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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

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

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SUMMARY

Introduction Sclerosing angiomatoid nodular transformation is a benign splenic pseudotumorous multinodular vascular proliferation. In the past, it was usually reported as splenic hamartoma, multinodular hemangioma or splenic hemangioendothelioma. Since it was defined in 2004, a total of 150 cases have been reported. We will present our experience with a 58-year-old female patient who underwent splenectomy due to the tumorous change in the upper pole of the spleen, histopathologically characterized as sclerosing angiomatoid nodular transformation of the spleen.

Case outline A 58-year-old women presented with abdominal pain, anemia, elevated C-reactive protein and fibrinogen level. Abdominal ultrasound and MDCT scan found a well-circumscribed, homogeneous, low-density tumor in the upper pole of the spleen. As the nature of the tumorous change could not be accurately determined and malignancy could not be excluded, splenectomy was performed. Histological findings showed multiple similar nodular foci, hardly discernible from splenic parenchyma, angiomatoid nodules surrounded and separated by partly collagenized fibroblastic areas admixed with mononuclear inflammatory infiltrate in various proportions. All findings were characterized as the coexistence of sclerosing angiomatoid nodular transformation of the spleen and splenic inflammatory pseudotumor.

Conclusion Splenectomy, laparoscopic or open, is an acceptable therapeutic and at the same time diagnostic method. Considering the important role of the spleen in the immune system, partial splenectomy is also an option, especially in children. However, the coexistence of sclerosing angiomatoid nodular transformation of the spleen and inflammatory pseudotumor indicates a careful treatment decision, given the tendency of inflammatory pseudotumor to relapse, and, rarely, the possibility of malignant transformation.

Keywords: spleen; splenectomy; SANT; inflammatory pseudotumor

INTRODUCTION

Sclerosing angiomatoid nodular transformation (SANT) is a benign splenic pseudotumorous multinodular vascular proliferation. This is a rare clinical entity, which was defined quite recently in a study published by Martel et al. [1] in 2004. Searching bibliographic databases (Pubmed, Scopus), a total of 150 cases have been reported 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 found by coincidence as an incidental finding during imaging diagnostics due to some other medical condition. Radiologically, it appears as a peculiar splenic tumor, whose nature cannot be accurately determined, despite the use of modern radiological imaging techniques. The diagnosis may be established only after histopathological and immunohistochemical analyses of the 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 still remains unclear. There are no reported cases of relapse after splenectomy.

In this paper, we present our experience with a 58-year-old female patient who underwent splenectomy due to the tumorous change in the upper pole of the spleen, histopathologically characterized as SANT. Written informed consent was obtained from the patient.

CASE REPORT

The patient was admitted to the Clinic for Digestive Surgery within the Clinical Center of Serbia on December 15, 2015 due to chronic dull abdominal pain. A few days earlier, an abdominal ultrasound examination 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 was treated for hypertension with a combination of an angiotensin-converting-enzyme inhibitor and diuretic, non-toxic nodular goiter, and pain in the joints. On admission, she was afebrile with

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normal vitals, and no associated nausea, vomiting, or fever was present. Laboratory examinations, including complete blood count, revealed moderate microcytic anemia [hemoglobin (HGB) 97 g/L, red blood cells (RBC) 3.88×10^{12} /L, mean corpuscular volume (MCV) 79 fL, hematocrit (HCT) 0.3, mean corpuscular hemoglobin (MCH) 24.9 pg, mean corpuscular hemoglobin concentration (MCHC) 315 g/L]. Tumor 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 the patient was euthyreotic. Biochemistry test results showed some features of the chronic inflammatory response through moderately elevated C-reactive protein and fibrinogen level, 44.6 mg/L and 5.6 g/L, respectively. Also, beta-2 microglobulinemia was present (2.91 mg/L).

Multiple detector computed tomography (MDCT) examination of the abdomen and pelvis found a moderate enlargement of the spleen of 152 mm in craniocaudal diameter with a well-circumscribed, homogeneous, low-density tumorous change in the upper pole of the spleen, 30 × 42 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 stones in the gallbladder were also seen.

Due to peculiar radiological characteristics, the nature of the splenic mass could not be precisely determined nor could the malignancy be excluded. Therefore, we opted for a splenectomy. During an intraoperative abdominal exploration, we found a tumorous mass in the upper pole of the spleen and gallstones. A splenectomy *in situ* and cholecystectomy was performed. The spleen was sent for histopathological examination. After the surgery, reactive thrombocytosis occurred, but, generally, the postoperative period was uneventful. 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, laboratory workup showed improvement of anemia (HGB 107 g/L, RBC 4.38×10^{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 respective ranges. Four years after the surgery, there has been no evidence of recurrence.

The resected spleen measuring 152 × 110 × 60 mm and weighing 400 g revealed a 20 mm nonencapsulated multinodular mass with a yellow-tan fibrotic central starry scar in the upper pole. Multiple similar nodular foci were found throughout, hardly discernible from splenic parenchyma (Figure 2). Histological findings showed angiomatoid nodules surrounded and separated by partly collagenized 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 a mixture of sinusoidal, capillary, and

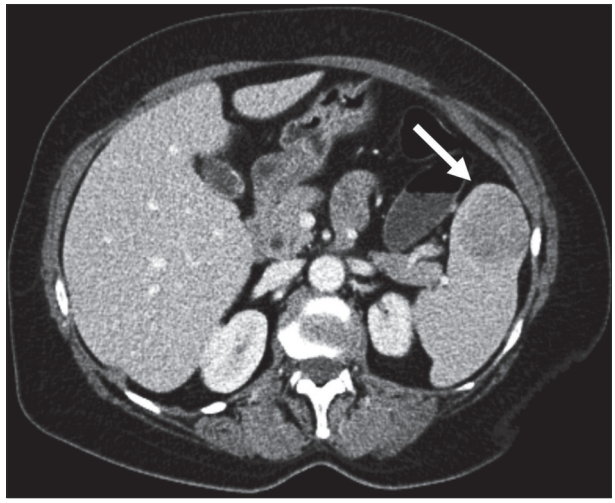

Figure 1. Abdominal computed tomography scan; the arrow points to the change in the upper pole of the spleen

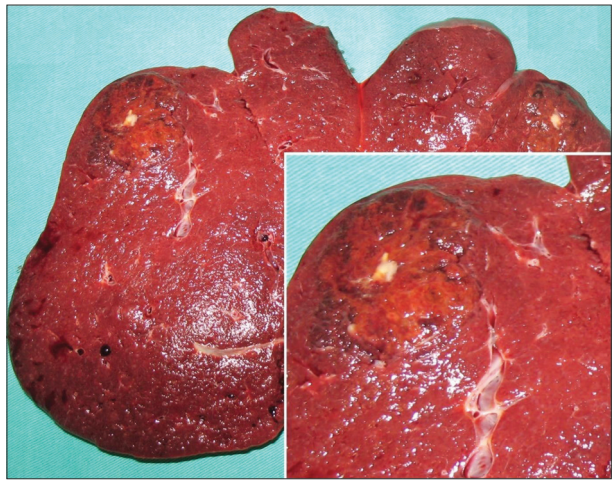

Figure 2. Macroscopic appearance of sclerosing angiomatoid nodular transformation on the cross-section of the spleen

veinlike 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 nonhomogenous 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 tumor (Figure 3).

DISCUSSION

In the past, SANT was usually described as splenic hamartoma, multinodular hemangioma, or splenic hemangioendothelioma. In 2004, in an analysis of 25 cases, a new name was defined by Martel et al. [1] – sclerosing

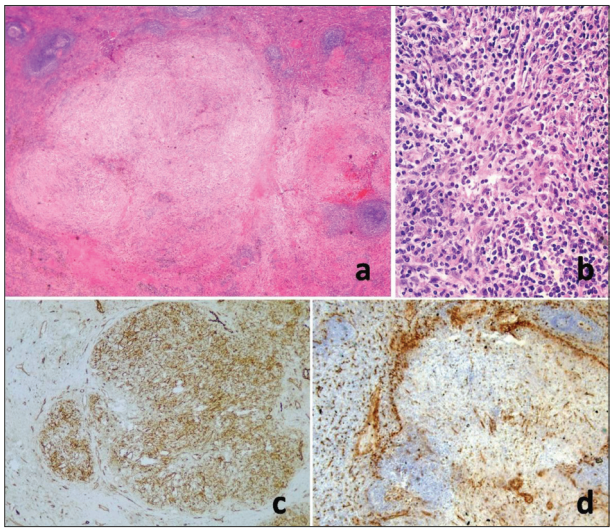

Figure 3. Histological examination of sclerosing angiomatoid nodular transformation clearly depicts nodular transformation of splenic parenchyma (a: H&E, 5×) and in some areas is associated with cellular areas consisting of spindle stromal cells and prominent lymphoplasmacytic infiltrate consistent with inflammatory myofibroblastic tumor (b: H&E, 20×); sclerosing angiomatoid nodular transformation is a 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 (d) antigen

angiomatoid nodular transformation of the spleen. In 95% of cases, SANT manifests itself as a solitary splenic lesion. Only five cases of multifocal SANT have been reported to date [5]. In one case report, only the accessory spleen was primarily affected [6].

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

In our patient, SANT coexisted with splenic inflammatory pseudotumor. Other authors also reported cases of concomitant occurrence of SANT and inflammatory pseudotumors, giving rise to the hypothesis on the close connection between SANT and inflammatory pseudotumor, which show an extremely rare yet possible malignant transformation [10, 11, 12].

Case reports published so far do not offer the possibility to distinguish a prominent clinical characteristic that can be associated with SANT. The most common symptoms that the patients experienced are a sense of abdominal discomfort and occasional dull abdominal pain [13]. 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 the study by Diebold et al. [7], three patients out of 16 had laboratory findings indicating inflammation. For one patient, Martel et al. [1] proved a high erythrocyte sedimentation rate, and occasional febrile episodes without a clear cause in two other patients. The existence of moderate iron deficiency anemia and its improvement after splenectomy detected in the case of our patient was also described in the case presented by Budzyński et al. [14].

SANT cannot be radiologically easily distinguished from other vascular lesions, such as the desmoplastic transformation of the splenic red pulp in response to metastatic carcinoma, littoral cell angioma, hemangioendothelioma, lymphangioma, angiosarcoma, hamartoma, and inflammatory pseudotumor. It can be misdiagnosed with splenic abscess [15]. Several cases of splenectomy due to suspected metastatic carcinoma in the spleen have also been described in the literature. However, a histopathologic analysis found SANT, which implies the coexistence of SANT with malignant diseases [8, 16]. Even in the most up-to-date radiological diagnostics such as (^{18}F-labeled fluoro-2-deoxyglucose) positron emission tomography / computed tomography used to follow-up the results of treatment for malignant diseases, radiopharmaceutical accumulation may sometimes falsly detect metastatic disease in the spleen, only to, later, after a splenectomy, establish that it was actually SANT [17]. Macroscopically, on the cross-section of the spleen, the change has a starry aspect. In a large number of reports, the starry shape of SANT has the "spoked wheel" appearance in MDCT and T2-weighted MRI images [18, 19, 20]. However, characteristic and pathognomic radiological findings, which could help unequivocally diagnose SANT, have not been defined yet.

Histopathological findings indicated that SANT can occur simultaneously with splenic inflammatory pseudotumor. Immunohistochemically, one portion of the splenic mass was described as SANT, while the remainder is an inflammatory myofibroblastic tumor. Budzynski et al. [14] reported a case of a patient who had undergone a laparoscopic partial splenectomy due to a splenic tumor, which was later, histopathologically, characterized as SANT. The follow-up proved that this was a satisfactory treatment option. Occasional coexistence of SANT and inflammatory myofibroblastic tumor compromise partial splenectomy as a treatment option. A careful decision should be made, given that an inflammatory pseudotumor can also have recurrence potential, and that rare cases of malignant transformations have been described as well.

Weinreb et al. [4] considered a splenic biopsy to be a reasonable and useful diagnostic method for diagnosing SANT, which is a lesion of vascular nature. Therefore, apart from possible splenic rupture and bleeding, considering coexistence with other inflammatory changes, a splenic biopsy may not be reliable. Angiosarcoma can have very similar radiological findings. Possible peritoneal dissemination 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 a 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. Considering the important role of the spleen in the immune system, partial splenectomy is also a treatment option, especially in children due to the higher risk of postsplenectomy sepsis [21]. However, the coexistence of SANT of the spleen and inflammatory pseudotumor indicates a careful treatment decision, given the tendency of inflammatory pseudotumor to relapse, and, rarely, the possibility of malignant transformation.

Conflict of interest: None declared.

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Склерозирајућа ангиоматозна трансформација слезине – ретка псеудотуморска промена слезине

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САЖЕТАК

Увод Склерозирајућа ангиоматозна нодозна трансформација слезине је бенигна псеудотуморска мултинодуларна пролиферација. Промена је раније најчешће описивана као хамартом, мултинодуларни хемангиом или хемангиоендотелиом слезине. Од 2004. године, када је дефинисан нови назив за ову промену – склерозирајућа ангиоматозна нодозна трансформација слезине, до данас је у литератури описано око 150 случајева. Овај текст, кроз приказ случаја, представља преглед литературе и актуелних сазнања о овом ретком клиничком ентитету.

Приказ болесника Болесница стара 58 година хоспитализована је због хроничних болова у трбуху, анемије умереног степена и умерено повишених вредности *C*-реактивног протеина и фибриногена. Ултразвучним прегледом и мултислајсном компјутеризованом томографијом абдомена виђена је јасно ограничена, хомогена туморска промена у горњем полу слезине. С 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 ангиоматозне 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 за постојање удружених промена, склерозирајуће ангиоматозне трансформације слезине и псеудоинфламаторног тумора.

Закључак Склерозирајућа ангиоматозна нодозна трансформација слезине се радиолошки презентује као тумор слезине нејасне природе. Спленектомија, лапароскопска или отворена, истовремено је метода избора за лечење и начин да се постави дефинитивна дијагноза. Имајући у виду значајне имунолошке функције слезине, парцијална спленектомија се може размотрити, нарочито код деце. Случајеви удруженог постојања склерозирајуће ангиоматозне нодозне трансформације и инфламаторног псеудотумора упућују да одлуку о парцијалној спленектомији треба доносити опрезно, имајући у виду могућност рецидива инфламаторног псеудотумора и његову ретку али могућу малигну трансформацију.

Кључне речи: слезина, спленектомија, склерозирајућа ангиоматозна нодозна трансформација, инфламаторни псеудотумор