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Case report / Приказ болесника

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Sclerosing angiomatoid nodular transformation of the spleen – an uncommon splenic pseudotumorus variant

Склерозирајућа ангиоматоидна нодозна трансформација слезине – ретка псеудотуморска промена слезине

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SUMMARY

Introduction Sclerosing angiomatoid nodular transformation (SANT) is a benign splenic pseudotumorus multinodular vascular proliferation. In the past, SANT was usually described as splenic hamartoma, multinodular hemangioma, or splenic hemangioendothelioma. Since it was defined in 2004, 150 cases have been described so far. In this case, report we provide literature review and current knowledge of this rare clinical entity.

Case outline A 58-year-old women presented with chronic dull abdominal pain, moderate microcytic anemia, moderately elevated C - reactive protein, and fibrinogen level. Abdominal ultrasound and computed tomography scan detected well-circumscribed, homogeneous, and low-density tumor in the upper pole of the spleen. Nature of the change on the spleen could not be established with precision nor could a malignancy be excluded. Therefore, we opted for a splenectomy. Histological findings showed multiple similar nodular foci, hardly discernible from splenic parenchyma, angiomatoid nodules surrounded and separated by partly collagenised fibroblastic areas admixed with mononuclear inflammatory infiltrate in various proportions. There were also areas with myofibroblastic proliferation, hypervascularity and hemosiderosis, findings highly indicative of coexistence of sclerosing angiomatoid nodular transformation of spleen and splenic inflammatory pseudotumor.

Conclusion SANT is usually discovered radiologically presenting as a splenic tumor of unknown nature and origin. Splenectomy, laparoscopic or open, is an acceptable therapeutic and at the same time diagnostic method. Partial splenectomy is justified for certain reasons in children but coexistence of SANT and inflammatory pseudotumour indicates careful decision, given the tendency of inflammatory pseudotumour to relapse, and rarely, the possibility of malignant transformation.

Keywords: spleen, splenectomy, SANT, inflammatory pseudotumour

САЖЕТАК

Увод Склерозирајућа ангиоматоидна нодозна трансформација слезине (САНТ) је бенигна псеудотуморкса мултинодуларна пролиферација порекла крвних судова. САНТ је раније описиван као хамартом, мултинодуларни хемангиом или хемангиоендотелиом слезине.Откако је дефинисан 2004. године у литератури је описано 150 случајева. Овај текст, кроз приказ случаја, представља преглед литературе и актуелних сазнања о овом ретком ентитету.

Приказ болесника Пацијенткиња стара 58 година хоспитализована је због хроничних тупих болова у трбуху, микроцитне анемије умереног степена и умерено повишених вредности *C*-реактивног протеина и фибриногена. Мултидетекторским компјутеризованим томографијским и ултразвучним прегледом абдомена виђена је јасно ограничена, хомогена туморска промена у горњем полу слезине. Обзиром на нејасну природу промене и немогућност да се са сигурношћу искључи малигнитет, одлучено је да се уради спленектомија. Хистопатолошка анализа показала је постојање мултиплих нодуларних зона које је веома тешко разликовати од нормалног паренхима слезине, затим ангиоматоидне нодулусе који су окружени и раздвојени комбинацијом делимично колагенизованих фибробластних фокуса и мононуклеарног инфламаторног инфилтрата у различитим односима. Такође су виђене зоне миофибробластне пролиферације, хиперваскуларизације и хемосидерозе, што је индикативно запостојање удружених промена, склерозирајуће ангиоматоидне трансформације слезине и псеудоинфламаторног тумора.

Закључак САНТ се радиолошки презентује као тумор слезине нејасне природе. Спленектомија, лапароскопска или отворена, истовремено је метода избора за лечење и постављање дефинитивне дијагнозе. Примена парцијалне спленектомије се може размотрити код деце. Случајеви удруженог постојања САНТ-а и инфламаторног псеудотумора упућују да одлуку о парцијалној спленектомији треба доносити опрезно, имајући у виду рецидивни потенцијал инфламаторног псеудотумора и његову ретку, али могућу малигну трансформацију.

Кључне речи: слезина, спленектомија, САНТ, инфламаторни псеудотумор

INTRODUCTION

Sclerosing angiomatoid nodular transformation (SANT) is a benign splenic pseudotumorus multinodular vascular proliferation. This is a rare clinical entity, which was defined quite recently in a study published by Martel et al. in 2004 [1]. Searching bibliographic databases (Pubmed, Scopus), a total of 150 cases have been described so far. It is more frequent in middle-aged women, but it can also occur in children [2, 3]. SANT rarely manifests clinical symptoms. It is usually discovered by coincidence as an incidental finding during imaging diagnostics due to some other medical condition. Radiologically, it is seen as splenic tumour, whose nature cannot be described with precision by means of modern radiological diagnostics. In such cases, a surgeon usually indicates splenectomy, while the right diagnosis may be established only after a histopathological and immunohistochemical analyses of tissue specimen. SANT is composed of angiomatoid nodules immersed in a fibrosclerotic stroma [4]. It can be viewed as more of a pathological diagnosis, since clinically; its nature remains unclear. There are no reported cases of relapse after splenectomy. In this paper, we will present our experience with a 58-year-old female patient, with moderate splenomegaly and a tumorous change in the upper pole of the spleen during an ultrasound and multidetector computed tomography (MDCT) examination of the abdomen, carried out due to abdominal pain and a suspected lymphoproliferative disease.

CASE REPORT

The patient was admitted to the Clinic for Digestive Surgery within the Clinical Center of Serbia on 15th December 2015 due to chronic dull abdominal pain. An ultrasound examination of the abdomen conducted few days earlier in a regional medical institution revealed a hypoechogenic tumorous change in the upper pole of the spleen together with cholelithiasis. By examining her medical documentation, we found out that the patient is

treated for hypertension with combination of an ACE inhibitor and diuretic, non-toxic nodular goiter and pain in the joints. On admission, she was afebrile with normal vitals, and no associated nausea, vomiting, or fever was present. Laboratory examinations, including complete blood count, revealed moderate microcytic anemia (HGB 97 g/L, RBC 3.88 $x10^{12}$ /L, MCV 79.0 fL, HCT 0.3, MCH 24.9 pg, MCHC 315 g/L). Tumour markers (CA 19-9, CEA, AFP, CA 125, CA 15-3, CA 72-4) were all unremarkable. Evaluation of free thyroid hormones in the serum (FT3, FT4) and thyrotropic hormone TSH confirmed that patient is euthyreotic. Biochemistry test results showed some features of chronic inflammatory response through moderately elevated C-reactive protein and fibrinogen level, 44.6 mg/L and 5.6 g/L, respectively. In addition, beta-2 microglobulinemia was present (2.91 mg/L).

MDCT examination of the abdomen and pelvis detected a moderate enlargement of the spleen of 152 mm in craniocaudal diameter with a well circumscribed, homogeneous, and low-density tumorous change in the upper pole of the spleen, 30x42 mm in size (Figure 1). Para-aortic and interaortocaval lymph nodes were enlarged with a maximal size of 10 mm. Partial wall calcification and multiple small calculi in gallbladder were also seen.

Due to peculiar radiological characteristics, the nature of the change on the spleen could not be established with precision nor could a malignancy be excluded. Therefore we opted for a splenectomy. During an intraoperative abdominal exploration, we detected a change in the upper pole of the spleen and cholelithiasis. A splenectomy “in situ” was performed along with cholecystectomy. The spleen was completely removed and sent to the pathological department within our clinic for histopathological examination. After the surgery, postsplenectomy reactive thrombocytosis occurred, but generally, there were no complications during the postoperative period. On the seventh postoperative day, the patient was discharged from the hospital. Vaccines against pneumococci, meningococci, and influenza viruses were prescribed in order to prevent a postsplenectomy infection.

Three months after the surgery, the patient underwent laboratory workup which showed improvement in her anemia (HGB 107 g/L, RBC 4.38 x10^{12} /L, MCV 80.3 fL, HCT 0.35, MCH 24.4 pg). Both C-reactive protein (4.8 mg/l) and fibrinogen (3.4 g/L) were within the normal range. In the 4 years since the surgery, there has been no evidence of recurrence.

The resected spleen measuring 152x110x60 mm in diameter and weighing 400 g revealed in the upper pole a 20 mm nonencapsulated multinodular mass with a yellow-tan fibrotic central starry scar. Multiple similar nodular foci were found throughout, hardly discernible from splenic parenchyma (Figure 2). Histological findings showed angiomatoid nodules surrounded and separated by partly collagenised fibroblastic areas admixed with mononuclear inflammatory infiltrate in various proportions. In addition, there were areas with myofibroblastic proliferation, hypervascularity, and hemosiderosis. No significant nuclear atypia, mitotic activity, or necrosis was found. Immunohistochemical examination showed mixture of sinusoidal, capillary, and vein like vessels. Using CD34, CD31, and CD8 antibodies, there were complex endothelial phenotypes resembling splenic sinusoids (CD34-/CD31+/CD8+), capillaries (CD34+/CD31+/CD8-), and small veins (CD34-/CD31+/CD8-). Mesenchymal component revealed non-homogenous smooth muscle actin immunophenotype and significant immunoreactivity for CD14, CD163, and F-XIIIa. Other antibodies did not express significant reactivity, including desmin, S100 protein, CD117, CD21, CD35, HHV8, fascin, ALK protein, D2-40, and EMA. A portion of mesenchymal proliferation was morphologically and immunohistochemically consistent with inflammatory myofibroblastic tumour (Figure 3).

DISCUSSION

In the past, SANT was usually described as splenic hamartoma, multinodular hemangioma, or splenic hemangioendothelioma. In 2004, in his analysis of 25 cases, a new

name was defined by Martel et al. - Sclerosing angiomatoid nodular transformation of the spleen [1]. In 95% of cases, SANT manifests as a solitary splenic lesion. Only 5 cases of multifocal SANT have been described [5]. In one case report, the change primarily affected only the accessory spleen [6].

Etiopathogenesis of SANT has remained unclear to this day. Various authors tried to explain the nature of this lesion. Martel et al. believe that angiomatoid nodules are a transformation of splenic red pulp in response to interruption of circulation in splenic blood vessels [1]. Diebold et al. constructed the hypothesis that the intrasplenic blood flow disturbance in the red pulp may be a mechanism for the formation of angiomatoid nodules [7]. Weinreb et al. were first to discern a connection between this disease and Epstein-Barr virus infection [4]. The most recent studies show that SANT results from sclerotic changes accompanied by IgG4-related inflammatory diseases [8]. SANT also can be accompanied by malignant and hematologic diseases, such as polyclonal gammopathy and myelodysplastic syndrome [9].

In our patient, SANT is accompanied by splenic inflammatory pseudotumour (IPT). Other authors also describe cases of concomitant occurrence of SANT and IPTs, giving rise to the hypothesis on close connection between SANT and inflammatory pseudotumours, which show an extremely rare, yet possible malignant transformation[10][11].

Examination of the case reports published so far does not offer the possibility of isolating a prominent clinical characteristic, which can be associated with SANT. The most common problems that the patients report are a sense of abdominal discomfort and occasional dull abdominal pain [12]. Pain in the joints and laboratory analyses of our patient with high levels of C-reactive protein, fibrinogen, and leukocytes may indicate the existence of some type of general inflammatory response. In Diebold's study, three patients, out of 16 who were proved to suffer from SANT, had laboratory findings indicating inflammation [7]. For one

patient, Martel et al. proved high erythrocyte sedimentation rate, and an occasional febrile state without a clear cause in two other patients [1]. Existence of moderate iron deficiency anaemia and its improvement after splenectomy detected in the case of our patient was also described in the case presented by Buzyncki et al. [13].

SANT cannot be easily distinguished from other vascular lesions, such as desmoplastic transformation of the splenic red pulp in response to metastatic carcinoma, littoral cell angioma, hemangioendothelioma, lymphangioma, angiosarcoma, hamartoma, and inflammatory pseudotumour. Several cases of splenectomy due to suspected metastatic carcinoma in the spleen have also been described in the literature. However, a histopathologic analysis indicated SANT, which implies that SANT can be combined with other malignant diseases [14][8]. Even in the most up-to-date radiological diagnostics such as (^{18}F-FDG) PET-CT used to follow-up the results of treatment for malignant diseases, radiopharmaceutical accumulation may sometimes wrongly indicate a metastatic disease in the spleen, only to later, after a splenectomy, establish that it was actually SANT [15]. Macroscopically, on the cross section of the spleen, the change has a starry aspect. Studies indicated that in a large number of cases, the starry shape of a change has the “spoked wheel” appearance in MDCT and T2-weighted MRI images [16][17]. However, characteristic and pathognomic radiological findings, which could help unequivocally diagnose SANT, have not been defined yet.

Histopathological diagnosis indicated that SANT can occur simultaneously with splenic inflammatory pseudotumour. Immunohistochemically, one portion of the change was described as SANT, while the remainder is inflammatory myofibroblastic tumour. Budzynski et al. presented a case of a patient who had underwent a laparoscopic partial splenectomy due to a splenic tumour, which was later, histopathologically, characterised as SANT [13]. Follow-up proved that this was a satisfactory treatment option. Our case indicates that, due to

occasional coexistence of SANT and inflammatory myofibroblastic tumour of the spleen, one should be careful when deciding that a patient should undergo partial splenectomy, given that inflammatory pseudotumour can also have recurrence potential, and that rare cases of malignant transformations have been described as well.

Weinreb et al. consider a splenic biopsy to be a reasonable and useful diagnostic method for diagnosing SANT [4]. SANT is a lesion of vascular nature; therefore, apart from possible ruptured spleen and bleeding, coexistence with other inflammatory changes indicates that results of a splenic biopsy may not be reliable. Possible peritoneal dissemination in case a biopsy of an angiosarcoma is performed, which angiosarcoma can have a very similar aspect in radiological findings, is another reason why this biopsy is not advisable. We believe that splenectomy, either classical or laparoscopic, is at the same time the best diagnostic and therapeutic method.

SANT is a clinical entity with favorable prognosis. Relapse has not been reported yet. Given that preoperative diagnostics is inconclusive, splenectomy, either laparoscopic or open, is an acceptable therapeutic and at the same time diagnostic method. An exception to this are children, where partial splenectomy is justified for certain reasons given that their spleen still has active immune functions and that there is a increased risk of postsplenectomy sepsis. Coexistence of SANT and inflammatory pseudotumour indicates that one should be careful when deciding that a patient should undergo partial splenectomy, given the tendency of IPT to relapse, and rarely, the possibility of malignant transformation.

Conflict of interest: None declared

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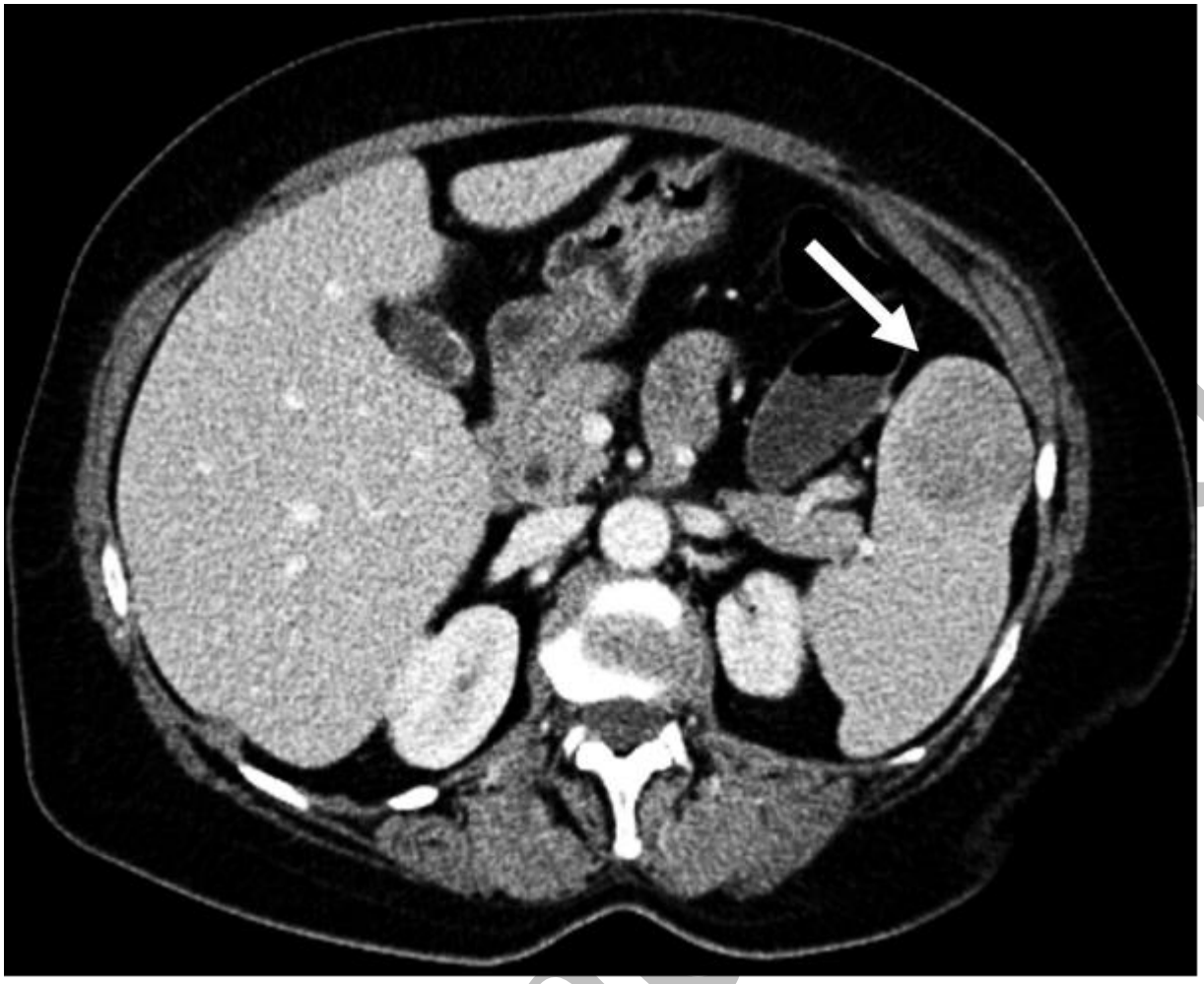

Figure 1. Abdominal CT scan. The arrow points to the change in the upper pole of the spleen

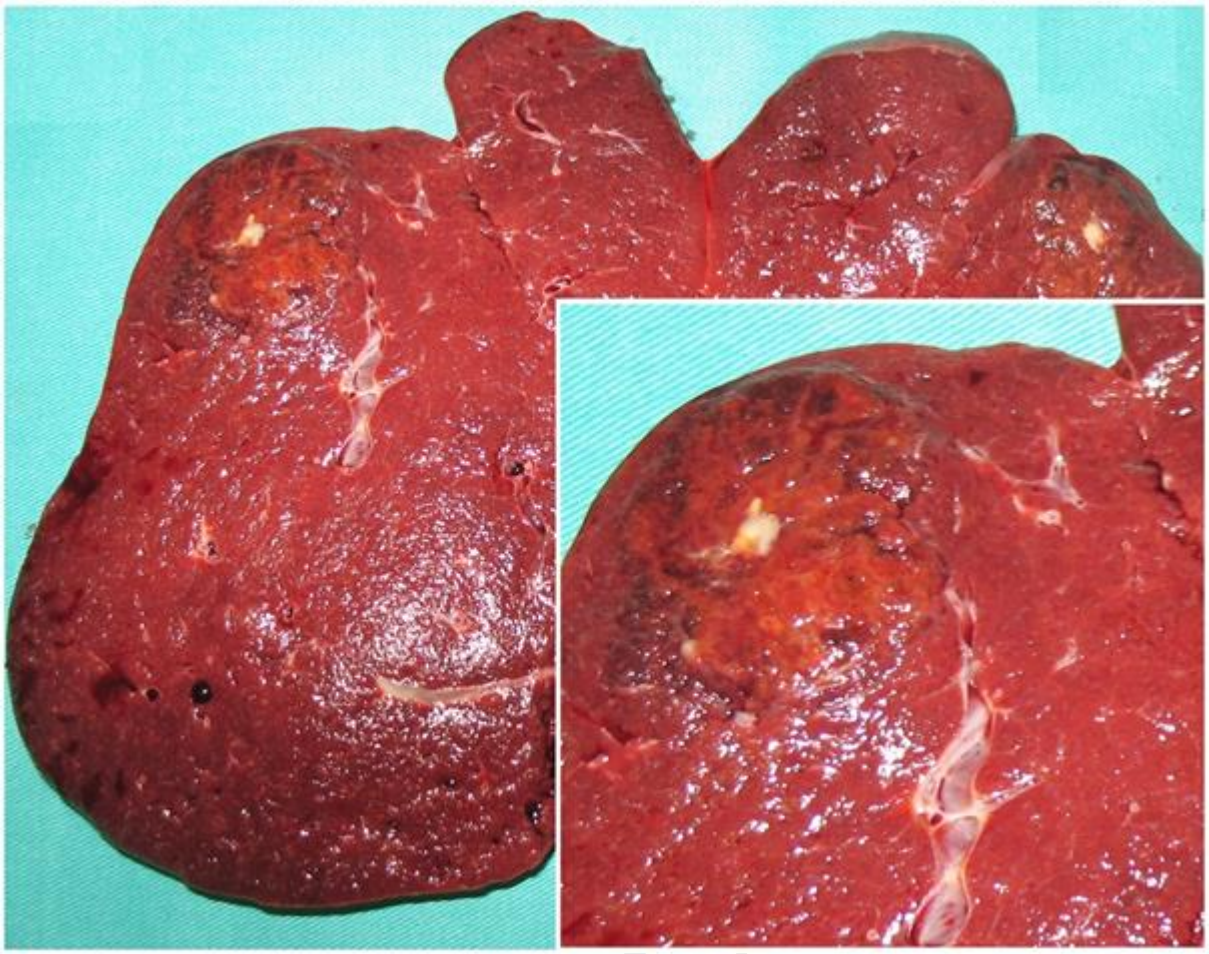

Figure 2. Macroscopic appearance of SANT on the cross section of the spleen

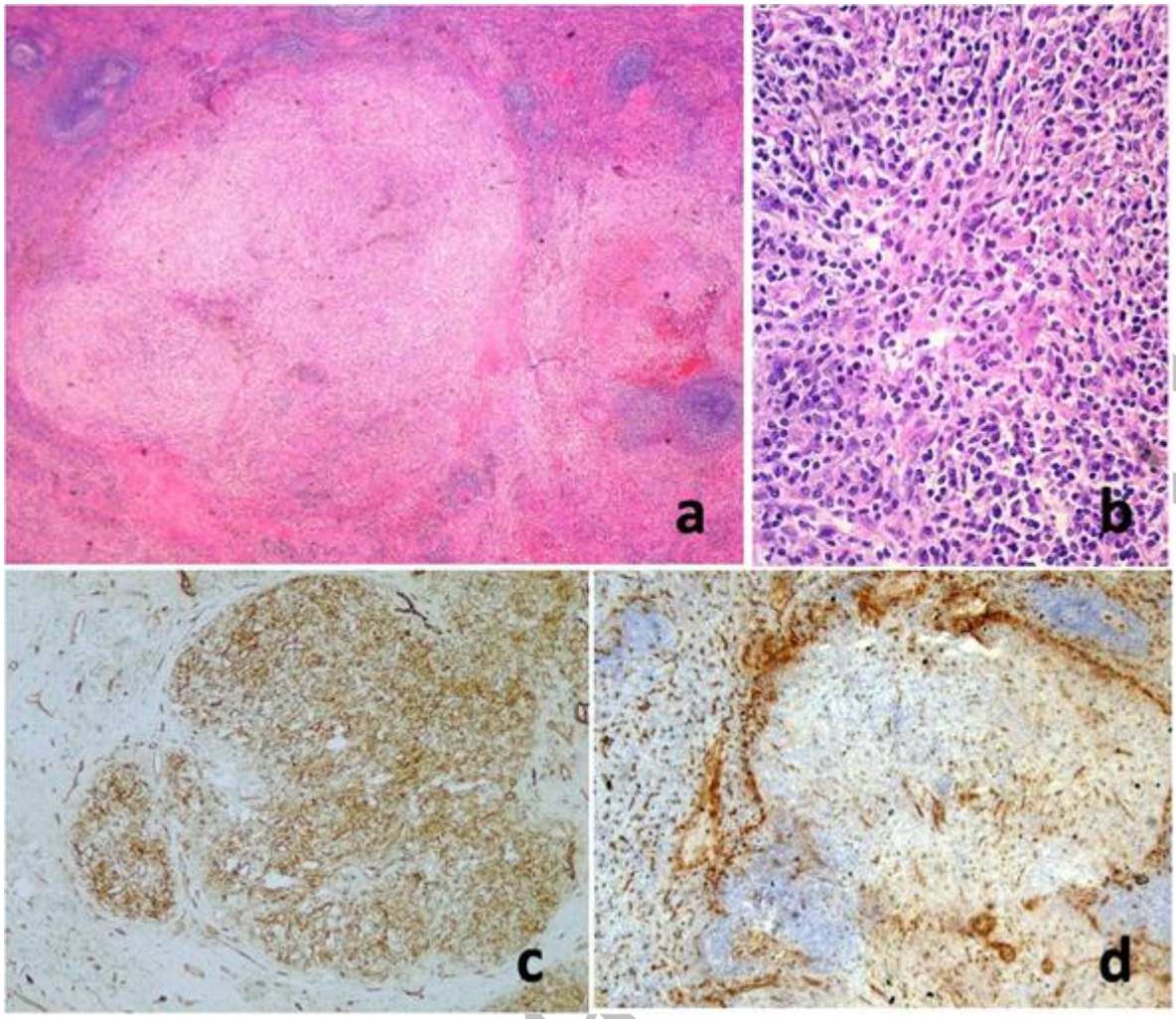

Figure 3. Histological examination of SANT clearly depicts nodular transformation of splenic parenchyma (a: H&E, 5x) and in some areas is associated with cellular areas consisted of spindle stromal cells and prominent lymphoplasmacytic infiltrate consistent with inflammatory myofibroblastic tumor(b: H&E, 20x). SANT is result of peculiar reactionary nodular angiomatoid transformation of red pulp with various types of vessels and immunohistochemical expression of vascular antigens such as CD31 (c) and CD34 antigen (d).

