

Angiofibroma stimulation in a transgender person receiving gender-affirming testosterone



Jeffrey A. Buble, MD,^a Howa Yeung, MD,^a Emily Cole, MD,^a Mariam Amin, MD,^a Douglas Parker, MD,^a and Jack L. Arbiser, MD, PhD^{a,b}
Atlanta and Decatur, Georgia

INTRODUCTION

We report a case of a transgender male patient, assigned female at birth, with multiple endocrine neoplasia type 1 who developed eruptive angiofibromas while receiving gender-affirming testosterone. This case is of significance because it demonstrates the possibility of a persistent angiofibroma precursor cell that exists well into adulthood and can be activated by testosterone. In addition, as more individuals undergo hormonal therapy for gender affirmation, the incidence of this complication is expected to increase.

CASE REPORT

A 26-year-old transgender male patient, assigned female at birth, with a medical history of multiple endocrine neoplasia type 1, asthma, and bipolar I disorder presented to our dermatology clinic for removal of cosmetically bothersome lesions on the face. These lesions were present for 2 to 3 months before presentation and were asymptomatic, but the patient wanted them removed because they were cosmetically bothersome. It was reported that at approximately aged 8 to 9 years, he developed several red papules on the nose and cheeks and underwent biopsy and treatment by a dermatologist. Shave biopsy in childhood showed the lesions to be angiofibromas, according to patient report. He had no other notable skin growths or pigmented lesions. Testosterone cypionate 100 mg intramuscular injections every 7 days were started 4 months before

presentation to our clinic, approximately 1 to 2 months before the growth of the angiofibromas (Fig 1).

The patient's brother and father have similar facial papules, and his father had a benign intracranial tumor and multiple endocrine neoplasia type 1 diagnosis. The patient received a diagnosis of multiple endocrine neoplasia type 1 after he was found to have a parathyroid adenoma. Blood testing at the time showed a testosterone level of 398.1 ng/dL (normal male range 320-1000 ng/dL) and a calcium level of 11.6 mg/dL (normal 8.9-10.3 mg/dL), which led to an evaluation that revealed a parathyroid hormone level elevated to 181.9 pg/mL. Parathyroid gland with increased radioactive uptake on scan led to subsequent parathyroidectomy of the left inferior parathyroid gland, which revealed a hypercellular gland consistent with parathyroid adenoma on histology. Vasoactive intestinal polypeptide, insulinlike growth factor 1, adrenocorticotrophic hormone, morning cortisol, prolactin, and gastrin levels were all within normal limits. This patient met familial criteria for the diagnosis of multiple endocrine neoplasia type 1 in accordance with clinical practice guidelines for multiple endocrine neoplasia type 1 by the Endocrine Society.¹

The patient was unable to afford compounded topical sirolimus cream and thus underwent shave removal and subsequent pulsed dye laser treatment of the lesions in our clinic (Fig 2). Histology of 3 nasal and medial cheek papules proved them to be angiofibromas (Fig 3).

From the Department of Dermatology, Emory University School of Medicine, Atlanta^a; and Veterans Affairs Medical Center, Decatur.^b

Funding sources: Supported by National Institutes of Health grant AR47901.

Conflicts of interest: None disclosed.

Correspondence to: Jack L. Arbiser, MD, PhD, Department of Dermatology, Emory University School of Medicine, Atlanta VAMC, WMB 5309, 101 Woodruff Circle, Atlanta, GA 30322.
E-mail: jarbise@emory.edu.

JAAD Case Reports 2020;6:1101-3.

2352-5126

Published by Elsevier on behalf of the American Academy of Dermatology, Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.jidcr.2020.06.016>

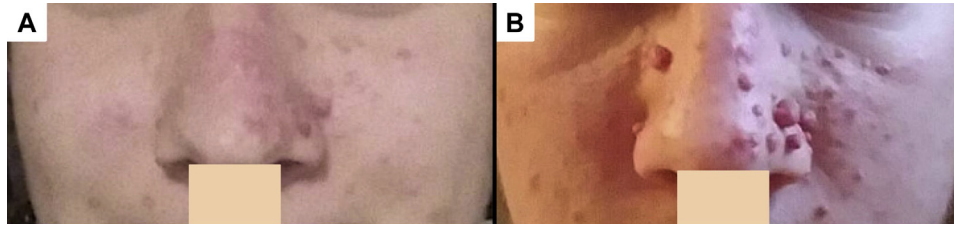


Fig 1. A 26-year-old transgender male patient, assigned female at birth, with eruptive angiofibromas after initiating testosterone therapy 4 months before. These images were patient provided and show (A) shortly before the initiation of gender-affirming testosterone, and (B) 2 to 3 months after initiation of testosterone.

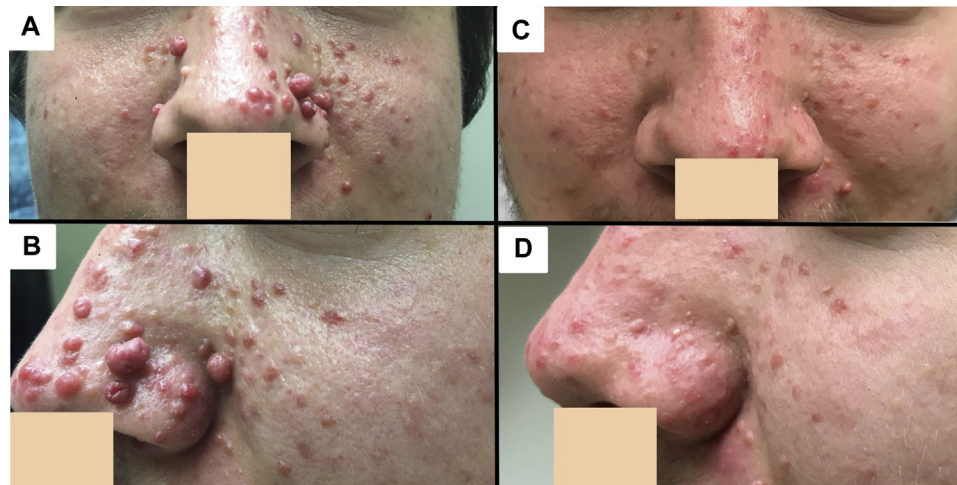


Fig 2. A and B, Photographs from our clinic on initial presentation, approximately 4 months after initiation of gender-affirming testosterone therapy. C and D, A subsequent follow-up visit after shave removal of a majority of the lesions and treatment with pulsed dye laser.

DISCUSSION

We present a case of a transgender male patient receiving therapeutic doses of testosterone with angiofibroma eruption. Paternal history of multiple endocrine neoplasia type 1, angiofibromas, and parathyroid adenoma confirmed a clinical diagnosis of multiple endocrine neoplasia type 1. The patient had normal prolactin and insulinlike growth factor 1 levels. Magnetic resonance imaging of the brain did not show pituitary mass.

Angiofibromas are benign neoplasms that often occur sporadically, but are highly associated with 3 autosomal-dominant disorders, tuberous sclerosis, Birt-Hogg-Dube syndrome, and multiple endocrine neoplasia type 1. Facial angiofibromas are one of the diagnostic hallmarks of tuberous sclerosis and are often pivotal in the diagnosis of tuberous sclerosis. This patient was evaluated for TS, including Wood's lamp examination and renal ultrasonography, results for both of which were negative and did not support this diagnosis.

Most genetically associated angiofibromas originate as red papules that expand during puberty and then gradually are replaced by scar tissue.²⁻⁴ The angiofibromas are often cosmetically disfiguring and are treated either topically with mammalian target of rapamycin inhibitors (rapamycin) or with physically destructive modalities, including shaving, laser, and cryotherapy. Systemic rapamycin/sirolimus has been used for treatment of patients with angiofibromas and other TS-related complications such as renal angiomyolipoma.

Peak of endogenous sex hormones at approximately puberty may account in part for the peripubertal eruption of angiofibromas. Endogenous sex hormone levels decrease over time, and this decrease is thought to explain the stable course of angiofibromas, with little growth observed in most cases after aged 20 years. This case is notable in that the patient developed an eruption of angiofibromas in his late 20s after initiation of gender-affirming testosterone. This implicates the possibility of the persistence of

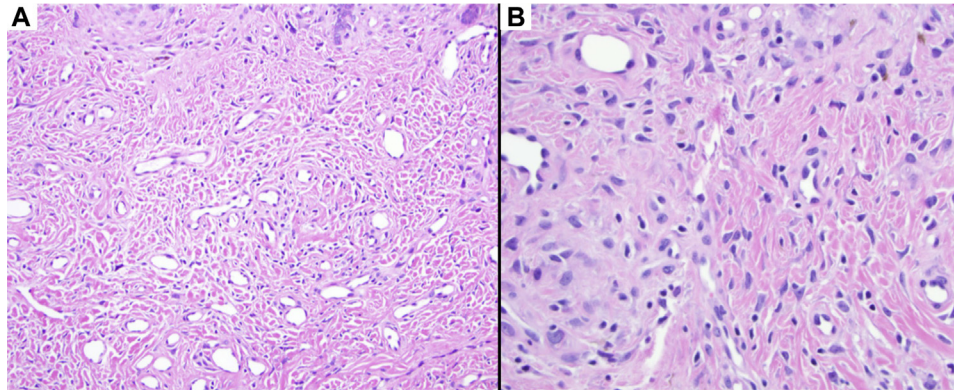


Fig 3. Histology of the patient's facial lesions. **A**, Coarse collagen bundles (magnification $\times 10$). **B**, Typical spindled cells surrounding blood vessels observed in angiofibromas (magnification $\times 20$).

angiofibroma “2-hit” cells that can respond to high levels of exogenous sex hormones, and these precursors likely persist well into adulthood. Testosterone has been implicated in the promotion of epidermal neoplasms,⁵ and a recent study has shown a similar mechanism in neurofibromas, in which NF1^{-/-} double-mutated Schwann cells are inducible in the presence of testosterone, estradiol, and human chorionic gonadotropin.⁶ This case highlights the importance of the hormonal pathogenesis of angiofibromas, and how studying the transgender community can lend insight into the role exogenous sex hormones play in various skin conditions.

REFERENCES

1. Thakker RV, Newey PJ, Walls GV, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). *J Clin Endocrinol Metab.* 2012;97(9):2990-3011.
2. Vortmeyer AO, Böni R, Pack SD, Darling TN, Zhuang Z. Perivascular cells harboring multiple endocrine neoplasia type 1 alterations are neoplastic cells in angiofibromas. *Cancer Res.* 1999;59(2):274-278.
3. Darling TN, Skarulis MC, Steinberg SM, Marx SJ, Spiegel AM, Turner M. Multiple facial angiofibromas and collagenomas in patients with multiple endocrine neoplasia type 1. *Arch Dermatol.* 1997;133(7):853-857.
4. Pack S, Turner ML, Zhuang Z, et al. Cutaneous tumors in patients with multiple endocrine neoplasia type 1 show allelic deletion of the MEN1 gene. *J Invest Dermatol.* 1998;110(4):438-440.
5. Zackheim HS. Effect of castration on the induction of epidermal neoplasms in male mice by topical methylcholanthrene. *J Invest Dermatol.* 1970;54(6):479-486.
6. Pennanen P, Peltonen S, Kallionpää RA, Peltonen J. The effect of estradiol, testosterone, and human chorionic gonadotropin on the proliferation of Schwann cells with NF1 or NF1 genotype derived from human cutaneous neurofibromas. *Mol Cell Biochem.* 2018;444(1-2):27-33.