A Vexing Diagnosis: When a somatic mutation results in sustained inflammation

Patrick Stauffer, MD[1]; Derek Galligan, MD[1,2], Kenneth Scalapino MD[1,2]

1. Oregon Health and Science University, Department of Medicine, Portland, OR
2. VA Portland Health Care System, Portland, OR

Case Presentation

A 60 year-old male with a complex history of relapsing polychondritis, possible GCA, APLS complicated by thrombosis resulting in compartment syndrome and amputation of LLE, and chronic macrocytosis with symptoms including recurring restrictive lung disease, joint pain, eye pain, diplopia, fevers and throat pain. Empiric treatment trials included methotrexate, anti-TNF agents, rituximab and mycophenolate mofetil without control of symptoms or systemic inflammation. Chronic high dose prednisone (> 20 mg daily) reduced symptoms, but notably did little to normalize ESR or CRP. A unifying diagnosis had eluded his care team until he underwent genotype testing for the recently described VEXAS syndrome (vacuoles, E1 enzyme, X-linked, Auto-inflammatory, Somatic), for which he was found to have the defining mutation. He presents to the hematology clinic for discussion of possible treatment with allogeneic stem cell transplantation (alloHSCT).

Discussion

- VEXAS syndrome is a newly defined disorder described as an adult-onset inflammatory syndrome driven by a somatic mutation affecting methionine-41 (p.Met41) in *UBA1*, the major E1 enzyme that initiates ubiquitylation.[1,2,3]
- Presentation: males with late adulthood onset of fevers, cytopenias (anemia and macrocytic anemia), pulmonary inflammation, chondritis, episcleritis and vasculitis.[2]
- A unifying characteristic is that symptoms are usually **treatment refractory to DMARDs and other immunosuppressants.**
- The patients described in the sentinel study carried presumed rheumatologic and hematologic diagnoses for many years.[1]
- Our patient has been symptomatic for nearly 9 years and continues to suffer sequalae of chronic prednisone and is at an elevated risk to develop myelodysplastic syndrome.
- Treatment: A lasting and efficacious treatment has yet to be identified.
- Based on a small clinical trial of alloHSCT that shows possible effectiveness the patient is not undergoing evaluation for this possible treatment.[4]

This case also underscores the importance for internists to question a diagnosis that presents as a variant of the typical illness script. It also highlights a potential future in medical research that more appropriately characterizes heterogenous diagnoses as a consortium

Key Points:

Consider **VEXAS** in the differential of **adult onset systemic inflammation** refractory to first-line therapies

Question the diagnosis that presents as a variant of the typical illness script

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stauffep@ohsu.edu

@p_stauffer

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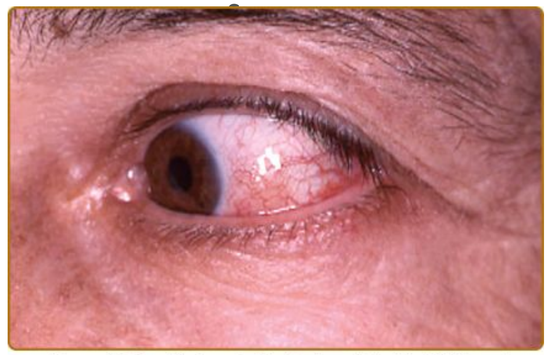
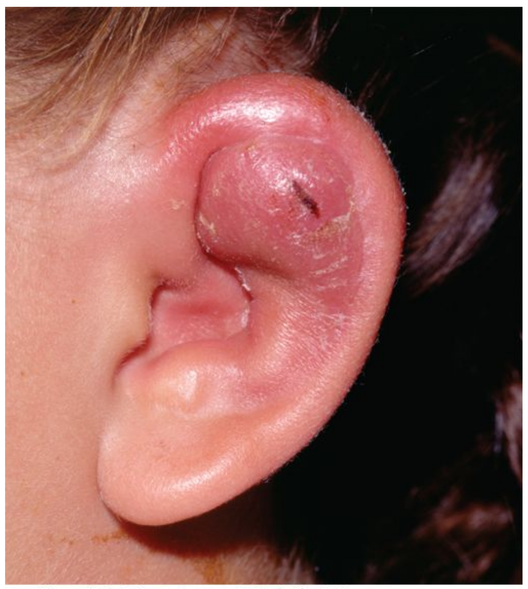


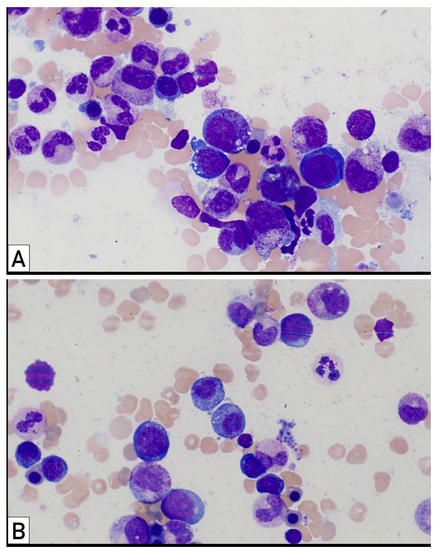
Source: S. Kang, M. Amagai, A.L. Bruckner, A.H. Enk, D.J. Margolis, A.J. Mcmichael, J.S. Orringer: Fitzpatrick's Dermatology, Ninth Edition

Periauricular Chondritis



Source: Kevin J. Knoop, Lawrence B. Stack, Alan B. Storrow, R. Jason Thurman: The Atlas of Emergency Medicine, 5e

Vacuolization of Myeloid Precursor before and after alloHSCT[3]



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