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Reversible aquagenic pruritus associated with testosterone-induced erythrocytosis

To the Editor: A 59-year-old healthy man presented for evaluation of new-onset aquagenic pruritus. He started testosterone replacement therapy (200 mg daily) 7 months before presentation for low testosterone level of unknown cause; testicular biopsy at that time revealed normal findings. Four months after beginning testosterone replacement, he noticed generalized intense burning and pruritus, specifically during and after showering, without evidence of rash. Empiric use of emollients and antifungal cream did not alleviate the pruritus. He could not tolerate antihistamines because of drowsiness. On evaluation, his full-body skin examination revealed normal findings. This history and examination are consistent with aquagenic pruritus, which typically presents without cutaneous signs.[1] Because aquagenic pruritus is most often associated with polycythemia vera (PCV),[2] hematologic studies were performed, revealing an elevated hematocrit of 51.2%, notably higher than his normal baseline of 46.5%. The remainder of his complete blood cell count and differential, renal and liver function tests, antinuclear antibody, and thyroid studies were normal.

Because the aquagenic pruritus tightly coincided with the initiation of his testosterone replacement therapy, the patient's testosterone dose was tapered to 50%, which resulted in significant improvement in his symptoms; his hematocrit also normalized to baseline levels (Fig 1). Given that his erythrocytosis and his symptoms were improving, the patient was recommended to continue routine monitoring of his hematocrit levels and did not undergo further diagnostic evaluation for hematologic malignancy.

Although most patients with aquagenic pruritus do not have underlying disease, when associated with systemic conditions, PCV is diagnosed in approximately 30% of cases of aquagenic pruritus.[3,4] Aquagenic pruritus is reported by approximately 5% to 69% of patients with PCV and may precede the diagnosis of PCV by many years.[3,4] Aquagenic pruritus may also occur in the setting of myelofibrosis, malignancy, medications (bupropion, antimalarials), and lactose intolerance.[4] However, little is known about the mechanism or pathophysiology of aquagenic pruritus. One study looking at skin biopsy specimens taken from patients with PCV and aquagenic pruritus demonstrated increased skin mast cells, mononuclear cells, and eosinophils.[3]

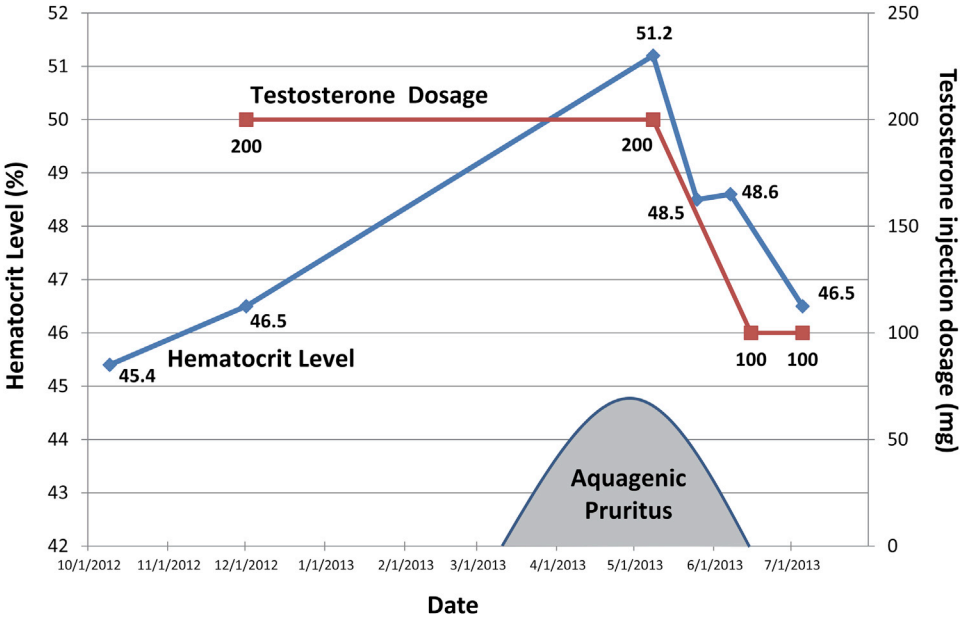

Fig 1. Aquagenic pruritus associated with testosterone-induced erythrocytosis: clinical course, hematocrit level, and testosterone dosage.

Additional studies revealed that these mast cells may be functionally different from those in healthy control subjects. Specifically, release of increased levels of pruritogenic factors by mast cells, including interleukin-31, histamine, and leukotrienes, is postulated to mediate pruritus. Homozygous JAK2V617F mutation—one of the mutations that causes PCV—has also been correlated with a higher incidence of pruritus among 58 patients with PCV (69% vs 38%, $P = .04$), compared with heterozygotes.[3]

Testosterone replacement therapy has been associated with erythrocytosis because of its ability to stimulate erythropoietin and its direct effect on erythroblasts in bone marrow.[5] Increase in hemoglobin is the most common adverse effect of testosterone treatment in men.[5]

To our knowledge, this is the first report of testosterone-induced erythrocytosis associated with PCV-like aquagenic pruritus. This case highlights the concept that erythrocytosis in a setting other than PCV may also cause aquagenic pruritus and common pathophysiologic mechanisms may contribute to aquagenic pruritus in both conditions; lowering the hematocrit by removing or reducing the cause of erythrocytosis may reverse the symptoms.

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