Familial secondary hyperhidrosis associated with tumor necrosis factor–alpha inhibitor treatment

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INTRODUCTION

Hyperhidrosis is a disorder caused by overactivity of the eccrine glands and characterized by excessive sweating beyond what is essential for thermoregulation.[1] Its prevalence is 3% in the US population and affects men and women equally.[1,2] Hyperhidrosis can be classified as either primary, which tends to be focal, or secondary, which tends to be more generalized.[2] Primary hyperhidrosis specifically affects the palms, soles, axillae, and face in a bilateral, symmetric distribution; begins in adolescence; and does not occur during sleep. In contrast, secondary hyperhidrosis typically presents in adults, affects a wider distribution of the body asymmetrically during both waking and sleeping hours, and is caused by either underlying medical conditions or medications.[2]

Abbreviation used:

TNF: tumor necrosis factor

CASE REPORT

A 31-year-old man with uveitis and colitis previously managed on prednisone developed severe generalized malodorous hyperhidrosis on his trunk, arms, and legs shortly after starting adalimumab treatment (40-mg injection every 14 days). He described episodes of hyperhidrosis throughout his adalimumab therapy, occurring mostly during the day, precipitated by light activity such as walking and required that he change his clothes frequently. Because of his lack of therapeutic response to adalimumab, he was prescribed infliximab infusions (5 mg/kg every 6 to 8 weeks) and azathioprine (100 mg daily). The patient described profuse sweating occurring during the first 3 weeks after each infusion and subsiding shortly before the next infusion. He experienced good therapeutic response for his colitis and uveitis on this new treatment regimen and was able to taper his prednisone dose from 80 mg to 4 mg every day. However, he continued to experience similar levels of hyperhidrosis on infliximab. The addition of glycopyrrolate (1 mg twice daily) alleviated the severity of sweating.

The patient's family history was notable for a 26-year-old female sibling with HLA-B27– and HLA-B51–negative Crohn's disease who also reported experiencing new-onset severe generalized hyperhidrosis when treated with adalimumab. Her symptoms occurred mostly at night and required her to sleep on a towel. Because of this side effect, she switched her treatment to certolizumab with good disease control and improved symptoms of hyperhidrosis. She never received infliximab treatment. Neither patient experienced associated symptoms of infection such as cough, joint pain and swelling, weight loss, or reported symptoms associated with diseases that may cause hyperhidrosis, including hyperthyroidism, diabetes, or heart failure. The patients denied a family history of hyperhidrosis or other medical conditions except colitis and uveitis.

DISCUSSION

In this report, we describe a case of secondary hyperhidrosis associated with tumor necrosis factor–alpha (TNF-α) inhibitor treatment. Given the timing of the onset of symptoms and initiation of treatment, TNF-α blockade is most likely the cause of hyperhidrosis in both the patient and his sibling. Moreover, the persistence of hyperhidrosis during

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both types of TNF-α inhibitor treatment, and the severity of hyperhidrosis tightly correlated to the frequency of anti—TNF-α treatment supports the hypothesis of medication-induced hyperhidrosis. It is important to consider whether other medications may have contributed to hyperhidrosis in this case. The patient's medical history was notable for depression for which he was being treated with duloxetine. Duloxetine is known to cause hyperhidrosis via perturbation of serotonin and norepinephrine in the central nervous system and periphery.[3] Because the sweating occurred only after initiation of therapy for uveitis and colitis, duloxetine is unlikely the causative trigger of his hyperhidrosis. Prednisolone, a metabolite of prednisone, is also associated with hyperhidrosis but presumably because of its action on the glucocorticoid receptor and downstream effects of increased sympathetic activity.[3] Of note, prednisolone therapy has been used successfully to treat acquired idiopathic generalized anhidrosis.[4] Prednisone was initiated with adalimumab and could have contributed to the hyperhidrosis. However, the patient reports that the symptoms of hyperhidrosis remained the same even after tapering of the prednisone dose and initiated therapy on infliximab. Azathioprine is not associated with hyperhidrosis.[3]

The mechanisms by which medications induce hyperhidrosis likely entail a broad spectrum of pathways involved in eccrine gland regulation and thermoregulation, including the complex interplay between hormonal mediators and neurologic mechanisms, such as the corticolimbic system, hypothalamus-pituitary-adrenal axis, autonomic nervous system, and the external environment. Some mechanisms of drug-induced hyperhidrosis have been elucidated. For example, cholinesterase inhibitors induce hyperhidrosis by inhibiting breakdown of acetylcholine in the cholinergic-innervated eccrine glands.[3] Antidepressants induce hyperhidrosis by inhibiting reuptake of serotonin and dopamine in the central nervous system and norepinephrine at the sympathetic ganglia.[3]

Hyperhidrosis occurring in 2 related individuals strongly suggests possible genetic determinants of TNF-α—induced hyperhidrosis. Members of the TNF family of ligands (ectodysplasin, TNF, Rank ligand) are found to play a pivotal role in epithelial appendage morphogenesis from initiation to differentiation.[5] It is intriguing to consider a role for TNF family ligands not only in the development of eccrine glands but also in the ongoing homeostatic regulation of gland activity, as suggested by patients with ectodermal dysplasia (caused by ectodysplasin gene mutations) who present with hypohidrosis.[5] Homeostatic sweat regulation by TNF-α is likely complex and may result in reduced or increased sweating depending on the balance of cytokine networks. Overproduction of TNF-α may contribute to excessive sweating in cachectic patients in association with malignancy or infection.[6] A critical role for TNF-α in sweat regulation is suggested by the observation that thalidomide, which is found to decrease TNF-α production, may benefit cachectic patients from distressing sweating in clinical trials.[7] However, in genetically susceptible individuals, such as those described in this report, TNF-α alpha inhibitors may paradoxically result in secondary hyperhidrosis. This paradoxical impact of TNF-α blockade parallels reported cases of psoriasis or lupus erythematosus induced by TNF-α inhibitors,[8,9] which are in some cases effective treatments for these diseases; in these cases, the pathogenesis involves a disruption in cytokine balance, allowing unopposed interferon-alfa production, which may further stimulate T cells to generate TNF-α.[8]

The recent discovery of genetic factors associated with multiple drug-induced reactions predicts that additional genetic polymorphisms underlying TNF-α inhibitor—induced hyperhidrosis may be discovered.[10] Hyperhidrosis significantly impacts quality of life and presents a clinically challenging scenario; we highlight the successful management of our patient's hyperhidrosis with the anticholinergic drug, glycopyrrolate.

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