CASE REPORT

Genital vasculitis secondary to all-trans-retinoic-acid

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SUMMARY

Acute promyelocytic leukaemia is among the most curable haematological malignancies after the introduction of differentiating agents (arsenic trioxide (ATO) and all-trans-retinoic-acid (ATRA)). Despite excellent cure rates, approaching 85–95% in various series, APL is associated with significant early mortality and morbidity. ATRA-related side effects partly contribute to this morbidity, which commonly presents as differentiation syndrome, pseudo tumour cerebri, dermatitis, gastrointestinal disorders, liver dysfunction (raised transaminases) and dryness of skin/eyes. Rarely, ATRA can lead to hypercalcaemia, genital vasculitis, erythaema nodosum and Sweet's syndrome. We present two cases of ATRA-associated genital vasculitis while being managed with a combination of ATO with ATRA therapy. Both patients developed these lesions despite being on prophylactic steroids (0.5 mg/kg). We also discuss the pathophysiology, clinical manifestations, differential diagnosis and treatment of genital vasculitis as a rare adverse event of ATRA.

BACKGROUND

Acute promyelocytic leukaemia (APL) is a unique subtype of acute myeloid leukaemia (AML), with characteristic clinical and molecular features. It accounts for 10% of AML cases and is one of the curable haematological malignancies after the advent of targeted therapy (all-trans-retinoic-acid (ATRA)) in the 1980s. The cure rates have approached 85–95% in patients treated with ATRA-based protocols. ATRA, despite its excellent clinical outcomes, can have adverse effects. Common side effects include differentiation syndrome (also known as ATRA syndrome), pseudo tumour cerebri, dermatitis, gastrointestinal disorders, liver dysfunction (raised transaminases) and dryness of skin/eyes. Scrotal ulceration has been reported in the literature as a rare adverse event of ATRA. At our institution, we have managed 124 patients of APL as part of a prospective therapeutic design with an ATO/ATRA combination without chemotherapy irrespective of their risk stratification over the past 10 years (Dual Inducing Differentiating agents Indian Trial: DID-IT, universal trial number: U1111-1176-8493).¹ We observed three cases of genital vasculitis among these 124 patients (2.4%).

We present two of these cases of genital vasculitis secondary to ATRA. Both patients were induced with ATRA@45 mg/m² and arsenic trioxide (ATO) @0.15 mg/kg for APL. We also reviewed the literature on incidence, differential diagnosis and treatment of ATRA-associated vasculitis.

CASE PRESENTATION (CASE 1)

A 50-year-old man, a farmer by occupation, with no known comorbidities, presented with complaints of easy fatigability of 2 months duration and bleeding manifestations of 1 month duration. Evaluation at a peripheral centre revealed haemoglobin (Hb)—6 g/dL, leucocyte count—9600/μL and platelet—10 000/μL, with atypical cells in the peripheral smear, for which he was referred to our tertiary care centre.

Clinically at admission to our centre, the patient was mesomorphic with a body mass index of 23.2 kg/m²; vitals were stable except for mild increase in heart rate (98/min). General physical examination revealed moderate pallor, gum hypertrophy and ecchymotic patches over the limbs and chest. Systemic examination revealed a haemic murmur and mild splenomegaly (3 cm below left costal margin). Peripheral smear revealed 84% promyelocytes and blasts. The patient was empirically started on ATRA (45 mg/m²) and ATO (0.15 mg/kg) as a case of intermediate risk APL. He was given regular component support to maintain Hb>8 g/dL, platelet>40 000/μL and fibrinogen>150 mg/dL.

He developed painless, punched out scrotal ulcers on day 8 of ATRA therapy (figure 1A). This was not associated with any concurrent features of differentiation syndrome (weight gain, tachypnoea, fever and pulmonary infiltrates) or any other adverse effect of ATO/ATRA.

INVESTIGATIONS (CASE 1)

Ultrasonography of the testes revealed no abnormality. Swab culture from the ulcers grew skin commensals. The lesions were biopsied, the results of which were suggestive of vasculitis with polymorphonuclear infiltrate in vessel walls and intravascular thrombosis (figure 1B). Herpes simplex virus (HSV) serology and Tzanck smear were negative.

CASE PRESENTATION (CASE 2)

A 17-year-old girl, a student, with no known comorbidities, presented with complaints of fever and menorrhagia of 30 days duration with cough, haemoptysis and diminution of visual acuity of 15 days duration. She was admitted to a local hospital where she was detected to have severe pancytopenia (Hb 3.3 g/dL, leucocyte count 32 600/μL, absolute neutrophil count 800/μL and platelet 17 000/μL), coagulopathy (international normalised ratio 1.59) with clinical/radiological evidence of community acquired pneumonia. She was given component therapy (2ØPRBC, 4ØFFP, 6ØRDP), started on antibiotics (cefoperazone+sulbactam 1.5 g intravenous q8 h) and referred to our tertiary care centre for further evaluation.

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Figure 1 (A) Clinical photograph showing punched out ulcers on the scrotum on day 8 of ATRA therapy. (B) Histopathological examination (HPE)—punch biopsy from the scrotal ulcers. Vessel wall and background showing polymorphonuclear infiltrate, suggestive of vasculitis. Also seen in the picture is intravascular thrombus. (C) Clinical photographs of the involved area on day 18 of starting induction therapy illustrating resolved ulcers. ATRA, all-trans-retinoic-acid.

Clinically at admission to our centre, she was bed-ridden, extremely fatigued and severely pale. She had tachycardia (110/min), tachypnoea (28/min) and fever (102°F). On physical examination, she had bleeding manifestations in the form of gum bleeding, petechiae, ecchymosis, fundal haemorrhages and consolidation in right infrascapular/infraaxillary regions. An urgent peripheral blood smear revealed 93% promyelocytes with blasts. She was started on ATRA (45 mg/m²) and ATO (0.15 mg/kg) as a case of high-risk APL based on the study protocol.¹ Bone marrow and flow cytometry performed later confirmed the diagnosis of APL. She was given prophylactic steroids (prednisolone—0.5 mg/kg). She was also given component support to maintain Hb > 8 g/dL, platelet > 40 000/μL and fibrinogen > 150 mg/dL. Her antibiotics were modified to piperacillin/tazobactam 4.5 g intravenous q6 h. Her general condition improved gradually, with fever and features of pneumonia resolving on therapy.

On day 9 of ATO/ATRA therapy, she developed painful redness and swelling of both labia majora (figure 2A), with swelling gradually increasing in severity. This was not associated with any local/per-vaginal discharge. She had no concurrent menstruation and was not preceded by any per-vaginal examination. She had no features of differentiation syndrome nor of any other adverse effect of ATO/ATRA concurrently.

INVESTIGATIONS (CASE 2)

Blood cultures and vaginal swab culture taken during this episode were sterile. Markers of acute inflammation were elevated (C reactive protein 10.2, erythrocyte sedimentation rate 44 with Hb of 11.2 g/dL). Procalcitonin levels (0.24 ng/mL) were normal. Punch biopsy taken from the inflamed labia majora was suggestive of local vasculitis (figure 2B). Tzanck smear was negative.

Figure 2 (A) Clinical photograph showing inflamed bilateral labia majora in the second patient as on day 11 of starting ATRA therapy. Note: the biopsy mark on the right labia majora is not an ATRA-induced ulcer. (B) HPE showing polymorphonuclear infiltrate in the vessel wall, suggestive of vasculitis. ATRA, all-trans-retinoic-acid.

DIFFERENTIAL DIAGNOSIS

Differential diagnoses of genital lesions in an immunocompromised host (as in APL) are many. Misdiagnosis can lead to unnecessary evaluation, prolong hospital stay with financial implications, and lead to significant morbidity and mortality. Differential for painless punched out scrotal ulcerations include tropical infections, autoimmune disorders and Sweet's syndrome.² Phenotypically, vasculitic lesions secondary to ATRA closely mimic erythema nodosum and Sweet's syndrome, which can only be differentiated on histopathological examination. Some consider these three disorders to be part of a continuous spectrum with steroids being the choice of therapy for all these immunological disorders, questioning the relevance of biopsy to differentiate them.

Local inflammation as seen in the second case can be secondary to vascular disorders and infections. Infections can be causative or superadded, which necessitates simultaneous antibiotics. Herpes is a major differential in patients with similar lesions and should be ruled out by HSV serology, direct immunofluorescence or Tzanck smear. Poor hygiene, local injury, ill-fitting undergarments and abnormal sexual activities can also, rarely, lead to local inflammation, mimicking these lesions.

TREATMENT

In both patients, ATRA was continued under cover of prednisolone (1 mg/kg × 14 days)/amoxicillin (1 g/dL × 7 days), with which the lesions started healing (figure 1C showing healed scrotal ulcer). The steroids were slowly tapered to 0.5 mg/kg and continued throughout ATRA induction.

OUTCOME AND FOLLOW-UP

Following therapy, both the patients recovered in a time span of 7–10 days. There was no recurrence of lesions. In both patients, secondary causes of local inflammation were ruled out and there

were no other ATRA-related side effects. The induction was successfully completed and both achieved haematological and molecular remission during postinduction. Both the patients underwent consolidation in three cycles with ATO/ATRA. The first patient developed some redness of the scrotum during the first cycle of consolidation with ATRA, for which his dose of ATRA was decreased to 25 mg/m². He has completed maintenance now for 4 years and is still in molecular remission. The second patient is undergoing the fourth cycle of maintenance and was in molecular remission at her last evaluation.

DISCUSSION

APL is a subtype of AML with characteristic genetic translocation of t(15:17) leading to production of abnormal oncoprotein promyelocytic leukemia-retinoic acid receptor alpha (PML-RAR α). It constitutes 10% of all AML cases and is characterised by a clinical phenotype with predominant coagulopathy. Targeted therapy in the form of ATRA has revolutionised the clinical outcome of APL. ATRA is the drug of choice in treating APL, which, in combination with ATO/anthracyclines, achieves complete remission in 85–95% cases. Common side effects secondary to ATRA include differentiation syndrome, bone marrow necrosis, thromboembolic events, xerosis, headache and hepatic dysfunction. Rare side effects include hypercalcaemia, genital vasculitis, erythema nodosum, Sweet's syndrome and pseudotumour cerebri.^{3 4}

Sun⁴ first reported this adverse event in a Chinese patient in 1993 among a series of patients with APL managed with ATRA. Vasculitis can present as cheilitis, lingual ulcerations, pulmonary capillaritis, and skin and genital lesions.^{5–8} Genital vasculitis presents as local inflammation, scrotal/vaginal/vulval ulcers and Fournier's gangrene.⁹ Biopsy is not always necessary as the disorder is self limiting and responsive to steroid therapy. Its incidence is dwindling due to routine steroid-prophylaxis in APL inductions. There are no similar reports in the literature of genital vasculitis while the patients are on prophylactic steroids. Owing to the painless nature of the scrotal ulcers and their location, they are frequently underreported. Recurrence on reintroduction of ATRA during consolidation is not uncommon. In both our cases, fever was absent at the presentation of genital vasculitis, contrary to what has been reported in the literature, which could possibly be explained by the prophylactic low-dose steroids.

The exact aetiopathogenesis is obscure. Immune mechanisms (cytokine-mediated) are postulated based on responses to steroids and histopathological evidence of inflammatory infiltrate from ulcer margins. Important cytokines implicated are tumour necrosis factor α and interleukin (IL)-1, IL-6 and IL-8, which lead to ulcerations by stimulating peripheral leucocytes.¹⁰ ATRA per se has also been implicated by activating peripheral leucocytes and leading to superoxide production. Some authors have proposed activated neutrophils derived from the differentiating APL cells as a pathophysiological basis for the development of these lesions.^{11 12} In addition, the literature implicates the role of ATRA in increased transcription of leucocyte adhesion molecules in the aetiopathogenesis of drug induced Sweet's syndrome and ATRA vasculitis.¹³ The authors also suggest the role of granulocyte colony stimulating factor (G-CSF) levels in differentiating Sweet's syndrome from ATRA-induced vasculitis.¹⁴ Cytokine-mediated injury of various target organs from the cytokines released from differentiating APL cells play a central role in most adverse events secondary to ATRA, including vasculitis.³

ATRA need not be stopped if steroids/antibiotics are promptly started.¹¹ Steroids can be given either topically or systemically.

It is up to the physician's discretion whether to withhold ATRA and determine the mode of steroid administration based on the severity of lesions and presence of other concurrent ATRA-related side effects. If they are not treated in time, these ulcers can get secondarily infected and progress to Fournier's gangrene. If steroids are unable to control the progression of the genital lesions or other concomitant ATRA-related side effects, ATRA administration should be withheld temporarily so as to prevent life threatening Fournier's gangrene and ATRA syndrome.^{5 6}

On review of the literature, most of the case reports/series on genital vasculitis/vasculitis/scrotal ulcers are based on patients managed with ATRA/chemotherapy.^{4–12} We report these lesions in patients managed with a combination of ATO and ATRA; the literature on this is scarce. But, the addition of ATO to ATRA has not led to any increase or decrease in incidence of this adverse complication, as studied in our series of 124 patients of all risk categories managed with ATO+ATRA, with only three patients (2.4%) having this adverse event.¹

Learning points

- ▶ Genital vasculitis is a rare but significant side effect that, if not recognised in time, can progress to Fournier's gangrene.
- ▶ Prompt steroid and antibiotic therapy may allow uninterrupted all-trans-retinoic-acid therapy during acute promyelocytic leukaemia induction.

Contributors UY, AK and PM were involved in managing both the cases. UN was the histopathologist reporting the slides. All the authors were actively involved in drafting the manuscript.

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