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Sweet syndrome associated with differentiation syndrome in a patient with acute promyelocytic leukemia – a case report and review of literature

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Introduction

Sweet Syndrome (SS) (acute febrile neutrophilic dermatosis) is an inflammatory disorder characterized by the appearance of painful, edematous, and erythematous papules, plaques, or nodules on the skin. It might also cause fever and internal organs' involvement. There are three clinical settings in which SS has been described: classical or idiopathic, malignancy-associated and drug-induced. (1) SS is described in patients with acute promyelocytic leukemia (APL), and is a rare side effect of all-trans retinoic acid (ATRA), which causes differentiation of promyelocytes and used in therapy of APL. ATRA may also cause Differentiation Syndrome (DS), previously called retinoic acid syndrome, and there is overlap with SS. (2)

There is a limited number of case reports describing SS in association with DS. We present here a case of SS associated with DS in a patient with APL treated with ATRA.

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Case presentation

A 43-year-old Filipina female, previously healthy, presented with easy fatigue and bruises for two weeks preceded by fever and sore throat. Her physical exam revealed bruises in the lower limbs, and retinal dot hemorrhages. Her complete blood count (CBC) on presentation: white blood cells (WBCs) 1.4 $x10^3$/µL (4.0 – 10.0), hemoglobin (Hb) 8.0 gm/dL (12.0 – 15.0), platelets (Plts) 63 $x10^3$/µL (150 - 400), peripheral smear showed leukopenia with marked neutropenia and abnormal leukemic promyelocytes ~ 4%, with features of early disseminated intravascular coagulation, elevated d-dimer of 15.51 mg/L (0.0 – 0.49) and low fibrinogen level of 0.8 gm/L (2.0 – 4.1) but normal coagulation profile. Bone marrow, cytogenetics and FISH confirmed Acute Promyelocytic Leukemia with PML-RARA, considered low risk.

Started on ATRA 45 mg/m^2/day as part of PETHEMA protocol. On day eight she developed painful non-pruritic rash, started on the dorsum of the right hand, and later spread to involve the whole body including the face and neck (papular and vesicular with some subcutaneous nodules), most lesions were several millimeters in diameter except the lesion on the dorsum of the right hand, ~ 2 centimeter in diameter (see Figure 1). On day nine she spiked fever with chills. Started on meropenem and acyclovir as the skin lesions were suspected to be herpetic. All cultures were negative, as well as herpes simplex and herpes zoster IgM. Over the next four days she didn't improve, as she continued to spike fever which became high grade and rash spread all over the body. Until this stage there was no weight gain and she didn't have any respiratory symptoms. On day fifteen started having dry cough which progressed rapidly over few hours to become severe and continuous with tachypnea (40 breaths/minute), tachycardia (126 beats/minute) and drop in saturation (88% on room air). SS +/- DS was suspected, so started on dexamethasone 10 mg BID, and ATRA held, Chest X-Ray (CXR) showed development of new widespread infiltrates in both lung fields (see figure 2). WBC count was starting to recover – 3.3. She got transferred to medical intensive care unit for further management. After two days, she was back on room air, afebrile, rash started to fade gradually, and she was transferred back to medical floor.

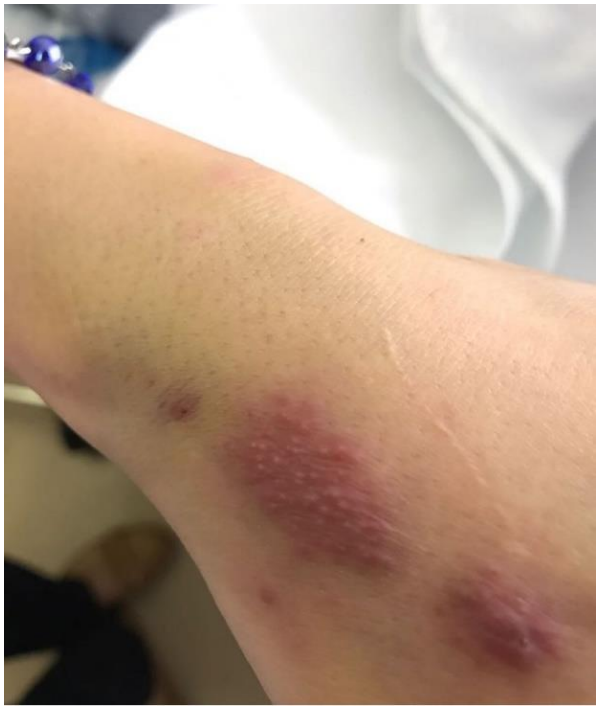

Figure 1: Shows the rash that first appeared on the dorsum of the right hand

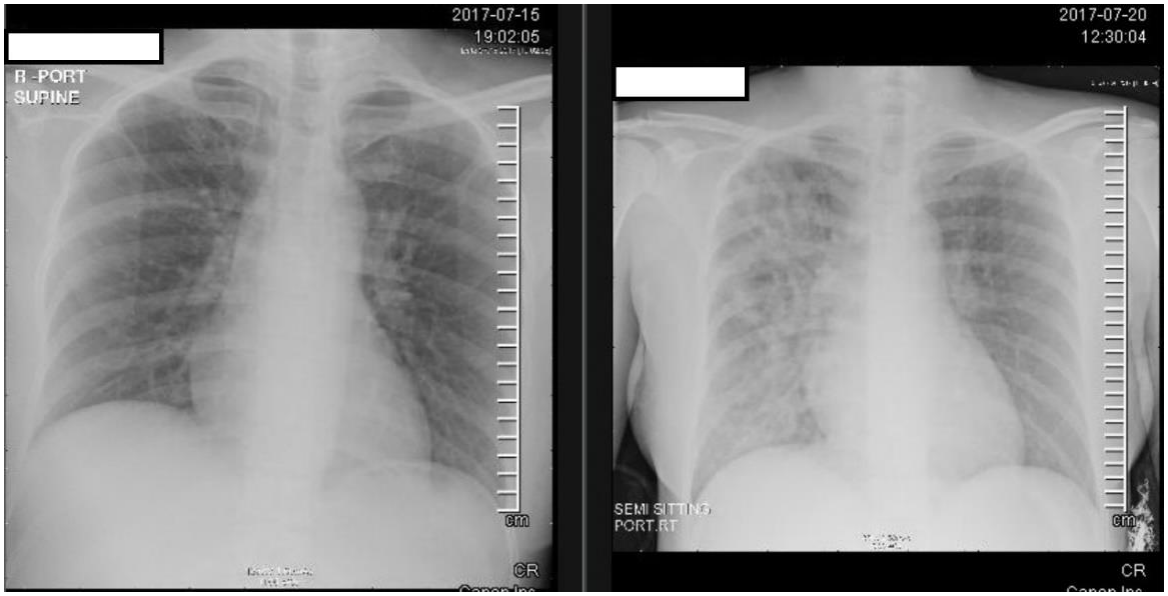

Figure 2: CXR on day 10 (Left side), CXR on day 15 with clinical deterioration (right side)

Discussion

Differentiation syndrome (DS), is a potentially life-threatening complication in up to a quarter of patients with APL during induction therapy with ATRA or arsenic trioxide (ATO). Clinical manifestations include unexplained fever, weight gain, peripheral edema, dyspnea with interstitial pulmonary infiltrates, pleuropericardial effusion, hypotension, and acute renal failure. (3)

Pathogenesis is not fully understood, but involves release of inflammatory vasoactive cytokines, linked to the differentiation and maturation of promyelocytes induced by ATRA or ATO, causing capillary leak, fever, edema, rash, and hypotension. Also, tissue infiltration by the maturing cells. (4)

SS seems to share pathogenesis with DS is described in association with ATRA. Both respond well to steroid therapy, typically dexamethasone 10 mg BID, with temporary discontinuation of ATRA in severe cases. (1-6)

There are 3 case reports describing SS in association with DS. Summary of characteristics in table 1.

Table 1: Case of SS associated with DS in patients with APL treated with ATRA

Reference	Age (years) / Sex	Location of skin lesions	Onset of skin lesions after initiation of ATRA (days)	Onset of DS after initiation of ATRA (days)	DS presentation	Steroid response	Time till improvement (hours)
Takada et al (7)	49/F	Arms	18	28	Respiratory distress	Yes	24
Astudillo et al (8)	46/M	Trunk, limbs	6	NA	Weight gain	Yes	NA
Solano-López et al (5)	50/M	Trunk, lower limbs	21	25	Respiratory distress, hypotension	Yes	48
This case	43/F	All over	8	15	Respiratory distress	Yes	24

The differential diagnosis for painful vesicular rash and fever in an immunocompromised patient, is herpes viral infection. However, given the fact that the rash worsened with acyclovir therapy and progressed to have respiratory distress and infiltrates in the lungs, then quickly responded to dexamethasone and withholding ATRA, makes the diagnosis of SS associated with DS the most likely diagnosis.

Because we didn't have skin biopsy to prove our assessment of SS with DS in the clinical context of our case, to assess the probability of this adverse drug reaction, we used the Naranjo Adverse Drug Reaction Probability Scale (Table 2) (9); the calculated score of 5 indicated that ATRA was the probable cause for SS associated with DS.

Table 2: Naranjo Adverse Drug Reaction Probability Scale: Items and score.

Question	Yes	No	Don't know	Patient's score
1. Are there previous conclusive reports on this reaction?	+1	0	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was administered?	+1	0	0	0
4. Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	+2
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drug in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1

Scoring • >9 = definite ADR • 5–8 = probable ADR • 1–4 = possible ADR • 0 = doubtful ADR

References

1. Raza S, Kirkland RS, Patel AA, Shortridge JR, Freter C. Insight in-to Sweet's syndrome and associated-malignancy: a review of the current litera-ture. Int J Oncol. 2013 May;42(5):1516-22. doi: 10.3892/ijo.2013.1874. Epub 2013 Mar 28.
2. Tallman MS, Altman JK. How I treat acute promyelocytic leukemia. Blood. 2009 Dec 10;114(25):5126-35. doi: 10.1182/blood-2009-07-216457.
3. Montesinos P, Bergua JM, Vellenga E, Rayón C, Parody R, de la Serna J, León A, Esteve J, Milone G, Debén G, Rivas C, González M, Tormo M, Díaz-Mediavilla J, González JD, Negri S, Amutio E, Brunet S, Lowenberg B, Sanz MA. Differentiation syndrome in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and anthracycline chemotherapy: characteristics, out-come, and prognostic factors. Blood. 2009 Jan 22;113(4):775-83. doi: 10.1182/blood-2008-07-168617. Epub 2008 Oct 22.
4. Rego EM, De Santis GC. Differentiation syndrome in promyelocytic leukemia: clinical presentation, pathogenesis and treatment. Mediterr J Hematol Infect Dis. 2011; 3(1): e2011048. Published online 2011 Oct 24. doi: 10.4084/MJHID.2011.048
5. 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 Feb 16; 3(2): 196–198. Published online 2015 Feb 16. doi: 10.12998/wjcc.v3.i2.196

6. Yan ZS, Li DP, Jiang EL, Zhou CL, Liu EB, Chen HS, Feng SZ, Han MZ. Devel-opment of Sweet syndrome in an acute promyelocyte leukemia patient during treatment with all-trans retinoic acid--case report and literature review. Zhong-hua Xue Ye Xue Za Zhi. 2007 Jul;28(7):462-5.
7. Takada S, Matumoto K, Sakura T, Shiozaki H, Miyawaki S. Sweet's syndrome followed by retinoic acid syndrome during the treatment of acute promyelocytic leukemia with all-trans retinoic acid. Int J Hematol. 1999 Jul;70(1):26-9.
8. Astudillo L, Loche F, Reynish W, Rigal-Huguet F, Lamant L, Pris J. Sweet's syn-drome associated with retinoic acid syndrome in a patient with promyelocytic leukemia. Ann Hematol. 2002 Feb;81(2):111-4. Epub 2002 Jan 10.
9. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981 Aug;30(2):239-45.