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Histiocytoid Sweet's Syndrome During Induction Therapy with All-trans Retinoic Acid for Acute Promyelocytic Leukemia: A Case Report

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Abstract

Histiocytoid Sweet's syndrome is a recently described histopathologic variant of Sweet's syndrome. This is the first case report describing histiocytoid variant of Sweet's syndrome caused by all-trans retinoic acid in a patient with acute promyelocytic leukemia. We present a 30-year-old man with newly diagnosed acute promyelocytic leukemia who received induction chemotherapy containing all-trans retinoic acid and developed fever and painful erythematous cutaneous papules on day 13 of therapy. A diagnosis of histiocytoid Sweet's syndrome was made. All-trans retinoic acid was considered the culprit drug to induce this event. Treatment with corticosteroids improved the systemic and cutaneous signs. A literature search identified only 17 cases of Sweet's syndrome during all-trans retinoic acid therapy, but none were of the histiocytoid variant. The presented clinical course resembles previously reported cases of Sweet's syndrome. This case emphasizes the rare effect of all-trans retinoic acid therapy causing histiocytoid Sweet's syndrome manifesting as fever and skin papules. (J Intern Med Taiwan 2021; 32: 199-203)

Key Words: Acute promyelocytic leukemia, Sweet's syndrome, Retinoic acid, Drug-related side effects, Case report

Background

Sweet's syndrome, also called acute febrile neutrophilic dermatosis, is characterized by abrupt onset of painful erythematous skin nodules associated with fever. It has been regarded as a paraneoplastic syndrome, a therapy-related dermatosis, or concurrent leukemia cutis in patients with hematologic disorders. Histiocytoid Sweet's syndrome, first described in 2005, is a rare histopathologic variant of Sweet's syndrome, with a dermal infiltrate composed of mononulear cells and histiocytoid immature cells of myeloid lineage[1]. All-trans-retinoic acid (ATRA) induces disease remission in acute promyelocytic leukemia (APL) patients by triggering terminal differentiation of leukemic immature promyelocytes into granulocytes.

Here we report the first case of histiocytoid Sweet's syndrome induced by ATRA therapy for APL.

Case presentation

A 30-year-old man presented with dyspnea on exertion to our hospital. The complete blood

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count showed a hemoglobin level of 9.6 g per deciliter, a platelet count of $31x10^9$/L, and a white blood cell count of $3x10^9$/L with 67% promyelocytes, 5% neutrophils, and 18% lymphocytes. There was no coagulopathy. Bone marrow aspiration and biopsy showed hypercellular marrow full of hypergranulated promyelocytes containing multiple Auer rods. Immunophenotyping by flow cytometry showed that CD33, CD13, and partial MPOc were expressed in those promyelocytes. *PML-RARA* rearrangement was detected. A diagnosis of APL was made. Induction chemotherapy with ATRA at a dose of 80 mg per day (45 mg/m^2) was initiated. Peripheral blood data showed signs of differentiation since day 4 of ATRA therapy. On day 4, idarubicin for 3 days was added to the regimen. On day 13, he developed fever with painful erythematous papules and pustules on the four limbs and trunk (Figure 1).

At that point, his white blood cell count increased to 5.83 $x10^9$/L, with 58% neutrophils, 9% monocytes and 0% promyelocytes. There were

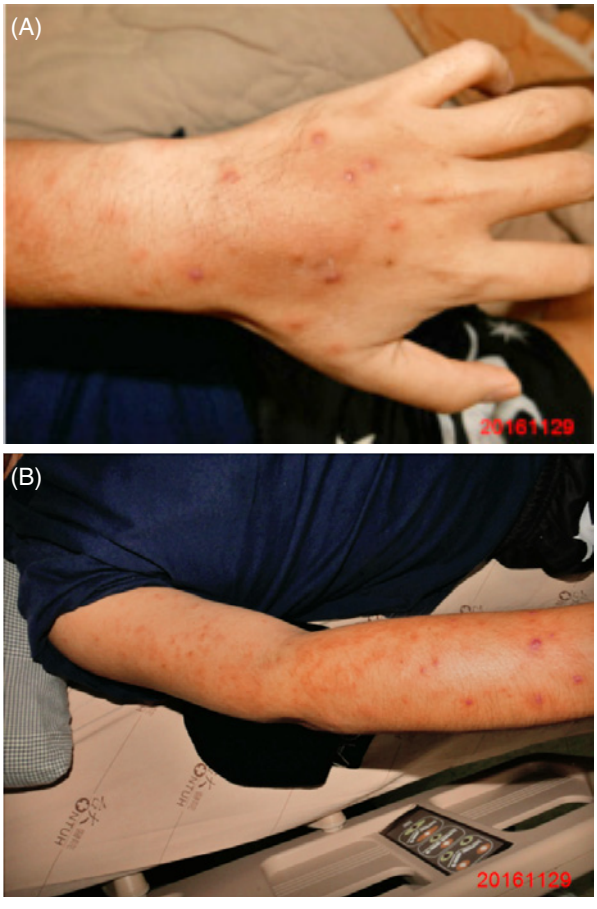

Figure 1. (A) Cutaneous lesions of the patient's left hand showing erythematous papules and pustules. (B) Cutaneous lesions of the right arm in a generalized distribution.

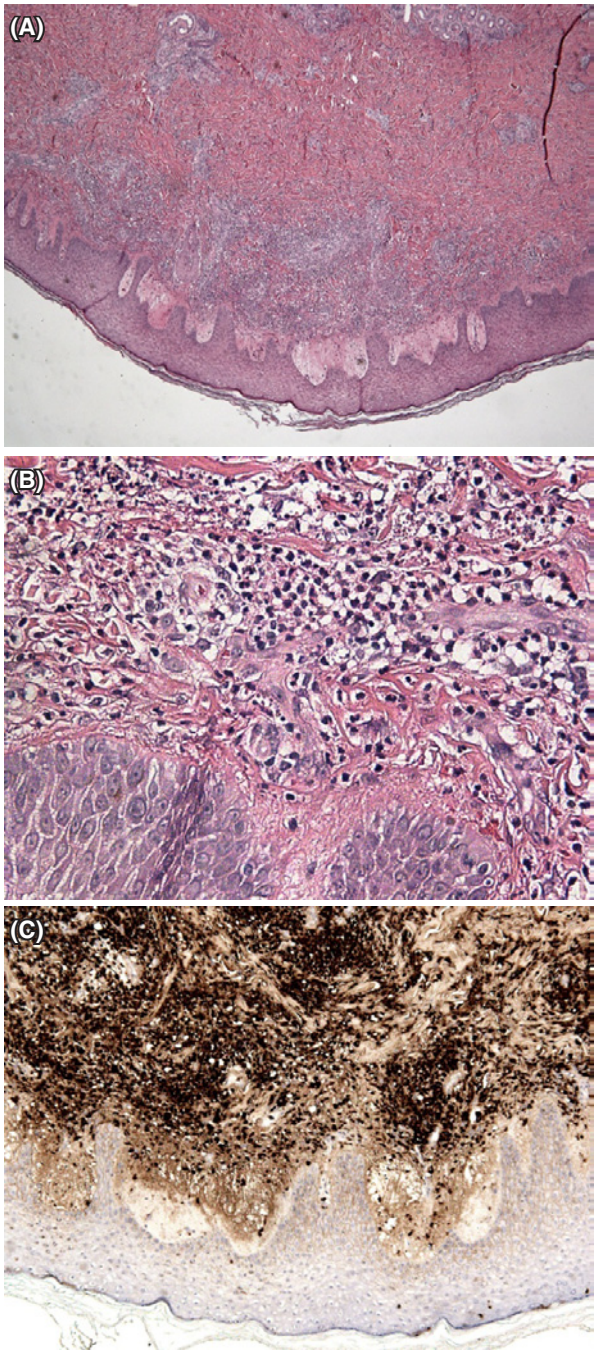

Figure 2. (A, B) Biopsy specimen of the left hand lesions showing diffuse infiltrate of mononuclear cells and histiocytoid cells with dermal edema (HE stain, A 40x, B 400x). (C) Some cells of the infiltrate express MPO in their cytoplasm.

no symptoms related to ATRA syndrome such as dyspnea, weight gain, pulmonary infiltrates, or pleuropericardial effusion. Blood and wound culture studies were performed, and no pathogens were isolated. A biopsy on day 20 of his hand skin lesions revealed infiltration by neutrophilic granulocytes, histiocytoid cells and immature granulocytes (positive for MPO and CD68) with dermal edema (Figure 2). No microorganisms were present. The clinical constellation and histopathologic findings were consistent with histiocytoid Sweet's syndrome. The Naranjo scale for adverse drug reaction (ADR) probability was 7 for ATRA, suggesting it was the probable ADR-inducing drug. Further FISH demonstrated a small proportion (10%) of the infiltrating cells positive for *PML-RARA* fusion gene (Figure 3), most of them in leukocytoclasis. Prednisolone 30 mg and colchicine 0.5 mg every 12 h were started and then with tapering doses. ATRA therapy was continued.

The patient became afebrile. His skin lesions improved over 14 days since the onset. His white blood cell count decreased to 3.05 $x10^9$/L then. Complete hematological remission was achieved 2 months after initiation of ATRA. The patient completed induction and consolidation therapies with ATRA and idarubicin and was in complete molecular remission at follow-up of 20 months later and is still on maintenance therapy with ATRA, methotrexate, and 6-mercaptourine.

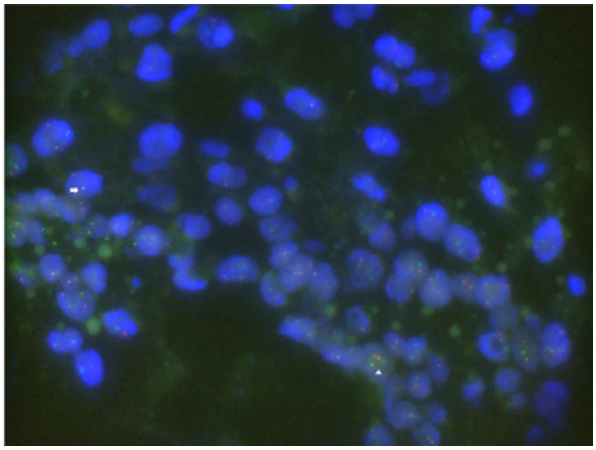

Figure 3. FISH test of the skin pathologic specimen for *PML* (15q22-24, red fluorescence) and *RARA* (17q21, green fluorescence) gene regions. In brief, the FISH probes are intended to detect the t(15;17)(q22;q21.1). A cell without translocation (arrowhead) is expected to show two red and two green signals, whereas a yellow signal (arrow) (merged color from red and green signals) indicates positivity for *PML-RARA* fusion gene in the cells.

Discussion

Few medications were associated with drug-induced Sweet's syndrome, such as trimethoprim-sulfamethoxazole, bortezomib, lenalidomide, G-CSF, furosemide, celecoxib, all-trans retinoic acid, and 13-cis-retinoic acid[2]. None of the patient's concurrent medications at the onset of Sweet's syndrome except ATRA were known to cause Sweet's syndrome. In addition, this case exhibited a temporal relationship between drug administration and typical clinical presentation. Systemic corticosteroid was effective, thus meeting the criteria for drug-induced Sweet's syndrome. Accordingly, ATRA was the most likely culprit drug for this adverse event.

Sweet's syndrome associated with APL during ATRA treatment are very rare, and only 17 cases have been reported previously (Table 1)[3-5]. Proposed mechanisms include increased G-CSF and interleukin-1ß expression in the presence of ATRA, and altered migratory capabilities[3,5]. The course is usually benign and continuation of ATRA can be considered in absence of severe differentiation syndrome. Studies to rule out infections are advised. Most patients responded to systemic corticosteroids. To the best of our knowledge, this patient is the first reported case of a patient with APL to develop histiocytoid variant of Sweet's syndrome during ATRA treatment. In this case of histiocytoid variant, the clinical course resembled classical Sweet's syndrome.

Several diagnostic entities warrant consideration in the differential diagnosis of erythematous

Table 1. Case reports of ATRA-associated Sweet's syndrome

	Age, sex	WBC at onset x10^9/L	Days of ATRA therapy
Piette 1994	50, F	4.9	21
Cox 1994	57, F	0.9	7
Tomas 1994	84, F	5.6	34
Shirono 1995	53, M	8.4	23
Christ 1996	28, F	18	9
Christ 1996	48, F	23	17
Arun 1998	50, M	12.4	26
Takada 1999	49, F	23	18
Levi 1999	58, F	5.71	11
Van der Vliet 2000	39, M	21.4	18
Ueno 2000	54, F	3.7	20
Park 2001	35, F,	2.5	24
Astudillo 2002	46, M	17.2	6
Jagdeo 2007	19, M	Not stated	Not stated
Yan 2007	49, F	2.66	23
Munoz 2012	48, M	Not stated	15
Solano-Lopez 2015	50, M	Not stated	21
Our case	30, M	5.83	13

cutaneous findings here[2,4]. Cutaneous infections (bacterial, fungal, mycobacterial), drug eruptions, vasculitis, other neutrophilic dermatoses (pyoderma gangrenosum), and malignancy (leukemia cutis) should be considered. Dermal infiltrate of characteristic mononulear cells and histiocytoid immature cells was compatible with histiocytoid Sweet's syndrome. Other diagnostic entities would not explain the pathologic findings. In this case, the skin biopsy, together with essential clinical information and established criteria, has led to a diagnosis and exclusion of other diagnoses[2,4,5]. Histiocytoid Sweet's syndrome was clearly associated with ATRA treatment in this case but the association with concurrent underlying hematologic malignancy could not be fully excluded.

A small proportion of infiltrating neutrophils were positive for *PML-RARA* by FISH in this patient. Their presence has been attributed to differentiated acute promyelocytic leukemia cells or, being less likely, concurrent leukemic infiltrates[6,7]. The detection of some bystander myeloid cells with *PML-RARA* translocation by FISH in the tissue is possible in APL patients. The reason why there were no leukemia cells by morphology is that the immature leukemia cells have undergone differentiation by medications. As those cells differentiate, before completing apoptosis, the *PML-RARA* fusion gene was still visible by FISH. Therefore, there were cells with *PML-RARA* fusion gene but they were not coined "leukemia cells" based on the differentiated morphology. Clinically, by the time of development of skin rash and skin biopsy, the hemogram of the patient has already improved after effective antileukemic therapy. Leukemia cutis would not develop at this time point of hematologic improvement. Moreover, leukemia cutis appears nodular and violaceous/gray-blue in color. Based on the above description, leukemia cutis is not an appropriate diagnosis[1].

Histiocytoid Sweet syndrome is distinct from classical Sweet's syndrome at least histopathologically[1,2,6]. The entity was first described in 2005, with clinical features of Sweet's syndrome but a dermal infiltrate composed of mostly mononuclear cells. The rare variant of Sweet's syndrome was studied further according to a clinicopathologic, immunohistochemical, and molecular features, showing that these infiltrating cells in the dermis was immature and of myeloid lineage, but should not be interpreted as leukemic cutis[1]. This histopathologic variant of Sweet syndrome was shown to be associated with hematologic malignancy with the same frequency as classic neutrophilic Sweet syndrome[1]. No data on its prognostic role was found. Further studies are necessary to delineate the pathogenesis and clinical significance of histiocytoid Sweet's syndrome.

Conclusions

For clinical practice, our patient's case empha-

sizes awareness of drug-induced Sweet's syndrome as a rare differential diagnosis for fever and skin rashes during ATRA therapy. With biopsy and early accurate diagnosis of the skin lesions, proper treatment of leukemia with curative intent could can be ensured. This case report is notable as it describes the first patient of APL in the literature developing histiocytoid variant of Sweet's syndrome during ATRA treatment.

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急性前骨髓性白血病接受ATRA治療合併類組織細胞Sweet症候群：病例報告

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摘　要

類組織細胞Sweet症候群(Histiocytoid Sweet's syndrome)是近期描述的一種Sweet症候群之組織病理變異型。本病案描述文獻上第一例之由全反維他命A酸(all-trans retinoic acid)在急性前骨髓性白血病病人引起之類組織細胞Sweet症候群。患者為30歲男性，新診斷急性前骨髓性白血病，在接受包含全反維他命A酸的前導性化學治療後第13天產生發燒、疼痛性皮膚丘疹。診斷為由全反維他命A酸引起之類組織細胞Sweet症候群。經由類固醇治療後，系統性及皮膚狀況改善。文獻回顧只有17例由全反維他命A酸在急性前骨髓性白血病病人引起之Sweet症候群，但其中並無案例屬於類組織細胞變異型Sweet症候群。本案例強調全反維他命A酸引起類組織細胞Sweet症候群之罕見副作用，其以發燒及丘疹為臨床表現。