【 CASE REPORT 】

Sclerosing Angiomatoid Nodular Transformation of the Spleen: Lessons from a Rare Case and Review of the Literature

Ryohei Nomura [1], Hiromi Tokumura [1], Yu Katayose [1], Fumie Nakayama [2], Noriyuki Iwama [2] and Makoto Furihata [3]

Abstract:

Sclerosing angiomatoid nodular transformation (SANT) of the spleen is an extremely rare benign lesion. We herein report a case of asymptomatic SANT of the spleen in a middle-aged woman with early breast carcinoma and an undiagnosed splenic mass, which was successfully treated by laparoscopic splenectomy and diagnosed postoperatively. We also review the literature on SANT to help make knowledge more accessible when clinicians encounter a splenic tumor. The present case taught us the following lesson: the presence of a splenic lesion during follow-up for malignancy is not always indicative of metastasis. Therefore, SANT should be considered in the differential diagnosis.

Key words: sclerosing angiomatoid nodular transformation, spleen, laparoscopic splenectomy, malignancy, case report

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Introduction

Sclerosing angiomatoid nodular transformation (SANT) of the spleen is an extremely rare benign splenic lesion. The lesion was first alluded to, under the designation of cord capillary hemangioma, in an abstract by Krishnan et al. in 1993 (1). Martel et al. first established this benign splenic angiomatoid lesion as SANT in 2004 (2). To date, 167 cases of SANT have been described in the English literature; however, it is not widely known to clinicians, including physicians, surgeons, and radiologists, due to its extreme rarity.

In general, splenic lesions are commonly encountered and often incidental in nature (3). Benign vascular neoplasms are often observed in the spleen, with benign hemangioma being the most common entity. Other benign splenic vascular neoplasms include hamartoma, lymphangioma, littoral cell angioma, hemangioendothelioma, angiomyolipoma, extramedullary hematopoiesis, and SANT. A variety of primary and secondary malignant diseases can also occur in the spleen.

The most common primary non-hemato-lymphoid malignancy is angiosarcoma, while lymphoma and myeloma are among the hematological malignancies encountered in the spleen. In addition, several extrasplenic primary diseases with systemic metastases can also involve the spleen (3). It is difficult to diagnose splenic tumors preoperatively on the basis of conventional imaging studies (4). There is no sensitive, specific way to diagnose splenic tumors, including SANT, without a tissue sample.

We herein report a rare case of asymptomatic SANT of the spleen in a middle-aged woman with early breast carcinoma and an undiagnosed splenic mass, which was successfully treated by laparoscopic splenectomy and diagnosed postoperatively. We also review the literature on SANT to help make knowledge of this lesion more accessible to clinicians when they encounter a splenic tumor.

Case Report

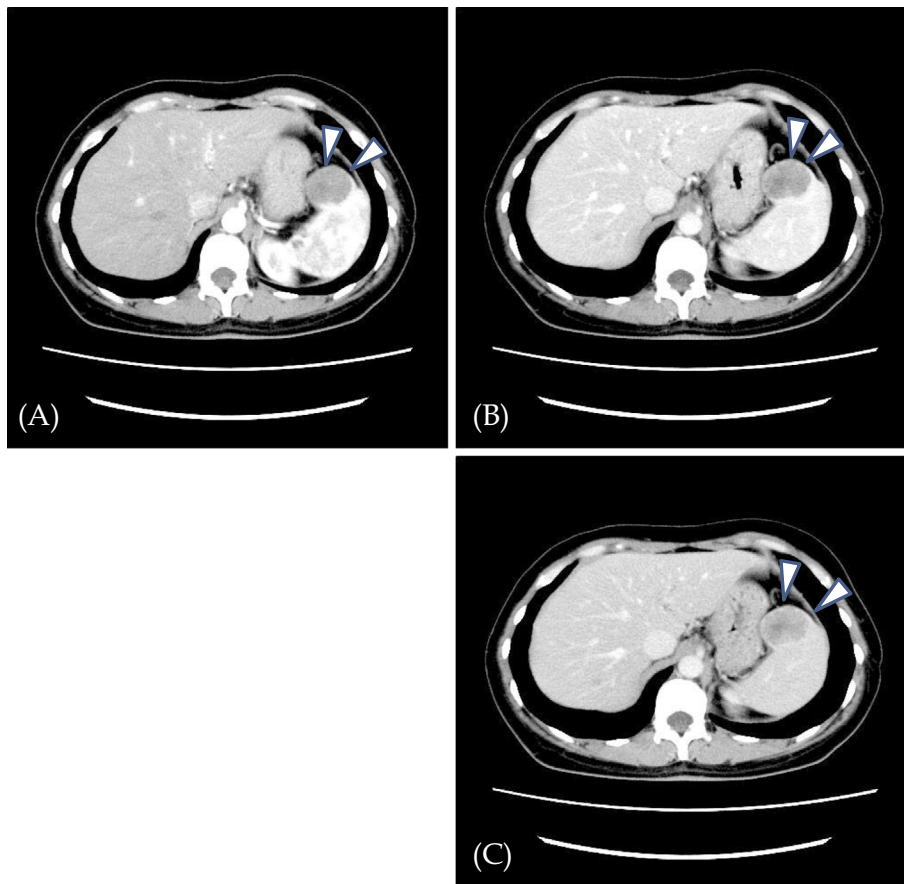A 41-year-old woman with no history of disease was re-

Figure 1. Abdominal CT revealed a solid lesion (white arrowheads) measuring 40 mm in diameter in the periphery of the spleen (A). The lesion was less contrast-enhanced than the spleeparenchyma in the early and portal phases (B). The densities of the mass and the surrounding spleen were similar in the delayed phase (C).

ferred to our institution for a further investigation upon suspicion of early breast cancer. A physical examination revealed no palpable mass in the abdomen, bilateral breast, or underarm. She had not noticed any symptoms. All hematological parameters were within normal ranges, including serum levels of carcinoembryonic antigen (1.8 ng/mL; normal range: <5.0 ng/mL), carbohydrate antigen (CA)15-3 (11.4 U/mL; normal range: <5.0 U/mL), breast carcinoma-associated antigen (BCA)225 (30.7 U/mL; normal range: < 160 U/mL), Nation Cancer Center-Stomach (NCC-ST)-439 (1.3 U/mL; normal range; <7.0 U/mL), and soluble inter-leukin (IL)-2 receptor (322 U/mL; normal range: 145-519 U/mL).

Mammography revealed a high-density mass with clustered microcalcifications in the inferior lateral segment of the right breast, which was suspected to be malignant. On chest computed tomography (CT), a well-enhanced solid mass was detected at the same position with no axillary lymph node metastases. A cytological examination using ultrasonography-guided fine-needle aspiration, performed for the definitive diagnosis of the right breast mass, indicated class V cytology, which was suggestive of malignancy.

Abdominal ultrasonography (US) revealed a heterogeneous hypoechoic mass with some blood signals on color Doppler protruding from the spleen. Abdominal CT, performed for the further evaluation of metastasis, revealed a solid lesion measuring 40 mm in diameter at the periphery of the spleen (Fig. 1A). The lesion was less contrast-enhanced than the parenchyma of the spleen in the early and portal phases (Fig. 1B). The densities of the mass and the surrounding spleen were similar in the delayed phase (Fig. 1C). Consistent with CT imaging, the lesion demonstrated a similar intensity to the splenic parenchyma on both T1- and T2-weighted magnetic resonance imaging (MRI) (Fig. 2A and B) and was slowly but progressively filled centripetally with contrast medium 10 minutes after injection (Fig. 2C). The mass reached almost the same intensity as that of the background spleen (Fig. 2D). We therefore performed positron-emission tomography-CT (PET-CT) for the evaluation of the splenic mass. PET-CT revealed no significant avidity for ^{18}F-fluorodeoxyglucose (FDG), excluding the previously diagnosed cancer in the right (Fig. 3). Differential benign diagnoses of the splenic mass included hemangioma, lymphangioma, littoral cell angioma, hamartoma, angiosarcoma, and inflammatory pseudotumor.

As a result of the preoperative examinations, the preoperative diagnosis of the right breast cancer was T1N0M0, stage I, according to tumor-node-metastasis (TNM) classifi-
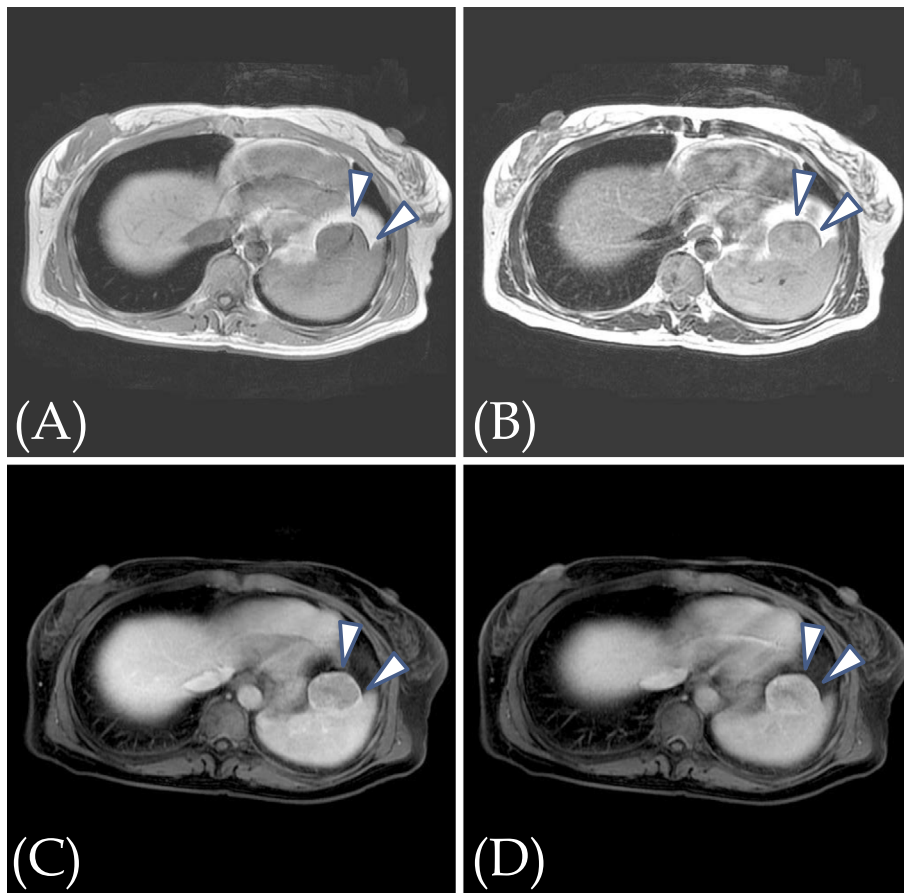
Figure 2. Consistent with CT imaging, the lesion (white arrowheads) showed almost the same intensity as the splenic parenchyma on both T1- and T2-weighted MRI (A, B) and was slowly but progressively filled centripetally with contrast medium 10 minutes after injection (C). The mass reached a similar intensity to the background spleen (D).
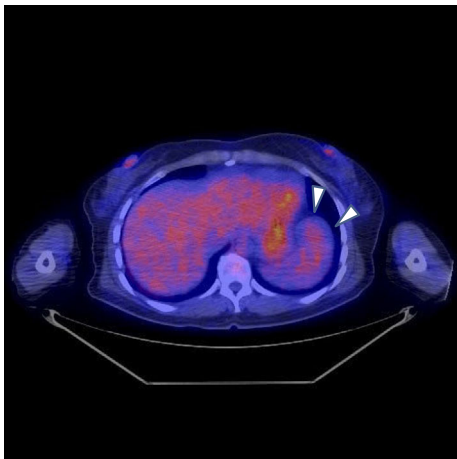

Figure 3. PET-CT showed no significant avidity for FDG in the splenic mass (white arrowheads).

cation (5); however, we were unable to establish a definitive preoperative diagnosis. In addition, we were unable to rule out the possibility of solitary splenic metastasis of the breast cancer or another malignant lesion, such as malignant lymphoma. Therefore, we decided to perform partial mastectomy of the right breast with axillary sentinel node dissec-

tion and laparoscopic splenectomy simultaneously to reach a therapeutic diagnosis.

With regard to the breast cancer, a pathological examination revealed invasive ductal carcinoma negative for sentinel lymph node involvement. The resected specimen of the spleen is shown in Fig. 4. The well-circumscribed solitary lesion contained a central white stellate structure. Thus, SANT was suspected macroscopically. On Hematoxylin and Eosin staining, the multiple angiomatoid nodules were separated by fibrous or fibrosclerotic stroma (Fig. 5A). Proliferation of both collagen fiber (Fig. 5B) and microvessels was observed, with inflammatory cell infiltration (Fig. 5C). On immunohistochemical staining, three types of vessels were observed, which is a characteristic of SANT: (1) sinusoid type, both CD8- and CD31-positive but CD34-negative vessels; (2) small vein type, CD31-positive but CD8- and CD34-negative vessels; and (3) cord capillary type, both CD34- and CD31-positive but CD8-negative vessels (Fig. 6A-C). In the stroma, myofibroblastic spindle cells had proliferated, showing positivity for α-smooth muscle actin (Fig. 6D).

We performed immunohistochemical staining for IgG and IgG4 to confirm the relationship with IgG4-related disease. The mean IgG4/IgG ratio was 10%, which is lower than the
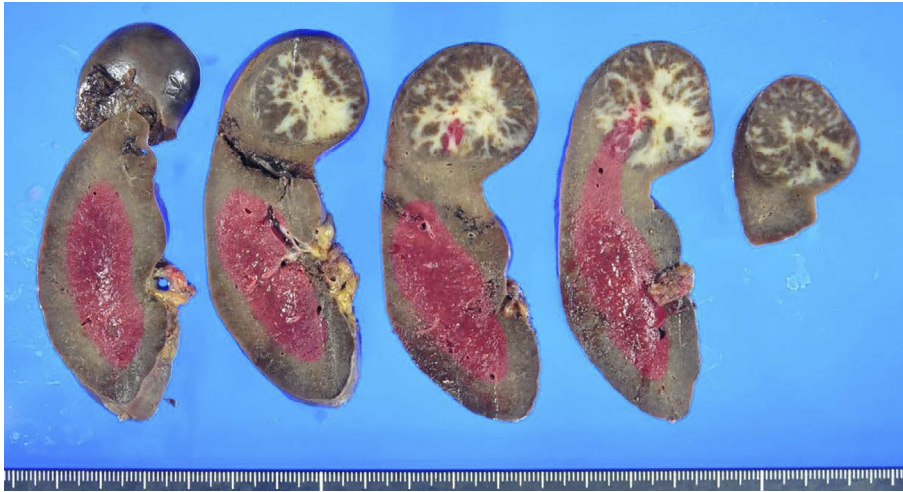
Figure 4. The resected specimen of the spleen is shown. The well-circumscribed solitary lesion, measuring 40 mm in diameter, contained a central white stellate structure, which is characteristic of SANT.
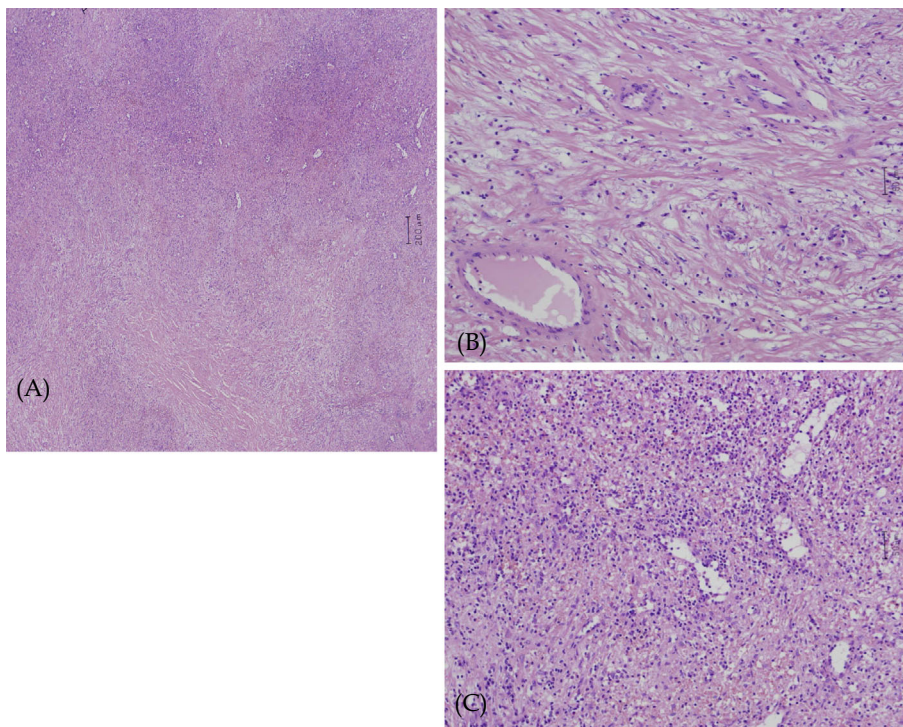

Figure 5. Hematoxylin and Eosin staining revealed multiple angiomatoid nodules separated by fibrous or fibrosclerotic stroma (A). Proliferation of both collagen fiber (B) and microvessels was observed, with inflammatory cell infiltration (C).

diagnostic criterion (>40%) for IgG4-related disease (6). In addition, the present lesion was negative for Epstein-Barr virus (EBV)-encoded small RNA (EBER). Thus, on a pathological examination, the final diagnosis of the lesion was SANT of the spleen. Metastatic cancer was not indicated. The patient has been well since hospital discharge. The postoperative radiological work-up showed no evidence of recurrence over the two-year follow-up period.

Discussion

Martel et al. first described and defined the pathological features of splenic SANT in a series of 25 patients (2). SANT is a morphologically distinctive lesion of unknown etiology. Thus, far, SANT has been known to occur only in the spleen. It is probable that SANT had been diagnosed as various other vascular lesions, such as hamartoma, hemangioma, or hemangioendothelioma (4), until Martel et al. established this new entity of splenic lesions. Because the ves-
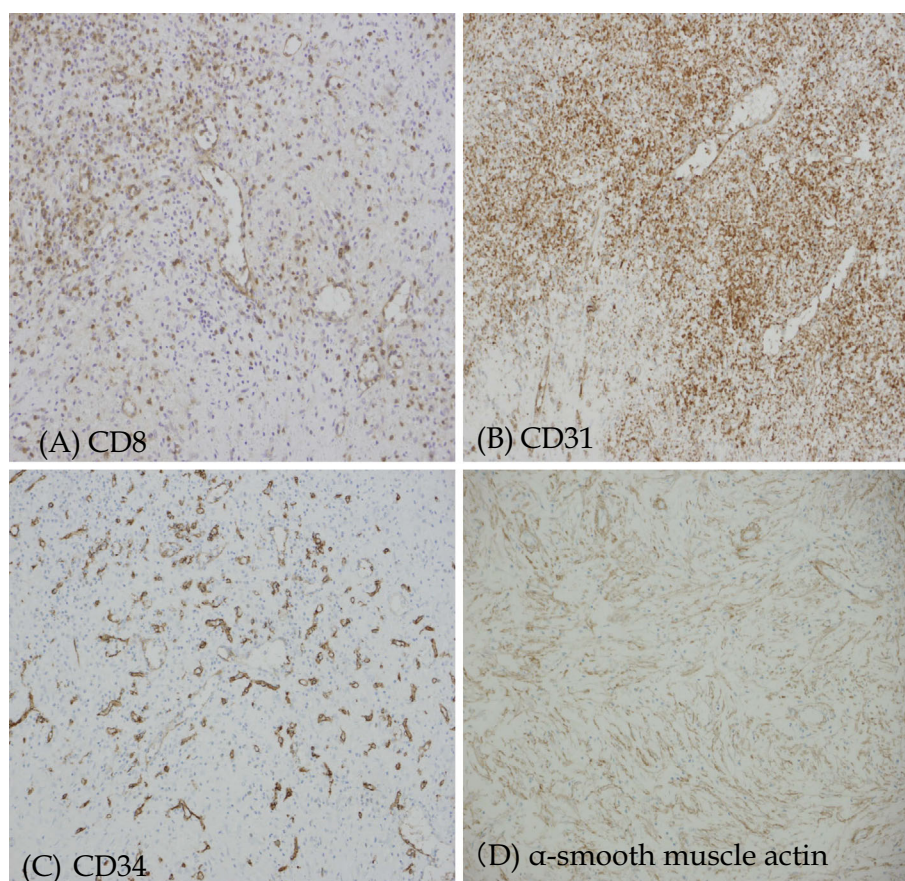
Figure 6. On immunohistochemical staining, three types of vessels were observed, which is characteristic of SANT: (1) sinusoid type, both CD8- and CD31-positive but CD34-negative vessels (A); (2) small vein type, CD31-positive but CD8- and CD34-negative vessels (B); and (3) cord capillary type, both CD34- and CD31-positive but CD8-negative vessels (C). In the stroma, myofibroblastic spindle cells had proliferated, showing positivity for α-smooth muscle actin (D). These immunohistochemical findings were definitive in confirming the exact diagnosis.

sels within the nodules are markedly cellular, SANT had been previously interpreted as a condition of multinodular hemangioma; however, it is classified with 'other primary tumors and tumorlike conditions' of the spleen in the latest 10th edition of Rosai and Ackerman's Surgical Pathology textbook (7). Collectively, the most important distinguishing features of SANT are its typical vascular characteristics and lack of other features that are typical of granuloma (4). We herein review the current literature on SANT in the context of the present case.

To date, 167 patients with SANT have been reported in the English literature. We decided to mainly review the 71 cases of SANT, including the present case, that have been reported between 2011 and 2018, since Falk et al. collected the sporadic reports of 97 cases (8). The clinical data, symptoms, treatment, radiological characteristics, pathological data, and references for these 71 cases are presented in Table. The cases consist of 27 men and 44 women. The resultant female-to-male ratio of 1.63 is similar to those reported by Wang et al. and Falk et al. (1.25 and 1.4, respectively) (4, 8). The mean age of the 71 cases was 46.0 years (range, 21 to 82 years). Thus, SANT appears to predomi-

nantly affect middle-aged women, as in the present case. The reported comorbidities in this case series seem nonspecific to SANT, as two patients had hypertension, four each had diabetes and hepatic cysts, two had anemia, and other comorbidities appeared in single patients. SANT has been reported to coexist with abdominal or extra-abdominal tumors in up to 14% of cases (9).

In the present review, coexistent malignancy (2 cases each of colon cancer and breast cancer and 1 each of ovarian cancer, cervical carcinoma, ductal carcinoma of the pancreas, intracystic papillary carcinoma, hypopharynx carcinoma, early gastric cancer with gastrointestinal stromal tumor of the jejunum, and papillary thyroid carcinoma) was present in 11 of 71 cases (15.5%), which is quite similar to the previously reported rates (9). As in the present case, it is likely that the diagnostic modalities used during follow-up or staging estimation contributed to the detection of incidental SANT in terms of the frequency of associated neoplastic lesions. Therefore, the association between SANT and malignancy is tenuous. With regard to symptoms, 33 of 71 cases (46.5%) were asymptomatic, 27 cases (38.0%) were symptomatic, and the remaining 11 cases (15.5%) were not

Table. The Characteristics and Diagnostic Features of SANT.

History		
☐	Number of reported cases	☐ 167 cases
☐	First review and year	☐ Martel et al. 2004
Characteristics		
☐	Mean age of onset	☐ 46 years (range, 21 to 82) (Wang et al. [4]: 44 years; range of majority, 30 to 60)
☐	Sex distribution	☐ 27 males and 44 females
☐	Female to male ratio	☐ 1.63 (Wang et al. [4]: 1.25, Falk et al. [8]: 1.4)
☐	Benign comorbidities	☐ Hypertension, diabetes, hepatic cysts, anemia, others
☐	Percentage of intercurrent malignant comorbidities	☐ 15.5% (11 of 71 cases) (Cafferata B et al. [9]; 14%)
☐	Types of intercurrent malignant comorbidities	☐ colon cancer and breast cancer and one each of ovarian cancer, cervical carcinoma, ductal carcinoma of the pancreas, intracystic papillary carcinoma, hypopharynx carcinoma, early gastric cancer with gastrointestinal stromal tumor of the jejunum, and papillary thyroid carcinoma
☐	With or without symptoms	☐ Symptomatic 38.0% (27 of 71 cases); asymptomatic 46.5% (33 cases)
☐	Types of symptoms	☐ Abdominal pain, abdominal or back discomfort, weight loss, fatigue, development of fever, deep breath pain
☐	Mean maximal diameter	☐ 49.5 mm (range, 3.83 to 175 mm)
☐	Number of nodules	☐ Solitary 87.3% (62 of 71 cases); two or three 9.9% (7 cases); more than four 2.8% (2 case)
☐	Mean growth rate	☐ 0.75 mm/month (range, 0 to 1.77 mm/month)
Radiological and imaging findings		
☐	US	☐ Heterogenous hypoechoic mass with bright liner echoes accompanied by acoustic shadow in the center.
☐	CT	☐ Lesion is well circumscribed and of lower attenuation compared to the background spleen.
		☐ The mass becomes isodense in the delayed phase [4, 10, 11].
☐	PET-CT	☐ Reports concerning as the findings of SANT on PET-CT are sporadic, and the typical features have not been conclusively established.
☐	MRI	☐ It appears that the typical features of SANT on MRI are not definitive.
		☐ Karaosmanoglu et al. reported that SANT presented as a central hyperintense area consistent with hemorrhage on fat-saturated precontrast T1-weighted images.
		☐ On T2-weighted images, the lesion appeared as a spoke and wheel pattern, which was similar to the pattern obtained by CT multiphase imaging.
Final diagnosis and treatment	☐	Diagnostic splenectomy is required. Laparoscopic splenectomy was performed in 15 cases out of all the cases (21.1%). FNA or CNB can be an alternative.
Prognosis	☐	SANT with atypia or recurrence has never been observed during follow-up (mean duration of 20.9 months; range, 2-70 months).

described. However, not all of the reported symptoms, which include abdominal pain, flank pain, abdominal or back discomfort, weight loss, fatigue, pain on deep breathing, and development of a fever, may be attributed to SANT itself. Overall, it is probable that SANT is mainly detected incidentally due to the expansion of opportunities to perform radiological examinations.

The maximal size of the mass ranges from 3.83 to 175 mm, with a mean diameter of 49.5 mm. Sixty-two of 71 cases (87.3%) involved a solitary nodule, while 7 involved 2 or 3 nodules (9.9%), and 2 had more than 4 nodules. Based on these characteristics, the present case appears to be typical of SANT. Based on the available follow-up data, the growth rate of SANT is estimated at 0.75 mm per month, with a range of −0.08 to 1.77 mm per month, indicating that SANT has gradual growth potential.

With regard to imaging findings, the present case also demonstrated imaging patterns typical of SANT. US shows a heterogeneous hypoechoic mass with bright linear echoes accompanied by an acoustic shadow in the center (4, 10, 11). The present case also demonstrated a hypoechoic mass with slight color signals on a Doppler analysis.

CT shows a solitary splenic mass that is well circumscribed and of lower attenuation than the background spleen (3, 4) in the early and porto-venous phases, which becomes isodense in the delayed phase. Furthermore, as Wang et al. mentioned, a number of SANT lesions demonstrate a 'spoke and wheel pattern' (4, 12), which reflects the central stellate fibrous stroma with fibrous septa that separate the nodules (4, 10, 11). Indeed, in the present case, a septum from the center could be faintly visualized. The findings of the present case were also consistent with all other features reported on CT (Fig. 1A-C). 'Well circumscribed' and 'spoke and wheel pattern' findings on CT and MRI corresponded to a well-demarcated mass and central fibrous stroma with septa on macroscopic findings, respectively. These typical radiological findings in the present case were compatible with the macroscopic findings of the resected specimen.

Reports concerning the findings of SANT on PET-CT are sporadic. Imamura et al. reviewed the features of SANT in

2016 (13) and reported that 10 of 11 cases showed the uptake of FDG in SANT, suggesting that PET-CT can be considered to provide an accurate diagnosis. However, this finding is not consistent with the present case (Fig. 3).

In the present case, the mass had a similar signal to the surrounding spleen on both T1- and T2-weighed MRI (Fig. 2A and B). It appears that typical features of SANT on MRI are not also definitive. Karaosmanoglu et al. first described the findings of SANT on MRI (4, 12). They reported that SANT presented as a central hyperintense area consistent with hemorrhaging on fat-saturated precontrast T1-weighted images and as a spoke and wheel pattern, similar to the pattern obtained with CT multiphase imaging, on T2-weighted images. Thipphavong et al. described the mass as hyperintense at the center, with hyporadiation bands corresponding to areas of fibrosis (3). Although the findings on MRI in the present case are not consistent with these previous reports, dynamic enhancement MRI revealed centripetal and progressive enhancement (Fig. 2C), which was similar to the pattern obtained by multiphase CT.

Although CT and MRI were consistent with the typical imaging pattern of SANT, these diagnostic modalities were not conclusive for a qualitative preoperative diagnosis. In the present review, a core needle biopsy (CNB) was used in 4 of 71 cases (5.6%). The final diagnosis was revealed after splenectomy in the remaining 66 cases (93.0%). Exceptionally, a clinical diagnosis was made without surgery in only 1 case (1.4%). Basically, surgery was required to reach a therapeutic diagnosis, and SANT could not be definitively diagnosed until removal of the lesion.

For the treatment, we selected laparoscopic splenectomy for the definitive diagnosis of the splenic mass because metastasis from the right breast cancer could not be excluded. Splenectomy can be replaced by less-aggressive methods, such as fine-needle aspiration (FNA) or a percutaneous biopsy, to establish the diagnosis of solitary splenic metastasis; FNA has a low complication rate of 0-2% (14, 15). However, we opted for splenectomy due to the risk of possible tumor dissemination in the case of metastasis. Furthermore, splenectomy, if performed, is fundamentally a palliative procedure for metastatic splenic tumors. Laparoscopic splenectomy as a minimally invasive surgery was performed in 15 of the 71 reviewed cases (21.1%), which is in line with current trends, as no SANT with atypia or recurrence has been observed during follow-up (mean duration of 20.9 months; range, 2-70 months). Therefore, we believe that laparoscopic splenectomy may be a possible alternative therapy for a mass that satisfies the characteristics of SANT listed in Table. The characteristics and diagnostic features of SANT summarized in Table should therefore be considered in the differential diagnosis of splenic tumors.

In general, SANT appears as of a solitary well-demarcated lesion with a stellate white mass at the center. A macroscopic examination of the resected specimen in our case was consistent with the generally reported gross examination findings of SANT (4). Microscopically, the classic characteristics of SANT are as follows: 1) a multinodular growth pattern composed of a variable mixture and sieve-like arrangement of vascular spaces that are often surrounded by dense collagen fibrosis and fibroid rims; 2) individual nodules that include slit-like, round, or irregular-shaped vascular spaces lined by plump endothelial cells and interspersed by a population of spindly or ovoid cells; 3) the presence of numerous red blood cells as well as scattered inflammatory cells, while nuclear atypia and mitotic figures are rare, and necrosis is absent; and 4) internodular stroma consisting of variably myxoid to dense fibrous tissue with scattered plump myofibroblasts, plasma cells, lymphocytes, and siderophages. SANT is composed of jumbled small blood vessels of three immunophenotypically distinct types, recapitulating the normal composition of the red pulp: cord papillaries (CD34+/CD8-/CD31+), sinusoids (CD34-/CD8+/CD31+), and small veins (CD34-/CD8-/CD31+) (2). The present case contained all of these blood vessel types, and these immunohistochemical findings are the most important points for arriving at the definitive diagnosis of SANT. These characteristics suggest that SANT is a distinctive nonneoplastic vascular lesion occurring in the spleen.

In addition, some investigators have suggested that SANT is related to IgG4 sclerosing lesions or inflammatory pseudotumors with stromal cells positive for EBV. The morphologic features and reports of stromal cells positive for EBV in SANT overlap with inflammatory pseudotumor-like follicular dendritic cell tumor (16-18). In addition, SANT may contain many IgG4-positive plasma cells, suggesting the possibility of a relationship with IgG4-related disease (16, 19, 20). Although SANT is classified among 'other primary tumors and tumorlike conditions' of the spleen (7), Chang et al. analyzed 22 cases of SANT in women using human androgen-receptor α and concluded that SANT is a polyclonal, reactive lesion rather than a neoplasm. The also observed no cases associated with IgG4 disease, although 11% of SANT samples had increased IgG4^{+} cells (16). In the present review, 28 cases (39.4%) were examined for EBER, and none were positive, suggesting no relationship between EBV and SANT. Overall, SANT is currently considered not a neoplasm but a reactive vascular lesion that follows a non-progressive clinical course. Clinicians should build their knowledge of SANT as a possible diagnosis of benign splenic tumors.

Splenic metastasis should be considered when establishing the diagnosis of an undiagnosed splenic mass in patients with advanced malignancy. Splenic metastasis of breast cancer is very rare in the literature. Splenic metastases from solid tumors, defined as parenchymal lesions, are considered exceptional. Nevertheless, the number of case reports has been increasing due to improvements in imaging techniques and the long-term follow-up of patients with cancer. Splenic metastases occur in the context of multivisceral disseminated cancer or as a solitary lesion. The most common primary sources of splenic metastasis are breast, lung, colorectal, and ovarian carcinomas and melanoma in cases of multivisceral

cancer and colorectal and ovarian carcinomas in cases of solitary splenic lesion.

The relative rarity of splenic metastases can be explained by anatomic factors and the inhibitory effect of the splenic microenvironment on the growth of metastatic cells. An analysis of clinical case reports suggested that solitary splenic metastases may result from the growth of an early blood-borne micrometastasis following a period of clinical latency, often several years after the diagnosis of the primary tumor (14). Dutta et al. reported a case of SANT masquerading as metastatic breast carcinoma, which is similar to the present case. They avoided splenectomy by preoperatively diagnosing SANT based on FNA cytology (21). Mueller et al. also reported a case involving SANT and simultaneous metachronous liver metastasis after colon cancer surgery and concluded that, in cancer patients, splenic lesions should be treated as metastatic lesions.

Therefore, a histological examination is recommended in most cases for the diagnosis and treatment of splenic lesions (22). Such decisions might affect subsequent clinical decisions regarding therapy and can alter the staging of cancer progression. We believe that splenectomy is not routinely required; however, splenectomy can be useful if there is a tumor of the spleen in a patient with existing malignancy. However, even if SANT is suggested as the definitive diagnosis, as in the present case, splenectomy may be essentially inevitable in patients with malignancy, as metastases cannot be excluded. The definitive diagnosis of splenic mass cannot be achieved until the removal of the spleen. Laparoscopic splenectomy is a feasible and minimally invasive procedure for cancer patients. Clinicians should establish the definitive diagnosis of splenic disease with consideration of the clinical presentation, key imaging findings, and histopathological features based on knowledge concerning the anatomy and histology of the spleen.

Conclusion

In conclusion, when clinicians encounter a splenic lesion in which metastasis cannot be excluded, laparoscopic splenectomy is feasible, and SANT should be considered in the differential diagnosis.

The authors state that they have no Conflict of Interest (COI).

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