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Periorbital necrotizing sweet syndrome: A report of two cases mimicking necrotizing soft tissue infections

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ABSTRACT

Purpose: Two cases are described of necrotizing Sweet syndrome (nSS), a rare variant of acute febrile neutrophilic dermatosis that mimics necrotizing soft tissue infections.
Observation: A 74-year-old female with myelodysplastic syndrome (MDS) presented with isolated periorbital nSS that closely mimicked necrotizing fasciitis (NF); she displayed pathergy to debridement, was exquisitely responsive to corticosteroids, and underwent successful first-stage reconstruction of the eyelid with full-thickness skin grafting. A second 40-year-old female patient with relapsed acute myelogenous leukemia (AML) presented with multifocal nSS most prominently involving the eyelid. Positive herpes zoster virus (HSV) PCR and bacterial superinfection complicated the diagnosis. She improved with chemotherapy for AML and corticosteroid therapy.
Conclusion: nSS is rare and a high level of clinical suspicion as well as an understanding of its distinguishing features is necessary to avoid undue morbidity. Identification of pathergy, histopathology, microbiology, and clinical context are critical to avoid misdiagnosis of infection.

1. Introduction

Classic Sweet syndrome (SS) is a neutrophilic dermatosis along a spectrum with pyoderma gangrenosum that typically presents acutely with fever and multifocal, tender, erythematous, cutaneous plaques or nodules, often with overlying vesicles.[1] The etiology of SS remains elusive, but the disease process is thought to stem from a cytokine mediated hypersensitivity reaction that may be idiopathic or triggered by an infection, medication, or malignancy.[1] Hematologic malignancies have been found to be most frequently associated with SS, in particular acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS).[1] Considering the immunocompromised status of these patients and the somewhat overlapping clinical presentation of SS with infection, including fever and leukocytosis with neutrophilia, SS may be misdiagnosed as a skin or soft tissue infection.[1] Necrosis is rare in SS; however a necrotizing variant has also been recognized which can mimic necrotizing fasciitis (NF). Limited reports have documented necrotizing Sweet syndrome (nSS), with only two involving the periorbital region.[2–4] NF is primarily treated with aggressive surgical debridement. SS, as with other neutrophilic dermatoses, shows pathergy and is instead treated with corticosteroids and immunosuppression. It is therefore crucial to establish diagnostic distinction. Herein, we discuss two patients with hematologic malignancies who presented with atypical cases of periorbital SS mimicking infection. This report includes the first presentation of the reconstruction of a patient with SS who initially underwent serial debridement for suspected NF. These cases emphasize the importance of early recognition of SS and alert ophthalmologists and ophthalmic pathologists to include neutrophilic dermatoses in the differential diagnosis of a necrotizing soft tissue process, along with infection.

Case 1. A 74-year-old female with high-risk MDS actively treated with azacytidine was transferred from an outside hospital for progressive worsening of a presumed left upper eyelid (LUL) necrotizing soft tissue infection (Fig. 1A). At transfer, she had received 5 days of systemic antibiotics, including intravenous (IV) clindamycin, and had undergone incision and drainage of a LUL abscess with drain placement (Fig. 1B). She denied any inciting event, including trauma or an insect bite, or lesions elsewhere on her body. On presentation, she was febrile to 103 °F

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and tachycardic, with exquisite LUL tenderness. Examination revealed diffuse edema, induration and erythema of the eyelid skin with scattered vesicles, extending to the frontalis and pre-auricular skin. The area surrounding the prior incision site was violaceous with a necrotic appearing crust. Visual acuity (VA) was 20/20 in the right eye (OD) and 20/100 in the left eye (OS) without a relative afferent pupillary defect (rAPD), and intraocular pressures (IOPs) were 14- and 25-mm Hg, respectively. She had left conjunctival injection and chemosis, and her dilated examination was normal in both eyes (OU). Computed tomography (CT) of the orbits demonstrated thickened, edematous left preseptal tissues with interval increased inflammatory changes, interval extension of inflammation into the left facial superficial soft tissue, as well as a new 2.5 cm enhancing hypodensity near the drain abutting the anterior aspect of the globe, when compared to imaging from three days prior. Her laboratory values were notable for a white blood cell count (WBC) of 7.48 K/μL (59.9% neutrophils, absolute neutrophil count of 4.48 K/μL), hemoglobin of 7.8 g/dL, markedly elevated C-reactive protein of 299.6 mg/L, and a Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score of 8, with a positive predictive value of 93.4%, suggestive of NF. She was continued on broad spectrum IV antibiotics; antiviral and antifungal medications were also added. Due to the rapid progression of periorbital necrosis and induration over the course of several hours, the patient was taken for additional urgent debridement.

Intraoperatively, she was found to have pale and firm necrotic tissue with "dishwater fluid" drainage, and surgical instruments could be passed freely through the left periorbital soft tissue planes. A subcutaneous debridement was performed initially. Post-operative assessment within 12 hours revealed marked progression of affected tissue (Fig. 1C) with firm induration extending well past the areas of prior debridement associated with persistent fevers, prompting a second urgent and more aggressive debridement (Fig. 1D). Expedited pathology showed extensive full-thickness epidermal, dermal, and soft tissue necrosis (Fig. 2A) with a very dense dermal neutrophilic inflammatory infiltrate, edema, and vascular damage in the form of endothelial cell atypia and erythrocyte extravasation (Fig. 2B) without microorganisms. The differential diagnosis of a neutrophilic dermatosis was raised, particularly given the patient's known MDS, and the fact that she was worsening with additional debridement. Bacterial and fungal cultures from both institutions showed no growth. Dermatology was consulted and felt the character of the adjacent viable skin was indeed consistent with a neutrophilic dermatosis; punch biopsy adjacent to the necrotic area showed papillary dermal edema and a dense dermal neutrophilic infiltrate without vasculitis (Fig. 2C). Following multidisciplinary discussion, IV methylprednisolone was initiated at 75 mg, which resulted in marked and rapid clinical improvement with resolution of spreading erythema, pain, and fevers within two days. The patient was transitioned to oral prednisone with a slow taper. After ten days of corticosteroid treatment, a first-stage reconstruction of the left upper and lower eyelids and upper cheek utilizing a divided anterior chest wall full thickness skin graft (FTSG) was performed (Fig. 3A and B). During post-operative month one, her MDS progressed, postponing her planned stem cell transplant. At 3.5 months, the FTSG appeared healthy, and she demonstrated retention of some left orbicularis and levator function (Fig. 3C**);** second-stage reconstruction is planned.

Case 2. A 40-year-old female with a history of relapsed, refractory AML presented with acute tenderness, erythema, and swelling of the right upper eyelid (RUL), in the setting of evolving multifocal tender upper and lower extremity papules. She was afebrile with a white blood cell count of 1.59 K/μL (28% neutrophils and absolute neutrophil count of 0.45 K/μL). One year prior, she had been diagnosed with herpes simplex virus (HSV) as well as SS of the RUL and extremities, treated with antiviral and oral corticosteroid therapy. Examination revealed an indurated, edematous RUL with overlying weeping vesicles and a deep violaceous hue (Fig. 4A). Her VA was 20/20 OU without an APD, and IOPs were 12 and 15 mmHg OD and OS. She had full EOMs and normal dilated fundus examination. CT of the orbits demonstrated preseptal soft tissue changes extending to the zygomatic region. In addition, she was found to have tender, erythematous papules of the left upper extremity and bilateral lower extremities, presumed to be insect bites occurring during a recent outdoor exposure. Biopsies and cultures performed on the RUL lesions returned positive for HSV-1 and coagulase negative staphylococcus. She received IV acyclovir and broad-spectrum antibiotics but became febrile to 103 °F while her facial lesions became necrotic and developed an eschar (Fig. 4B). Additional areas of involvement developed at venipuncture sites (Fig. 5A–D). Lesions on her right temple and lower extremity were biopsied by dermatology.

Pathology revealed dermal neutrophilic infiltrates with areas of necrosis, no microorganisms of both sites, and no vasculitis, most consistent with SS, particularly given her history of such. She was initiated on IV methylprednisolone 80 mg daily and maintained on a slow taper of IV

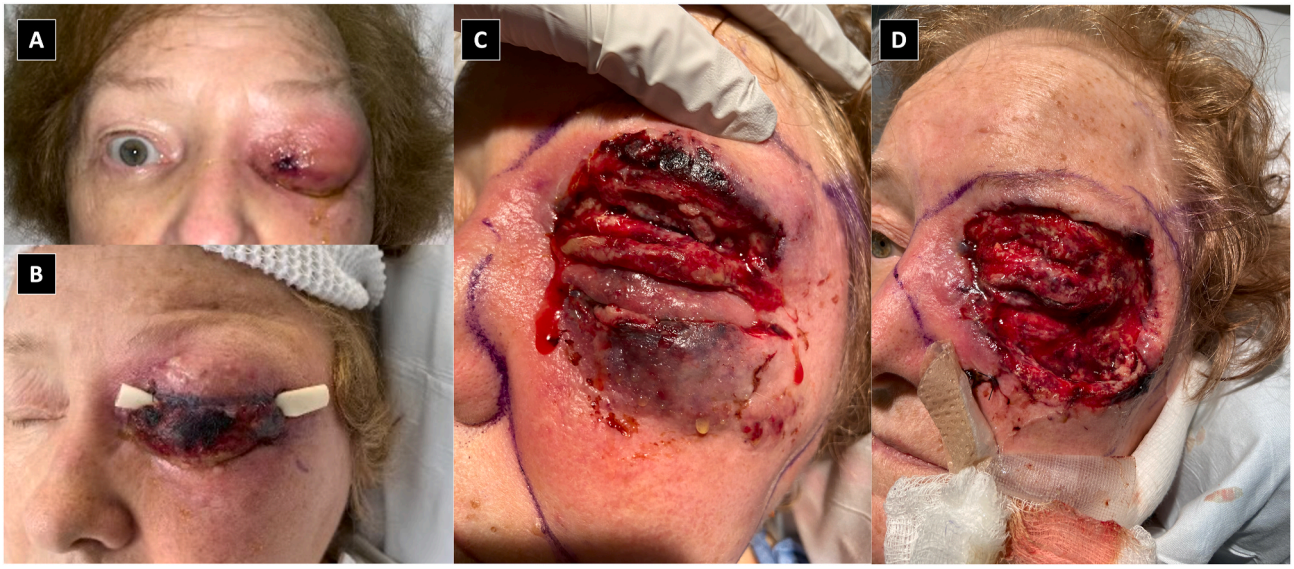

Fig. 1. Case 1 clinical photographs. A) Left upper eyelid (LUL) swelling, erythema, and edema with vesicular lesions and foci of necrosis at initial presentation to the outside hospital; B) LUL following initial incision and drainage at outside facility with Penrose drain in place, C) LUL following first debridement, D) LUL following second debridement one day after the first debridement.

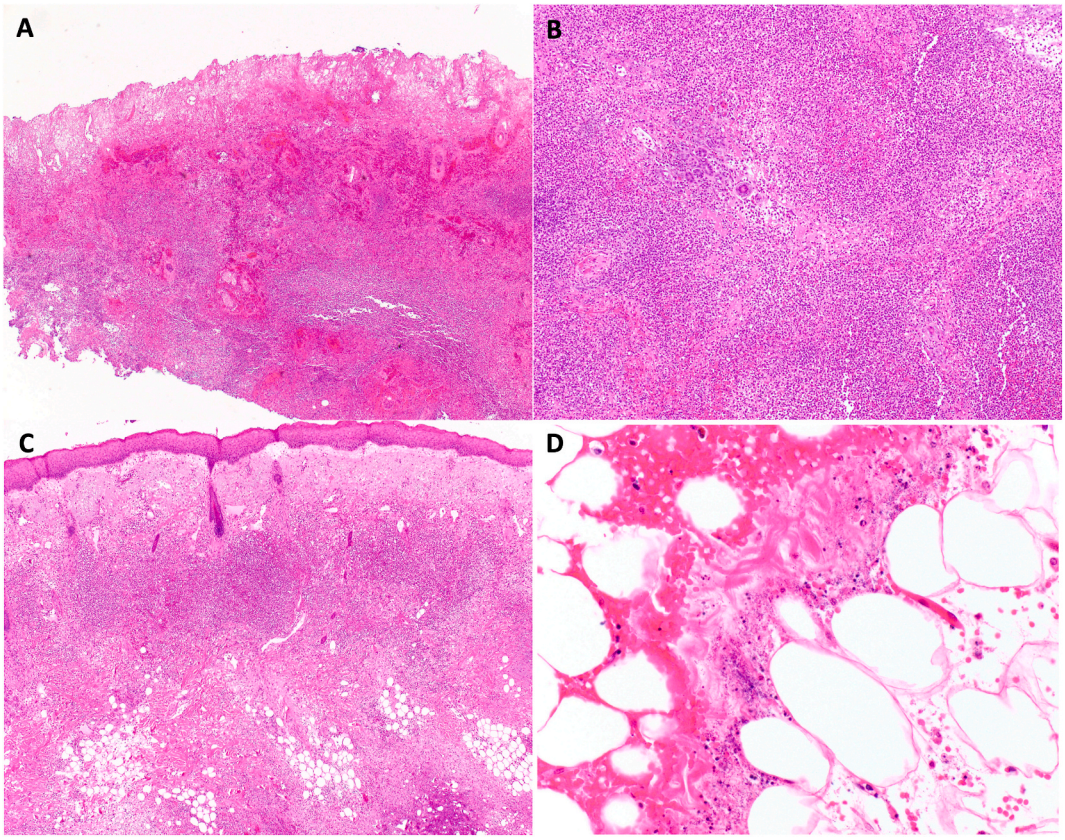

Fig. 2. Histopathology, Case 1. A) Debrided tissue shows full-thickness epidermal, dermal and soft tissue necrosis with a dense inflammatory infiltrate. B) The inflammatory infiltrate is neutrophilic in nature with leukocytoclasia and vascular damage. C) Adjacent to the necrosis, there is papillary dermal edema as well as a marked dermal neutrophilic infiltrate. D) In necrotizing fasciitis (different patient), bacterial cocci are readily identifiable in devitalized tissue; the inflammatory infiltrate is much more subtle. (A-D, hematoxylin and eosin, 4x, 10x, 4x, 60x).

corticosteroids over the next two weeks. Simultaneously, she was initiated on FLAG-IDA-venetoclax for maximal immunosuppression and management of her underlying relapsed AML, per oncology. Over the course of a few days, she developed new areas of necrosis over the right face crossing over her nasal bridge. Following that, she began to show clinical improvement over the subsequent weeks with sloughing of her eschars revealing underlying vitalized tissue and without significant sequelae to the RUL structure or function (Fig. 6A–C). She remained admitted for AML treatment and her oral prednisone was tapered over several weeks.

2. Discussion

Initially described as a distinct variant of classical SS in 2012 by Kroshinsky et al., nSS is marked by the characteristic clinical features of SS such as tender, erythematous plaques and nodules, accompanied by fever and systemic symptoms.[2] In contrast to classic SS, significant tissue necrosis is also present. The acute and rapidly progressive clinical presentation can closely resemble NF. Therefore, a high level of clinical suspicion for nSS is crucial, particularly in patients with myeloid neoplasms who show clinical features of pathergy or altered tissue reactivity in response to minor trauma. Pathergy was apparent in both patients in this series but manifested differently. Patient 1 demonstrated pathergy in the form of worsening, rather than improving, clinical examinations following sequential debridement. The second patient developed additional lesions at venipuncture sites, in addition to at the site of an HSV outbreak.

Histopathology is also helpful; a very dense neutrophilic infiltrate in the absence of microorganisms, particularly in the setting of papillary dermal edema, also supports the diagnosis of a neutrophilic dermatosis. Rapid histopathologic assessment or consideration of use of frozen sections and/or intraoperative gram stain should be considered.[5] Alternatively, if the suspicion for nSS is high and debridement is not pursued, a punch biopsy of adjacent indurated, but non-necrotic skin, may be performed. In typical necrotizing fasciitis (Fig. 2D), initial gram stain is typically revealing, and cultures grow rapidly. In angioinvasive fungal infections, hyphae are readily visible on histopathology. The absence of such features should raise alternative differential diagnostic considerations. It is also important to consider that infection and SS are not mutually exclusive. An additional clinical feature that may serve as a helpful diagnostic clue is the presence of vesicles or pustules, which were noted in both patients described herein. This feature is included as an occasional finding in the proposed major diagnostic criteria for SS.[6]

While the immunocompromised state of hematologic malignancies is associated with SS, immunocompromise is also associated with NF. The treatment of periorbital NF can range from medical therapy alone to orbital exenteration. In a series of 17 periorbital NF cases presented by Wladis et al. three patients required orbital exenteration to obtain disease control and one patient died from NF.[7] Such cases highlight the importance of accurate diagnosis and aggressive treatment of periorbital NF, and suggest evaluating a response to initial limited debridement as well as initial microbiologic studies before more extensive surgery. Since SS is exquisitely steroid responsive, response to a single dose of IV corticosteroid may be considered as diagnostic confirmation.

To our knowledge, there have only been two prior reports of nSS involving the periorbital region.[3,4] One patient had very focal necrosis limited to the eyelid margin; SS in this case was felt to be associated with inflammatory bowel disease and psoriatic arthritis, and was successfully treated with oral corticosteroids.[3] The other patient had a history of AML, and his initial presentation resembled NF which was

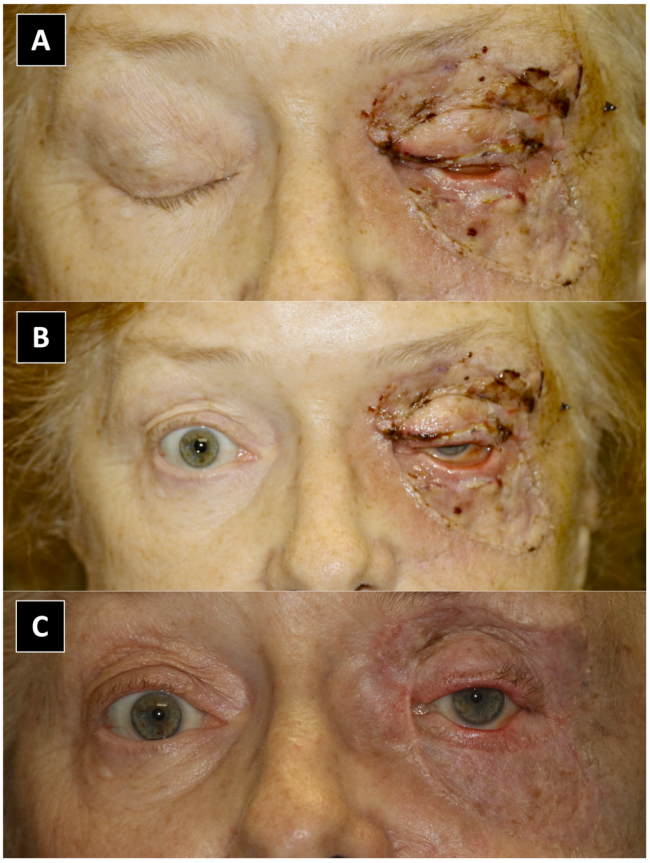

Fig. 3. Case 1 clinical reconstruction. A-B) Post-operative week 1 following reconstruction of left upper and lower eyelids and upper cheek with an anterior chest wall full thickness skin graft; C) Post-operative month 3.5 following reconstruction.

nonresponsive to antimicrobials and serial debridement; he also improved with corticosteroid treatment.[4] Notably, the latter patient underwent canthotomy-cantholysis during debridement and was initiated on eye pressure-lowering drops for an elevated IOP of 35 mmHg.[4] Direct ocular manifestations of SS, such as elevated IOP, conjunctivitis, and other forms of ocular/orbital inflammation, have been well documented in the literature.[8] One study with biopsy data of ocular tissue affected by SS reported histopathology that resembled that of the cutaneous lesions.[8] Consistent with this, Patient 1 presented to the authors institution with chemosis and increased IOP relative to the unaffected eye, without other orbital signs or post-septal involvement on imaging, suggesting direct ocular involvement. The specific cause of her transient decreased VA during her active SS is unknown but excess pressure on the left eye when raising her upper eyelid with a retractor or ointment may have contributed to refractive error and/or blurred vision.

Successful reconstruction of the eyelid after debridement for nSS necessitated a balance between minimizing the risk of tissue contraction and infection with the risk of additional pathergy, while simultaneously optimizing the health of the tissue bed to enhance graft vascularization. The patient in Case 1 remained on high dose corticosteroids, which are known to impair wound healing. Intraoperatively, the wound was thoroughly cleansed, necrotic and granulation tissue removed until petechial bleeding was encountered, and the FTSG was adequately thinned to optimize success. Given the defect size and location, the patient's immunocompromised status, and ongoing high corticosteroid requirement, a flap was not pursued. At post operative month three, the patient continued to have a healthy appearing FTSG although, not surprisingly, some medial canthal webbing and lower lid ectropion had developed.

Patient 2 is unique in that the diagnosis was complicated by the presence of positive HSV PCR and bacterial growth on cultures at the site where her nSS initially presented; her prior diagnosis of SS and continued pathergy helped refine the clinical picture. Case 2 also emphasizes the importance of aggressive management of the underlying malignancy. Patients with suspected nSS should be managed closely with oncology for this reason, as well as to appropriately adjust chemotherapy regimens to avoid other exacerbators of SS, such as granulocyte colony stimulating factors (G-CSF).[1] However, this treatment was not felt to be a contributing factor in this series of patients. Patient 1 never received G-CSF. Patient 2 had their first episode of SS prior to the introduction of G-CSF. Her current and subsequent episode was spatially distant to the G-CSF treatment she had received one year prior.

3. Conclusion

nSS is an unusual form of the more commonly encountered neutrophilic dermatoses of classical SS and pyoderma gangrenosum. It is a challenging diagnostic entity due to its overlapping features with NF and the rarity of necrosis in SS. It is therefore crucial to maintain a high level of clinical suspicion, especially in the presence of pathergy, characteristic histopathological findings, and largely negative wound cultures.

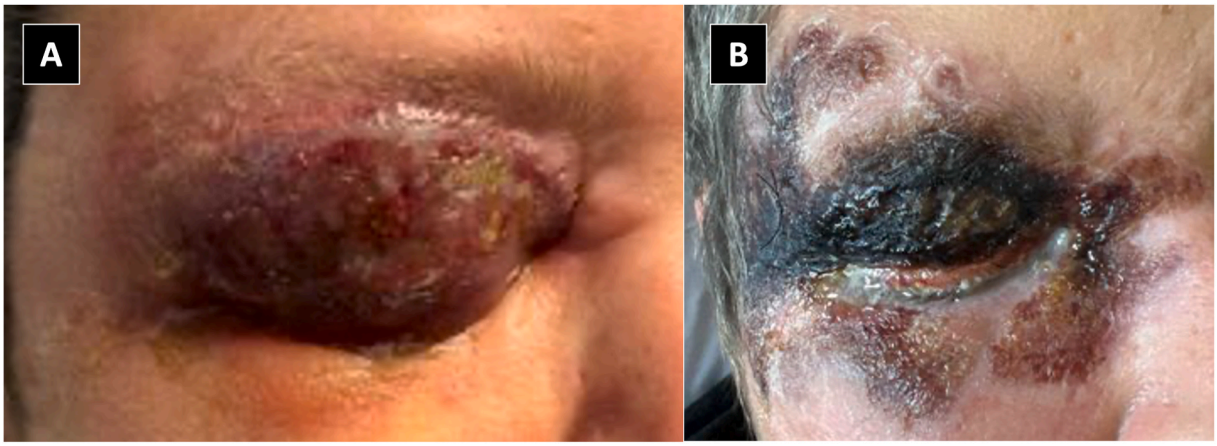

Fig. 4. Case 2 clinical photographs. A) Right upper lid (RUL) with ptosis, edema, overlying weeping vesicles, and a deep violaceous hue upon presentation; B) Evolution of RUL necrosis with involvement of right lower eyelid (RLL), temple, and nasal bridge.

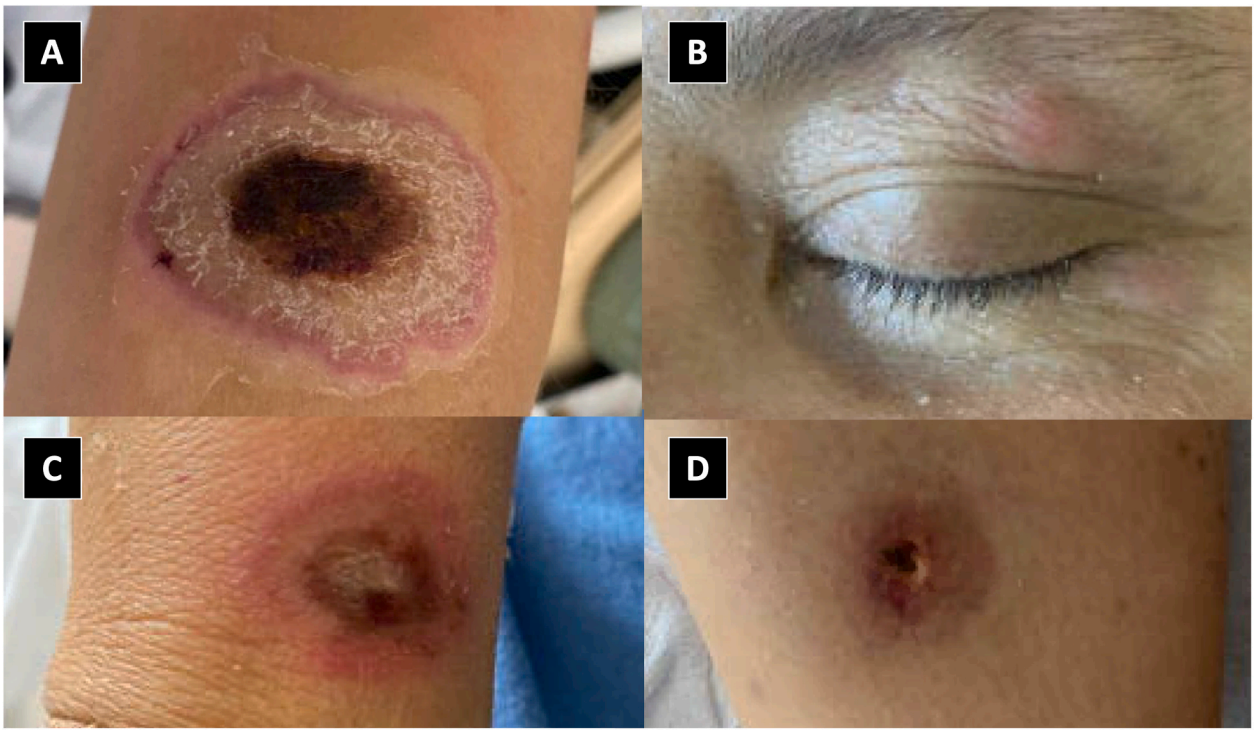

Fig. 5. Case 2, extra-orbital manifestations. A) Left upper extremity subcutaneous nodule with eschar, B) Pink papules on left upper and lower eyelid, C) Right wrist subcutaneous nodule with evolving eschar, D) Right lower extremity lesion with eschar.

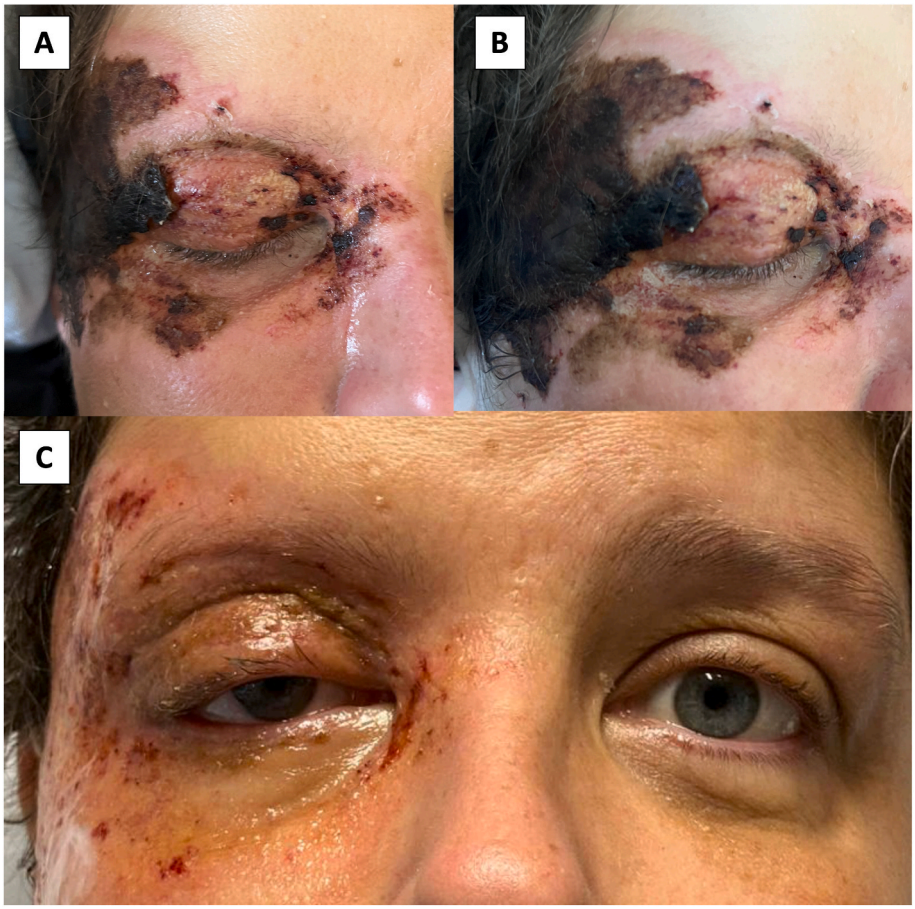

Fig. 6. Case 2, post-treatment. A and B) Following steroid initiation, right upper eyelid (RUL) eschars began sloughing off revealing healthy tissue. C) Complete resolution of RUL eschar with intact eyelid structure underneath.

Patient consent

The patients provided written consented for publication of the cases.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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