Abstract

All-trans retinoic acid (ATRA) is effective in approximately 90% of the cases of acute promyelocytic leukemia (APL) with a low incidence of adverse effects. We report a patient with APL who developed skin ulcers of the scrotum concomitant with high fever during treatment that included ATRA. Severe fever was promptly alleviated with discontinuation of ATRA, while the ulcers improved gradually over 3 months. As the clinical features are similar to those of Sweet’s syndrome, we should be aware of the possibility that this rare adverse effect may occur in the treatment with ATRA.

(Key words: all-trans retinoic acid, localized scrotal ulcers, severe fever, acute promyelocytic leukemia)

Introduction

Approximately 90% of acute promyelocytic leukemia (APL) cases achieve complete remission (CR) in response to treatment with all-trans retinoic acid (ATRA). ATRA is well tolerated by most patients and its adverse effects, such as dryness of the skin and lips, gastrointestinal disturbance and hyperlipidemia, are minimal. It is known, however, that the “ATRA syndrome”, which consists of high fever, respiratory distress, and transient pulmonary infiltrates on radiology in conjunction with leukocytosis can occur during ATRA treatment (1). On the other hand, Sweet’s syndrome, which consists of high fever and skin rash (2–8), may also occur during ATRA treatment. The ATRA syndrome is the more serious complication and sometimes can be fatal. However, scrotal ulcer as a specific adverse effect of ATRA has been reported only in extremely rare cases (9–15). We report here a case of APL featuring scrotal ulcers accompanied by high fever during induction therapy which included ATRA.

Case Report

A 38-year-old man was admitted to our hospital because of gingival swelling and bleeding, leg purpura and high fever in November 2003. Hematological studies showed that white blood cell count (WBC) was 2,100/μl (88% promyelocytes), hemoglobin level 5.6 g/dl and platelet count 0.5×10⁴/μl. Coagulatory examination results indicated 13 seconds of prothrombin time (PT), 223 mg/dl fibrinogen, 29.4 g/ml FDP and 35.8 μg/ml D-dimer. Bone marrow aspiration showed that 95% of promyelocytes were abnormal, and flow cytometry revealed that the immunophenotype of the promyelocytes was CD13+, CD33+, HLA-DR+. Double-color fluorescence in situ hybridization (DC-FISH) analysis showed the presence of t (15; 17) in 98% of the marrow nucleated cells. The patient was eventually diagnosed as having APL and daily oral administration of ATRA 45 mg/m² was initiated. Because the WBC count increased to 1,200/μl on the second day, we administered idarubicin (IDA; 12 mg/m²/day ×3 days), and Ara-C (80 mg/m²/day ×5 days) in addition to ATRA. The patient became febrile on the fourth day and, in spite of the administration of antibiotics and an anti-fungal agent, high fever continued. Blood marrow aspiration showed that 95% of promyelocytes were abnormal, and flow cytometry revealed that the immunophenotype of the promyelocytes was CD13+, CD33+, HLA-DR+. Double-color fluorescence in situ hybridization (DC-FISH) analysis showed the presence of t (15; 17) in 98% of the marrow nucleated cells. The patient was eventually diagnosed as having APL and daily oral administration of ATRA 45 mg/m² was initiated. Because the WBC count increased to 1,200/μl on the second day, we administered idarubicin (IDA; 12 mg/m²/day ×3 days), and Ara-C (80 mg/m²/day ×5 days) in addition to ATRA. The patient became febrile on the fourth day and, in spite of the administration of antibiotics and an anti-fungal agent, high fever continued. Blood culture was negative and the origin of the fever remained unclear.

Painful scrotal vesicles appeared on day 12; the number of vesicles increased gradually and eventually they converged and converted into four ulcers (Fig. 1). We discontinued ATRA on day 23, after confirming that only 9% of the
promyelocytes remained in bone marrow. High fever was gradually alleviated, and the scrotal ulcers were cured slowly over 12 weeks. Histopathologic study of the biopsied scrotal skin on day 24 showed diffuse epidermal infiltration of neutrophils, lymphocytes, and histiocytes but not leukemic cells (Fig. 2), while bone marrow aspiration detected 3% promyelocytes and DC-FISH 2% of t(15;17) on day 36. The patient remained CR without treatment of ATRA.

Discussion

This report concerns a rare case of multiple ulcers localized in the scrotum and accompanied by high fever, which occurred during induction therapy with ATRA. Fever promptly improved with discontinuation of ATRA, followed by healing of the scrotal ulcers. These clinical features are also seen in Sweet’s syndrome (2–8). However, the case reported here also presented with a painful skin rash that was confined to the scrotum.

Thirteen cases with scrotal ulcers only occurring during ATRA therapy have been documented (9–15) (Table 1). In all 13 cases, the ulcers occurred on day 9–29 of ATRA therapy, slowly improving over 3 weeks to 3 months. In 10 out of 14 (71%) cases (including the present case) high fever was noted; the reports of the remaining cases did not mention whether fever occurred. In cases no. 9 and 11, corticosteroid was administered after discontinuation of ATRA, and scrotal ulcers of case no. 11 were resolved in three weeks. In case no. 13, where corticosteroid was administered concomitantly with ATRA, scrotal ulcers healed more quickly, within only two weeks. Because scrotal ulcers may progress to Fournier’s gangrene (11), we wish to emphasize that the recognition of this peculiar adverse effect is important for an early and accurate diagnosis.

In terms of histopathology, Sweet’s syndrome and drug-induced Sweet’s syndrome (16) are characterized by dense neutrophilic infiltration of the dermis. In fact, skin biopsy for genital lesions of the previously reported cases of Sweet’s syndrome showed dense neutrophilic infiltrate in two out of three cases (17–19). On the other hand, in the 14 cases with scrotal ulcers, skin biopsy was performed in only two cases. In case no. 9, the biopsy specimen showed dense dermal neutrophilic infiltrate, which may be compatible with one of the histological characteristics of Sweet’s syndrome. In the present case, skin biopsy was performed after discontinuation of ATRA. It is reported that in the later stages of Sweet’s syndrome, histiocytes and lymphocytes accompanied by leukocytoclasis predominate in the infiltrate (20). Our patient’s ulcer lesion was not in the acute phase, however, and this may have accounted for the fact that the biopsy specimen did not show dense neutrophilic infiltration. Thus, histopathological evidence is not conclusive for establishing the adverse effects of ATRA.

The clinical course featuring scrotal ulcers accompanied by fever and the prompt improvement in response to steroid treatment is characteristic of both Sweet’s and ATRA syndrome. In terms of skin lesions, however, the scrotal lesions of the present case appeared first in the form of vesicles, which later fused and converted into ulcers. Sweet’s syndrome is typified by a red skin rash and sharply demarcated plaques. In some cases, however, vesicular patterns are seen at first, and these typically fuse later on. These symptoms therefore do not constitute sufficient evidence for distinguishing the adverse effects of ATRA from Sweet’s syndrome. Skin biopsy in the early phase is thus important when scrotal ulcers first appear during ATRA therapy in order to establish an accurate diagnosis for the treatment of the
scrotal ulcers.

It was previously established that 1) transcription of the gene coding the leukocyte adhesion molecule is promoted by ATRA (21), 2) ATRA produces superoxide (22) and cytokines such as TNF-α, IL-1, IL-3, IL-6, IL-8 G-CSF, GM-CSF, interferon γ activating leukocytes, which directly injure tissues (20, 23–26). It has been reported that in some cases scrotal ulcers appeared concurrently with recovery of the WBC count. In the present case, the WBC count increased rapidly from the nadir state at the onset of fever and scrotal ulcer. These findings support the hypothesis of the existence of a relationship between scrotal ulcer and G-CSF. However, such a mechanism has been hypothesized for Sweet’s syndrome. Therefore, cytokines must be investigated to precisely differentiate the adverse effect of ATRA from Sweet’s syndrome.

### References


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**Table 1. Scrotal Ulcer during Treatment of APL with ATRA**

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Onset</th>
<th>Duration</th>
<th>ATRA</th>
<th>WBC at Cr</th>
<th>Fever</th>
<th>Biopsy</th>
<th>Prognosis</th>
<th>Author</th>
<th>Ref</th>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Sun GL et al</td>
<td>9)</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>Day 17</td>
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<td>&gt;10,000</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Tajima K et al</td>
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<td>3</td>
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<td>10 w</td>
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<td>&gt;10,000</td>
<td>–</td>
<td>–</td>
<td>CR</td>
<td></td>
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<tr>
<td>4</td>
<td>37</td>
<td>9</td>
<td>8 w</td>
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<td>–</td>
<td>Gangrane</td>
<td>Goto H et al</td>
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<td>6</td>
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<td>17</td>
<td>–</td>
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<td>3,700</td>
<td>+</td>
<td>–</td>
<td>CR</td>
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<td>18</td>
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<td>Stopped for 5 days (steroid added)</td>
<td>5,700</td>
<td>+</td>
<td>+</td>
<td>CR</td>
<td></td>
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<tr>
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<td>13</td>
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<td>Continuous</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>CR</td>
<td>Esser AC et al</td>
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<tr>
<td>11</td>
<td>20</td>
<td>9</td>
<td>3 w</td>
<td>Stopped (steroid added)</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>Charles KS et al</td>
<td>14)</td>
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<td>CR</td>
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<td>14</td>
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<td>+</td>
<td>+</td>
<td>CR</td>
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Scrotal Ulcers with ATRA Treatment