 43-year-old woman, a hepatitis B virus carrier, was noted to have a hypoechoic splenic tumor during a routine ultrasonography examination in February 2004. Four months later, she began to feel left flank pain and lost 9 kg within 6 months thereafter. She was admitted to the National Taiwan University Hospital for evaluation. Laboratory examinations including complete blood count, biochemistry test, CA-19-9, and C-reactive protein were all unremarkable, but splenomegaly was noted on physical examination. Computed tomography (CT) showed two lobulated low-density masses in the spleen (Figure 1). Magnetic resonance imaging (MRI) revealed that the tumors were of low signal on T2-weighted images and of mild low signal on T1-weighted images, without definite enhancement. Thrombosed hemangioma, lymphoma, or chronic abscess was suspected. The patient received total splenectomy in January 2005. On operation, some small white nodules were also found over the gastric wall and omentum, and they were removed completely. No recurrence was noted during postoperative follow-up.

Grossly, the spleen weighed 180g. Upon cutting, two well-circumscribed round tumors were found in the spleen, measuring 3.5 × 3.5 × 3.0 cm and 3.0 × 2.0 × 2.0 cm in size, respectively. The tumors comprised some hemorrhagic nodules, which were separated by thick fibrotic septa (Figure 2). Four mesenteric tumors were also submitted, and they were white and elastically firm, measuring up to 1.4 cm in diameter. Microscopically, the splenic tumors comprised multiple nodules arranged in a lobular pattern. These nodules had a central vascular core and were surrounded by a fibroedematous cortical zone and an outermost fibrotic shell (Figure 3). On high power examination, three types of vascular structure were found in the tumor. First, capillary-like vessels, which were the most frequent vascular component and mainly located within the vascular core. Histologically, they were characterized by the presence of erythrocytes within the lumen. Second, larger vessels, which had open and empty lumina and resembled the sinusoids in the red pulp. Third, ectatic veins, which usually had a well-defined vascular wall. Immunohistochemically, different vessels in the tumor had distinct immunophenotypes (Figure 4). The capillaries and ectatic veins were reactive to CD31 and CD34 but negative for CD8. The sinusoid-like vessels were positive for CD31 and CD8, but negative for CD34. The spindle-shaped cells of the tumor were negative for desmin, CD1a, S-100, CD21, and anaplastic lymphoma kinase (ALK)-1.
In addition, *in situ* hybridization for Epstein Barr Virus (EBV)-encoded small RNA (EBER) was also negative.

The separated mesenteric nodules were fibrotic and well circumscribed (Figure 5A). Microscopically, they were composed of thick hyalinized collagen bundles arranged in whorls or haphazard patterns admixed with scanty bland-looking spindle cells. Occasional psammoma bodies and dystrophic calcifications were present in these nodules. Focal lymphocytic infiltration with lymphoid follicle formation was also noted (Figure 5B). Immunohistochemically, the spindle cells were reactive to factor XIIIa (Figure 6) and vimentin, but negative for CD34, CD68, desmin, S-100 protein, epithelial membrane antigen (EMA), muscle-specific actin, calretinin, ALK, CD117, and bcl-2. *In situ* hybridization for EBER was also negative. The microscopic features and immunohistochemical characteristics of the
mesenteric nodules were consistent with the diagnosis of CFPT.

Discussion

Vascular tumors are the most common neoplasms of the spleen, and they include several different entities, some of which are unique to that organ. SANT is a novel vascular lesion of the spleen, and it must be differentiated from other vascular tumors or tumor-like lesions of the spleen, including hamartoma, littoral cell angioma (LCA), inflammatory pseudotumor, and follicular dendritic cell tumor (FDC).

Hamartoma is a tumor composed of a disorganized overgrowth of mature cells and tissues that are normally present within the organ. Splenic hamartoma is an overgrowth of sinus-like structures of the red pulp, which is immunoreactive to CD8. In contrast, SANT contains three types of vessels, i.e., capillaries, sinusoids, and small veins. Each vascular type has a distinct phenotype and recapitulates the normal vascular structure of splenic red pulp. The capillaries of SANT are usually CD31+, CD34+, and CD8−, resembling the capillaries in the cord of normal splenic red pulp. The sinusoids are CD31+, CD34−, and CD8+, reminiscent of the sinusoids in the normal red pulp. The small veins are also CD34+, CD31+, and CD8−. Therefore, SANT can be regarded as a variant of splenic hamartoma5,8 with an overgrowth of all three types of vessels in the red pulp.

LCA is a unique vascular neoplasm of the spleen. Grossly, it usually presents as a nodular lesion with sponge-like vascular spaces. Microscopically, LCA comprises anastomosing sinusoidal vascular channels lined by tall endothelial cells. Immunohistochemically, these tall endothelial cells usually express both endothelial (factor VIII,
CD31, and CD34) and histiocytic markers (CD68, KP-1) but are negative for CD8. Therefore, it is easy to differentiate LCA from SANT by gross, microscopic, and immunohistochemical examinations.

Inflammatory pseudotumor is a myofibroblastic proliferative lesion with an edematous myxoid background rich in blood vessels and inflammatory cells. Because of the angiomatoid or “granulation tissue-like” core and a fibromyxoid cortex, SANT has been thought to be a variant of inflammatory pseudotumor. Unlike the conventional inflammatory pseudotumor, SANT has fewer inflammatory cells and myofibroblasts. In addition, the EBV genome is usually present in the tumor cells of splenic inflammatory pseudotumor but not in SANT. Therefore, there are still certain distinct histologic and immunohistochemical differences between SANT and inflammatory pseudotumor.

In addition, SANT has to be differentiated from FDC, which can also be found in the spleen occasionally. FDC is characterized by a proliferation of oval to spindle cells that form fascicles and whorls. Immunohistochemically, the spindle cells of FDC usually express CD21, S-100 protein, and CD35. Thus, FDC can be differentiated from SANT by immunohistochemical staining. Although cavernous hemangioma is the most common vascular neoplasm of the spleen, it is not difficult to differentiate splenic hemangioma from SANT by gross and microscopic examinations.

Because SANT is a recently described entity and only a limited number of cases have been reported, the pathogenesis of SANT is unknown. Whether it is a neoplasm or a reactive lesion is still unclear. Several hypotheses have been proposed for the formation of SANT. First, the angiomatoid nodule of SANT is similar to an organized hematoma. SANT may thus have evolved from a hematoma. Second, since the angiomatoid nodules of SANT comprise red pulp elements only, SANT may be considered a variant of splenic hamartoma that has undergone a peculiar form of sclerosis. Third, the internodular zones of SANT are often indistinguishable from inflammatory pseudotumor. Therefore, SANT may be a peculiar variant of inflammatory pseudotumor. Finally, in some patients with space-occupying lesions in the spleen, nodular transformation of the red pulp can be found. Therefore, the angiomatoid nodules of SANT may also represent a peculiar transformation of the red pulp in response to an exaggerated stromal proliferation. The above observations suggest that SANT is more like a reactive lesion rather than a true neoplasm. We also agree with this hypothesis because patients with SANT have a relatively high prevalence (20%) of concurrent diseases at other sites; our patient also had multiple CFPTs on the mesentery.

CFPT is an uncommon tumor-like lesion first described by Rosenthal and Abdul-Karim in 1988. In 1993, Fetsch et al added 10 additional cases and proposed the designation "calcifying fibrous pseudotumor". The tumor usually arises from the peritoneal subserosa or the soft tissue. Lesions of the soft tissue tend to occur in childhood, while lesions of the peritoneum can be found in both children and older patients. This implies that the two groups of CFPT may have different mechanisms of tumorigenesis.

Grossly, CFPT usually presents as a well-circumscribed gray–white elastic tumor. On the serosal surface, it may grow as a pedunculated tumor. Its size is variable, ranging from less than 1 cm to more than 10 cm. Lesions in the soft tissue tend to be larger than those in the peritoneum.

Microscopically, CFPTs are characterized by four components: (1) dense hyalinized collagen bundles; (2) bland spindle-shaped fibroblasts; (3) lymphoplasmacytic infiltrations; and (4) psammomatous or dystrophic calcifications. The collagen bundles are often arranged haphazardly or in whorls. The lymphoid infiltration may aggregate as lymphoid follicles or germinal centers. Immunohistochemically, the spindle-shaped fibroblastic cells in CFPT are usually positive for vimentin and factor XIIIa. They are also variable for smooth muscle actin and CD68 but negative for cytokeratin, desmin, S-100, EMA, calretinin, ALK, CD117, and bcl-2.

The etiology of CFPT is still unknown. Some researchers suggest that CFPT might arise from
an inflammatory myofibroblastic tumor (IMT), since both lesions coexist in some patients, and transformation between IMT and CFPT has also been reported.12,13 However, there are still some differences between the two tumors. First, calcification is a common feature of CFPT but rare in IMT. Second, up to 60% of IMTs express immunoreactivity for ALK-1,14,15 which is rare in CFPT. Third, EBV infection is frequently detected in intra-abdominal IMTs but never described in CFPT. Therefore, the relationship between IMT and CFPT remains controversial, although there might be a small subgroup of IMT that evolves to CFPT.

Clinically, both SANT and CFPT are benign lesions and generally do not cause mortality. Most of them were found incidentally or presented as palpable masses. Peritonitis was reported in some patients with abdominal CFPTs, and in rare cases symptoms related to superior vena cava and trachea compression have also been described. No recurrence of SANT following splenectomy has been reported, but recurrence of CFPT was reported in eight patients and three of them had multiple lesions. Accordingly, the present case is at higher risk of CFPT recurrence.

In summary, we reported a unique case with coexistence of CFPT and SANT. Both lesions are closely associated with IMT/inflammatory pseudotumor. The coexistence of the two rare entities in our patient may not be just a coincidence, and a common reactive mechanism contributory to both lesions is more likely.

References


3. Krishnan J, Danon A, Frizzera G. Use of anti-factor VIII-related antigen (F8) and QBEN10(CD34) antibodies helps classify the benign vascular lesions of the spleen. Mod Pathol 1993;6:94A.


