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Case Presentation

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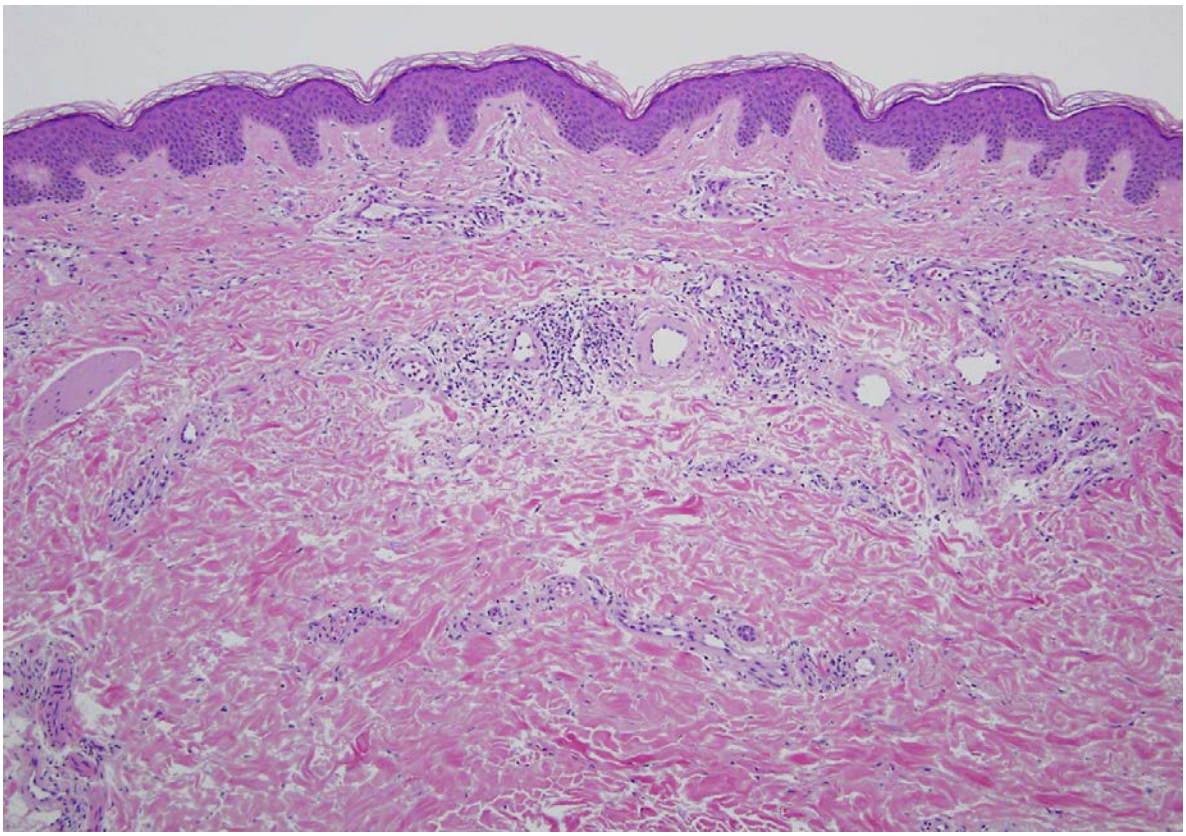
Abstract

A 35-year-old man initially was referred for management of recalcitrant urticaria. Owing to his long history of arthritis and sensorineural hearing loss, genetic testing was performed. The test showed a D305N heterozygous mutation in the *NLRP3* gene, which is consistent with the diagnosis of Muckle-Wells syndrome. We discussed the rationales behind the use of the interleukin-1 antagonist anakinra in this autoinflammatory disorder.



Case synopsis

A 35-year-old man was referred to New York University Dermatologic Associates for evaluation of recalcitrant generalized urticaria that had been present since childhood. He had been treated with numerous antihistamines in the past but continued to experience daily flares. Review of systems included intermittent joint pain, which predominantly involved his ankles, proximal interphalangeal joints, and the small joints of his feet. Past medical history included sensorineural hearing loss since childhood. He denied shortness of breath, nausea, vomiting, or abdominal pain. There is no family history of autoinflammatory or autoimmune diseases, which included rheumatoid arthritis and systemic lupus erythematosus. After consultation with the rheumatology service, anakinra 100 mg daily and methotrexate 10 mg weekly were started. His symptoms improved rapidly on this regimen and as of his last follow up examination, he continued to report good control of urticaria. Joint pain has since resolved and his hearing loss has stabilized.

Physical Examination: Diffuse, erythematous, edematous plaques on a background of generalized, faintly erythematous patches were noted.

Laboratory Data: A complete blood count, comprehensive metabolic panel, and C-reactive protein level were normal. The patient is heterozygous for a D305N mutation in the *NLRP3* gene.

Histopathology: Beneath a normal epidermis, there is a perivascular and interstitial infiltrate of neutrophils, eosinophils, lymphocytes, and scattered plasma cells.

Diagnosis: Muckle-Wells syndrome

Comment: First described in 1962, Muckle-Wells syndrome (MWS) is a rare, autoinflammatory disease with autosomal dominant inheritance [1]. It is characterized by recurrent urticaria, progressive sensorineural hearing loss, inflammatory eye disease, cutaneous vasculitis, arthritis, lymphadenopathy, abdominal pain, and recurrent fevers [2]. This constellation of symptoms was eventually linked to the *NLRP3* gene locus (also called *CIAS1*), which is also mutated in a related disorder called familial cold autoinflammatory syndrome [3]. The identification of *NLRP3* has revolutionized our understanding of MWS and ultimately led to the use of an IL-1 receptor antagonist as a therapeutic intervention.

The *NLRP3* mutation that was identified in MWS alters functions of its gene product cryopyrin, which is a key component of the inflammasome. In animal models, antigen presenting cells (APCs) of mutant mice produce massive amounts of the pro-inflammatory cytokine IL-1β in response to normally sub-threshold stimulation of APCs [4]. In humans, macrophages isolated from MWS patients spontaneously secrete the pro-inflammatory cytokine IL-1β [5]. Taken together, these findings led to the hypothesis that IL-1 inhibition might be beneficial in the treatment of MWS.

The efficacy of IL-1 receptor antagonists, particularly anakinra, in the treatment of MWS now has been documented in a number of case series. In 2003, Hawkins and Lachman reported that inflammatory symptoms abated after one subcutaneous injection of anakinra at a dose of 100 mg daily in two patients with MWS [6]. Furthermore, serum levels of the acute phase proteins serum amyloid protein, whose production is stimulated by IL-1β, and C-reactive protein, became normal within one week after starting anakinra [2, 6]. In a cohort study of 12 severe MWS patients, the disease activity score, which reflected the organ involvement in MWS, decreased from 12.8 at baseline to 3.2 at two weeks and to 3.9 at last follow up ($p < 0.05$, median follow-up time: 11 months, range: 5 to14 months) [7]. In two of these patients, an improvement in hearing loss also was documented.

References

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