Granulation Tissue as a Rare Side Effect of Isotretinoin Treatment: A Case Report

Only a few cases of an impressive granulation reaction at sites of previous acne lesions have been described since the 1980s.

BY SHAYNA C. RIVARD, MD AND MARY HURT, MD

Though a rare side effect, granulation tissue may occur following treatment with isotretinoin for acne vulgaris. Isotretinoin is commonly known for side effects such as elevated liver enzymes and teratogenicity; however, cutaneous manifestations may appear less often and should be recognized as a potential limiting factor. We report the findings of a 25-year-old male started on isotretinoin for management of cystic acne who two months later had developed excessive crusted lesions with granulation tissue at the base. Discontinuation of isotretinoin and initiation of minocycline and prednisone taper eventually improved the patient’s initial presentation, though hypertrophic scarring remained.

CASE REPORT
A 25-year-old active duty male initially presented with cystic acne since age 14, which had caused scarring on his back and chest. He was unresponsive to a previous five-month trial of 100mg doxycycline daily. The patient was started on 80mg isotretinoin. Three weeks into therapy, he began to develop crusted nodules on his back and chest, which were initially attributed to the expected flare associated with isotretinoin treatment. The patient noted that it was particularly difficult to sleep due to pain and that the sites would bleed occasionally.

Two to three months into therapy, the patient had a greater extent of crusted nodules and had to discontinue wearing his uniform due to the associated pain. The patient was given an intramuscular injection of 80mg of kenalog and his isotretinoin dosage was subsequently decreased to 40mg daily with initiation of a 10-day course of keflex. Two weeks later when no improvement was seen, a hydrogen peroxide and water soak was performed, and an extensive amount of granulation tissue was found at the nodule base.

After recognition of this rare side effect, the patient was advised to discontinue all isotretinoin therapy and was started on 100mg minocycline twice daily, advised to apply compresses, and provided a three-week prednisone taper starting at...
Isotretinoin is most commonly prescribed for the treatment of severe, nodulocystic acne. Many side effects have been reported, with the most common being liver function and lipid abnormalities, depression, teratogenic effects, and mucocutaneous changes. An exuberant granulation tissue reaction, especially around nailfolds, has also been well documented and is listed as a side effect on the safety warning for isotretinoin. However, only a few cases involving such an impressive reaction at sites of previous acne lesions have been described since the 1980s.

In prior case reports, most symptoms of this abnormal tissue proliferation started later than the six-week mark when an early acne flare typically would have already occurred. Based on Exner’s observations, those with crusted acne lesions prior to initiation of therapy appear particularly prone to these cutaneous manifestations; however, this reaction does not appear to be related to the cumulative dose of isotretinoin.

The histologic findings of the above granulation tissue reactions include increased capillary formation with plasma cells and lymphocytes comprising an inflammatory infiltrate. Retinoids, both topical and oral, have been shown to promote increased dermal blood vessel formation. In addition, it is known that retinoids have effects on wound healing and fibroblast proliferation. Several studies have demonstrated a reduced proliferation of fibroblasts and decreased fibroblast collagen synthesis. However, others report increased collagen production, angiogenesis, and granulation tissue with tretinoin treatment. In addition, studies on wound healing have shown enhanced angiogenic activity in the granulation tissue of the dermis with vitamin A-treated wounds as well as enhanced neutrophilic inflammatory response and fibroblast proliferation.

A proposed mechanism for periungual pyogenic granulomas according to Armstrong is that disruption of keratinocyte connections and weakened nail structure from systemic retinoid effects may create susceptibility to foreign body embedment or trauma. Such trauma initiates cytokine processes for healing with resulting angiogenesis and inflammatory mechanisms ultimately responsible for excess granulation tissue. It is unclear if increased skin fragility and trauma to existing acne lesions from friction could play a role in our patient’s presentation. It is known that this reaction does not develop from traumatic injury, however. Delay in reepithelialization due to retinoids could also be significant in granulation tissue overgrowth. Treatment can prove rather difficult. In one prior case when the lesions were surgically removed, they grew again to their previous size in 72 hours. Similarly in a case of periungual disease, electrodesiccation was ineffective with prompt reoccurrence. Instead, discontinuation of the medication can be effective. According to Miller, in those cases which do not respond to discontinuation, cryotherapy with clobetasol-17-propionate (Dermovate), which is known to decrease vasodilation and fibroblast and collagen activity, can be helpful. Unresponsive lesions despite medication discontinuation have also resolved with 50% trichloroacetic acid or silver nitrate application. Again, in most cases, however, like ours, discontinuation of the medication alone proves quite effective.

**CONCLUSION**

Acne vulgaris is a very common condition treated with isotretinoin by dermatologists worldwide. Screening programs for the most common side effects associated with isotretinoin usage are already in effect; however, in addition, the clinician should be aware of the rare side effect of excessive granulation tissue and crusting, which may form at sites of previous acne lesions. As Exner reports, great care should be taken to be aware of this side effect in those who already have crusted acne prior to initiation of therapy. Prompt discontinuation of the drug should occur when this rare side effect is encountered during regular follow-up visits.

Dr. Rivard, General Medical Officer at Camp Pendleton, CA, is employed by the United States Navy. Dr. Rivard has no relevant financial or nonfinancial relationships to disclose.

Dr. Hurt, Dermatologist at Naval Hospital Camp Pendleton, CA, is employed by the United States Navy. Dr. Hurt has no relevant financial or nonfinancial relationships to disclose.