CASE REPORT

Guillain-Barré syndrome as first presentation of systemic lupus erythematosus: a rare manifestation complicated by IVIg-induced splenic infarct

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SUMMARY

A 44-year-old woman presented with progressively worsening neurological symptoms of 1 week duration. Physical examination revealed absent reflexes of the lower extremities and proximal muscle weakness, bilaterally. Cerebrospinal fluid analysis and electrophysiological studies were consistent with the diagnosis of Guillain-Barré syndrome (GBS) and the patient was started on intravenous immunoglobulin infusion. Along with positive neurological findings, rheumatological work up revealed elevated antinuclear antibody titres, positive double-stranded DNA and anti-Smith antibodies. These results, in conjunction with positive clinical findings, confirmed an underlying diagnosis of systemic lupus erythematosus (SLE). The patient's hospital course was complicated by an episode of severe left upper quadrant abdominal pain, fever, tachycardia and elevated inflammatory markers. CT scan of the abdomen revealed a splenic infarct following completion of IVIg infusion, making this a contributor to thrombus formation in the setting of an already thrombophilic state, and a rare complication of an approved method of treatment.

BACKGROUND

Confirmation for the diagnosis of systemic lupus erythematosus (SLE) can frequently be difficult, as the presentation may not always be typical for the disease. Guillain-Barré syndrome (GBS) is a rare initial presenting manifestation of SLE, and requires intense treatment and thorough physical rehabilitation. The American Academy of Neurology guidelines suggest that treatment of GBS may consist of either plasma exchange or IVIg. IVIg has been noted to cause rare complications including venous thrombosis, myocardial infarction and stroke. In our patient, we describe the occurrence of splenic thrombosis provoked by the initiation of IVIg treatment in the setting of undiagnosed SLE and suspected secondary antiphospholipid syndrome (APS), a unique finding that has not yet been reported.

CASE PRESENTATION

A 44-year-old woman presented to the emergency department, with postural instability and difficulty with ambulation. The medical history was negative. Her symptoms began 1 week prior to admission, manifesting as painful cramps of the calves and feet. Three days before admission, she felt an overwhelming sense of weakness of the lower extremities, as well as increasing pain of the hand joints,

to the extent that she could not grip household items. The patient denied numbness of the lower extremities, urinary or bowel incontinence, recent trauma, neck pain or back pain. She also denied shortness of breath, blurry vision, headache, fever, recent illness and unintentional weight loss. The patient was a native of Haiti, but had not visited that country in over 15 years. She denied a recent travel history, local or international. She was a G2P2 with no complications during those pregnancies, and did not describe any loss of pregnancy in the past. She denied a family history of autoimmune diseases, communicable diseases or cancer.

The patient was alert and oriented to person, place and time, with no signs of head or vertebral trauma noted. She had no facial asymmetry and no pronator drift, and performed an intact finger-to-nose test. Physical examination revealed proximal muscle weakness with hip and knee extensor strength graded as a 3 and 4 on a scale of 5, respectively. Cardiovascular, pulmonary and abdominal examinations were unremarkable.

Following initial work up, the patient was diagnosed with GBS, and IVIg infusion was administered for a total of 4 days. Approximately 2 days after the completion of this regimen, the patient began reporting severe, sharp abdominal pain located at the left upper quadrant. This pain was accompanied by fever, tachycardia, hypotension and a significant elevation of the white cell count (WCC).

INVESTIGATIONS

Laboratory findings on admission included a normal complete blood count (WCC 4.6 μ L and haemoglobin 13.6 g/dL). Renal function was within normal limits (creatinine of 0.7 mg/dL). Serum vitamin B₁₂ was also within normal limits (176 pg/mL). Erythrocyte sedimentation rate (ESR) was grossly elevated at 145 mm/h. Rapid HIV testing was non-reactive. CT scan of the head was negative for haemorrhage, masses and other intracranial pathology. Lumbar puncture revealed elevated cerebrospinal fluid (CSF) protein (78 mg/dL) and WCC (27 UL) with lymphocyte predominance of 99%. CSF was positive for the presence of oligoclonal bands. Neurological work up demonstrated an abnormal electromyography and nerve conduction study with electrophysiological evidence of an acute demyelinating polyneuropathy. Owing to high suspicion of GBS, the patient was started on IVIg at 0.5 mg/kg/day for 4 days.

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The elevated ESR, without obvious signs of infection, raised concern for additional diagnoses, including autoimmune disease, vasculitis and neoplasm. Also, an elevated ESR in the setting of CSF lymphocyte pleocytosis raised concern for lymphoma. CT of the chest/abdomen/pelvis was performed to rule out neoplasm, and revealed prominent axillary lymph nodes. Lymph node biopsies were obtained. Laboratory data included positive titres of antinuclear antibody (1:320 speckled pattern). Additional rheumatological studies were revealed for positive antidouble-stranded (ds) DNA, anti-ribonucleoprotein (RNP) and anti-Smith antibodies, all suggestive of a diagnosis of SLE. The patient's renal function remained within normal limits. Urine dipstick was negative for protein, and the urine protein-to-creatinine ratio was 0.08, indicating that there was no significant renal impairment at the time of diagnosis.

Forty-eight hours following the last dose of IVIg, the patient experienced severe left upper quadrant abdominal pain. The patient was febrile to 104.4°F (obtained rectally), with a heart rate of 120 bpm. Mean arterial pressure (MAP) dropped from the previous range of 88–96 to 71–81 after this event. Peripheral WCC was 32.8 μ L (compared to 7.8 μ L the morning prior) with 21% neutrophil band count. Two sets of blood cultures were negative. A CT of the abdomen/pelvis was performed shortly after symptom onset, demonstrating an area of infarct at the posterior/superior portion of the spleen, with normal overall size of the organ (figure 1). The patient had no prior history of manifestations of a hypercoagulable state including miscarriages, previous thrombosis or known family history of clotting disorders. A hypercoagulable work up was initiated, including an echocardiogram, which was negative for valvular vegetations. The patient was also negative for Factor V Leiden mutation, protein C and S antigen, lupus anticoagulant screening assay, anti-cardiolipin antibody (IgG, IgM and IgA) and anti- β 2 glycoprotein I antibody (IgG and IgM). The patient's

serum was positive for IgA anti- β 2 glycoprotein I antibody; however, this antibody is often positive in patients with SLE and it does not fulfil the criteria for primary antiphospholipid syndrome.^{1–5} The patient's axillary lymph node biopsy later returned as reactive lymphadenitis and negative for lymphoma, consistent with an underlying inflammatory condition, which, in a case such as this, may be attributed to both GBS and SLE.⁶

DIFFERENTIAL DIAGNOSIS

On initial presentation, the differential diagnoses for a middle-aged woman presenting with proximal muscle weakness, absent reflexes and inability to walk included stroke, acute inflammatory demyelinating polyneuropathy, transverse myelitis, multiple sclerosis, vitamin B₁₂ deficiency (causing subacute combined degeneration of the spinal cord) and HIV infection. Along with a splenic infarct, patients who present with acute left upper quadrant pain should be evaluated for peptic ulcer disease with possible perforation, pancreatitis and pyelonephritis.

TREATMENT

CT imaging revealed a splenic infarct, but the patient's hypercoagulable work up was negative; therefore, anticoagulation was not indicated following this thrombotic event. Hydroxychloroquine sulfate 200 mg twice daily was initiated for the patient's newly diagnosed SLE.

OUTCOME AND FOLLOW-UP

The patient was discharged to a subacute rehabilitation centre for continued physical therapy and close monitoring. She was seen for a follow-up at the neurology clinic, where she described overall improvement of her lower extremity weakness. The patient continues to participate in outpatient physical therapy twice a week.

DISCUSSION

GBS is a rare manifestation of SLE, falling under the category of neuropsychiatric SLE (NPSLE).^{7–11} The exact pathophysiology of this relationship is widely unknown; however, it is believed that there may be cross-reactivity between autoantibodies associated with SLE and those formed against myelin tissue. This process, along with the inflammation of neuronal tissue, is further exposed in an immunosuppressed patient with underlying SLE.⁷ The patient's initial diagnosis of GBS was confirmed by CSF analysis, electromyography and nerve conduction studies, as well as by a strong clinical suspicion. The American Academy of Neurology recommendations for treatment of GBS includes the use of either plasma exchange or intravenous immunoglobulin.¹² IVIg is considered superior to plasma exchange for GBS, while also being the preferred treatment for GBS associated with lupus.^{13 14} The use of pulsed glucocorticoids (eg, prednisone and methylprednisolone) is the treatment of choice for management of NPSLE, especially in those experiencing an acute or severe flare. Cyclophosphamide is yet another immunosuppressive agent used to control central nervous system manifestations of SLE, in addition to its use in lupus nephritis.¹¹ With regard to this particular patient, the diagnosis of SLE was not initially identified and, therefore, she was not started on these preferred treatment options. The diagnosis became apparent, however, following rheumatological work up: 4 of 11 ARA criteria for SLE were met, including positive anti-dsDNA and anti-Smith antibodies, arthralgia of the hand joints and neurological symptoms.¹⁵

Figure 1 (A) The initial CT scan showing a normal appearing spleen. (B) Obtained 48 h after the completion of IVIg infusion revealing an infarction located at the posterior aspect of the spleen (yellow arrow).

Aside from its use in the treatment of GBS, IVIg has shown significant benefit in the treatment of other conditions as well, including idiopathic thrombocytopenic purpura, idiopathic inflammatory myopathies, ANCA-associated vasculitides, Kawasaki disease and chronic inflammatory demyelinating polyneuropathy.^{13–16} Generally considered a benign treatment, IVIg carries with it the rare, but serious, risk of thrombosis, which may manifest as a myocardial infarction, cerebral vascular infarct or even end-organ ischaemia.^{17–18} The cause of thrombus formation is likely multifactorial. Proposed mechanisms include increased viscosity postinfusion, platelet aggregation, increased activation of specific coagulation factors, localised vasoconstrictive cytokine release and subsequent vasospasm.¹⁸ It has been suggested that, along with a reduction of IVIg infusion flow rate, patients may benefit from prophylactic treatment with antiplatelet or anticoagulant therapy; however, there is not enough evidence to support the efficacy of these interventions.

The signs and symptoms exhibited by this patient, including left upper quadrant pain and tenderness, fever and leucocytosis, are entirely consistent with splenic infarction, which was later identified through radiological imaging.¹⁹ After tracing the sequence of events during the patient's hospital course, it was determined that the likely cause for this infarction was due in large part to IVIg infusion used in the treatment of GBS. To the best of our knowledge, this is the first report of splenic infarction caused by intravenous immunoglobulin infusion. Before arriving at this conclusion, we first were required to exclude thromboembolic causes from a cardiac source, as well as from an underlying hypercoagulable state. The results of these tests returned negative; however, the patient's laboratory work up was revealing for a positive IgA anti- β 2 glycoprotein I antibody. Studies have shown a close correlation between this particular antibody in patients with SLE, some even considering it a pos-

sible marker for pro-thrombotic risk. While this marker does not fulfil the Sapporo Criteria for diagnosis of APS in a traditional sense, similar to SLE, it is often positive in those with APS. Therefore, an underlying diagnosis of secondary APS should not be overlooked as a possible contributing factor leading to this patient's thrombotic complication.^{1–5}

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Learning points

- ▶ Guillain-Barré syndrome (GBS) is a rare initial presenting manifestation of systemic lupus erythematosus (SLE).
- ▶ IVIg is considered superior to plasma exchange in hastening recovery from lupus-associated GBS.
- ▶ Thrombosis is a rare, yet serious, risk factor of intravenous immunoglobulin infusion, which may manifest as a myocardial infarction, cerebrovascular accident or end-organ ischaemia.
- ▶ IgA anti- β 2 glycoprotein I antibody is often positive in patients with SLE.
- ▶ Thromboembolic causes from either a cardiac source or hypercoagulable source must first be ruled out before attributing such an event to IVIg infusion.

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