A case of neutrophilic dermatosis with MEFV gene variant and abnormal activation of peripheral blood monocytes: a case report

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ABSTRACT
A healthy 32-year-old man had a fever and elevated levels of white blood cells (WBC) and C-reactive protein (CRP). In addition, he presented with a skin rash on his forehead, around the neck, and from the anterior chest to the abdomen. His laboratory findings showed elevated levels of hepatic enzyme, CRP, and ferritin; therefore, he was suspected to have adult-onset Still’s disease (AOSD) and referred to our department. We ruled out hematological malignancy and established diagnosis of AOSD according to Yamaguchi’s criteria and treated with 20 mg/day prednisolone. His clinical condition did not improve, therefore, we increased the dosage of prednisolone to 40 mg/day; however, his rash gradually expanded with papules and plaques. A cervical skin biopsy revealed neutrophil dermatosis and analysis of the MEFV gene revealed a heterozygous variant in exon 2 (E148Q). We found an elevated percentage of CD86+CD14+CD16– classical monocytes in the peripheral blood using flow cytometry. We added oral potassium iodide as a treatment for neutrophil dermatosis. Despite this treatment, his eruption and fever did not subside, therefore, we changed potassium iodide to colchicine, this improved his clinical condition. This case suggests the importance of autoinflammation-related gene abnormalities and macrophage activation in the pathogenesis of neutrophil dermatosis.

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1. Introduction
Neutrophilic dermatoses comprise a group of non-infectious skin diseases characterized by fever and arthritis. The characteristic histologic features of Sweet syndrome include abundant neutrophil infiltration in epidermis, dermis, and subcutaneous tissue. Representative examples of neutrophilic dermatoses include Sweet’s disease and pyoderma gangrenosum; however, neutrophil dermatosis reportedly occurs even in autoinflammatory diseases [1] and is associated with mutations/variations in the MEFV gene, known to cause familial Mediterranean fever (FMF) [2].

Hallmarks of autoinflammatory diseases, including FMF and adult-onset Still’s disease (AOSD), are the presence of activated macrophages. The pathological roles of monocytes and macrophages in neutrophilic dermatoses have not been fully clarified. However, some case reports indicating the co-existence of AOSD and Sweet’s disease [3] suggest that activated macrophages may be involved in the pathogenesis of neutrophilic dermatoses.

Herein, we report a case of neutrophil dermatosis that presented MEFV gene abnormality along with activation of monocytes in the peripheral blood.

2. Case report
A healthy 32-year-old man with no family history of periodicity of fever or refractory rash had a fever and sore throat at the beginning of June 2018. He was diagnosed with acute tonsillitis because of high body temperature, inflammation in the pharynx, and elevated white blood cell (WBC) count (18400/µL) and C-reactive protein (CRP) (9.9 mg/dL) level. Despite treatment with ABPC/SBT 9 g/day, his fever...
persisted. In addition, he presented with a skin rash on his forehead, around the neck, and from the anterior chest to the abdomen, with pain in both knee joints. His laboratory findings showed elevated levels of hepatic enzyme, CRP, and ferritin (2586 ng/mL); therefore, he was suspected to have AOSD and was referred to our department for further investigation on June 26.

On admission, his body temperature was 37.6°C, blood pressure was 97/51 mmHg, and heart rate was 68 beats/min. A physical examination showed swollen lymph nodes in the left neck, they were soft, movable, and non-tender. Further, he had erythema in the forehead, neck, and abdomen with infiltration. Laboratory investigations revealed the following results: hemoglobin (Hb) 11.4 g/dL, WBC 12200/μL (neutrophils 87.8%), platelet count 420 × 10^3/μL, lactate dehydrogenase 198 IU/L, alkaline phosphatase 423 U/L, aspartate aminotransferase 41 IU/L, alanine aminotransferase 118 IU/L, γ GTP 110 IU/L, blood urea nitrogen 9 mg/dL, creatinine 1.89 mg/dL, ferritin 1728 ng/ml, and CRP 11.27 mg/dL. The titers of anti-streptolysin O antibody (ASO) and anti-streptokinase antibody (ASK) were 1024 and 20,480, respectively.

The following immunological and serological results were all negative: rheumatoid factor, antinuclear antibody (ANA), proteinase-3 anti-neutrophil cytoplasmic autoantibodies (PR3-ANCAs), and myeloperoxidase anti-neutrophil cytoplasmic autoantibodies (MPO-ANCAs). HLA typing showed A2, A24, B39, and B61 positivity. An examination with contrast-enhanced computed tomography from the neck to the pelvis showed multiple lymphadenopathies at the bilateral neck, right armpit axilla, and bilateral inguinal regions. A bone marrow aspiration smear revealed no abnormality in the cell density of three systems, including WBCs, red blood cells, and platelets. Moreover, there was no increase in the dysplasia or blast cells.

We diagnosed AOSD as per Yamaguchi’s criteria [4] and administered treatment with 20 mg/day prednisolone. His clinical condition did not improve; therefore, we increased the prednisolone dosage to 40 mg/day. However, his rash gradually expanded with papules and plaques (Figure 1). A cervical skin biopsy revealed dense infiltration of neutrophils in the upper and mid-dermis with no evidence of vasculitis (Figure 2). Inguinal lymph node biopsy revealed dermatopathic lymphadenopathy with no evidence of malignant lymphoma.

Histopathological findings suggested the possibility of Sweet’s disease and autoinflammatory diseases other than AOSD. Notably, pyrin-associated autoinflammation with neutrophilic dermatosis (PAAAND) syndrome with neutrophilic dermatosis based on the MEFV gene mutation has been recently reported [5]. Although our patient did not present with periodic fever and accompanying serositis, acne, or gastrointestinal symptoms suspected of pyoderma gangrenosum, we performed genetic testing for MEFV gene. Analysis of the MEFV gene revealed no mutations in Exon 2 (S242R or E244K) found in PANND syndrome or Exon 10 mutations; however, a heterozygous missense variant was found in exon 2 of the MEFV gene (E148Q). He met the diagnostic criteria for Sweet’s disease [6]; therefore, we added oral potassium iodide as a treatment for Sweet’s disease. Despite this treatment, his eruption and fever persisted; therefore, we changed potassium iodide to colchicine; there was a gradual improvement in the eruption and the CRP level. The clinical course of the patient has been shown in Figure 3. At the time of writing this report, we had tapered the PSL to 7.5 mg/day and the patient’s clinical remission had been maintained for >6 months. Although this patient was responsive to colchicine, the absence of family history, absence of periodic fever, and absence of erysipelas-like erythema did not meet the Hel Hashomer criteria and led to a diagnosis of FMF.

We investigated the percentage of CD86^+CD14^+CD16^- classical monocytes in the peripheral blood using flow cytometry and found that this case presented an increased percentage of CD86^+CD14^- monocytes before treatment; however, the percentage decreased gradually 2 months after the treatment (Figure 4). We also examined the percentage of CD86^- cells among intermediate (CD14^-CD16^+) and non-classical (CD14^+CD16^-) type of monocytes and found that there was a modest expression (<1%) of CD 86^- cells in these subsets before treatment.

3. Discussion

We experienced the case of a patient with neutrophilic dermatosis with E148Q heterozygous variant in the MEFV gene that developed with AOSD-like clinical symptoms and the patient presented with fever, arthralgia, sore throat, and an elevated level of serum ferritin. In addition to Yamaguchi’s criteria for AOSD, this patient also met the diagnostic criteria for Sweet’s disease based on skin findings, laboratory findings, and pathological findings; however, his painless erythema was not typical for Sweet’s disease. In addition, because neutrophilic dermatosis can occur in AOSD patients [7,8], it is difficult to differentiate AOSD and other neutrophilic dermatosis such as Sweet’s disease by the histological findings. Accordingly, we could not exclude the possibility of neutrophilic dermatosis...
associated with autoinflammatory disease including AOSD.

Sweet’s disease is a prototype of neutrophil dermatosis, with an elevation of granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), and type 1 T helper (Th1) related cytokines [9]. It is assumed that these cytokines may promote infiltration of neutrophils into the dermis. Sweet’s disease can be divided into the following three subtypes as per their etiology: (1) classical, (2) malignancy-associated including myelodysplastic syndrome (MDS), and (3) drug-induced [10]. In the present case, we suspected that the precedent of hemolytic streptococcal infection was associated with the development of Sweet’s disease. An association with HLA-B54 has been reported in Japanese patients with Sweet’s disease [11]; however, HLA-B54 was not found in this case.

Our patient showed an E148Q heterozygous variant in the MEFV gene exon 2. This variant was detected in around 20% of healthy individuals in

**Figure 1.** Photographs of the patient’s the back of the neck (A) and the lower back (B) (after treatment with prednisolone 40 mg/day).

**Figure 2.** Histological examination of the patient’s cervical skin before treatment (HE: Hematoxylin and Eosin staining, original magnification A: ×40, scale bars: 100 µm, B: ×100, scale bars: 100 µm).

**Figure 3.** Clinical course of the patient. Graphs display the severity of the rash, fever, and C-reactive protein (CRP), ferritin as well as the treatment interventions.
Japan [12]. Pyrin encoded by the \textit{MEFV} gene is a protein involved as a suppressor of inflammasome and several \textit{MEFV} mutations causing autoinflammatory diseases other than FMF have been reported [13]. Among them, a mutation of exon 10 (M694I) has been proposed as a risk factor for the development of AOSD [14] and MDS associated with Sweet’s disease [15]. Although this patient did not have a mutation of M694I in the \textit{MEFV} gene, E148Q variant may contribute to the onset and pathology of neutrophil dermatosis.

First, we considered that our patient developed AOSD based on clinical manifestations, such as atypical rash, hyperferritinemia, polyarthritic pain, and fever; he also met Yamaguchi’s criteria [4]. Although the pathology of AOSD has not been completely understood yet, previous studies have suggested that IL-1β, IL-18, and IL-6 are important cytokines for onset and pathogenesis. Among these inflammatory cytokines, IL-18 activates Th1 cells, produces IFN-γ, and promotes macrophage activation, resulting in amplifying inflammasome-mediated inflammation. In contrast, activated macrophages induce differentiation into Th17 cells as well as Th1 cells. Thus, since IL-17 that promotes the recruitment and activation of neutrophils is produced by Th17 cells, neutrophil infiltration into the skin is also observed in AOSD patients [16]. Therefore, we speculate that T cells-mediated activation of macrophages is involved in the pathology of neutrophil dermatosis.

Once activated, macrophages express the costimulatory molecules CD80 and CD86 that are necessary for the activation of naive T cells on the cell surface. CD80/86 binds CD28 on the T cell surface and differentiates T cells. Our patient showed a higher percentage of activated CD86^+CD14^+ than healthy individuals ($n = 5$, the mean percentage of CD86^+CD14^+ cells was $6.3 \pm 0.7\%$); therefore, it was suggested that macrophages interact with T cells and that activated T cells contribute to the activation of neutrophils via IL-17 production.

Our patient responded well to colchicine treatment. The primary mechanism of action of colchicine is tubulin disruption leading to inhibition of neutrophil adhesion and recruitment to inflamed tissue [17]. More recently, mechanisms include various inhibitory effects on macrophages including the inhibition of the NACHT-LRRPYD-containing protein 3 (NALP3) inflammasome [18,19]. This case suggests that colchicine not only inhibited neutrophil activation but also directly affected the expression of CD86 by macrophages.

Thus, we experienced the case of a patient with neutrophil dermatosis successfully controlled in remission under the low-dose of corticosteroids plus colchicine. Our case revealed the E148Q variant in the \textit{MEFV} gene and elevated percentage of CD14^+CD86^+ monocytes in the peripheral blood. These observations suggest the importance of autoinflammatory-related gene abnormalities and macrophage activation usually observed in AOSD patients.

\textbf{Figure 4.} Representative flow cytometric staining profile for CD14^+ cells in healthy individuals and the present case. The percentages of activated macrophages (CD14^+CD86^+) cells in the peripheral blood were improved after the induction of prednisolone and colchicine therapy.
in the pathogenesis of neutrophil dermatosis. Further research is required to determine the precise mechanisms by which MEFV gene mutation and activated macrophage develop and accelerate neutrophil dermatoses.

**Ethical approval**

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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