CASE REPORT

Neuro-Ophthalmic Presentation of Neuro-Sweet Disease

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ABSTRACT

Acute febrile neutrophilic dermatosis (Sweet syndrome) is a systemic inflammatory condition usually associated with autoimmune or neoplastic processes and characterised by inflammatory dermatologic lesions such as erythematous plaques and papules associated with fever and leukocytosis. Neurological and ophthalmological involvement is rare. The authors describe an unusual case of Sweet syndrome associated with microscopic polyangiitis presenting with papilloedema, anterior uveitis, and skin rash. Years later, he developed acute posterior multifocal placoid pigment epitheliopathy. Treatment with immunosuppressive medications led to a relapsing remitting course with maximum benefit from use of steroids. The authors describe the difficulties in diagnosis and treatment of this rare case.

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APMPPE; microscopic polyangiitis; neuro-Sweet; papilloedema; Sweet syndrome

Introduction

Sweet syndrome (SS) or acute febrile neutrophilic dermatosis is a systemic inflammatory disease, first described by Dr. Robert Douglas Sweet in 1964.¹ It is characterised by dermatologic lesions such as erythematous plaques and papules accompanied by fever and leukocytosis.^{1,2} SS along with pyoderma gangrenosum and erythema elevatum diutinum forms a group of diseases called neutrophilic dermatoses. Diagnosis is established by a skin biopsy that shows characteristic features of deep dermal infiltration of mature neutrophils, spared epidermis, and absence of vasculitis. SS is usually associated with an underlying autoimmune or neoplastic process. Ocular manifestations may be seen in a third of SS, and neurological manifestations are uncommon. We present a unique case of SS associated with microscopic polyangiitis who initially presented with papilloedema, anterior uveitis, and skin rash.

Materials and methods

A 62-year-old obese white male with no pertinent past medical history developed headache, blurred vision, redness, and watering in both eyes 2 weeks after

starting male enhancement pill, Extenze. Extenze is an over-the-counter nutritional supplement containing a combination of male prohormone blend (dehydroepiandrosterone, pregnenolone), bio-enhancement blend (black pepper, piper longum, and ginger root), sexual response enhancement blend (yohimbe bark, licorice extract, pumpkin, L-arginine hydrochloride, γ -aminobutyric acid, etc.), zinc, and folic acid. He denied symptoms of transient visual obscurations, pulsatile tinnitus, or diplopia. Three months earlier, he was evaluated for malaise and weight loss and found to have lymphopenia, elevated thyroid-stimulating hormone (TSH; 20.3 uIU/ml) and antithyroid peroxidase antibody, and normal T3 levels. His primary care felt he had inflammation secondary to “unknown viral infection” and treated him with a course of antibiotics and methylprednisolone. Ophthalmic examination obtained after he developed visual blurring revealed normal visual acuity with no afferent pupillary defect, quiet anterior segment, and papilloedema in both eyes. Visual fields showed enlarged blind spots in both eyes and an infero-nasal defect in the right eye. Contrast-enhanced magnetic resonance imaging (MRI) of the brain and orbit and MR venogram were normal. Lumbar

puncture on two occasions revealed opening pressures of 36 and 42 cm H₂O, respectively. Cerebrospinal fluid (CSF) formulation was normal on both occasions. He was treated with acetazolamide for “pseudotumor cerebri”. Within a week, he developed rash on his legs that was attributed to “poison ivy”. However, the rash was resistant to treatment with topical steroids and quickly spread to his abdomen and arms. A skin biopsy was reported to be inconclusive. Both Extenze and acetazolamide were discontinued due to suspicion of drug allergy within 6 weeks of initiation. No other medication for lowering intracranial pressure was added. He was referred to neuro-ophthalmology for evaluation.

Results

Neuro-ophthalmic examination about 2 months from onset of visual symptoms revealed visual acuity of 20/30 right eye and 20/20 left eye. Right pupil showed sluggish reaction without relative afferent pupillary defect (RAPD). Slit-lamp examination showed keratic precipitates, anterior chamber flare, and anterior vitreous cells in the right eye. Funduscopy examination revealed Frisén scale grade 3 papilloedema on the right and grade 2 papilloedema on the left with no haemorrhages, exudates, or cotton wool spots in either eye. Fluorescein angiogram showed disc leakage in both eyes, but otherwise unremarkable. He

was seen by a uveitis specialist, who felt topical steroids were not warranted. Systemic evaluation revealed pustular eruption, with necrosis and scab crusting on a pink-red inflammatory base distributed in a serpiginous fashion across his chest and extremities (Figure 1A). A repeat skin biopsy of the lesions revealed mixed dermatitis pattern with features of granuloma annulare and neutrophilic dermatosis consistent with Sweet syndrome (Figure 1B–D). He was treated with oral steroids, which resulted in improvement of the skin rash and uveitis but led to development of steroid-induced diabetes.

A month later, he developed hoarseness of voice and shortness of breath. Laryngoscopy revealed laryngitis and an ulcer on the epiglottis. High-resolution chest computed tomography (CT) showed interstitial lung disease. Pulmonary function testing revealed forced vital capacity (FVC) of 85% and forced expiratory volume in 1 s (FEV₁)/FVC of 92%. Right lobe wedge biopsy of the lung confirmed chronic obliterative bronchiolitis most likely secondary to collagen vascular disease.

Autoimmune evaluation showed elevations of erythrocyte sedimentation rate (ESR; 114 mm/h), C-reactive protein (CRP; 8 mg/dL), anti-nuclear antibody (ANA; 1:320), myeloperoxidase antibody (MPO), and perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA), with normal double-stranded DNA antibody levels. He was diagnosed

Figure 1. (A) Skin rash distributed in a serpiginous fashion across chest and extremities. (B, C) Skin punch biopsy (haematoxylin and eosin stain); (B) low-power magnification 2× and (C) medium-power magnification 20× showing pustular necrosis with inflammatory cells within the pustule, multinucleated giant cells at the interface, and overlying thin epidermis with thinned keratin on the roof of the pustule with sparing of deep dermis. (D) Skin biopsy (haematoxylin and eosin stain) high-power magnification 40× showing granuloma annulare in dermis consisting of mixed cells—lymphocytes, macrophages, giant cells, and collagen necrobiosis.

to have atypical microscopic polyangiitis and treated with immunomodulators (azathioprine, mycophenolate mofetil, and subsequently rituximab). Within 3 months of treatment, papilloedema and uveitis had resolved in both eyes. He had normal visual acuity, colour vision, and pupillary reaction. Visual fields continued to show nonspecific inferonasal field defect in the right eye and enlarged blind spot in the left eye.

A follow-up contrast-enhanced MRI of brain and orbit was normal. A follow-up lumbar puncture (performed for headache) showed normal opening pressure (11 cm H₂O) and elevated CSF protein (85 mg/dl).

Three years later, he returned with worsening skin lesions and blurred vision in both eyes. Ophthalmology examination revealed visual acuity of 20/30 in both eyes, RAPD in the right eye, mutton fat keratic precipitates in both eyes, vitreous flare and cells in the right eye, and multiple pale creamy white subretinal lesions involving the macula of the right eye (Figure 2A). Fundus examination of the left eye was normal. No disc oedema was noted in either eye. There was disc pallor in the right eye. Visual fields showed worsening, with nasal defects in both eyes. Retinal nerve fibre layer thickness on optical coherence tomography (OCT) showed global thickness of 72 µm on the right and 86 µm on the left. Fundus fluorescein angiogram showed hyper-autofluorescent lesions with early blocking and late staining in the right eye (Figure 2 B, C). He was diagnosed with acute posterior multifocal placoid pigment epitheliopathy (APMPPE). Prednisone 60 mg/day was added, which resulted in resolution of posterior uveitis and skin rash. Rituximab was discontinued, and he is now being treated with methotrexate.

Discussion

Neuro-Sweet syndrome (NSS) is an uncommon entity first reported in 1999,³ with fewer than 70 cases reported in literature.^{4–6} Nervous system involvement is believed to occur due to aseptic neutrophilic infiltration resulting in meningoencephalitis and can lead to raised intracranial pressure.⁷ NSS is more prevalent in patients of Asian origin, males, and in the age group 30–60 years. Neurological signs and symptoms include headache and altered consciousness and may precede development of skin lesions.⁸ Ophthalmic manifestations may be seen in approximately a third of SS. These occur due to inflammation of the ocular, orbital, and periorbital tissues leading to dacryoadenitis, conjunctivitis, episcleritis, scleritis, limbal nodules, keratitis, uveitis (anterior, posterior and panuveitis), glaucoma, retinal vasculitis, and optic neuropathy.^{1,8,9}

Our case report highlights the diagnostic difficulty for rare presentations of systemic conditions. Presentation with papilloedema and elevated CSF pressure with normal contents led to the falsely reassuring diagnosis of idiopathic intracranial hypertension and treatment with acetazolamide, despite tell-tale signs of a systemic inflammatory process—constitutional symptoms, headache, skin rash, uveitis, and elevated inflammatory markers. Skin rash was attributed to his exposure to “poison ivy” and later to drug allergy. Delay in initiating treatment with immunosuppressive medications likely resulted in increased morbidity from uveitis, epiglottitis, and interstitial lung disease. Diagnosis of SS was established with demonstration of characteristic features on skin biopsy.

Figure 2. (A) Fundus photo of the right eye showing multiple pale creamy white subretinal lesions involving the macula of the right eye. (B, C) Fundus fluorescein angiogram of the right eye showing hyper-autofluorescent lesions with early blocking (B) and late staining (C).

Common involvement of uvea, retina, and meninges from inflammatory processes is seen in a group of heterogeneous disorders collectively called “uveo-meningeal syndrome”. These include infectious, autoimmune, neoplastic, and paraneoplastic processes. Autoimmune processes commonly associated with uveo-meningeal syndrome include microscopic polyangiitis (MPA), sarcoidosis, Behçet’s disease, Vogt-Koyanagi-Harada (VKH) disease, and APMPE.¹⁰ Several cases of SS in literature describe simultaneous occurrence of intraocular and central nervous system (CNS) inflammation, which suggests that SS may be a cause of uveo-meningeal syndrome.⁸ We believe that our patient most likely had uveo-meningitis at presentation. Although the initial CSF results were “normal”, we believe that CSF pressure was elevated due to aseptic meningitis. The cell count may have falsely normalised as he was treated with steroids for “unknown viral infection”. A subsequent lumbar puncture showed elevated protein (85 mg/dl), which supports this hypothesis.

Majority of the cases of SS are associated with an underlying systemic disorder.^{8,11} Classical SS occurs in patients with autoimmune diseases such as sarcoidosis and Behçet’s and may be associated with human leucocyte antigen (HLA) B54.¹² SS is also associated with underlying systemic malignancy and may be induced by certain types of medications.¹³ In our patient, SS was associated with an underlying autoimmune condition: microscopic polyangiitis (MPA). MPA is one of the three main conditions constituting a group of rare and potentially fatal diseases called ANCA-associated vasculitis (AAV), the others being granulomatosis with polyangiitis (GPA; also called Wegener’s disease) and eosinophilic GPA (EGPA). Although skin lesions are common in AAV, the specific association of neutrophilic dermatosis (specifically SS) with AAV is uncommon. In an excellent case series and literature review of 50 patients with AAV and neutrophilic dermatosis, de Boysson et al. identified MPA in 11 patients of whom 5 had SS.¹⁴ Of these 5 cases, 3 had peripheral nervous system involvement whereas none had central nervous system manifestations. To the best of our knowledge, there are no known reports of neurological or neuro-ophthalmological

presentations of MPA with SS, although SS has been reported in MPA.¹⁵

Scleritis and episcleritis are the most common ophthalmic manifestations in AAV. Other manifestations include retinal vein occlusion, optic neuropathy, acute posterior multifocal placoid pigment epitheliopathy (APMPPE), anterior ischaemic optic neuropathy (AION), and multifocal choroiditis.^{16,17} Interestingly, our patient developed APMPPE while being treated with rituximab without adjunct treatment with steroids. Although there are no known reports of the association of SS with APMPPE, there are reports of APMPPE in patients with AAV.^{17,18} The association of APMPPE with cerebral vascular inflammation is well known.^{19,20} Although reports of association between AAV, SS, and APMPPE are vanishingly rare, this might be simply due to the difficulty in diagnosing SS and APMPPE due to lack of expertise at centres where such subspecialists may not be readily available. Such challenges were experienced in the management of our patient who steadily flowed through seven different subspecialists and his primary care before being diagnosed and managed appropriately using multidisciplinary care (rheumatology, dermatology, ophthalmology, neuro-ophthalmology, dermatopathology, pulmonary medicine, and retina/uveitis). This case highlights the difficulties in accurate diagnosis of systemic inflammatory conditions with protean manifestations likely related to common underlying immunological mechanisms and perhaps antigen target.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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