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CASE REPORT

A case of periodic-fever-syndrome-like disorder with lipodystrophy, myositis, and autoimmune abnormalities

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Abstract A 24-year-old Japanese woman had been suffering from a periodic fever since 10 months of age. She developed deformities in her fingers, with severe atrophy of subcutaneous adipose tissue, myositis, and frostbitten hands. She showed elevated C-reactive protein, creatine kinase, and γ-globulin. She was also positive for antinuclear, anti-DNA, anti-SS-B, and anti-U1RNP antibodies. Her myositis was similar to amyopathic dermatomyositis rather than juvenile dermatomyositis. Although consanguineous marriage of her parents and early onset of disease suggested her disease as a hereditary disorder with periodic fever, her clinical feature and laboratory tests were unlike any known periodic fever syndromes. Her disease was regarded as a unique type of periodic-fever-syndrome-like disorder with autoimmune abnormalities.

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Introduction

Hereditary periodic fever syndromes (HPFs) are a subset of autoinflammatory diseases characterized by recurrent attacks of fever and serositis, synovitis, and cutaneous inflammation. HPFs include tumor necrosis factor (TNF) receptor-1 associated periodic syndrome (TRAPS), familial Mediterranean fever (FMF), hyper-immunoglobulin D (IgD) syndrome, periodic fevers with aphthous stomatitis pharyngitis and adenitis (PFAPA) syndrome, and three overlapping syndromes related to mutations in the cryopyrin protein [1]. HPFs are extremely rare in Japan [2], and about 20 cases of HPFs have been reported [3–5]. PFSs associated with autoimmune diseases are rare when an associated viral/bacterial infection or malignancy are absent. Here, we describe a unique case similar to but distinct from these PFSs. In addition to periodic fevers, her clinical and radiological features included subcutaneous adipose tissue atrophy, myositis, basal ganglia calcification, and autoimmune disorders such as positive antinuclear autoantibody. Here, we report her unique clinical features and discuss the differences between her case and other related disorders.

Case report

A 24-year-old Japanese woman had been in good health until 10 months of age, at which time she experienced periodic high fever >39°C for a few hours a day accompanied by nasal erythema. Her parents were

consanguineous, but there was no family history of collagen vascular diseases or PFSs. At the age of 2 years, she had difficulty in walking, which was manifested by walking on tiptoe, and was admitted to a hospital for the first time. Physical examination revealed corpulence of bilateral gastrocnemius muscle and shortening of the Achilles' tendons. At the age of 12 years, she developed deformities of the fingers and frostbitten hands but had no major functional disturbance. At the age of 19 years, she suffered bilateral knee and shoulder pain. Prednisolone (5 mg day^{-1}) and anti-inflammatory drugs were begun, but those were not efficacious in resolving the joint pains and fever. At the age of 24 years, she visited our outpatient clinic and was admitted to our hospital. She reported fatigue and joint pains only for the few hours a day that she had high fever >38–39°C. Physical examination revealed deformities of fingers and toes, frostbitten hands (Fig. 1a), and edematous erythema on her eyelids (Fig. 1b). She had tenderness of both elbows, joint pains in both shoulders, knees, wrists, and feet, but had no swelling or local fever in these joints. Her shoulders, elbows, wrists, and finger joints were contractile. She showed mild atrophy of subcutaneous adipose tissues, especially in her face, fingers, and calves. On neurological examination, she had neither muscle weakness nor cranial nerve abnormality. Her verbal IQ on the Wechsler Intelligence Scale (WAIS) was 94 (normal range). She had no Sicca syndrome, lymphadenopathy, or cardiac murmur.

Abnormal laboratory findings included C-reactive protein of 5.3 mg dl^{-1} (normal < 0.5 mg dl^{-1}), creatine kinase of 361 IU l^{-1} (normal < 180 IU l^{-1}), hemoglobin of 10.3 g dl^{-1}, and white blood cell count of 5,200 μl^{-1} (neutro 49%:eosino 4%:baso 9%:lymph 37%), but platelet count of 2.54×10^5 μl^{-1} was normal. Serum levels of immunoglobulin G (IgG) (3,440 mg dl^{-1}) and IgE (13,715 IU ml^{-1}) were elevated, whereas that of IgM (291 mg dl^{-1}) was decreased, and those of IgA and IgD were normal. Levels of liver enzymes, blood urea nigrogen, creatinine, ferritin, and complements C3, C4, CH50 were normal. Antinuclear antibody was positive at 1:640 dilution (homogenous type). Anti-DNA (RIA) (32.9 IU ml^{-1}) and anti-SS-B antibodies were positive on enzyme immunoassay (EIA). Anti-Sm, anti-SS-A, anti-Jo-1, and anti-Scl-70 antibodies were negative on EIA. Anti-U1RNP antibody was weakly positive, but anti-U2RNP, anti-U3RNP, anti-U4/U6RNP, anti-7-2RNP, anti-SRP, anti-OJ, anti-EJ, anti-PL-7, anti-PL-12, anti-KS, and anti-ribosome antibodies were negative on immunoprecipitation assays.

We also examined her peripheral blood natural killer (NK) cell activity, which showed remarkably low activity of NK cell (effector:target ratio 50:1, 7.4%; 20:1, 4.6%; 10:1, 3.1%). Human leukocyte antigen (HLA) typing demonstrated the presence of antigen DR8. The enzyme-linked immunosorbent assay (ELISA) for TNF-α, soluble TNF-alpha receptor superfamily 1A (sTNFRSF-1A), sTNFRSF-1B, and interleukin 6 (IL-6) showed elevated titers with the serum samples, which were drawn from peripheral blood when she had high fever (Table 1). The nucleotide sequencing analysis for all exons of the *TNFRSF-1A* gene showed no mutation (data not shown).

A brain computed tomography (CT) scan showed calcification of basal ganglia (Fig. 2a). An abdominal CT scan showed hepatosplenomegaly. A ^{67}Ga scintigraphy showed increased uptake at parotid and submandibular glands, but no remarkable uptake at the other sites. A bone scintigraphy [^{99m}Tc-methylene diphosphonate (MDP)] revealed increased uptakes in bilateral shoulder, knee, elbow, wrist, and foot joints (Fig. 2b), of which she had tenderness. An electromyogram showed myogenic changes. A magnetic resonance image (MRI) of the distal thighs revealed low signal intensity lesion of T1-weighed coronal image and a high signal intensity lesion of both T2-weighed coronal

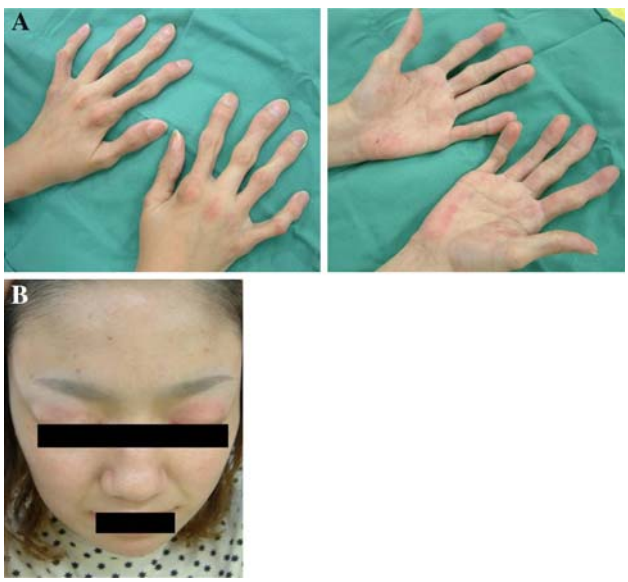

Fig. 1 **a** Deformities of fingers and frostbitten hands. **b** Edematous erythemas on the eyelids

Table 1 ELISA for TNF-α, sTNFRSF-1A, sTNFRSF-1B, and IL-6 of serum samples drawn from peripheral blood of the patient when having high fever

	Peak of fever	Normal range
TNF-α (pg ml^{-1})	30.0	11.9 ± 6.4
sTNFRSF-1A (ng ml^{-1})	4.0	1.2 ± 1.1
sTNFRSF-1B (ng ml^{-1})	15.5	3.0 ± 1.3
IL-6 (pg ml^{-1})	35.4	<4.0
IL-1β (pg ml^{-1})	0.263	<10.0

TNF tumor necrosis factor, *sTNFRSF-1A* soluble TNF-alpha receptor super family 1A, *sTNFRSF-1B* soluble TNF-alpha receptor super family 1B, *IL* interleukin

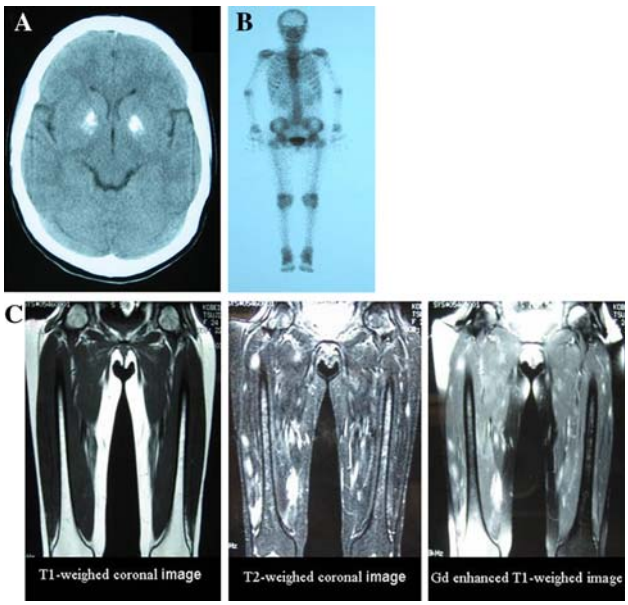

Fig. 2 **a** A comuted tomography scan of the brain showed calcification in basal ganglia. **b** Bone scan (^{99m}Tc-methylene diphosphonate) revealed increased uptake in bilateral shoulder, knee, elbow, wrist, and foot joints. **c** Magnetic resonance images of the distal thighs. *Left* T1-weighed image, *middle* T2-weighed image, and *right* gadolinium-enhanced T1-weighed image

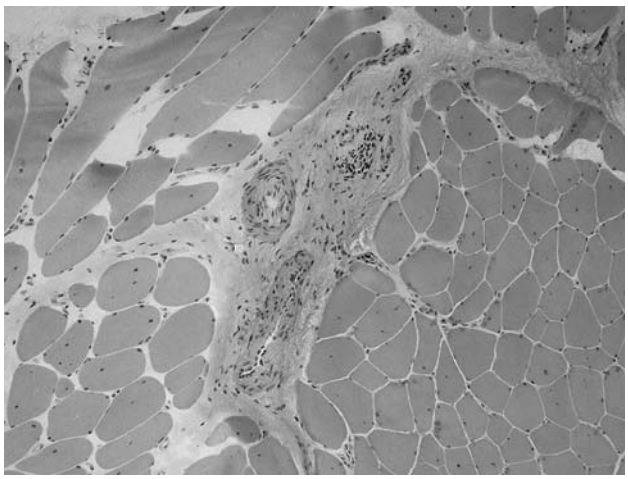

Fig. 3 A biopsy specimen from the thigh showed a few foci with mild perivascular infiltration of mononuclear cells. The most prominent field with perivascular infiltration is shown. Perifascicular atrophy of muscle fibers was rarely observed in her muscle biopsy specimen

image and gadolinium (Gd)-enhanced T1-weighed image (Fig. 2c). Bilateral MRI of elbows and shoulders showed no evidence of synovitis. A biopsy specimen from the thigh showed a few foci of mild perivascular infiltration of mononuclear cells in connective tissue, but mononuclear cells did not infiltrate into muscle fibers (Fig. 3). A biopsy specimen from a subcutaneous nodule on the left hand showed that there was focus of mononuclear cells in corium, and no amyloid deposit. No abnormality was detected by urine analysis, stool examination, chest radiography, electrocardiogram (ECG), echocardiogram, neuron conduction test, and bone marrow aspiration.

The patient had been receiving prednisolone (5 mg day^{-1}) since the age of 19 years to reduce her symptoms, but it had not been effective in preventing periodic fever and joint contracture. As her general status was stable enough for her to perform daily social life, and we did not change her immunosuppressive therapy.

Discussion

We describe a case with periodic fever accompanied by myositis, partial atrophy of subcutaneous adipose tissue, and immunological disorders. Partial lipodystrophy is known to be accompanied by congenital metabolic abnormalities or other collagen vascular diseases [6]. Partial lipodystrophy is classified into face-sparing lipodystrophy, familial partial lipodystrophy, Barraquer–Simons' syndrome, and other rare cases that include repeated pressure against the body, and a manifestation of anti-HIV protease inhibitors. Our patient had no family history of congenital metabolic disease, and she had no abnormal laboratory test indicating metabolic diseases. On the other hand, autoimmune diseases accompanied by partial lipodystrophy include dermatomyositis (DM), Sjogren syndrome [7, 8], systemic lupus erythematosus (SLE) [9], scleroderma [10], myasthenia gravis [11], and glomerulonephritis [12, 13]. Although she had polyarthritis and high titers of antinuclear and anti-DNA antibodies, which might suggest the overlapping of SLE, she had no organ involvement other than muscles and subcutaneous adipose tissue. Therefore, her disease lacked symptoms to be diagnosed as any particular autoimmune disease except DM.

Lipodystrophy and muscle atrophy caused by DM are sometimes associated with panniculitis, as seen in Weber–Christian syndrome [14]. Our case had an erythema-like heliotropism of the eyelids, elevated serum creatinine kinase, and myopathic findings on electromyogram and MRI, which were compatible with DM [15]. Common clinical manifestations of DM, such as myalgia and muscle weakness, were absent. Although perivascular infiltration of mononuclear cells in muscle tissue was observed, other histological findings typical in DM, such as perifascicular atrophy of muscle fibers, necrotic muscle fibers, and regeneration were almost absent. These mild histological findings might support the diagnosis of amyopathic DM but did not strongly support the diagnosis of typical DM because of her long disease history of more than 20 years. On the other hand, the biopsy specimen from her thigh showed no lobular panniculitis, which is characteristic

histological finding in Weber–Christian syndrome. From a different perspective, her clinical symptoms were atypical for juvenile DM. Juvenile DM is characterized early in its course by an immune-complex vasculitis of varying severity and later by the development of calcinosis. An acute onset of proximal muscle weakness accompanied by the characteristic dermatitis is pathognomonic for juvenile DM. The absence of muscle weakness at the onset and the presence of digital deformities with frostbitten hands in our case are unlike the features of juvenile DM.

HPFs are a candidate to explain her disorder. Of these, TRAPS may most resemble our case. TRAPS is characterized by episodes of periodic fever and localized inflammation, such as arthritis, pleuritis, myositis, and skin involvement [16]. Genetic mutations in the *TNFRSF-1A* gene have been reported in Japanese TRAPS cases by Ida et al. [17]. Their laboratory tests showed high titers of serum TNF-α and sTNFRSF-1B, which are considered as the specific features for TRAPS with TNFRSF-1A mutation. TRAPS is also characterized by episodes of fever, which typically last more than 5 days; abdominal pain; and an autosomal dominant inheritance. Although our patient's profile of TNF-α/TNFRSF-1 and some of her clinical features were similar to those of TRAPS, her case failed to meet TRAPS diagnosis according to Hull's criteria [16]. Amyloid A (AA) amyloidosis is the main complication of hereditary PFSs [18]. Her clinical symptoms and findings detected by chest radiography, ECG, echocardiogram, MRI, and skin biopsy did not show evidence of AA. Moreover, genetic examination of her and her families did not reveal any mutation in the *TNFRSF-1A* gene.

Cryopyrin-associated periodic syndromes also resembled our case in that they have intermittent episodes of fever, rash, and joint pain, and their attacks resolve in 24–36 h. However, cryopyrin-associated disorders, such as systemic inflammatory response in exposure to generalized cold, sensorineural deafness, and amyloidosis with nephropathy, were absent in our case. In addition, her serum level of IL-1β was extremely low, which is unlikely for cryopyrin-associated disorders.

Tanaka et al. [19] proposed a syndrome that has common features. They reported 13 Japanese patients with common manifestations as follows: loss of subcutaneous adipose tissue and muscle atrophy in the same region, severe contractures of joints, steroid-responsive skin eruptions, mental retardation, macroglossia, hepatosplenomegaly, bilateral extensor plantar reflexes, elevated erythrocyte sedimentation rate (ESR), hyper-γ-globulinemia, reduced NK activity, calcification of basal ganglia, abnormal ECG findings, and autosomal recessive inheritance suggested by parents' consanguineous marriages. The ages of disease onsets ranged from 2 months to 23 years. Although many symptoms described in their cases were quite similar to those in our case, their detailed description failed to indicate the existence of periodic fever and autoantibodies.

In summary, we presented the case of a 24-year-old Japanese woman with periodic fever, and her clinical, radiological, and histological features did not completely fit the features of any known disease or syndrome. Accumulation and extensive genetic interventions in our case and similar patients are anticipated to elucidate the differences or concordance of their genetic backgrounds.

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