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Case Report

Response of Bone Marrow Edema and Parotitis to Canakinumab in a Woman with Neonatal-Onset Multisystem Inflammatory Disease: A Case Report

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Abstract

Background: A patient is 50-year-old woman developed pyrexia, conjunctival hyperemia, and urticarial rash at the age of 2 months. In addition to these symptoms, multiple arthralgia, abdominal pain, and aseptic meningitis recurred. Mental developmental regression, sensorial deafness, ulnar side deformities in both hands, and dry mouth also gradually progressed. Marked increases in neutrophil counts and serum C-reactive protein levels persisted. She was clinically diagnosed with neonatal-onset multisystem inflammatory disease at the age of 44 years.

Methods: She underwent whole-exome sequencing analysis of the NLRP3 gene. A point mutation was determined in c.1060G>A.

Results: After the administration of anti-interleukin-1β antibody, her symptoms and acute-phase inflammatory markers markedly improved. Arthralgia after cold exposure and dysphagia persisted; however, they were reduced by improvements in lifestyle factors. Parotid salivary smears continued to show high neutrophil counts and some monocytes, whereas the evidence of bone marrow edema, present before treatment, was no longer observed on magnetic resonance imaging scans.

Conclusions: The latter finding suggests that interleukin-1β play the main role in developing bone marrow edema. To date, no studies have investigated bone marrow edema and salivary neutrophils in patients with neonatal-onset multisystem inflammatory disease.

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Keywords: Neonatal-Onset Multisystem Inflammatory Disease; Bone Marrow Edema; Salivary Neutrophil; Interleukin-1β; Canakinumab.

Introduction

Cryopyrin-associated periodic syndrome (CAPS) is an autoinflammatory disease in which interleukin-1β (IL-1β) is overexpressed owing to abnormalities in the NLRP3 gene [1-3]. The most severe type of CAPS is neonatal-onset multisystem inflammatory disease (NOMID) [1-3]. A 50-year-old woman with recurrent fever, conjunctival hyperaemia, and urticarial rash from early infancy was clinically diagnosed with NOMID. Whole-exome sequencing analysis of the NLRP3 gene was analysed and a point mutation was identified at the age of 44 years. After the administration of anti-IL-1β antibody (i.e., canakinumab), her severe symptoms disappeared, and acute-phase inflammatory marker levels improved, whereas arthralgia caused by cold exposure, dry mouth, sensorial deafness, and mild mental retardation remained. Herein, we present and discuss the first two sets of clinical manifestations, which have not been reported previously.

Methods

The patient had no family history of genetic abnormalities. At the age of 2 months, she developed pyrexia, conjunctival hyperemia, and urticarial rash, all of which were recurrent. Based on these symptoms, anterior uveitis and optic neuritis were diagnosed and symptomatic treatment was initiated. She subsequently complained of pain in multiple joints. Therefore, she was diagnosed with juvenile idiopathic arthritis. She received treatment with steroids and anti-inflammatory drugs. Although the treatment was continued and immunosuppressive agents were administered during exacerbation, her symptoms did not improve. Moreover, aseptic meningitis and abdominal pain recurred. She was repeatedly hospitalized for several days at that time. Mental developmental regression, sensorial deafness, and buttonhole and ulnar side deformities in both hands gradually progressed. At 22 years of age, she visited our hospital so that appropriate treatment could be determined.

Results

Blood tests showed marked increases in white blood cell counts and serum levels of C-reactive protein, amyloid A, and matrix metalloproteinase-3 (Table 1). Her serum antinuclear antibodies (ANA) have been positive for more than 20 years after visiting our hospital, and only the anticentromere antibody was positive in the ANA classification type. Scleroderma was suspected at the age of 40 years because of the development of dysphagia and anticentromere antibody positivity. However, scleroderma was not diagnosed because no sclerotic skin was observed, and normal esophageal findings were noted in the barium study and upper endoscopy. She complained of dry mouth in addition to dysphagia; therefore, a smear examination of her salivary sample from the mouth was performed. The smear examination results revealed high neutrophil counts. The salivary sample selectively collected from the parotid duct opening contained a mixture of mucus and serous fluid. The smear examination showed neutrophils without bacterial phagocytosis and some monocytes, but no bacteria were observed. In the bacterial culture tests, no pathogenic bacteria, other than some oral commensal bacteria, were isolated from the saliva sample. Saliva samples could not be collected from the duct openings of the submandibular and sublingual glands. Ultra sonographic findings showed several small, round, and hypoechoic areas with internal hyperechoic spots in the obscure heterogeneous structures of both parotid glands. Differentiating between the parotid glands and the surrounding tissues was difficult. Sjögren syndrome was not diagnosed because of both negative serum anti-SS-A and anti-SS-B antibody test findings and the absence of dry eyes. These findings suggested that dysphagia was caused by a decrease in serous saliva production due to persistent inflammation of the parotid glands. Meanwhile, pain and swelling at the deformed joints of the index and middle fingers on both sides were observed during cold exposure. Therefore, magnetic resonance imaging (MRI) of the hands was conducted. Bone marrow edema (BME) was noted in the asymptomatic state (Figure 1a) and was exacerbated after cold stimulation (Figure 1b). No findings indicated arthritis. Based on these manifestations, NOMID was clinically diagnosed rather than autoimmune disease. Genetic testing results revealed a c.1060G>A point mutation (A352T) in the NLRP3 gene. The serum levels of interleukin-1β, interleukin-2, tumour necrosis factor-α, and interferon-γ in the acute phase were within the normal range. Treatment with canakinumab was initiated for the patient at the age of 44 years after discontinuing the administration of steroids and immunosuppressive agents. Consequently, recurrent fever, conjunctival hyperemia, and the urticarial rash disappeared, and arthralgia and abdominal pain were alleviated. Six years after the start of treatment, laboratory tests were performed to evaluate the therapeutic effects. Blood test results showed normalized white blood cell counts and decreased levels of serum C-reactive protein, amyloid A, and matrix metalloproteinase-3 (Table 1). The serum ANA titer showed a four-fold increase compared to that before treatment, whereas no significant findings were obtained for the other autoantibodies. The patient continued to complain of pain in the index and middle fingers without swelling after cold exposure; however, no evidence of BME was found on MRI scans (Figures 1c and 1d). Avoiding cold exposure reduced arthralgia. The number of neutrophils in the parotid saliva did not decrease, although she no longer complained of dysphagia after frequent gargling, tooth-

brushing, and gum-chewing. Her sensorineural deafness did not improve; however, she wore a hearing aid to resolve interference in daily life. Brain MRI findings showed moderate dilatation of the sulcus and lateral ventricles. These findings were not changed compared to those before treatment. She could become independent in daily life, although her mental retardation did not improve. The mild osteoporosis findings noted before treatment did not change after that. At present, treatment with canakinumab alone continues. No adverse effects have been observed and hospitalization is no longer required. Approval from the hospital ethics committee and consent from the patient and her family were obtained for publication of this report.

Blood test (Reference value)	Pre-treatment	Post-treatment
White blood cell (3,000-8,900 /μL)	25,000	6,000
Neutrophil (54-62 %)	57	73
Lymphocyte (21-35 %)	23	11
C-reactive protein (<0.4 mg/dL)	8.11	1.02
Serum amyloid A (<8.0 μg/dL)	551.4	11.8
MMP-3 (17.3-59.7 ng/mL)	204	60.2
Rheumatoid factor (<15 IU/mL)	negative	negative
Antinuclear antibody (<1:80)	1:320	1:1280
Anticentromere antibody (<1:80)	1:640	1:380
Anti-Scl70 antibody (<7.0 IU/mL)	<7.0	<7.0
Anti-Jo1 antibody (<7.0 IU/mL)	<7.0	<7.0
Anti-DNA antibody (<2.6 IU/mL)	<2.6	<2.6
Anti-SS-A antibody (<7.0 IU/mL)	negative	negative
Anti-SS-B antibody (<7.0 IU/mL)	negative	negative
Anti-RNP antibody (<10.0 IU/mL)	negative	negative
MMP-3, matrix metalloproteinase-3; Scl70, scleroderma 70; SS-A/B, Sjöegren syndrome A/B; RNP, Ribonucleoprotein		

Table 1: Results of blood tests before and after treatment.

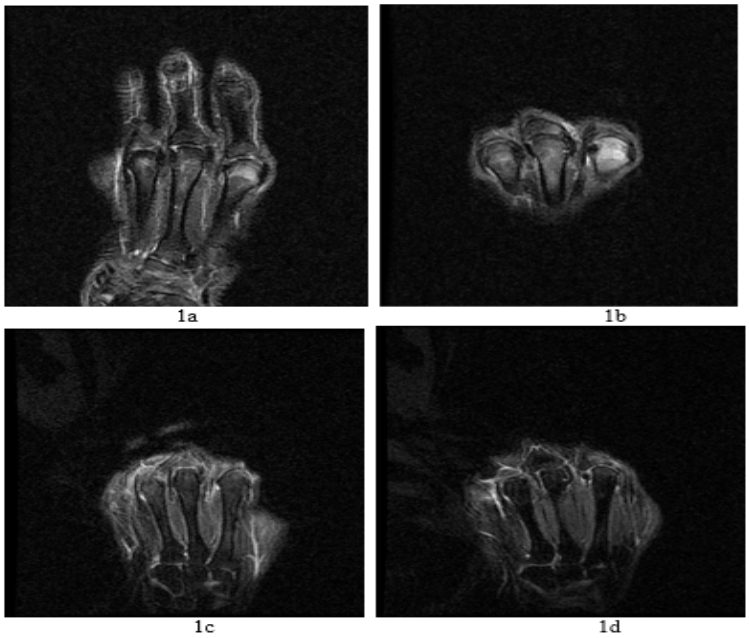

Figure 1: The T2-weighted fat-suppression images show high signals at the distal site of the right second metacarpal bone before the cold stimulation (a) and higher signals at the same site after the stimulation (b). The high signals disappear before (c) and after (d) the stimulation in a lull after treatment.

Discussion

In the present case report, the patient's recurrent symptoms and clinical manifestations from infancy were consistent with the characteristics of NOMID [1-3]. Moreover, this diagnosis was confirmed by determining a point mutation in the NLRP3 gene. The same point mutation has been previously reported, but the details of the clinical manifestations, as noted in our patient, have not been described [4].Autoantibodies are not involved in the pathology of CAPS [1,2,5]. The patient's serum anticentromere antibody test result was positive before and after treatment; this finding may be due to the long-term effects of sialadenitis or its fluctuation range in healthy individuals.6 Differentiating CAPS from autoimmune diseases is necessary, as seen in the present case. IL-1β is primarily produced by immunocytes and vascular endothelial cells [3]. In this patient, serum IL-1β concentration measured in the acute phase before the administration of canakinumab was within the normal range. One reason for this result may be that IL-1β, which is produced only by immunocytes in extravascular tissues, did not enter the systemic circulation or the measurement time was late. In this patient, steroids and immunosuppressive agents were ineffective, whereas canakinumab was markedly effective in relieving physical symptoms. The patient no longer faced problems in daily life due to each impediment, although dry mouth, arthralgia due to cold exposure, mental retardation and sensorineural hearing loss persisted. We believe that early treatment with canakinumab is important to further improve the prognosis of patients with NOMID. In Japan, only canakinumab has been approved for the treatment of auto inflammatory diseases, and the treatment cost is very high. Combined administration of anakinra, an IL-1β receptor inhibitor, is expected to improve treatment efficacy and reduce costs. Both scleroderma and Sjögren syndrome were excluded because the patient had neither sclerotic skin nor dry eyes and negative anti-SS-A and anti-SS-B antibody test findings, although this patient complained of dysphagia before the definitive diagnosis. In addition, given that the parotid gland saliva contained a mixture of mucus and neutrophils without bacterial phagocytosis, no pathogenic bacteria were isolated, and the internal structure of the parotid glands was heterogeneous on ultrasonography; thus, we considered that the etiology of par otitis was persistent inflammation caused by NOMID. This consideration is supported by the fact that dysphagia resolved after canakinumab treatment and lifestyle changes. Patients with NOMID suffer from pain in many joints [1-3]. This patient's most severe arthralgia developed in the index and middle fingers. We considered those fingers to be susceptible to cold exposure. In the bone marrow, myeloid cells containing abundant IL-1β receptors on the cell surface proliferate, and many types of immunocyte-

producing IL-1β coexis [3]. In this patient, we speculate that these immunocytes released excessive IL-1β after cold stimulation, that the nearby myeloid cells were activated, and that this hyper activated state was noted as evidence of BME on MRI scans.

BME develops in rheumatoid arthritis, gout, and non-specific arthritis [7]. The patient's MRI scans of the hands before treatment showed evidence of BME without arthritis. BME on MRI of her hands disappeared after treatment with canakinumab, while arthralgia due to cold stimulation persisted. Further investigation is needed to understand the relationship between BME, IL-1β, and arthritis in various diseases associated with arthralgia. Careful observation may help to elucidate the pathophysiology of injured organs in patients with CAPS. Accumulation of case reports is required to examine the relationship between the mutation site in the NLRP3 gene and disease phenotype.

Disclosure: The authors declare no conflict of interest.

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References

1. Welzel T, Kuemmerle-Deschner JB. (2021) Diagnosis and management of the cryopyrin-associated periodic syndromes (CAPS): what do we know today? J Clin Med. 10:128.
2. Hoffman HM, Kuemmerle-Deschner JB, Goldbach-Mansky R. Cryopyrine-associated periodic syndromes (CAPS). In: Hashkes PJ, Laxer RM, Simon A (eds). (2019) Textbook of Autoinflammation. Springer, Berlin/Heidelberg, Germany, 2019: 347-365.
3. Verbsky JW. (2020) Hereditary periodic fever syndromes and other systemic autoinflammatory diseases. In: Kliegman RM, Blum NJ, Shah SS, et al. (eds). The Textbook of Pediatrics, 21st edn. Elsevier, Philadelphia, Pennsylvania, 2020: 1293-1304.
4. Parker T, Keddie S, Kidd D, Lane T, Maviki M, et al (2016) Neurology of the cryopyrin-associated periodic fever syndrome. Eur J Neurol. 23:1145-1151.
5. Lachmann HJ. (2017) Periodic fever syndromes. Best Pract Res Cli. Rheumatol. 31:596-609.
6. Hayashi N, Koshiba M, Nishimura K, Sugiyama D, Nakamura T, et al. (2008) Prevalence of disease-specific antinuclear antibodies in general population: estimates from annual physical examinations of residents of a small town over 5-year period. Mod Rheumatol. 18:153-160.
7. Akhavan S, Martinkovich SC, Kasik C, DeMeo PJ. (2020) Bone marrow edema, clinical significance, and treatment options: a review. J Am Acad Orthop Surg. 28:e888-e899.