Neuro-Sweet disease

A case of recurrent encephalitis and febrile neutrophilic dermatosis

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Practical Implications

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Case report

A 49-year-old African American woman developed acute confusion followed by speech arrest, right face and arm weakness, and hemineglect that spontaneously resolved 1 hour from onset. Brain MRI showed fluid-attenuated inversion recovery (FLAIR) hyperintensities and cortical thickening in bilateral cingulate gyri and left insular and frontal cortex (figure 1, A and B). Her examination showed a Montreal Cognitive Assessment (MoCA) score of 8/30. CSF showed 327 nucleated cells/ μ L (lymphocyte predominant) and protein 120 mg/dL. Erythrocyte sedimentation rate (ESR) was 36 mm/h, C-reactive protein (CRP) 5.3 mg/L, peripheral leukocyte count 14.3 K/mm^3 with 67% neutrophils. No infectious etiology was identified. Pertinent negatives included the following: CSF and serum paraneoplastic panel; CSF herpes simplex virus, cytomegalovirus, and varicella-zoster virus PCRs, and West Nile virus immunoglobulin M; CSF and serum protein electrophoresis; and serum thyroid-stimulating hormone, TPO antibody, HIV, rapid plasma reagin, antinuclear antibodies, extractable nuclear antigen, and antineutrophil cytoplasmic antibodies. CSF cytology and body PET/CT demonstrated no malignancy. EEG showed left hemispheric slowing. Levetiracetam was started given the presenting transient deficits. After 5 g of IV methylprednisolone (empiric treatment for presumed autoimmune encephalitis), she was discharged on oral prednisone with an improved MoCA score of 18.

The patient was readmitted 11 days later with transient confusion and fevers to 39.5°C after errantly tapering her prednisone off within 1 week of discharge. A 1 cm erythematous papule was noted above her lip. A repeat EEG was normal; repeat brain MRI and CSF analysis showed interval improvement. Oral prednisone was restarted. In clinic on the last day of her planned steroid taper, she was doing well, but memory, language, and executive dysfunction persisted (MoCA 16). Brain MRI showed resolution of the FLAIR changes (figure 1, C and D). Her skin lesion had disappeared. Because of a mild headache and depressed mood, venlafaxine was started.

A week later, the patient re-presented with a temperature of 39.1°C and no identifiable infectious etiology; however, tender, edematous violaceous papules had erupted over all her limbs and abdomen (figure 2, A and B). Her neurologic examination was unchanged. Venlafaxine was stopped with concern for a drug allergy. ESR was 73 mm/h. A skin biopsy revealed dermal neutrophilic infiltration and septal panniculitis without vasculitis, diagnostic of Sweet syndrome (figure 2, C and D). The rash cleared with

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Figure 1 MRI findings before and after corticosteroids

Fluid-attenuated inversion recovery hyperintensities from the initial encephalitis admission present in the bilateral cingulate gyri and left frontal cortex (A) and the left insular cortex (B) had resolved by the end of 2 courses of prednisone (C, D).

prednisone 60 mg daily. She was diagnosed with NSD and discharged on a slow steroid taper. She has been on low-dose prednisone since then without recurrence of neurologic disease.

DISCUSSION

NSD is a rare entity presenting with neurologic symptoms and fever that precede, coincide with, or follow acute neutrophilic dermatosis,¹ making the diagnosis and management challenging. An extreme example of this temporal dissociation was the first patient assigned a diagnosis of neuro-Sweet syndrome, who had recurrent meningitis for 2.5 years before dermatologic manifestations led to a diagnosis.¹ NSD should be considered in cases of idiopathic meningoencephalitis when common infectious or autoimmune etiologies are ruled out. Other CNS manifestations include headaches, epilepsy, hemiparesis, dysarthria, and ataxia.¹ They are usually transient, recurrent, and steroid-responsive.¹ While most NSD is benign, the association between Sweet syndrome and malignancy warrants cancer screening, especially for myelodysplastic disorders.^{1,2} Lymphocytic pleocytosis and elevated CSF protein are common, as are elevated ESR and CRP.² Brain MRI can be normal or include T2 hyperintensities in cortical or subcortical regions (without site predilection), often with asymmetries, and meningeal enhancement/thickening may also be present.³ Proposed diagnostic criteria for probable NSD stipulate that neurologic symptoms respond to steroids and that tender erythematous plaques with pathology characteristic of Sweet syndrome are found on skin biopsy (criteria fulfilled by our patient).^{2,3} Diagnosis may have been expedited had the face lesion been biopsied during the patient's second admission.

Clinically, NSD and Neuro-Behçet disease (NBD) may coincide,^{4,5} which presents another diagnostic challenge. In both conditions, meningoencephalitis is a common neurologic presentation and mucocutaneous and ocular involvement can occur.⁴ CNS deficits of NBD are more likely to persist and progress. Distinctly, dermatologic and CNS biopsies in NBD show vasculitis, a finding absent in NSD, where pathologic data are limited to one autopsy study that showed histiocytic perivascular cuffing without vasculitis,⁶ underscoring the importance of early skin biopsy. The MRI abnormalities in NBD have a predilection for the brainstem and deep gray nuclei.²⁻⁴ Importantly, steroids, which are extremely effective in NSD, can aggravate mucocutaneous lesions in NBD.^{2,3}

NSD attacks may recur with steroid discontinuation. Other therapies used for Sweet syndrome include topical steroids, dapsone, cyclosporine, and colchicine, but there are no established therapies beyond corticosteroids for NSD.⁷

Figure 2 Leg rash and skin pathology

Tender violaceous papules on the lower extremities (pictured are lesions over the medial left leg at the knee and proximal right posterolateral thigh/buttocks) (A), one of which was biopsied (right anteromedial thigh, not visible in A) (B), resolved with oral prednisone. Low-power (40 $\times$) view of a hematoxylin & eosin (H&E) stain of the skin biopsy of the leg lesion (C) shows neutrophilic infiltration of the dermis/subcutaneous fat (arrow) without evidence of vasculitis, characteristic of Sweet syndrome. Grocott methenamine silver, acid-fast bacilli, Fite, and Gram stains were negative for microorganisms. A higher-power (400 $\times$) view shows a neutrophilic focus within the dermis/subcutaneous fat (arrow) (D).

Our patient's persistent cognitive impairment prevents her from returning to work. Longitudinal studies are needed to identify the neurologic sequelae of delayed diagnosis, risk factors for recurrence, and the efficacy of steroid-sparing agents in preventing relapses.

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