Received: 15 December 2020 | Accepted: 6 May 2021

DOI: 10.1111/1346-8138.15975

THE JOURNAL OF DERMATOLOGY

LETTER TO THE EDITOR

Case of Muckle–Wells syndrome with obesity

Dear Editor,

Muckle–Wells syndrome (MWS) is one of the cryopyrin-associated periodic syndromes (CAPS), an autosomal dominant autoinflammatory disease characterized by genetic mutations in NOD-like receptor family pyrin domain containing 3 (*NLRP3*) and increased interleukin-1β (IL-1β) levels. Urticarial rash, recurrent fever, arthralgia, and fatigue are major clinical features of MWS. Sensorineural hearing loss and renal amyloidosis can occur in the course of the disease.[1,2] Here, we demonstrate a case of MWS whose prominent clinical symptoms occurred with bodyweight gain.

A 14-year-old Japanese boy presented with a 10-year history of untreated repeated asymptomatic erythema on his face, trunk, and limbs with heel pain. Of note, recurrent fever had occurred with his bodyweight gain 5 years before visiting our department (Figure S1). His mother and grandmother had a history of similar repeated erythema and hearing impairment. His grandmother had also obesity and diabetes. Physical examination revealed wheal-like erythema or papules on his trunk and limbs (Figure 1a,b). His weight was 71.3 kg and height 160.5 cm. Body mass index was 27.6 kg/m^2. Abnormal laboratory results were as follows: white blood cells, 129 × 10^2/μL; blood platelets, 52.5 × 10^4/μL; erythrocyte sedimentation rate (1 h), 41 mm; C-reactive protein, 1.29 mg/dL; serum amyloid A (SAA), 82.9 μg/mL; and triglycerides, 158 mg/dL. The following laboratory results were within normal limits: creatinine, 0.60 mg/dL; and hemoglobin A1c, 5.8%. Histological examination of a tissue specimen biopsied from the erythema showed perivascular and periadnexal infiltration of inflammatory cells, mainly lymphocytes and neutrophils in the dermis (Figure 1c,d). Otorhinolaryngological hearing test showed a mildly elevated threshold in the mid- to high frequencies in his left ear. Obtaining informed consent from the patient, a hybridization capture-based next-generation sequencing was performed by using the patient's genomic DNA purified from peripheral blood cells,[3] and the c.1043C>T (p.Thr348Met) mutation was identified in *NLRP3*.[4] MWS was diagnosed, and IL-1β blockade therapy with canakinumab (150 mg every 8 weeks) had been started. The laboratory data concerning inflammatory reaction and SAA levels was improved after 4 months (Figure 1e). The frequency of fever was reduced, heel pain had completely disappeared, and erythema was observed only in the limited area on his back and abdomen. His bodyweight was increased from 71.3 to 77.1 kg, presumably due to leaving his sports team.

The pathophysiological roles of *NLRP3* mutation and IL-1β have been considerably identified, and IL-1β blockade therapy is now clinically utilized for the patients with CAPS. Although the activation of the NLRP3 signaling pathway has been implicated in the pathogenesis of various diseases including atherosclerosis, diabetes, and obesity,[5] these diseases are not reported as comorbidities of CAPS. In our patient, recurrent fever had occurred with his bodyweight gain, suggesting that obesity-associated inflammation might increase the serum IL-1β levels by activating the NLRP3 signaling pathway together with the gain-of-function in *NLRP3* mutation. Since the effects of canakinumab were limited, losing weight may be necessary in our patient. However, since clinical data from CAPS

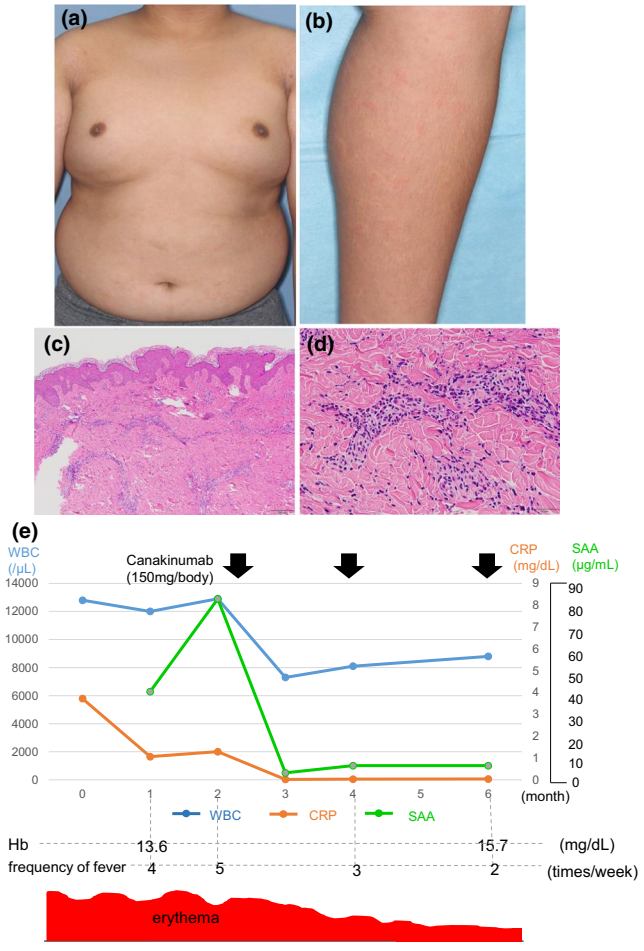

FIGURE 1 (a,b) Clinical manifestations of the patient at first visit. Wheal-like erythema or papules were observed on his trunk and limbs. (c,d) Histological features of biopsy specimen showed perivascular and periadnexal infiltration of inflammatory cells, mainly lymphocytes and neutrophils in the dermis (hematoxylin–eosin, original magnifications: [c] ×40; [d] ×400). (e) Clinical course of the patient Abbreviations : CRP, c-reactive protein; Hb, Hemoglobin; SAA, Serum amyloid A; WBC, white blood cells;

are limited, further clinical reports are required to verify the complication and/or correlation between CAPS and obesity.

CONFLICT OF INTEREST

None declared.

Erina Fukumura[1]
Kozo Nakai[1]
Sayaka Togo[1]
Sadao Tokimasa[2]
Nobuo Kanazawa[3]
Daisuke Tsuruta[1]

[1]*Department of Dermatology, Osaka City University Graduate School of Medicine, Osaka, Japan*
[2]*Department of Pediatrics, Osaka City University Graduate School of Medicine, Osaka, Japan*
[3]*Department of Dermatology, Hyogo College of Medicine, Nishinomiya, Japan*

Correspondence
Kozo Nakai, Department of Dermatology, Osaka City University Graduate School of Medicine, 1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan.
Email: nakai.kozo@med.osaka-cu.ac.jp

ORCID

Erina Fukumura https://orcid.org/0000-0002-3021-8292
Kozo Nakai https://orcid.org/0000-0001-5214-2308
Nobuo Kanazawa https://orcid.org/0000-0003-3000-9711

REFERENCES

1. Tran TA. Muckle-Wells syndrome: clinical perspectives. *Open Access Rheumatol*. 2017;9:123–9.
2. Kuemmerle-Deschner JB, Ozen S, Tyrrell PN, Kone-Paut I, Goldbach-Mansky R, Lachmann H, et al. Diagnostic criteria for cryopyrin-associated periodic syndrome (CAPS). *Ann Rheum Dis*. 2017;76:942–7.
3. Fujiki R, Ikeda M, Yoshida A, Akiko M, Yao Y, Nishimura M, et al. Assessing the accuracy of variant detection in cost-effective gene panel testing by next-generation sequencing. *J Mol Diagn*. 2018;20:572–82.
4. Dodé C, Le Dû N, Cuisset L, Letourneur F, Berthelot J-M, Vaudour G, et al. New mutations of CIAS1 that are responsible for Muckle-Wells syndrome and familial cold urticaria: a novel mutation underlies both syndromes. *Am J Hum Genet*. 2002;70:1498–506.
5. Wang Z, Zhang S, Xiao Y, Zhang W, Wu S, Qin T, et al. NLRP3 inflammasome and inflammatory diseases. *Oxid Med Cell Longev*. 2020. 2020. https://doi.org/10.1155/2020/4063562

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.