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Is recurrent Kikuchi-Fujimoto disease a precursor to systemic lupus erythematosus?

TARO HORINO[1], OSAMU ICHII[2], YOSHIO TERADA[1]

[1]Department of Endocrinology, Metabolism and Nephrology, Kochi Medical School, Kochi University, Kohasu, Oko-cho, Nankoku, Kochi 783-8505, Japan
[2]Laboratory of Anatomy, Department of Biomedical Sciences, Graduate School of Veterinary Medicine, Hokkaido University, Kita 18, Nishi 9, Kita-Ku, Sapporo, 060-0818, Japan

Kikuchi-Fujimoto disease (KFD), also known as histiocytic necrotizing lymphadenitis, is a rare, benign, self-limiting disease characterized by cervical lymphadenopathy and fever. Since KFD was first reported in 1972, the validity of this clinical entity has been controversial and its aetiology remains unknown. Herein, we report a case of a patient with KFD, which was believed to be associated with systemic lupus erythematosus.

Keywords: Kikuchi-Fujimoto disease, systemic lupus erythematosus, FDG-PET/CT, enhanced CT.

INTRODUCTION

Kikuchi-Fujimoto disease (KFD), also known as histiocytic necrotizing lymphadenitis, is a rare, benign, self-limiting disease characterized by cervical lymphadenopathy and fever [1]. KFD was first reported in 1972 almost simultaneously by Kikuchi [2] and Fujimoto [3] as a lymphadenitis in which histology reveals a focal proliferation of histiocytic cells and abundant nuclear debris [1]. Although the validity of this clinical entity is controversial and its aetiology is unknown, an infectious or auto-immune process has been suggested, especially linking it to systemic lupus erythematosus (SLE).

CASE REPORT

A 21-year-old woman presented with progressive and persistent high fever, night sweats, painful swelling of the neck, polyarthralgia, and weight loss. She had a history of persistent high fever and painful swelling of the neck 5 years ago and again 3 years ago, after which she recovered spontaneously. On admission, physical examination revealed multiple enlarged cervical, supraclavicular, and axillary lymph nodes that were matted and moderately tender to palpation. Body temperature was 38.0°C. As shown in Table 1, laboratory data revealed elevated levels of C-reactive protein, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, ferritin, and soluble interleukin 2 receptor, as well as lymphopenia. Serological tests were positive for ANA and Sm Ab and negative for others. Serology for infectious agents did not reveal a current infection and all tumour markers were within normal ranges. Enhanced computed tomography (CT) revealed multiple lymphadenopathies in the cervical, supraclavicular, and axillary areas (Supplementary Figure 1) in addition to an intranodal unenhanced area and a suspicious necrotic lesion in the cervical region (Figure 1c). ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) revealed hepatosplenomegaly in addition to multiple lymphadenopathy with FDG uptake in the cervical, supraclavicular, axillary, and pelvic lymph nodes (Figure 1a, 1b, Supplementary Figure 2). A biopsy specimen from the right cervical lymph node revealed numerous lymphohistiocytic cells (Figure 1d) and karyorrhectic debris (Figure 1d, 1e) compatible with histiocytic necrotizing lymphadenitis. Based on these findings, she was diagnosed with Kikuchi-Fujimoto disease (KFD) and subsequently treated with 10 mg daily of oral prednisolone (PSL). Her symptoms and laboratory values immediately improved. PSL was tapered down to 5 mg/dL and she was followed up for 8 years without a relapse.

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Table 1

Laboratory data on admission

CBC			Reference range	Blood chemistry			Reference range	Infection			Reference range
RBC	396	x 10^4/μL	(386–492)	TP	7.3	g/dL	(6.6–8.1)	HCV Ab	(-)		(-)
Ht	34.0	%	(35.1–44.4)	FBS	92	mg/dL	(73–109)	HBs Ag	(-)		(-)
Hb	11.3	g/dL	(11.6–14.8)	Alp	187	U/L	(106–322)	HIV Ab	(-)		(-)
Plt	25.3	x 10^4/μL	(15.8–34.8)	t-Cho	192	mg/dL	(142–322)	HTLV-1 Ab	(-)		(-)
WBC	5.0	x 10^3/μL	(3.3–8.6)	γ-GTP	32	U/L	(13–64)	EBV VCA IgG	160	x	(<10)
ban	9.0	%	(0–11)	t-Bil	0.4	mg/dL	(0.4–1.5)	EBV VCA IgM	<10	x	(<10)
seg	71.0	%	(47–70)	d-Bil	0.1	mg/dL	(<0.4)	EBV VCA IgA	<10	x	(<10)
lym	17.0	%	(20–40)	ChE	287	U/L	(240–486)	EBV EBNA	40	x	(<10)
mon	3.0	%	(1–8)	Glb	3.4	g/dL	(2.2–3.4)	CMV Ag	(-)		(-)
eos	0.0	%	(1–4)	Alb	3.9	g/dL	(4.1–5.1)	PVB19 Ab	(-)		(-)
bas	0.0	%	(0–2)	ALT	53	U/L	(10–42)	rubella IgG	(+)		(-)
Proteinogram				AST	40	U/L	(13–30)	rubella IgM	(-)		(-)
IgG	1404	mg/dL	(861–1747)	LDH	365	U/L	(124–222)	measles IgG	(+)		(-)
IgA	530	mg/dL	(93–393)	CPK	20	U/L	(59–248)	measles IgM	(-)		(-)
IgM	410	mg/dL	(50–269)	SCr	0.46	mg/dL	(0.65–1.07)	TP Ab	(-)		(-)
IgE	270.5	IU/mL	(<100.0)	BUN	11	mg/dL	(8–20)	RPR	(-)		(-)
IgD	<1.0	mg/dL	(<12.6)	UA	4.6	mg/dL	(3.7–7.8)	ASO	29	IU/mL	(<160)
Urinalysis				Amy	45	U/L	(44–132)	ASK	80	x	(<2560)
protein	(-)		(-)	Serological tests				β-D-glucan	<6.0	pg/mL	(<11)
occult	(-)		(-)	CRP	0.9	mg/dL	(<0.14)	Tumour markers			
Electrolytes				CH50	48.4	U/mL	(30–45)	NSE	6.4	ng/mL	(<10)
Na	140	mmol/L	(138–145)	C3	112.8	mg/dL	(73–138)	α-FP	3.2	ng/mL	(<7.0)
K	4.1	mmol/L	(3.6–4.8)	C4	27.4	mg/dL	(11–31)	CEA	1.0	ng/mL	(<3.4)
Cl	104	mmol/L	(101–108)	ANA	80	x	(< 40)	CA19-9	17.4	U/mL	(<37)
Ca	9.8	mg/dL	(8.8–10.1)	(speckled)				SCC	<0.5	ng/mL	(<1.5)
Mg	2.2	mg/dL	(1.8–2.3)	anti-DNA Ab	<80	x	(<80)	Span-1	12	U/mL	(<30)
P	3.3	mg/dL	(2.7–4.6)	Sm Ab	(+)		(-)	DUPAN-2	29	U/mL	(<150)
Fe	63	mg/dL	(40–188)	MPO-ANCA	(-)		(-)	Others			
TIBC	254	μg/dL	(251–398)	PR3-ANCA	(-)		(-)	ACE	9.3	U/L	(7.0 - 25.0)
ferritin	337.7	ng/mL	(6.2–138)	sIL2R	966	U/mL	(145–519)	lysozyme	6.0	μg/dL	(5.0 - 10.0)

CBC, complete blood cell count; RBC, red blood cell count; Hb, haemoglobin; Ht, haematocrit; Plt, platelet; WBC, white blood cell count; ban, band cells; seg, segmented cells; lym, lymphocytes; mon, monocytes; eos, eosinophils; bas, basophils; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M; IgE, immunoglobulin E, IgD; immunoglobulin D; Na, sodium; K, potassium; Cl, chlorine; Ca, calcium; P, phosphorus; Mg, magnesium; Fe, iron; TIBC, total iron-binding capacity; TP, total protein; FBS, fasting blood sugar; Alp, alkaline phosphatase; t-Cho, total cholesterol; γ-GTP, γ-glutamyltransferase; t-Bil, total bilirubin; d-Bil, direct bilirubin; ChE, cholinesterase; Alb, albumin; Glb, globulin; ALT, alanine transaminase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CPK, creatine phosphokinase; SCr, serum creatinine; BUN, blood urea nitrogen; UA, uric acid; Amy, amylase; CRP, C-reactive protein; CH50, complement activity; C3, complement 3; C4, complement 4; ANA, anti-nuclear antibody; anti-DNA ab, anti DNA antibody (RIA); Sm Ab, anti-Smith antibody; MPO-ANCA, myeloperoxidase-anti-neutrophil cytoplasmic antibody; PR3-ANCA, serine proteinase3-anti-neutrophil cytoplasmic antibody; sIL2R, soluble interleukin 2 receptor; HCV Ab, hepatitis C virus antibody; HBs Ag, hepatitis B surface antigen; HIV Ab, human immunodeficiency virus antibody; HTLV-1 Ab, human T-cell leukaemia virus type 1 antibody; EBV, Epstein-Barr virus; VCA, virus capsid antigen; EBNA, EBV nuclear antigen; CMV Ab, cytomegalovirus antibody; PVB19 Ab, human parvovirus B19 antibody; rubella IgG/IgM, rubella IgG/IgM antibody; measles IgG/IgM, measles IgG/IgM antibody; TP Ab, treponema pallidum antibody; RPR, plasma reagin test; ASO, anti-streptolysin O antibody; ASK, antistreptokinase antibody; NSE, neuron specific enolase; α-FP, alpha-fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; SCC, squamous cell carcinoma antigen; Span-1, s-pancreas antigen-1; DUPAN-2, duke pancreatic monoclonal antigen type 2; ACE, angiotensin-converting enzyme.

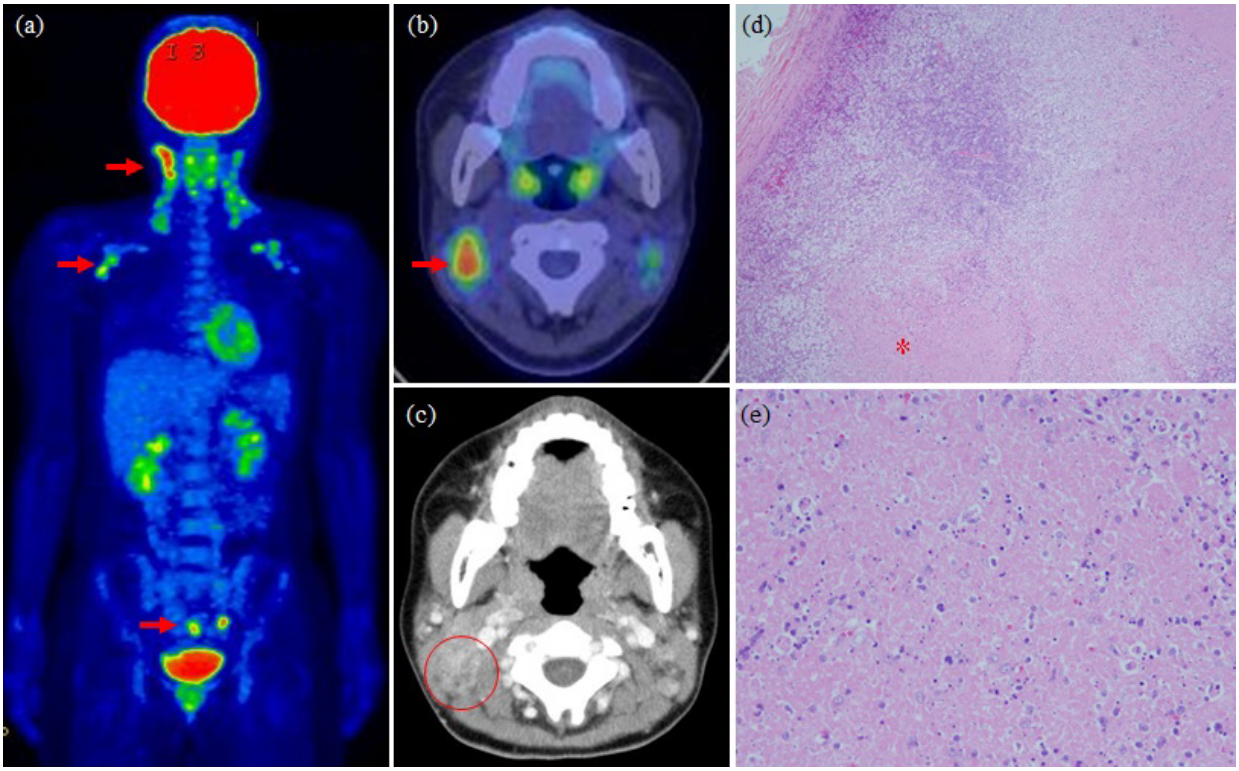
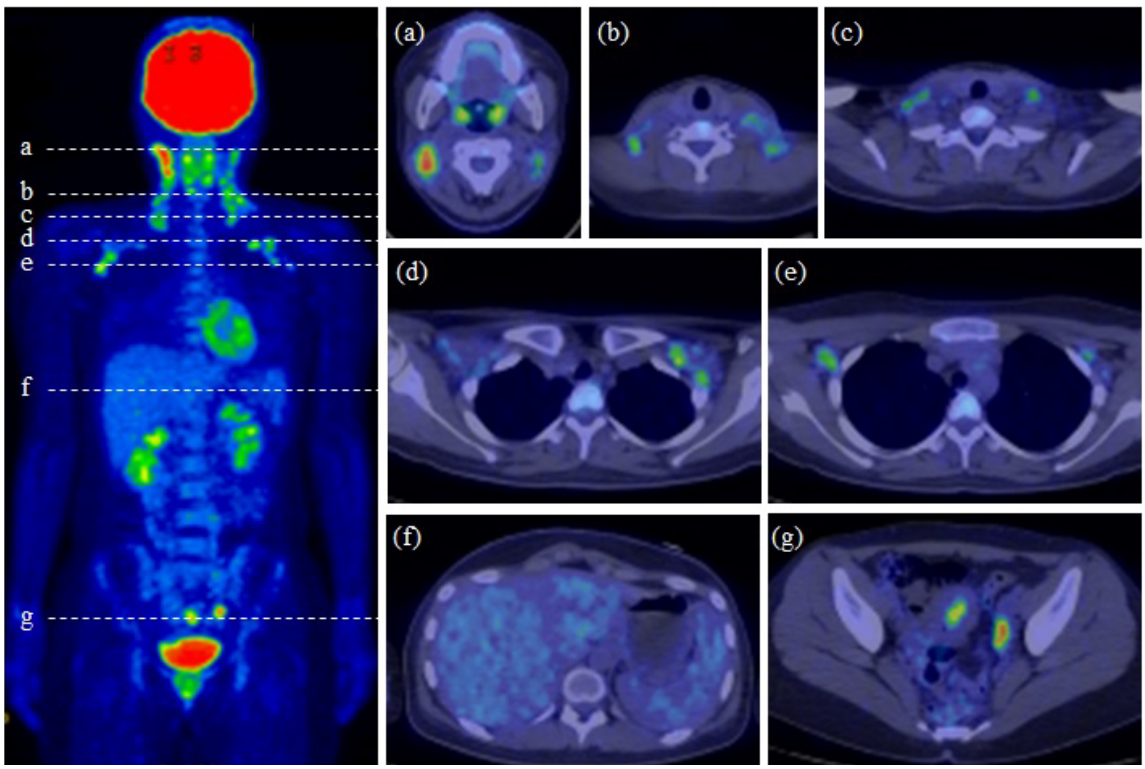
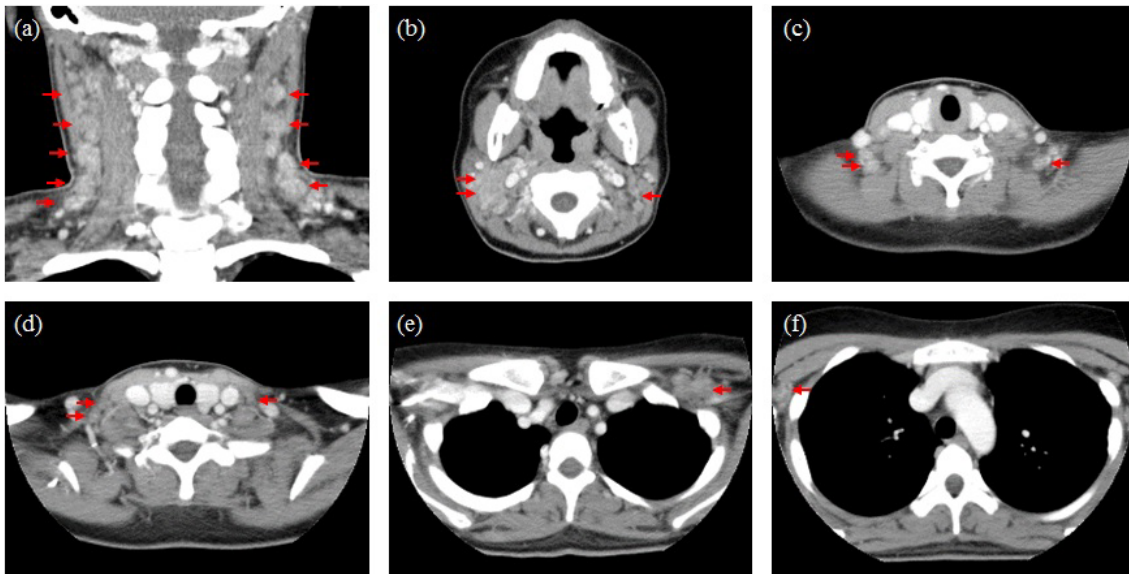


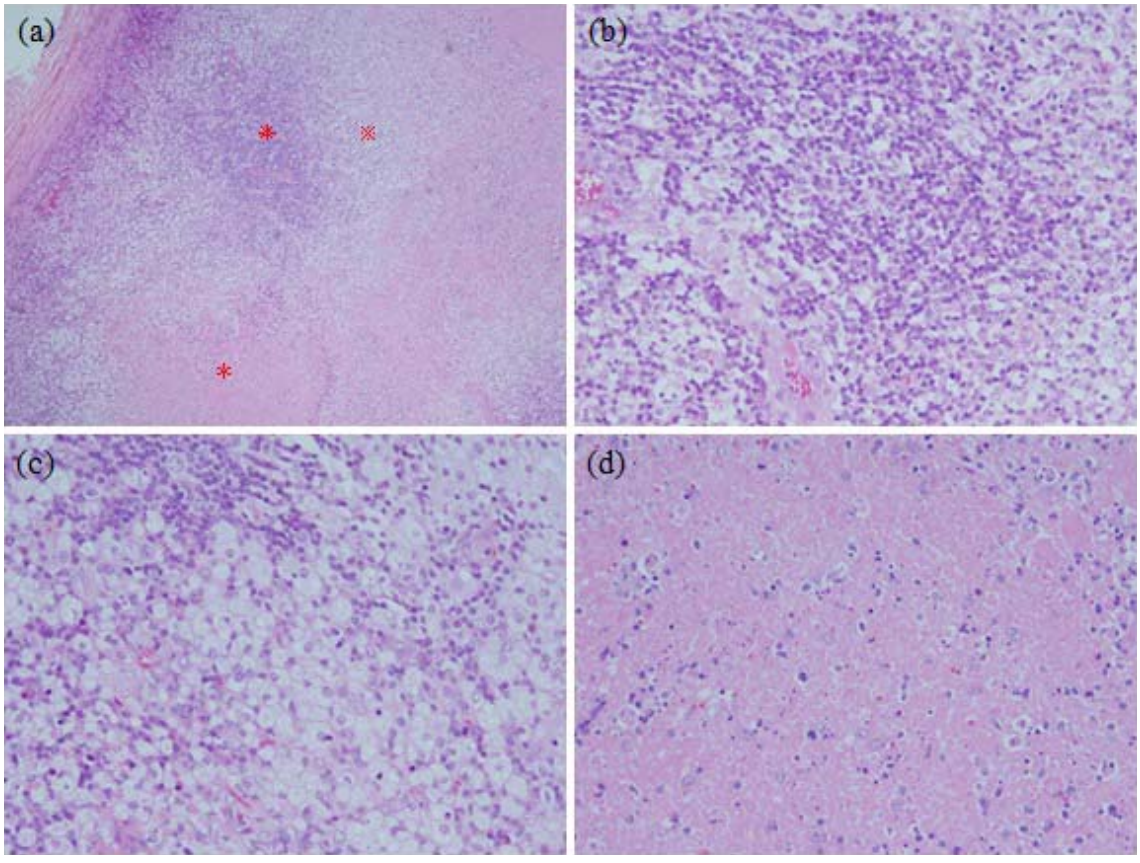
Figure 1. Findings of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography and enhanced computed tomography and pathohistological findings of biopsy specimen from the right cervical lymph following nodectomy (a) ^{18}F-fluoro-deoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) imaging shows active uptake of FDG by lymph nodes in the cervical, axillary, and pelvic regions (arrow). (b) FDG-PET/CT imaging shows that the region of most active uptake of FDG is by the right cervical lymph node (arrow). (c) Enhanced CT findings show an enhanced lesion in the right cervical lymph node with a focal unenhanced lesion (circle). (d) The biopsy specimen reveals histiocytic necrotizing lymphadenitis with numerous lymphohistiocytic cells and karyorrhetic debris compatible with Kikuchi-Fujimoto disease findings. (e) Karyorrhectic debris with eosinophilic necrosis and apoptotic bodies without granulocytes (*).



Supplementary Figure 1. ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography reveals hepatosplenomegaly in addition to multiple lymphadenopathies with ^{18}F-fluorodeoxyglucose uptake in the cervical, supraclavicular, axillary, and pelvic lymph nodes.



Supplementary Figure 2. Enhanced computed tomography demonstrates multiple lymphadenopathies in the cervical, supraclavicular, and axillary areas (red arrows).



Supplementary Figure 3. Pathohistological findings of biopsy specimen from the right cervical lymph following nodectomy (a) The biopsy specimen reveals histiocytic necrotizing lymphadenitis with numerous lymphohistiocytic cells and karyorrhetic debris compatible with Kikuchi-Fujimoto disease findings. (b) Numerous lymphohistiocytic cells (1*). (c) Numerous lymphohistiocytic cells (1※). (d) Karyorrhectic debris with eosinophilic necrosis and apoptotic bodies without granulocytes (1*).

DISCUSSION

KFD was reported to be frequently associated with infectious and autoimmune diseases, especially SLE [4]. Although the cause of KFD remains unclear, it is generally considered to be an autoimmune-mediated disorder or an exaggerated immune reaction to an underlying infectious agent. Recent studies revealed that some patients with KFD met the criteria for diagnosis of SLE during their episode and

shared several clinical and laboratory manifestations [5, 6]. About 12-59% of patients with SLE develop lymphadenopathies at some point during the course of their disease, and histological and ultrastructural findings of lymph node biopsy specimens cannot distinguish KFD from lymphadenopathy associated with SLE [6]. In our case, although fever, arthralgia, and leukopenia are nonspecific symptoms reported in other febrile diseases, the patient met the diagnostic criteria of SLE according to ANA and Sm Ab positivity. Therefore, we considered the possibility that KFD may be associated with SLE or may even be a subtype of SLE.

Sopeña B *et al*. recently reported that patients with KFD associated with SLE can present with fever, arthritis, cutaneous rash, leukopenia, neurologic involvement, severe KFD, haemophagocytic lympho-histiocytosis (HLH) and recurrence at a higher rate than those with KFD alone, and need treatment with high or immediate doses of corticosteroids [6]. In our patient, HLH-like symptoms and laboratory findings were identified and continuous corticosteroid treatment was deemed necessary.

KFD is frequently misdiagnosed as a malignant lymphoma or an inflammatory disease [7]. Previous studies concluded that although FDG-PET/CT was unable to distinguish KFD from malignant lymphoma using maximum standardized uptake values, it may help guide the decision on appropriate biopsy sites [8, 9]. In our case, FDG-PET/CT revealed the location of the largest uptake of FDG and enhanced CT showed a strong enhancement in the right cervical lymph node. We believe that combining FDG-PET/CT and enhanced CT in patients with KFD may be useful in detecting active lesions to determine the appropriate biopsy site for accurate diagnosis of KFD. Furthermore, FDG-PET/CT helps in identifying the extent of lesion spread to the deep lymph nodes throughout the body, which we could not have detected otherwise. It was reported that KFD associated with SLE is more severe than KFD alone. We believe that FDG-PET/CT might be useful in assessing disease severity and accordingly determining corticosteroid treatment.

In conclusion, we report a case of a patient with KFD, which was believed to be associated with SLE. Our case suggests that KFD may be a subtype of SLE. Combining FDG-PET/CT and enhanced CT may be useful in determining the appropriate biopsy site for the accurate diagnosis of KFD.

Research ethics board approval was not required for the publication of this case report.

Declaration of interest: The authors declare that there are no conflicts of interest.

Boala Kikuchi-Fujimoto disease (KFD), cunoscută şi sub denumirea de limfadenită histiocitică necrotizantă, este o boală rară, benignă si autolimitativă caracterizată prin adenopatii laterocervicale şi febră. Etiologia a rămas necunoscută deşi primele cazuri au fost raportate in 1972. Prezentăm cazul unui pacient cu KFD care fusese suspicionat de lupus sistemic eritematos.

Correspondence to: Taro Horino, MD, PhD, Department of Endocrinology, Metabolism and Nephrology, Kochi Medical School
Kohasu, Oko-cho, Nankoku, Kochi 783-8505, Japan, Tel: +81-88-880-2343, Fax: +81-88-880-2344
E-mail: horinott@yahoo.co.jp

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