LETTERS TO THE EDITOR

STIFF PERSON SYNDROME IMPROVEMENT WITH CHEMOTHERAPY IN A PATIENT WITH CUTANEOUS T CELL LYMPHOMA

A 57-year-old Caucasian woman developed diffuse erythematous subcutaneous induration at 40 years of age. She was found to have peripheral blood lymphocytosis, and subsequent skin biopsy confirmed T-cell lymphoma. Pan–computed tomography (CT) scans and other comprehensive malignancy work-ups were negative. Skin lymphoma was treated with high-dose oral steroids and later in combination with hydroxychloroquine for the next 6 years. In addition to skin lesions (Fig. 1), she had persistent fatigue with low-grade fever, malaise, and weight loss. At 44 years of age, she developed episodes of painful back and abdominal muscle spasms resulting in tripping episodes and the need for a cane. Worsening of truncal muscle stiffness and disabling spasms correlated with skin tumor flare-ups. The patient also began to exhibit an exaggerated startle response to unexpected auditory and tactile stimuli. She was found to have elevated anti–glutamic acid decarboxylase 65-kDa isoform (anti-GAD65) antibody (6.4 U/ml, normal $\leq$1.0 U/ml), whereas amphiphysin antibody and a comprehensive paraneoplastic panel were negative.

Symptomatic therapy with baclofen and diazepam was initiated with some improvement of stiffness. In addition, she was treated with plasma exchange and pulse intravenous dexamethasone on 4 separate occasions for autoimmune stiff person syndrome (SPS), with marginal improvement. For exacerbation of skin lymphoma, the patient then received a course of monthly cyclophosphamide infusions followed by a standing dose of tacrolimus, with remarkable improvement of skin lesions as well as SPS symptoms for several months thereafter. After 2 years of being only on symptomatic therapy, she developed steady deterioration of gait, and yearly rituximab treatment was administered for the next 3 years. She had significant improvement that allowed her to ambulate without assistance. Thirteen years later, a standard dose of alemtuzumab was administered once for lymphoma relapse with the most robust improvement of both cutaneous lymphoma and SPS symptoms. During the past 4 years and without further chemotherapy, the patient has been walking unaided without tripping. A repeat GAD antibody titer was 4.6 U/ml.

In SPS associated with tumor, either cryptogenic or paraneoplastic, cross-reactive binding of serum antibodies with malignant cells expressing neuronal antigens, such as GAD and amphiphysin, may be responsible for triggering the autoimmune response.[1,2] Although the complex autoimmune processes involved in these patients are not fully understood, cancer-specific therapies in addition to immunomodulating agents may synergistically benefit both conditions. Recognition of the neurological syndrome and associated autoantibodies should prompt and direct diagnostic work-up for malignancy. Although SPS in our patient may or may have not been a paraneoplastic manifestation of her cancer, early and continuous treatment of lymphoma with chemotherapeutic agents resulted in marked resolution of her neurological symptoms. Use of B-cell–depleting therapies in SPS and other humoral immunity-related neurological disorders, such as myasthenia gravis and IgM neuropathies, should be considered in refractory patients who do not respond to standard symptomatic and immune therapies.[3–7] T-cell–depleting therapies have a potential to confer more robust and long-lasting modulation of immune processes in SPS, but the safety and efficacy in GAD-associated neurological disorders not associated with malignancy needs to be studied prospectively.

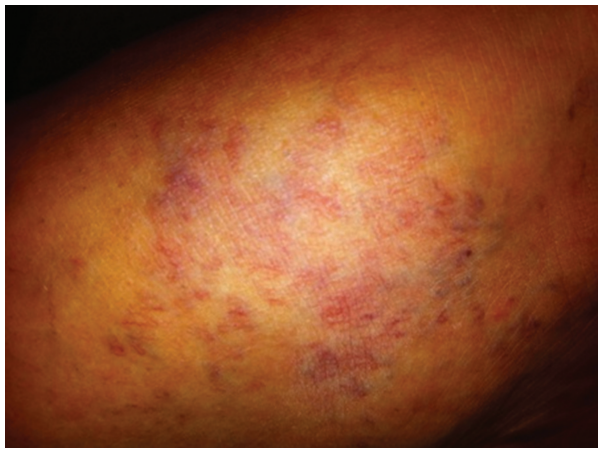

FIGURE 1. Primary cutaneous T-cell lymphoma.

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FLEXOR HALLUCIS BREVIS SPASM

A 30-year-old man presented with a 2-year history of painless involuntary muscle "twitches" affecting the instep of his right foot. There was no causative trigger nor any consequent functional deficit. He was not taking regular medications and did not smoke or drink excess alcohol. There was no family history of neuromuscular disease.

Neurological examination was normal except for conspicuous spontaneous, tonic, continuous, and irregular muscle activity in the instep of his right foot with wrinkling of overlying skin and repetitive flexion of his right great toe (see video online). This movement was not distractible nor entrainable. The clinical impression was that of a hitherto unreported flexor hallucis brevis (FHB) muscle spasm; a condition that would be analogous to palmaris brevis spasm syndrome in the hand.

Routine blood tests were unremarkable. The absence of structural pathology in the distribution of the medial plantar neurovascular bundle (which supplies the FHB muscle) was confirmed by normal ankle and foot radiographs plus an MRI scan. Electromyography showed high-frequency motor unit potential discharges with normal duration, amplitude, and morphology. These were transient, spontaneous, and irregularly recursive. They exclusively affected the right FHB muscle. Other lower limb muscles sampled (including gastrocnemius and tibialis anterior) were electrically silent during the spasmodic episodes. Motor and sensory nerve conduction studies were normal, specifically in the tibial nerve, and F-wave latencies were normal. Peripheral nerve electrophysiology thus excluded the possibility of an underlying entrapment neuropathy (tarsal tunnel syndrome). To exclude the remote possibility of focal motor seizures we performed electroencephalography, which was normal. We concluded that this condition was hitherto unreported FHB spasm.

DISCUSSION

The FHB muscle arises from the medial aspect of the cuboid bone, the third cuneiform, and the prolongation of the tibialis posterior tendon. It divides into 2 portions, which insert into the medial and lateral sides of the base of the first phalanx of the great toe. FHB is innervated by the medial plantar nerve, which is the larger of 2 terminal divisions of the tibial nerve. The condition we describe may result from entrapment of the first branch of the medial plantar nerve where it pierces the plantar fascia on the way to FHB. It likely resembles other focal muscular hyperactivity syndromes, including palmaris brevis syndrome, focal dystonia–blepharospasm, and hemifacial spasm. Typically, these are benign conditions involving spontaneous tonic contractions of a single muscle group causing "dimpling" in the skin superficial to the affected muscle. There are usually no specific triggers. The spasms are not under voluntary control, but they are exacerbated by stress and alleviated by rest.[1] The extent to which motor unit potential size or recruitment pattern determine susceptibility to develop these conditions has yet to be established. We propose that this spectrum of disorders includes blepharospasm and hemifacial spasm,[2] hence providing some rationale for using botulinum toxin therapeutically. In our patient, FHB could be targeted if the symptoms progress to become functionally incapacitating.

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