Journal of Pathology Research
ISSN: 0976-8068 & E-ISSN: 0976-8076, Volume 3, Issue 1, 2014, pp.-049-053.
Available online at http://www.bioinfopublication.org/jouarchive.php?opt=&jouid=BPJ0000276

SCLEROSING ANGIOMATOID NODULAR TRANSFORMATION OF THE SPLEEN - A REPORT OF TWO CASES AND REVIEW OF LITERATURE

EL DEEB N.M.F.[1]*, HASSAB H.A.[2], ASAL M.F.[2] AND HASSAB T.H.[3]

[1]Department of Pathology, Faculty of Medicine, Alexandria University, Alexandria, Egypt.
[2]Department of Surgery, Faculty of Medicine, Alexandria University, Alexandria, Egypt.
[3]Department of Surgery, Medical Research Institute, Alexandria, Egypt.
*Corresponding Author: Email- nevineldeeb@yahoo.com

Received: November 12, 2013; Accepted: February 27, 2014

Abstract- Sclerosing angiomatoid nodular transformation (SANT) is a rare benign, proliferative vascular lesion affecting the spleen. Only a few cases have been reported to date. In this study, two cases of SANT are presented with their clinical and pathological features, and review of the related literature. The first case is a 34-year-old woman who presented with right hypochondrial pain. She gave a history of mild left hypochondrial discomfort that started 2 years prior to presentation. Computed tomography (CT) showed gall stones together with a 9 cm-sized solitary well-defined hypodense splenic mass. She underwent splenectomy and cholecystectomy. The second case is a 22-year-old man who was evaluated for a 6-months history of left hypochondrial pain. An 8 cm-sized solitary splenic mass was detected on CT scan; and contrast-enhanced magnetic resonance imaging (MRI) revealed a spoke-wheel pattern of enhancement. Splenectomy was performed. In both cases, the spleen showed grossly a well-circumscribed solid mass with a multinodular hemorrhagic cut surface. Microscopically, the mass consisted of multiple angiomatoid nodules surrounded by collagen bundles with a lymphoplasmacytic infiltrate. Immunohistochemically, CD31, CD34 and CD8 were detected in the endothelial cells of the angiomatoid nodules. Smooth muscle actin and CD68 expression was noted as well, but there was no reactivity for CD21. SANT has an excellent prognosis with splenectomy being curative.

Keywords- SANT, splenic mass, angiomatoid nodules, immunohistochemistry

Introduction

Sclerosing angiomatoid nodular transformation (SANT) of the spleen is a recently recognized, rare, tumour-like vascular splenic lesion of uncertain histologic nature [1]. Its particular gross and histological appearance, immunophenotype, as well as its benign clinical course indicate that it is a distinctive non-neoplastic vascular lesion of the spleen, specifically, of the red pulp [2]. SANT demonstrates a complex heterogeneous mixture of blood vessels lined by three types of endothelial cells; cord capillary endothelium, sinusoidal endothelium, and small vein endothelium, resembling the vascular structure of the normal red pulp of the spleen [3]. SANT has a benign clinical course and is cured by means of splenectomy [1,2].

To date, fewer than 100 cases have been reported in the English medical literature [4]. In this article, we report two new cases of SANT of the spleen which were treated with surgical resection, with their clinicopathological features, and review of the related literature.

Case Report

Case 1

A 34-year-old woman complained of right hypochondrial pain, which started 2 months ago and progressively increased. She gave a history of mild left hypochondrial discomfort that started 2 years prior to presentation. Abdominal ultrasonography demonstrated stones in the gall bladder, as well as a well-defined, hypoechoic lesion in the spleen. Computed tomography (CT) revealed a solitary, well-defined hypodense mass in the spleen. Surgical exploration was done, splenectomy and cholecystectomy were performed. The gall bladder showed gross and microscopic evidence of chronic calcular cholecystitis. The spleen showed a solitary mass measuring 9 cm in maximum dimension.

Case 2

A 22-year-old man complained of left hypochondrial pain that started 6-months before presentation. Abdominal ultrasonography demonstrated a sharply-demarcated, hypoechoic splenic mass. CT showed a solitary hypodense splenic mass. Contrast-enhanced magnetic resonance imaging (MRI) revealed a solitary and round lesion at the anterior aspect of the spleen with progressive filling in enhancement (from periphery to centre) in the consequent dynamic phases displaying a spoke wheel pattern, with presence of a central non-enhancing area [Fig-1A]. Splenectomy was performed. The spleen showed a solitary mass measuring 8 cm in maximum dimension.

The two reported cases showed similar gross (apart from the size of the splenic lesion), microscopic and immunophenotypic features, so these aspects are described together.

On gross examination, the resected spleen showed a solitary well-circumscribed, unencapsulated, roughly round-shaped, solid mass, bulging the capsular surface of the spleen. On sectioning, the mass was formed of multiple dark red hemorrhagic nodules separated by stellate-shaped gray-white scar-like fibrous bands [Fig-1B].

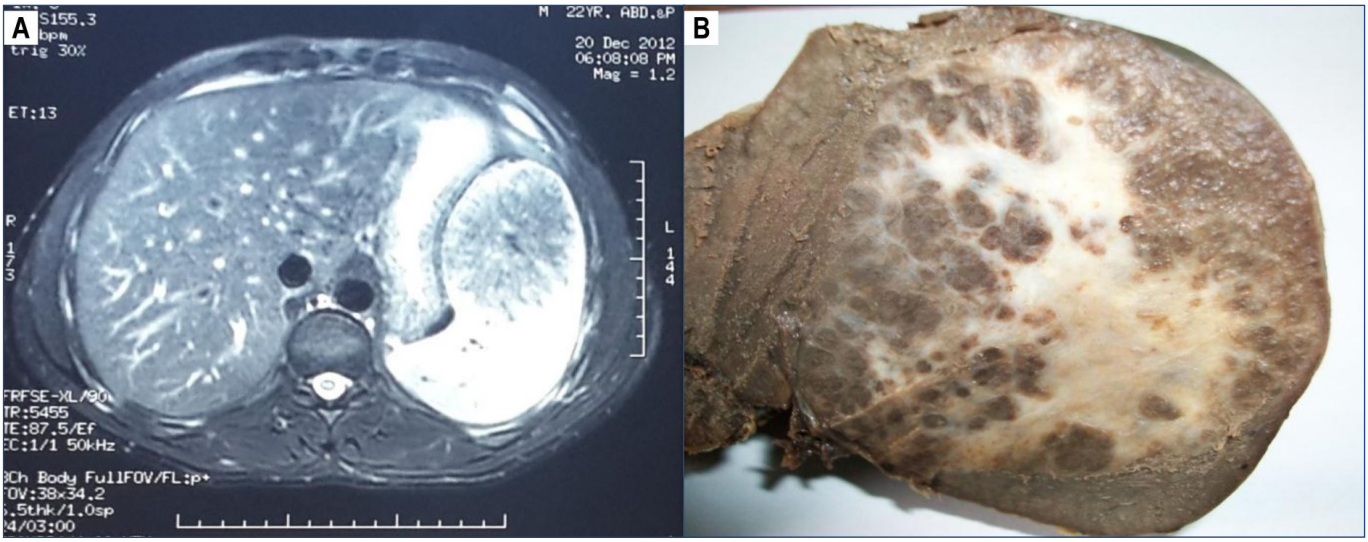

Fig. 1- (A) Contrast-enhanced magnetic resonance imaging demonstrating a solitary mass in the spleen, with spoke-wheel pattern of enhancement. **(B)** Spleen showing a round, well-circumscribed unencapsulated lesion. The cut surface shows multiple dark red nodules separated by stellate-shaped gray-white fibrous bands.

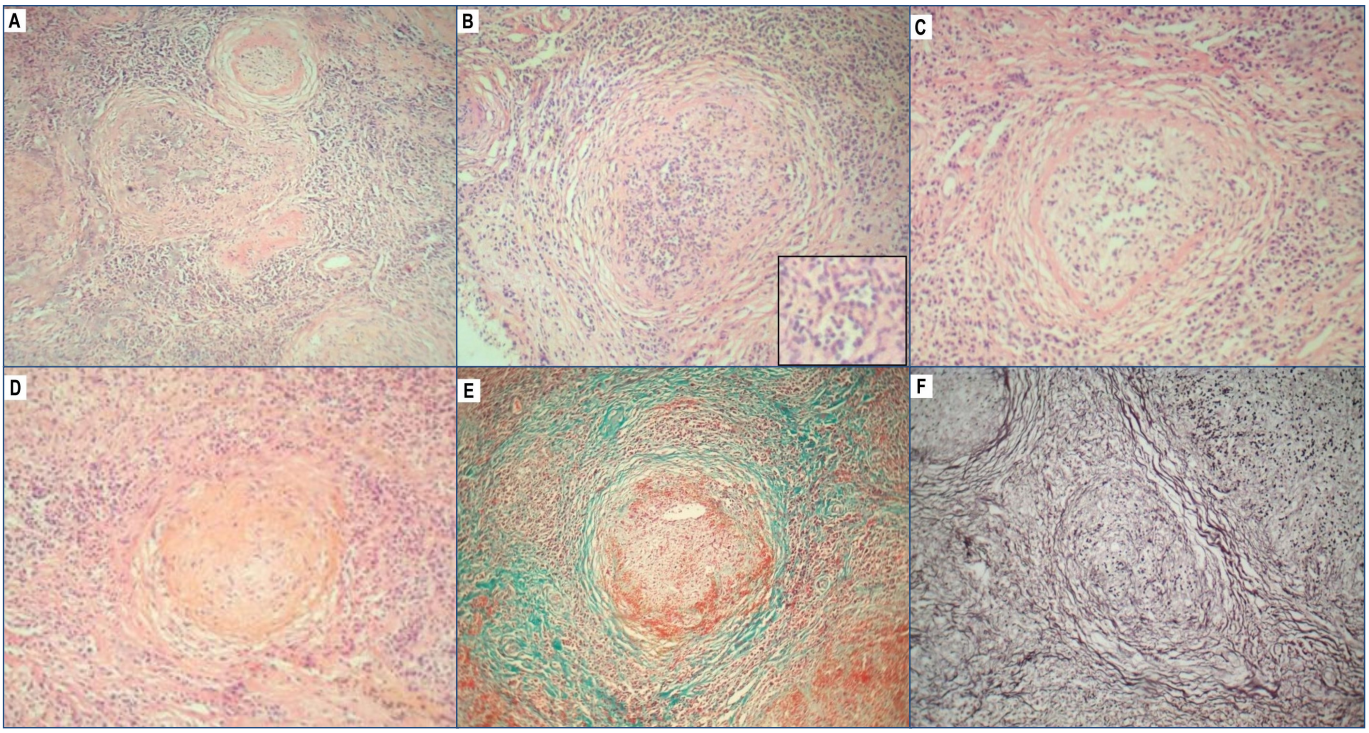

Fig. 2- (A) The lesion is formed of angiomatoid nodules surrounded by a dense fibrocollagenous stroma; **(B)** The angiomatoid nodule shows slit-like or irregularly-shaped vascular channels interspersed by spindle-shaped or ovoid cells. Inset: The endothelial cells lining the vascular channels are plump, without cellular atypia; **(C)** An angiomatoid nodule delimited by a rim of fibrin, resulting in a necrotizing vasculitic appearance; **(D)** A nodule with a haemorrhagic appearance. Note the presence of extravasated red blood cells and hemosiderin-laden macrophages; **(E)** Masson-trichrome stain demonstrating the dense collagen deposition in the interangionodular areas; **(F)** Reticulin stain highlighting the intricate vascular network within the nodules as well as the sinusoid-like structures. Original magnifications: **(A)** x100; **(B)** x 200, inset x 400; **(C-F)** x 200.

Microscopic examination revealed that the lesion was formed of multiple well-circumscribed individual and confluent vascular/ angiomatoid nodules of various sizes embedded in a fibrosclerotic stroma [Fig-2A]. At higher magnification, each nodule was composed of slit-like or irregular vascular structures intermingled with spindle cells as well as inflammatory cells, mainly lymphocytes and plasma cells [Fig-2B]. The endothelial cells lining the vascular channels were plump and bland-looking without cellular atypia [Fig-2B, (inset)]. Some nodules were surrounded by dense concentric collagen fibers, producing a granuloma-like appearance, whereas others showed a fibrin rim resulting in a necrotizing vasculitic appearance [Fig-2C]. Still, other nodules appeared haemorrhagic, with extravasated red blood cells and hemosiderin-laden macrophages seen both within and around the nodules [Fig-2D]. The internodular stroma was dense fibrous, formed of proliferative spindle cells and showed infiltration by lymphocytes, plasma cells, fibroblasts and

macrophages. No necrosis was present in the lesion. The adjacent splenic tissue showed no pathologic abnormality. Masson-trichrome staining demonstrated dense collagenous fibrous tissue in the inter-angionodular areas [Fig-2E]. The intricate vascular network within the nodules as well as the sinusoid-like structures were highlighted by a reticulin stain [Fig-2F].

Using immunohistochemistry, staining for CD31 highlighted numerous cells within the angiomatoid nodules [Fig-3A], including individual interspersed cells, as well as cells lining recognizable vascular channels [Fig-3B]. CD34 immunostaining displayed the endothelial cells lining the narrow, well-formed capillaries [Fig-3C], but positively-stained cells varied in different nodules. Overall, CD31-positive capillaries and endothelial cells were considerably more than CD34-positive ones. Few CD8-positive cells [Fig-3D] were detected in the endothelial lining of some sinusoid-like structures without CD34 expression. Focal expression of CD68 was detected within the nodules in some of the vascular lining cells. In addition, CD68 highlighted numerous interspersed cells between the vessels within the nodules, and scattered cells in the internodular stroma [Fig-3E].

Alpha-smooth muscle actin (SMA) immunostaining was positive in cell clusters seen between vascular spaces, and in some spindle cells of the interangionodular areas [Fig-3F]. Staining for CD21 was negative. Based on these results, the splenic mass was diagnosed as SANT.

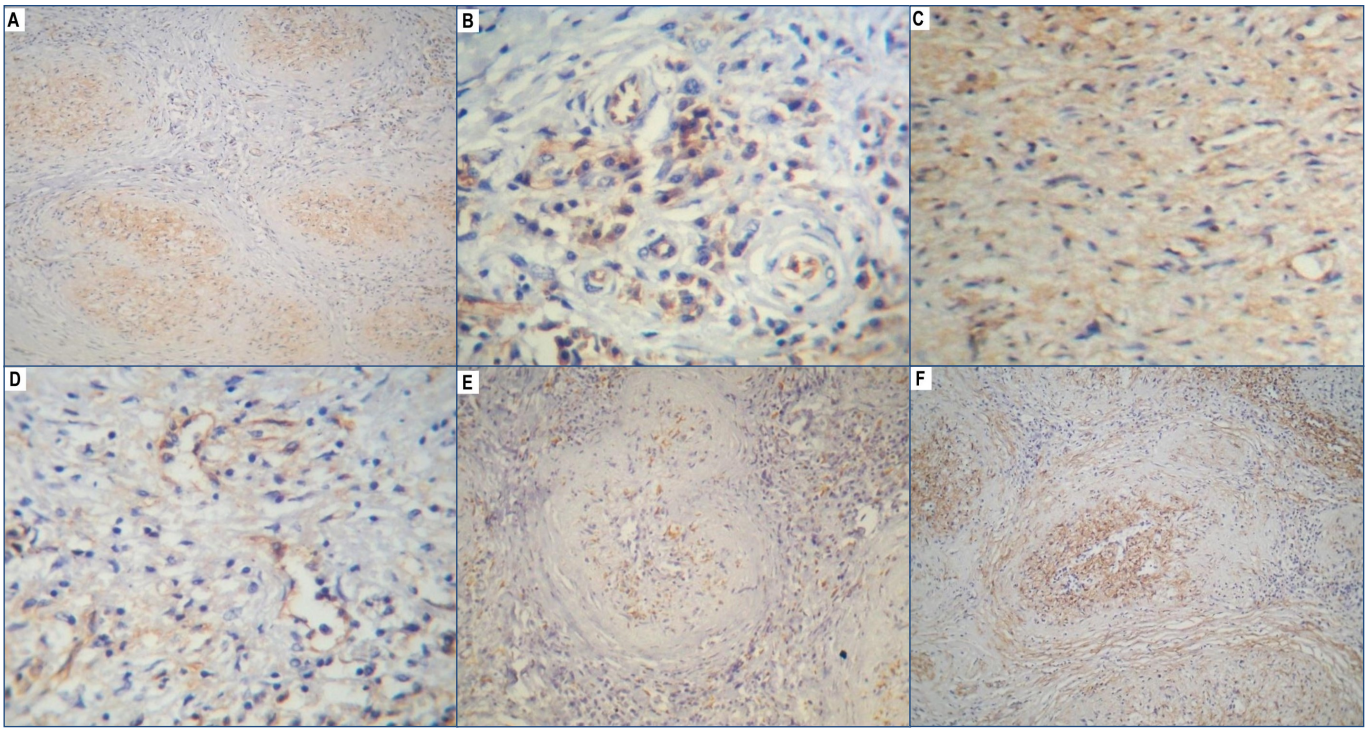

Fig. 3- Immunohistochemical staining: (A) CD31, showed nodular positive staining ;(B) CD31, high power view, positive reaction in the plump endothelial lining of vascular spaces; (C) CD34 stained the endothelial cells lining the narrow, well-formed capillaries; (D) CD8-positive cells were detected in the endothelial lining of some sinusoid-like structures; (E) CD68 highlighted few vascular lining cells, numerous interspersed cells between the vessels within the nodules, and scattered cells in the internodular stroma; (F) Alpha SMA positively stained cell clusters between vascular spaces, and some spindle cells of the interangionodular areas. Original magnifications: (A) x100, (B-D) x 400, (E-F) x 200.

Discussion

Martel, et al. [1] described a distinctive tumor-like vascular lesion of the spleen, which they termed *sclerosing angiomatoid nodular transformation* (SANT), based on the characteristic histological features and immunophenotype. Some isolated cases that had been previously reported under the terms *splenic hamartoma* [5,6], *cord-capillary hemangioma* [7] and *hemangioendothelioma* [8] might also belong to this category. Kraus and Dehner [9] and Karim, et al. [10] described this lesion as a benign vascular neoplasm of the spleen with myoid and angioendotheliomatous features. It is referred to as "multinodular hemangioma" in *Rosai and Ackerman's Surgical Pathology* [11], emphasizing the most characteristic features of the lesion; the presence of multiple nodules and the angiomatous nature.

Only a few reports have detailed the clinicopathological aspects of SANT of the spleen [1-3,12]. These reports mention that SANT is most commonly encountered in middle-aged adults, with a fairly wide age range for presentation of 22-82 years [3]. An evident female predominance of cases was reported, with a female-to-male ratio of 2:1 [1,2,12]. Most patients were asymptomatic and the splenic mass was discovered incidentally during laparotomy or during imaging studies for unrelated conditions [1,2,13]. Some patients complained of abdominal pain or discomfort. Fever, increased erythrocyte sedimentation rate and splenomegaly were encountered in a minority of patients [1,3]. Abdominal ultrasonography, CT scan, and MRI usually reveal a solitary hypodense, multinodular splenic mass [2]. In accordance with these data, both cases presented herein were within the reported age range (34 and 22 years old). The first case complained mainly of right hypochondrial pain and sought medical advice because of her gall bladder condition, and the splenic mass was incidentally discovered during abdominal imaging. The patient gave a 2-years history of mild left upper quadrant discomfort, which was not severe enough to make her seek medical advice. On the other hand, the second case presented with a complaint related to the splenic lesion, left hypochondrial pain.

At gross inspection, patients with SANT often have a normal-sized or slightly enlarged spleen [13]. The lesion itself usually appears as a solitary, unencapsulated but well- circumscribed mass with multinodular cut section featuring red brown nodules of variable size separated by fibrous bands radiating from a central stellate scar [3,13].

The most characteristic microscopic feature of SANT is the presence of multiple angiomatoid nodules, composed of irregularly-shaped vessels lined by prominent bland-looking endothelial cells. The nodules are surrounded by a dense fibrocollagenous stroma with a variable lymphoplasmacytic infiltrate [2,3].

Immunohistochemical analysis of SANT usually displays a complex heterogeneous mixture of three distinct endothelial phenotypes that resemble the normal vascular structure of the red pulp: cord capillaries (CD34+/CD8-/CD31+), sinusoids (CD34-/CD8+/CD31+) and small veins (CD34-/CD8-/CD31+) [1]. Positive staining for CD68 is also typical in splenic SANT [12,13], whereas CD21 staining has been consistently negative [1,12]. Positive staining for SMA has been reported within nodules and in the internodular stroma [14].

The gross and microscopic features of the splenic lesion in the two cases reported in this article were similar to those described for SANT in literature, and the diagnosis was confirmed by immunohistochemical analysis, which revealed variable expression of markers for splenic sinusoidal, capillary-like, and small vein-like endothelial cells, including CD31, CD34, and CD8 in the endothelial lining of the vascular channels within the angiomatoid nodules. Some lining cells were focally positive for CD68 as well. SMA staining was observed in the spindle cells interspersed between the vascular channels and in the internodular stroma. Reactivity for CD21 was not identified. These immunohistochemical results are in agreement with the immunophenotype of SANT described in previous studies [1,14].

The differential diagnosis of SANT includes other splenic vascular lesions such as splenic hamartoma, hemangioma, littoral cell angioma, hemangioendothelioma, as well as inflammatory myofibroblastic tumor and nodular transformation of the splenic red pulp in association with metastatic carcinoma [2,3,14,15].

Hamartoma of the spleen is a tumor-like lesion formed of structurally-disorganized mature red pulp elements [2]. Grossly, the outlines of hamartomas are usually less defined than SANT [12]. Microscopic examination reveals disorganized vascular channels lined by plump endothelial cells resembling splenic sinuses, with intervening red pulp-like stroma and absence of malpighian follicles [5,15]. The endothelial cells in hamartomas show an immunophenotype similar to normal sinusoids, that is, CD31+/CD34-/CD8+ [5,16] and are negative for CD68 and CD21 [15]. Although the possibility that SANT represents a splenic hamartoma that has undergone a peculiar form of sclerosis cannot be totally excluded, in their classical definition hamartomas consist of only sinusoid-type vessels and do not show a striking angiomatoid nodular pattern [15].

Splenic hemangioma is the most common benign tumour arising from sinusoidal epithelial cells. The cavernous type is more common than the capillary type [14,15]. The endothelial cells often express CD31 and CD34, but not CD8, CD21 or CD68 [15]. Although infarction, thrombosis with organization, cystic degeneration and fibrosis may be seen, especially in larger lesions [14,15], they do not display the distinctive angiomatoid nodular changes of SANT [17].

Littoral cell angioma is a vascular tumor arising from littoral cells originating from splenic sinuses [15,16,18]. It usually appears as multiple hemorrhagic nodules involving the red pulp, and is formed of variable-sized, irregular anastomosing vascular sinus-like channels lined by columnar cells having vesicular nuclei, open chromatin, and small nucleoli [18]. Sometimes, papillary fronds, cellular vacuolization, evidence of hemophagocytosis, and focal aggregates of eosinophilic globules may be also seen in this tumor [2]. The cells lining the vascular channels are positive for both endothelial and histiocytic markers, CD31 and CD68, whereas they are negative for CD34 and CD8 [2,14,15]. CD21 is exclusively positive in littoral cell angioma [2,15]. SANT lacks all the typical morphologic features associated with littoral cell angioma, namely the monotonous vascular composition, pseudopapillary growth pattern, plumper appearance of the lining cells and absence of sclerosis [2,19]. In addition, SANT nodules lack CD21 expression. Unlike SANT, littoral cell angioma is negative for CD8 and CD34 [16].

Hemangioendothelioma is considered a lesion of intermediate histology between hemangioma and angiosarcoma [14,15]. Epithelioid, spindle, and a combination of these two patterns have been described [2,20]. The cells lining the vascular channels show mild to moderate atypia, and are usually positive for CD31 and factor VIII–related antigen, and variably express CD34, but not CD8 [14,15]. In contrast, SANT does not show an epithelioid morphology and is composed of a mixture of three types of blood vessels as mentioned before [2].

Inflammatory myofibroblastic tumor appears grossly as a gray-white mass with a well-defined border [14]. Microscopically, this lesion is composed of spindle cells with features of fibroblasts/ myofibroblasts, a mixed inflammatory infiltrate and a hypocellular fibrocollagenous stroma [21]. Although the internodular areas of SANT may resemble inflammatory myofibroblastic tumor, the latter lacks the angiomatoid nodular pattern of SANT [2,14]. Smooth muscle actin and CD68 are invariably expressed in this lesion, but endothelial markers are typically negative [9,14].

Nodular transformation of the splenic red pulp in response to metastatic carcinoma is an occasional finding, where metastasis may induce prominent fibrosis with a nodular appearance [22]. The splenic red pulp becomes replaced by multiple nodules separated by fibrous tissue featuring a lymphohistiocytic infiltrate, metastatic malignant cells, and hemorrhage [2]. None of the SANT cases reported to date has been associated with metastatic carcinoma in the spleen [2].

The pathogenesis of SANT is still obscure [3]. In the literature, about 20% of the reported cases of SANT were found to be accompanied by other diseases [14], such as hypertension, chronic lymphocytic leukemia, as well as various malignancies, such as carcinomas of the kidney, lung and gastrointestinal tract without metastasis to the spleen [1]. However, no strong correlation with another disease process was identified [1,19].

Martel, et al. [1] postulated that the angiomatoid nodules in SANT originate from splenic red pulp and represent a peculiar nodular transformation of the red pulp in response to an exaggerated stromal proliferation. Diebold, et al. [23] suggested that disturbance of the circulation in the red pulp may be a possible mechanism of formation of angiomatoid nodules. The presence of CD68 positivity may point to an active phagocytic process in response to increased splenic activity [12], adding further evidence to support the non-neoplastic nature of this lesion. SANT may also represent a peculiar

form of hamartoma of the spleen because it is composed of red pulp elements [1]. Teng, et al. [14] described the coexistence of SANT and a hamartoma-like lesion together with nodules showing transitional features in one of the cases they reported. This, together with the overlap in immunophenotypic and morphologic features made them suggest that SANT may represent a variant of splenic hamartoma. Lee, et al. [19] reported the coexistence of SANT and calcifying fibrous pseudotumor, and proposed that these two lesions may have a common mechanism. Pathologically, SANT has been thought to be a variant of inflammatory pseudotumor, because in some of the reported cases the interangionodular areas showed an inflammatory pseudotumor-like appearance [23]. Furthermore, two reports have mentioned the coexistence of a hepatic angioma and SANT [14,24].

It remains to be determined whether SANT is a de novo lesion or the final common pathway of different benign splenic conditions [14]. Although its histogenesis and denomination are still poorly understood, SANT appears to be a benign condition, and splenectomy was found to be curative in all of the reported cases [1,12]. Our two new cases are in accordance with the pathological criteria described by Martel, et al. [1], supporting the suggestion that SANT may represent a nodular transformation of the red pulp in response to an exaggerated stromal proliferation.

Conflicts of Interest: None declared.

References

[1] Martel M., Cheuk W., Lombardi L., Lifschitz-Mercer B., Chan J.K., Rosai J. (2004) *Am. J. Surg. Pathol.*, 28(10), 1268-1279.

[2] Awamleh A.A. and Perez-Ordonez B. (2007) *Arch. Pathol. Lab Med.*, 131, 974-978.

[3] Lee H.J., Choi S.Y., Huang S.M., Sul J.Y. and Kim J.M. (2011) *The Korean Journal of Pathology*, 45, 111-114.

[4] Kim H.H., Hur Y.H., Koh Y.S., Kim J.C., Kim H.J., Kim J.W., Kim Y., Lee J.H. and Cho C.K. (2013) *Surg. Today*, 43(8), 930-936.

[5] Krishnan J. and Frizzera G. (2003) *Semin. Diagn. Pathol.*, 20, 94-104.

[6] Silverman M.L. and Livolsi V.A. (1978) *Am. J. Clin. Pathol.*, 70, 224-229.

[7] Krishnan J., Danon A. and Frizzera G. (1993) *Mod. Pathol.*, 6, 94A.

[8] Kaw Y.T., Duwaji M.S., Knisley R.E. and Esparza A.R. (1992) *Arch. Pathol. Lab. Med.*, 116, 1079-1082.

[9] Kraus M.D. and Dehner L.P. (1999) *Histopathology*, 35, 328-336.

[10] Karim R.Z., Ma-Wyatt J., Cox M. and Scolyer R.A. (2004) *Int. J. Surg. Pathol.*, 12, 51-56.

[11] Rosai J. (2011) *Spleen*. *Rosai and Ackerman's Surgical Pathology*. 10th ed., Edinburgh, Elsevier Inc, 1917.

[12] Li L., Fisher D.A. and Stanek A.E. (2005) *Am. J. Surg. Pathol.*, 29, 839-841.

[13] Thacker C., Korn R., Millstine J., Harvin H., Van Lier Ribbink J.A. and Gotway M.B. (2010) *Abdom. Imaging*, 35, 683-689.

[14] Teng X., Yu X., Wang G., Xu L. and Lai M. (2008) *Anal Quant Cytol. Histol.*, 30, 125-132.

[15] Lee H. and Maeda K. (2009) *Arch. Pathol. Lab. Med.*, 133, 147-151.

[16] Arber D.A., Strickler J.G., Chen Y.Y. and Weiss L.M. (1997) *Am. J. Surg. Pathol.*, 21, 827-835.

[17] Di Blasi A., Boscaino A., De Dominicis G. and Marino-Marsilia G. (2005) *Pathologica*, 97, 124-129.

[18] Falk S., Stutte H.J. and Frizzera G. (1991) *Am. J. Surg. Pathol.*, 15, 1023-1033.

[19] Lee J.C., Lien H.C. and Hsiao C.H. (2007) *J. Formos. Med. Assoc.*, 106, 234-239.

[20] Suster S. (1992) *Am. J. Surg. Pathol.*, 16, 785-792.

[21] Neuhauser T.S., Derringer G.A., Thompson L.D., Fanburg-Smith J.C., Aguilera N.S., Andriko J., Chu W.S. and Abbondanzo S.L. (2001) *Arch. Pathol. Lab. Med.*, 125, 379-385.

[22] Fakan F. and Michal M. (1994) *Histopathology*, 25, 175-178.

[23] Diebold J., Le Tourneau A., Marmey B., Prevot S., Müller-Hermelink H.K., Sevestre H., Molina T., Billotet C., Gaulard P., Knopf J.F., Bendjaballah S., Mangnan-Marai A., Brière J., Fabiani B. and Audouin J. (2008) *Histopathology*, 53, 299-310.

[24] Cao J.Y., Zhang H. and Wang W.P. (2010) *World J. Gastroenterol.*, 16(29), 3727-3730.