Staring at an abscess, but lupus stares back…

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Abstract

We report a case of a 12-year-old male who initially presented with active systemic lupus erythematosus (SLE) with lupus nephritis and secondary macrophage activation syndrome (MAS). He went on to develop left-sided upper motor neuron (UMN) facial palsy secondary to lupus-related tumefactive demyelination. Tumefactive lesions secondary to demyelination are a very rare manifestation in neuropsychiatric SLE. This child responded to aggressive immunosuppression with steroids and cyclophosphamide.

Keywords: central nervous system lupus, brain abscess, tumefactive demyelination

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Introduction

Systemic lupus erythematosus (SLE) affecting the nervous system is a well described clinical manifestation with prevalence ranging from 14–75% in various cohorts.[1] The neuropsychiatric syndromes of SLE (NPSLE) can be polymorphic and are classically divided into two groups:[2]

1. NPSLE affecting the central nervous system: aseptic meningitis, cerebrovascular disease, cognitive dysfunction, headache, movement disorders, seizures, acute confusional state, anxiety disorder, mood disorder, psychosis, demyelinating syndrome, myelopathy
2. NPSLE affecting the peripheral nervous system: autonomic disorder, mononeuropathy, cranial neuropathy, plexopathy, polyneuropathy, GBS, myasthenia gravis

Tumefactive lesions secondary to demyelination, while described in multiple sclerosis,[3] are a very rare manifestation in lupus. Demyelination in NPSLE is often associated with anti-aquaporin-4 related neuromyelitis optica, but this is not always the case. We report a young male who presented with lupus-related tumefactive demyelination.

Case presentation

An adolescent boy was referred to us with fever, altered sensorium, malar rashes and hard palatal ulcers for the previous month. Routine evaluation showed anaemia with 4+DCT with a peripheral smear showing microcytic hypochromic anaemia with left shift and leukoagglutination along with platelet clumps, neutropenia (for a prolonged period before his hospital stay) along with nephrotic-range proteinuria and haematuria. C-reactive protein (CRP) was 0.1 mg/dl, hypocomplementemia (C3 18.8 mg/dl and C4 6.1 mg/dl), antinuclear antibody (ANA) by immunofluorescent assay (IFA) showing 4+ homogeneous pattern, anti-dsDNA163.0 IU/ml with negative antiphospholipid syndrome (APS) workup and a normal chest X-ray. He also had features suggestive of MAS with hyperferritinaemia (14,969 ng/ml), high LDH (1159 IU/l), hypertriglyceridemia, transaminitis (serum AST/ALT was 1037/415 IU/l) and hypofibrinogenemia. He was diagnosed as a case of juvenile SLE with lupus nephritis with cytopenias and secondary MAS. He was admitted in the ICU and started on pulse methylprednisolone (30 mg/kg) under broad spectrum antibiotic cover (until the neutropenia improved). Prednisolone was continued (1.5 mg/kg/day) and his clinical and biochemical parameters improved.

During this improving period he also developed bradycardia secondary to SA nodal dysfunction (lupus related) (Figure 1) and an episode of haemoptysis (evolving diffuse alveolar haemorrhage vs infection). Workup for infection with inflammatory markers (CRP and procalcitonin), blood and sputum cultures were negative. Along with additional immune suppression (IV methylprednisolone 250 mg pulse followed by 1.5 mg/kg/day), he was treated with isoprenaline, cardiac monitoring and broad spectrum antibiotics respectively and improved.

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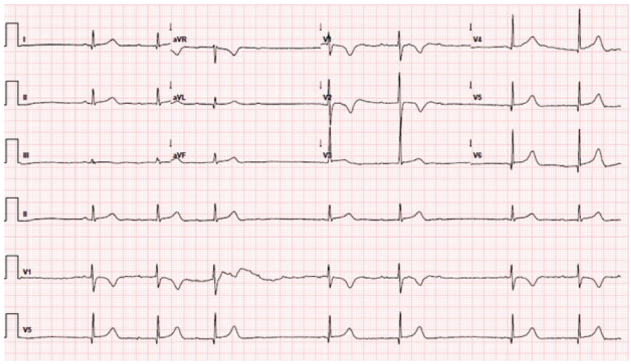
Figure 1 ECG shows heart rate of 44, absent P waves, normal QRS. Suggestive of SA node dysfunction



He then developed acute onset left-sided UMN facial palsy without other neurological deficits. MRI brain (contrast) showed a well circumscribed T2 hyperintense lesion in the right frontal lobe with mild perilesional oedema and ring enhancement on contrast imaging (Figure 2A) without meningeal enhancement. The child was well otherwise with no fever or neurological or other systemic symptoms. Given the background of initial prolonged neutropenia followed by immunosuppression for lupus and the unilateral nature of the lesion, the possibilities considered were brain abscess (bacterial/fungal) or tuberculoma. He was started on intravenous linezolid, meropenem and amphotericin (later changed to voriconazole) with levetiracetam for seizure prophylaxis. Repeat blood cultures and serum inflammatory markers (CRP and procalcitonin) were negative. Simultaneous workup for an extracranial infectious foci as a cause of CNS dissemination with whole body CT scan and sputum studies (in view of recent lower respiratory tract infection) was negative. In spite of this potent antibiotic regimen, the repeat MRI brain showed increasing lesional oedema and size along with a new similar lesion with similar enhancement.

Brain biopsy was considered, but deferred after discussion with the family due to possible complications from the lesion's proximity to internal capsule and low sensitivity. Also, MR imaging pattern and lesion characteristics were consistently opined as suggestive of a non-neoplastic process. The possibility of a bacterial/fungal focus was very unlikely as the patient had worsened on high-end broad spectrum antibiotics and antifungals. Thus the possibility of tumefactive demyelination (secondary to lupus) was considered.

Consequently, he was hiked on immunosuppression with IvIg (60 gm over 3 days) followed by IV cyclophosphamide 500 mg/m^2 in view of the good response to IvIg. IV cyclophosphamide was continued for a total of 6 doses following improvement. The UMN palsy improved with no clinical deterioration and radiologically, on repeat MRI, the lesional oedema reducing first, followed by the lesional size (Figure 2B). During this period, the haemogram, urinary sediments and other evidence of disease activity of lupus also normalised. He continued to be stable on maintenance mycophenolate mofetil (1 g daily) and hydroxychloroquine (200 mg daily).

Discussion

Tumefactive demyelination (TD) is a very rare presentation of NPSLE. However, this is a well described clinical entity in other autoimmune CNS diseases, namely multiple sclerosis. The clinical presentation of patients with TD is variable and is related to the lesion size and its location. The gold standard investigation for TD diagnosis is MRI. TD is usually a solitary demyelinating lesion larger than 2 cm, mimicking brain neoplastic lesions.

Neuroimaging characteristics of these demyelinating lesions show predominantly white matter lesions with ill-defined borders, little mass effect, perilesional oedema, and incomplete or open-ring enhancement. The high T2 signal and relatively low T1 signal with the relative lack of mass effect or vasogenic oedema given the size of the lesions is also often a clue to the diagnosis on MRI.[3] The various differentials and their characteristics are discussed in Table 1. Only a single case has been reported showing development of TD in NSPLE and this was in a 13-year-old girl who presented with a right parietal lobe lesion with mass effect.[12] She also improved with aggressive immunosuppression with IV steroids and cyclophosphamide. Thus no large case series are available regarding the treatment of TD. However, as it can be considered as a major CNS manifestation, the authors

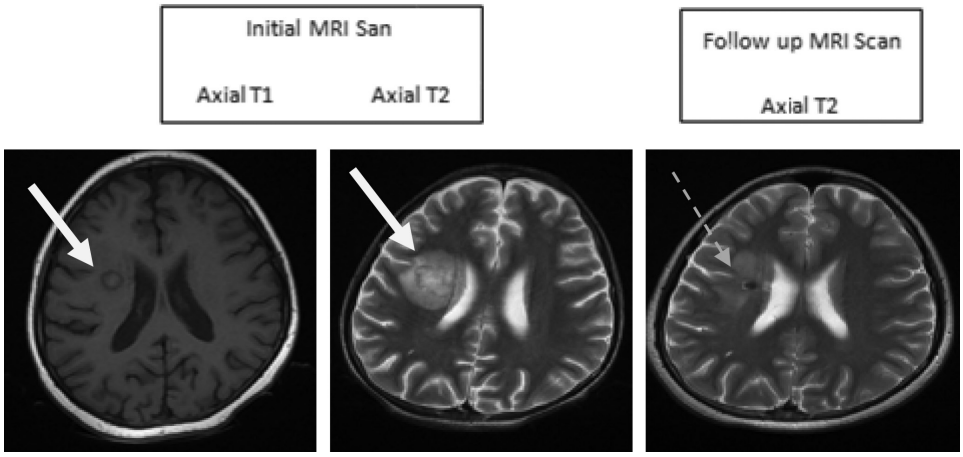


Figure 2 A) Initial MRI showing lesion (white solid arrow) in right lobe adjacent to the body of right lateral ventricle that is hypointense in T1 and hypertense with surrounding white matter vasogenic edema in T2. B) Follow up MRI showing reduction in size of the lesion and perilesional edema in T2 (white dotted arrow)

Table 1 The various differential diagnosis for a patient presenting with tumefactive demyelinating lesions and its differentiating lesions

Disease	Coexistent MTI findings (besides the TD lesions)	Coexistent clinical features
Multiple sclerosis	Multiple hyperintense lesions in the white matter-periventricular, juxtacortical/asymmetrical[4] 'Open-ring' enhancement pattern[4]	CNS-dominant presentations with optic neuritis, diplopia, dysarthria, vertigo, ataxia, bowel & bladder impairment, paraparesis or quadriparesis
Systemic lupus erythematosus	Large infarcts and multifocal white matter T2-hyperintense lesions (exhibit a vascular distribution) Reduced cerebral & corpus callosal volume Leptomeningeal enhancement Bilateral involvement of basal ganglia, along with punctuate enhancement[5]	Extra-CNS manifesations (serositis, arthritis, cutaneous LE, cytopenias, haematuria proteinuria, seizures neuropathy, oral ulcers, photosensitivity) are often coexistent
Primary Sjögren's syndrome	Nonspecific T2-weighted white matter hyperintensities Demyelination – brain or spinal chord[6]	Optic neuritis, kerato-conjunctivitis sicca, xerostomia, recurrent parotitis, fever, arthralgia
Tuberculosis	Nodular or smoothly enhancing basal leptomeningitis. TB abscess shows central zone of necrosis tuberculomas – smooth, thick, round capsular and non-enhancing lesions and can be solitary or multiple[7]	Coexistent pulmonary TB (fever, chronic cough) or extrapulmonary TB (pleural effusion, lymph node etc.) with constitutional symptoms
Fungal infections	Intracranial aspergilloma will have extra axial masses involving the anterior/ middle cranial fossa arising in close proximity to paranasal sinues[8]	More likely in immune-compromised patients and can be CNS (meningitis/ abscesses; infarcts/ haemorrhage, aneursyms, mass lesions) or other systemic fungemia
Glioma	Has T2/FLAIR hyperintense, expansile lesions involving both cortex and underlying white matter with vasogenic oedema[9]	CNS-dominant presentations with headache, focal seizures, focal neurodeficits, cortical sensory loss
Antiphospholipid syndrome	Stroke and transient ischemic attacks (TIA) are the most common manifestations. Demyelination - multiple T2 hyperintense lesions, subcortical, unilateral optic neuritis[10]	Obstetric complications, arterial or venous thrombosis
Behçet's disease	Lesions commonly in brain stem. T1 hypointense, T2 hyperintense, associated with vasogenic oedema, meningoencephalitis, cerebral vein thrombosis[11]	Recurrent oral ulcers, genital ulcers, uveitis

recommend aggressive treatment with pulse glucocorticoids (30 mg/kg/dose methylprednisolone for 3 days followed by 1 mg/kg/day oral prednisolone). Cyclophosphamide (750 mg/m2) can be considered as the second-line agent given its proven efficacy in other NPSLE manifestations.[13] Also, in severe cases not responding to the above treatment, Ivig has been proven to have a role in NPSLE manifestations affecting the brain parenchyma.[14] We recommend slow tapering of steroids over 6 months along with a total of 6–9 doses of IV cyclophosphamide which should be followed by maintenance therapy.

Of note, there were a few limitations in our approach to this case. As the patient was on broad spectrum antibiotics, along with the low pick up rate of CSF TB PCR /nucleic acid amplification test (NAAT) and lack of parental consent, CSF studies were deferred, which was not ideal. Another drawback was that MR spectroscopy was not done due to unavailability. An odd point to note in the case was normal CRP in the presence of features suggestive of MAS (cytopenias, transaminitis, elevated LDH and triglycerides, hyperferritinaemia >10000 mg/ml, hypofibrinogenemia).

Conclusion

Although it is desirable to have diagnostic tests that establish a specific diagnosis of neuropsychiatric lupus, such tests do not exist. Thus the approach to patients with neuropsychiatric symptoms in lupus consists of investigations that establish active systemic lupus whilst distinguishing between organic and functional manifestations and excluding symptoms not due to lupus. In such a patient, and keeping in mind the classical logical principle of Occam's razor, any new symptom or sign in a patient with a known disease, the possibility of another manifestation of the same disease should be thought of and ruled out before attributing it to another new entity. Though rare in lupus, tumefactive demyelination is suggestive of an aggressive presentation. This aggressive nature was evident in our patient in whom the lesions progressed even with IV steroids. Treatment with aggressive immunosuppression (IV cyclophosphamide) is the best treatment in this scenario of severe NPSLE.[13]

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