Case Report

Eruptive Sebaceous Hyperplasia: A Case Report and Review of the Literature

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Abstract

Introduction
Eruptive sebaceous hyperplasia (ESH) is a benign process characterized by the acute onset and rapid proliferation of sebaceous glands, typically on the face. Although historically attributed to cyclosporine therapy, the preponderance of reports over the past 2 decades suggests a more complex etiology. There is increasing thought a combination of multiple medications as well as a genetic component contribute to ESH's clinical presentation. Despite these theories, the exact cause of ESH in immunosuppressive therapy is poorly understood.

Case Presentation
To our knowledge, we report the third case of ESH arising in multimodality immunosuppressive therapy, consisting of tacrolimus, mycophenolate mofetil, and prednisone, affecting a renal transplant patient. Our patient began cyclosporine monotherapy at an early age but did not see eruption of lesions until years later after following a multimodal therapy.

Conclusion
We discuss the association of ESH with other medical conditions and treatments. We hope this case sheds light on a possible complication of multimodal immunosuppressive therapy in renal transplant patients. This will allow patients and providers to be better informed of the pros and cons of different treatment options for immunosuppressive therapy in renal transplant patients.

Keywords
cyclosporine; eruptive sebaceous hyperplasia; sebaceous gland diseases; immunosuppression therapy; mycophenolate mofetil; prednisone; renal transplant; sebocytes; tacrolimus

Introduction
Eruptive sebaceous hyperplasia (ESH) most commonly presents on the face as multiple pink- to yellow-tinged papules with central umbilication.[1-4] ESH was originally reported among renal transplant patients and is believed to be a complication of cyclosporine therapy (affecting up to 30% of this group).[1,3] More recently, multiple cases outside the renal transplant setting have been reported, suggesting a more complex etiology (**Table 1**). Over the past 2 decades, 13 cases of ESH have been reported in the English medical literature. Five of these cases affected non-renal transplant patients.

Case Presentation
A 38-year-old male with a history of 2 renal transplants for congenital hydronephrosis presented for evaluation of multiple facial lesions that developed over 2 years. The patient underwent his first renal transplant in 1984 when he was started on cyclosporine. He underwent a second renal transplant in 2007, at which time he was started on a multimodality immunosuppressive regimen consisting of prednisone (5 mg daily), tacrolimus (0.5 mg), and mycophenolate sodium (360 mg). In 2017, he noted the acute onset of raised lesions on his face that slowly increased in number. His most recent ex-

Table 1. Cases of ESH Reported in the English Medical Literature

Reference	Age/Sex	Medications	History
Marini et al, 2001[5]	41/M	• Cyclosporine (3 mg/kg qd) • Prednisone (unknown dose)	**Bone marrow transplant** Chronic myeloid leukemia ESH developed 5 years after BMT
Boschnakow et al, 2003[6]	33/M	• Cyclosporine (2 mg/kg qd) • Prednisolone (0.07 mg/kg qd) for 10 years	**Renal transplant** ESH developed 9 years after first kidney transplant
	66/M	• Cyclosporine (2.5 mg/kg qd) • Prednisolone (0.06 mg/kg qd) for 23 years	**Renal transplants** (1978, 1991) ESH developed 7 years after second kidney transplant
Yamamoto et al, 2009[2]	68/M	• Medically managed • No immunosuppression or transplant history	**Chronic renal failure** (Cr 7.8 mg/dl, BUN 82 mg/dl) ESH developed prior to hemodialysis
	58/M	• Managed with dialysis • No immunosuppression or transplant history	**Chronic renal failure** (Cr 12.3 mg/dl, BUN 97 mg/dl) ESH developed after initiation of dialysis
Yayli et al, 2010[7]	55/M	• Cyclosporine (5 mg/kg qd) with gradual reduction over 1 year (to 2 mg/kg qd) • Prednisolone (unknown dose) for 9 years	**Renal transplant** ESH developed 4 years into treatment
McDonald et al, 2011[8]	36/M	• Cyclosporine (60 mg bid) • Azathioprine (75 mg qd) • Prednisolone (5 mg qd) • Doxycycline (50 mg qd)	**Renal transplant** ESH developed 15 years into cyclosporine, azathioprine, and prednisolone treatment. Patient was taking doxycycline for rosacea during presentation of ESH
	45/M	• Cyclosporine for 9 years, then discontinued • Prednisolone (5 mg qd), followed by • Tacrolimus (3 mg bid) • Mycophenolate mofetil (1.5 g qd) • Doxycycline (50 mg qd)	**Renal transplants** (1991, 2003) ESH developed during cyclosporin treatment; lesions increased in number after discontinuation of cyclosporine and initiation of prednisone/tacrolimus/mycophenolate mofetil
Cortés et al, 2016[4]	69/M	• Cyclosporine (350 mg qd)	**Bone marrow transplant** Acute myeloid leukemia ESH developed 7 months after initiation of cyclosporine
Jung et al, 2016[9]	40/M	• Cyclosporine (350 mg qd) • Prednisolone (7.5 mg qd) for 11 years followed by • Tacrolimus (6 mg qd) • Prednisolone (5 mg qd) for 4 years	**Renal transplant** ESH developed during treatment with cyclosporine and prednisolone; lesions increased in number after discontinuation of cyclosporine and initiation of tacrolimus and prednisolone therapy
Levandoski et al, 2017[1]	29/M	• Tacrolimus (6 mg bid), • Mycophenolate mofetil (500 mg qid) • Prednisone (20 mg qd)	**Renal transplants** (2006, 2015) ESH developed 2 weeks after initiation of immunosuppressive therapy
Ranasinghe et al, 2018[3]	46/M	• Prednisone (40 mg qd) • Long standing cholestyramine and mercaptopurine therapy	**Crohn's disease** ESH developed two weeks after starting prednisone therapy
Steinmetz et al, 2023	38/M	• Cyclosporine (unknown dose) during childhood, discontinued 20+ years ago • Prednisone (5 mg qd) • Tacrolimus (0.5 mg qd) • Mycophenolate sodium (360 mg qd) • Amlodipine (5 mg qd) • Febuxostat (40 mg qd) • Terazosin (2 mg daily)	**Renal transplants** (1984, 2007) ESH developed 2-3 years ago (10 years after initiating immunosuppressive therapy consisting of tacrolimus, prednisone and mycophenolate sodium

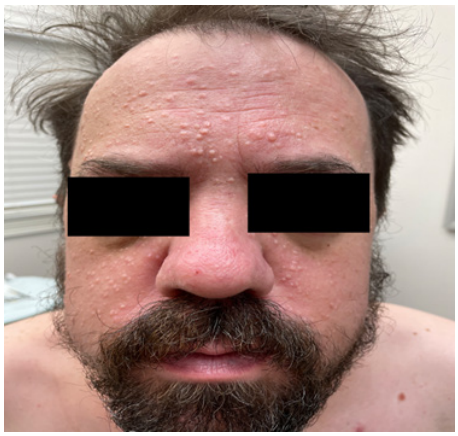

Figure 1. A 38-year-old male presented with numerous pink-yellow papules diffusely distributed over his face.

amination was notable for numerous pink-yellow papules with central umbilication diffusely distributed over his entire face (**Figure 1**). Currently, there is no definitive treatment for ESH. All treatment is purely cosmetic. A biopsy of a characteristic lesion showed histologic findings consistent with sebaceous hyperplasia (**Figure 2**).

Discussion

To date, 13 cases of ESH have been reported in the English medical literature. All cases affected men either being managed for chronic renal failure (CRF) or being treated with systemic immunosuppressive medications in the setting of allogeneic transplantations (renal and bone marrow) and autoimmune disease (ie, Crohn's disease). Of note, patients with existing or pre-existing renal disease (eg, chronic renal failure and renal disease resulting in transplantation) accounted for the majority (10/13; 77%) of cases, both in the presence or absence of immunosuppression. The predominance of ESH among adult men has been attributed to undefined genetic factors and unique characteristics of the pilosebaceous unit.[4-7] In support of this assertion, no cases of ESH have been reported among women (or children). An autosomal dominant pattern has also been reported within families, suggesting a heritable component.[5]

At the onset of his ESH, our patient was on a multimodal immunosuppressive regimen consisting of tacrolimus, mycophenolate mofetil, and prednisone. Among all reported cases, ESH arose or was exacerbated in the setting of this regimen (3/13; 23% of patients; **Figure 3**). Among patients with pre-existing ESH attributed to the use of cyclosporine (2/13; 15% of cases), those treated with this combination of medications experienced a worsening of their condition. In both cases, tacrolimus, mycophenolate mofetil, and prednisolone were substituted for cyclosporine (with or without prednisolone), suggesting that these medications were suffi-

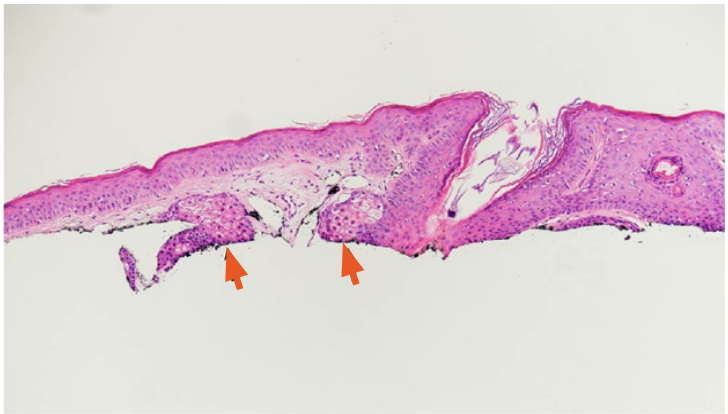

Figure 2. A shave biopsy of a representative lesion shows the superficial portion of enlarged mature sebaceous glands (orange arrows) in close proximity to the epidermis and a follicular unit (HE stain, 10x magnification).

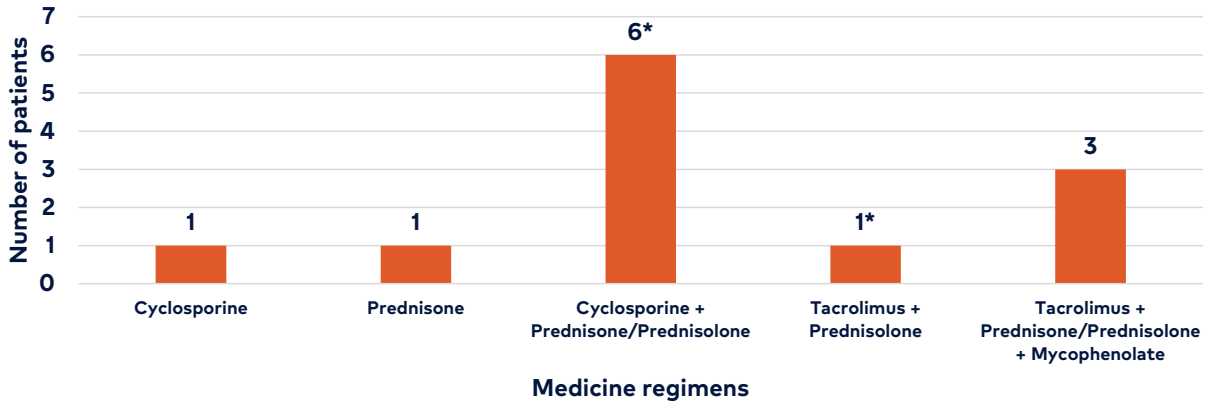

Figure 3. A graph shows the medication(s) regimes associated with the occurrence of ESH.
*Includes a patient represented twice. The subject patient developed ESH on a treatment regimen consisting of cyclosporine and prednisone; tacrolimus was eventually substituted for cyclosporine at which time the patient experienced disease progression.

cient to sustain the proliferation of sebaceous glands in the absence of cyclosporine. In our case report, cyclosporine was administered after the patient's first transplant (during early childhood) and discontinued decades before the onset of his cutaneous findings, suggesting either an unlikely delayed reaction to cyclosporine or a response to the multimodal regimen.

It has been hypothesized that lipophilic drugs (such as cyclosporine, prednisone, and tacrolimus) promote their accumulation in sebaceous glands, stimulating hyperplasia. Tacrolimus and cyclosporine share many physiochemical properties. Both are calcineurin inhibitors that suppress the production of proinflammatory cytokines.[9] The high lipid solubility of these drugs promotes their accumulation in the skin, resulting in abnormal epithelial cell proliferation.[9] It has also been postulated that the effect of prednisone on the reduction of systemic androgens leads to a reduction in sebocyte turnover.[3] The absence of any reported cases of ESH associated with prednisone monotherapy suggests that prednisone alone is not sufficient to induce this condition.

We have presented a novel report on ESH arising in the setting of mycophenolate monotherapy. Through our literature search, we could not identify another case quite like ours. Among reported cases, it has always been prescribed with tacrolimus, either in combination with or without prednisone. Because systemic tacrolimus is rarely used as a monotherapy, it is difficult to determine the full extent of its contribution to ESH pathogenesis.

It is difficult to draw a definitive link between ESH and specific disease states. However, there does appear to be an association between ESH and renal failure (**Figure 4**). Two cases of ESH were reported in patients with chronic renal failure (in the absence of immu-

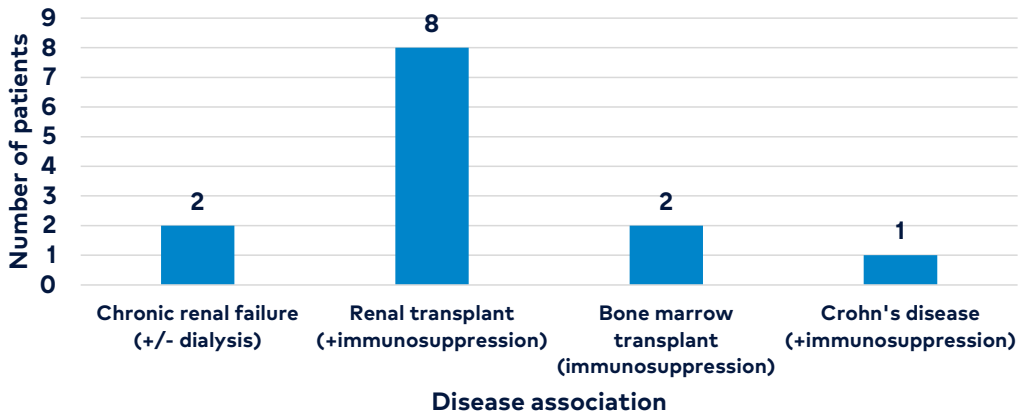

Figure 4. A graph shows reported disease states occurring with ESH.

nosuppressive therapy or renal transplantation). In one case, the patient was being treated with hemodialysis. It has been postulated that the interaction between blood and the dialytic membrane releases cytokines that stimulate sebocyte proliferation.[2]

Although 1 case of ESH was reported in a patient afflicted with Crohn's disease, there have been no other reports of ESH arising in the setting of inflammatory bowel disease. We suspect the patient's immunosuppressive regimen (prednisone and mercaptopurine) may have contributed to the onset of his ESH. In this case, the authors hypothesized that decreased androgen production due to prednisone therapy, age, and drug deposition in the sebaceous glands predisposed the patient to this condition.[3]

To date, there are no definitive treatments available for ESH. Management is aimed at cosmetic improvement. Strategies encompass those currently used to manage sebaceous hyperplasia, ranging from destructive techniques (eg, electrocautery, cryotherapy, CO_2 laser) to systemic treatments (eg, isotretinoin), and photodynamic therapy.[10]

Conclusion

ESH appears to be a disease limited to men and is strongly associated with drug-induced immunosuppression in multiple clinical settings. These drugs include cyclosporine, prednisone, mycophenolate mofetil, and tacrolimus. Further study is warranted to characterize the complex interactions and mechanisms underlying the onset and progression of ESH in the setting of renal disease, allogeneic transplantation, and other systemic inflammatory disorders requiring immunosuppression.

Conflicts of Interest

The authors declare they have no conflicts of interest.

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