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Sarcoidal granulomas in the spleen associated with multiple carcinomas

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Abstract. Sarcoid reactions are relatively rare manifestations of epithelioid cell granulomas associated with malignancy; they are especially found in the lymph nodes draining malignant tumors, but rarely found in other organs. We present a case of a 60-year-old female with sarcoid reactions in the spleen identified during the consecutive diagnosis and management of ovarian, breast, and thyroid carcinomas during a period of about 2 years. The symptoms and laboratory data suggestive of systemic sarcoidosis were absent except for a slight mediastinal lymphadenopathy detected only by a computed tomographic scan. The splenic granulomas were accompanied by dendritic cells of mature and immature types, the latter being different from the reported nodal counterparts. To our knowledge, this is the first reported case of splenic sarcoid reactions associated with multiple cancers, and the first reported immunohistochemical detection of dendritic cells in splenic granuloma. *(Sarcoidosis Vasc Diffuse Lung Dis 2010; 27: 153-159)*

Key words: splenic sarcoidosis. sarcoid reactions, epithelioid cell granuloma, dendritic cell

Abbreviation List

ACE:	Angiotensin-converting enzyme
CT scan:	Computed tomographic scan
DC	Dendritic cell
FDG-PET:	F-18 fluorodeoxyglucose positron emission tomography
LN:	Lymph node
IPT:	Inflammatory pseudotumor

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Introduction

Sarcoidosis is a systemic disorder of unknown etiology characterized by noncaseating epithelioid cell granulomas in the involved organs (1). Apart from sarcoidosis, patients with malignant tumors may show sarcoid-like granulomas in the stroma or the neighborhood of the tumor as well as in lymph nodes (LNs) draining malignant neoplasms, but they are rarely seen in other organs (2). Granulomas that are associated with malignancy but are not indicative of systemic sarcoidosis have been termed "sarcoid reactions". In cases where epithelioid cell granulomas are identified in a patient with malignancy, making a differential diagnosis between sarcoid reactions and systemic sarcoidosis is often problematic (2). Sarcoidal granuloma in the spleen is rare (3), and further, it is extremely rare that splenic granuloma is found in an individual who have multiple carcino-

mas. We report here a case in which splenic sarcoidal granulomas were identified in the course of the diagnosis and management of multiple cancers and present the immunohistochemical study in the context of maturation of dendritic cells (DCs).

Case Report

A 60-year-old female patient is presented. Her past medical history was unremarkable. A right ovarian tumor was discovered during a complete physical check-up when she was 58 years old in March, 2006. Hysterectomy with bilateral salpingo-oophorectomy was performed in June, 2006. Although the omentum was resected, LNs were not dissected. The right ovarian tumor, 10 cm in diameter, presented as a unilocular cyst that was histologically composed of both mucinous adenocarcinoma and endometrioid adenocarcinoma cells, thus it was diagnosed as a mixed epithelial tumor (Fig. 1a, b).

Further, when she underwent a complete physical check-up in 2007, a mammography was performed, and a calcification in the left breast was found. A left partial mastectomy with sentinel LN biopsy was performed in July, 2007. Histologically, a minute noninvasive ductal carcinoma was identified, but the surgical margin was negative for cancer (Fig. 1c, d). Neither cancer metastasis nor sarcoid reaction was detected in the dissected sentinel LN. Postsurgical radiation (60 Gy) to the left breast was performed.

Cervical ultrasonography was performed in September, 2007, when she was referred for brain check-up, and a mass lesion in the left lobe of the thyroid was incidentally discovered, but it was judged a benign lesion and subsequently followed up. Multiple nodules in the spleen were identified by abdominal computed tomographic (CT) scan performed as a follow-up of the ovarian cancer in February, 2008. A chest CT scan, performed in April, 2008, revealed bilateral hilar and mediastinal slight lymphadenopathy up to 1 cm in diameter that was not obvious on chest X-ray films (Fig. 2). Neither axillary nor abdominal lymphadenopathy was identified. No liver lesion was detected by abdominal CT scan. F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) was performed, and uptake within the spleen and thyroid was recognized. Left lobectomy of the thyroid was performed in June, 2008. A grayish white nodule, 1.3 cm in diameter, of the left lobe of the thyroid was histologically diagnosed as papillary carcinoma with invasion beyond the thyroidal capsule, but the surgical margin was negative for cancer (Fig. 1e, f).

Laparoscopic splenectomy was further performed to investigate the splenic nodules in July, 2008. The resected spleen weighed 80 g, measured 10 x 7 x 4 cm, and was accompanied by multiple grayish white nodules, up to 1.3 cm in diameter. Histologically examined, the nodules turned out to be epithelioid cell granulomas without caseous necrosis (Fig. 3). No microorganism was detected by Ziehl-Neelsen, periodic acid-Schiff, and Grocott stainings. Although this patient presented with multiple non-caseous granulomas in the spleen, her serum angiotensin-converting enzyme (ACE) was within normal limit, and ocular or cardiac or other systemic lesions were not detected. Therefore, she was followed up without further medication. Twelve months after the splenectomy, she is uneventful without recurrence of the cancers.

Additional staining and immunohistochemistry were performed on the spleen tissue (Fig. 4). Fibrosis was observed inside the granulomas, visualized by reticulin staining. Immunohistochemistry was performed on paraffin-embedded sections using microwave antigen retrieval and avidin-biotin-peroxidase complex reactions, according to standard methods. The primary antibodies were directed to CD1a, CD3, CD20, CD21, fascin (Dako, Denmark), CD83 (Novocastra, Newcastle upon Tyne, UK), and polyclonal S100 (Nichirei Histofine, Tokyo, Japan) with dilutions between 1/40 and 1/400. Immunohistochemically, $S100^+$ DCs and $CD1a^+$ immature DCs as well as $fascin^+$ and $CD83^+$ mature DCs were identified but $CD21^+$ follicular DCs were not identified inside or in the vicinity of the granulomas. In the background spleen, mature DCs in the T-cell area and sinus as well as follicular DCs in germinal centers were recognized, but $CD1a^+$ immature DCs were not identified (Table 1). $CD3^+$ T-lymphocytes were detected, but no $CD20^+$ B-lymphocytes were found inside the granulomas.

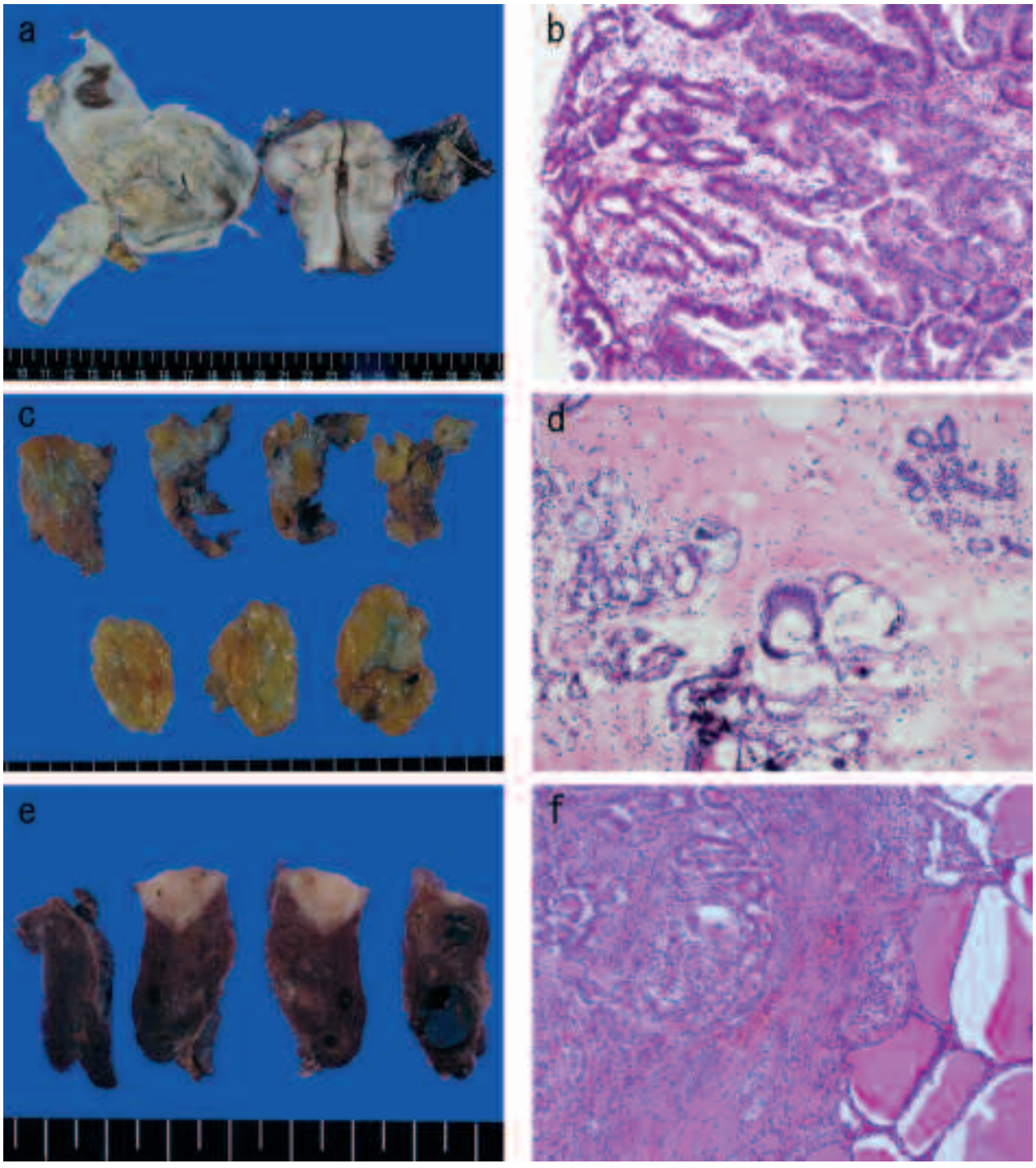

Fig. 1. Gross and histological (H&E staining, 100 x) features of multiple carcinomas. Right ovarian tumor (a, b). a, Resected uterus and bilateral adnexa. Right ovarian unilocular cyst is accompanied by multiple nodules. b, Atypical glands are composed of those with abundant mucin as well as those showing columnar epithelium with squamous differentiation. Left breast tumor (c, d). c, Serial cut surface of the resected specimen. Macroscopically, the tumor is not obvious. d, Microscopically, focal noninvasive ductal carcinoma with microcalcification, lower left, exhibits irregular glands along with enlarged nuclei, in contrast to normal ducts, upper right. Thyroid tumor (e, f). e, Serial cut surface of the left lobectomy specimen of the thyroid with yellowish white nodule. f, The nodule is composed of atypical thyroid follicles with colloid-like and papillary structure.

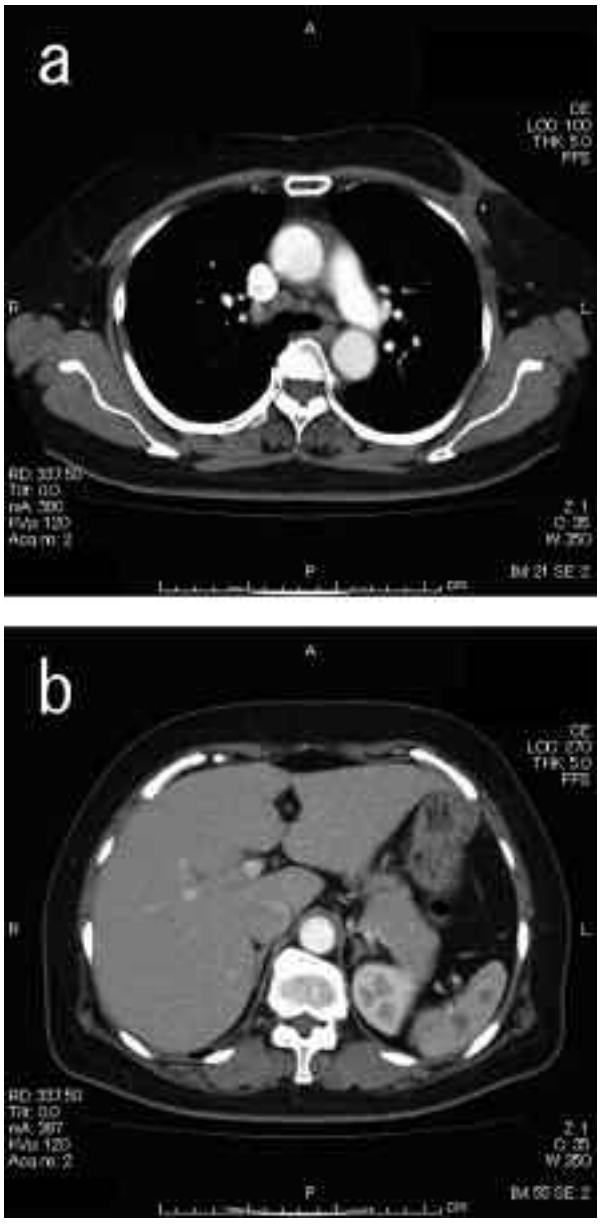

Fig. 2. Thoracic and abdominal computed tomographic (CT) scan. a, Chest CT scan shows bilateral hilar and mediastinal slight lymphadenopathy. b, Abdominal CT scan shows multiple nodules in the spleen, but no lesion is identified in the liver.

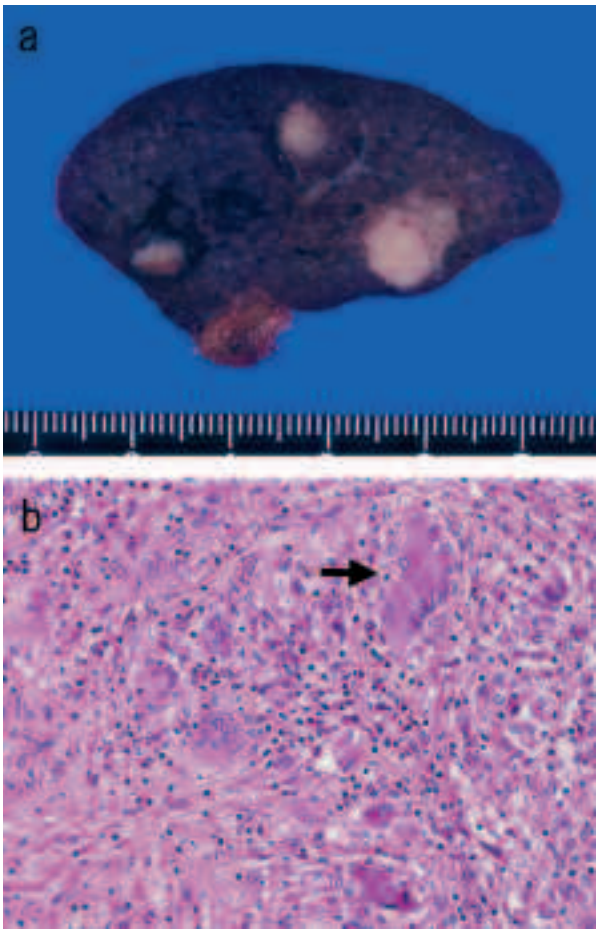

Fig. 3. Splenic granulomas. a, The cut surface of the spleen presents with multiple nodules, up to 1.3 cm in diameter. b, The histology of the nodules is epithelioid cell granuloma with multinucleated giant cells and partially asteroid bodies (arrow), but without caseous necrosis (200 x).

Discussion

This patient presented with multiple sarcoidal granulomas in the spleen during the consecutive diagnosis and management of ovarian, breast, and thyroid carcinomas during a period of about 2 years. Splenic granuloma is rare, and has not been recorded in archival files in our institute for the latest 15 years. Further, to our knowledge, splenic granuloma associated with multiple cancers has not been reported previously, so it is a topic that deserves discussion. A benign tumor-like lesion occurring in a woman of advanced age with nonspecific symptoms was reminiscent of inflammatory pseudotumor (IPT) (4). Furthermore, although extremely rare, granulomatous IPTs have been reported, in which an exuberant granulomatous reaction accompanied the IPT (5). IPT is characterized by a mixed inflammatory infiltrate that includes B-lymphocytes, plasma cells, and usually spindle cells of myofibroblastic or follicular dendritic cell origin (4,5). However, the lesions in the present case were not accompanied by

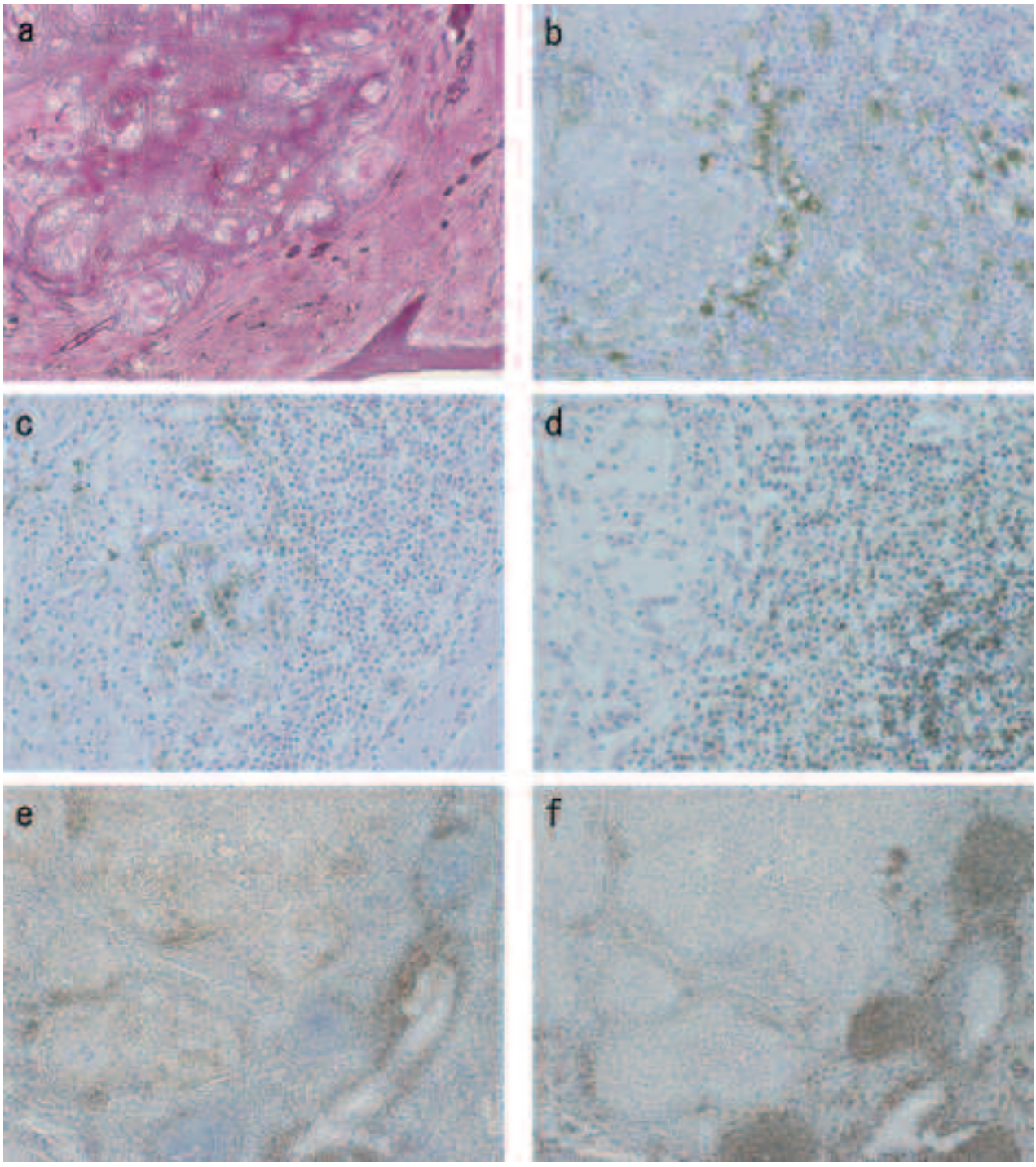

Fig. 4. Reticulin staining and immunostaining of the splenic granuloma (upper-left in each figure). a, Reticulin staining visualizes the fibrosis, an admixture of collagen and reticular fibers, inside the granuloma. b, Fascin$^+$ dendritic cells (DCs) scattered inside and around the granuloma as well as T-cell area of normal spleen (200 x). c, CD1a$^+$ immature DCs inside the granuloma but not in normal spleen (200 x). d, CD21$^+$ follicular DCs in germinal center, but not inside the granuloma (200 x). e, Numerous CD3$^+$ T-lymphocytes inside or in the vicinity of the granulomas (40 x). G, CD20$^+$ B-lymphocytes in the white pulp, but not identified inside the granulomas (40 x).

Table 1. Immunohistochemical detection of dendritic cells in the spleen in the present case.

Antibody	Inside granuloma	Background spleen		
		Germinal center	T-cell area	Sinus
S100	+	+	+	+
fascin	+	-	+	+
CD83	+	-	+	+
CD1a	+	-	-	-
CD21	-	+	-	-

+: present, -: absent

these cells, as evidenced by negative immunostaining of CD20 and CD21. Therefore, the lesions in the present case were diagnosed as pure granulomas. Granulomas usually form from an accumulation of nondegradable products or in connection with delayed-type hypersensitivity. Therefore, the etiology of granuloma includes infectious agents, environmental agents, and autoimmune disorders (6). Since this patient did not exhibit infections, such as tuberculosis, had not been exposed to environmental antigens such as beryllium, and did not have any autoimmune diseases such as Wegener's granulomatosis, the main differential diagnosis within the granulomatous disorders is systemic sarcoidosis and tumor-related sarcoid reactions.

Bilateral hilar and mediastinal lymphadenopathy suggest systemic sarcoidosis with splenic involvement. However, in our patient the lymphadenopathy was slight, and the FDG-PET was negative in these mediastinal sites, although FDG uptake in sarcoidosis has been well documented (7). Furthermore, it has been reported that in cases of systemic sarcoidosis with splenic involvement, liver nodules are observed in 50% and serum ACE is elevated in 91% of the patients, but this patient did not show such manifestations. In addition, systemic symptoms are often observed in systemic sarcoidosis with splenic involvement, but such symptoms were not apparent in this patient (3). The age of this patient is higher than usual for the first occurrence of systemic sarcoidosis, which is most commonly seen in the second to third decade of life (1). Therefore, the possibility of systemic sarcoidosis is unlikely, although not completely excluded.

Tumor-related sarcoid reactions are relatively rare findings, the average frequency being 4.4% in carcinomas, which manifest as epithelioid cell granulomas in the stroma or the neighborhood of the tumor, in LNs draining malignant neoplasms, and rarely in other organs such as bone marrow, spleen, and skin (2). The occurrence of splenic sarcoid reactions in gastric cancers was formerly reported to be 5 out of 100 cases, and less than 13 out of 100 cases of regional LNs (8). The pathogenesis of sarcoid reactions is thought to be a local T-cell mediated immune response to the soluble antigens shed by tumor cells or released in tumor necrosis (2,9). Antigen-presenting cells such as $CD83^+$ and/or $fascin^+$ mature DCs as well as T-cells were identified inside and in the periphery of granulomas of the LNs in sarcoid reactions as well as in systemic sarcoidosis (9). The splenic granulomas in this patient showed the same immunohistochemical results, including the absence of B-cells and $CD21^+$ follicular DCs, which play a major role in maintaining B-cell homeostasis (10), suggesting that the common pathway of antigen-presentation is associated with the formation of splenic granulomas.

However, $CD1a^+$ immature DCs were also identified inside the splenic granulomas of this patient, in contrast to sarcoid reactions in the LNs, in which $CD1a^+$ immature DCs were not identified (9). CD1a, first reported in Langerhans cells, serves as a well-established marker of immature DCs (11). Immature DCs are capable of antigen uptake and processing, but are unable to stimulate naive T-cells. As a consequence of antigen uptake, DCs generally begin to mature en route through lymph vessels or lymphatic organs, expressing molecules that will lead to binding and stimulation of naive T-cells (12). Therefore, the reason for the discrepancy between LNs and spleen concerning the presence of CD1a may be related to the absence of afferent lymph vessels in the spleen (13) or the difference in stromal cell environment in these 2 organs (14). Although little is known about DCs in human spleen, a high turnover of splenic DCs with a half-life of 2-3 days has been demonstrated in mice (14). It is noteworthy that no immature DCs were identified in the background spleen in this patient. Since immature DCs are widely distributed throughout the body (15), migrating immature DCs in the blood vessels may have been captured in the spleen, differentiated in situ to their mature counterparts, and acted as antigen-presenting cells in this case. Although it is intriguing to discern whether CD1a immunostaining can distinguish sarcoid reactions from systemic sarcoidosis, we

could not confirm it since splenic granuloma in systemic sarcoidosis has not been recorded in archival files in our institute for the latest 15 years. However, we suggest that the emergence of immature DCs in the formation of splenic granuloma is a common phenomenon, partly because the appearance of $CD1a^+$ cells has been reported in splenic granulomatous IPT (5), and partly because we earlier failed to identify the difference between the two disorders in LNs despite detailed immunohistochemistry (9).

In summary, we have presented a case of splenic granulomas associated with multiple cancers. Immunohistochemical analysis of DCs demonstrated that $CD1a^+$ immature DCs were found inside these granulomas, which is different from the situation in the nodal counterparts.

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References

1. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med 2007; 357: 2153-65.
2. Brincker H. Sarcoid reactions in malignant tumours. Cancer Treat Rev 1986; 13: 147-56.
3. Warshauer DM. Splenic sarcoidosis. Semin Ultrasound CT MR 2007; 28: 21-7.
4. Oz Puyan F, Bilgi S, Unlu E, et al. Inflammatory pseudotumor of the spleen with EBV positivity: report of a case. Eur J Haematol 2004; 72: 285-91.
5. Zhang MQ, Lennerz JK, Dehner LP, Brunt LM, Wang HL. Granulomatous inflammatory pseudotumor of the spleen: association with Epstein-Barr virus. Appl Immunohistochem Mol Morphol 2009; 17: 259-63.
6. Kobayashi K, Kaneda K, Kasama T. Immunopathogenesis of delayed-type hypersensitivity. Microsc Res Tech 2001; 53: 241-5.
7. Reilly TB, Schuster DM, Starsiak MD, Kost CB, Halkar RK. Sarcoid-like reaction in the spleen following chemotherapy for non-Hodgkin's lymphoma. Clin Nucl Med 2007; 32: 569-71.
8. Kojima M, Nakamura S, Fujisaki M, et al. Sarcoid-like reaction in the regional lymph nodes and spleen in gastric carcinoma: a clinicopathologic study of five cases. Gen Diagn Pathol 1997; 142: 347-52.
9. Kurata A, Terado Y, Schulz A, Fujioka Y, Franke FE. Inflammatory cells in the formation of tumor-related sarcoid reactions. Hum Pathol 2005; 36: 546-54.
10. Laurent C, Meggetto F, de Paiva GR, et al. Follicular dendritic cell tumor of the spleen associated with diffuse large B-cell lymphoma. Hum Pathol 2008; 39: 776-80.
11. Caux C, Vanbervliet B, Massacrier C, et al. CD34+ hematopoietic progenitors from human cord blood differentiate along two independent dendritic cell pathways in response to GM-CSF+TNF alpha. J Exp Med 1996; 184: 695-706.
12. Wilson NS, Villadangos JA. Lymphoid organ dendritic cells: beyond the Langerhans cells paradigm. Immunol Cell Biol 2004; 82: 91-8.
13. Mueller SN, Ahmed R. Lymphoid stroma in the initiation and control of immune responses. Immunol Rev 2008; 224: 284-94.
14. Tan JK, O'Neill HC. Concise review: Dendritic cell development in the context of the spleen microenvironment. Stem Cells 2007; 25: 2139-45.
15. Perez L, Shurin MR, Collins B, Kogan D, Tourkova IL, Shurin GV. Comparative analysis of CD1a, S-100, CD83, and CD11c human dendritic cells in normal, premalignant, and malignant tissues. Histol Histopathol 2005; 20: 1165-72.