CLINICAL VIGNETTE

Histiocytoid Sweet Syndrome and Myelodysplastic Syndrome

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Clinical Case

A 61-year-old male with chronic leukopenia presented to rheumatology for a second opinion on his Rheumatoid Arthritis treatment. One year prior he had developed fever, right lower extremity and ankle erythema and swelling and presented to the Emergency Department. Deep vein thrombosis was ruled out, and he was treated for cellulitis. One month later these same symptoms recurred, and he was managed with another course of antibiotics. He subsequently developed rashes and mouth sores thought to be a reaction to the antibiotics. He also developed severe pain and swelling in the bilateral feet and ankles without involvement of other joints. Further evaluation revealed positive ANA and rheumatoid factor, leading to a diagnosis of Rheumatoid Arthritis. He was treated with Prednisone 20mg daily and all symptoms improved. He was started on hydroxychloroquine as a disease modifying agent. Two months later he developed worsening leukopenia and thrombocytopenia and discontinued hydroxychloroquine. Bone marrow biopsy revealed myelodysplastic syndrome (MDS).

The patient was not able to reduce his prednisone below 20mg daily without recurrence of erythema, pain and swelling in the ankles and feet. He was unable to take sulfasalazine due to a sulfa allergy and unable to take methotrexate due to leukopenia and thrombocytopenia. He was started on Etanercept by an outside rheumatologist and experienced severe allergic reaction. Tofacitinib was then tried and was ineffective. He presented for a second opinion and appeared cushingoid. He was taking 20mg Prednisone daily and he had no tender or swollen joints and no rashes on physical exam. His labs were significant for positive ANA 1:40 homogenous pattern and a positive rheumatoid factor at 51. His inflammatory markers were elevated with a sedimentation rate of 22 and a C-Reactive Protein of 14. His white blood cell count was low at 2.8, hemoglobin normal at 14.6 and platelets low at 88. Radiographs of his feet and ankles were normal without joint space narrowing or erosions. A repeat bone marrow biopsy by his hematologist showed stable MDS. VEXAS testing was negative.

Infusions with Rituximab were initiated as a steroid sparing agent which was complicated by a severe flare a month later with foot pain and swelling. MRI of the foot indicated soft tissue swelling *without* findings of an inflammatory arthritis. Given the MRI findings and lack of response to RA therapy, it was suspected that the patient did not have RA and that the positive ANA and RF serologies were instead reflective of the underlying MDS. The patient was also having atypical RA features including increasing fever, night sweats and lower extremity rashes. Skin biopsy during a flare indicated histiocytoid sweets syndrome. Prednisone was increased with initial improvement of symptoms, but symptom flares continued despite moderate to high doses of steroids. Additional treatment for sweets syndrome with NSAIDS, colchicine, dapsone and potassium iodide were all ineffective. His MDS was initially thought to be "low risk," not requiring therapy, however due to the ongoing flares, and lack of responsiveness to multiple therapies for Sweet's, the decision was made to treat the MDS with decitibine. With the MDS chemotherapy, his flares began to subside with resolution of fevers, night sweats, rashes and improvement of pain and swelling, enabling him to taper his prednisone.

Discussion

Sweet Syndrome was first described in 1964 by Robert Sweet as a constellation of clinical findings he described as an "acute febrile neutrophilic dermatosis." Symptoms include sudden onset of painful erythematous plaques or nodules. Sites frequently involved include the face, neck and extremities.[1] The rashes may be difficult to distinguish from bacterial cellulitis,[2] and suspect that occurred at initial presentation. Other salient features include fever, leukocytosis, elevated neutrophil count, and prompt clinical improvement following the initiation of steroid therapy. Arthralgias, myalgias, headaches and malaise can also be associated symptoms.[1] On histopathologic exam, a predominant neutrophil infiltrate is seen in the dermis with the absence of vasculitis features.[2] Histiocytoid Sweets syndrome is a histological variant of sweets syndrome that is characterized by a dermal infiltrate mainly composed of histiocytoid cells.[3]

Sweets syndrome has been further categorized into 3 subtypes; the "classic" presentation, the "malignancy-associated" presentation and the "drug-induced" presentation where symptoms are precipitated by a medication. The classic presentation may be associated with an upper respiratory or gastrointestinal infection, inflammatory bowel disease or pregnancy. In the malignancy associated presentation, the dermatosis is either the presenting manifestation of an undiagnosed cancer or a sign of malignancy complication or recurrence.[1] Approximately 21% of patients with sweets syndrome have an underlying malignancy. More and more cases have been associated with MDS

and less frequently with other hematologic malignancies or solid tumors.[2]

Ghoufi et al. conducted a comparative study of 62 patients with histopathologic coded diagnosis of sweets syndrome between 2005 and 2014. Overall, 22 (35.5%) had histiocytoid sweets syndrome and 40 (64.5 %) had neutrophilic sweets syndrome. The median age, sex ratio and presenting clinical features were similar between the two groups. They noted recurrent forms of sweets syndrome were significantly more frequent in the histiocytoid group. MDS was also significantly more prevalent in the histiocytoid group, occurring in one third of the patients. Hematologic disease was diagnosed before or at the time of the occurrence of the cutaneous lesions. However, in 3 histiocytoid patients with MDS, the skin lesions preceded the MDS diagnosis by up to 6 months. This highlights the importance of monitoring for development of hematologic malignancy in patients with sweets syndrome, especially if the histiocytoid variant is diagnosed.[3]

The clinical course of sweets syndrome can vary from acute non-relapsing to a chronic relapsing and remitting course. The acute non-relapsing forms of sweets syndrome generally have an identifiable preceding trigger and are more common in drug-induced forms where the symptoms respond dramatically to cessation of the medication with or without a short course of steroids. The chronic recurring forms are associated with more severe systemic upset and debility. The condition can respond to systemic steroids but will relapse as the dosage is reduced and tends to be more recalcitrant to other therapies as seen in this patient. This form of sweets syndrome was found to be more associated with MDS even if the MDS was considered "low risk."[4]

Systemic corticosteroids are the mainstay of therapy for sweets syndrome. Other potential therapies include high potency topical steroids, intralesional corticosteroids, clofazimine, colchicine, cyclosporine, dapsone, indomethacin and potassium iodide.[1] There have also been reports of successful treatments with methotrexate, etanercept, and infliximab although response to immunosuppressive therapy is variable. It has also been suggested that MDS-associated histiocytoid sweets syndrome may respond better to hypomethylating agents such as azacitidine and decitabine.[2] For our patient, treatment of the MDS with decitabine was the only intervention that successfully treated his histiocytoid sweets syndrome.

REFERENCES

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