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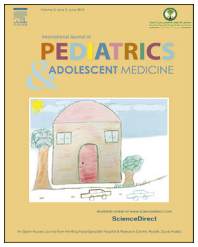

WHAT'S YOUR DIAGNOSIS

Answer: Cyclosporine A hypertrichosis in a patient with hemophagocytic lymphohistiocytosis

Jeylan El Mansoury [a], Joyce N. Mbekeani [b,c,*]

[a] *Dept of Ophthalmology, KFSH&RC, Riyadh, Saudi Arabia*
[b] *Dept of Surgery, Jacobi Medical Center, North Bronx Health Network, Bronx, NY, USA*
[c] *Dept of Ophthalmology and Visual Sciences, Albert Einstein College of Medicine of Yeshiva University, Bronx, NY, USA*

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1. Answer: Cyclosporine-A hypertrichosis in a patient with hemophagocytic lymphohistiocytosis

Hypertrichosis is defined as the excessive growth and thickness of hair in the normal distribution of hair and should be distinguished from hirsutism or excessive hair growth in females distributed in the male pattern [1]. It may be congenital, acquired, localized, or diffuse and associated with underlying dermatologic changes and pigmentation. Acquired hypertrichosis has been associated with conditions such as atopic dermatitis and vernal keratoconjunctivitis, HIV, porphyria, hypothyroidism, anorexia nervosa, paraneoplasia, systemic lupus, and trauma [1—3]. Hemophagocytic lymphohistiocytosis is a rare group of disorders manifesting as immune disregulation. Familial, autosomal recessive and acquired forms are diagnosed by fulfilling specific criteria and can be triggered by infections, malignancies, and autoimmune diseases [4]. Characteristic

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* Corresponding author. Dept of Surgery, Jacobi Medical Center, 1400 Pelham Parkway, Bronx, NY 10461, USA. Tel.: +1 718 918 4784; fax: +1 718 918 7379.
E-mail address: jnanjinga@yahoo.com (J.N. Mbekeani).

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impaired natural killer and cytotoxic T cell function results in excessive cytokines that lead to the accumulation of T cell lymphocytes and histiocytes (macrophages) in multiple organs including lymph nodes, the liver, and spleen [4]. To date, HLH has not been associated with hypertrichosis or hursutism. In addition to a significant temporal relation with hospitalization and chemotherapy, it seems the likely cause of hypertrichosis in our patient is acquired and iatrogenic.

Drugs associated with hypertrichosis include, cyclosporine A, minoxidil, phenytoin, steroids, epidermal growth factor inhibitors, tyrosine kinase inhibitors, interferon A, tacrolimus, and prostaglandin analogues used for glaucoma, such as latanoprost and travaprost [1—3,5]. Of the medications administered for HLH and pre-BMT management, the most likely culprit causing hypertrichosis and eyelash trichomegaly is cyclosporine A with possible potentiation by simultaneous prednisolone therapy [2,6]. Cyclosporine A, a potent immunosuppressive agent that specifically downregulates T cell-mediated immunity through interleukin-2 (IL2) inhibition can be administered as part of therapeutic regime for various auto-immune disorders, malignancies and to ameliorate allogeneic graft rejection. In this patient, it was utilized as part of the HLH-2004 treatment protocol [7] and in preparation for potentially curative BMT. Known complications of CSA therapy include nephrotoxicity, hepatotoxicity, various infections, tremors, gingival hyperplasia and hypertrichosis [6]. The frequency of CSA hypertrichosis and eyelash trichomegaly varies with different reports [2,6,8]. Although higher frequencies are noted in pediatric and female patients and at higher doses of CSA [2,6], this side effect does not occur universally in all patients, suggesting an element of idiosyncrasy.

The mechanism for excessive hair growth has not been conclusively elucidated. Takahashi and Kamimura [9] in their studies of cultured murine hair epithelial cells found that CSA at various doses stimulated hair and epidermal keratinocyte growth, when compared to control cells, and simultaneously down-regulating certain protein kinase C isoenzymes. Since protein kinase C, a key enzyme system influencing cell proliferation and differentiation, has known negative hair-growing effects, they speculated that this might be the pathway that leads to CSA hypertrichosis. Interestingly, the downregulation of protein kinase C isoenzymes is thought also to be the means by which CSA inhibits IL2 and thus T cell immunity, thereby causing immune modulation. If indeed CSA exerts potent immunosuppression and hypertrichosis effects by a similar mechanism, the question that begs to be answered is why there is selective vulnerability to hypertrichosis and trichomegaly.

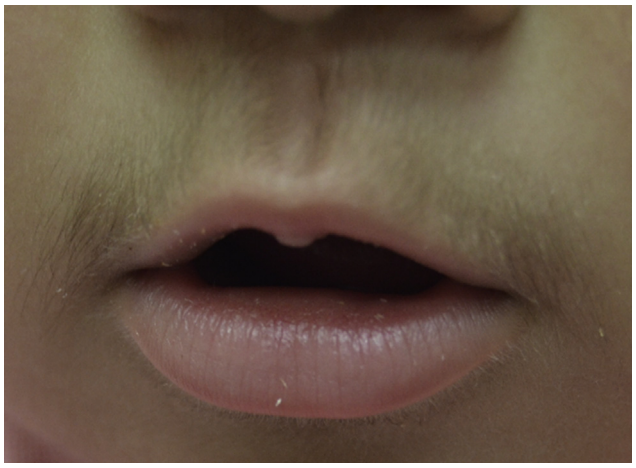

Figure 2 CSA-induced hypertrichosis of upper lip and face manifesting as a moustache, sideburns and downy facial hairs.

Our patient, a vulnerable candidate, exhibited diffuse hypertrichosis, and eyelash trichomegaly, likely associated with systemic cyclosporine and steroid administration.

Although occasionally of cosmetic concern, this well-recognized side effect is rarely of clinical significance and resolves on termination of therapy. Rarely does iatrogenic hypertrichosis require intervention and hair trimming, shaving, plucking, or application of depilating creams can be used in severe cases. These measures might be considered, in our patient, in the unlikely event of dystrichiasis [10], (misdirected accessory eyelashes towards the globe), or should cyclosporine need to be employed post-BMT, to ameliorate graft vs host disease, with unacceptable cosmesis from excessive hypertrichosis. A case of a patient with HLH and similar CSA-hypertrichosis after HLH-2004 therapy, has been described who displayed the expected resolution upon cessation of therapy [11]. Likewise, we fully expect complete resolution of hypertrichosis and trichomegaly

Figure 1 CSA-induced hypertrichosis with eyelash trichomegaly and unibrow. Head hair, eyelashes and brow hairs are unusually long, thick and dark.

without intervention and will continue to review this patient at regular intervals during his clinical course (Figs. 1 and 2).

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Hasan Omairah AAS, COT, OCT-C, CRA, Senior Ophthalmic Photographer, Dept of Ophthalmology, KFSH&RC, Riyadh, KSA.

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