A Woman with an Urticarial Eruption, Fevers, Arthralgias and Hearing Loss

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Introduction
Muckle-Wells Syndrome (MWS) also known as hereditary periodic fever syndrome is a rare autosomal dominant disease caused by a heterozygous mutation on chromosome 1q44 affecting the NLRP3 (CIAS1) gene which encodes the protein cryopyrin. This protein serves as a scaffold for assembly of the NALPs inflammasome complex. This complex is responsible for the activation and amplification of the proinflammatory cytokines IL-1β and IL-18 which induce and maintain inflammation. Hyperactivity of cryopyrin in MWS can be demonstrated clinically by episodic fevers, urticaria, hearing loss and kidney damage.

History
A 35-year-old Caucasian woman presented with redness of the eyes and a transient pruritic rash on her bilateral upper extremities, chest and back. These clinical findings and associated arthralgias, oral ulcers and low-grade fevers had been present for approximately 20 years. She admitted to new onset hearing loss with associated tinnitus. The urticaria was transient and lasted roughly 24 hours. There was no history of angioedema. The patient reported a family history of similar symptoms present in her brother, mother and grandmother.

Examination
Physical examination revealed well-circumscribed, blanchable, erythematous, edematous papules and plaques on her bilateral upper extremities, chest and back. Additionally, her sclerae were injected bilaterally without associated discharge. No oral ulcers were identified.

Laboratory
Laboratory evaluation included an elevated CRP of 1.4 (normal-0.5) and an elevated thyroid peroxidase antibody at 108 (normal-9) with a normal CBC, CMP, ANA, hepatitis B antigen, hepatitis C antibody, ESR, free T4 and anti-thyroglobulin antibody. Protein electrophoresis revealed beta-gamma bridging and increased IgA.

Course and Therapy
The patient was treated with cyclosporine, methotrexate, and colchicine 0.6 mg twice daily. She was referred to genetics for further evaluation and confirmation of her condition.

Discussion
Muckle-Wells Syndrome is classified on a spectrum amongst two other cryopyrin associated periodic syndromes (CAPS) caused by the same NLRP3 mutation: familial cold autoinflammatory syndrome (FCAS) and neonatal-onset multisystem inflammatory disease (NOMID). These three interleukin-1 autoinflammatory disorders or cryopyrinopathies have a prevalence of 1 in 360,000 individuals. FCAS demonstrates the least severity, its inflammatory component does not typically cause permanent damage. In contrast, NOMID demonstrates the worst severity causing permanent inflammatory damage throughout most areas of the body including joints, brain, ears and eyes. MWS falls in between these two variants in terms of severity.

With roughly 135 cases of MWS reported, diagnostic criteria have not been established, creating difficulty in proper diagnosis. However, clinical features well described in MWS include recurrent urticaria, episodic fever and sensorineural deafness. Additionally, patients may present with conjunctivitis, episcleritis, abdominal pain, myalgias, arthralgias, digital clubbing, chronic fatigue, and headaches. Severe presentations exhibit papilledema, optic atrophy or chronic meningitis. Males may demonstrate sterility. Symptoms occur spontaneously or in response to stress, temperature change or fatigue. Renal amyloidosis resulting in proteinuria and chronic renal insufficiency will occur in 25% of patients.

Two clinical variants can be seen in MWS. These include inflammatory and organ disease phenotypes. The inflammatory type is often seen in children experiencing episodic fevers and abdominal pain while the organ disease type is primarily observed in adults experiencing chronic fatigue with sensorineural hearing loss.

In the laboratory evaluation of MWS patients, elevated levels of CRP, ESR, serum amyloid protein and IL-6 are characteristic. Genetic analysis confirms the diagnosis of MWS through identification of the NLRP3 gene mutation. Cryopyrin hyperactivity contributes to increased levels of IL-1, which is responsible for the promotion of inflammation in MWS. Anakinra, an IL-1 receptor antagonist, canakinumab, a monoclonal IL-1 antibody, and rilonacept, an IL-1 signaling blocker have shown remarkable efficacy in decreasing inflammatory markers, reversing amyloidosis and improving hearing loss in MWS.

Conclusion
In conclusion, Muckle-Wells Syndrome is a rare autosomal dominant cryopyrinopathy. The classic triad of recurrent urtiaria, episodic fever and sensorineural deafness can identify patients with this condition. Early recognition and utilization of IL-1 receptor antagonists is key for symptomatic treatment and prevention of further amyloidosis and hearing loss progression.