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Case Presentation

Improvement of pruritus associated with erythrocytosis in transmasculine patients undergoing gender-affirming therapy with phlebotomy: a report of two patients

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Abstract

Gender-affirming hormone therapy with testosterone may be a component in the treatment plan for transmasculine individuals. Secondary erythrocytosis induced by testosterone therapy and its subsequent complications, such as pruritus, have been reported in the literature in cisgender men. This report presents two transmasculine patients who developed generalized pruritus shortly after initiating testosterone therapy for gender-affirming care. Both patients exhibited elevated hemoglobin and hematocrit levels indicative of testosterone-induced erythrocytosis. Despite treatments, including topical corticosteroids, antihistamines, gabapentin, and benzodiazepines, their symptoms persisted. Symptomatic relief was achieved through therapeutic phlebotomy. The occurrence of polycythemia vera-like pruritus underscores a significant but less commonly recognized side effect of testosterone therapy. Balancing effective gender-affirming care and patient goals with the management of associated side effects is essential for optimizing patient outcomes.

plan may involve the administration of exogenous testosterone. Testosterone therapy induces virilization, cessation of menses, increased facial and body hair, deepening of the voice, increased sexual desire, clitoral enlargement, and changes in body composition.² Therefore, the goals of hormonal therapy are to lower endogenous sex hormone levels, thereby diminishing the secondary sex characteristics associated with the individual's assigned gender at birth and to replace these hormones with ones consistent with the individual's gender identity. In this report, we present two transmasculine patients who developed pruritus shortly after initiation of testosterone for gender-affirming hormone therapy. Both patients reported improvements in pruritus after therapeutic phlebotomy.

Case Synopsis

Patient one, aged 48, presented with generalized pruritus without rash approximately 6 months after starting testosterone cypionate injections ([Table 1](#)). His pruritus was exacerbated with heat exposure and hot showers. Although he had a history of atopic dermatitis, no evidence of eczema was observed during visits. Prior to phlebotomy, he underwent treatments including triamcinolone 0.1% ointment, gabapentin, diphenhydramine, cetirizine, fexofenadine, hydroxyzine, and alprazolam, none of which provided complete relief.

Patient two, aged 30, presented with generalized pruritus without rash approximately 6 to 12 months after commencing testosterone cypionate injections. His pruritus intensified in the evening, disrupted his sleep, and was aggravated by heat and hot showers. He had a history of cigarette smoking. Medications he had tried prior to phlebotomy included gabapentin, cetirizine, hydrox-

Introduction

Gender plays a crucial role in shaping personal identity. Experiencing gender differently from sex assigned at birth may prompt individuals to seek care in a gender-affirming health program.¹ For transmasculine individuals, who are recorded female sex at birth, the treatment

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Table 1. Patient Demographics and Disease Characteristics

Patient	1	2
Age	48	30
BMI	24	24
Clinical manifestations	Generalized pruritus without rash	Generalized pruritus without rash Worse in the evening Affecting sleep
Aggravators	Heat Hot showers	Heat Hot showers
Form of testosterone	Testosterone cypionate	Testosterone cypionate
How long after starting testosterone did symptoms start	6 months	6 months – 1 year
History of cigarette smoking	No	Yes
History of atopy (atopic dermatitis, asthma)	Yes	No
History of thrombosis	No	No
Other specialties involved	Dermatology, allergy and immunology, neurology, hematology	Hematology
Medication history	Triamcinolone 0.1% ointment, gabapentin, diphenhydramine, cetirizine, fexofenadine, hydroxyzine, alprazolam	Gabapentin, cetirizine, hydroxyzine, lorazepam
Most effective treatment	Phlebotomy	Phlebotomy

Table 2. Summary of Laboratory Findings and Investigations

Patient	1	2
Hemoglobin (at peak)	15 g/dL	17 g/dL
Hematocrit (at peak)	51%	48%
Erythropoietin	N/A	15.2 mU/mL
<i>JAK2</i> , <i>CALR</i> , <i>MPL</i> mutation	N/A	Negative
Creatinine	Normal	Normal
Liver function tests	Normal	Normal
Splenic ultrasound	N/A	Normal

JAK2, Janus kinase 2; *CALR*, Calreticulin; *MPL*, myeloproliferative leukemia virus

yzine, and lorazepam, none of which offered complete alleviation of symptoms.

Prior to phlebotomy, both patients displayed evidence of elevated hemoglobin and/or hematocrit while on testosterone (Table 2). Both patients were referred to the hematology department. Work-up including complete blood cell count and differential, renal function tests, and liver function enzymes were normal for both patients. The cause of erythrocytosis in both individuals was attributed to exogenous testosterone.

Case Discussion

Erythrocytosis (polycythemia) refers to an abnormal elevation of hemoglobin and/or hematocrit in peripheral blood. Erythrocytosis is divided into relative erythrocytosis (eg, volume depletion) and absolute erythrocytosis. Absolute erythrocytosis is further divided into primary erythrocytosis and secondary erythrocytosis. There are no exact lab value cutoffs for erythrocytosis, but the criteria for polycythemia vera (PV), a subtype of primary erythrocytosis, is often used as a prototype. The World Health Organization criteria for PV are a hemoglobin and hematocrit of 16.5g/dl and 49% in cisgender men and 16g/dl and 48% in cisgender women.³

Testosterone therapy is a cause of hematocrit increases and secondary erythrocytosis in cisgender men.^{4,5} In one of the largest randomized-controlled trials (RCT) involving testosterone-replacement therapy comprising 2601 men randomized to testosterone, four participants (0.15%) exceeded the hematocrit threshold of 54% even after titration to the lowest dosage.⁶ In an RCT evaluating testosterone treatment to prevent or revert type 2 diabetes in men, hematocrit increased to 54% in 106 (22%) of 480 testosterone randomized participants.⁷ It is important to note that these two RCTs differed in testosterone vehicle used (gel versus testosterone undecanoate injection) and both had hematocrit cutoffs of 54% for treatment discontinuation. Testosterone-replacement therapy was associated with a relative risk of 8.14 (95% confidence interval 1.87, 35.40) of developing erythrocytosis (hematocrit > 54%) based on a meta-analysis of four RCTs in hypogonadal men.⁵

Erythrocytosis also occurs in transmasculine patients receiving testosterone. The largest increase in hematocrit is seen within the first year of therapy. Other factors reported to increase erythrocytosis in this population include tobacco use, testosterone injections (compared with gel and transdermal administration), younger age of initiation, increased body mass index, and pulmonary conditions associated with erythrocytosis.⁸ A cohort of 192 transmasculine patients undergoing gender-affirming hormone therapy showed a prevalence of secondary erythrocytosis (hematocrit > 50%) in 11.5% of individuals.⁷ In a 20-year follow-up study of 1073 transgender men, erythrocytosis occurred in 11%, 3.5%, and 0.5% of patients as determined by hematocrit 50%, 52%, and 54%, respectively.⁸ The guidelines on the management of secondary erythrocytosis in transmasculine men on testosterone recommends cessation of testosterone therapy, dose reduction, longer injection intervals, or therapeutic phlebotomy when hematocrit levels exceed 54%.²

Pruritus is a common manifestation of PV, with aquagenic pruritus specifically occurring in approximately

40% of cases.⁹ The exact cause of PV-associated pruritus is unknown, however studies looking at skin biopsies taken from patients with this phenomenon demonstrated increased numbers of mononuclear cells and eosinophils after exposure to warm water.⁹ The management of PV-associated pruritus is empirical and has included antihistamines, interferon alfa, phototherapy, serotonin reuptake inhibitors, and phlebotomy.⁹⁻¹¹ Testosterone-induced erythrocytosis associated with PV-like aquagenic pruritus in a 59-year-old cisgender man receiving testosterone replacement therapy has been reported in the literature.¹² In that report, his pruritus improved by tapering his testosterone dose by 50%. To date, there are no reports of successful treatments of PV-like pruritus in individuals receiving testosterone injections for gender-affirming care.

Conclusion

In conclusion, we present two transmasculine patients undergoing gender-affirming hormone therapy with testosterone that experienced PV-like pruritus. Both patients found relief from symptoms after receiving therapeutic phlebotomy. In this population of patients, stopping or decreasing the dose of testosterone may not align with their goals of care. These cases highlight the need for healthcare providers to be vigilant in recognizing and addressing the unique health challenges faced by transgender individuals. Further research is warranted to develop optimal management strategies of such adverse effects in this population. Healthcare professionals should strive to provide comprehensive and inclusive care for this historically underserved population within the field of medicine.

Potential conflicts of interest

The authors declare no conflicts of interest.

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