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【 CASE REPORT 】

Repeated Necrotizing Lymphadenitis with *MEFV* Gene Mutations

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Abstract:
We herein report a 36-year-old man with repeated necrotizing lymphadenitis due to *MEFV* gene mutations. The patient's chief complaints were a fever and painful cervical lymphadenopathy. We diagnosed him with necrotizing lymphadenitis based on the pathological findings of the lymph nodes and the exclusion of other differential diseases. The same episode recurred four times. We speculated the involvement of autoinflammatory backgrounds and detected *MEFV* gene mutations of E148Q (homo), P369S, and R408Q. Considering the elevation of interleukin-18, these mutations probably played roles in the repeated necrotizing lymphadenitis.

Key words: necrotizing lymphadenitis, *MEFV* gene mutation, autoinflammatory disease, inflammasome

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Introduction

Necrotizing lymphadenitis, which was described in 1972 by Masahiro Kikuchi, is characterized by self-limiting episodes of a fever and painful lymphadenitis. The pathological findings of lymph node biopsies show non-specific necrotizing lymphadenitis. Necrotizing lymphadenitis is commonly seen in young children and adolescents and is rare among people over 50 years old (1, 2). Recurrence of necrotizing lymphadenitis is rare (3-4% according to previous reports) (3, 4).

We herein report a case of repeated necrotizing lymphadenitis with *MEFV* gene mutations. *MEFV* is a candidate gene of Familial Mediterranean Fever (FMF). Because our case showed a different clinical course from FMF with its atypical fever cycle and the defect of serositis, we diagnosed this case to have necrotizing lymphadenitis and not FMF.

MEFV mutations cause functional changes in pyrin and induce the activation of inflammasomes. Based on the elevated interleukin-18 (IL-18) levels, we suspected that the *MEFV* gene mutations would contribute to the recurrent clinical features of necrotizing lymphadenitis in this case.

Case Report

A 36-year-old Japanese man presented with a fever and cervical lymphadenopathy. He had a history of infectious mononucleosis, which had occurred 15 years ago. There was no family history of any fever of unknown origin. All of his relatives were Japanese. No history of allergy, pet breeding, or foreign travel was noticed.

Fifteen years ago (X-15 years), the patient had had a fever and cervical lymphadenopathy. He had been diagnosed with infectious mononucleosis by serological tests. Eight years ago (X-8 years), he had developed a fever and cervical lymphadenopathy again and been diagnosed with necrotizing lymphadenitis, evidenced by pathological findings of the

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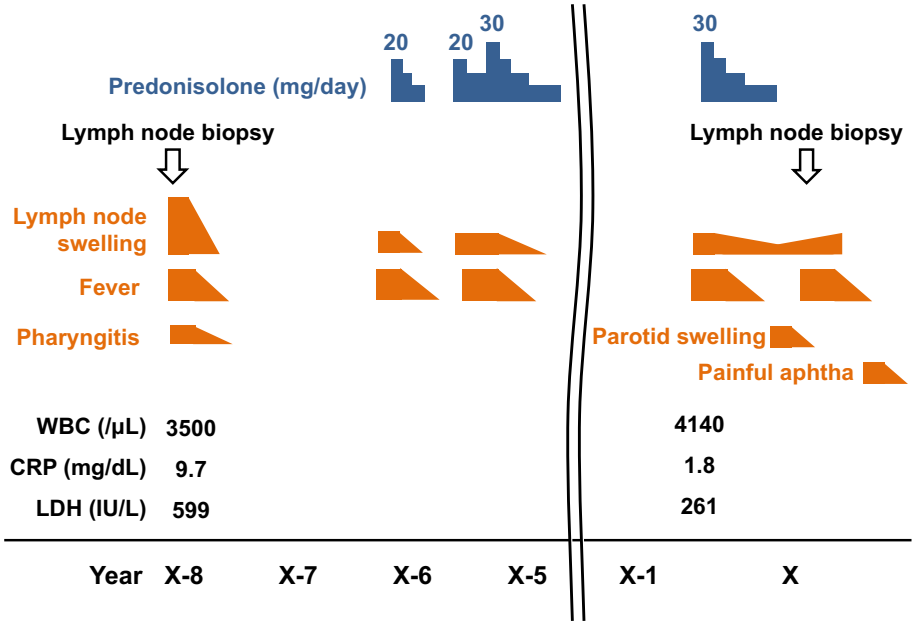

Figure 1. **Clinical course of the case. WBC: white blood cell, CRP: C-reactive protein, LDH: lactate dehydrogenase**

cervical lymph nodes; he recovered naturally within two weeks. He also had had similar clinical courses five and six years ago (X-5, X-6 years). At these episodes, prednisolone (PSL) had been used for two months and discontinued after tapering.

The previous October (X-1 year), he had developed a fever with cervical lymphadenopathy again. Recurrence of necrotizing lymphadenitis was speculated. Treatment with oral PSL was initiated, and his symptoms improved. Fluorodeoxyglucose-position emission tomography (FDG-PET) showed an increased FDG uptake in the right neck and right hilar lymph node of the lung and bilateral parotid glands. Late in the following February (X year), oral PSL treatment was discontinued. Four days after this discontinuation, he developed a fever and cervical lymphadenopathy and was admitted to our hospital for a close examination (Fig. 1).

A physical examination showed normal findings of the chest and abdomen. The patient's body temperature was 38.3 °C. He showed swelling of painful lymph nodes at the submental, submandibular, preauricular, superficial lateral cervical, deep lateral cervical, and supraclavicular nodes on the left. The lymph nodes were soft and mobile, measuring 0.3-1.0 cm in diameter. The axillary and inguinal lymph nodes were not palpable. He did not suffer from joint pain or skin lesions.

A urinary analysis showed no abnormalities. A blood analysis showed mild leukopenia and mildly elevated C-reactive protein levels but no increase in lactate dehydrogenase (LDH) or procalcitonin (Table).

Neck-pelvic enhanced computed tomography revealed no malignancy or infection foci. FDG-PET showed hotspots in the right neck, right hilar lymph node of the lung, and bilateral parotid glands (Fig. 2). Serological examinations revealed no evidence of autoimmune disease or infection but did show that the patient had previously suffered from Epstein-Barr virus (EBV), cytomegalovirus (CMV), and mumps virus infections. Assays for toxoplasma antibodies, HIV antibodies, and interferon gamma release were all negative. The titer of anti-nuclear antibody was 40 (Speckled pattern). However, tests for specific antibodies, such as anti-RNP antibodies, anti-Sm antibodies, anti-SSA antibodies, and anti-Scl-70 antibodies, were all negative. The serum levels of IgG4 were 110 mg/dL. There was no evidence suggesting malignancy on ultrasound or upper gastrointestinal endoscopy.

To clarify the etiology of the fever and cervical lymphadenopathy, a lymph node biopsy was performed. The pathological findings of the lymph nodes in X-8 year revealed that the lymphoid follicle structure was intact (Fig. 2). In contrast, the pathological findings of the lymph nodes in X year showed that the follicular structure of the lymph nodes had been lost, with an area of patchy necrotic distribution noted. Histiocytes and lymphocytes were detected around the necrotic area. Karyorrhectic debris were also observed. Immunostaining revealed that CD68-positive cells were dominant in the necrotic area (Fig. 2). The pathological diagnosis of the lymph nodes was non-specific necrotizing lymphadenitis.

In the cytokine profile analysis, the neopterin and IL-18 levels were elevated to 26.0 nmol/L (normal range <5 nmol/L) and 6,500 pg/mL (normal range 829-2,262 pg/mL), respectively. Soluble Tumor Necrosis Factor-Receptor II (sTNF-RII) was slightly elevated at 680 pg/mL (normal range <500 pg/mL) (Fig. 3). These findings were similar to those of typical necrotizing lymphadenitis. In an *MEFV* gene analysis, the patient was found to have *MEFV* gene mutations of E148Q (homo), P369S, and R408Q (Fig. 4). In

Table. **Laboratory Findings.**

Urinalysis		Blood chemistry		Serology			
pH	7.5	Na	140 mEq/L	IgG	1,250 mg/dL	HBs Ag	<0.1
Glucose	-	K	4.4 mEq/L	IgG4	110 mg/dL	HCV Ab	<0.1
Protein	-	Cl	103 mEq/L	IgA	181 mg/dL	HIV Ab	<0.1
Occult blood	-	Ca	9.0 mg/dL	IgM	222 mg/dL	TP Ab	0.2
WBC	<1 /HPF	P	3.0 mg/dL	IgE	153 mg/dL	VCA-IgM Ab	<10.0
RBC	<1 /HPF	BUN	9 mg/dL	CH50	69 U/mL	EBNA Ab	20
		Cr	0.66 mg/dL	C3c	122 mg/dL	CMV-IgM Ab	0.26
Complete blood cell count		UA	6.5 mg/dL	C4	55 mg/dL	CMV-IgG Ab	17.7
WBC	3,850 /μL	AST	19 IU/L	RF	<10 IU/mL	Mumps IgM	0.26
Neu	60.5 %	ALT	13 IU/L	ANA	×40	Mumps IgG	6.3
Lymph	27.0 %	LDH	185 IU/L	Anti SS-A Ab	<10.0 U/mL	Txoplasma-IgM Ab	0.1
Mo	11.7 %	γGTP	22 IU/L	Anti SS-B Ab	<15.0 U/mL	Parvovirus B19-IgM	0.58
Eos	0.3 %	T-Bil	0.4 mg/dL	Anti ds-DNA Ab	<12.0 IU/mL	QuantiFERON	-
Baso	0.5 %	TP	7.4 g/dL	Anti Sm Ab	<7.0 U/mL		
RBC	502×10^4 /μL	Alb	4.3 g/dL	Anti RNP Ab	<15.0 U/mL		
Hb	14.5 g/dL	T-cho	148 mg/dL	MPO-ANCA	<10.0 EU		
Ht	43.2 %	TG	107 mg/dL	PR3-ANCA	<10.0 EU		
Plts	20.3×10^4 /μL	Amy	111 IU/L	ACE	12.3 IU/mL		
		CK	62 IU/L	sIL-2R	396 U/mL		
		CRP	1.01 mg/dL				
		ESR	12 mm/h				
		Procalcitonin	<0.02 ng/mL				
		Ferritin	104 mg/dL				

WBC: white blood cell, RBC: red blood cell, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, CRP: C-reactive protein, RF: rheumatoid factor, ANA: anti-nuclear antibody, MPO-ANCA: myeloperoxidase anti-neutrophil cytoplasmic antibody, PR3-ANCA: serine proteinase 3 anti-neutrophil cytoplasmic antibody, ACE: angiotensin-converting enzyme, sIL2-R: soluble interleukin-2 receptor, TP: *Treponema pallidum*, CMV: cytomegalovirus

accordance with the diagnosis of necrotizing lymphadenitis, non-steroidal anti-inflammatory drugs (NSAIDs) were used. His fever of 39 °C improved gradually and returned to a normal body temperature within 2 weeks. The swelling of the cervical painful lymph nodes improved over the same time course.

Discussion

We encountered a case of repeated necrotizing lymphadenitis. The patient had experienced recurring episodes four times over eight years. Although it is necessary to consider the possibility of other diseases, serological and pathological examinations showed no findings of other diseases. The patient was found to have *MEFV* gene mutations [E148Q (homo), P369S, and R408Q].

The differential diagnosis is important for this case because he had suffered four repeated recurrences of necrotizing lymphadenitis over eight years. Differential diagnoses for a fever and cervical lymphadenopathy are usually infection, malignancy, autoimmune disease, IgG4 related disease, Castleman disease, sarcoidosis, and autoinflammatory diseases. However, because serological and pathological examinations showed no findings suggestive of these diseases, we made a diagnosis of necrotizing lymphadenitis. Recurrence of necrotizing lymphadenitis is relatively rare (3-4% in previous reports) (3, 4). Patients with recurrent episodes are usually prone to show a subacute onset (≥2 weeks) and are likely to have a fever (≥38 °C), cough, fatigue with frequent extranodal involvement (such as skin lesions), arthritis, and oral cavity lesions at the initial presentation. Furthermore, patients with recurrent episodes are usually more likely to show high anti-nuclear antibody levels (5).

In the present study, the patient had a subacute onset, a fever (≥38 °C), cough, fatigue, and extranodal involvement, including pharyngitis and tonsillitis. Skin lesions, arthritis, and high anti-nuclear antibodies are findings reminiscent of autoimmune disease. Some cases of repeated necrotizing lymphadenitis have been reported to develop autoimmune disease by a merger or after the diagnosis of necrotizing lymphadenitis (6, 7). In particular, systemic lupus erythematosus (SLE) is similar to necrotizing lymphadenitis both pathologically and clinically (8-10). Follow-up of this case will be important in order to rule out other autoimmune diseases.

The present patient had *MEFV* gene mutations of E148Q (homo), P369S, and R408Q, which are in exons 2 and 3. The *MEFV* gene encodes a pyrin (11) and regulates the activation of the inflammasome negatively via the NOD-like receptor family pyrin domain containing 3 (NLRP3). *MEFV* mutations cause functional changes of pyrin and induce the activation of the inflammasome (12). The *MEFV* gene has

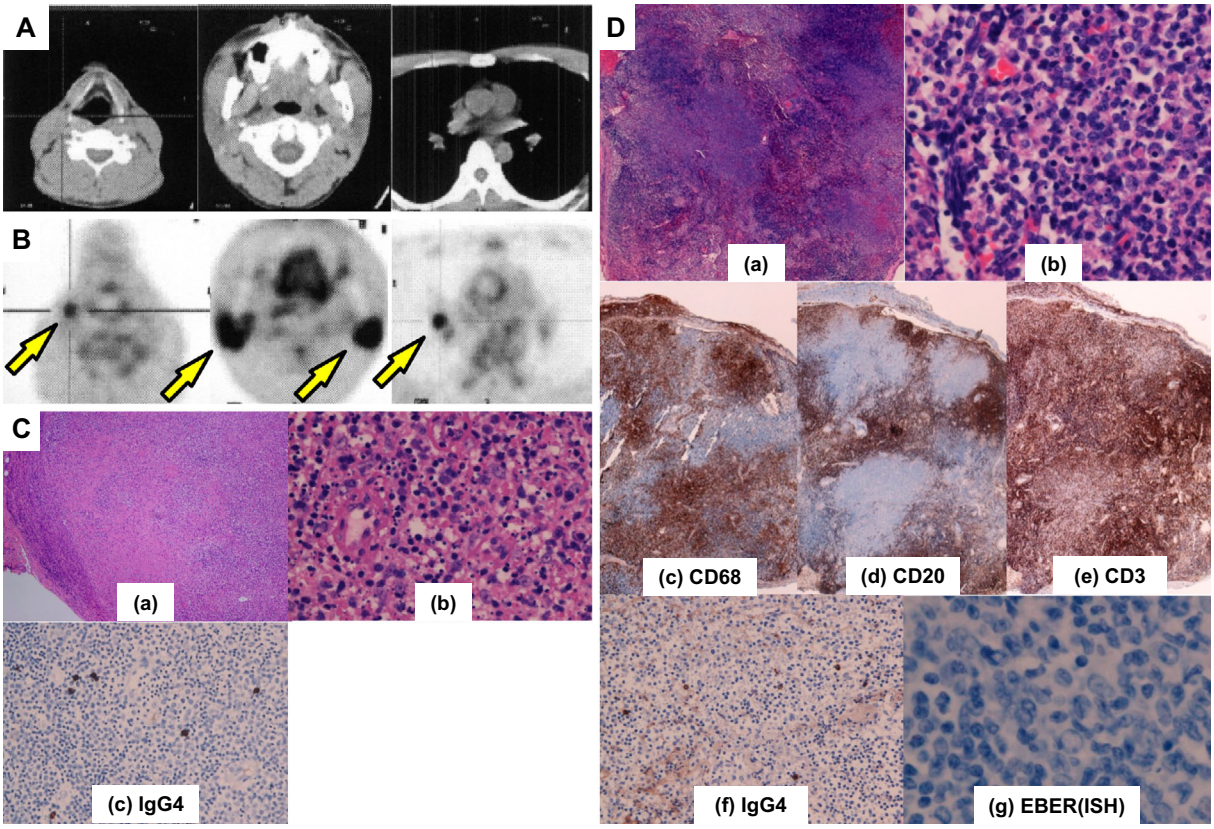

Figure 2. **Computed tomography, FDG-PET, and pathological findings. A, B: Plain CT (A) and FDG-PET (B) findings of the parotid glands, cervical lymph nodes, and mediastinum. Plain CT of the neck showed bilateral parotid gland enlargement, which is in the physiological range of phenomena, and no malignancy or infection foci. FDG-PET showed hotspots in the right neck, right hilar lymph node, and bilateral parotid glands (arrows). C: Pathological findings of lymph nodes in X-8 year. (a) Patchy pale lesions of histocytic necrotizing lymphadenitis are seen in the paracortical area of the lymphoid follicle. Hematoxylin and Eosin (H&E) staining ×40. (b) The lesions are composed of mononuclear cells with karyorrhectic debris and phagocytosis. H&E staining ×400. (c) A majority of the lesional cells are negative for IgG4. IgG4 ×400. D: Pathological findings of lymph nodes in X year. (a) The follicular structure of the lymph node was lost. The necrotic area was distributed patchily. H&E staining ×100. (b) Histiocytes and lymphocytes were detected around the necrotic area. Karyorrhectic debris were also observed. H&E staining ×400. (c)-(e) Immunohistochemical study. CD68-positive cells were dominant in the necrotic area. Very few CD20-positive cells and a few CD3-positive cells were observed, but monoclonal proliferation was not observed. CD68 (c) CD20 (d) CD3 (e) ×100. (f)-(g) A majority of the lesional cells were negative for IgG4 (f) and EBV-encoded RNA (EBER) (g). ×400.**

been recognized as a candidate gene of FMF (13). Although typical FMF has an *MEFV* mutation in exon 10, the coexistence of *MEFV* exon 2 variants induce the elevation of serum IL-18 levels and more severe phenotypes in patients with FMF with an *MEFV* exon 10 mutation (14). Furthermore, *MEFV* mutations are involved in FMF and various inflammatory diseases. Patients with a fever of unknown origin showed a higher frequency of *MEFV* gene mutations than healthy individuals (15). The present patient had mutations in exons 2 and 3, and the clinical course was different from that of typical FMF with mutations in exon 10. Given that IL-18, which is a marker of the inflammasome, was increased compared with healthy controls, *MEFV* gene mutations might have played a role as disease modifiers, resulting in the exacerbation of the inflammatory condition.

Our patient showed a self-limited fever with cervical lymphadenopathy, pharyngitis, and aphtha repeatedly. The clinical features are similar to those of periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome although the duration and intermittent period of the fever as well as the age of the onset are atypical (16). Furthermore, the patient also had symptoms similar to those of Behçet's disease. Although he did not meet the diagnostic criteria of Behçet's disease due to the lack of typical main symptoms, such as uveitis, mucocutaneous lesions, and gastrointestinal lesions, this patient may have had a pathological condition due to the activation of the inflammasome, which is also known to be involved in PFAPA syndrome and Behçet's dis-

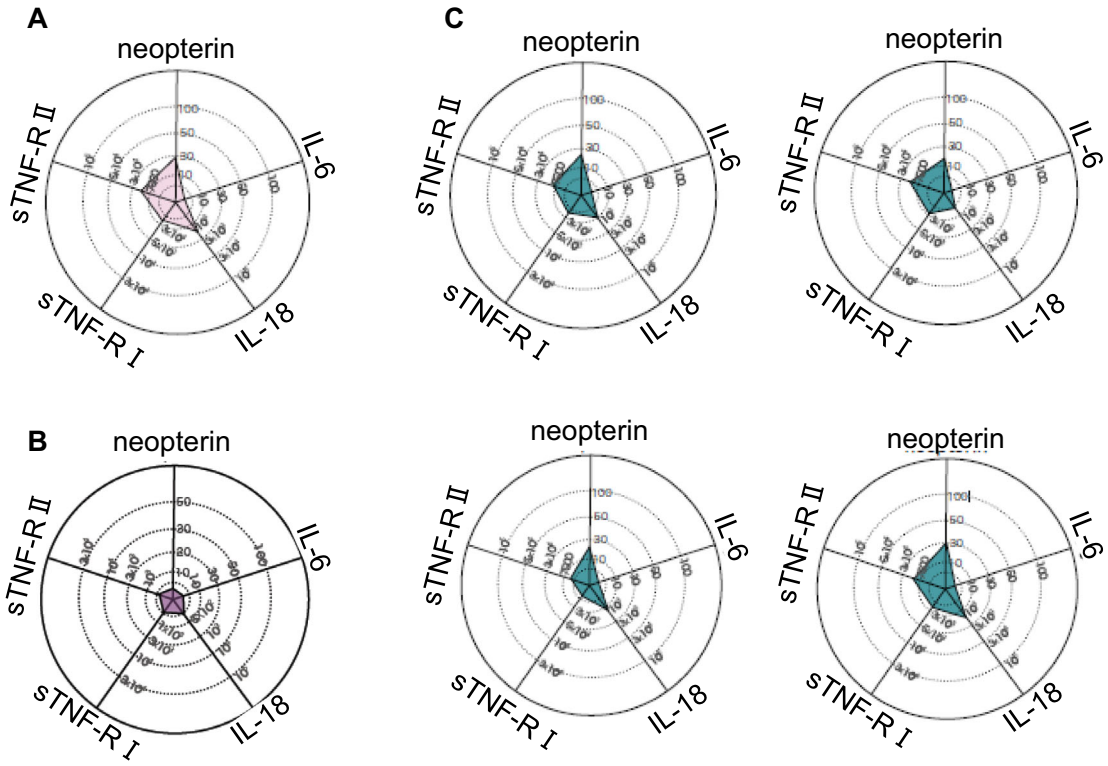

Figure 3. **Cytokine profile in the present case (A), healthy control (B), and another typical case of necrotizing lymphadenitis (C). In the present case and other cases of necrotizing lymphadenitis, neopterin levels were significantly high, and sTNF-RII and IL-18 levels were mild. In the present case, IL-6 was 5 pg/mL, neopterin was 26.0 nmol/lL, TNF-α was <5 pg/mL, sTNFα1 was 1,380 pg/mL, sTNF-RII was 6,530 pg/mL, and IL-18 was 680 pg/mL.**

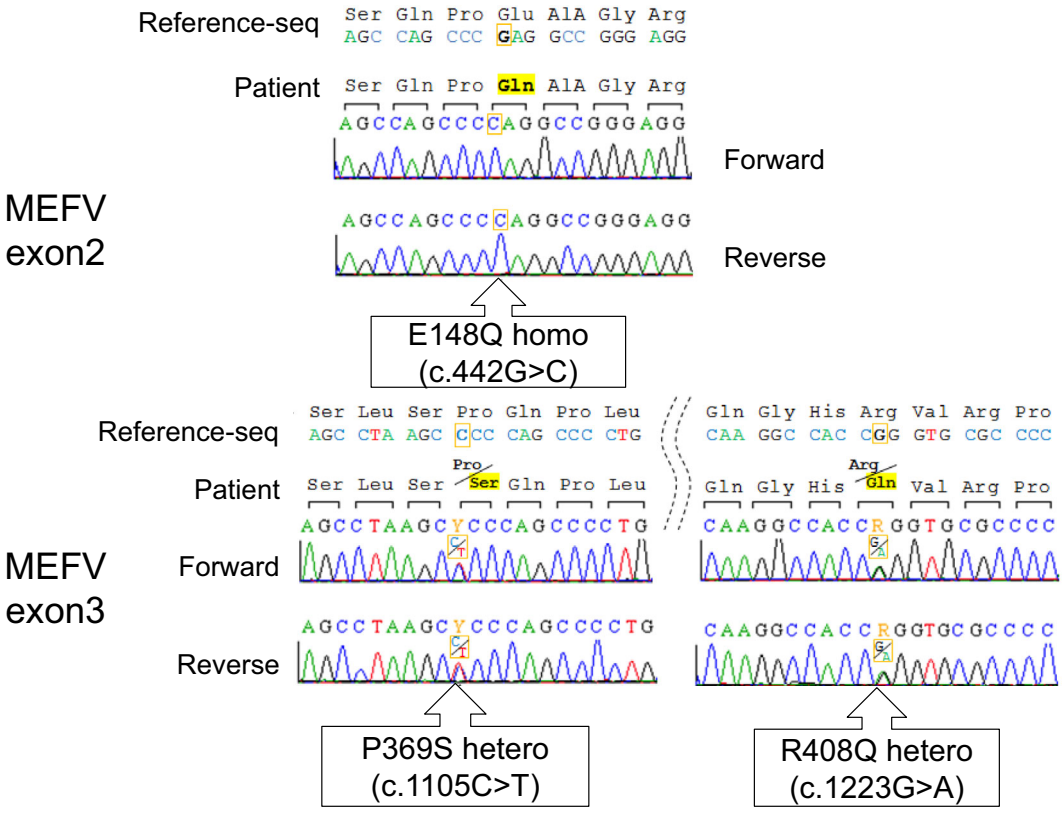

Figure 4. **Results of a *MEFV* gene analysis in the present case. E148Q homozygous, P369S heterozygous, and R408Q heterozygous mutations were demonstrated in the present case.**

ease (17-19). Some PFAPA and Behçet's disease patients have *MEFV* mutations (20, 21). Colchicine have been recognized as a way to regulate inflammasome activation and reported as a treatment for PFAPA syndrome and Behçet's disease (22, 23). Should recurrence occur again in this patient, it may be necessary to consider the administration of colchicine for treatment, based on his pathological condition.

In summary, we encountered a case of repeated necrotizing lymphadenitis. Necrotizing lymphadenitis complicates autoimmune diseases in some cases. Although this patient had no findings typical of autoimmune disease, careful follow-up will be necessary in the future. Furthermore, this case also showed *MEFV* gene mutations. We need to consider the involvement of inflammasome conditions, including *MEFV* gene mutations, in cases of repeated necrotizing lymphadenitis, as this knowledge may help treat recurrent necrotizing lymphadenitis based on the pathological condition of each patient.

This article does not contain any studies with human participants performed by any of the authors.

Informed consent was obtained from the participant included in this article.

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

References

1. Kikuchi M. Lymphadenitis presenting a specific tissue image. Nihon Ketsueki Gakkai Zasshi (Acta Hematol Jpn) **35**: 379-380, 1972 (in Japanese).
2. Fujimoto Y. Subacute necrotizing lymphadenitis in the neck. Naika (Intern Med) **30**: 920-927, 1972 (in Japanese).
3. Tsang WY, Chan JK, Ng CS. Kikuchi's lymphadenitis. A morphologic analysis of 75 cases with special reference to unusual features. J Surg Pathol **18**: 219-231, 1994.
4. Bosch X, Guilabert A, Miquel R, Campo E. Enigmatic Kikuchi-Fujimoto disease: a comprehensive review. Am J Clin Pathol **122**: 141-152, 2004.
5. Song JY, Lee J, Park DW, et al. Clinical outcome and predictive factors of recurrence among patients with Kikuchi disease. Int J Infect Dis **13**: 322-326, 2009.
6. Cheng CY, Sheng WH, Lo YC, Chung CS, Chen YC, Chang SC. Clinical presentations, laboratory results and outcome of patients with Kikuchis disease: emphasis on the association between recurrent Kikuchis disease and autoimmune disease. J Microbiol Immunol Infect **43**: 366-371, 2010.
7. Sopeña B, Rivera A, Vázquez-Triñanes C, et al. Autoimmune manifestations of Kikuchi disease. Semin Arthritis Rheum **41**: 900-906, 2012.
8. Yilmaz M, Camci C, Sari I, et al. Histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto's disease) mimicking systemic lupus erythematosus: a review of two cases. Lupus **15**: 384-387, 2006.
9. Kim SK, Kang MS, Yoon BY, et al. Histiocytic necrotizing lymphadenitis in the context of systemic lupus erythematosus (SLE): is histiocytic necrotizing lymphadenitis in SLE associated with skin lesions? Lupus **20**: 809-819, 2011.
10. Pilichowska ME, Pinkus JL, Pinkus GS. Histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto disease): lesional cells exhibit an immature dendritic cell phenotype. Am J Clin Pathol **131**: 174-182, 2009.
11. El-Shanti H, Majeed HA, El-Khateeb M. Familial Mediterranean fever in Arabs. Lancet **367**: 1016-1024, 2006.
12. Chae JJ, Komarow HD, Cheng J, et al. Targeted disruption of pyrin, the FMF protein, causes heightened sensitivity to endotoxin and a defect in macrophage apoptosis. Mol Cell **11**: 591-604, 2003.
13. Masters SL, Simon A, Aksentijevich I, Kastner DL. Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease. Annu Rev Immunol **27**: 621-668, 2009.
14. Endo Y, Koga T, Hara K, et al. The possession of exon 2 or exon 3 variants in the *MEFV* gene promotes inflammasome activation in Japanese patients with familial Mediterranean fever with a heterozygous exon 10 mutation. Clin Exp Rheumatol **38** (Suppl 127): 49-52, 2020.
15. Migita K, Ida H, Moriuchi H, Agematsu K. Clinical relevance of *MEFV* gene mutations in Japanese patients with unexplained fever. J Rheumatol **39**: 875-877, 2012.
16. Kusuhara K. Periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome. Nihon Rinsho Meneki Gakkai Kaishi (Jpn J Clin Immunol) **34**: 401-407, 2011 (in Japanese).
17. Theodoropoulou K, Vanoni F, Hofer M. Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome: a review of the pathogenesis. Curr Rheumatol Rep **18**: 18-24, 2016.
18. Nara K, Kurokawa MS, Chiba S, et al. Involvement of innate immunity in the pathogenesis of intestinal Behçet's disease. Clin Exp Immunol **152**: 245-251, 2008.
19. Musabak U, Pay S, Erdem H, et al. Serum interleukin-18 levels in patients with Behçet's disease. Is its expression associated with disease activity or clinical presentations? Rheumatol Int **26**: 545-550, 2006.
20. Kubota K, Ohnishi H, Teramoto T, et al. Clinical and genetic characterization of Japanese sporadic cases of periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome from a single medical center in Japan. J Clin Immunol **34**: 584-593, 2014.
21. Wu Z, Zhang S, Li J, et al. Association between *MEFV* mutations M694V and M680I and Behçet's disease: a meta-analysis. PLoS One **10**: e0132704, 2015.
22. Gaggiano C, Rigante D, Sota J, Grosso S, Cantarini L. Treatment options for periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome in children and adults: a narrative review. Clin Rheumatol **38**: 11-17, 2019.
23. Bettiol A, Hatemi G, Vannozzi L, Barilaro A, Prisco D, Emmi G. Treating the different phenotypes of Behçet's syndrome. Front Immunol **10**: 2830, 2019.