CASE REPORT

Systemic lupus erythematosus with secondary thrombotic thrombocytopenic purpura and acute parkinsonism: A case report

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Abstract

Systemic lupus erythematosus (SLE) is an autoimmune disease that has certain characteristic features but can also present with misleading signs and symptoms especially when it is of late-onset. Various case reports address its association with thrombotic thrombocytopenic purpura (TTP), however, its association with parkinsonism remains unclear. We present the case of a 58-year-old male who reported with acute-onset parkinsonism along with some gastrointestinal symptoms. Detailed laboratory investigations unmasked the underlying SLE with an overlapping picture of TTP. This unusual presentation in a resource-constrained setting created challenges and subsequent delays in the diagnosis and management of the patient. Despite urgent care, the patient's age, presence of overlapping conditions, and multi-organ involvement were some of the factors due to which the treatment failed and he could not survive. We report the association of SLE with secondary TTP and parkinsonism. More studies are needed to provide a greater understanding of these associations and various risk factors that drive them.

Keywords: Late-onset systemic lupus erythematosus, Systemic lupus erythematosus in males, Thrombotic thrombocytopenic purpura, Parkinsonism.

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Introduction

Systemic lupus erythematosus (SLE) is an immune-mediated inflammatory condition characterised by the presence of autoantibodies directed against nuclear antigens. Despite multifactorial aetiology, genetic predisposition and environmental triggers remain the most common aetiological factors. Though more common in young females, it can also affect children and the elderly. Late-onset SLE is defined as a disease occurring at or after 50 years of age, with this group making up 10-20% of all the cases with SLE.[1] Previous case studies report late-onset SLE to have a different clinical presentation and a much more insidious onset than that presenting in early ages.[1] The characteristic features of SLE such as fever, cutaneous lesions, and renal and nervous system impairment are less commonly seen; however, arthritis, lung involvement, pericarditis, thrombocytopenia, and sicca syndrome account for more frequent presentations of late-onset SLE.[1]

Thrombotic thrombocytopenic purpura (TTP) is a rare blood disorder characterised by a pentad of fever, microangiopathic haemolytic anaemia, thrombocytopenia, renal and nervous system dysfunction that is followed in later stages by a diffuse circulatory collapse.[2] TTP can occur either due to congenital or acquired deficiency of a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13 (ADAMTS13) enzyme.[3] ADAMTS13 is synthesised in the liver and is responsible to cleave large von Willebrand factor (VWF) multimers into smaller ones that are less adhesive to platelets.[3] Consistently, low levels of this enzyme devoid the body of its protective mechanism leading to an increased risk of microthrombi formation and subsequent end-organ ischaemia and damage. The most common organ systems affected by TTP are renal and central nervous systems. The less common congenital TTP results from ADAMTS13 mutations; however, autoantibody formation triggered by human immunodeficiency virus (HIV) infection or connective tissue diseases (CTDs) causes the more common acquired TTP.[4] Among all CTDs, SLE remains the most frequent cause of secondary TTP.[4]

Consistent with this well-recognised association between SLE and TTP, our patient was also diagnosed with late-onset SLE overlapping with secondary TTP during the course of hospitalisation, though at the time of admission he did not present with any symptoms pertaining to SLE or thrombocytopenia. In fact, he presented predominantly with features of parkinsonism, i.e. rigidity, bradykinesia, postural instability, and resting tremors. Following the diagnosis of SLE, the patient's parkinsonism could be attributed to the neuropsychiatric variant of underlying SLE (NPSLE), although movement disorder such as parkinsonism is an unusual and rarely reported

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manifestation of NPSLE.[5] The more common features of NPSLE include headache, psychoses, seizures, and cerebrovascular diseases.[5] Regardless, possible mechanisms of parkinsonism overlapping with SLE have been hypothesised. These include cytokine or autoantibody-mediated neurotoxicity and thrombotic-vasculopathy mediated by anti-phospholipid antibodies, each causing damage to the dopaminergic neurons of the basal ganglia.[5]

Herein, we report an unusual case of a middle-aged man who presented to Dr Ruth K. M. Pfau, Civil Hospital, Karachi (CHK) with vivid characteristics of Parkinson's disease along with some indistinct gastrointestinal (GI) symptoms, all possibly precipitated by underlying SLE. This case study reports the association of SLE with acquired TTP as well as parkinsonism; however, the primary focus lies on the rarely reported coexistence between two pathologies i.e. SLE and parkinsonism.

Case Summary

A 58-year-old man presented to CHK in September 2019 with a fever of 100o F, disturbed bowel habits for the last one and a half month including few nocturnal episodes of loose stools, mild lower abdominal pain, multiple episodes of vomiting, all associated with decreased appetite and weight loss. Earlier, he had consulted a nearby physician for his symptoms but his condition did not improve. Besides those symptoms, he also developed new-onset pill rolling tremors at rest involving both upper and lower limbs about 20 days back. The patient denied the consumption of alcohol and tobacco smoking and had an insignificant past medical and surgical history.

On examination, the patient appeared pale and drowsy, had a mask-like face, altered behaviour with a Glasgow Coma Scale of 13/15. His blood pressure was high (160/100 mmHg), heart rate was 100 beats/min, respiratory rate was 22 breaths/min with raised jugular venous pressure, and generalised oedema. He had non-blanchable purpuric rashes on both the upper and lower extremities. Chest examination revealed decreased breath sounds at the lung bases bilaterally with normal heart sounds. The abdomen was soft, non-tender, and distended. There was increased muscle tone with generalised cogwheel rigidity in both upper and lower limbs.

His blood analysis done at the time of admission showed pancytopenia, raised lactate dehydrogenase and bilirubin levels and schistocytes on peripheral smear, all in the presence of a negative Coombs test (Table-1). These findings suggested the presence of non-autoimmune haemolytic anaemia.[4] The blood, stool, urine, and sputum cultures were negative suggesting an absence of any infection. However, urinalysis reported significant pyuria, haematuria, and nephrotic-range proteinuria (Table-2), consistent with decreased serum proteins seen on blood test reports (Table-1). These, together with raised serum urea and creatinine, suggested deranged renal function

Table-1: Initial laboratory findings.

Laboratory Tests	Results	Normal Values
Hb (g/dL)	6.6	Men: 13.5-17.5 Women: 12-15.5
MCV (fL)	77	80-100
TLC (cells/L)	2.62	4.5-11
Neutrophils (%)	82	34.9-76.2
Lymphocytes (%)	9.7	17.5-45
Platelets (units/L)	53,000 (53 × 109)	150,000-400,000 (150-400 × 10^9)
Reticulocyte (%)	5.09	0.5 - 2.5
ESR (mm/hour)	23	0-20
CRP (mg/L)	56	<10
LDH (U/L)	571	140-280
Coombs (direct)	Negative	-
ADAMTS13 level	15%	>=68%
Total Bilirubin (µmol/L)	2.14	1.71-20.5
Direct Bilirubin (µmol/L)	0.54	1.7-5.1
Indirect Bilirubin (µmol/L)	1.6	3.4-12
AST (U/L)	39	May-40
ALT (U/L)	61	Jul-56
Iron (µg/dL)	43	65 to 176
Vitamin B-12 (pg/mL)	1248	160-950
Folate (ng/mL)	4.4	2.7-17.0
PT (seconds)	13.1	11-12.5
aPTT (seconds)	30.7	30-45
INR	1.25	0.8-1.1
Blood culture	Negative	-
Stool culture	Negative	-
Urine culture	Negative	-
Sputum culture	Negative	-
Total Protein (g/dL)	4.2	8-Jun
Albumin (g/dL)	2	3.5-5.0
Globulin (g/dL)	2.2	2.0-3.5
Anion gap (mEq/L)	23	11-Mar
BUN (mg/dL)	124	20-Jul
Creatinine (mg/dL)	4.4	0.9-1.3
Sodium (mEq/L)	120	135-145
Potassium (mEq/L)	5.2	3.5-5.5
Chloride (mEq/L)	75	96-106
Calcium (mg/dL)	7.7	8.6-10.3
RBS (mg/dL)	104	80-130
HIV	Negative	-

Hb= haemoglobin; MCV= mean corpuscular volume; TLC= total leukocyte count; ESR= erythrocyte sedimentation rate; CRP= C-reactive protein; LDH= lactate dehydrogenase; ; ADAMTS13= a disintegrin and metalloproteinase with thrombospondin type 1 motifs, member 13; AST= aspartate transaminase; ALT= alanine transaminase; PT= prothrombin time; aPTT= activated partial thromboplastin time; INR= international normalised ratio; BUN= blood urea nitrogen; RBG=Randon Blood Glucose; HIV= human immunodeficiency virus.

Table-2: Urine detailed report (D/R).

Laboratory Tests	Result	Normal Values
pH	5	4.5-8.0
Protein	3+	None-traces only
Red blood cells/hpf	18	0-4
Pus cells/hpf	6-8	2-3
Cast	Nil	-
Protein/Creatinine Ratio	5.03	<0.2

Table-3: Autoimmune profile of the patient.

Laboratory Tests	Results	Normal Values
ANA (Units)	5000 (raised)	<20 = Negative 20-60 = Moderate Positive >60 = Strong Positive
Anti-dsDNA antibody (IU/mL)	6.0 (raised)	<=4 (Negative) 5-9 (Intermediate) >=10 (Positive)
Other auto-immune profile	Negative	-
C3 (g/L)	1.6	0.8-1.6
C4 (g/L)	0.38	0.16-0.48

ANA: Anti-nuclear antibody; Anti-dsDNA: anti double-stranded DNA.

Table-4: Laboratory test results on the second day of admission.

Laboratory Tests	Results	Normal Values
Hb (g/dL)	6.9	Men: 13.5-17.5 Women: 12-15.5
MCV (fL)	74	80-100
TLC (cells/L)	5.9	4.5-11
Platelets (U/L)	35,000 (35×10^9)	150,000-400,000 ($150\text{-}400 \times 10^9$)
LDH (U/L)	432	140-280
Reticulocyte (%)	0.18	0.5-2.5
BUN (mg/dL)	100	20-Jul
Cr (mg/dL)	5.8	0.9-1.3
Protein/Cr Ratio	4.07	<0.2
Sodium (mEq/L)	128	135-145
Potassium (mEq/L)	4.9	3.5-5.5

Hb= haemoglobin; MCV= mean corpuscular volume; TLC= total leucocyte count; LDH= lactate dehydrogenase; BUN= blood urea nitrogen; Cr= creatinine.

(Table-1). The chest radiograph showed bilateral pleural effusion, more marked on the right side (Figure-1). Ultrasound abdomen showed bilaterally small echogenic kidneys with parenchymal changes and moderate ascites. CT of the brain showed age-related atrophic changes with no gross findings (Figure-2). This clinical picture of fever, thrombocytopenia, microangiopathic haemolytic anaemia, impaired renal function and neurological symptoms strongly led to a differential diagnosis of TTP. Furthermore, mildly low blood ADAMTS13 levels provided support to this suspicion (Table-1). This finding

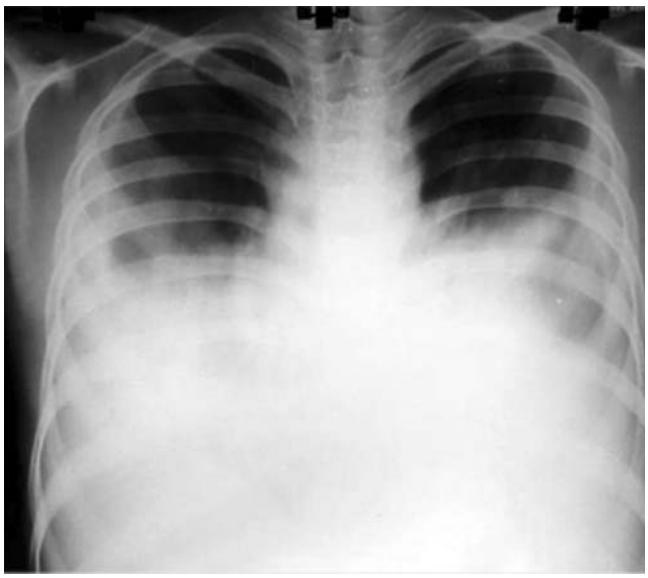

Figure-1: A chest X-ray showing bilateral pleural effusion.

was alarming and necessitated a thorough workup to investigate any primary condition precipitating the TTP. Among all known causes, two potentially important conditions that drive secondary TTP are HIV and CTDs.[4] Since our patient tested negative for HIV (Table-1), a detailed evaluation of his autoimmune profile was done on the next day of his admission that gave positive markers for active SLE, a CTD (Table-3). Additionally, considering the urine analysis report, renal biopsy was also planned to exclude lupus nephritis but was not done because consent was not given by the patient and his attendant.

Immediately on his admission, the patient was catheterised and was started on intravenous infusion of normal saline along with intravenous analgesics and broad-spectrum antibiotics for fever and diarrhoea and anti-secretory drug (proton-pump inhibitor) for GI ulcer prophylaxis. He received a total of three packed red blood cells transfusion in three days. Following the provisional diagnosis of TTP, he was started on 1-gram intravenous Methylprednisolone on the day of admission and plasma exchange was added in the treatment plan. His pancytopenia persisted on the second day of his admission while his renal functions deteriorated further (Table-4) with a massive increase in oedema for which he underwent 3-4 sessions of haemodialysis. Despite all these interventions and strict monitoring, there was no improvement in his condition. Concurrently, even with continual efforts, it was practically impossible to arrange plasma exchange on an urgent basis due to limited resources in our government setup and a restricted supply. Though it was arranged by the third day of his

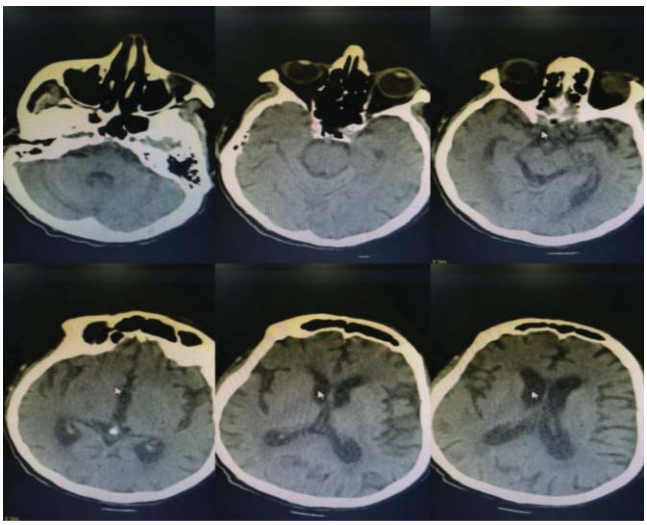

Figure-2: CT scan brain showing no gross findings.

admission it was of no use as the patient collapsed haemodynamically and expired before he could undergo the session of plasma exchange scheduled on the same day.

Discussion

SLE is a disease that predominantly affects females of child-bearing age; however, this is not always true as neither gender nor any age group is spared from this autoimmune multi-organ disease which has diverse presentations and prognosis. The prognosis of an SLE patient depends highly on the age of presentation and the extent of organ involvement. SLE occurring in children tends to be more serious and demands aggressive intervention,[6] whereas late-onset SLE has a more insidious onset and a slower disease course, yet it carries a higher risk of poor disease outcomes specially in terms of mortality.[6] Thus, the later the presentation, the more lethal the disease is, of which our case is a strong evidence.

In our case of SLE in a middle-aged male, the diagnosis was impeded because of the predominant presence of two sets of symptoms — parkinsonism strongly hinting towards a neurodegenerative disorder, whereas fever and GI symptoms suggested some infectious cause such as tuberculosis, inflammatory bowel disease (IBD) or any GI malignancy. A thorough blood workup was done to evaluate underlying conditions that were possibly precipitating this presentation. The laboratory test results concluded the diagnosis of TTP. TTP could be congenital or acquired; however, the latter is much more common. Among all known causes of acquired TTP, HIV and CTDs remain the most frequent ones. The association of TTP with CTD was first reported in 1961 where a diagnosed case of SLE, a CTD developed TTP.[4] Consistently, the detailed workup of our patient unmasked the underlying hidden SLE. On this basis, it was concluded that TTP and probably parkinsonism as well, had been precipitated chiefly by SLE.

It is hypothesised that patients with acquired TTP secondary to SLE tend to have lower than normal ADAMTS13 levels in blood[4] as they form autoantibodies against ADAMTS13; a VWF cleavage enzyme which cleaves large precursors of VWF into smaller units with less adhesive surface for platelets. Due to the deficiency of ADAMTS13, a high concentration of large multimeric forms of VWF accumulate in the blood and provide potent adhesive surfaces for the formation of platelet-rich thrombi that narrows the lumen of arterioles. This results in microangiopathic haemolysis of the red blood cells as they are subjected to sheer stress while squeezing past these blood clots resulting in damage to their membranes.[4] In addition, these microthrombi can disrupt the blood supply leading to end-organ ischaemia and damage. This hypothesis of antibody-mediated destruction of ADAMTS13 is supported by Knecht ME, et al[7] who also claimed a low serum ADAMTS13 levels in SLE patients. Our case further supports this hypothesis as blood ADAMTS13 levels in our patient were also low when evaluated on the day of admission, albeit the overall validity of this concept is still inconclusive.

On the contrary, strong evidence of an association between SLE and Parkinson's disease (PD) is not found in the current relevant literature. Considering the neuropsychiatric variant of SLE (NPSLE), headache, psychoses, seizures, and cerebrovascular diseases remain the most frequent presentations[5] whereas, parkinsonism secondary to NPSLE is very rare and unusual.[5] Regardless, there are plausible explanations for this association between NPSLE and parkinsonism. Either it's the formation of autoantibodies against the dopaminergic neurons in the basal ganglia or the association is driven by the underlying antiphospholipid antibody-mediated thrombotic-vasculopathy.[5] The latter results in multiple infarcts in the small vessels of basal ganglia causing disruptions in the motor pathways.[8] Furthermore, inflammatory mediators such as cytokines can play a key role in the pathogenesis of parkinsonism. These inflammatory mediators produced by the autoimmune disease process are potentially neurotoxic as they can enter and trigger an inflammatory process in the brain tissue leading to the degeneration of the dopaminergic neurons.[5] Contrarily, CT scan of our patient (Figure-2) ruled out infarcts or any degenerative changes in basal nuclei which makes these equivocal theories inconclusive

and less supportive.

The management of our patient became very challenging because the link between his indistinct symptoms was difficult to derive at the time of admission and required a detailed workup to reach a specific conclusion. Consistently, the laboratory test results guided our management plan. Following initial resuscitation for haemodynamic stability, the patient was started on intravenous steroids, preferably high-dose Methylprednisolone which was continued for three days. Though the use of Methylprednisolone as a first-line treatment for TTP does not hold a firm basis, it is mainly preferable because of its immunosuppressive property as claimed by Blombery P, et al.[9] The drug weakens the immune system and eventually antagonises antibody production and subsequently, the destruction it mediates.

Following the initiation of steroids, the next step in the management of our patient was to arrange plasma exchange which has now been recognised as the most effective intervention for TTP, as also reported in the study conducted by Hassan AT, et al.[10] Concurrently, Blombery P, et al[9] also concluded plasma exchange as the cornerstone of the management of acquired TTP and suggested that it should be commenced even in cases suspected of TTP. However, considering the resource-constrained tertiary hospital setup that our patient was managed in, the time required for the arrangement of this procedure was longer than the time the patient could remain stable. Despite urgent care, his pancytopenia and renal functions worsened on the day following his admission. Even though, plasma exchange was set up on the third day of his admission, the patient's condition suddenly deteriorated as he collapsed haemodynamically and expired before receiving the session of plasma exchange scheduled for that day.

Conclusion

It is not uncommon to see patients presenting with unusual and poorly related symptoms that mask major underlying culprit. Our case is one such example where features of overlapping diseases i.e., TTP and PD masked underlying SLE. Though, detailed laboratory evaluation eventually revealed the diagnosis of SLE; it was too late to save the life of our patient. This case report should acutely alert health care professionals to be very vigilant of complex late-onset SLE cases that carry potential to bear clinical presentation of overlapping diseases, so as to avoid delays in diagnosis. However, in real essence, this report warrants the need of high-quality literature to help understand disease associations highlighted herein better and potential risk factors that drive them; paving way for standard guidelines focused on proactive management of such cases to improve chances of survival and subsequent quality of life.

Consent: A proper written consent was taken from the patient's son (his attendant) in for publication of this case report.

Disclaimer: None to declare.

Conflicts of Interest: The head of the department who signed the letter of approval for the case report is also a co-author of this manuscript.

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