Editorial Comment: Sweet Syndrome—A Diagnosis Seeking a Cause

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By AIDS Reader [1]

Dermatological disorders may occur in more than 90% of persons infected with HIV. In this setting, skin disorders tend to be more frequent as immunodeficiency progresses. The spectrum of cutaneous diseases includes inflammatory dermatoses, drug reactions, infections, and neoplasms. Johnson and colleagues present an unusual case of Sweet syndrome in a 37-year-old HIV-positive man coinfected with Treponema pallidum. Sweet syndrome was originally described by the late English dermatologist Dr Robert Sweet (1917 to 2001) in 1964 in the August-September issue of the British Journal of Dermatology. In this seminal article, he summarized the features of “acute febrile neutrophilic dermatosis” that he had encountered in 8 women during a 15-year period. In 1968, Whittle and colleagues reported a similar case that they termed “Sweet syndrome,” which then became the accepted eponym for such acute febrile neutrophilic dermatosis.

There are hundreds of non–HIV-associated cases of Sweet syndrome reported in the literature. Apart from the case presented by Johnson and colleagues, we are aware of only 7 other HIV-associated cases of Sweet syndrome (Table). In one of these cases, Sweet syndrome was the initial manifestation of HIV infection. Classic Sweet syndrome demonstrates a female predilection. Age at onset is most common in the fourth to seventh decades, but the syndrome can occur in infants, children, and the elderly. In the published cases of HIV-associated Sweet syndrome (Table), patients were, on average, 43 years of age (range, 3 months to 54 years) and were more frequently male. The mean CD4+ cell count in this HIV-infected group of patients was 307/µL (range, 50 to 530/µL).

Cutaneous lesions in Sweet syndrome often begin as tender, nonpruritic, erythematous papules, which typically enlarge and coalesce to form plaques with an irregular surface. Owing to the presence of marked papillary dermal edema, these plaques may exhibit a pseudovesicular or bullous clinical appearance. Frank bullae may eventually form, leading to epidermal ulceration. Such lesions usually present on the head, neck, and upper extremities, particularly the dorsal aspect of the hands. The distribution of such skin lesions was documented in all of the HIV-associated cases (Table). However, in the 3-month-old infant, macerated white papules were also noted on the tongue and palate. One of the HIV-infected women also had associated dysphagia and moderate diarrhea.
Lesions may occur anywhere, particularly in patients with Sweet syndrome associated with an underlying malignancy. Pathergy, the induction of clinical lesions secondary to wounding injuries, such as abrasions and wounds resulting from venipuncture procedures, may also develop. Multiple indurated red plaques with bullae and necrosis were described at the vaccination site in one HIV-positive case. The most common systemic manifestations of Sweet syndrome, occurring in the majority of patients, are fever and leukocytosis. Less common (20% to 50%) presentations include arthralgia; myalgia; and ocular involvement, such as conjunctivitis, episcleritis, limbal nodules, and iridocyclitis.

Despite typical clinical features, a skin biopsy is often required to confirm the clinical suspicion and remains one of the major criteria for the diagnosis of Sweet syndrome. Histological findings of papillary dermal edema and a dense, superficial sterile infiltrate that consists predominantly of mature neutrophils, without evidence of leukocytoclastic vasculitis, are not pathognomonic. These findings may also be seen in infections, rheumatoid neutrophilic dermatoses, and bowel-associated dermatosis-arthritis syndrome. The pathological findings of Sweet syndrome can also occur in extracutaneous sites.

Much like anemia, which is a diagnosis seeking a cause, so, too, should the diagnosis of Sweet syndrome prompt a search for a possible cause. Sweet syndrome may be subdivided into 5 groups based on its cause: (1) infection-associated; (2) malignancy-associated (paraneoplastic); (3) autoimmune/inflammatory-associated; (4) drug/vaccine-induced; and (5) pregnancy-related. The most common associated infections are those of the upper respiratory tract (eg, streptococcal infections) and GI tract (eg, salmonellosis and yersiniosis). Apart from HIV, other infectious triggers may include Chlamydia, mycobacteria, cytomegalovirus, and hepatitis viruses. Syphilis, as pointed out in the preceding case report, can be added to the list of infectious associations. Approximately 10% to 20% of patients with Sweet syndrome may have an associated malignancy. Acute myeloid leukemia, usually of the myelomonocytic type, is by far the most common malignancy associated with Sweet syndrome. However, solid tumors (mainly, carcinomas of the genitourinary system, breast, and GI tract), lymphoma, or myeloma may also be present. Only 1 of the HIV-positive patients shown in the Table was reported to have a malignancy (Kaposi sarcoma). The most common autoimmune/inflammatory conditions associated with Sweet syndrome include Crohn disease and ulcerative colitis. Rheumatoid arthritis, sarcoidosis, relapsing polychondritis, lupus erythematosus, subacute thyroiditis, and Behet syndrome may also be present as well as chronic granulomatous disease and primary T-cell immunodeficiency.

Medications associated with drug-induced Sweet syndrome include antibiotics (eg, trimethoprim/sulfamethoxazole [TMP/SMX], minocycline), antiepileptics, antihypertensives (eg, hydralazine), diuretics (eg, furosemide), NSAIDs (eg, celecoxib, diclofenac), contraceptives, antineoplastics (eg, imatinib), antipsychotics (eg, clozapine), propylthiouracil, retinoids, and colony-stimulating factors (eg, granulocyte colony-stimulating factor [G-CSF]). Sweet syndrome may also occur following vaccination. Sweet syndrome is assumed to represent an immunological hypersensitivity rash caused by an underlying trigger. Enhanced chemotaxis has been reported in several cases, which may help explain the dermal aggregate of neutrophils. Some investigators have shown that the pathogenesis is probably mediated through CD4+ helper T cell type 1 cytokines (interleukin-2 and interferon-γ). The mechanism(s) underlying Sweet syndrome in HIV-infected persons is unclear. HIV-induced immune disturbances are thought to create a favorable background for the occurrence of Sweet syndrome. Potential triggers that have been linked with HIV-associated Sweet syndrome include infection, medications (eg, G-CSF, NSAIDs, furosemide, TMP/SMX), and influenza vaccination. Apart from the case being reported by Johnson and colleagues, only 2 other cases in HIV-infected persons were associated with exposure to antiretroviral drugs. Bevilaqua and colleagues document the onset of Sweet syndrome 1 month after their patient received an antiretroviral drug regimen of zidovudine, zalcitabine, and saquinavir. Del Giudice and colleagues noted the onset of clinical features 2 months following the start of a regimen containing lamivudine, nelfinavir, and abacavir; symptoms improved 48 hours after abacavir was stopped. It is plausible that immune restoration in these cases may have had a role in the onset of Sweet syndrome. It will certainly be interesting to observe whether similar clinical findings will constitute part of the immune restoration inflammatory syndrome (IRIS) in the current HAART era.

Sweet syndrome, by itself, is a benign condition, which if left untreated may persist for weeks or months. Recurrence (with or without treatment) is common, occurring in approximately 30% of cases. Antibiotics are not usually indicated, unless a specific infection is identified. The most effective treatment is the use of systemic corticosteroids, which usually gives prompt relief of
cutaneous and extracutaneous manifestations. In fact, the excellent response to systemic corticosteroids is one of the minor criteria for the diagnosis of Sweet syndrome. In an HIV-positive person, a thorough search for an inciting event provoking Sweet syndrome is mandated. Initial investigations should focus on concomitant new infections, underlying malignancy, pregnancy, new medications, and possibly IRIS.

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