Diplopia as the Initial Manifestation of Cerebral Vasculitis in a Patient with Systemic Lupus Erythematosus: Diagnostic Approach and Challenges

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Abstract

The term Neuropsychiatric systemic lupus erythematosus (NPSLE) encompasses all neurologic and or psychologic symptoms arising in patients with SLE after other causes have been ruled out. Cerebral vasculitis as a manifestation of NPSLE is a rare case with a very broad spectrum of clinical presentation and severity. We report a case of a female with cerebral vasculitis presenting with diplopia as its early manifestation. Diagnosing cerebral vasculitis remains challenging given that biopsy as the gold standard is an invasive procedure and may not be available in many settings. A high suspicion of diagnosis requires clinicians' judgement in reviewing combination of detailed history taking, physical examination, neuroimaging, and other available supporting modalities.

Keywords: *Cerebral vasculitis, diplopia, nerve VI palsy, systemic lupus erythematosus*

Introduction

The term Neuropsychiatric systemic lupus erythematosus (NPSLE) encompasses all neurologic and psychologic symptoms arising in patients with SLE after other causes have been ruled out. Due to its broad features, it is crucial to promptly determine whether any neurologic or psychologic complaint arising during the course of the disease is a primary disorder, secondary to increased SLE disease activity, or to other systemic manifestations which is not related to SLE through thorough exclusion process [1]. The prevalence of NPSLE varies widely ranging between 37-95% depending on the diagnostic criteria used, study design, and other baseline characteristics[2].

Double vision, or diplopia, is a disturbance of visual focus which can occur as a result of either ophthalmologic or neurologic disorder with many possible aetiologies ranging from mild diseases such as refractive error or dry eyes to the lethal ones namely intracranial injuries [3]. With regards to that, it is vital to localize the underlying pathology of diplopia in a timely manner, particularly in SLE patients, to confirm the diagnosis and establish whether it is a manifestation of NPSLE or not. Patients with NPSLE generally have poorer prognosis, therefore, an early diagnosis and adequate treatment is required to prevent further life-threatening complications [4]. In this report, we illustrate the diagnostic steps of NPSLE manifesting as cerebral vasculitis with diplopia as the early complaint.

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Case Report

A 24-year old Indonesian female was admitted to the emergency department with sudden complaint of shortness of breath since two days before admission. She also complained of cough since 1 week before admission and joint pain in her elbows and knees. There was not any fever. Two days ago, she started to experience double vision. She had been diagnosed with SLE since 4 years ago and routinely takes mycophenolate sodium 180 mg BID and methylprednisolone 4 mg QD. She had a history of being diagnosed with pneumonitis lupus one year ago and have completed six sessions of cyclophosphamide chemotherapy in which she achieved complete clinical response.

On physical examination, her general appearance was ill with severe dyspnoea, blood pressure 110/80 mmHg, respiratory rate 28 times per minute, heart rate 112 times per minute, and body temperature 37.1^0 C. Rhonchi was found in middle side of right hemithorax. Regarding the presence of double vision, the first approach is to promptly determine whether it is a monocular or binocular diplopia. During the eye examination, the patient claimed that the double vision resolved when either eye was covered establishing a binocular type diplopia. The most common cause for binocular diplopia are neurologic. We continued to perform neurologic examination to the patient covering motoric, sensory, reflexes, and cranial nerves function. It was found that the motoric, sensory, and reflexes were normal. However, during the cranial nerves examination, the patient failed to move her left eye's gaze to lateral side indicating that she may have cranial nerve VI palsy.

Blood test showed haemoglobin level 6.4 g/dL, leukocytes 2740 cells/mm3, neutrophil 77.3%, lymphocytes 18%, random plasma glucose 102 mg/dL, BUN 31 mg/dL, creatinine serum 1.04 mg/dL, CRP 30.49 mg/dL, potassium 4.7 mmol/L, ESR 20, C3 45 mg/dL, C4 13 mg/dL, and blood gas analysis as follows: pH 7,51, pCO_2 24,9 mmHg, pO_2 139 mmHg, HCO_3 20 mmol/l, BE -3,2 mmol/l, SO_2 99,4%. The chest x-ray showed infiltrates in right paracardial. She was initially assessed with suspected case of pneumonitis lupus with bacterial pneumonia as its differential diagnosis, and suspected case of NPSLE manifesting as cranial nerve VI palsy. Consequently, she was planned to have sputum and blood culture examination to determine the true cause of the pneumonia; and brain CT scan to evaluate the cranial neuropathy. She was also planned to have lipid profile and electrocardiography to screen possible microvascular risk factors. Meanwhile, she was treated with oxygenation support, intravenous methylprednisolone 1 mg/kg body weight, levofloxacin 750 mg intravenous QD as empirical antibiotics for possible infection, and blood transfusion.

The CT scan of the brain with contrast conducted on the second day of treatment discovered: multiple small hypodense lesion in right and left basal ganglia and calcification of left basal ganglia suggesting a vasculitis with lacunar infarction in basal ganglia. The blood test done earlier showed normal lipid profile (total cholesterol 141mg/dL, low density lipoprotein 79mg/dL, high density lipoprotein 28mg/dL, and triglycerides 132mg/dL); the electrocardiography only recognized a sinus tachycardia; while the sputum and blood culture examination required at least 5-7 days of processing. A diagnosis of cerebral vasculitis as a manifestation of NPSLE was added. In the time she was diagnosed with cerebral vasculitis, a blood examination to inspect the presence of antiphospholipid (aPL) antibodies was also performed in order to rule out the possibility of coexisting antiphospholipid syndrome (APS). The result showed normal aCL (aCL IgG 3 and aCL IgM <2), normal LA (47,4 seconds), and negative IgG and IGM of anti-$\beta_2$glycoprotein-1.

On the grounds that there was a possible bacterial infection existing due to pneumonia in this patient, determining the management brought a dilemmatic situation as both pneumonitis lupus and NPSLE requires high dose of glucocorticoids and cyclophosphamide

which are strong immunosuppressants. Considering the minimal clinical features of infection and sepsis found in this patient, it was decided to increase the methylprednisolone dose to a pulse of 500 mg daily for 3 consecutive days with close monitoring. By the time the sputum and blood culture revealed no signs of bacteria on the sixth day of treatment, the patient was immediately treated with cyclophosphamide. Nonetheless, the cough and dyspnoea worsened and her condition was deteriorating with signs of oxygen desaturation. She refused to be treated with ventilation support and passed away due to respiratory failure on the 8th day of treatment.

Discussion

Cerebral vasculitis as one of NPSLE's manifestation is rare of which prevalence fell below 7% in post-mortem studies [5]. It is defined as inflammation occurring in cerebral blood vessels with very diverse early clinical manifestations and may resemble common neurology symptoms such as loss of consciousness, headaches, seizures, stroke, and optic or cranial neuropathies. A case-series report conducted in a health centre in Portugal discovered that during 10 years of observation, there were only 4 cases of cerebral vasculitis in SLE patients of which each has different initial manifestation, covering: cognitive dysfunction, lower limb monoparesis, seizure, and diplopia [6]. Brain vessel biopsy is its diagnostic gold standard, however, it is an invasive procedure and may not be available in many settings. It requires complex technique, particularly when affected site is difficult to access resulting in varying sensitivity rates [7,8]. As a result, high suspicion of the disease is usually made by experts' clinical judgement in the field after reviewing detailed history-taking, physical examination, neuroimaging, and other supporting modalities. Given the unpredictable course of the disease, the diagnostic process may pose as challenges for clinicians, especially those in low-resource settings.

When this patient was discovered with diplopia, it is crucial to quickly determine the underlying cause. The first step toward a patient with diplopia is to ascertain whether it is a monocular or binocular type by asking the patient to close their eyes alternately. Monocular diplopia is generally a result of ophthalmologic disorders while binocular diplopia is due to neurologic problems. In monocular diplopia, the double vision disappears when the affected eye is covered but returns when the normal eye is covered. While in binocular diplopia, the double vision disappears when either eye is covered. When the examination revealed a binocular type, the differential diagnosis narrows down to neurologic causes, therefore, a thorough neurologic physical examination was conducted [3,9,10].

After the examination showed a cranial nerve VI (abducens nerve) palsy, this case drifted us to a whole new diagnostic algorithm to follow. With its long course between lower pons and the eye, the abducens nerve is very much susceptible to injuries. The past publications have established that immediate neuroimaging examination is not recommended due to its lack of diagnosis benefit and cost-effectiveness. The evaluation of nerve VI palsy begins with excluding history of trauma or physical injuries. After trauma has been excluded, it is advisable that we conduct evaluation of vasculopathy risk factors (i.e. diabetes, hypertension, hyperlipidaemia, and coronary artery disease) as microvascular ischemic disease is a frequent underlying cause of cranial nerve VI palsy. Most cases of cranial nerve VI palsy due to vasculopathies ameliorate within 3-6 months after treatment, however, if improvement was not observed within the timeframe or symptoms worsen, neuroimaging examination is then advised. Conversely, patients without microvascular risk factors are suggested to have immediate neuroimaging examination to evaluate other possible aetiologies. MRI is more preferred to CT scan due to its higher sensitivity. Brain CT scan is hardly representative because it generally can only display large ischemic

infarcts, however, in some cases it may show brain calcifications within old ischemia, similar to what we discovered in this case [11,12].

This patient was planned to have brain CT scan because history of trauma and microvascular risk factors have been excluded, and emergency MRI examination was not available at the time. After the CT scan result supported a diagnosis of cerebral vasculitis, the patient was treated accordingly.

The therapy of NPSLE depends on the underlying mechanism whether it is inflammatory or ischaemic/thrombotic. The management of NPSLE with inflammatory process includes high dose of intravenous glucocorticoids in combination with monthly cyclophosphamide therapy, while NPSLE with the latter mechanism requires anticoagulant and antithrombotic if aPL antibodies are present. It is not uncommon that both mechanism may even coexist in the same patient. When the inexistence of aPL antibodies were proven by normal results of aCL, LA, and anti-$\beta_2$glycoprotein-1, it was clear that the patient did not require additional anticoagulant or antithrombotic treatment. Meanwhile, this patient had pneumonia either due to lupus pneumonitis or infection as a comorbid of which exact aetiology was still being evaluated. The mainstay of pneumonitis lupus treatment is similar to NPSLE consisting of high dose of steroids followed by cyclophosphamide. It is important to note that administration of high dose steroid in combination with cyclophosphamide may suppress immune system thus requiring extra cautious in patients with suspected infections [13,14].

This patient was treated with pulse dose of methylprednisolone for three days followed by administration of cyclophosphamide after the culture result indicates no sign of bacterial infection. Nonetheless, at the same time the patient's condition has deteriorated and she eventually died of respiratory failure due to severe lupus pneumonitis. Cerebral vasculitis in SLE is generally a reversible case, however, pneumonitis lupus has poor prognosis with mortality rate as high as 50% [6,15].

Conclusion

In summary, an SLE patient with diplopia was unexpectedly discovered to have cerebral vasculitis through thorough history taking, physical examination, laboratory, and neuroimaging examination. Cerebral vasculitis as manifestation of NPSLE is a rare case with very broad clinical features and prognosis, thus requiring good clinical judgement and experience in the field. Therefore, it is important that clinicians are able to conduct diagnostic investigation by processing all subjective and objective findings to arrive at a safe clinical-decision that benefits the patients, such as deciding the examinations that need to be taken (taking cost-effectiveness and patients' convenience into consideration), therapy to give, and even decision to immediately refer when diagnostic modalities are limited.

Patient Informed Consent

Patient consent was obtained from patient and family for writing this case report.

Funding: Self-funded

Conflicts of Interest: The authors declare no

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