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Improvement of neurological symptoms and memory and emotional status in a case of seronegative Sneddon syndrome with cyclophosphamide

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Abstract

Sneddon syndrome (SS) is characterized by livedo racemosa, recurrent ischemic strokes, and often progressive vascular dementia. Treatment options for SS center on either anticoagulation or immunosuppression to prevent strokes and to dissipate the skin findings, with these modalities based historically on the presence or absence of antiphospholipid antibodies (APA) respectively. However, few effective treatments have been reported to reverse the cognitive decline in SS. We report a case of a woman with seronegative SS (absence of APA) with cognitive decline who demonstrated objective and subjective improvements in her memory and emotional functioning after treatment with cyclophosphamide.

Keywords

Seronegative Sneddon syndrome; Cognitive decline; Cyclophosphamide; Dementia in the young

1. Introduction

Sneddon syndrome (SS) is a disease characterized by livedo racemosa and ischemic strokes. This disease occurs mostly among women in their third decade. In addition to stroke symptoms, SS presents with renal failure, seizures, headache, and vertigo [1]. Additionally, dementia in young individuals without clinical strokes can be the presenting symptom of SS [2–5]. While the prevalence of cognitive decline in this condition is unknown, impairments in concentration and memory are often observed in SS. Cumulative infarcts are hypothesized to account for the cognitive decline [6]. The natural history of SS includes continued cognitive decline and progression of leukoencephalopathy, causing subcortical dementia [1–6]. Therefore, aggressive treatment should be sought to prevent future disability. Limited reports exist on the anticoagulant, warfarin, in the treatment of the cognitive decline in SS with unclear effects [2,4,5]. We report a case of SS who demonstrated improvements in her

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Conflict of interest

The authors have reported no conflicts of interest.

neurological symptoms and her memory and emotional functioning after 8 months of monthly intravenous cyclophosphamide therapy.

2. Case report

A 46-year-old, right-handed Caucasian woman with a history of hepatitis C and hypertension presented with acute onset of leftsided weakness and numbness. She was brought to the emergency room 3 h after the onset of her symptoms. She had developed a painless rash in her bilateral lower extremities and abdomen 6 months prior to the presentation and was treated with prednisone for several weeks without improvement. She also experienced transient left hand and leg weakness 3 days prior to the presentation, lasting for only a few minutes. On examination, her pulse was 63 beats per minute, and her blood pressure was 188/74 mmHg. No heart murmur was appreciated. Lace-like maculopapular skin eruptions were noted on the bilateral lower extremities and abdomen (Fig. 1A). On neurological examination, she appeared to be impulsive and disruptive to the examiner. Mini-Mental Status Exam was 28/30, in which she missed one point for orientation and another for shortterm recall. She had hemiparesis with Medical Royal Council (MRC) scale 4/5 strength in the left upper and lower extremities. Sensory perception was diminished to light touch and temperature on the left face, arm, and leg. Deep tendon reflexes were hyper-reflexic on the left side with negative Babinski's signs bilaterally. The rest of the neurological examination was unremarkable. Her medications consisted of prednisone 50 mg daily for her rash and metoprolol XR 50 mg daily for hypertension. She had a 20-year-pack smoking history, but denied alcohol or intravenous drug use. Her family history was notable for a cousin with multiple sclerosis, but was otherwise unremarkable for neurological disease. She denied any history of arthritis, malar rashes, asthma, or hemoptysis.

An unenhanced computer tomography (CT) scan of the brain in the emergency department revealed multiple foci of white matter hypodensities. A subsequent magnetic resonance imaging (MRI) showed hyperintensity in these lesions in the diffusion weighted imaging (DWI), consistent with ischemic infarcts in the bilateral middle cerebral artery (MCA) territories (Fig. 2A). Digital subtraction angiogram (DSA) showed distal narrowing of intracranial blood vessels consistent with vasculitis (Fig. 2B–D). Cerebrospinal fluid (CSF) analysis showed 1/mm³ white blood cell, 14/mm³ red blood cell, 65 mg/dL glucose, and 25 mg/dL protein without increased immunoglobulin G synthesis rate. Echocardiogram showed normal left heart function without thrombus or patent foramen ovale. However, the patient's right atrium and right ventricle were both dilated with high pulmonary artery pressure consistent with pulmonary hypertension. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were not elevated, and both cryoglobulins and antiphospholipid antibodies (APA) were absent. A hypercoagulable workup was unremarkable. Other laboratory studies including serum anti-nuclear antibody, p-anti-neutrophil cytoplasmic antibody (p-ANCA), c-ANCA, and Lyme titers were all negative. Serum hepatitis C ribodeoxy-nucleic acid (RNA) was undetectable. Based on the livedo racemosa, multifocal strokes, lack of serum APA, and the absence of alternative diagnoses, the patient was diagnosed with seronegative Sneddon syndrome. The patient was initially treated with high

dose intravenous methylprednisone for several days but developed hyperglycemia as an acute effect of the steroids, and thus the treatment was discontinued.

The patient's initial neuropsychological assessment occurred 80 days following the discontinuation of her steroid treatment. She earned her GED and was a few courses short of earning an Associate's degree. She worked primarily as a window cleaner and was functional in this capacity until 5 months prior to the presentation when she stopped working due to a decline in her cognitive abilities. She complained of impaired attention and concentration, as well as memory loss, misplacing possessions and repeating herself in conversations. She described episodes of "mind foginess" and her "mind going blank" which lasted for several hours. In addition, she reported feeling disoriented at times, with increased irritability and anxiety. On the initial neuropsychological testing, she demonstrated low-average to borderline impaired learning of both verbal and visual material, verbal long-term recall, confrontational naming, lexical and semantic fluency, visuo-spatial construction, visuo-motor information processing speed and set-shifting. Normative data that corrected for the influence of gender, ethnicity and level of education were used when available. Mild symptoms of depression and minimal symptoms of anxiety were also reported at the initial evaluation (Table 1).

Following the neuropsychological evaluation, she began treatment with daily intravenous cyclophosphamide dosed at 750 mg/m² body surface area for 3 days and then monthly for 8 months. Her skin rash improved (Fig. 1B), and her muscle strength returned to normal with residual hyper-reflexia on her left side. The patient reported subjective improvement of her neurological condition after 2–3 doses of cyclophosphamide. A repeat brain MRI showed only hyperintense lesions in the T2 sequence corresponding to the old strokes in the prior MRI. No DWI signal changes indicated new strokes.

Follow-up neuropsychological testing, performed 8 months after the onset of her treatment, revealed improvements in verbal learning and learning and retention of visually presented material to the average range, with a mild decline in attention. Visuo-construction with 3-dimensional blocks remained impaired and a mild decline in attention was revealed, both of these findings are likely associated with the MCA vascular changes noted on her MRI (Table 1). Moreover, our patient reported subjective improvements in her cognitive functioning following treatment, noting that she "didn't have any more brain lapses or mind fogs," and that her depression and anxiety had improved. She reported plans to return to work within 2 weeks at her previous place of employment. The neuropsychological scores were further examined using reliable changes indexes (RCIs), a statistical method which adjusts for practice effects and test–retest reliability [7]. A 95% confidence interval (CI) adjusted for neuropsychological practice effects was calculated revealing reliable improvements in the previously mentioned cognitive domains. The declines in attention were not statistically reliable declines according to the RCI values (Table 1). Although she endorsed a mild level of symptoms of depression at follow-up, the number of symptoms had reduced over time. This improvement in mood may have also influenced her changes in memory. However, her attention scores, which are typically affected by mood changes, did not improve following treatment.

3. Discussion

SS is characterized by livedo racemosa in combination with multiple cerebrovascular ischemic insults as originally described by Sneddon in 1965 [8]. SS most commonly occurs among women between the ages of 20 and 40 and is associated with neurological symptoms such as headaches, vertigo, seizure, progressive dementia and stroke, in addition to other clinical findings such as hypertension, heart valve abnormalities, and renal involvement [1,6]. The skin findings of livedo racemosa may precede other clinical findings [1]. Strokes occur most frequently in the MCA territory, resulting in hemiparesis, sensory disturbances and aphasia [1,6]. SS is a progressive condition, and the long-term functional status is usually related to the cumulative burden of repeated ischemic infarcts [1,6,9]. Prognosis of untreated SS is poor, and about half of the patients suffer long-term disability [6,9].

This 46-year-old woman with livedo racemosa had multi-focal strokes. Though a history of smoking and hypertension can contribute to strokes, multi-focal acute strokes in a young woman are very unusual. Her DSA showed vasculitic changes; therefore, a brain biopsy was not performed. In addition, brain biopsy is rarely pathognomonic in SS, with prior studies in the literature showing diverse patterns including granulomatous leptomeningeal infiltrates [10], multiple vascular thrombosis without vasculitis [5], or multiple healed necrotic foci in the gray and white matter without inflammation or vascular thrombosis [3]. As a result of her livedo racemosa, multi-focal strokes, lack of serum APA, and absence of alternative diagnosis based on laboratory data and imaging, this patient was diagnosed with seronegative SS.

Though some familial cases of SS are reported [11], the debates on the pathophysiology of SS mainly center on whether SS is an inflammatory or prothrombotic disease. Approximately 40% of SS patients have antiphospholipid antibody, raising the question of whether SS overlaps with primary antiphospholipid antibody syndrome (APS) and systemic lupus erythematosus (SLE) [9,12]. SS with no antiphospholipid antibody (seronegative SS) has a larger fishnet pattern of livedo racemosa, less frequent seizures and slower progression, and milder clinical manifestations [9,12]. The etiology of SS is not completely understood. Skin biopsies of livedo racemosa reveal a vascular inflammation process manifested by lymphocytic and polymorphonuclear infiltrations in the capillary vessels [13]. Brain biopsies of patients with SS have shown either vasculitic or thrombotic changes [3,5,10]. The small number of pathological studies makes it difficult to determine whether SS is inherently an inflammatory vasculitic or occlusive thrombotic disease.

The treatment of SS is divided into either anticoagulation or immunosuppression based on the assumptions of either thrombotic or inflammatory etiologies. Anticoagulation therapy is usually based on the recommended treatment for primary APS, specifically to keep international normalized ratio (INR) greater than 3. Angiotensin converting enzyme inhibitors (ACEI) and prostaglandin E1 (PGE1) have also been used in the treatment of SS [14]. Corticosteroids, cyclophosphamide, and azathioprine are the commonly used immunosuppressants in treatment of SS with variable results [14]. In the case of our patient, we chose immunosuppressants based on the absence of antiphospholipid antibodies and multi-focal irregularity of cerebral vessels by angiogram similar to a vasculitic pattern.

Approximately 77% of SS patients have subjective neuropsychiatric complaints [1], and SS can also be a cause of dementia in the young [2–5]. Very limited evidence exists regarding effective treatment of cognitive decline in SS; to our knowledge, only five reports are available. Kume et al. treated a 24-year-old man with SS with cyclophosphamide, prednisolone, and prostaglandin with improvement of psychiatric symptoms and a decreased anti-cardiolipin level. However, the authors reported the patient's mental abilities remained "subnormal," and the patient required low doses of haloperidol to control psychotic symptoms. No objective neuropsychological testing was performed [15]. Flöel et al. also reported a 29-year-old woman with SS who continued to decline cognitively when treated with steroids, azathioprine, and aspirin. The therapy was switched to aspirin plus clopidogrel, and the regimen stabilized cognitive function on neuropsychological tests [14]. However, the patient experienced medically refractory epilepsy and was on multiple anti-epileptic medications, which were known to cause cognitive dysfunction and to interfere with neuropsychological test interpretation [14]. Three other studies reported cases with SS and progressive dementia that were treated with warfarin, however, detailed descriptions regarding the effects of this therapy on cognitive function were not provided [2,4,5].

In conclusion, previous studies showed potential therapeutic options for the neurological and cognitive declines in SS patients, but these studies did not demonstrate objective and subjective improvements of memory and behavioral functions on neuropsychological evaluation. In the present case, we used a treatment of cyclophosphamide for 8 months in a patient with seronegative SS and cognitive and behavioral decline, who demonstrated a subsequent improvement in subjective and objective memory and emotional status. Therefore, we propose that cyclophosphamide should be considered among first line treatment options for patients with SS and cognitive impairment. Future research in a controlled study should investigate the effectiveness of this treatment and identify potential subgroups of patients who may be good responders. If further research replicates these initial findings, it may be possible to identify another potential reversible cause of dementia in the young.

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Fig. 1.
The patient had livedo racemosa with lace-like rashes on her bilateral lower extremities at presentation (A), and the rashes lessened after 8 months treatment of cyclophosphamide (B).

Fig. 2. Brain magnetic resonance imaging (MRI) showed multi-focal subcortical hyperintensities in the diffusion weighted imaging (DWI) consistent with acute ischemic strokes (A). Digital subtraction angiogram (DSA) revealed multi-focal distal narrowing (arrows) of intracranial blood vessels (B–D).

Table 1

Neuropsychological scores before and after cyclophosphamide treatment.

Measure by cognitive domain	Baseline		Follow-up		95% RCI criterion	Difference between baseline and follow-up
	Raw	T-score	Raw	T-score		
Mental status						
MMSE (0–30)	28	NA	29	NA	1.30	1.0
Verbal memory						
HVLT-R Total (0–36)	25	43	34	63	0.74	9.0*
HVLT-R LTM (0–12)	11	55	11	55	0.66	0.0
Visual memory						
BVMT-R Total (0–36)	21	42	30	60	5.60	9.0*
BVMT-R LTM (0–12)	7	38	11	59	2.20	4.0*
Language						
BNT (0–60)	51	42	51	42	2.70	0.0
Lexical Fluency (no max)	37	47	38	51	12.0	1.0
Semantic Fluency (no max)	18	46	16	41	4.10	–2.0
Visuo-spatial						
Clock Drawing (0–10)	9	NA	10	NA	0.80	1.0*
Block Design (0–68)	30	25	28	25	3.22	–2.0
ROCF (0–36)	34	41	35	51	1.22	1.0
Attention/info. processing						
Digit Span (0–30)	17	50	16	37	1.90	–1.0
Trails A (0–300s)	29	41	27	46	9.30	–2.0
TSAT (0–480 s)	66	71	57	60	18.87	–9.0
Executive functions						
Trails B (0–300s)	61	47	56	47	20.9	–5.0
WCST Persever Errors (0–64)	4	55	5	53	8.30	1.0
Affective functioning						
BDI (0–63)	18	Mild	6	Mild	NA	NA
BAI (0–63)	10	Minimal	4	Minimal	NA	NA

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Mini-Mental Status Exam (MMSE); WAIS-III Similarities; Trail Making Part A (Trails A); WAIS-III Digit Span; Test of Sustained Attention (TSAT); Verbal Fluency (FAS); Category Fluency-Animals; Boston Naming Test (BNT); Hopkins Verbal Learning Test-Revised (HVLT-R); Brief Visual Memory Test-Revised (BVMTR); Wisconsin Card Sorting Test (WCST); Trail Making Part B (Trails B); Clock Drawing; WAIS-III Block Design; Rey-Osterrieth Complex Figure (ROCF); Beck Depression Inventory-II (BDI); Beck Anxiety Inventory (BAI).

* Significantly reliable difference between baseline and follow-up testing.