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Case Report

Distinct Characteristics of Sweet's Syndrome of the Scrotum Caused by All-*trans* Retinoic Acid in a Patient with Acute Promyelocytic Leukemia

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Keywords
Acute promyelocytic leukemia · All-*trans* retinoic acid · PML-RARα · Differentiation syndrome · Sweet syndrome · Neutrophil infiltration · Scrotal ulceration

Abstract
Induction therapy with all-*trans* retinoic acid (ATRA) is effective for acute promyelocytic leukemia (APL). ATRA induces neutrophil differentiation and its associated side effects. The differentiation syndrome is the most characterized ATRA-induced adverse effect. Sweet's syndrome, also known as neutrophilic dermatosis, is another form of ATRA-associated disease characterized by neutrophil infiltrating erythema that develops with fever. This is a case of a 34-year-old Japanese man diagnosed with APL. At the onset, the patient did not have skin involvement of APL cells. He was treated with ATRA and induction chemotherapy with idarubicin and cytarabine. Scrotal skin rash occurred at day 14, which developed into scrotal ulceration up to day 28 even after eliminating APL cells in his peripheral blood. Sweet's syndrome is a pathological diagnosis of scrotal skin ulceration representing neutrophil infiltration. The infiltrating neutrophils showed PML-RARα rearrangement. The patient was diagnosed with ATRA-associated Sweet's syndrome with skin ulcer. His cutaneous lesion did not respond to intravenous prednisolone therapy; thereby, ATRA was discontinued. After the cessation of ATRA, the skin lesion improved in the next week. We confirmed he achieved a complete response after induction chemotherapy. In our observation, ATRA-associated Sweet's syndrome is characterized by the following clinical manifestations: preferable occurrence in the scrota, tend to progress into skin ulcer, and pathogenicity associated with PML-RARα-positive

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matured neutrophils. The etiology, pathogenesis, and risk factors of ATRA-associated scrotal ulceration were discussed in the literature review.

Introduction

Acute promyelocytic leukemia (APL) is an acute leukemia with promyelocyte proliferation caused by promyelocytic leukemia/retinoic acid receptor alpha (PML-RARα) fusion protein [1]. An effective standard treatment regimen for APL is the induction therapy with all-*trans* retinoic acid (ATRA) [2]. ATRA induces neutrophil differentiation and is associated with various adverse events [3], with the retinoic acid syndrome [3]/differentiation syndrome (DS) as representative manifestations [4]. Sweet's disease (SD)/Sweet's syndrome (SS), also known neutrophilic dermatosis, is characterized by neutrophil infiltrating erythema that develops with fever [5, 6]. Myeloid cell differentiation induced by ATRA is associated with 2 compilations: DS [4] and ATRA-associated SS [7].

ATRA-associated SS is considered as a syndrome pathologically similar to that of the cutaneous disease infiltrated with neutrophils caused by various inducers, such as neutrophil proliferation, cytokine release, and biological activity of neutrophils. In addition, SD is a more precise clinical entity of neutrophilic cutaneous infiltration by idiopathic etiology including autoimmune mechanism. Capillary leak syndrome is the essential pathogenesis of retinoic acid syndrome/DS [3, 4], which reflects the pathological infiltration of neutrophils in the lung. SD/SS is substantially established by neutrophil infiltration to the skin and soft tissues [5, 6]. Notably, whether SD/SS-associated neutrophils are disease specific or not remains clinically controversial. In addition, cutaneous infiltration in APL is practically complicated. PML-RARα fluorescence in situ hybridization (FISH) was used to analyze the etiology of infiltrating neutrophils in the skin lesion of ATRA-induced SS.

Case Report/Case Presentation

This is a case of a 34-year-old Japanese man complaining of fever and oral/subcutaneous bleeding 4 days before hospital consultation. On his visit to a nearby physician, his blood test showed abnormal cells with Auer bodies and a decreased platelet count. On the next day, he was referred to our hematology department and was urgently hospitalized for suspected acute leukemia. The patient's medical history includes asthma since childhood; smoking history of 10–20 sticks/day (20–32 years), but currently is a nonsmoker; occasional alcohol drinking; and no food or drug allergies. The patient was conscious upon admission with grade 2 performance status due to severe fever and fatigue, with the following vital signs: temperature, 38.3°C; blood pressure, 160/78 mm Hg; heart rate, 86 bpm in regular rhythm; and oxygen saturation, 98% in room air. The patient's height was 178.6 cm, and weight was 102.7 kg (BMI 32.2 kg/m^2). Upon admission, he represented left conjunctival hemorrhage, bleeding of tongue and buccal mucosa, subcutaneous hemorrhage in the left lower abdomen, and nonpalpable liver and spleen.

Clinical data upon admission are shown in Table 1. Peripheral blood morphology is also presented in Figure 1. Bone marrow aspiration detected prominent proliferation of promyelocytes (67.0%), cytogenetical and molecular biological examination revealed

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Table 1. The patient's clinical data on the onset of acute promyelocytic leukemia

WBC	5,840	/μL
Neu	7.2	%
Eos	0.2	%
Baso	0.0	%
Lym	28.6	%
Mono	0.6	%
Myelo	0.8	%
Blast	62.6	%
RBC	30.4	$\times 10^4/\mu L$
Hb	10.2	g/dL
Ht	26.4	%
MCV	86.8	fL
MCH	33.6	pg
MCHC	38.6	%
PLT	1.2	$\times 10^4/\mu L$
RET	7.57	$\times 10^4/\mu L$
CRP	0.51	mg/dL
TP	7.6	g/dL
ALB	5.2	g/dL
T-Bil	1.6	mg/dL
D-Bil	0.5	mg/dL
AST	34	U/L
ALT	31	U/L
ALP	223	U/L
LDH	532	U/L
γ-GTP	55	U/L
BUN	18.4	mg/dL
Cre	0.90	mg/dL
UA	6.0	mg/dL
Na	140	mmol/L
K	4.0	mmol/L
Cl	106	mmol/L
Ca	9.3	mmol/L
IP	2.2	mg/dL
PT	57	%
PT-INR	1.34	ratio
APTT	26.2	sec
Fib	82	mg/dL
ATIII	119	%
D-dimer	8.5	μg/mL
FDP	46.3	μg/mL

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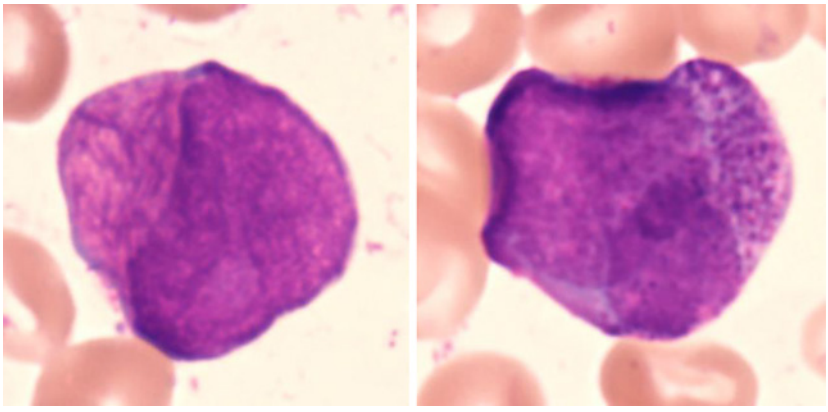

Fig. 1. Leukemia cells in the peripheral blood. Promyelocytes have irregular nuclear and cytoplasmic Auer's body.

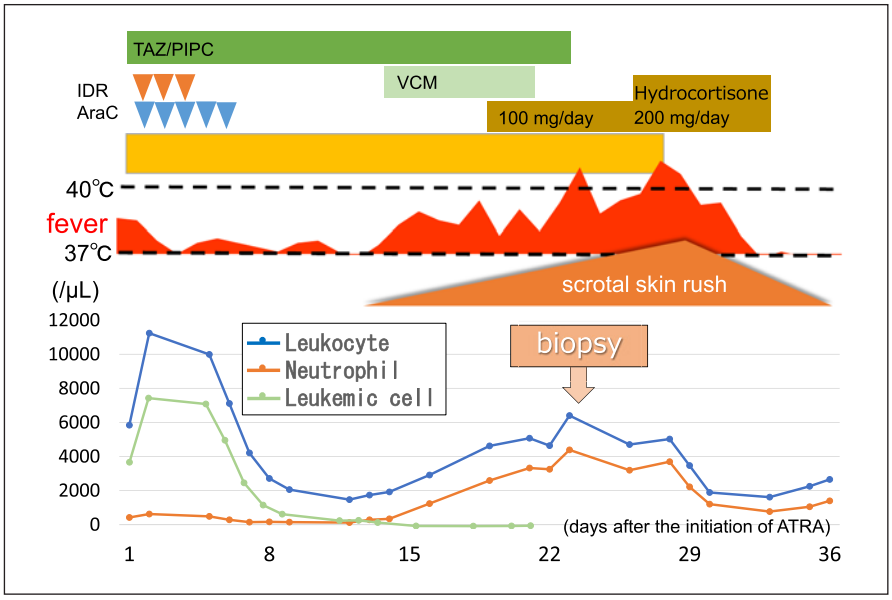

Fig. 2. Clinical course of the patient. The patient was treated with ATRA 45 mg/m^2, followed by IDR and AraC. He was febrile since admission and then was treated with TAZ/PIPC. The scrotal skin rash occurred on day 14, accompanied with high fever spikes. The fever exacerbated through on day 28, which did not respond to hydrocortisone (100–200 mg/day) and regressed after the ATRA discontinuation. Scrotal skin biopsy was performed on day 24. AraC, cytarabine; ATRA, all-*trans* retinoic acid; IDR, idarubicin; TAZ/PIPC, tazobactam/piperacillin; VCM, vancomycin.

t (15;17), and chromosomal and FISH analyses detected PML-RARα fusion genes. Based on these findings, we diagnosed the patient with APL. Induction therapy with ATRA was initiated, followed by idarubicin and cytarabine. He was initially treated with 45 mg/m^2 ATRA upon admission and received cytotoxic agents, that is, idarubicin and cytarabine, thereafter. Initial fever decreased after administration of antimicrobial tazobactam/piperacillin.

The patient's clinical course is indicated in Figure 2. He complained of scrotal skin rash with fever on day 14 from the initiation of chemotherapy, which exacerbated through

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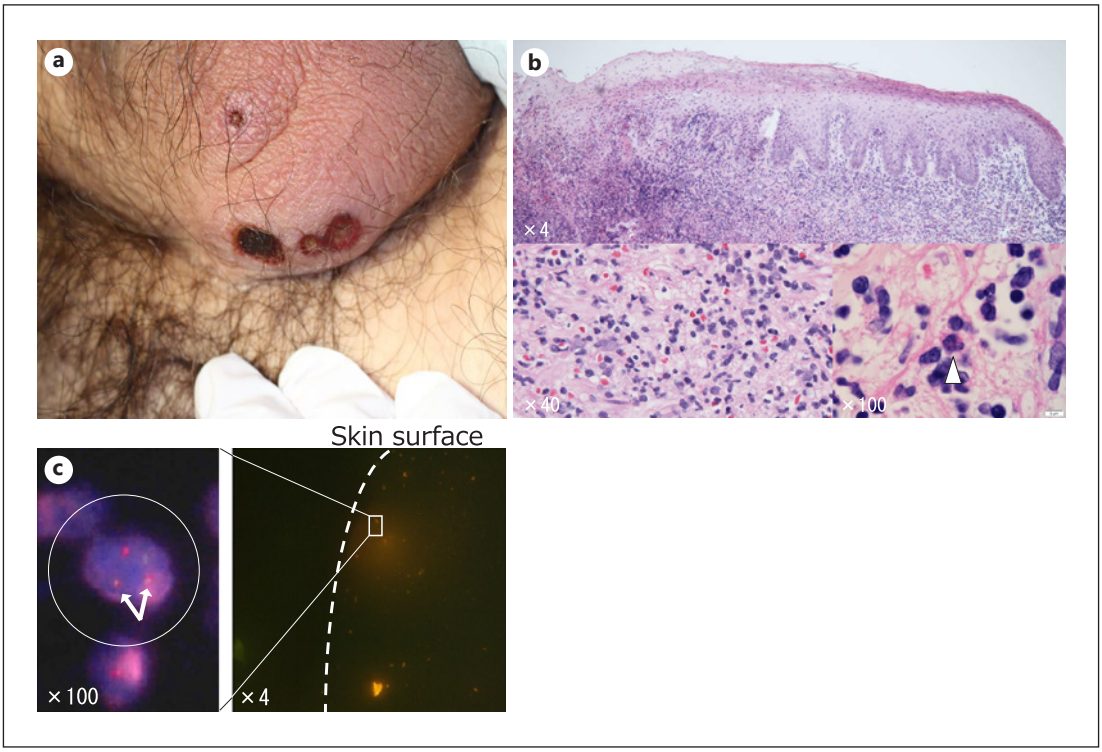

Fig. 3. Pathology and cytogenetics of the patient's scrotal skin. **a** The patient's scrota indicated skin rash progressing to ulceration. **b** The pathological finding of the patient's scrota revealed severe neutrophil infiltration (upper panel, HE. ×4) with nuclear dusts, erythrocyte extravasation, and fibrillization (lower left panel, HE. ×40). At the bottom of the ulceration, granulocytes with solid and rough granules were scattered (arrow head, lower right panel, HE. ×40). **c** PML-RARα FISH analysis showed fusion signal (yellow spots, assigned by 2-head arrow in white) in some neutrocytes at the bottom of the ulceration. FISH, fluorescence in situ hybridization.

day 28. An image of the scrota (shown in Fig. 3a) and the pathological image of the scrotal skin (shown in Fig. 3b) are shown. Pathological diagnosis was consistent with that of SS. FISH analysis using the PML-RARα gene probe indicated APL cells positive for fusion signal of PML-RARα were detected in the patient's scrotal subcutaneous tissues (shown in Fig. 3c). Corticosteroid (hydrocortisone) was ineffective for the patient's symptoms (shown in Fig. 2). However, scrotal lesion and fever improved immediately after the ATRA discontinuation on day 28. His disease achieved complete response after induction chemotherapy.

Discussion/Conclusion

Table 2 indicates characteristics of ATRA-associated scrotal ulceration, which was searched in PubMed with the keywords "ATRA" and "scrotal ulcer." A total of 33 cases of scrotal ulcers associated with ATRA were summarized [8–28]. Fever was observed in all patients but one [26]. The concomitant occurrence of ATRA syndrome, characterized by fever, weight gain, and respiratory distress, was observed only in 3 patients [12, 17, 19] and considered low association. Neutrophil infiltration was observed in all 13 patients who underwent biopsy, which was considered to be SD [11, 13–15, 17–20, 24, 26–28]. In many

Table 2. The summary of the cases reported as "ATRA-associated scrotal ulceration" in PubMed

Summary of 33 cases	Median (range)	In our case
Age	31 (13–78)	35
Onset day (after ATRA therapy)	17 (8–30)	14
Duration	36.5 (10–84)	31
Febrile	All cases but 1	+
Complication with differentiation syndrome, % (*n*)	6.0 (2/33)	-
Biopsy performed, % (*n*)	36.4 (13/33)	+
Pathology, % (*n*)		
Neutrophil infiltration	84.6 (13/13)	+
Vasculitis	7.7 (1/13)	-
Developed to Fournier's gangrene	In 3 cases	-
Ameliorate after ATRA discontinuation	In all cases	Yes
ATRA retreatment	In 7 cases	-
Recurrence after ATRA retreatment	1 case (14.3%, 1/7)	–

ATRA, all-*trans* retinoic acid.

cases, the onset and exacerbation were accompanied by increased leukocyte/neutrophil levels [11, 13–15, 17–20, 24, 26–28], and no recurrence of ATRA-associated ulceration was observed in 6 cases after ATRA readministration [15, 22, 23, 26–28]. Early treatment is important for 3 cases that progressed to Fournier's gangrene [9, 14, 20], and 1 case among them had to undergo orchiectomy [14].

Figure 4 shows the distribution of ATRA-related skin lesions. Compared with other unspecific SD (common on face and limbs), lesion distribution in ATRA-induced SD is different. Therefore, ATRA-induced SD is characterized by its prevalence in the scrotum, and the onset mechanism may be different. APL cells infiltrating subcutaneously have been reported to be positive for PML-RARα by FISH [29]. Efficacy of FISH has been reported to evaluate the evidence of cutaneous involvement by APL diseases. We applied this investigation technique to differentiate APL cell association or infiltration into the affected tissues. Although we detected fusion signals of PML-RARα FISH in the patient's scrotal tissue, it does not directly mean the cutaneous involvement, that is, extramedullary APL lesion. We hypothesize the result to suggest differentiating APL cell chemotaxis to the subcutaneous tissue due to proinflammatory cytokines, such as interleukin (IL)-1β, TNF-α, and IL-6. Observation of scrotal ulcers revealed its contact with the thighs and scrotum, areas prone to stimulation. Anatomical features of the scrotum include thin skin, in addition to its susceptibility to external stimuli.

ATRA can induce differentiation of neutrophils from APL cells, active oxygen production from neutrophils [30], neutrophil increase due to IL-1β, granulocyte-colony-stimulating factor production from APL cells [31], and vascular endothelium of APL cells [32]. Adhesion to cells and extracellular matrix was reported to be enhanced by production of these cytokines [32]. The mechanism of ATRA-associated ulceration was summarized (presented in Fig. 5). Effects may be caused by scrotal vulnerability to external stimuli, possibly resulting in scrotal ulceration.

In conclusion, during ATRA treatment, the patient experienced SD characteristics with scrotal ulceration. We advocate that ATRA-induced SD is different from normal SD, due to an abnormal mechanism of neutrophil hyperplasia/infiltration based on PML-RARα gene abnormality.

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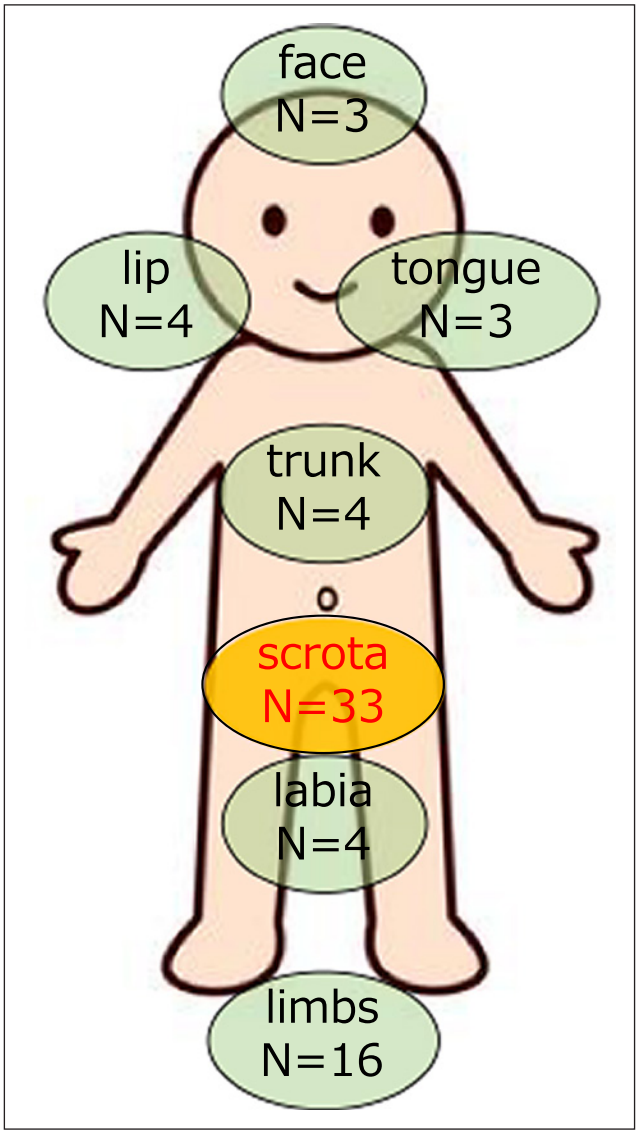

Fig. 4. ATRA-related skin lesions. We reviewed ATRA-associated Sweet syndrome ($N = 64$). Among those cases, the scrota is the primary site of the skin lesion in 33 cases (51.6%, 33/64). ATRA, all-*trans* retinoic acid.

Appropriate measures such as discontinuation of ATRA are necessary if fever, scrotal eruptions, or ulcers during ATRA use develop to Fournier's gangrene.

Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The subject has given written informed consent to publish this case (including publication of images). Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

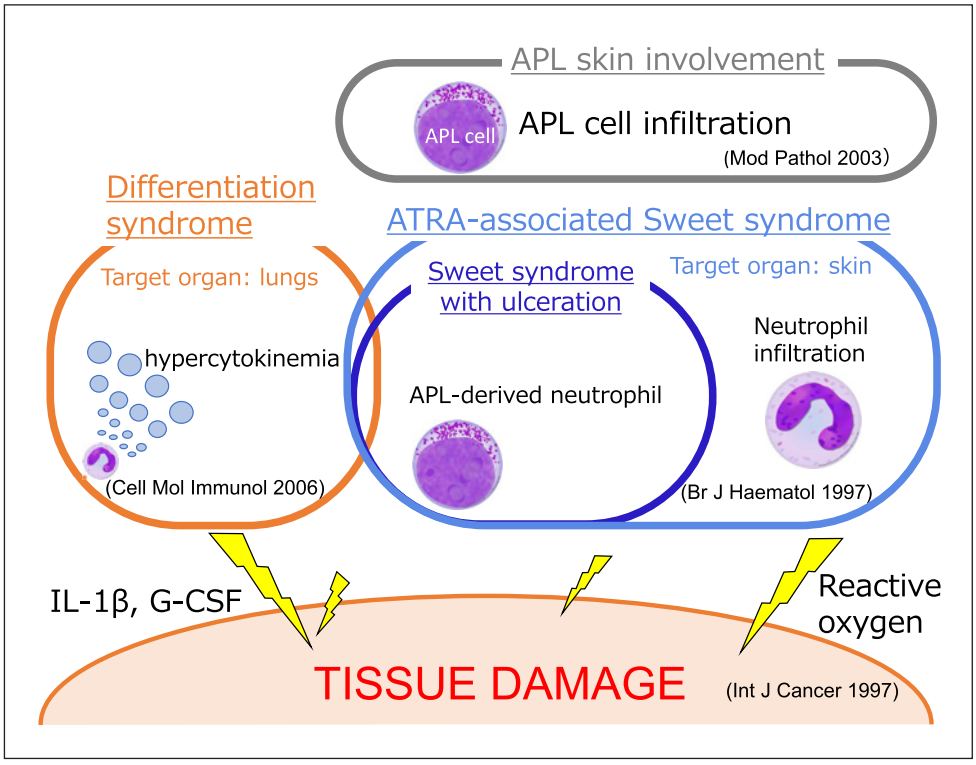

Fig. 5. The mechanism of ATRA-associated ulceration. We advocate 3 entities of ATRA-associated adverse disease: one is APL cell skin involvement, another is differentiation syndrome, and the last is ATRA-associated Sweet syndrome. The ATRA-associated Sweet syndrome with ulceration is a special subtype of the last one. We speculate this form of ATRA-associated Sweet syndrome is caused by the APL-derived neutrophils. The evidence of tissue damage was found using PML-RARAα-positive neutrophil infiltration into the ulceration. We speculate the APL-derived neutrophils exert more toxic features to the skin with serous and cellular maneuver in each milieu. ATRA, all-*trans* retinoic acid; APL, acute promyelocytic leukemia.

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Author Contributions

O.I., S.Y., and J.I.K. managed the patient's case, contributed to the literature search, and wrote the manuscript. M.U. made substantial contributions to the concept and design of this report. T.K. qualified the patient's data and suggested important intellectual content. H.K. and H.F. took part in critical discussions. N.K. was involved in supervision of the manuscript and managed the research. All authors approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this published article.

References

1 Wang ZY, Chen Z. Acute promyelocytic leukemia: from highly fatal to highly curable. Blood. 2008;111:2505–15.
2 Chen SJ, Zhu YJ, Tong JH, Dong S, Huang W, Chen Y, et al. Rearrangements in the second intron of the RARA gene are present in a large majority of patients with acute promyelocytic leukemia and are used as molecular marker for retinoic acid-induced leukemic cell differentiation. Blood. 1991;78:2696–701.
3 Frankel SR, Eardley A, Lauwers G, Weiss M, Warrell RP Jr. The "retinoic acid syndrome" in acute promyelocytic leukemia. Ann Intern Med. 1992;117:292–6.
4 Stahl M, Tallman MS. Differentiation syndrome in acute promyelocytic leukaemia. Br J Haematol. 2019;187:157–62.
5 Tomas JF, Escudero A, Fernandez-Ranada JM. All-trans retinoic acid treatment and sweet syndrome. Leukemia. 1994;8:1596.
6 Piette WW, Trapp JF, O'Donnell MJ, Argenyi Z, Talbot EA, Burns CP. Acute neutrophilic dermatosis with myeloblastic infiltrate in a leukemia patient receiving all-trans-retinoic acid therapy. J Am Acad Dermatol. 1994;30:293–7.
7 Christ E, Linka A, Jacky E, Speich R, Marincek B, Schaffner A. Sweet's syndrome involoving the musculoskeletal system during treatment of promyelocytic leukemia with all-trans retinoic acid. Leukemia. 1996;10:731–4.
8 Sun GL. Treatment of acute promyelocytic leukemia (APL) with all-trans retinoic acid (ATRA): a report of five-year experience. Zhonghua zhong liu za zhi. 1993;15:125–9.
9 Lévy V, Jaffarbey J, Aouad K, Zittoun R. Fournier's gangrene during induction treatment of acute promyelocytic leukemia, a case report. Ann Hematol. 1998;76:91–2.
10 Tajima K, Sagae M, Yahagi A, Akiba J, Suzuki K, Hayashi T, et al. [Scrotum exfoliative dermatitis with ulcers associated with treatment of acute promyelocytic leukemia with all-trans retinoic acid]. Rinsho Ketsueki. 1998;39:48–52.
11 Mori A, Tamura S, Katsuno T, Nishimura Y, Itoh T, Saheki K, et al. Scrotal ulcer occurring in patients with acute promyelocytic leukemia during treatment with all-trans retinoic acid. Oncol Rep. 1999;6:55–8.
12 Charles KS, Kanaa M, Winfield DA, Reilly JT. Scrotal ulceration during all-trans retinoic (ATRA) therapy for acute promyelocytic leukaemia. Clin Lab Haematol. 2000;22:171–4.
13 Esser AC, Nossa R, Shoji T, Sapadin AN. All-trans-retinoic acid-induced scrotal ulcerations in a patient with acute promyelocytic leukemia. J Am Acad Dermatol. 2000;43:316–7.
14 Fukuno K, Tsurumi H, Goto H, Oyama M, Tanabashi S, Moriwaki H. Genital ulcers during treatment with ALL-trans retinoic acid for acute promyelocytic leukemia. Leuk Lymphoma. 2003;44:2009–13.
15 Gettinger S, Shapira I, Scheinfeld N, Grossbard M. Complications of therapy in cancer patients: case 2. Scrotal ulceration during all-trans-retinoic acid therapy for acute promyelocytic leukemia. J Clin Oncol. 2004;22:4648–9.
16 Pavithran K, Arjun R, Aruna R, Thomas M. Scrotal ulceration during induction therapy of acute promyelocytic leukemia with ATRA. Am J Hematol. 2004;75:260–1.
17 Mourad YA, Jabr F, Salem Z. Scrotal ulceration induced by all-trans retinoic acid in a patient with acute promyelocytic leukemia. Int J Dermatol. 2005;44:68–9.
18 Shimizu D, Nomura K, Matsuyama R, Matsumoto Y, Ueda K, Masuda K, et al. Scrotal ulcers arising during treatment with all-trans retinoic acid for acute promyelocytic leukemia. Intern Med. 2005;44:480–3.
19 Wrede JE, Sundram U, Kohler S, Cherry AM, Arber DA, George TI. Fluorescence in situ hybridization investigation of cutaneous lesions in acute promyelocytic leukemia. Mod Pathol. 2005;18:1569–76.
20 Naithani R, Kumar R, Mahapatra M. Fournier's gangrene and scrotal ulcerations during all-trans-retinoic acid therapy for acute promyelocytic leukemia. Pediatr Blood Cancer. 2008;51:303–4.
21 Lee HY, Ang AL, Lim LC, Thirumoorthy T, Pang SM. All-trans retinoic acid-induced scrotal ulcer in a patient with acute promyelocytic leukaemia. Clin Exp Dermatol. 2010;35:91–2.
22 Tazi I, Rachid M, Quessar A, Benchekroun S. Scrotal ulceration following all-trans retinoic Acid therapy for acute promyelocytic leukemia. Indian J Dermatol. 2011;56:561–3.
23 Al Huneini M, Wasim F, Al Farsi K, Al-Khabori M, Al Kindi S. Genital ulcer development in patients with acute promyelocytic leukaemia treated with all-trans retinoic acid: a case series. Oman Med J. 2013;28:207–9.
24 Drago MJ, Kim BS, Bennett D, Elder D, Rosenbach M. All-trans-retinoic acid-induced scrotal ulcers in a patient with acute promyelocytic leukemia. Cutis. 2013;91:246–7.
25 Sutherland J, Kempton CL, Curry MA. Continuation of all-trans retinoic acid despite the development of scrotal ulcerations in a black male. J Oncol Pharm Pract. 2015;21:393–5.
26 Yanamandra U, Khadwal A, Saikia UN, Malhotra P. Genital vasculitis secondary to all-trans-retinoic-acid. BMJ Case Rep. 2016 Jan 20;2016:bcr2015212205.
27 Foley CC, Marren P. Scrotal ulceration and pyrexia. JAMA Dermatol. 2017;153:1181–2.
28 Buligon MP, Mielke JC, Chiesa J, Ferrazzo KL. Rare labial ulcer related to the use of all-trans retinoic acid in a patient with acute promyelocytic leukemia. Spec Care Dentist. 2018;38:234–8.
29 Wrede JE, Sundram U, Kohler S, Cherry AM, Arber DA, George TI. Fluorescence in situ hybridization investigation of cutaneous lesions in acute promyelocytic leukemia. Mod Pathol. 2005;18:1569–76.
30 Taraboletti G, Borsotti P, Chirivi RG, Vergani V, Falanga A, Barbui T, et al. Effect of all trans-retinoic acid (ATRA) on the adhesive and motility properties of acute promyelocytic leukemia cells. Int J Cancer. 1997;70:72–7.
31 Bi KH, Jiang GS. Relationship between cytokines and leukocytosis in patients with APL induced by all-trans retinoic acid or arsenic trioxide. Cell Mol Immunol. 2006;3:421–7.
32 Marchetti M, Falanga A, Giovanelli S, Oldani E, Barbui T. All-trans-retinoic acid increases adhesion to endothelium of the human promyelocytic leukaemia cell line NB4. Br J Haematol. 1996;93:360–6.