

INTRODUCTION

VEXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) syndrome was first described in December 2020 in 25 men who developed a late-onset systemic inflammatory syndrome with involvement of the hematologic, dermatologic, ocular, cardiovascular, pulmonary, nervous, gastrointestinal, genitourinary, and musculoskeletal systems. VEXAS is caused by somatic mutations in the *UBA1* (Ubiquitin-like Modifier-Activating Enzyme 1) gene at p.Met41, which results in vacuoles in myeloid and erythroid precursors.(1)(2)(3) Clinically, VEXAS can mimic numerous other diseases, including small vessel vasculitis, rheumatoid arthritis, Sweet syndrome, relapsing polychondritis, polyarteritis nodosa, and giant cell arteritis.(4) Histopathologically, skin lesions can resemble erythema nodosum, neutrophilic dermatoses, vasculitis, urticarial reaction, or chronic panniculitis.(5). We present a case series of three men with VEXAS syndrome who were initially diagnosed with and treated for tumid lupus.

INITIAL CASE PRESENTATION

Patient 1: 64 year old immunocompetent man presented with two years of a rash on the trunk and extremities not associated with pruritis or pain. He reported lesions would resolve with prednisone but reoccur if tapered below 15 mg. Also reported pain/stiffness in the Achilles and knuckles. He had 3 biopsies suggestive of tumid lupus or histiocytoid Sweet syndrome.

Treatment before diagnosis: hydroxychloroquine 200 mg twice daily, mycophenolate mofetil 1000 mg twice daily, belimumab 200 mg subcutaneous weekly, anifrolumab 300 mg monthly

Patient 2: 70 year old immunocompetent man presented with 6 months -of a recurrent rash occurring on the trunk, and extremities, but sparing the face. Each individual lesion would last for 2 weeks then fade to a lighter color, and were associated with mild tenderness, but no pruritis. He denied identifiable triggers. He had a biopsy showing an interface dermatitis with superficial and deep inflammation, suggestive of connective tissue disease, including lupus.

Treatment before diagnosis: topical triamcinolone and clobetasol; hydroxychloroquine 200 mg twice daily for 2 months followed by 300 mg twice daily for 3 months; chloroquine 250 mg daily for 4 months

Patient 3: 71 year old immunocompetent man presented with 2 years of a rash on the trunk, extremities, and face, associated with mild pruritis, no pain. Each lesion would last 2-3 days then resolve with pigment changes. Denies other symptoms or triggers. Initial biopsy showed superficial and deep perivascular inflammation consistent with collagen vascular disease. Subsequent biopsies were suggestive of urticarial vasculitis, histiocytoid Sweet syndrome or palisading neutrophilic and granulomatous dermatosis.

Treatment before diagnosis: colchicine 0.6 mg daily for 6 months, hydroxychloroquine 400 mg daily for 2 years, methotrexate 10 mg weekly for 1 month, mycophenolate mofetil 1000 mg twice daily for 3 months, dapsone 50-75 mg daily for 8 months

LABORATORY WORKUP

P1: ANA, RF, anti-ds DNA Ab, anti-CCP Ab, C3, C4, ESR (all WNL)

P2: ANA, anti-ds DNA Ab, anti-SA/SSB Ab (all WNL)

P3: ANA, RF, anti-ds DNA Ab, anti-CCP Ab, C3, C4, ESR (all WNL)

P1: platelets 108-135*, MCV 97-101*, CMP WNL, CRP 52.1

P2: platelets 369-416, MCV WNL, Hgb 13, RDW 17.7, CMP WNL

P3: platelets 190-295*, MCV 99-108*, Hgb 10.9-13.6, Lymph #0.6-1.0, CRP 16

*Platelets < 200 and elevated MCV > 100 are often associated with VEXAS.

CLINICAL PHOTOS

Patient 1



Patient 2

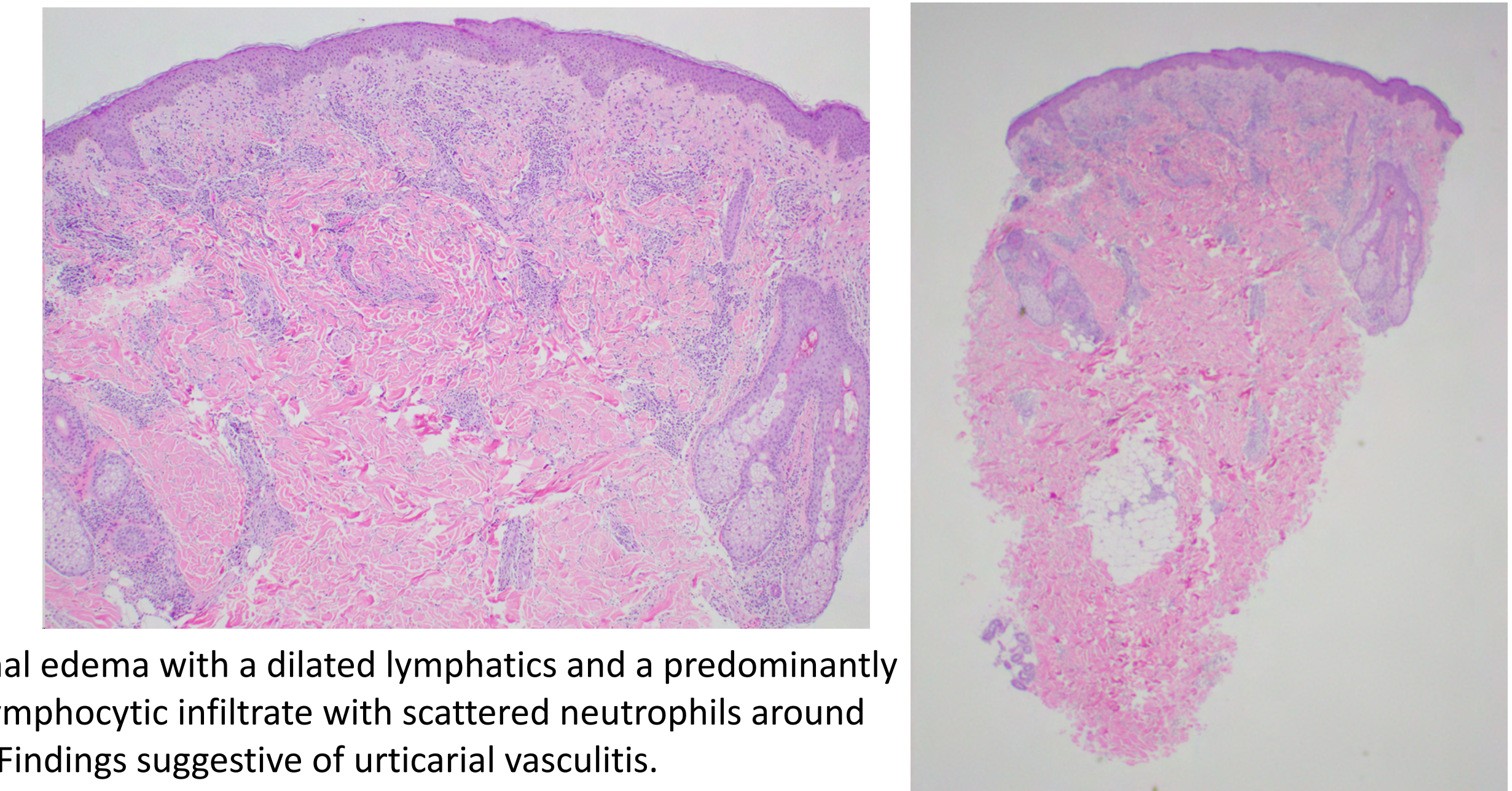


Patient 3



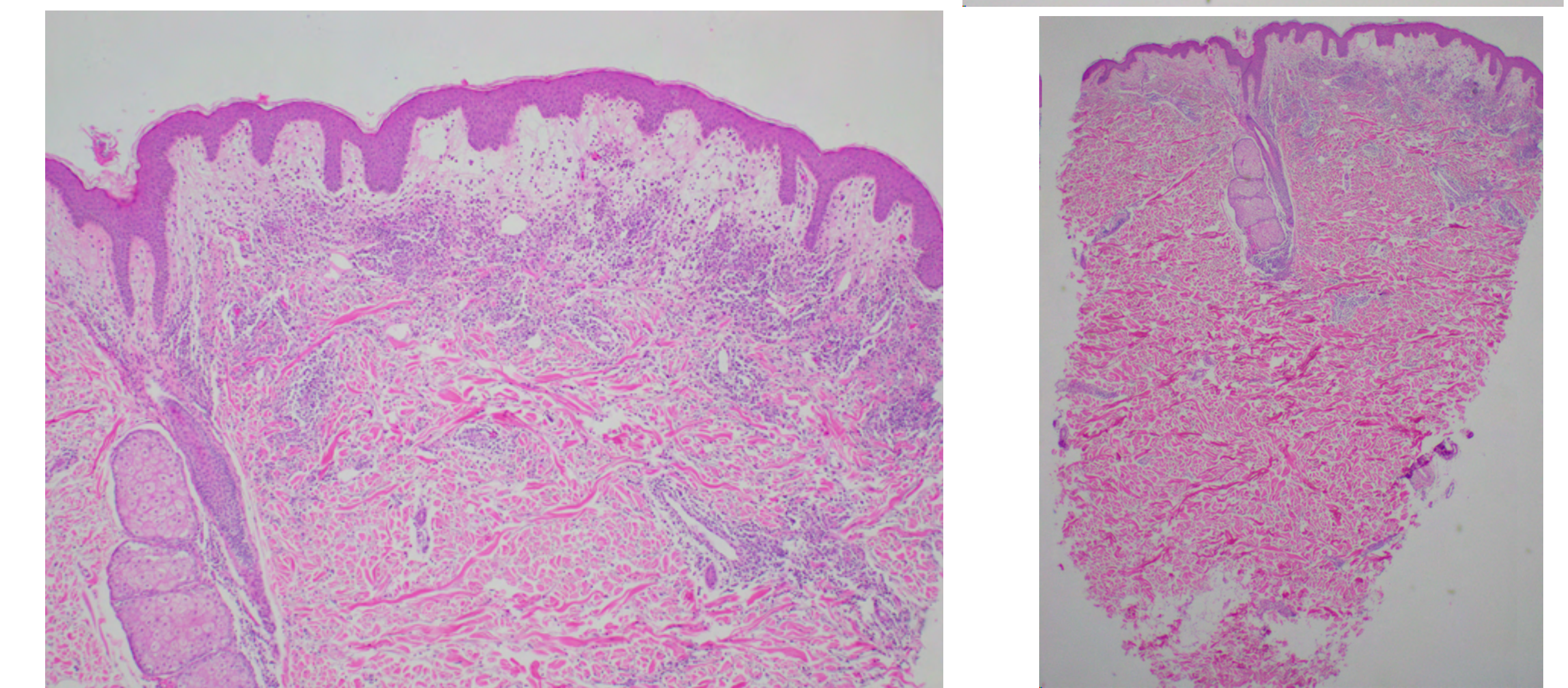
REPRESENTATIVE HISTOPATHOLOGY

Patient 3 Biopsy 2



Papillary dermal edema with a dilated lymphatics and a predominantly perivascular lymphocytic infiltrate with scattered neutrophils around small vessels. Findings suggestive of urticarial vasculitis.

Patient 3 Biopsy 3



Normal epidermis. Papillary dermal edema associated with a superficial and mid infiltrate of histiocytes, highlighted by CD163 stains, admixed with neutrophils and lymphocytes. Histiocytes present interstitially around collagen fibers. Lymphocytes predominantly T-cell, retention of CD7. Findings suggestive of palisading neutrophilic and granulomatous dermatosis, the histiocytoid variant of Sweet's syndrome (neutrophilic dermatosis) and cutaneous infection.

DISCUSSION

The severity of VEXAS syndrome is related to the specific *UBA1* mutation; about 50% of published cases show the p.Met41Thr substitution, while 20% consist of the p.Met41Val or p.Met41Leu mutations. (6) All 3 mutations decrease cytoplasmic *UBA1* protein production, but the p.Met41Val is associated with the lowest *UBA1* translation, highest disease severity, and worst prognosis. (2)(6) The p.Met41Leu substitution is a less inflammatory and milder phenotype, with less lung involvement, lymphadenopathy, venous thromboembolic disease, constitutional symptoms (for example: fevers, weight loss), and elevated CRP. Patients with p.Met41Leu show a 5-year survival of 100% in comparison to 76.7% for p.Met41Val and 83.1% with p.Met41Thr. (7) Our 3 patients had the p.Met41Leu mutation and considerable skin involvement refractory to numerous prior treatments, but only mild systemic disease. All 3 patients had evidence of mild bone marrow myelodysplasia and CBC abnormalities, and the patient with costochondritis symptoms also had an elevated CRP. However, they did not have ocular, lung, cardiovascular, neurologic, genitourinary, or gastrointestinal symptoms (to the best of our knowledge), and were never hospitalized for VEXAS. Tocilizumab has been utilized as treatment due to its targeting of the IL-6 receptor, a pathway that is upregulated in VEXAS syndrome. Ruxolitinib, which targets JAK1/JAK2 and TYK2, has been found to produce complete clinical remission after 6 months of treatment in one case series. (4). If our three patients' symptoms are refractory to tocilizumab, we plan to prescribe ruxolitinib. We recommend that testing for VEXAS be considered for any male over the age of 60 with a presumptive diagnosis of tumid lupus, especially if associated with costochondritis, elevated MCV or decreased platelets, or if the cutaneous lesions are responsive to moderate doses of oral steroids (15-20 mg) but refractory to other immunosuppressive agents.

FURTHER WORKUP AND TREATMENT

Genetics: All positive for *UBA1* mutation (p.Met41Leu).

Bone Marrow Biopsy: **P1)** possible dysplasia consistent with myelodysplasia with multilineage dysplasia - not requiring treatment; **P2:** marrow hypercellularity and subset megakaryocytes with MDS-like features - not requiring treatment; **P3:** normocellular marrow and maturing trilineage hematopoiesis, erythroid lineage with mild dyserythropoiesis and megaloblastic changes, myeloid lineage with occasional hypogranular cytoplasm.

Current Treatment: **P1)** tocilizumab 162 mg SC weekly, prednisone 15 mg daily; currently unclear if improving, working on tapering prednisone; **P2:** tocilizumab 162 mg SC weekly, chloroquine 250 mg daily; **currently improving after 2 months of tocilizumab;** **P3:** tocilizumab 162 mg SC weekly, prednisone 9.5 mg daily; only minimal improvements after 7 months of tocilizumab.

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