Response of necrobiotic xanthogranuloma to venetoclax in the setting of chronic lymphocytic leukemia complicated by IgG lambda monoclonal gammopathy

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BACKGROUND

Necrobiotic xanthogranuloma (NXG) is a rare histiocytic disease that is often associated with monoclonal gammopathy secondary to either a plasma cell dyscrasia or lymphoproliferative disorder.[1] NXG typically presents with indurated, yellow papules, nodules, and/or plaques most commonly in a periorbital distribution. A skin biopsy demonstrates granulomatous nodules with zones of necrosis, lipidized histiocytes, multinucleated giant cells, neutrophilic debris, and cholesterol clefts in the dermal and subcutaneous layers.[1] There are no controlled clinical studies to guide the therapy of NXG. As such, treatment of NXG is often challenging and refractory to multiple treatment modalities. Surgical excision of NXG lesions is not recommended due to high recurrence rates. Some cases of NXG have shown promising results to intravenous immunoglobulin (IVIG) and intermittent systemic steroids.[1] Ultimately, the most important aspect of treatment is targeting the underlying malignancy or monoclonal gammopathy that is potentially triggering a patient's NXG.

CASE

A 61-year-old male presented with progressive eruption of the arms and legs along with induration and discoloration involving both eyelids (Figure 1). Outside biopsies of the extremity eruption showed superficial and deep granulomatous inflammation. He was subsequently treated with tacrolimus 0.1% and clobetasol 0.05% ointment, which resulted in no improvement. Many of the lesions on his extremities and periorbital area progressed and ulcerated (Figure 1).

Repeat biopsies demonstrated pan-dermal palisaded granulomatous inflammation with cholesterol clefts in association with a nodular lymphoid infiltrate and variable numbers of Touton giant cells (Figure 2).

He underwent several weeks of high dose intermittent systemic steroids, which resulted in minimal improvement. Introduction of IVIG, which was started as 0.5 g IVIG/kg for 4 consecutive days for 4 weeks resulted in rapid improvement and permitted steroid tapering (Figure 3A).

He was started on chemotherapy for CLL under the direction of Heme/Onc. Initially, he was started on a single agent, obinutuzumab (anti-CD20 monoclonal antibody) but still had residual disease after 6 cycles. Then, zanubrutinib (Bruton's tyrosine kinase [BTK] inhibitor) was started but was discontinued due to cardiac toxicity. Finally, he was started on venetoclax (BCL-2 inhibitor), which led to complete hematologic remission, and subsequently, complete resolution of NXG (Figure 3B).

CLINICAL PRESENTATION AND PROGRESSION

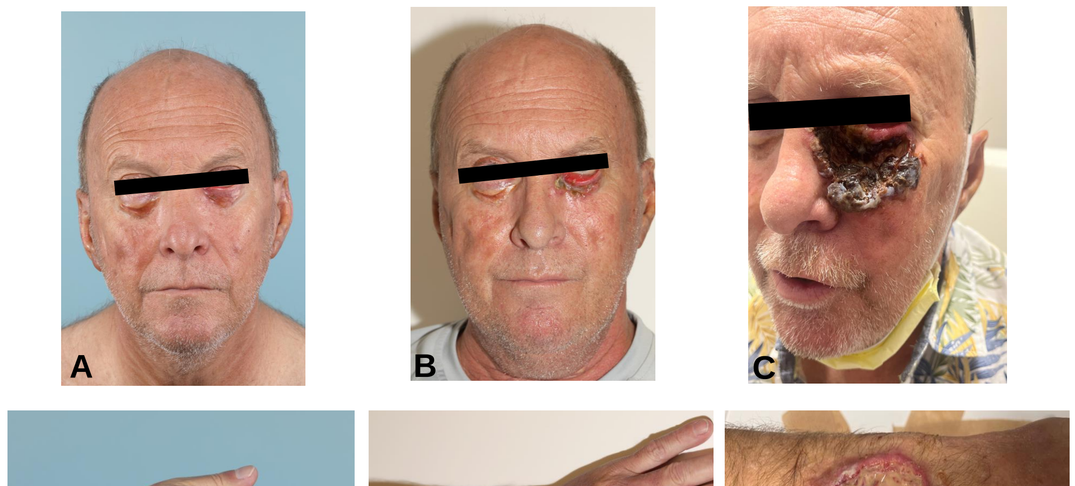

Figure 1. A & D, Initial presentation showed yellow-orange infiltrated smooth plaques involving the left and right lower eyelids and well-defined, annular, erythematous smooth plaques of the extremities. B & E, Rapid progression with ulceration and overt ectropion of the left lid and ulceration of plaques on extremities. C & F, Fulminant progression with extensive deep ulceration of the left peri-ocular face and cheek, as well as deep ulceration on the extremities

HISTOPATHOLOGY

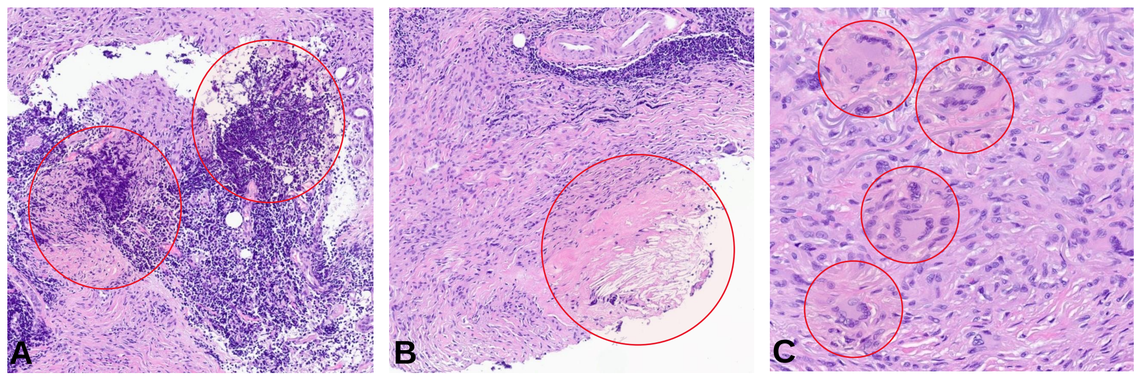

Figure 2. H&E (original magnification ×10). A 5 mm punch biopsy showed necrobiotic granulomatous inflammation with multi-focal dense nodular lymphoid aggregates (A), cholesterol cleft formation in areas of necrobiosis (B), and Touton giant cells within areas of granulomatous inflammation (C).

STABILIZATION AND REMISSION

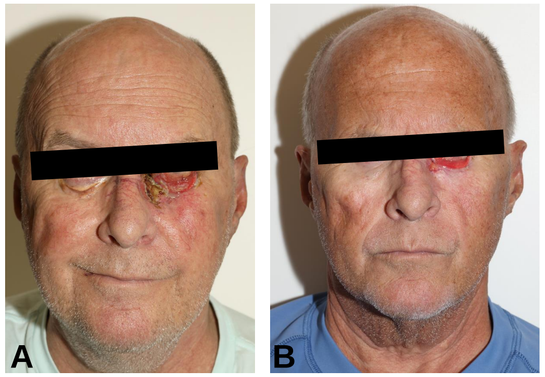

Figure 3. A, Stabilization with rapid regression and re-epithelialization of previously ulcerated areas after treatment with IVIG 0.5 g/kg for 4 consecutive days for 4 weeks. B, Remission of NXG after treatment of underlying CLL with venetoclax. He has residual post-inflammatory ectropion with planned oculo-plastics repair.

SUMMARY

- Patient's advanced NXG was initially stabilized with IVIG
- Treatment in targeting the underlying malignancy with reduction of the monoclonal gammopathy led to complete clearance of NXG
- Venetoclax is used to treat CLL and works by selectively binding to BCL-2, displacing pro-apoptotic proteins and triggering events that lead to apoptosis
- This case highlights the role dermatologists play in identifying NXG as a paraneoplastic phenomenon and the importance of multi-disciplinary modalities in successful treatment

REFERENCES

1. Nelson CA, Zhong CS, Hashemi DA, et. al. A Multicenter Cross-Sectional Study and Systematic Review of Necrobiotic Xanthogranuloma With Proposed Diagnostic Criteria. JAMA Dermatol. 2020 Mar. PMID: 31940000.