All-trans-retinoic Acid–Induced Scrotal Ulcers in a Patient With Acute Promyelocytic Leukemia

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Practice Points
• All-trans-retinoic acid therapy may be associated with scrotal ulcers.
• Patients may develop secondary infectious complications.

Case Report
A 42-year-old black man was diagnosed with acute promyelocytic leukemia (APL). The patient was started on all-trans-retinoic acid (ATRA) (45 mg twice daily) as a part of his induction chemotherapy regimen, which included cytarabine and daunorubicin. Approximately 3 weeks following initiation of ATRA therapy, the patient developed multiple painless scrotal ulcerations (Figure). He had a nonreactive rapid plasma reagin test for syphilis and negative direct fluorescent antibody test for herpes simplex virus. A biopsy specimen demonstrated ulceration with a mixed inflammatory cell infiltrate including neutrophils, lymphocytes, and histiocytes. Special stains for microorganisms were negative, and a lesional tissue culture showed no growth of bacteria, fungi, or atypical mycobacteria after 6 weeks.

A diagnosis of ATRA-induced scrotal ulcerations was considered. The patient required continuation of ATRA treatment as a standard of care for APL. Despite continuation of ATRA therapy, his scrotal ulcerations gradually improved over the course of several weeks without intervention.

Comment
Acute promyelocytic leukemia is an uncommon subtype of leukemia characterized by a specific translocation involving the retinoic acid receptor. Targeted ATRA therapy has led to dramatically improved therapeutic responses and a complete remission rate greater than 90% when combined with traditional chemotherapy. In 1993, Sun first described scrotal ulcerations as a side effect of ATRA therapy in China. The majority of subsequent reports have been published primarily in Asia, with the first case in a white male reported in 2000 by Esser et al.
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Ramzi et al\(^5\) reported ATRA-induced scrotal ulcerations in a black patient in Tunisia in 2007. All-trans-retinoic acid–induced scrotal ulcers are described as multiple painless ulcers occurring 9 to 29 days after initiation of chemotherapy.

Ulceration usually is associated with preceding leukocytosis, fever, and negative infectious evaluation, and frequently is associated with exfoliative dermatitis of the scrotum. Prior reports describe patients ranging in age from 8 to 63 years. Ulcers typically are self-limited and last for 2 to 12 weeks, regardless of continued ATRA therapy; however, relapse of APL requiring rechallenge with ATRA has been reported to cause recurrence of scrotal ulcerations. No treatment is necessary, but 2 cases have shown that corticosteroid therapy resulted in faster resolution.\(^1\) Complications from these ulcers predominately involve infection, with some cases progressing to Fournier gangrene.\(^4\) Notably, ATRA therapy also has been associated with the development of pyoderma gangrenosum.\(^3\) In this case, the presence of multiple small, painless, circular ulcers limited to the scrotum; lack of a pathergic response; and resolution without treatment while continuing ATRA therapy made it less likely for the patient’s scrotal ulcers to be caused by pyoderma gangrenosum.

Conclusion

The ongoing use of ATRA therapy combined with chemotherapy for successful treatment of APL demands that dermatologists be aware of ATRA-induced scrotal ulcerations as a possible side effect of treatment. Familiarity with this occurrence will help promote rapid diagnosis, avoid extensive diagnostics, and may prevent patients from exposure to unnecessary systemic antimicrobials.

REFERENCES