中文題目：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

英文題目：Histiocytoid Sweet's syndrome during induction therapy with all-trans retinoic acid for acute promyelocytic leukemia: a case report

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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 is a recently described rare variant of Sweet's syndrome, with a dermal infiltrate composed of histiocytoid immature cells of myeloid lineage and numerous mature neutrophils (*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.

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

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 no symptoms related to RA 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. The clinical constellation and histopathological 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 leukocytoclasis and a small proportion (10%) of the infiltrating cells positive for *PML-RARA* fusion gene. 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, MTX, and 6-MP.

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 (*3*). 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 (*4-6*). 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. Little is known about its mechanisms. 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. Unlike prior published cases, a small proportion of infiltrating neutrophils were positive for *PML-RARA* by FISH in this patient. Their presence was attributed to differentiated acute promyelocytic leukemia cells (*7*) or, being less likely, concurrent leukemic infiltrates (8) as shown in the literature. Further studies are necessary to delineate the pathogenesis.

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