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Case Series

Pathology Section

Sclerosing Angiomatoid Nodular Transformation: A Series of Four Cases

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ABSTRACT

Among the primary non haematopoietic neoplasms of the spleen, vascular neoplasms are the most common. These vascular neoplasms consist of haemangiomas, littoral cell angiomas, lymphangiomas, Splenic Hamartomas (SHs), haemangioendotheliomas, angiosarcomas and Sclerosing Angiomatoid Nodular Transformation (SANT). SANT is a recently described, rare non neoplastic vascular entity of the spleen. The majority of patients are asymptomatic and are incidentally picked up on Computed Tomography (CT) or Magnetic Resonance Imaging (MRI), but the diagnosis can mimic malignant lesions of the spleen on imaging studies. SANT is considered a female-predominant disease with a wide age distribution. Majority of cases have been reported in the adult age group, in paediatric age it is very rare. Hereby, the authors present a case series of four patients diagnosed with SANT in tertiary care hospital. Two of them were in the paediatric age group (four-year-old boy and 14-year-old girl), while the other two were middle-aged adults (46-year-old female and 41-year-old male). Both paediatric patients presented with symptoms of abdominal pain and discomfort and underwent an Ultrasonographic (USG) examination, which showed a well-circumscribed hypoechoic mass. Laboratory findings showed increased Erythrocyte Sedimentation Rate (ESR) and anaemia. Based on the clinical and radiological findings, diagnosis of splenic hamartoma and inflammatory pseudotumour were made in these cases. Unlike the paediatric patients, both adult patients were asymptomatic and diagnosed incidentally during routine radiological examinations. The USG examination showed a well-circumscribed hypoechoic mass, with a difference in the size of the lesions. Light microscopic examination and immunohistochemical staining confirmed the diagnosis of SANT in all cases. The patients were followed for six months, during which no recurrences occurred. Although SANT is a benign tumour, it can sometimes be misdiagnosed by radiological studies, so surgical removal followed by histopathological and immunohistochemical examinations is required for an accurate diagnosis.

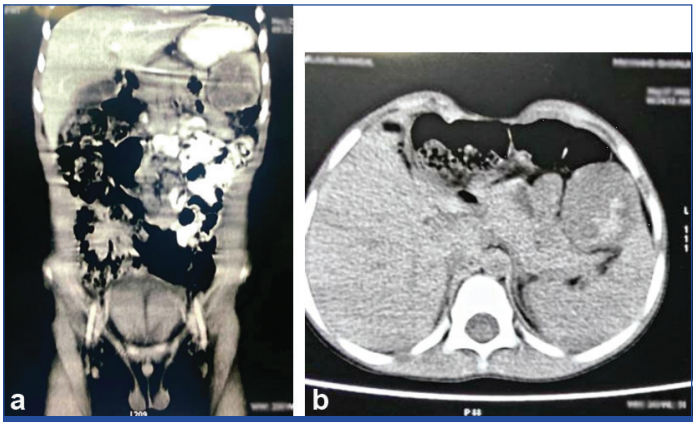
Keywords: Histopathology, Immunohistochemistry, Non haematopoietic, Splenic proliferation

INTRODUCTION

The Sclerosing Angiomatoid Nodular Transformation (SANT) is a rare non haematopoietic primary splenic proliferation that is often missed or misdiagnosed in routine histopathological practice. Martel M et al., first described SANT as a distinct diagnostic entity in 2004, based on a series of 25 cases [1]. In a recent systematic review of the literature by Aziret M et al., 230 cases of SANT were found to be published from 2004 to 2020 [2]; but only a few cases have been found in children [3]. The majority of these cases were reported outside of India. Indian data on SANT in the adult age group is very limited and in paediatric age group only three cases have been reported from the western part of the country by Kale KA et al., Vyas M et al., and Agrawal M et al., [4-6]. Differentiating SANT from other benign primary tumours and tumour-like lesions of the spleen can only be achieved by a thorough histopathological examination with the use of immunomarkers. We conducted a retrospective study from January 2012 to December 2023 in the Pathology Department of present tertiary care hospital in eastern India. In present series, authors discussed four cases of SANT diagnosed and treated during this period, among them two were paediatric age and two were adult cases.

Case 1

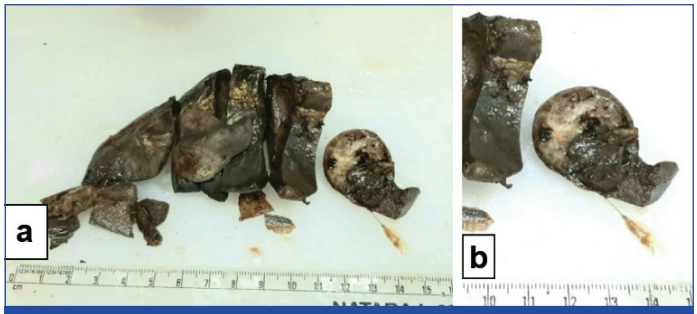
A four-year-old male child presented to the Paediatric Department with intermittent dull pain in the left upper quadrant of the abdomen, without other symptoms. Haematological parameters, along with liver and kidney function tests, were unremarkable, except for an increased level of Erythrocyte Sedimentation Rate (ESR). An abdominal ultrasound revealed a hypoechoic mass lesion in the spleen and a probable diagnosis of a benign vascular lesion was given. Which on CECT scan showed a comparatively hypovascular center with an enhancing rim and radiating vascularised tissue penetrating from the periphery toward the center of the lesion. "Spoke Wheel" pattern on delayed imaging is thought to a result from contrast penetrating the centre of the lesion from the peripheral vascular rim [Table/Fig-1a,b]. The patient was then referred to the Paediatric Surgery Department, where a laparoscopic splenectomy was done for further evaluation and the specimen was sent to present department.



[Table/Fig-1]: CECT images of four-year-old male child: (a) Axial unenhanced CT image shows a well-circumscribed, solid lesion in the spleen; (b) Coronal contrast enhanced CT shows a predominantly hypodense splenic mass.

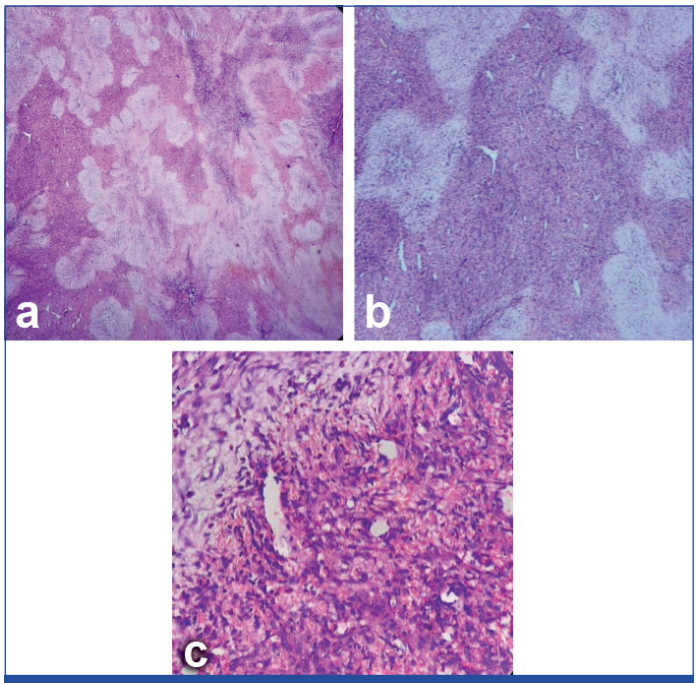
On gross examination, the splenectomy specimen measured 11×6×4 cm, with the cut section showing a well-circumscribed, non encapsulated bosselated mass measuring 3×2.5×2 cm. which on cut section showed firm, tan-white nodules separated by satellite fibrous areas and foci of haemorrhage [Table/Fig-2a,b].

Microscopic examination showed splenic parenchyma was replaced by multiple well-circumscribed nodules of varying sizes, surrounded by a variable fibrosclerotic stroma. The nodules were composed



[Table/Fig-2]: Gross pictures of Sclerosing Angiomatoid Nodular Transformation (SANT) of four-year-old male child: a) Total specimen; b) Cut section showed firm, tan- white nodules separated by satellite fibrous area and foci of haemorrhage with adjacent rim of normal spleen tissue.

of vascular spaces of different calibers, ranging from capillaries to sinusoid-like spaces lined by bland to plump endothelial cells without any atypia, necrosis, or mitotic figures. The intersecting fibrous septa showed bands of fibroblasts and myofibroblasts with abundant chronic inflammatory cells, like lymphocytes, plasma cells and haemoseridin-laden macrophages [Table/Fig-3a-c].



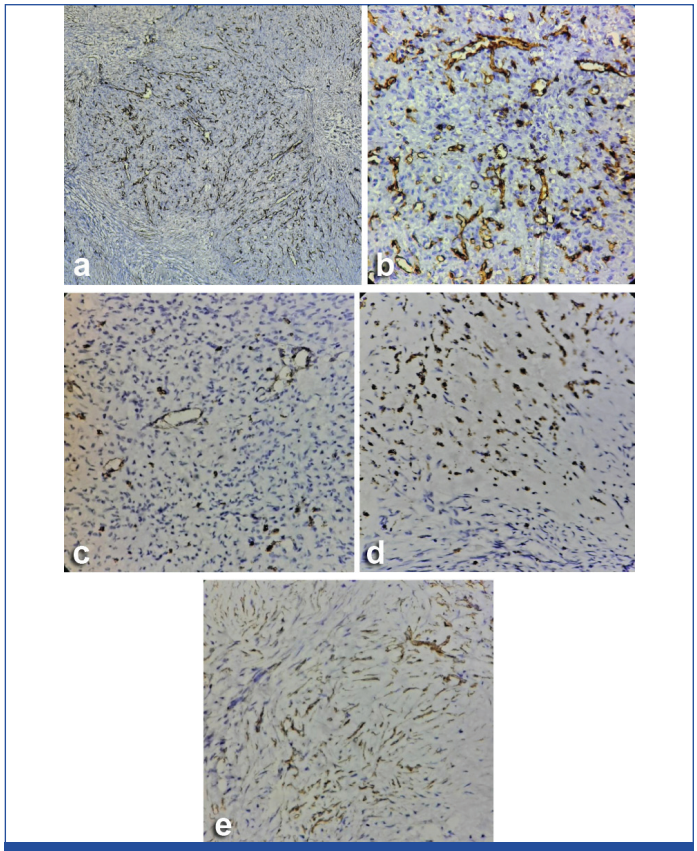
[Table/Fig-3]: Histopathological features of Sclerosing Angiomatoid Nodular Transformation (SANT) of four-year-old male child. (a) Photomicrograph showing multiple angiomatoid nodules of varying size separated by sclerotic stroma {Haematoxylin and Eosin (H&E)}; (b) Photomicrograph showing the nodules were composed of vascular spaces of different caliber ranging from capillaries to sinusoid like spaces (H&E, 10X); (c) Photomicrograph showing sinusoid like spaces lined by bland to plump endothelial cells without any atypia, necrosis and mitotic figures. The intersecting fibrous septa showed band fibroblast and myofibroblast with abundant chronic inflammatory cells like lymphocytes, plasma cells, haemosiderin laden macrophages (H&E, 10X).

To confirm the diagnosis, Immunohistochemical (IHC) staining was performed, which showed CD31 positivity in all capillaries and small veins, whereas CD34 staining highlighted only the capillaries. CD8 immunostaining showed positivity only in occasional sinusoid-like spaces but not in capillaries and small veins. Smooth Muscle Actin (SMA) staining highlighted the myofibroblastic stroma. Also, CD68 highlighted the spindle cell component and histiocytes [Table/Fig-4a-e].

On the basis of clinical presentation, radiological findings, histopathological results and immunohistochemical findings, a diagnosis of SANT was made. The patient was followed-up for one year after the surgery, with no recurrence reported.

Case 2

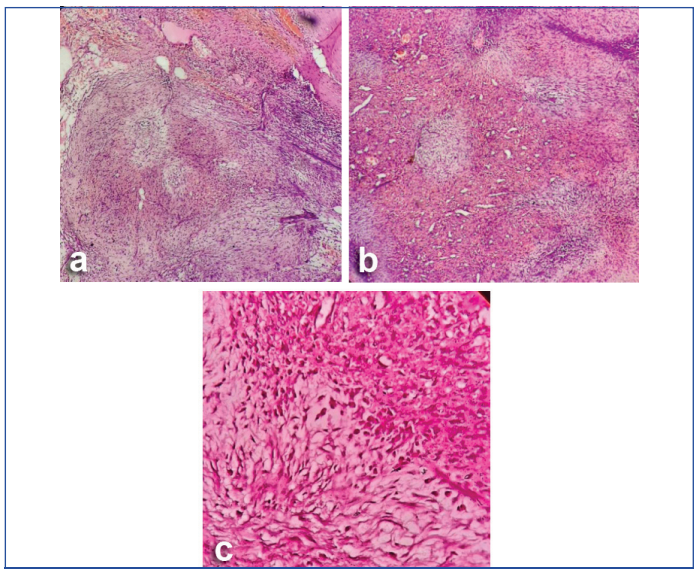
A 14-year-old female presented with left upper abdominal pain for six months and anaemia. Ultrasonography revealed a hypoechoic lesion in the spleen. A clinical diagnosis of inflammatory



[Table/Fig-4]: Immunohistochemistry of Sclerosing Angiomatoid Nodular Transformation SANT) of four-year-old male child. (a) Photomicrograph showing CD 34 positivity in capillaries; (b) Photomicrograph showing CD31 positively stained in small veins and capillaries; (c) Photomicrograph showing CD8 positively stained in splenic sinusoids; (d) Photomicrograph showing CD68 positive histiocytes in the internodular areas; (e) SMA staining highlights the myofibroblasts in stroma.

pseudotumour was given. CT scan or MRI was not performed. Laparoscopic splenectomy was performed and the tissue was sent for histopathological examination. The spleen was measuring 10×8 centimeters and had a circumscribed multinodular mass measuring 5×3 cm. The cut section appeared congested, with whitish fibrous strands in the parenchyma forming nodules.

Histopathological examination showed multiple nodules composed of vascular spaces, capillaries and sinusoid-like vessels of varying sizes within dense fibrotic stroma. The fibrous tissue was infiltrated by inflammatory cells, mainly lymphocytes and plasma cells [Table/Fig-5a-c].



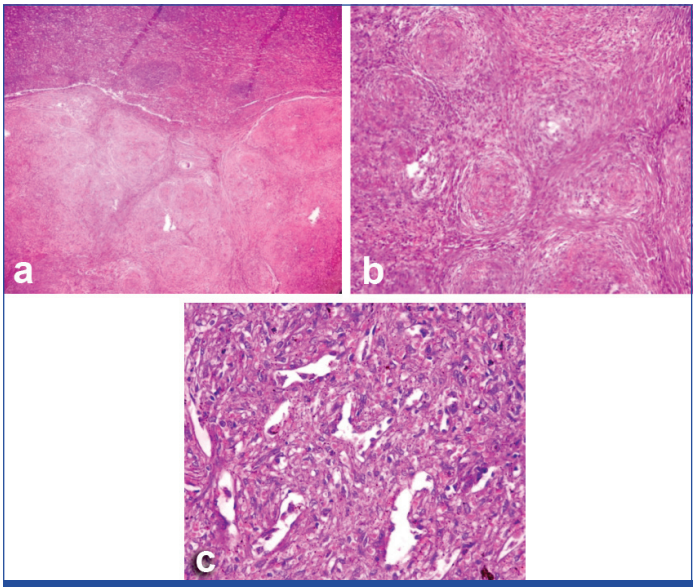
[Table/Fig-5]: Histopathological features of Sclerosing Angiomatoid Nodular Transformation SANT) of 14-year-old female child. (a) Photomicrograph showing nodules of varying size separated by sclerotic stroma (H&E, 4X); (b) Photomicrograph vascular spaces like capillaries to sinusoid (H&E, 10X); (c) Photomicrograph showing sinusoid lined by plump endothelial cells and inflammatory cells (H&E, 40X).

Immunohistochemistry was performed and revealed positivity for CD34, CD31 and CD8. CD34 positivity was observed in capillaries, CD8 positivity in sinusoids and CD31 positivity in all capillaries and small veins. CD68 highlighted the histiocytes and SMA was present in the myofibroblastic stroma. On the basis of histopathological and immunohistochemical findings, a diagnosis of SANT was offered. The follow-up period was uneventful.

Case 3

A 46-year-old female came to Surgery Department for further investigations of a solid tumour of the spleen. The mass was diagnosed by a routine ultrasonography performed by a private practitioner. The patient's medical and family history was unremarkable. On physical examination, she was in good general condition without anorexia, fever, night sweats, or hepatomegaly. A provisional clinicoradiological diagnosis of splenic haematoma was made. Laparoscopic resection was performed and the specimen was sent to present Department.

On gross examination, a splenic mass measuring 6×5 cm with a haemorrhagic cut surface separated by fibrous tissue was seen. Histological examination showed a well-demarcated multinodular lesion surrounded by a reactive fibrous tissue, primarily composed of vascular spaces of different sizes [Table/Fig-6a-c].

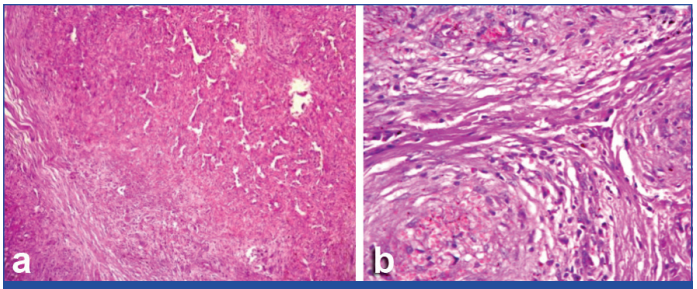


[Table/Fig-6]: Histopathological features of Sclerosing Angiomatoid Nodular Transformation (SANT) of 46-year-old female. a,b) Photomicrographs showing multiple variably sized angiomatoid nodules within the red pulp separated by fibrosclerotic septa (H&E, 4X, 10X, respectively); (c) Photomicrograph showing well-formed capillaries arranged in a lobular pattern, sinusoid-like spaces, inflammatory cells and histiocytes (H&E, 10X).

Immunohistochemical staining showed that capillaries expressed CD31 and CD34, while small vessels and sinusoids expressed CD31 and CD8, respectively. These findings were similar to those of a SANT. The patient's follow-up course was uneventful.

Case 4

A 41-year-old diabetic male patient came to the Surgery Outpatient Department with a splenic mass, which was diagnosed as a splenic hamartoma by a Radiologist. After the resection of the mass, it was sent to present Department. On gross examination, it was a well-circumscribed lesion measuring 8×5×4 cm, with nodules surrounded by collagen fibers. Microscopically, multiple nodular vascular lesions presented in a fibrocollagenous connective tissue background. The lesion is composed of three types of blood vessels and capillaries [Table/Fig-7a,b]: CD31+/CD34+/CD8-; sinusoids, that are CD31-/CD34-/CD8+; and small veins, which are CD31+/CD34-/CD8-. All cases have been summarised in [Table/Fig-8].



[Table/Fig-7]: Histopathological features of Sclerosing Angiomatoid Nodular Transformation (SANT) of 41-year-old male. (a) Photomicrograph showing angiomatoid nodule composed of vascular networks with extravasted red blood cells (H&E, 4X); (b) Photomicrograph showing the nodules were composed of vascular spaces, separated by fibrous septa and inflammatory cells (H&E, 40X).

DISCUSSION

In literature, initially, these lesions were considered a special type of splenic hamartoma [7,8]. It was Martel M et al., concluded, in their case series of 25 patients, concluded SANT is a separate neoplasm of the spleen [1]. They described SANT as a well-circumscribed, nodular solitary lesion of the spleen with a characteristic immunostaining profile. The nodules in SANT develop from the splenic red pulp due to extensive stromal proliferation, causing small vascular disruptions and proximal vascular tract hyperplasia. It is a form of splenic hamartoma as it is made up of red pulp tissue [1].

The SANT is a relatively uncommon splenic lesion coming under non haematopoietic vascular tumours of the spleen, along with other entities like, splenic hamartoma, haemangioma, haemangioendotheliomas and littorel cell angiomas. It is more prevalent in adults but can be occur in the paediatric age group. After an extensive search of the literature, we found only 15 cases of SANT in the paediatric age group worldwide [3]. Demographic and clinical data of all previously reported paediatric cases are summarised in [Table/Fig-9]. Only three cases were reported in India: one by Kale KA et al., presented in a 13-year-old female; second by Vyas M et al., in an 11-year-old boy; and a third case by Agrawal M et al., in a 12-year-old girl [4-6]. The majority of these cases were from outside of India [Table/Fig-9] [3-6,9-18].

No literature was found regarding paediatric involvement of SANT in present region. SANT were reported majority in girls than boys. In present cases, one was a girl and the other was a boy. In the paediatric age group, all most all patients presented with abdominal pain or discomfort. In present cases Clinical presentation was similar. In adults, SANT is considered a female-predominant lesion occurring in their fourth to seventh decades of life [19]. Most adult patients are asymptomatic, with the condition often detected incidentally detected on imaging studies. A very less proportion of patients present with vague symptoms of abdominal discomfort, abdominal pain, flank pain and abdominal distension. In diameter study, the adult patients were asymptomatic and diagnosed incidentally during routine radiological examinations.

The exact aetiology of SANT is not yet well understood, but it has been reported that SANT can be associated with Epstein-Barr Virus (EBV) infection and Immunoglobulin (Ig) G4-related sclerosing disease [20]. Later publications ruled out these hypotheses and concluded that SANT is a polyclonal reactive lesion [21]. Martel M et al., hypothesised that SANT shares similar features with inflammatory pseudotumours [1]. Authors took a thorough clinical and treatment history of present four cases but could not find out any IgG4-related disease or any history of past or present EBV infection.

Histopathological examination with radiological correlation is necessary for a definitive diagnosis of SANT. A CT scan typically shows a solitary, well-circumscribed, multilobulated mass with a hypo-vascular center and an enhancing rim in the post contrast phases. A "spoke wheel" pattern of progressive central enhancement can also be appreciated. In contrast to most of its differential diagnosis, a low signal intensity lesion can be appreciated of T2-weighted MRI [22]. T1-weighted

Age (years)	Gender	Clinical presentation	Laboratory data	Radiological finding	Clinical and radiological differential diagnosis	Surgical treatment	Gross-size Maximum diameter (cm)	Microscopic examination and IHC	Follow-up
4	Male	Abdominal pain	Increase ESR	USG- Hypoechogenic mass. CECT- Spoke wheel pattern.	Splenic hamartoma	Splenectomy	3	SANT	No recurrence
14	Female	Abdominal discomfort	Anaemia	USG- Hypoechogenic mass.	Inflammatory pseudotumour	Splenectomy	5	SANT	No recurrence
46	Female	Asymptomatic	Within normal limits	USG- Hypoechogenic mass.	Splenic hamartoma	Splenectom	6	SANT	No recurrence
41	Male	Asymptomatic	Within normal limits	USG- Hypoechogenic mass.	Splenic hamartoma	Splenectom	8	SANT	No recurrence

[Table/Fig-8]: Demographic data, clinical presentation, laboratory and radiological finding, treatment history, histopathological findings, differential diagnosis and follow-up.

Name of the author	Age (years)	Gender	Number of cases	Clinical presentation	Place of the study
Soleimani N et al., [3]	3	Female	1	Abdominal pain and constipation	Iran
Kale K et al., [4]	13	Female	1	Abdominal pain	India
Sanmoto Y et al., [9]	14	Female	1	Anaemia	Japan
Jamal A et al., [10]	8	Female	1	Abdominal distention	Pakistan
Idrissa S et al., [11]	14 and 4	Female and male	2	Asthenia and Abdominal pain	France
Zhang S et al., [12]	3		1	Abdominal pain	China
Bamboat ZM and Masiakos PT [13]	Adolescent	Male	1	Abdominal pain	USA
Kuybulu A et al., [14]	11	Female	1	Anaemia	Turkey
Vyas M et al., [5]	11	Male	1	Abdominal pain	Mumbai, India
Agrawal M et al., [6]	12	Female	1	Abdominal pain	Hyderabad, India
Pelizzo G et al., [15]	2	Female	1	Abdominal discomfort and rectal bleeding	Palermo, Italy
Delgado MA et al., [16]	4	Male	1	Recurrent vomiting	USA
Cao P et al., [17]	7	Male	1	Incidental finding	China
Abboud B et al., [18]	16	Male	1	Abdominal pain	Lebanon

[Table/Fig-9]: Demographic, clinical data and geographic distribution of SANT cases in paediatric age group [3-6,9-18].

images mostly show low to intermediate signal intensity, which, on adding contrast (gadolinium), reveals a spoke wheel pattern with a central stellate scar. There is very few published data on the role of Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) in diagnosing SANT [23]. On Single Photon Emission Computed Tomography (SPECT)-CT, lack of 99mTc-sulfur colloid is due to the absence of reticuloendothelial cells within the SANT [22].

Gross examination after splenectomy shows a well-circumscribed, non encapsulated mass with multiple confluent nodules interspersed with fibrotic stroma [24]. On microscopic examination, the stable low-power magnification appearance of SANT reveals multiple angiomatous nodules within a fibro-sclerotic stroma. The nodules are of variable size, generally round and widely separated by a sclerotic stroma, though occasional coalescence may occur [1]. Vascular spaces of three different calibres, lined by plump endothelial cells, can be appreciated within the nodules [1]. On immunohistochemistry, these nodules demonstrate heterogeneous mixture of immunomarkers. The inter-nodular stroma is usually fibro-sclerotic and contains chronic inflammatory infiltrate composed of lymphocytes, plasma cells, macrophages, along with myofibroblasts. Literature told that the spindle-shaped cells found inside and around the angiomatoid nodules are myofibroblasts, which express SMA [25].

Immunohistochemistry demonstrates (CD31+/CD34-/CD8+) splenic sinusoids, (CD31-/CD34+/CD8-) capillaries and (CD31+/CD34-/CD8-) small veins [1]. CD68+ dendritic phagocytic cells can also be demonstrated focally [26]. The main differential diagnosis of SANT includes other common benign vascular lesions and rare nodular transformations of splenic red pulp in response to metastatic carcinoma. Littoral cell angioma, a distinctive vascular neoplasm of the spleen, also shows multiple red pulp nodules composed of variably sized vascular channels. However, distinct nuclear features (vesicular nuclei, open chromatin and small nucleoli), the presence of haemophagocytosis and aggregates of eosinophilic globules, along with a specific immunophenotype (CD31, CD68, CD21 positivity), make it distinctly different from SANT. SH is also characterised by slit-like vascular channels resembling sinusoids but lacks the vascular spaces of capillaries and small veins seen in SANT. Other differential diagnosis include benign vascular lesions (haemangioendothelioma, haemangioma) and inflammatory myofibroblastic tumours of the spleen. Only one case of SANT has been reported in an accessory spleen [27].

Splenectomy (either open or minimally invasive) is the curative treatment for SANT [28]. Although most patients are asymptomatic and without any risk of malignant transformation, surgery is better indicated as some lesions that resemble SANT may be malignant in nature. Core biopsy can be done to distinguish SANT from other benign lesions, but there is a risk of profuse bleeding and the chance of intra-peritoneal seeding in cases of some conditions, such as angiosarcoma [29]. No evidence of recurrence has been reported during the follow-up period after splenectomy.

CONCLUSION(S)

The SANT of the spleen is a benign vascular lesion of the spleen with a wide range of age distribution, but it occurs more commonly in adults than in the paediatric age group. SANT should be included in the differential diagnosis of any patient presenting with an angiomatoid or inflammatory splenic lesion. It exhibits characteristic morphological and immunophenotypic findings, followed by an incidentally on imaging studies. Surgical histopathology is indicated, as the differential diagnosis for SANT includes some malignant conditions.

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