Journal of clinical and experimental hematopathology
Vol. 62 No. 4, 226-237, 2022

Case report

Diffuse large B-cell lymphoma in the course of systemic sarcoidosis: A case report and review of 30 Japanese patients with sarcoidosis-lymphoma syndrome

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We report a patient with sarcoidosis who developed diffuse large B-cell lymphoma. A 71-year-old woman with persistent cough was diagnosed pathologically with sarcoidosis by resection of the right upper lung lobe with a nodule after an unsuccessful attempt of transbronchial needle aspiration for mediastinal lymphadenopathy. She was referred for an eye examination and found to have spotty retinal degeneration on the lower fundi of both eyes, together with residual macular edema and vitreous opacity in the left eye. At 76 years, she underwent cataract surgery and vitrectomy to gain a visual acuity of 0.6 in the left eye. At 77 years, she developed a cough and fever, and showed leukopenia and thrombocytopenia. Computed tomography showed multiple small nodular lesions in both lungs, and bilateral hilar, mediastinal, and hepatic lymphadenopathy. Fluorodeoxyglucose positron emission tomography demonstrated high uptake in the liver, spleen, pancreatic head, and lymph nodes. Bone marrow biopsy was intact, but liver biopsy revealed anomalous large lymphoid cells in the sinusoids which were positive for CD20 and showed a high Ki-67 index, leading to the diagnosis of diffuse large B-cell lymphoma. Chemotherapy with 8 courses of THP-COP (cyclophosphamide, pirarubicin, vincristine, and prednisolone) with rituximab, followed by intrathecal injection of methotrexate, cytarabine, and dexamethasone, resulted in complete remission. She maintained complete remission for 10 years until 88 years old at present. The literature review found 30 patients, including this case, who developed lymphoma in the course of sarcoidosis. A novel pathological diagnosis is required in the setting of acute symptomatic changes and novel lesions on imaging in patients with sarcoidosis.

Keywords: sarcoidosis; diffuse large B-cell lymphoma; liver biopsy; lung lobectomy; literature review

INTRODUCTION

Sarcoidosis is a multiorgan granulomatous disease of unknown cause. It mainly involves the skin, eyes, lungs, and heart manifesting erythema nodosum in the lower extremities, granulomatous uveitis, granular lung-field lesions with bilateral hilar lymphadenopathy, and atrioventricular block, respectively. Plain chest X-ray films at health checkups and visual symptoms of uveitis are two major factors that lead to the diagnosis of sarcoidosis in Japan.[1,2] Sarcoidosis has been known to be complicated rarely with lymphoma, and the condition is designated as sarcoidosis-lymphoma syndrome.[3-11] In this report, we describe a patient with pathologically-proven sarcoidosis in the lung who later developed diffuse large B-cell lymphoma and showed a good response to chemotherapy. We also reviewed 30 Japanese patients, including this case, with sarcoidosis who developed lymphoma in the literature.[12-43]

CASE PRESENTATION

A 71-year-old woman with a persistent cough for three months underwent right upper lobectomy for a pulmonary nodule which was suspicious of lung cancer. However,

Received: May 25, 2022. Revised: July 1, 2022. Accepted: July 2, 2022. J-STAGE Advance Published: September 28, 2022
DOI:10.3960/jslrt.22015

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pathological examination revealed that the nodule was indicative of sarcoidosis (Fig. 1). She also had mediastinal lymphadenopathy, and preceding transbronchial needle aspiration ended up with an unsuccessful attempt to have a pathological diagnosis, leading thus to open thoracic surgery. She had no medication at that time, and her history was unremarkable except for appendectomy in her late twenties. She was referred to an ophthalmologist for examination of possible uveitis.

On her first visit to Okayama University Hospital, the best-corrected visual acuity was 1.2 in the right eye and 0.2 in the left eye. The intraocular pressure was 10 mmHg in both eyes. She had no active uveitis but had retinal spotty degenerations in the midperipheral fundi of both eyes as well as residual macular inflammatory change and vitreous opacity in the left eye. She had erythema nodosum in both lower extremities but had no electrocardiographic change. She was followed up for five years with no oral or topical medication until the age of 76 years when she underwent cataract surgery in the left eye, and then, after a month, underwent vitrectomy for vitreous opacity (Fig. 2, fundus photographs at A and B). The best-corrected visual acuity was 0.9 in the right eye and 0.6 in the left eye. She had no active inflammation of sarcoidosis systemically or ophthalmologically (Fig. 2, fundus photograph at C).

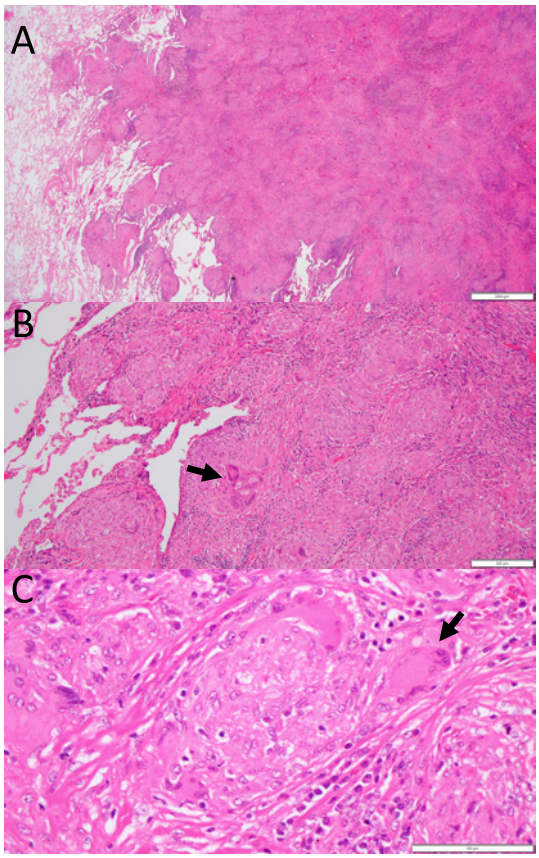

Fig. 1. Pathological diagnosis of sarcoidosis in the excised right upper lung lobe at the age of 71 years. Arrows indicate multinucleated giant cells. Hematoxylin-eosin stain. White scale bar = 2000 μm in ***A***, bar =200 μm in ***B***, and bar =100 μm in ***C***.

At 77 years old, she suddenly developed a dry cough and fever of 37 °C during the daytime which rose to 38-39 °C at night. A few days after admission to a local hospital, she showed thrombocytopenia and leukopenia, and was referred to another hospital. On this admission, she developed diarrhea with loss of appetite, but physical examinations revealed neither superficial lymphadenopathy nor hepatosplenomegaly. The complete blood cell counts showed red blood cells at 2.80 x 10^6/μL, platelets at 3.8 x 10^4/μL white blood cells at 3.3 x 10^3/μL with 53.0% neutrophils, 0.5% eosinophils, 22.5% lymphocytes, 22.0% monocytes, and 2.0% atypical lymphocytes. The reticulocyte index was 7.8%. The blood chemistry showed normal liver and renal functions including lactate dehydrogenase at 221 IU/L. The fibrin degradation product and D-dimer were not elevated at 3.3 μg/mL and 0.9 μg/mL, respectively. The serum calcium was elevated to 8.3 mg/dL and C-reactive protein to 6.98 mg/dL. The serum soluble interleukin-2 receptor (sIL-2R) was markedly high at 6933 U/mL. She did not experience weight loss or night sweats.

A computed tomographic scan showed multiple small ill-defined nodular lesions in the bilateral lung fields with bilateral hilar and mediastinal lymphadenopathy and multiple lymphadenopathies along the hepatic artery. A week later, whole-body 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) (Fig. 3A–3C) demonstrated high uptake in the spleen (maximum of standardized uptake value (SUVmax) = 16.21), liver (SUVmax = 5.35), pancreatic head (SUVmax = 5.38), and lymphadenopathy along the hepatic artery (SUVmax = 5.99). A relatively elevated uptake was also noted in the bilateral supraclavicular (SUVmax = 4.0 in the right, SUVmax = 1.89 in the left), mediastinal (SUVmax = 4.39), bilateral hilar (SUVmax = 4.96 in the right, SUVmax = 4.23 in the left) lymph nodes. The uptake in the lung-field small nodules was low (SUVmax = 1.66).

Bone marrow biopsy disclosed hypocellular marrow and no infiltration with anomalous cells. Spinal tap revealed no abnormalities. Skin biopsy showed no malignancy. Gastrointestinal endoscopy revealed no abnormalities. Liver biopsy disclosed sinusoidal infiltration with large anomalous lymphoid cells (Fig. 4A) which were positive for CD20 (Fig. 4B), bcl-6, MUM1 (Fig. 4D), and Ki-67 (Fig. 4E), but negative for CD3 (Fig. 4C), CD10, bcl-2, CD5, and CD30, indicative of diffuse large B-cell lymphoma. The International Prognostic Index (IPI) was high at 4 and the revised IPI was poor. She underwent 8 courses of THP-COP (cyclophosphamide 700 mg, pirarubicin 40 mg, vincristine 1.4 mg, and prednisolone 40 mg) in half a year with 80% doses in the second course, 70% doses in the fifth course, and 60% doses in the seventh course. Rituximab 500 mg in 8 courses was combined. After the first course, she showed no fever in response to the chemotherapy, and the serum sIL-2R decreased to 2963 U/mL. Ultimately, she underwent intrathecal injection of methotrexate at 15 mg, cytarabine at 40 mg, and dexamethasone at 3.3 mg, leading to complete remission half a year later (Fig. 3D–3F).

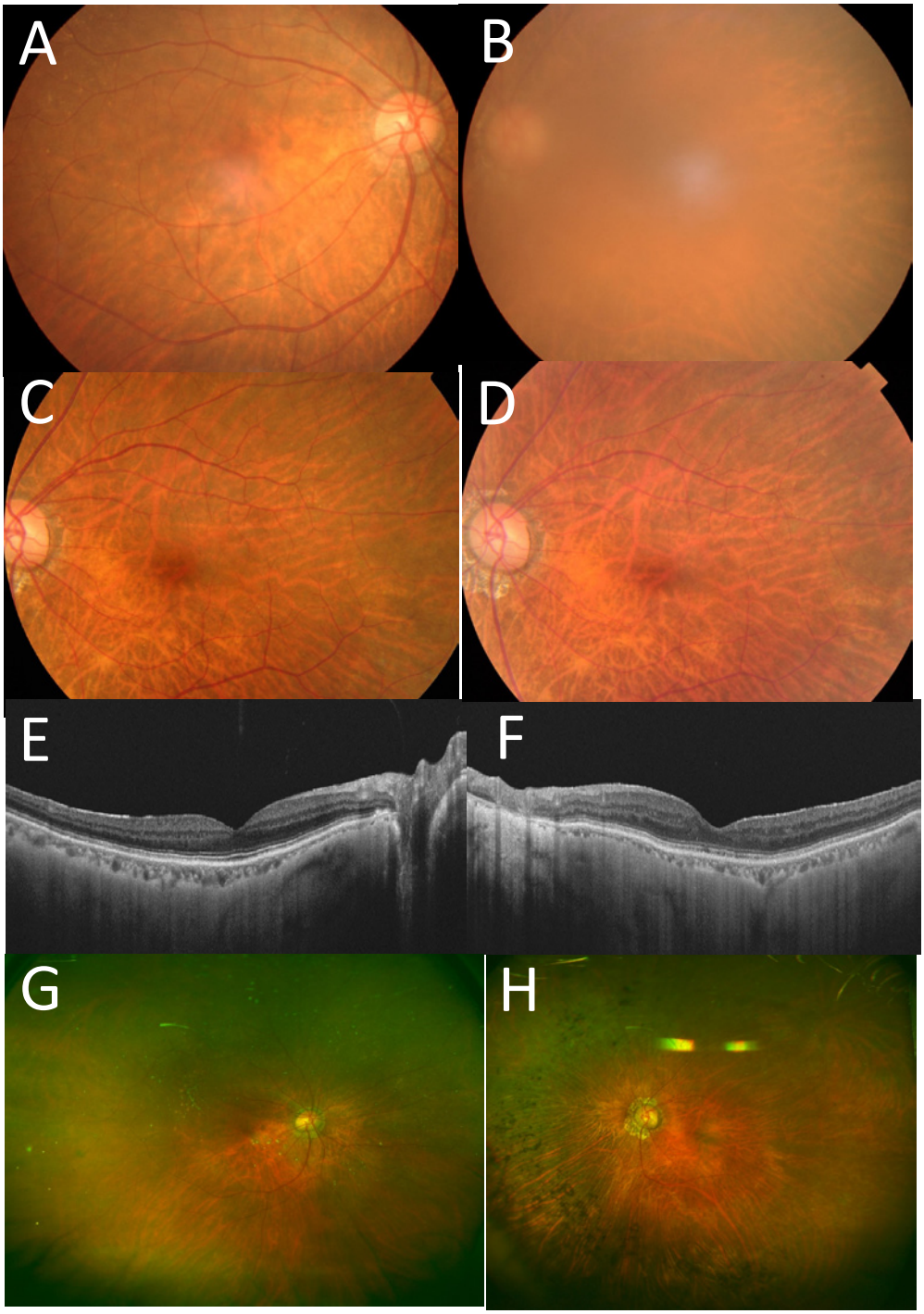

Fig. 2. Fundus photographs at the age of 76 years just before vitrectomy in the left eye (right eye: ***A***, left eye with vitreous opacity: ***B***), one month after vitrectomy (left eye with no vitreous opacity: ***C***), and at the age of 79 years one year after the end of chemotherapy (left eye: ***D***). Optical coherence tomography (right: ***E***, left: ***F***) and wide-view fundus photographs (right: ***G***, left: ***H***) at the age of 86 years, showing midperipheral spotty retinal degeneration with no active inflammation.

She was healthy and maintained complete remission with no medication for the following ten years until the age of 88 at the final visit in 2022. The small nodular lesions in the bilateral lung fields with bilateral hilar lymphadenopathy were stable without treatment (Fig. 5). She showed a normal range of blood angiotensin-converting enzyme activity but reduced renal function with serum creatine at 1.43 mg/dL and an estimated glomerular filtration rate of 30 mL/min/1.73 m^2. She showed no active iritis in the right eye while iritis in the left eye was stable with topical 0.1% betamethasone twice daily and 0.1% bromfenac twice daily (Fig. 2D–2H). The best-corrected visual acuity was 0.7 in the right eye and 0.4 in the left eye at the final visit.

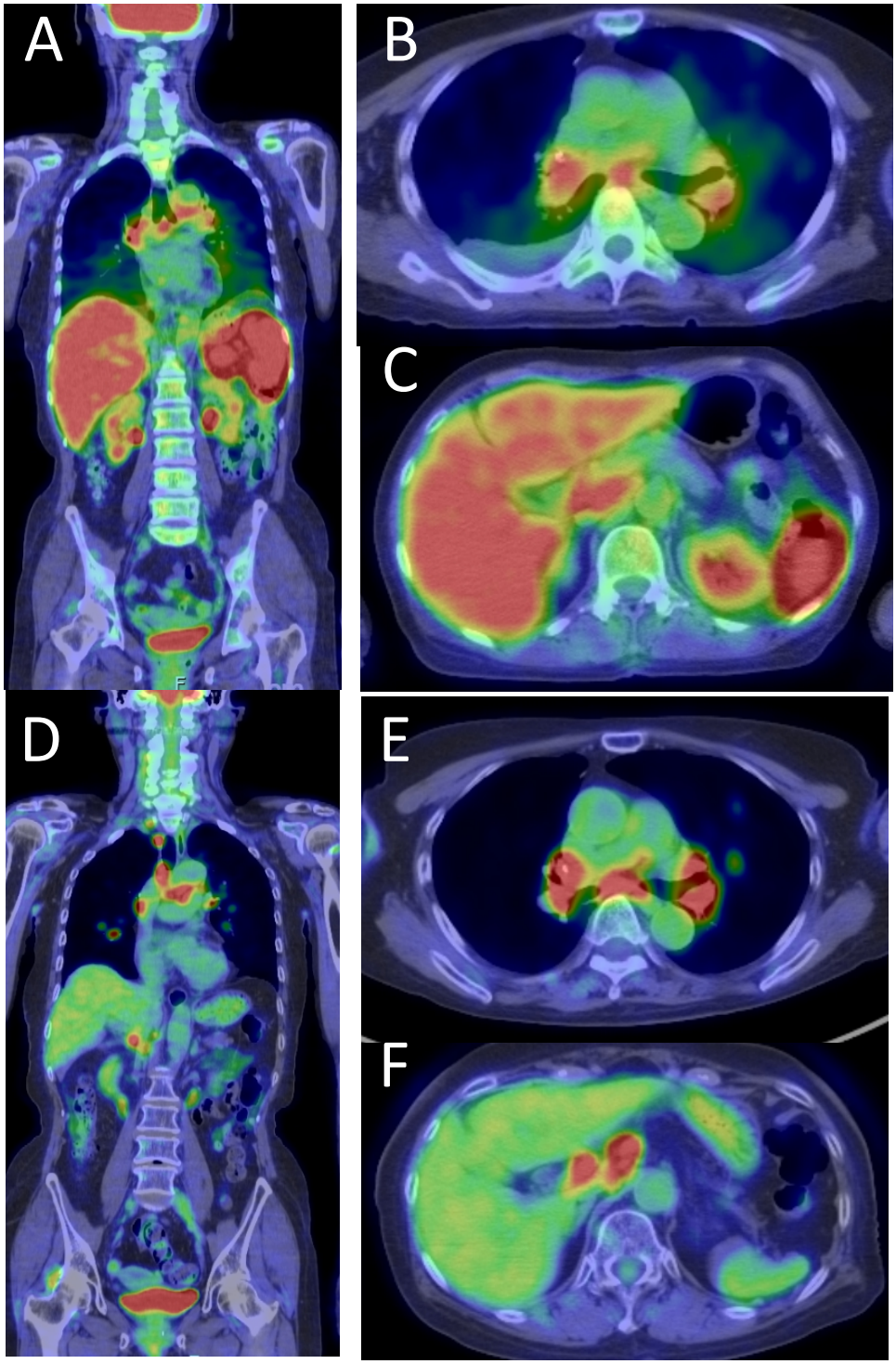

Fig. 3. Whole-body 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) combined with computed tomography (CT) at the age of 77 years (***A***, ***B***, ***C***), showing high uptake in the spleen (maximum of standardized uptake value (SUVmax) = 16.21), liver (SUVmax = 5.35), pancreatic head (SUVmax = 5.38), and lymphadenopathy along the hepatic artery (SUVmax = 5.99). A relatively elevated uptake was also noted in the bilateral supraclavicular (SUVmax = 4.0 on right, SUVmax = 1.89 on left), mediastinal (SUVmax = 4.39), bilateral hilar (SUVmax = 4.96 on right, SUVmax = 4.23 on left) lymph nodes. FDG-PET/CT at the age of 78 years after half a year of chemotherapy (***D***, ***E***, ***F***), showing uptake at the same levels in bilateral hilar, mediastinal, and hepatic lymphadenopathy with presumed involvement with sarcoidosis.

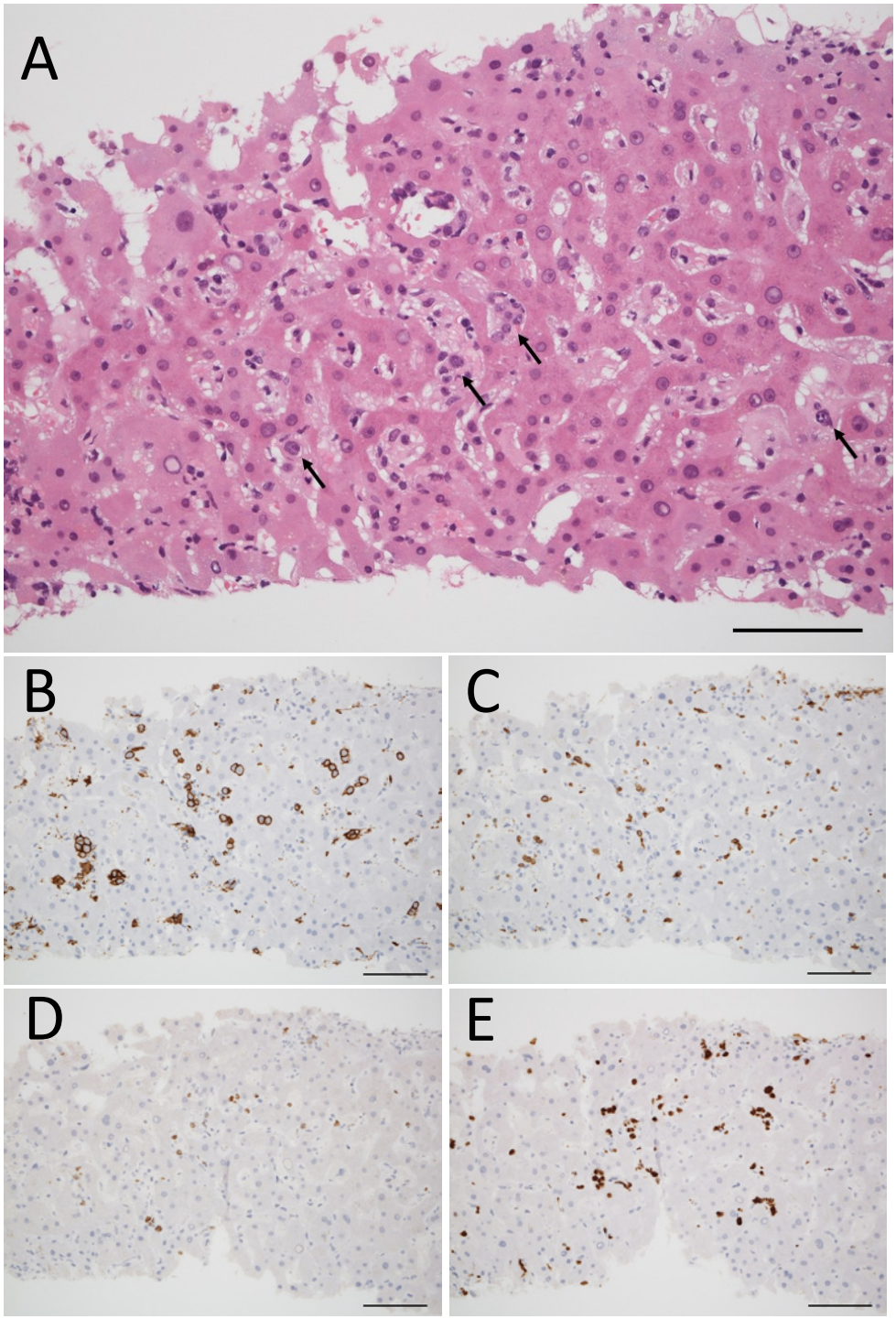

Fig. 4. Pathological diagnosis of diffuse large B-cell lymphoma by liver needle biopsy at the age of 77 years. Anomalous large cells (arrows in ***A***) in the hepatic sinusoids, positive for CD20 (***B***), MUM1 (***D***), and Ki-67 (***E***). CD3-positive T cells (***C***) are also found. Scale bar = 100 μm.

Methods

To analyze similar cases, we reviewed the Japanese literature with the keywords "*sarcoidosis* (in Japanese)" and "*lymphoma* (in Japanese)" in the bibliographic database of medical literature in Japanese (Igaku Chuo Zasshi, Japana Centra Revuo Medicina, Ichushi-Web), published by the Japan Medical Abstracts Society (JAMAS, Tokyo, Japan). Old literature was collected from the references cited in the articles identified during the literature search. PubMed and Google Scholar were also searched for the keywords "*sarcoidosis*" and "*lymphoma*". A sufficient description was found in 29 Japanese patients with sarcoidosis complicated with lymphoma (Table 1).[12-43]

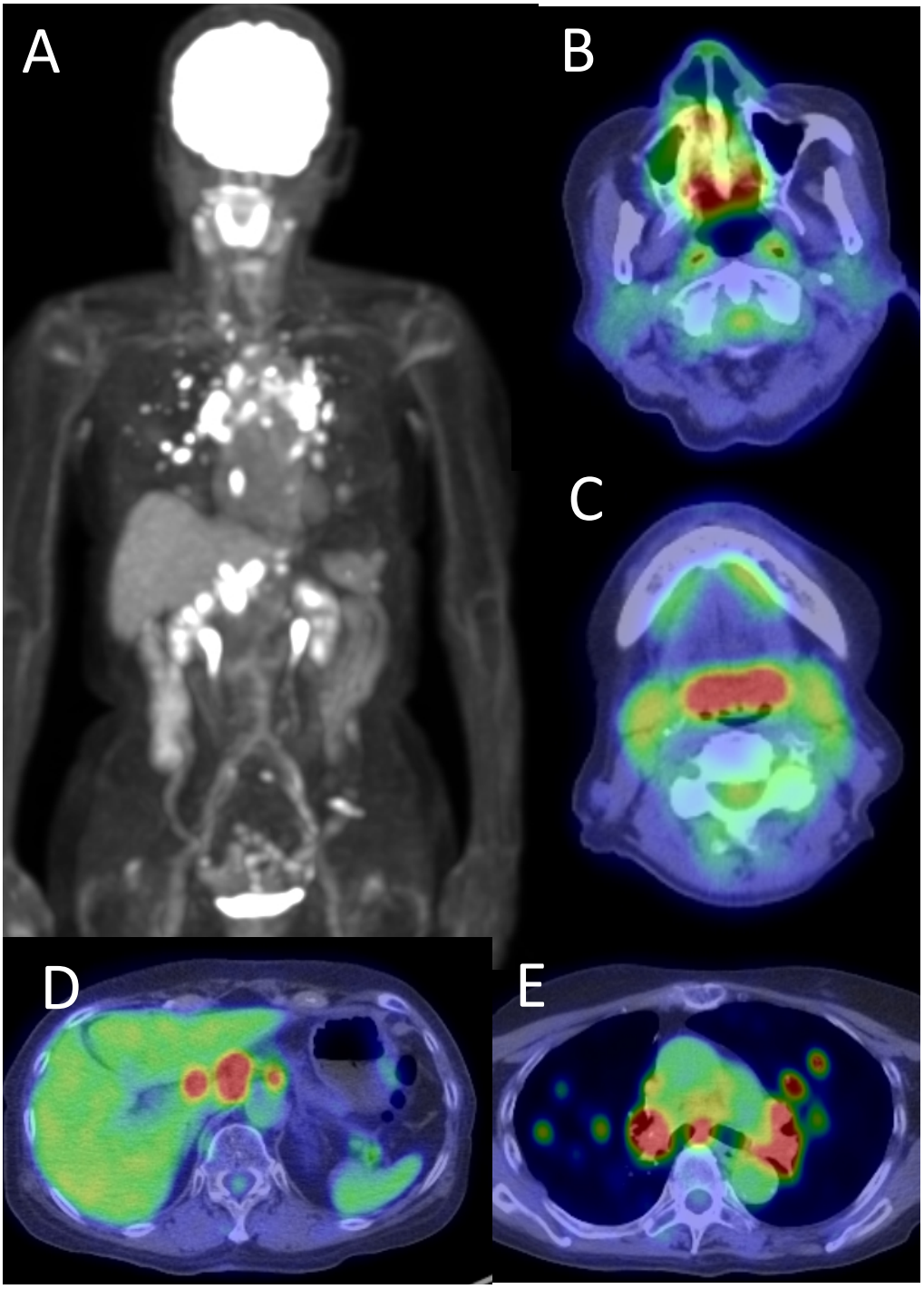

Fig. 5. Whole-body 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) (***A***) combined with computed tomography (CT) at the age of 81 years, 4 years after chemotherapy, showing relatively elevated uptakes at the same levels as just after the end of chemotherapy in bilateral hilar (***E***), mediastinal (***E***), hepatic (***D***) lymphadenopathy with presumed involvement with sarcoidosis. Uptake in the Waldeyer's tonsillar ring (***B***, ***C***) are considered physiological.

Results

We discovered 30 patients, including the present case, with sarcoidosis complicated with lymphoma (Table 1).[12-43] They were 20 women and 10 men with the age of diagnosis of sarcoidosis ranging from 8 to 79 (median, 56.5 years). The signs and symptoms of sarcoidosis were bilateral hilar or mediastinal lymphadenopathy in 14 patients, skin lesions in 9, uveitis in 7, subcutaneous nodules in 5, lung lobular nodules in 2, and the other lymphadenopathy in 2. The diagnosis of sarcoidosis was pathologically confirmed by lymph node biopsy in 12 patients, transbronchial lung biopsy in 9, skin biopsy in 8, nodule biopsy in 3, and lung lobectomy in 2.

Table 1. Review of 30 patients, including the present case, with sarcoidosis who developed lymphoma

Case No. /Sex	Age at diagnosis of sarcoidosis	Signs and symptoms of sarcoidosis	Diagnostic procedure for sarcoidosis	Timing of onset of lymphoma	Signs and symptoms of lymphoma	Procedure for pathological diagnosis of lymphoma	Pathological classification of lymphoma	Treatment of lymphoma	Other features	Author (Year)
1/Female	31	Erythema nodosum in the lower extremities, BHL, mediastinal lymphadenopathy	Skin biopsy, mediastinoscopic biopsy	4 years previously	Systemic skin rashes	Skin biopsy	Mycosis fungoides	CHOP Radiation	Mental delay	Shibuya[12] (1986)
2/Female	59	BHL	Abdominal lymph node dissection, splenectomy	10 years later	Epigastric pain	Gastrectomy, splenectomy, cholecystectomy	Lymphoma	Subtotal gastrectomy	Sarcoidosis in spleen and lymph nodes	Tamura[13] (1986)
3/Female	58	Skin rashes, nodules in the face, forearms, lower extremities	Skin biopsy, lymph node dissection	1.5 years later	Left axillary mass	Axillary mass biopsy	B-cell lymphoma	CHOP Radiation		Kobayashi[14] (1990)
4/Female	60	Paratracheal, parathyroid lymphadenopathy	Lymph node dissection	Concurrent	Anterior cervical swelling	Thyroidectomy	Thyroid lymphoma	40 Gy radiation		Mikuni[15] (1991)
5/Female	39	Left thigh skin scales, popliteal nodule	Skin biopsy	12 years later	Bilateral lower extremities skin rashes and ulcer	Skin biopsy	Cutaneous T-cell lymphoma	COP, VEPA	Dead of pneumonia in 1 year	Kobayashi[16] (1991)
6/Female	50	BHL uveitis	Cervical lymph node biopsy	15 years later	Epigastric pain	Proximal gastrectomy Splenectomy, gastric lymph node dissection	Diffuse large B-cell lymphoma	CHOP	Sarcoidosis in gastric lymph nodes	Masuda[17] (1992)
7/Male	8	Muscle nodule in the right upper arm Systemic skin rashes	Muscle nodule biopsy	23 years later	Right supraclavicular lymphadenopathy	Lymph node biopsy	T-cell lymphoma	CHOP with bleomycin Cisplatin or carboplatin with etoposide	Dead of pulmonary hemorrhage Sarcoidosis and lymphoma at autopsy	Banno[18] (1992) Takada[19,20] (1993)
8/Female	55	Skin, lung field change	Transbronchial lung biopsy, skin biopsy	12 years previously	Left femoral cutaneous nodule	Biopsy	B-cell lymphoma	Modified CHOP Radiation		Tada[21] (1993)
9/Female	44	BHL, erythema nodosum in the lower extremities	Scalene lymph node biopsy Skin Biopsy	24 years later	Disseminated intravascular coagulation and death	Autopsy	T-cell lymphoma	None		Harada[22] (1994)
10/Male	43	Stomach, gastric lymphadenopathy	Total gastrectomy, lymph node dissection	Concurrent	Epigastric pain	Total gastrectomy, Lymph node dissection	Diffuse large B-cell lymphoma	CHOP		Nakajima[23] (1996)

11/Male	46	uveitis	Skin biopsy Mediastinal lymph node biopsy	6 years later	Epigastric pain	Partial gastrectomy	B-cell lymphoma	CHOP with etoposide		Matsumoto[24] (1998)
12/Male	44	BHL	Not done	1.5 years later	Fever, Cervical, axillary & inguinal lymphadenopathy	Inguinal lymph node biopsy	Diffuse large B-cell lymphoma	CHOP DeVIC SEAM		Saito[25] (1999)
13/Female	55	Nodules in the thighs	Open nodule biopsy	1 year previously	Not described	Total gastrectomy	Diffuse large B-cell lymphoma	Chemotherapy		Nakamura[26] (2002)
14/Male	67	Abdominal pain	Transbronchial lung biopsy	6 years later	Right supraclavicular lymphadenopathy	Supraclavicular lymph node biopsy	Peripheral T-cell lymphoma	Procarbazine, cyclophosphamide	Dead of pneumonia	Terakawa[27] (2005)
15/Female	55	Uveitis, Sjogren syndrome, BHL, mediastinal lymphadenopathy	Transbronchial lung biopsy	1.5 years later	Left posterior cervical lymphadenopathy	Lymph node biopsy	Hodgkin lymphoma (mixed cellularity)	ABVD 38 Gy Radiation		Mori[28] (2008)
16/Female	61	Right hilar, mediastinal lymphadenopathy	Transbronchial lung biopsy	1.5 years later	Abdominal discomfort, systemic lymphadenopathy	Cervical lymph node biopsy	Hodgkin lymphoma	ABVD		Kyoraku[29] (2009)
17/Female	63	Cervical, mediastinal lymphadenopathy Lumbago (1.5 years later)	Lymph node biopsy Vertebral mass biopsy (1.5 years later)	2 years later	Dyspnea Pleural effusion	Gastric mucosal biopsy	B-cell lymphoma	R-CHOP		Mori[30] (2009)
18/Male	48	Fever, upper airway symptoms, uveitis	Transbronchial lung biopsy	5 years previously	Systemic lymphadenopathy	Lymph node biopsy	Follicular lymphoma	CHOP CHASER		Sakai[31] (2010)
19/Female	33	BHL, interstitial pneumonitis	Transbronchial lung biopsy	15 years later	Right cervical, inguinal lymphadenopathy	Lymph node biopsy	Diffuse large B-cell lymphoma	R-CHOP, methotrexate	Left lower lobe small cell carcinoma at 55 years old Dead of brain metastasis 2 years later	Kurosaki[32] (2012)
20/Male	55	Uveitis Mediastinal mass	Thoracoscopic biopsy	0.5 year previously	Left cervical lymphadenopathy	Lymph node biopsy	Diffuse large B-cell lymphoma	R-CHOP		Iino[33] (2012)
21/Female	76	Skin lesion	Skin biopsy	2 years later	Fever, lower abdominal pain, bloody bowel discharge	Emergency open abdominal surgery, ileocecal resection	Diffuse large B-cell lymphoma	THP-COP	Cardiac pacemaker at 69 years old	Uchihara[34] (2012)
22/Female	62	Nodules in lower extremities	Skin Biopsy	3 years previously	Not described	Inguinal lymph node biopsy	Follicular lymphoma	CHOP, CM	Mesenteric lymph node lymphoma relapse 1year later	Shiomi[35] (2012)
23/Male	60	BHL, mediastinal lymphadenopathy	Transbronchial lung biopsy Transbronchial needle biopsy of mediastinal lymph node	7 years previously	Right pharyngeal lymphadenopathy Right tonsillar enlargement	Lymph node biopsy Tonsillar biopsy (7 years later)	Diffuse large B-cell lymphoma	R-CHOP R-DHAP, ASCT (7 years later)	BHL after ASCT	Eguchi[36] (2015)

24/Female	79	Not described	Left inguinal lymph node biopsy (4 years later)	4 years later	Systemic lymphadenopathy Sudden death	Autopsy	Diffuse large B-cell lymphoma	None	Concurrent diagnosis of sarcoidosis and lymphoma in lung	Iizuka[37] (2017)
25/Female	60	Papules and ulcers in the right lower leg	Skin biopsy	Concurrent	Left inguinal, left axillary, right chest wall lymphadenopathy	Left inguinal lymph node biopsy	Folliculotropic peripheral T-cell lymphoma, NOS	Oral prednisolone	Sarcoidosis and lymphoma in the same tissue	Yoshida[38] (2017)
26/Male	63	Fever, cough	Lobectomy for nodular lesions	2 months later	Left hemiparesis	Right frontal brain lesion biopsy by craniotomy	Diffuse large B-cell lymphoma	High dose methotrexate Whole brain radiation	Alive in 2 years	Yamanaka[39] (2019) Ishihara[40] (2019)
27/Female	35	Right upper lobe large nodule	Transbronchial lung biopsy	Concurrent	Systemic lymphadenopathy	Left inguinal lymph node biopsy	Follicular lymphoma	Bendamustine, rituximab	Epilepsy	Kitaoka[41] (2018)
28/Male	73	Fever, cough, uveitis	Transbronchial lung biopsy	3 months later	Right scrotal swelling Mediastinal lymphadenopathy	Right orchidectomy Transbronchial needle aspiration of lymph node	Diffuse large B-cell lymphoma	R-CHOP Intrathecal methotrexate Radiation to left testicle		Hayama[42] (2019)
29/Female	59	BHL, Right supraclavicular lymphadenopathy	Right supraclavicular lymph node biopsy	6 years later	Left lower abdominal pain	Splenectomy	Diffuse large B-cell lymphoma (methotrexate-induced?)	R-CHOP without vincristine	Methotrexate for rheumatoid arthritis from 57 years old	Nakano[43] (2019)
30/Female	71	Right upper lobe nodule, BHL, mediastinal lymphadenopathy Uveitis, erythema nodosum	Right upper lobectomy	6 years later	Fever, leukopenia, thrombocytopenia	Liver biopsy	Diffuse large B-cell lymphoma	R-THP-COP Intrathecal methotrexate & cytarabine		This case

BHL, bilateral hilar lymphadenopathy; ASCT, autologous hematopoietic stem cell transplantation.
CHOP: cyclophosphamide, doxorubicin, vincristine, prednisolone; COP: cyclophosphamide, vincristine, methylprednisolone; VEPA: vindesine, cyclophosphamide, methylprednisolone, doxorubicin; ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; CHASER: cyclophosphamide, cytarabine, dexamethasone, etoposide, rituximab; CM: mitoxantrone, leustatin (cladribine); DHAP: dexamethasone, cytarabine, cisplatin; THP-COP: cyclophosphamide, pirarubicin, vincristine, prednisolone; DeVIC: dexamethasone, etoposide, ifosfamide, carboplatin; SEAM: semustine, etoposide, cytarabine, melphalan.

Lymphoma developed after the diagnosis of sarcoidosis in 19 patients in the period ranging from 2 months to 24 years (median, 6 years) while lymphoma developed earlier relative to the diagnosis of sarcoidosis in 7 patients in the period ranging from 0.5 years to 12 years (median, 4 years). Sarcoidosis and lymphoma were concurrently diagnosed in the remaining 4 patients. The signs and symptoms of lymphoma were lymphadenopathies in 15 patients, and skin lesions in 3 patients. The diagnosis of lymphoma was made by lymph node biopsy in 15 patients, gastrectomy or endoscopic biopsy in 6, skin biopsy in 3, splenectomy in 3, and autopsy in 2. The pathological diagnosis was diffuse large B-cell lymphoma or an unspecified description of B-cell lymphoma in 17 patients, follicular lymphoma in 3, T-cell lymphoma in 6, Hodgkin lymphoma in 2, and lymphoma with no specific description in 2. As the treatment for lymphoma, systemic chemotherapy was done in most patients.

DISCUSSION

The present patient at 71 years old with no marked past history complained of a dry cough, presented with a nodule in the lung field and mediastinal lymphadenopathy, and was diagnosed as pathologically-proven sarcoidosis by lung lobectomy during open chest surgery. She also had erythema nodosum in the lower extremities and showed inactive bilateral granulomatous uveitis with spotty retinal degenerations and vitreous opacity, which are characteristic of sarcoidosis. The patient fulfilled the clinical criteria for sarcoidosis as two or more organs were involved with typical clinical features, in addition to the pathological criteria. She was stable with no medication for the following 6 years until the age of 77 years when she developed novel acute-onset symptoms and signs, namely, fever, thrombocytopenia, and leukopenia. A computed tomographic scan, which showed lung-field small nodules and lymphadenopathy, supported the existing condition of sarcoidosis but did not explain the novel symptoms and signs. FDG-PET was helpful revealing an abnormally high uptake in the liver and spleen, and thus, leading to liver biopsy.

Diffuse large B-cell lymphoma was diagnosed by liver biopsy, based on CD20-positive anomalous large cells with a high Ki-67 index. These lymphoma cells were CD10-negative, bcl-6-positive, and MUM1-positive, leading to the designation as non-GCB (geminal center B-cell) type by the Hans classifier. It should be noted that hepatic sinusoidal involvement with large B-cell lymphoma suggests a differential diagnosis of intravascular large B-cell lymphoma.[44,45] Intravascular lymphoma is defined as lymphoma cells which proliferate only in the lumen of small blood vessels, without the evidence of extravascular mass formation such as lymphadenopathy.[44,45] Pathologically, lymphoma cells are frequently positive for CD5 in intravascular B-cell lymphoma.[46-48] In the present patient, lymphoma cells in the hepatic sinusoids were negative for CD5. Based on FDG-PET imaging, the liver and spleen were the two main organs involved with lymphoma in this patient, and pathological infiltration with lymphoma cells at other sites was not found by skin biopsy, bone marrow biopsy, or spinal tap. These clinical features are consistent with intravascular lymphoma.

A major diagnostic challenge in the present case is whether lymphadenopathy is due to sarcoidosis or lymphoma. Based on the fact that uptake in the lymph nodes did not decline immediately after chemotherapy with complete remission and also years after chemotherapy, bilateral hilar, mediastinal, and hepatic lymphadenopathy could be designated as the involvement of sarcoidosis. We think that this case is best regarded as intravascular large B-cell lymphoma. In the background of sarcoidosis, it is difficult to determine which organs are involved with newly-onset lymphoma from the viewpoint of clinical imaging; the involved organs may only be confirmed after long-term yearly observation.

According to the literature review,[12-43] sarcoidosis would serve as the background for the development of lymphoma. Diffuse large B-cell lymphoma is the most frequent entity to develop in combination with sarcoidosis, as shown in the present case, but the other entities of lymphomas, such as follicular lymphoma, Hodgkin lymphoma, and T-cell lymphoma, are also described in association with sarcoidosis. IgG4-related disease is also a precipitating condition for developing lymphoma.[49-52] Chronic inflammatory conditions, such as sarcoidosis, IgG4-related disease[49-52] and orbital inflammatory pseudotumor,[53] would give rise to lymphoma. On the other side of the coin, the complication with lymphoma in sarcoidosis might give a clue for understanding the unknown cause of sarcoidosis. A hint for the cause of sarcoidosis will also be obtained from a similar granulomatous disease, previously called early-onset sarcoidosis, which is now designated as Blau syndrome in the entity of autoinflammatory disease.[54] Coronavirus vaccination is also reported to underlay the development of sarcoidosis.[55]

CONFLICT OF INTEREST

The authors declare no conflicts of interest in this study. This study received no funding.

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