Oral tacrolimus for ocular involvement in pediatric neutrophilic dermatoses

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INTRODUCTION

Neutrophilic dermatoses (ND), including pyoderma gangrenosum (PG) and Sweet syndrome (SS), are rare in children. One study showed that only 2% of PG cases occurred in patients younger than 18 years old.[1] While both disorders are associated with extracutaneous features, ocular involvement is uncommon and often a diagnostic challenge. One French case series found ocular involvement in less than 15% of the 27 pediatric patients with PG or SS.[2] Ocular manifestations include conjunctivitis, iritis, scleritis, and retinal vasculitis.[3] Periorbital inflammation and eyelid lesions are also considered ocular manifestations, as eyelid lesions can lead to decreased visual acuity and occasionally vision loss.[4,5] Most of the current literature describes ocular involvement in adults and highlights the risk of misdiagnosis as cellulitis or other bacterial infections, chalazion, or malignancy, resulting in inappropriate treatment.[4,5] Early recognition and timely initiation of immunosuppressive therapy are imperative to prevent ocular damage and unnecessary antimicrobial exposure. To our knowledge, only 9 case reports have been published detailing the ocular manifestations of ND in pediatric patients,[6-10] and even more limited data exists regarding the optimal treatment. We report 2 additional children with ocular manifestations of ND, refractory to other immunosuppressants, with excellent response to systemic tacrolimus.

Abbreviations used:

ND: neutrophilic dermatosis
PG: pyoderma gangrenosum
SS: Sweet syndrome

CASE REPORT

Case 1 is a 15-year−old female with a history of dermatitis herpetiformis and juvenile idiopathic arthritis currently treated with subcutaneous methotrexate and intravenous tocilizumab, who presented with 2 weeks of worsening joint pain and new skin findings. Skin examination showed diffuse, indurated papules and plaques, a painless, violaceous nodule of the left upper eyelid (Fig 1, *A*), and right-eye conjunctivitis. Ophthalmologic examination showed normal visual acuity and intra-ocular pressures, but her right bulbar conjunctiva had an unusual follicular reaction inconsistent with viral conjunctivitis. Her left eyelid lesion was clinically suggestive of a chalazion. A biopsy of a leg papule demonstrated an intense superficial and deep dermal perivascular and interstitial infiltrate of neutrophils consistent with SS. She was then started on intravenous methylprednisolone with substantial improvement in her skin lesions, eyelid lesion, conjunctivitis, and joint pain. With the unusual follicular reaction of the bulbar conjunctiva and improvement with steroids, the eye findings were recognized as manifestations of SS, rather than a viral process or chalazion.

For her SS, topical clobetasol ointment and oral dapsone were added as prednisone was tapered. Simultaneously, and due to persistent arthritis, tocilizumab was replaced with rituximab infusions. Despite dapsone, methotrexate, and rituximab, she

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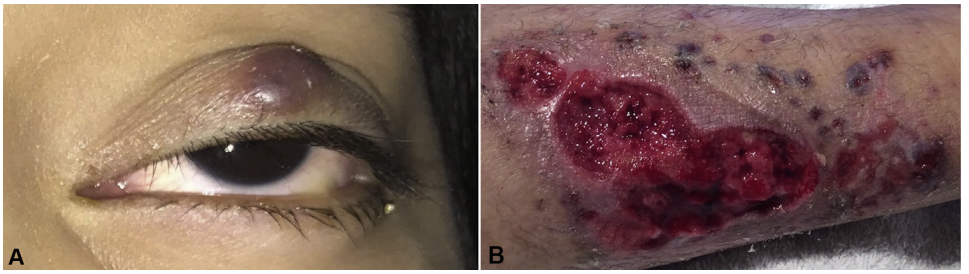

Fig 1. **A**, Eyelid lesion on presentation. **B**, Untreated leg ulcer.

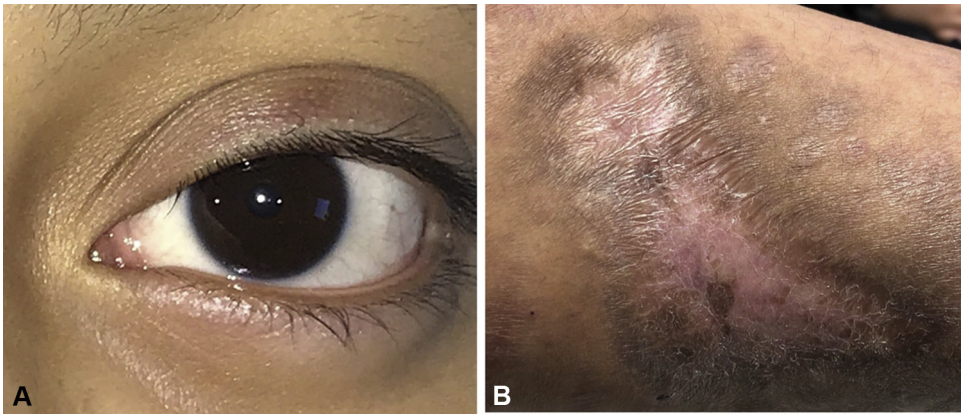

Fig 2. **A**, Eyelid lesion 6 months after initiation of tacrolimus. **B**, Leg ulcer 6 months after initiation of tacrolimus.

developed a persistent leg ulcer (Fig 1, *B*) and recurrence of her right-eye conjunctivitis when her prednisone was tapered off. Dapsone and methotrexate were then discontinued, and she was trialed on tacrolimus 3 mg orally twice daily. The addition of tacrolimus resulted in the resolution of ocular and cutaneous lesions over 6 months and spared her from additional systemic steroids (Figs 2, *A* and 2, *B*). She continued rituximab for juvenile idiopathic arthritis and resumed oral dapsone for a dermatitis herpetiformis flare. Three years after her SS diagnosis, the patient continues to do well with no exacerbations of SS, including ocular involvement, and no side effects from combination immunosuppressive therapy.

Case 2 is a 12-year–old girl with a history notable for juvenile idiopathic arthritis, previously treated with methotrexate, who was referred to dermatology for new acneiform facial lesions and recurrent skin lesions. Since she was 5 years old, she also had a history of presumed septic arthritis, recurrent, culture-negative cutaneous abscesses (including on the upper eyelids), and 1 episode of left eye periorbital cellulitis, all refractory to systemic antimicrobials. One particular eyelid abscess took over 2 months to resolve, despite treatment with prolonged topical and oral antimicrobials. Skin examination showed painful, erythematous, and ulcerated plaques on her chest and face and

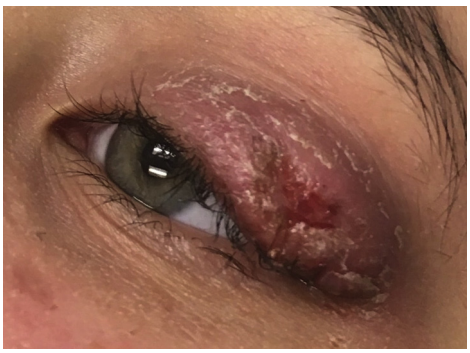

Fig 3. Eyelid lesion on presentation.

acneiform facial lesions. A biopsy of a left breast cutaneous lesion demonstrated dense mixed dermal inflammation with fibrosis, including areas of dense neutrophilic inflammation, consistent with PG. She was subsequently started on topical dapsone and clobetasol ointment, but continued to develop new skin and eyelid lesions (Fig 3). She was quickly escalated to oral steroids with only temporary improvement.

Five months after initial presentation, she was diagnosed with PAPA syndrome (pyogenic arthritis, PG, cystic acne) after sequencing identified a known pathogenic mutation in the *PSTPIP1* gene.[11] Adalimumab subcutaneous therapy was initiated

Table I. Cases of ocular involvement in pediatric neutrophilic dermatoses in the literature

Age, y	ND	Ocular involvement	Associated disease	Ineffective treatments	Regimen to achieve disease control	Study
2	SS	Scleral injection	Cutis laxa	N/A	Oral steroids	Guhamajumdar and Agarwala[6]
3	SS	Conjunctivitis	N/A	N/A	Oral steroids	Koppelhus et al[7]
3	PG	Eyelid lesion	N/A	N/A	Oral steroids	Bromeo and Suller[8]
6	SS	Erythematous swelling	*Mycoplasma*	N/A	Oral steroids	Hsieh, Yalcindag, and Coghlin[9]
9	SS	Eyelid lesion	CVID	IV and oral steroids Oral colchicine Oral dapsone SC anakinra Oral cyclosporine	IV tocilizumab + oral lenalidomide	Cook et al[10]
12	PG	Eyelid lesion	PAPA syndrome	IV and topical steroids Topical dapsone	SC adalimumab + oral tacrolimus	Present study
15	SS	Conjunctivitis, eyelid lesion	JIA	IV, oral, and topical steroids Oral dapsone SC methotrexate IV tocilizumab	IV rituximab + oral tacrolimus	Present study

CVID, Common variable immunodeficiency; *IV,* intravenous; *JIA*, juvenile idiopathic arthritis; *ND,* neutrophilic dermatosis; *PAPA*, pyogenic arthritis, pyoderma gangrenosum, cystic acne; *PG,* pyoderma gangrenosum; *SC,* subcutaneous; *SS,* Sweet syndrome.

and resulted in the improvement of existing lesions, but did not prevent new lesions. Tacrolimus 2 mg orally twice daily was added and titrated to 3 mg twice daily over 3 months. The addition of tacrolimus resulted in significant improvement over 6 months with resolution of the eyelid lesion and only rare cutaneous lesions now responsive to topical dapsone and topical steroids. Four years from her PAPA syndrome diagnosis, the patient maintains good disease control without recurrence of her ocular involvement, acne, or arthritis. The patient has also tolerated the combination of adalimumab and tacrolimus without adverse effects.

DISCUSSION

Ocular manifestations are uncommon presentations of ND, and reports of pediatric patients are very limited. Table I summarizes data from 5 articles reporting on the presentation and treatment of ocular manifestations in pediatric patients with ND. Four additional patients were described in the French cohort, but information on their underlying ND diagnosis and treatment was not included.[2] Of those patients with ND with ocular involvement, one quarter were less than 2 years old, highlighting that extracutaneous manifestations, including ocular ones, occur more frequently in infants than previously reported. Their presentations included scleritis, episcleritis, palpebral edema, conjunctivis, and superficial keratitis. Please see Appendix A (available via Mendeley at doi: 10.17632/vcstt8nwvs.1) for a detailed description of the literature search.

Due to disease rarity and variable presentations of ocular involvement in ND, patients often suffer delays in diagnosis and therapy. Relatedly, the cases described in the present study were initially misdiagnosed, specifically with a chalazion and viral conjunctivitis (Case 1) and an abscess (Case 2). Case 2 also received unnecessary and prolonged antimicrobial treatments prior to diagnosis.

Given the limited literature, little data exists regarding the optimal treatment of ND, particularly ocular manifestations in children. Oral steroids achieved disease control in all but 1 patient in Table I; that patient had underlying immunodeficiency. Systemic tacrolimus is an immunomodulating agent found to have positive outcomes in adults with ND and one pediatric patient with PG.[12,13] Notably, this pediatric patient was only 11 months old at diagnosis, again illustrating the importance of maintaining a high index of diagnostic suspicion in infants. Our cases demonstrate how both the skin and ocular manifestations of ND can be challenging to treat and potentially refractory to steroids and other immunosuppressants. Our patients achieved

remission only after adding systemic tacrolimus. Systemic tacrolimus was preferred over cyclosporine due to the success reported in the adult literature and its more favorable side effect profile with chronic use, including less hypertension, hypertrichosis, and gingival hyperplasia.[14]

In conclusion, ocular manifestations of ND are uncommon and underrecognized. Our cases add to the limited literature and suggest that oral tacrolimus may be helpful and well-tolerated. Further study is needed to fully define the role of tacrolimus in the treatment of ND.

Conflicts of interest

None disclosed.

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