Journal of Associated Medical Sciences 2023; 56 (1): 101-105

JAMS
Journal of Associated Medical Sciences

Scopus indexed & Thai-Journal Citation Index Centre (TCI)

Journal of Associated Medical Sciences

Journal homepage: https://www.tci-thaijo.org/index.php/bulletinAMS/index

Guillain–Barré Syndrome in a patient with systemic lupus erythematosus with underlying pituitary carcinoid: A rare presentation

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ARTICLE INFO

Article history:
Received 6 August 2022
Accepted as revised 2 October 2022
Available online 15 October 2022

Keywords:
GBS, SLE, Pituitary carcinoid, extra-gastric carcinoid.

ABSTRACT

Background: Guillain-Barré syndrome (GBS) is a rare neuropsychiatric symptom of systemic lupus erythematosus (SLE). GBS in individuals with SLE has distinct features than those without SLE. There is much heterogeneity in the treatment and clinical outcome. Even though GI carcinoids have been related with autoimmune illnesses, extra-gastrointestinal carcinoid coexisting with SLE has been documented only once, and coexistent GBS and SLE with pituitary carcinoid have never been reported previously to the best of our knowledge. Greater knowledge of how inflammation causes cytological alterations that contribute to the formation of a carcinoid might help explore newer pathological mechanisms and therapies.

Objectives: We report a middle-aged female who presented with sudden onset of weakness in all four limbs, long-standing history of arthralgia, flushing, dizziness, and a malar rash.

Materials and methods: The initial evaluation led to the diagnosis of GBS and SLE, for which the patient was treated. Further workup of patient revealed the presence of a carcinoid tumor in the pituitary.

Results: Patient was successfully treated with plasmapheresis, steroids, and injection octreotide.

Conclusion: In patients with SLE, neuropsychiatric illness may have a plethora of presentation including GBS. Recognizing such rare presentations and evaluating the possibility of a carcinoid tumor in presence of symptoms like a long-standing history of intermittent palpitation, dizziness, profuse sweating, and flushing, should alert the physician of an underlying carcinoid tumor, which could prove detrimental if left untreated.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune illness that affects various organ systems in our body. The presence of the central nervous system (CNS) involvement in SLE was first reported by Hebra and Kaposi in 1875. Neuropsychiatric symptoms are present in around 56.3 percent of SLE individuals.[1] The most common symptoms are cognitive dysfunction, headache and seizures.[2] Association of SLE with GBS has occasionally been reported in the literature.[3] Gastrointestinal (GI) carcinoids have been associated with autoimmune diseases like SLE.[4] Extra gastrointestinal carcinoids with SLE have been reported only once.[5] Here we possibly report the first case of GBS as an initial presentation of SLE with an underlying pituitary carcinoid.

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** **doi:** 10.12982/JAMS.2023.024
E-ISSN: 2539-6056

Case report

A 48-year-old lady came to our hospital with a history of frequent, short-lasting episodes of palpitation, dizziness, profuse sweating and flushing for the last four years, arthralgia affecting small and medium-sized joints for the last six months, shortness of breath not associated with chest pain or cough, and aggravated with exertion for last four months, and five days history of ascending weakness in all four limbs. She noticed difficulty climbing stairs and getting up from a sitting posture, which rapidly progressed to the weakness of both upper limbs in the form of holding and lifting objects, combing hair, and doing other routine activities. There was no bladder and bowel involvement. There were no complaints of diarrhea, abdominal pain, history of any dog bite, or recent vaccinations. She had no other comorbidities, and there was no similar presentation in the past. There was no history of abortions or stillbirth.

Clinical examination

The patient was attentive, aware, and communicative during the examination. There was mild pallor and an erythematous, non-itching malar rash. Icterus, cyanosis, clubbing, lymphadenopathy, and pedal edema were absent. Her pulse rate was 96 beats per minute, regular, and her blood pressure at the time of examination was 140/90 mmHg in the supine posture, and her respiratory rate was 26 cycles per minute. Examination of the central nervous system (CNS) revealed normal higher mental functions and no involvement of any cranial nerves. On motor system examination, the bulk was normal with hypotonia, and power was decreased (3/5) in all four limbs. All deep tendon reflexes (DTR) and superficial abdominal reflexes were absent, and plantar reflex was absent bilaterally. There were no signs of sensory, cerebellar, or meningeal involvement. The cardiovascular, respiratory, and per-abdomen examinations were normal.

Laboratory investigations

A complete blood count revealed hemoglobin (Hb) of 7.5 gm/dL, total leukocyte counts (TLC) of 3800 cells/µL, total red blood cell counts (TRBC) of $3.93x10^6$ cells/µL, and a peripheral smear showed microcytic hypochromic anemia. Urine routine and microscopy examination showed 3+ proteinuria and 1+ hematuria. Her fasting and postprandial blood sugar levels were 98 mg/dL and 120 mg/dL, respectively. Serum total bilirubin was 0.5 mg/dL, AST and ALT levels were 33 and 28 IU/L, respectively, serum sodium was 138 mEq/L, serum potassium was 3.5 mEq/L, ESR was 110, blood urea level was 28 mg/dL, serum creatinine was 1.2 mg/dL and eGFR 58 mL/min/m^2.

In view of ascending weakness of all 4 limbs with areflexia without bowel or bladder involvement, an urgent cerebrospinal fluid (CSF) analysis was done, which revealed albumin-cytological dissociation with a cell count of 5 cells/mm^3 and elevated CSF protein. A nerve conduction study (NCS) was also ordered, which revealed decreased distal motor amplitude and absent F waves, suggesting acute motor axonal neuropathy (AMAN) variety of GBS.

Considering clinical features such as arthralgia affecting small and medium sized joints, malar rash, and lab investigations suggestive of bicytopenia, proteinuria, microscopic hematuria suggestive of possible SLE, further workup was advised which revealed positive Antinuclear (ANA) and anti-ds DNA antibodies in high titers ≥1:100, nucleolar pattern, whereas C3 and C4 complement levels were decreased (0.3 gm/L, and 0.05 gm/L respectively) leading to a diagnosis of definite SLE according to 2019 European Alliance of Associations for Rheumatology (EULAR)/ American College of Rheumatology (ACR) classification criteria. Antibodies to HIV, hepatitis B, and C were negative.

In view of unexplained intermittent dizziness, palpitation, profuse sweating, and flushing, the remote possibility of a neuroendocrine tumor (NET) was suspected, and an endocrine consultation was sought. 24-hr urinary 5-hydroxy indole acetic acid was sent, which was 20 µmol/day (normal range -10-40 µmol/day). An upper GI endoscopy was done, which showed only antral erosions. With a strong suspicion of NET, plasma serotonin and chromogranin A was advised, which turned out to be positive with values of 284 nmol/L (normal <30 nmol/L) and 700.1 ng/mL (normal <76.30 ng/mL) respectively, which was suggestive of a NET.

To localize the site of NET, CECT abdomen and thorax were done, which were normal. MRI brain and pituitary with contrast was done to rule out any CNS pathology, which showed a bulky left lobe of the anterior pituitary gland with a small nodular lesion measuring 9.4x8.7 mm, causing a slight deviation of infundibulum towards the right. The lesion showed an iso intense signal on T1W, iso to slight hyperintense signal on T2W with small cystic spaces within. The lesion showed gradual post-contrast enhancement in the dynamic phase, suggestive of pituitary microadenoma with cystic changes (Figure 1). Somatostatin receptor scintigraphy (SRS) with radio-labeled Ga-68-DOTANOC PET scan was not done because of unavailability. A final diagnosis of GBS (AMAN variety) with SLE & pituitary carcinoid was made.

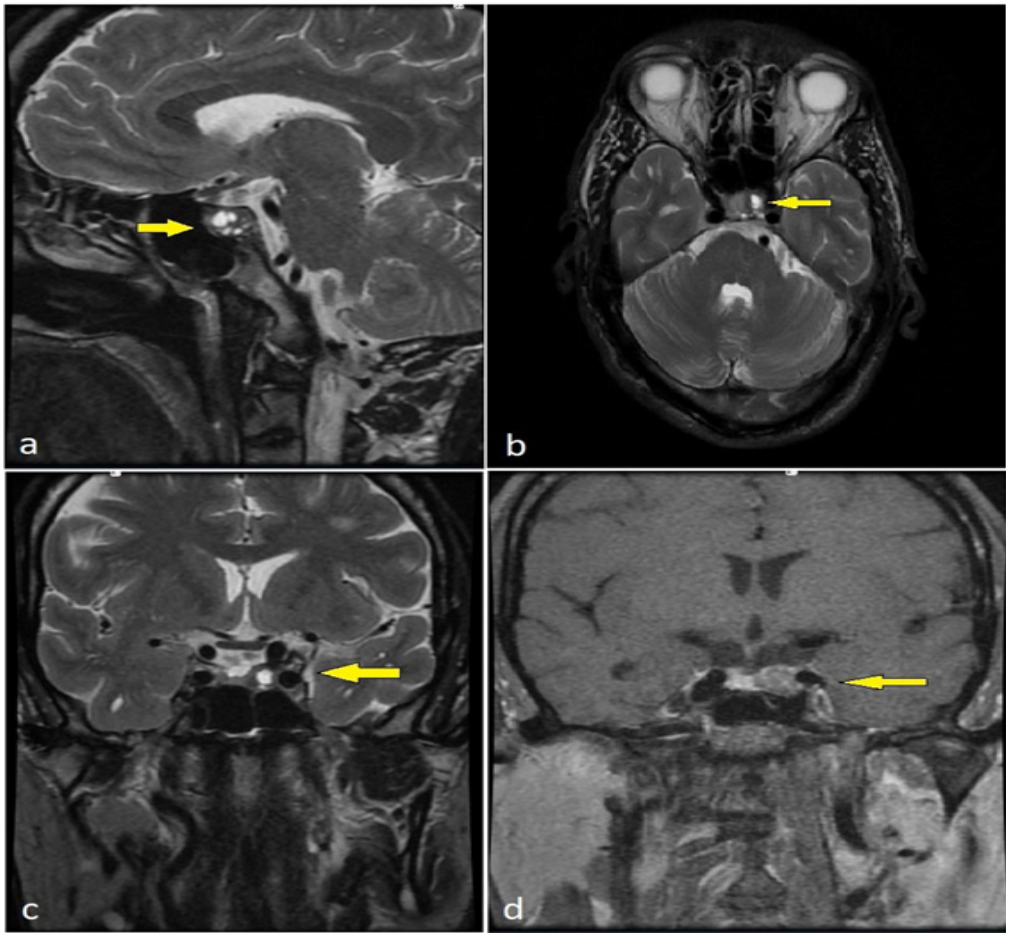

Figure 1. *MRI brain and pituitary with contrast showing a bulky left lobe of the anterior pituitary gland with a small nodular lesion measuring 9.4x8.7 mm, causing a slight deviation of infundibulum towards the right. a: sagittal T2, b: axial T2, c: coronal T2, d: coronal post-contrast enhancement in the dynamic phase suggestive of pituitary microadenoma with cystic changes.*

Treatment & follow up

For the initial five days, the patient received five cycles of plasmapheresis. The power of all four limbs started improving after the third cycle of plasmapheresis. By the end of the fifth cycle, her power had improved to grade 4/5. She was then given 1 gram of pulse methylprednisolone intravenously from day 6 to day 9. She was then started with oral prednisolone 40 mg/day, which was gradually reduced to 5 mg/day over the next 30 days.

At follow up after one month, there was a significant reduction in arthralgia. ESR was 22 mm, Hb improved to 9.9 gm/dL and TLC was 8600 cells/µL. Power and reflexes were also normal. For the treatment of pituitary carcinoid, after endocrinology consultation, injection Octreotide LAR 20 mg IM stat was given and planned for a repeat dose at the second month of follow up.

Discussion

GBS as a neurological complication is seen in 0.1% of patients of SLE.[1] GBS is often characterized by acute inflammatory demyelinating polyneuropathy, but in SLE, most GBS individuals have atypical features. Acute motor axonal neuropathy (AMAN) and acute motor-sensory axonal neuropathy (AMSAN) have been reported earlier in patients with SLE, where treatment with glucocorticoids and low-dose pulse cyclophosphamide has been beneficial.[6] Patients with SLE have been documented to have numerous neuropsychiatric manifestations like headache (most common), mood disorders, state of acute confusion, psychosis, cognitive dysfunction, cerebrovascular diseases, mono and polyneuropathy, seizures, autonomic disorder, myelopathy, cranial neuropathies, plexopathies, aseptic meningitis, demyelinating syndrome, movement disorders, and myasthenia gravis; being collectively referred as neuropsychiatric SLE (NPSLE).[7] A few cases of GBS as an initial manifestation of SLE has been reported in the literature.[3] Although the cause and mechanisms of GBS in lupus is unclear, it probably involves immunological pathways. As of now it's unclear whether GBS causes lupus flares or vice versa. Molecular mimicry leading to immune response because of cross-reactivity have been proposed as one of the mechanisms.[8] Second, a generalized and widespread immune response in SLE may result in the development of autoantibodies against gangliosides, which may cause demyelinating polyneuropathy resembling GBS. It is also hypothesized that complement activation and cell-mediated immunity play significant roles. Lupus vasculitis can lead to microangiopathy, and premature atherosclerosis which in turn accelerate ischemic demyelination triggering GBS.[9] Finally, host-specific variables including

genetics, ethnicity, and the environment may also be at play.

NPSLE is associated with high mortality rates despite aggressive immunosuppressive therapy making therapeutic plasma exchange (TPE) a safe and effective alternative.[10-11] Twenty-sex patients with SLE and CNS involvement who were given TPE alone or in conjunction with cyclophosphamide were analyzed by Neuwelt *et al*.[12] Following treatment, 74% of patients showed improvement, 13% were stable, and symptoms worsened in the rest 13%. The current American Society for Apheresis (ASFA) guideline considered TPE as a second-line therapy for SLE.[13]

Carcinoid syndrome is diagnosed by an excess of serotonin synthesis from a NET.[14] NETs are slow growing neoplasms with an incidence of 2.5 per 1,00,000 women and 2.0 per 1,00,000 men per year.[15] They originate most commonly from the gut, followed by the lungs, whereas 10% seem to have ectopic or an unknown origin.[16] Approximately 0.9% of patients with extra-pituitary NETs may develop pituitary metastases.[17] Urticaria, stomach pain, loose motions, edema of lips, bronchospasm, and variable blood pressure levels are common symptoms. Excessive urinary discharge of the 5-HIAA has generally been used to diagnose carcinoid with a sensitivity of 73% and specificity of 100%.[18-19] But in our case, 5-HIAA was normal which is often seen in an atypical carcinoid.[18] Consequently, a negative 5-HIAA result in a patient with clinical suspicion of carcinoid syndrome should be followed up with the measurement of plasma serotonin and chromogranin A levels, which are accepted as sensitive (90%) and specific (100%) markers of both functioning and non-functioning NET.[20-21] Due to the high expression of SSRs on NETs, receptor scintigraphy using somatostatin analogues as receptor ligands is a valuable diagnostic approach. Scintigraphy with 111-indium-marked octreotide or 68-Ga-DOTATOC provides a higher sensitivity (>90%) than CT/MRI for locating the primary lesion.[22]

Multiple studies have revealed a higher incidence of gastrointestinal carcinoids in autoimmune conditions like AIG.[23] The pathophysiology of the carcinoid-autoimmunity association can be explained by the fact that the patients with AIG have a chronic rise of serum gastrin due to gastric atrophy, which causes the development of gastric carcinoid.[23] However, this hypothesis explains the autoimmune mechanism for the gastric carcinoid only. None of the reported cases in the literature included development of extragastric carcinoids.

Carcinoid syndrome or NET are often misdiagnosed as irritable bowel syndrome (37%), intolerance to certain foods (18%) and psychiatric conditions (17%), or symptoms of menopause (5%), and the average delay in diagnosis is 5-7 years from the onset of the first recognizable symptom.[24-25]

This case is noteworthy for several reasons: the patient had intermittent flushing, sweating, dizziness, and dyspnea, which could be attributed to carcinoid disease. Pituitary carcinoid per se is uncommon, and its presence in a case of SLE-associated GBS is still rarer. A molecular understanding of how inflammation triggers cytological abnormalities that result in formation of carcinoids could lead to the development of novel therapeutic alternatives.

Conclusion

In patients with SLE, neuropsychiatric illness may have a subtle presentation ranging from confusion, lethargy, dementia, coma, and even GBS. Awareness of the likelihood of such rarer presentations, and a careful analysis of each documented clinical trait in individuals with a long-standing history of intermittent palpitation, dizziness, profuse sweating, and flushing in the presence or absence of hypertension, should alert the physician of a possible carcinoid tumor.

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