

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.

Acute promyelocytic leukemia (APL) accounts for 10% of acute myelocytic leukemias and is characterized by t(15;17) that produces the PML-RAR α (promyelocytic leukemia-retinoic acid receptor α) fusion oncoprotein. The discovery and implementation of all-trans-retinoic acid (ATRA) therapy for APL has led to complete remission rates greater than 90% when coupled with chemotherapy. We report a novel case of ATRA-induced scrotal ulcers in a black man with APL. The differential diagnosis of scrotal ulcerations in immunocompromised patients is lengthy, and misdiagnosis can lead to substantial morbidity and mortality. It is important for dermatologists to be aware of this potential complication of ATRA therapy.

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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.¹ In 1993, Sun² first described scrotal ulcerations as a side effect of ATRA therapy in China. The majority of subsequent reports have been published primarily in Asia,³ with the first case in a white male reported in 2000 by Esser et al.⁴

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The authors report no conflict of interest.

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Multiple scrotal ulcerations following all-*trans*-retinoic acid therapy for acute promyelocytic leukemia.

Ramzi et al⁵ 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.³ Complications from these ulcers predominately involve infection, with some cases progressing to Fournier gangrene.¹ 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.

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