Ulerythema ophryogenes in association with *MAP3K1*-mutated Swyer syndrome

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INTRODUCTION

Swyer syndrome, also known as 46,XY gonadal dysgenesis, is a rare disorder of sexual development, involving sequence variations in the testes-determining genetic pathway. Patients are phenotypically female at birth and diagnosed in adolescence on workup for primary amenorrhea and delayed secondary sexual development. In 13% to 18% of the cases, the causative sequence variation occurs in the *MAP3K1* gene.[1] Ulerythema ophryogenes (UO), also known as keratosis pilaris atrophicans faciei, is a separate, rare cutaneous disorder characterized by inflammatory keratotic papules in the outer portion of the eyebrows, leading to scarring and alopecia.

To our knowledge, UO has not previously been associated with Swyer syndrome, although it has been associated with cardio-facio-cutaneous syndrome and Noonan syndrome; 2 conditions also caused by dysfunction of the MAPK pathway.[2] We describe an individual with known Swyer syndrome presenting with UO.

CASE REPORT

A 17-year old girl with Swyer syndrome presented with a history of eyebrow loss, bumps on her arms, and skin tags on her face. The eyebrow loss was localized to the lateral thirds of both eyebrows and had progressed over 3 months. She also reported skin-colored bumps on her arms, forearms, and thighs that had been present for years. Finally, she recently noted several skin tags on her face. She denied any family history of these conditions, and none were associated with itching or tenderness. She had not attempted any treatments.

Abbreviation used:

UO: ulerythema ophryogenes

Her past medical history was significant for anxiety, primary amenorrhea, gonadal dysgenesis, and tall stature, with the latter 3 symptoms reflecting congenital Swyer syndrome caused by a 1016G>A sequence variation (Arg339Gln) of the *MAP3K1* gene (confirmed with genetic testing). In her previous workup for primary amenorrhea, when she was 16 years old, a wrist x-ray had revealed a bone age of 14 years, and transabdominal ultrasound revealed a very small uterus with absent ovaries. Recent laboratory tests showed normal dehydroepiandrosterone sulfate, α-fetoprotein, lactate dehydrogenase, prolactin, and thyroid hormone levels. Her medications included an estradiol transdermal patch, medroxyprogesterone, and vitamin D supplementation. She was also scheduled for a bilateral gonadectomy for gonadal tumor prophylaxis.

Physical examination revealed a 6'0"-tall, phenotypically female patient with follicular hyperkeratotic papules on the lateral aspects of the arms, forearms, thighs, face, and lateral thirds of eyebrows. The lateral thirds of her eyebrows were additionally noted to have 1 cm-sized, localized areas of hair loss (Fig 1). A few scattered, soft, 1 to 2 mm-sized, flesh-colored, pedunculated papules were present on the face and left eyelid.

Based on the findings of hyperkeratotic papules with localization to the lateral aspect of the eyebrows, a clinical diagnosis of UO was made, with additional findings of keratosis pilaris on her arms

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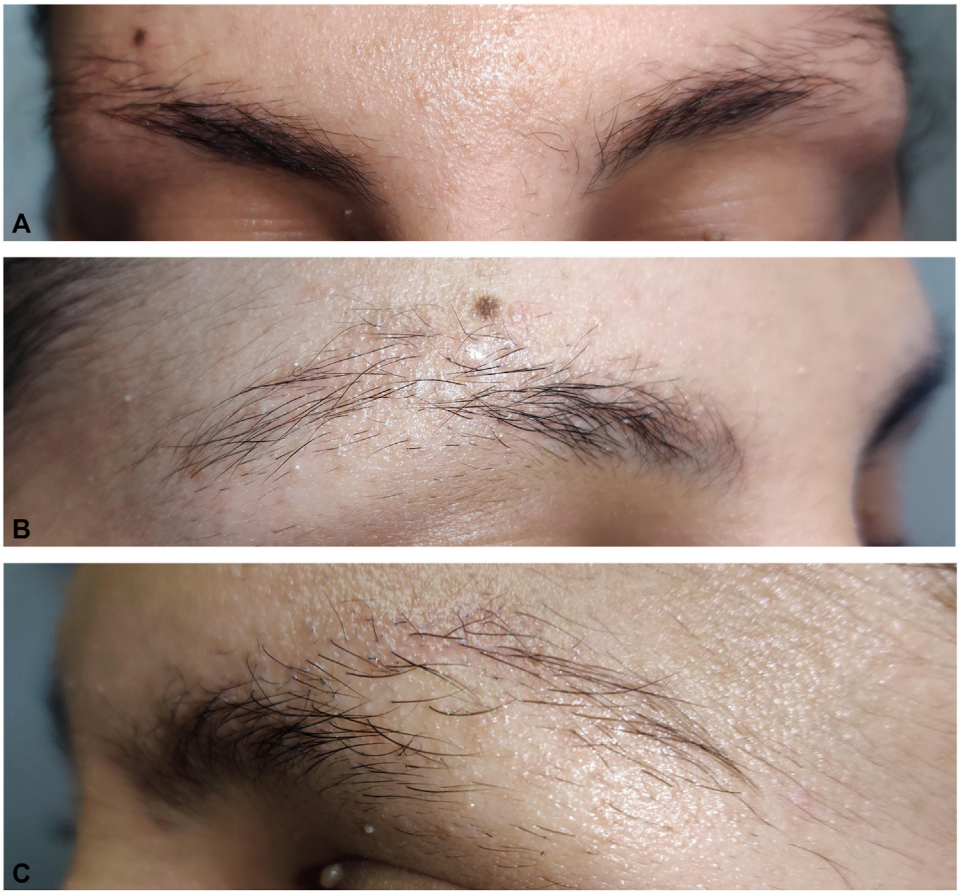

Fig 1. Ulerythema ophryogenes in a 17-year old patient with Swyer syndrome. Frontal aspect (**A**), lateral aspect of right side (**B**), and lateral aspect of left side (**C**) views of the eyebrows demonstrating alopecia and inflammatory keratotic papules in the outer portion of the eyebrows; findings characteristic of ulerythema ophryogenes also known as keratosis pilaris atrophicans faciei.

and legs, and skin tags on the face. Though UO typically improves after puberty, scarring in the affected areas can lead to permanent hair loss. The patient was prescribed adapalene gel mixed with desonide to apply to the eyebrows daily, and topical emollient containing α-hydroxy, β-hydroxy, and polyhydroxy acids to be applied twice daily to her arms, face, and thighs. The facial skin tags were monitored.

DISCUSSION

We describe a case of UO in a 17-year-old patient with Swyer syndrome (46,XY gonadal dysgenesis) caused by a missense sequence variation in *MAP3K1*. Neither have cutaneous manifestations of Swyer syndrome been previously described, nor has UO been documented in a patient with any disorder of sexual differentiation.

Although the etiology of UO is unclear, it has been associated with several other syndromes caused by sequence variations in the MAPK/Ras–signaling pathways, including, but not limited, to Noonan syndrome, cardio-facio-cutaneous syndrome, Rubinstein-Taybi syndrome, and Cornelia de Lange syndrome (Table I).[3-6] The patient described here had Swyer syndrome specifically caused by a 1016G>A sequence variation (Arg339Gln) in the *MAP3K1* gene, which has previously been described in only 1 patient.[7]

Hormone replacement therapy may have contributed to our patient's UO presentation. Although there are no documented cases of iatrogenically-induced UO, there is *in vitro*-based evidence that estrogen can promote keratinocyte proliferation, and our patient's UO symptoms roughly coincided with hormone replacement therapy.[8] However, our patient also had chronic keratosis pilaris preceding

Table I. RASopathies associated with cutaneous manifestations

Syndrome	Common gene sequence variations	Possible cutaneous manifestations
Noonan syndrome*	*PTPN11*, *SOS1*	Woolly or curly hair, plantar hyperkeratosis, ichthyosis, koilonychias, and multiple pigmented nevi, keratosis pilaris, sparse eyebrows, UO[5]
CFC syndrome*	*BRAF*, *MAP2K1*, *MAP2K2*, *KRAS*	Multiple melanocytic nevi, hair abnormalities; curly wavy, or scarce hair; keratinization disorders (KP, UO, palmoplantar hyperkeratosis)[2]
Costello syndrome‡	*HRAS*	Loose, redundant skin; cutaneous papillomas, palmoplantar hyperkeratosis, sparse eyebrows, keratosis pilaris[2]
Cornelia de Lange syndrome†	Various chromosomal rearrangements	Confluent eyebrows, curly eyelashes, general hirsutism, UO[6]
Rubinstein-Taybi syndrome†‡	*CREBBP*	Hirsutism, keloid formation, capillary hemangiomas, *café-au-lait* spots, abnormal dermatoglyphics, pilomatricomas, keratosis pilaris[4]
Swyer syndrome‡§	*MAP3K1*	Sparse eyebrows, UO, keratosis pilaris, facial skin tags

CFC, Cardiofaciocutaneous syndrome; *KP*, keratosis pilaris; *UO*, ulerythema ophryogenes.
*Strong association with cutaneous manifestations listed, including UO.
†Moderate association with cutaneous manifestations listed.
‡Possible association with UO.
§Present case.

therapy, therefore, the role of hormone replacement therapy in causing UO, if any, remains unclear.

Treatment of UO is challenging, and topical medications have been used with minimal success. Topical medications target multiple proposed mediators of the disease process, including topical steroids, tacrolimus, and pimecrolimus to decrease inflammation, retinoids to affect cell turnover, and topical keratolytics, such as urea, lactic acid, or salicylic acids to smoothen the skin and decrease follicular plugging. We treated our patient with a mild cleanser, low-potency topical steroids, a retinoid, and keratolytics. At her 3-month follow-up, the patient admitted to having difficulties adhering to her topical regimen. Although the patient's hair loss and inflammation did not progress, there was no significant improvement in the density of terminal hairs on the lateral aspect of the eyebrows or resolution of follicular hyperkeratosis.

Lasers have been trialed for the treatment of UO, including the pulsed-dye laser and intense pulsed-light lasers. Use of pulsed-dye laser at a 595-nm wavelength produced clinically significant improvement by reducing erythema, with complete resolution in 3/10 and >75% improvement in 7/10 included patients.[9] Although some cases may exhibit spontaneous resolution of associated inflammation and progression often halts after puberty, patients may experience permanent thinning or complete loss of hair from the lateral aspect of the eyebrows.[3]

In summary, we present a case of UO associated with Swyer syndrome. Our report adds to the growing knowledge about this rare and poorly understood condition and strengthens previous associations between UO and syndromes caused by sequence variations in the MAPK/Ras pathway. Research on the role of the MAPK/Ras pathway in keratinocyte survival, maturation, and differentiation may clarify the pathophysiology of UO and thus lead to more effective treatment options for this disease. Additionally, the recognition that patients with Swyer syndrome may be prone to developing UO provides an opportunity for early diagnosis and treatment to prevent permanent scarring and hair loss. Enhanced screening of patients with genetic disorders for cutaneous conditions may be warranted, especially for patients with syndromes that fall under the RASopathy umbrella.

Conflicts of interest

None disclosed.

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