

## Sweet syndrome and differentiation syndrome in a patient with acute promyelocytic leukemia

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**Author contributions:** Solano-López G contributed to manuscript writing and patients data collection; Llamas-Velasco M contributed to main idea, patients data collection; Concha-Garzón MJ contributed to patients data collection; Daudén E contributed to supervision.

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Received: June 9, 2014

Peer-review started: June 10, 2014

First decision: July 18, 2014

Revised: October 27, 2014

Accepted: November 17, 2014

Article in press: November 19, 2014

Published online: February 16, 2015

### Abstract

The differentiation syndrome is an inflammatory reaction with increased capillary permeability that occurs in up to 25% of patients with acute promyelocytic leukemia treated with all-trans retinoic acid. A 50-year-old man with acute promyelocytic leukemia underwent chemotherapy with idarubicin and all-trans retinoic acid. On day +21 the patient developed pruritic prepatellar papules as well as

several 10 mm subcutaneous nodules in both thighs accompanied by persistent fever. On the day +25 the patient presented with bilateral pulmonary crackles, infiltrates in the right lower lobe and severe hypotension which required dopamine infusion. Biopsy of one of the thighs nodules was performed. A Sweet syndrome associated to a differentiation syndrome was suspected. All-trans retinoic acid therapy was discontinued and dexamethasone was administered. In 48 h the patient showed remission of the fever and the infiltrates and the skin lesions acquired a residual aspect. It is debatable whether these two syndromes are distinct entities with common mechanisms or whether they are poles of the same spectrum. Dermatologists and hematologists must be aware of these two syndromes and its pathophysiologic association.

**Key words:** Differentiation syndrome; Sweet syndrome; Acute promyelocytic leukemia; All-trans retinoic acid

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**Core tip:** It is debatable whether the differentiation syndrome and the sweet syndrome are distinct syndromes with common mechanisms or whether they are poles of the same spectrum. We believe that there may be more cases of differentiation presenting with skin sweet syndrome lesions, which are underdiagnosed, overshadowed by the critical state of these patients. Dermatologists and hematologists must be aware of these two syndromes and its pathophysiologic association. It is very likely that these two specialties are staring the same phenomenon from two different points of view.

Solano-López G, Llamas-Velasco M, Concha-Garzón MJ, Daudén E. Sweet syndrome and differentiation syndrome in a patient with acute promyelocytic leukemia. *World J Clin Cases* 2015; 3(2): 196-198 Available from: URL: <http://www.wjgnet.com>

## INTRODUCTION

All-trans retinoic acid (ATRA) therapy induces the differentiation of the myelogenous leukemic cells in acute promyelocytic leukemia (APL). The differentiation syndrome (DS) is an inflammatory reaction with increased capillary permeability that occurs in up to 25% of patients with APL treated with ATRA. It is characterized by respiratory distress, fever, pulmonary infiltrates, pleuropericardic effusions, renal failure and hypotension, with a mortality of up to 30% without treatment<sup>[1]</sup>. The association of sweet syndrome (SS) and DS has been exceptionally described in the literature.

## CASE REPORT

A 50-year-old man presented with pancytopenia on a routine analysis. A bone marrow (BM) aspirate showed 73% of blasts; homogeneous medium to large cells with visible nucleoli in most cases and clasmotosis. Auer rods were also seen. The red series was decreased without megakaryocytes. The BM biopsy showed that the hematopoietic parenchyma was replaced by a proliferation of myeloid cells showing a monomorphic appearance. The neoplastic cells were positive for myeloperoxidase and CD117 and negative for CD34, TdT and Glycophorin. Thirty percent of BM cells were positive for PML-RARa by fluorescence *in situ* hybridization (FISH). Diagnosed of APL the patient underwent chemotherapy with idarubicin 12 mg/m<sup>2</sup> and ATRA 45 mg/m<sup>2</sup>. On day +21 of ATRA therapy, the patient developed pruritic erythematous 3-5 mm prepatellar papules as well as several 10 mm subcutaneous nodules in both thighs along with persistent fever (Figure 1). On day +25, the patient presented with bilateral pulmonary crackles, infiltrates in the right lower lobe and severe hypotension which required dopamine infusion. No features of disseminated vascular coagulation were present. The patient did not gain or lose weight and no renal or hepatic dysfunction was observed. Empirical antibiotic and antifungal treatment was started. A cutaneous biopsy of one papule showed moderate edema in the papillary dermis with perivascular infiltrates consisting predominantly of confluent neutrophils, without vasculitis or involvement of the adipose tissue (Figure 2). Blood, urine and biopsy cultures were negative. Skin lesions occurred along with the neutrophil count recovery and the disappearance of the promyelocytes in the BM smears. Based on the data, a diagnosis of SS associated with DS was made. ATRA therapy was discontinued and dexamethasone 10 mg every 12 h was administered. In 48 h the patient showed

remission of the fever and the pulmonary infiltrates and skin lesions cleared. On day +29, a new BM aspiration FISH study did not show the PML-RARa translocation.

Haematologists reintroduced ATRA as maintenance therapy for the APL along with corticosteroids without new recurrences.

## DISCUSSION

Cases of drug-induced SS associated with ATRA has been exceptionally described in the literature. Although systemic manifestations in SS are uncommon, there are cases of biopsy proven pulmonary involvement<sup>[2-4]</sup>.

As far as we are concerned, there are only 2 cases of SS associated with DS in patients with APL (Table 1)<sup>[2,5]</sup>.

It is debatable whether the DS and the SS are distinct syndromes with common mechanisms or whether they are poles of the same spectrum. They share common features such as fever, infiltration of neutrophils and improvement with steroid therapy. One of the differences between these two syndromes is that in most cases of SS, the involvement is limited to the skin while the main difference is the capillary leakage in the DS which is produced by the cytokine storm released by the promyelocytes as they mature. ATRA induces the differentiation of myelogenous leukemic cells into mature myeloid cells conferring them functional properties with modification of their migratory capability.

We know that these two syndromes are caused by ATRA therapy but we cannot rule out the possibility that they can be the sides of the same phenomenon with common mechanisms. For some authors, the SS and the DS are different inflammatory reactions with common mechanisms induced by ATRA therapy<sup>[6]</sup> while Ueno *et al.*<sup>[7]</sup> thought that the SS due to ATRA therapy could represent a partial form of the DS.

We believe that there may be more cases of DS presenting with skin SS lesions which are underdiagnosed, overshadowed by the critical state of these patients. Dermatologists and hematologists must be aware of these two syndromes and its pathophysiologic association. It is very likely that these two specialties are staring the same phenomenon from two different points of view.

## COMMENTS

### Case characteristics

A 50-year-old man with acute promyelocytic leukemia presented with erythematous prepatellar papules as well as several subcutaneous nodules in both thighs along with persistent fever, pulmonary crackles and hypotension.

### Clinical diagnosis

Sweet syndrome lesions and systemic symptoms in a patient who underwent chemotherapy with idarubicin and all-trans retinoic acid (ATRA).

### Differential diagnosis

Sepsis, drug reaction.

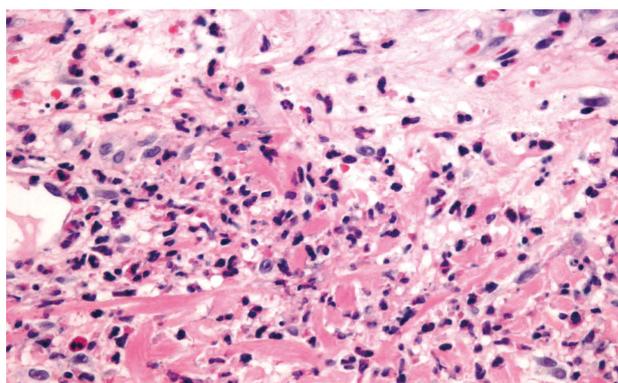
**Table 1** Cases of sweet syndrome associated with differentiation syndrome in patients with acute promyelocytic leukemia treated with all-trans retinoic acid

Ref.	Age(yr)/sex	Cutaneous location	Biopsy	Onset of skin lesions after ATRA induction therapy (d)	Onset of the DS after ATRA induction therapy (d)	DS signs and symptoms	Steroid response	Time until improvement
Takada <i>et al</i> <sup>[5]</sup>	49/F	Arms	Yes	18	28	Respiratory distress	Yes	24 h
Astudillo <i>et al</i> <sup>[2]</sup>	46/M	Trunk, arms, lower extremities	Yes	6	uk	Weight gain	Yes	Unknown
This case	50/M	Trunk lower extremities	Yes	21	25	Respiratory distress Hypotension	Yes	48 h

DS: Differentiation syndrome; ATRA: All-trans retinoic acid; M: Male; F: Female.



**Figure 1** Papules and nodules appeared on day +21 of all-trans retinoic acid therapy.



**Figure 2** Infiltrates consisting predominantly of neutrophils, without vasculitis (HE, x 20).

### Laboratory diagnosis

Blood, urine and biopsy cultures were negative.

### Imaging diagnosis

Pulmonary infiltrates in the right lower lobe on a chest radiography.

### Pathological diagnosis

A biopsy of a papule showed moderate edema in the dermis with perivascular infiltrates consisting predominantly of confluent neutrophils, without vasculitis or involvement of the adipose tissue.

### Treatment

Dopamine infusión, empirical antibiotics, ATRA therapy discontinued and dexamethasone 10 mg every 12 h.

### Related reports

As far as the author are concerned, there are only 2 cases of Sweet syndrome associated with differentiation syndrome in patients with acute promyelocytic leukemia.

### Term explanation

Sweet syndrome is an inflammatory neutrophilic skin condition characterized by a sterile infiltrate of normal polymorphonuclear leukocytes.

### Experiences and lessons

The authors believe that there may be more cases of differentiation syndrome presenting with skin sweet syndrome lesions which are underdiagnosed, overshadowed by the critical state of these patients.

### Peer review

In the submitted manuscript the authors described a rare disorder—a drug-induced sweet syndrome associated with ATRA therapy for a patient with acute promyelocytic leukemia (APL). The association of sweet syndrome and ATRA-induced differentiation syndrome is rarely observed in APL. The case in this report is well-described, along with relevant lab results.

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P- Reviewer: Dovat S, Sharma P S- Editor: Song XX  
L- Editor: A E- Editor: Lu YJ





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