DEVELOPMENT OF NASAL SKIN NECROSIS ASSOCIATED WITH RITUXIMAB TREATMENT FOR WALDENSTRÖM’S MACROGLOBULINEMIA AND SUBSEQUENT SPONTANEOUS RESOLUTION

Aaron N. Pearlman, MD; Frank P. Fechner, MD; Minas Constantinides, MD

Abstract
We report the unusual case of a 72-year-old man who developed acute and extensive necrosis of the nasal skin and soft-tissue envelope while undergoing chemotherapy for Waldenström’s macroglobulinemia, a lymphoproliferative disorder. The patient’s treatment involved infusions of rituximab, a chimeric monoclonal antibody that is directed against B cell surface membrane protein CD20. The patient refused surgery to restore the nose, and he was treated conservatively with wet-to-dry dressings and antibiotic ointment. Approximately 5 weeks after admission, the eschar had exfoliated, revealing that the underlying skin was pink and healthy; no significant areas of necrosis remained. Within weeks, the nose had healed completely without scarring. A good aesthetic result was achieved exclusively through healing by secondary intention. We wish to alert the medical community that (1) conservative management of even extensive nasal skin loss should be considered when clinically acceptable, and (2) there may be an association between anti-CD20 antibody therapy for Waldenström’s macroglobulinemia and skin necrosis.

Introduction
Nasal reconstruction poses a challenge to the facial plastic surgeon. The nose is a vital central facial structure, and its aesthetics and function require an optimal treatment algorithm. For the best outcome, three layers should be reconstructed: the internal lining, the bony-cartilaginous skeleton, and the skin. Reconstructive options for the skin envelope include secondary healing by granulation and placement of split-thickness and full-thickness skin grafts, local rotation/advancement flaps, regional pedicle flaps, and free flaps.

Most reconstructive surgeons today recommend early initiation of reconstruction. The reasons for this approach include optimization of outcomes and a shorter recovery process. We present an interesting case in which a patient developed skin necrosis of the entire nose. A good aesthetic result was achieved exclusively through healing by secondary intention.

Case report
A 72-year-old man with a history of Parkinson’s disease and newly diagnosed Waldenström’s macroglobulinemia was admitted to the hospital after he had undergone treatment with plasmapheresis and rituximab, a chimeric monoclonal antibody (dose 2 of 4). The indication for admission was unexplained fevers and chills. One week earlier, he had been treated with an initial dose of rituximab, and he had not experienced any significant side effects. Upon admission, the patient was pan-cultured, and vancomycin and cefepime therapy was initiated. His hematocrit value was 24.5%, and findings on urinalysis were significant for the presence of many bacteria. His monoclonal IgM level was greater than 5 g/dl.

On hospital day 4, the patient had been afebrile for more than 24 hours, and so the third dose of rituximab was infused. After approximately 150 ml of medication had been delivered, the patient developed rigors and his oxygen saturation level fell to 88%. The infusion was stopped, meperidine was administered to treat a febrile nonhemolytic reaction. The patient quickly stabilized, and the rituximab infusion was continued. Upon completion of the infusion, the patient’s fingers and toes had a mottled appearance.

Several hours after the completion of the chemotherapeutic treatment, the patient became acutely hypotensive and cyanotic, and ischemic changes were noted on his nose.
and digits. His laboratory values were significant for disseminated intravascular coagulation and acute renal failure. He was urgently transferred to the medical intensive care unit, and an otolaryngology consult was requested.

Close inspection of the nose revealed that the overlying skin was edematous and violaceous. The nose was tender to palpation. No active bleeding emanated from the nasal cavity, but clots were noted bilaterally. Ulceration and ecchymosis were evident over the soft palate, and they extended to the hard palate. Scattered petechiae of the buccal mucosa were seen bilaterally. Flexible diagnostic laryngoscopy performed transorally revealed the presence of an ecchymotic lesion on the left tip of the epiglottis. There was no active bleeding of the nasopharynx or oropharynx. The patient was intubated for airway protection, and a biopsy of necrotic tissue from the right first digit was performed by the dermatology service. The biopsy findings were significant for thrombotic vasculitis in the small and medium-sized vessels. Biopsy also revealed some leukocytoclasia that was consistent with thrombosis secondary to Waldenström’s macroglobulinemia rather than a septic embolic event.

Over the next week, the patient’s overall medical condition improved, and he was successfully extubated. The nasal necrosis had become sharply demarcated along the glabella and the facial-nasal junctions (figure 1). Purple eschar was evident along the dorsum, and it extended to the nasal tip. The necrosis was minimally debrided at the bedside. Bedside discussion with the patient and his family by the consulting facial plastic surgery service included a recommendation for nasal reconstruction with a paramedian forehead flap for coverage. However, the patient and his family refused any surgical intervention, so local wound care with wet-to-dry dressings and antibiotic ointment coverage was continued.

Approximately 5 weeks after admission, the eschar had exfoliated, revealing that the underlying skin was pink and healthy. No significant areas of necrosis remained, although a small anterior nasal septal perforation was noted. The patient’s monoclonal IgM concentration had fallen to 1.9 g/dl. Because the need for nasal reconstruction no longer existed, the patient was discharged to a rehabilitation hospital with follow-up as an outpatient. At the 12-week follow-up, the patient had healed completely without scarring (figure 2).

Discussion

The face is divided into aesthetic regions, with the nose being a distinct subunit. Nasal defects up to 15 or 20 mm can often be successfully repaired with local flaps. Larger lesions may require flaps taken from other aesthetic regions. The paramedian forehead flap is commonly used to achieve reconstruction of large nasal defects for large nasal defects that involve multiple nasal subunits, including the nasal tip.

The lesion in our patient was confined to the external nasalepithelium. The underlying cartilage and nasal mucosa remained viable, which made the paramedian forehead flap an appropriate recommendation for reconstruction. If our patient’s skin loss had extended to the alar margin, a cartilage graft might have been necessary to prevent external nasal valve collapse and alar retraction. Furthermore, if cartilaginous destruction had been present, the specific cartilage subunits would have required reconstruction for both functional support and aesthetic considerations.

The paramedian forehead flap is well suited for the reconstruction of the nose. The color, texture, and consistency of forehead skin are similar to those of nasal skin. In addition, the flap is a hardy one, owing to its well-vascularized pedicle. The donor site can be closed primarily in many cases and by secondary intention when necessary. The patient is left with an unobtrusive vertical scar that heals in the midline of the forehead. A second procedure is required to detach the pedicle.1

Our patient’s nasal defect was probably the result of his underlying medical condition and subsequent treatment. Waldenström’s macroglobulinemia is a lymphoproliferative disorder characterized by bone marrow infiltration by small lymphocytes, lymphoplasmacytic cells, and a monoclonal IgM serum peak.2,3 Most cases of Waldenström’s macroglobulinemia are diagnosed secondary to a finding of fatigue-related anemia. Patients may also present with lymphadenopathy, splenomegaly, hyperviscosity syndrome, cryoglobulinemia, peripheral neuropathy, cold agglutinin
hemolysis, autoimmune thrombocytopenia, von Willebrand’s disease and, in rare cases, amyloidosis. Hyperviscosity syndrome is caused by the binding of positively charged IgM molecules to red blood cells, which in turn leads to aggregation and ultimately rouleaux formation of these complexes. As a result, the viscosity of the blood increases secondary to increased protein concentration. Most often, patients with hyperviscosity syndrome present with oronasal bleeding, dizziness, and/or visual disturbances related to retinal bleeding. Reducing the amount of circulating M protein usually leads to the resolution of symptoms, although the relationship between hyperviscosity syndrome and M protein is not fully understood.

Rituximab, the chimeric monoclonal antibody, is directed against B cell surface membrane protein CD20. This agent has been useful in treating Waldenström’s macroglobulinemia because most affected lymphoplasmacytic cells express this protein. Approved by the Food and Drug Administration in 1997 for use in patients with low-grade or follicular, CD20-positive, B cell non-Hodgkin’s lymphoma, rituximab has been linked to an extensive list of reported side effects, including infusion reactions, tumor lysis syndrome, mucocutaneous reactions, hypersensitivity reactions, cardiac arrhythmias, angina, and renal failure. Furthermore, it has been shown that this medication can cause a sudden rise in serum IgM and viscosity levels, thereby placing patients at risk for hyperviscosity syndrome.

The true etiology of our patient’s nasal ischemia remains unclear. However, of all the possibilities, the infusion of rituximab is the most likely cause, based on the temporal association of this agent with the patient’s ischemia of the fingers and toes in addition to the nose. Of particular interest is the remarkable regeneration of the nasal skin that occurred despite minimal intervention. After 4 weeks of local wound care, approximately half of the nasal coverage had reepithelialized, and the remainder of the nose exhibited healthy granulation tissue. After an additional 3-week period, the nose healed completely by secondary intention with an optimal cosmetic result (the septal perforation remained). It is likely that the nasal skin necrosis was not a full-thickness necrosis, as we initially presumed; instead, it appears to have involved only the outer half of the dermis. If the necrosis had indeed affected the deeper dermis, then no doubt would have healed with scarring. Fortunately, no such scarring occurred.

Obtaining a nasal skin biopsy at the initial presentation would have been helpful in identifying the depth of necrosis early, and perhaps this would have prompted the surgeon to recommend a less aggressive restoration than a full nasal reconstruction with a forehead flap. But as it turned out, the unwillingness of the patient and his family to consider such a massive reconstruction spared the patient from what would have been, in retrospect, an unnecessary operation.

In conclusion, conservative management of even extensive nasal skin loss should be considered when clinically acceptable. Despite an expectation to the contrary, a very good cosmetic outcome may result. A skin biopsy may help to better define the depth of an apparently severe necrosis, thereby assisting the surgeon in assessment and surgical planning. Although the nature of the relationship of the necrosis to anti-CD20 antibody therapy for Waldenström’s macroglobulinemia remains unclear, the medical community should be aware of this possible association.

References