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CASE REPORT

Guillain–Barré syndrome occurring synchronously with systemic lupus erythematosus as initial manifestation treated successfully with low-dose cyclophosphamide

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Systemic lupus erythematous (SLE) is frequently encountered in clinical practice; a widespread immunological response can involve any organ system, sometimes leading to rare and diagnostically challenging presentations. We describe a 38-year-old female who presented with symmetric numbness and tingling of the hands and feet, and cervical pain. Imaging studies were not diagnostic of any serious underlying pathology. The patient developed ascending paresis involving lower extremities and cranial muscles (dysphagia and facial weakness). Guillain–Barré syndrome (GBS) was diagnosed on the basis of electromyography and lumbar puncture showing albuminocytologic dissociation. Intravenous immunoglobulins (IVIG) were administered for 5 days. Supported by anti-dsDNA antibody, oral ulcers, proteinuria of 0.7 g in 24 h, and neurological manifestation, she was diagnosed with lupus. After completion of IVIG, she received pulse-dose corticosteroids and one dose of low-dose cyclophosphamide. Her neurological symptoms improved and she had complete neurological recovery several months after her initial presentation. Literature search provides evidence of co-occurrence of lupus and GBS occurring mostly later in the course of the disease. However, GBS as initial manifestation of SLE is exceedingly rare and less understood. The association of GBS with lupus is important to recognize for rapid initiation of appropriate therapy and for consideration of immunosuppressive therapy which may affect the outcome.

Keywords: *Guillain–Barré syndrome*; *systemic lupus erythematosus*; *intravenous immunoglobulin*; *cyclophosphamide*; *electromyography*

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A 38-year-old female with a history of hypertension and cervical disc herniation was evaluated by a neurologist in the clinic for numbness and tingling in the hands and feet bilaterally and right-sided cervical pain for a duration of 3 days. An electromyography (EMG) was performed which revealed markedly prolonged latency with low amplitudes in the right median and tibial motor nerves. She presented to our hospital the next day due to worsening cervical pain that radiated to the face and jaw. Her vital signs included BP – 161/91 mmHg, HR – 115 per min, RR – 17 per min, and temperature – 98.2°F. Her cardiovascular, respiratory, abdominal, and musculoskeletal examinations were unremarkable. Motor strength and reflexes were intact. Cervical spine motion was limited due to pain. She was noted to have small oral ulcerations and a faint rash resembling livedo reticularis. Laboratory investigations were as follows: BUN – 10 mg/dl, Cr – 0.68 mg/dl, Na – 139 mEq/l, K – 4.3 mEq/l, Cl – 106 mEq/L, HCO^3 – 22 mEq/L, glucose – 88 mg/dl, aspartate aminotransferase (AST) – 45 U/l, alanine aminotransferase (ALT) – 64 U/l, alkaline phosphatase (ALP) – 82 U/l, total bilirubin – 0.6 mg/dl, C-reactive protein – 19.35 mg/l, white blood cells (WBC) – 9.6×10^3 per µl, hemoglobin (Hb) – 12.2 g/dl, and platelets – 284×10^3 per µl.

A computerized tomography (CT) scan of the cervical spine showed mild disc space narrowing and endplate spurring at C4-C5 without any fracture, neuroforaminal narrowing, or joint dislocation. Magnetic resonance imaging (MRI) of the brain and cervical spine were negative for demyelinating disorder. An initial workup for polyneuropathy excluded hypothyroidism, hypovitaminosis B12, Lyme disease, diabetes mellitus, and plasma cell dyscrasias. Connective tissue diseases, in particular

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systemic lupus erythematosus (SLE), were also considered. The patient was found to have mildly low complement C4 (14 mg/dl, normal range: 16–47 mg/dl) but normal complement C3 and total complement. A summary of rheumatological serologies is described in Table 1. A screen for antiphospholipid antibodies was done which demonstrated weakly present lupus anticoagulant and mildly elevated phosphatidylserine IgG antibody at 14 U/ml (normal <11 U/ml), while cardiolipin antibodies and phosphatidylserine IgA or IgM antibodies were negative. A 24-h urine protein quantification showed proteinuria of 700 mg. A diagnosis of SLE was made based on American College of Rheumatology Criteria for classification of SLE (oral ulcers, presence of anti-dsDNA antibody, proteinuria of 0.7 g/day, and neurological involvement in the form of mononeuritis multiplex).

Therapy for SLE was instituted as hydroxychloroquine and corticosteroids were initiated. The patient developed numbness and tingling involving the face with difficulty swallowing as well as weakness in the lower extremities. Lower-extremity muscle strength was 3/5 bilaterally, whereas strength was preserved in the upper extremities. Deep tendon reflexes were diminished in the lower extremities but intact in the upper extremities. A second EMG showed mixed sensory-motor pattern consistent with acute inflammatory demyelinating polyneuropathy (AIDP) as follows: right median motor nerve showed prolonged distal onset latency, reduced amplitude, and decreased conduction velocity; left peroneal motor, right peroneal motor, and right tibial motor nerves showed prolonged distal onset latency and reduced amplitude; right ulnar motor nerve showed prolonged distal onset latency; right median sensory nerve showed no response; left sural sensory nerve showed reduced amplitude; right sural sensory nerve showed prolonged distal peak latency and decreased conduction velocity; and right ulnar sensory nerve showed prolonged distal peak latency and decreased conduction velocity. Furthermore, a lumbar puncture demonstrated a WBC count of 5 (85% lymphocytes and 15% monocytes) and a protein level of 145 mg/dl (normal range: 15–40 mg/dl) consistent with albuminocytologic dissociation. Guillain–Barré syndrome (GBS) was diagnosed on the basis of clinical symptoms, EMG, and lumbar puncture. Further GBS workup, such as antiganglioside antibodies was not performed. The patient was started on intravenous immunoglobulins (IVIG) for 5 days. After the IVIG course was completed, pulse-dose methylprednisolone was initiated while hydroxychloroquine was continued. She was given one dose of low-dose cyclophosphamide (500 mg/m^2). Motor strength and facial weakness improved during the course of therapy; however, paresthesia and neuropathic pain persisted in the hands and feet up to knee at the time of discharge from the hospital. Gabapentin was commenced by outpatient neurologist for persistent acroparesthesias and neuropathic pain of all limbs. Her neurological symptoms recovered completely. From SLE standpoint, she was maintained on hydroxychloroquine and remained in clinical and serological remission.

Table 1. Serological studies

Serology	Result	Reference range
ANA	1:80 IU/ml	Not detected
SSA antibody	337 AU/ml	<100 AU/ml
SSB antibody	<100 AU/ml	<100 AU/ml
Anti-dsDNA antibody	569 IU/ml	<100 IU/ml
Anti-Smith antibody	<100 AU/ml	<100 AU/ml
ANCA antibody	<1:20 FIU	<1:20 FIU
Myeloperoxidase antibody	<9.0 U/ml	<9.0 U/ml
Proteinase 3 antibody	<3.5 U/ml	<3.5 U/ml
RNP antibody	<100 AU/ml	<100 AU/ml
SCL-70 antibody	<100 AU/ml	<100 AU/ml

ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; RNP, ribonucleoprotein; SCL, scleroderma; SSA, Sjögren's-syndrome-related antigen A; SSB, Sjögren's-syndrome-related antigen B.

Discussion

SLE is a disorder of immune dysregulation leading to autoimmunity involving virtually any organ. Being a multisystem disorder, there is a broad spectrum of clinical presentation, and it often presents a diagnostic dilemma (1). SLE has a yearly incidence of 1 to 10 cases per 100,000 individuals. It has peak prevalence in African American women of reproductive age in the United States (2). Mucocutaneous, musculoskeletal, and renal manifestations are most commonly seen. SLE also affects the central nervous system, the peripheral nervous system, and the autonomic nervous system and is associated with worse prognosis (3, 4). Neuropsychiatric manifestations of lupus may precede the onset of lupus, occur at the time of diagnosis or later in the course of the disease (3, 5). American College of Rheumatology has defined 19 primary neuropsychiatric syndromes in lupus (3). Secondary neuropsychiatric manifestations occur as a result of disease complications or treatment. Common presentations include headaches, cerebrovascular accidents, seizures, depression, and psychosis. Peripheral nervous system involvement is seen in less than 10% of all nervous system manifestations (5).

GBS is an autoimmune disorder characterized by symmetric extremity paralysis. It has an annual incidence of about two cases per 100,000 individuals, and is the most common cause of acute flaccid paralysis in the United State (6). GBS is rapidly progressive and can involve respiratory muscles, a potentially fatal complication. Antecedent infectious triggers leading to GBS have been identified including *Campylobacter jejuni*, cytomegalovirus, Epstein–Barr virus, *Mycoplasma pneumoniae*, and

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Haemophilus influenzae (6, 7). Associations of GBS have also been described with HIV infection, immunizations, lymphoma, and bone marrow and organ transplantation.

GBS as initial manifestation of lupus is exceedingly rare and has been reported in a few cases in the literature (8–12). We report a 38-year-old female who presented with AIDP as initial manifestation of SLE. Natural history of GBS is variable in terms of extent and severity of involvement (6). Therefore, it is of utmost importance to diagnose the condition in a timely manner to prevent potentially life-threatening complications. In our patient, suspicion for GBS was raised when the patient developed lower-extremity weakness. Diagnosis was made in a timely manner, and prompt treatment of GBS with IVIG was initiated. Furthermore, our patient was treated with a dose of cyclophosphamide to control SLE along with pulse-dose steroids. Eventually, she had complete neurological recovery approximately 8 months after the initial presentation.

GBS in lupus is a complex and poorly understood phenomenon but likely involves immunological mechanisms. Whether GBS unmasks an underlying autoimmune disorder or lupus flare triggers GBS is currently unknown. Several pathophysiological mechanisms can explain this. First, simultaneous occurrence of GBS and SLE can be explained by a common etiological trigger, for example, Epstein–Barr virus (13). Molecular mimicry where an immune response is triggered because of cross-reactivity is an implicated pathogenesis in GBS since many cases of GBS are preceded by infections (6). It is possible that cross-reacting epitopes not only invoke an immune response against neurons causing GBS but also against other organs and at the same time contribute to SLE-like presentation. It is noteworthy that our patient did not have any antecedent diarrhea, respiratory illness, or immunization; hence, this mechanism is not a likely explanation in this patient. Second, a widespread immunological response in SLE may cause autoantibody formation against gangliosides which can potentially elicit demyelinating polyneuropathy such as GBS (1). Elevated proinflammatory cytokines such as interleukin-6 and interleukin-8 have been found in patients with SLE with neurological symptoms (14). It is plausible that cell-mediated immunity and complement activation play important roles as well. Third, vascular phenomena in SLE including vasculitis, micoangiopathy, and premature atherosclerosis leading to ischemic demyelination may trigger a GBS-like response (15). It is interesting to note that our patient had lupus anticoagulant and phosphatidylserine IgG antibodies which, theoretically, may confer a hypercoagulable state causing microinfarction and demyelination. Last, host-specific factors such as genetics or ethnicity and environmental factors may be involved.

IVIG have shown efficacy against GBS and is the first line therapy along with plasmapheresis (6, 16). The exact mechanism of action of IVIG in GBS is unknown. Proposed mechanism involves antagonization of circulating pathological antibodies by anti-idiotypic antibodies. Besides, modulation of cell-mediated immunity and complement pathways are also possible (17). The present patient received IVIG for treatment of GBS in the background of another autoimmune disorder. Hydroxychloroquine is an antimalarial agent that has immunosuppressive properties. Its mechanism of action involves alteration in the lysosomal pH interfering with antigen presentation by macrophages. Inhibition of peptide-major histocompatibility complex (MHC) fails to stimulate T-helper lymphocytes, thereby causing downregulation of autoimmune response against autoantigens. Although hydroxychloroquine is the first line agent in SLE, it is not sufficiently immunosuppressive to control organ-threatening acute flares or severe neuropsychiatric SLE. In this regard, low-dose cyclophosphamide has demonstrated efficacy in the treatment of non-thrombotic neuropsychiatric lupus (18). Cyclophosphamide is an alkylating agent that inhibits DNA replication by adding alkyl radicals into DNA strands forming DNA cross-links. It exerts its immunosuppressive effects in SLE and other autoimmune disorders by suppressing both T- and B-lymphocytes. However, its use in the treatment of GBS in lupus has not been studied. It appears that low-dose cyclophosphamide combined with corticosteroids improved the overall outcome in patients with SLE where GBS was the initial presentation (9, 10, 12).

Conclusion

The association of GBS with lupus is extremely rare and likely has an immunological basis. It seems to have implications for both treatment and prognosis, and identification is important as it may imply important therapeutic decisions. Early diagnosis of GBS is extremely important to initiate therapy to limit morbidity and mortality. This case not only illustrates a rare and unusual presentation of a common disorder but also a complete neurological recovery after being treated with immunosuppressive therapy. Therefore, low-dose cyclophosphamide with corticosteroids should be considered when encountered with a similar situation.

Conflict of interest and funding

The authors have no conflicts of interest.

References

1. Tsokos GC. Systemic lupus erythematosus. N Engl J Med 2011; 365: 2110–21.
2. Pons-Estel GJ, Alarcón GS, Scofield L, Reinlib L, Cooper GS. Understanding the epidemiology and progression of systemic lupus erythematosus. Semin Arthritis Rheum 2010; 39(4): 257–68.

3. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 1999; 42: 599–608.
4. Muscal E, Brey RL. Neurological manifestations of systemic lupus erythematosus in children and adults. Neurol Clin 2010; 28(1): 61–73.
5. Hanly JG, Urowitz MB, Sanchez-Guerrero J, Bae SC, Gordon C, Wallace DJ, et al. Neuropsychiatric events at the time of diagnosis of systemic lupus erythematosus: An international inception cohort study. Arthritis Rheum 2007; 56(1): 265–73.
6. Yuki N, Hartung HP. Guillain-Barré syndrome. N Engl J Med 2012; 366(24): 2294–304.
7. Poropatich KO, Walker CLF, Black RE. Quantifying the association between *Campylobacter* infection and Guillain-Barré syndrome: A systematic review. J Health Popul Nutr 2010; 28(6): 545–52.
8. Fazio RM, Chen I, Somal N. Guillain-Barré syndrome as first presentation of systemic lupus erythematosus: A rare manifestation complicated by IVIg-induced splenic infarct. BMJ Case Rep 2015; 2015.
9. Okoh HC, Lubana SS, Langevin S, Sanelli-Russo S, Abrudescu A. A case of systemic lupus erythematosus presenting as Guillain-Barré syndrome. Case Rep Rheumatol 2015; 2015: 528026.
10. Santiago-Casas Y, Peredo RA, Vilá LM. Efficacy of low-dose intravenous cyclophosphamide in systemic lupus erythematosus presenting with Guillain-Barre syndrome-like acute axonal neuropathies: Report of two cases. Lupus 2013; 22(3): 324–7.
11. Hsu TY, Wang SH, Kuo CF, Chiu TF, Chang YC. Acute inflammatory demyelinating polyneuropathy as the initial presentation of lupus. Am J Emerg Med 2009; 27(7): 900.e3–5.
12. Vaidya S, Jasin HE, Logan J. Systemic lupus erythematosus and Guillain-Barre syndrome. J Clin Rheumatol 1999; 5(6): 349–53.
13. Tsokos GC, Magrath IT, Balow JE. Epstein-Barr virus induces normal B cell responses but defective suppressor T cell responses in patients with systemic lupus erythematosus. J Immunol 1983; 131(4): 1797–801.
14. Trysberg E, Carlsten H, Tarkowski A. Intrathecal cytokines in systemic lupus erythematosus with central nervous system involvement. Lupus 2000; 9(7): 498–503.
15. Hanly JG. Neuropsychiatric lupus. Curr Rheumatol Rep 2001; 3(3): 205–12.
16. Hughes RA, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barré syndrome. Cochrane Database Syst Rev 2014; 9: CD002063.
17. Jacob S, Rajabally YA. Current proposed mechanisms of action of intravenous immunoglobulins in inflammatory neuropathies. Curr Neuropharmacol 2009; 7(4): 337–42.
18. Stojanovich L, Stojanovich R, Kostich V, Dzjolich E. Neuropsychiatric lupus favourable response to low dose i.v. cyclophosphamide and prednisolone (pilot study). Lupus 2003; 12(1): 3–7.