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RESEARCH ARTICLE

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY IN AN ADULT PATIENT WITHSYSTEMICLUPUSERYTHEMATOSUS

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Abstract

We report a case of 40-year-old female who is known to have systemic lupus erythematosus (SLE) presenting with severe cognitive impairment with lymphopenia, proteinuria, and evidence of SLE serological activity. Initially, she was managed as a case of neuropsychiatric systemic lupus erythematosus (NPSLE) with Cyclophosphamide and pulse steroids. However, she has been deteriorating clinically in forms of right sided hemiparesis, blindness, and aphasia despite normalization of complements and anti-double stranded DNA antibodies levels. Diagnosis of progressive multifocal leukoencephalopathy (PML) was made based on her clinical manifestations with brain MRI findings of subcortical white matter lesions and detection of John Cunningham virus (JCV) in cerebrospinal fluid analysis. Immunosuppressive agents were discontinued aiming for immune system restoration.

Introduction:-

Systemic Lupus Erythematosus (SLE) is a heterogeneous autoimmune systemic disease that mostly affects child-bearing women. The disease often involves the central nervous system and causes varied neuropsychiatric manifestations that range from mild headache to cognitive impairment. (1)

Neuropsychiatric systemic lupus erythematosus (NPSLE) is considered the most common manifestations of lupus as the prevalence is reported to be around 80%. (2, 3) The American College of Rheumatology (ACR) has defined 19 neuropsychiatric syndromes. (4) NPSLE presentation is wide and non-specific, therefore its diagnosis and management are often delayed.

One of the challenging rheumatological diagnosis that sometimes is confused with NPSLE is progressive multifocal leukoencephalopathy (PML), which is a rare demyelinating disease of the central nervous system (CNS). It is caused by reactivation of polyomavirus John Cunningham virus (JCV) and carries a poor prognosis with a high mortality rate and permanent neurological complications. (5) Acquiring JCV occurs early during childhood as asymptomatic infection that gets reactivated during immunosuppression periods. (6) The disease was reported frequently during

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AIDS pandemic in 1980 as AIDS-defining illness. Since then, it was described in patients with malignancies, organ transplantation, and multiple sclerosis. (7, 8) However, PML is rarely reported in patients with rheumatic diseases. The diagnosis is usually made when an immunocompromised patient with subacute neurological deficit has demyelinating lesions in parieto-occipital or frontal lobes on brain MRI and either positive polymerase chain reaction (PCR) of JCV from cerebrospinal fluid (CSF) sample or brain biopsy. (9)
We herein describe a case of PML in SLE patient.

Case Presentation:
We report a 40-year-old female patient who was brought to the emergency room due to a three-week history of confusion. She has the background of SLE that was diagnosed 8 years earlier based on a score of 8 out of 17 ofSLICC classification criteria in terms of cutaneous manifestation, arthritis, leukopenia, lymphopenia, positive antinuclear antibody (ANA), positive anti-double stranded DNA antibody (anti-dsDNA), positive anti-smith, and low complements levels. She was on Prednisolone 5mg once daily, Hydroxychloroquine 200mg once daily, and Methotrexate 10mg once weekly.

The patient was in her usual state of health till she started to develop headache,that was followed by mood swings. Her symptoms have progressed to the point of poor appetite, sleep deprivation, lack of self-care, and confusion.

She denied any history of fever, seizure attacks, or visual or auditory hallucination. There was no history of joint pain, malar rash, oral or nasal ulcers, nor hair loss. Also, she did not describe any pleuritic chest pain,shortness of breath, hematuria,or frothy urine. She had no previous history of venous thromboembolism events or abortions.

Initially, the patient had sought medical advice in another hospital where they investigated her and did brain MRI which showed left subcortical parietal lobe white matter lesion (Figure. 1), after which she was referred to our tertiary-care center for further investigations and management.

On examination,her vital signs were within normal limitswith a blood pressure of 125/80, however, she was confused and disoriented to time, place, and person. She could not obey a 3-step command and had impaired short-term memory. Moreover, her long-term memory was impaired as she could not remember the king's name. Also, she had impaired comprehension plus impaired writing and calculation. Examination of the cranial nerves,and power and sensation in all limbs were normal. There were no meningeal signs and she did not have evidence of synovitis clinically. Chest and cardiovascular examinations were normal, and she had no evidence of organomegally upon abdominal examination.

Her initial laboratory investigations are shown in Table 1, and echocardiography was done and showed normal biventricular function with no evidence of vegetations. As part of her headache evaluation, she underwent brain CT with carotid CT angiography which showed evidence of SLE related vasculitis/vasculopathy of the intracranial vessels. (Figure. 2)

Therefore, the patient was admitted to the hospital with a presumed diagnosis of NPSLE based on acute confusional state and serological evidence of the disease activity, i.e., high anti-dsDNA, low complements levels, lymphopenia, and high urine protein/creatinine ratioand after ruling out focus of infection and electrolytes disturbance. Her SLEDAI score was 24 which indicated severe SLE flare, therefore, she was started immediately on Methylprednisolone 500 mg intravenously for 3 days followed by oral prednisolone 30 mg orally twice a day.

Three days later, the patient developed a tonic-clonic seizure that lasted for around 30seconds and was aborted spontaneously. Her blood pressure was 135/80 and she had a normal blood glucose level and no electrolytes disturbance. Urgent brain CT was requested, and it showed scattered hypodensities lesions involving cortical and subcortical white matter of both frontal lobes, both parietal, occipital & posterior temporal lobes suggesting posterior reversible encephalopathy syndrome (PRES). (Figure. 3) Clinically, the patient had cortical blindness on examination although she denied that in keeping with Anton syndrome. Few days later, Brain MRI was done and again showed features of PRES. (Figure 4).

The patient received Cyclophosphamide (CYC) 500 mg/m2 (lower-range dose of NIH protocol) and upon discharge, her cognitive function improved. Her discharge medications were Prednisolone 60 mg once daily, Calcium and Cholecalciferol, Alendronate, Trimethoprim/Sulfamethoxazole, and Hydroxychloroquine.

Two weeks after the first CYC dose, she was admitted in another hospital as a case of febrile neutropenia secondary to Salmonella bacteremia. Initially, she was treated with Piperacillin/Tazobactam and Vancomycin that were de-escalated to Ceftriaxone as per cultures' sensitivity and completed a total of 14-days course. During that period, she became more confused and aggressive. Therefore, she received the second dose of CYC that was given in a reduced dose due to her previous neutropenia complication.

Few days later, patient was hospitalized again due to worsening of her cognitive function. At that time, she started to have visual hallucination and decrease attention and awareness. She became more agitated with disorganized behaviors and dysarthric speech. However, she had no nuchal rigidity and no meningeal signs. Though she did not have gross focal neurological deficits, full neurological examination could not be completed as she was uncooperative. Her laboratory investigations are shown in Table 2.

Although patient's cognitive function has progressed and continued to deteriorate clinically in terms of progressive right-sided weakness, blindness, and aphasia, her brain CT showed stable appearance of multifocal areas of PRES-related changes.

One week later, brain MRI was done evaluating unexplained worsening of her neurological symptoms and it showed possibility of SLE-related cerebritis/encephalitis (Figure. 5) although her anti-dsDNA and complements levels were normalized, with decreasing sedimentation rate level, and elevated c-reactive protein along with poor response to high dose steroids, which were all going against the findings of SLE flare and raising the possibility of other differential diagnoses including malignancy, paraneoplastic syndromes, and PML. Therefore, another lumbar puncture was performed for further workup, meanwhile, paraneoplastic syndromes workup, namely, Anti Hu, anti Ri, and anti Yo came out negative. Also, anti-Ribosomal P-protein antibodies were negative. This time, JCV PCR was sent from CSF sample and turned out to be positive at 4550 copies/mL with negative HIV antigen/antibody test. After receiving the positive result of JCV, a repeated enhanced brain MRI was done and showed non-enhanced left subcortical frontoparietal white matter lesions which indicate PML. (Figure. 6)

After diagnosing the patient with PML, prednisolone dose was gradually tapered down to 5mg OD and no further CYC doses were prescribed.

The patient's condition has continued to progress as she has become bed-bound and dependent due to right-sided hemiparesis, blindness, and aphasia. Her clinical status remained the same for more than two months although she had a complicated hospital course with right hip avascular necrosis with septic arthritis and catheter-related thrombosis.

Discussion:-

PML is a rare disease that is caused by reactivation of the JCV and carries poor prognosis. Rarity of the condition is much pronounced in the context of rheumatic disease including SLE. (9) Reviewing the literature, few cases have been reported of SLE patients who developed PML since it was first described by Astrom et al. in 1958 as a rare complication in patient with hematological malignancy. (7) The incidence of PML in patients with SLE is considered higher than other rheumatic diseases or general population. (10)Molloy and Calabrese found the incidence to be 4for SLE and 0.4 for Rheumatoid Arthritis per 100,000 discharges, meanwhile its rate is 0.2 in the general population. (11)

Although immunosuppression is considered a risk factor for PML development, cases have been reported in literature for patients who received no immunosuppressive treatment as described thoroughly in a systematic review by Henegar et al. (6) They analyzed 35 case reports, and found only 23 patients had immunosuppression, five cases had minimal immunosuppression, and three PML cases had no immunosuppression.

Differentiating PML from other etiologies as the underlying cause of central nervous system involvement in SLE patients remains crucial and challenging in the same time, as patients with presumed NPSLE or lupus cerebritis for example, require intensification of their immunosuppressants as part of their management. Meanwhile, this step is in contrary to PML management which requires immediate discontinuation of immunosuppressive agents and reversing immunosuppression state. (12) Therefore, it is vital to revisit the diagnoses of NPSLE in patients who are not responding to CYC, especially with normalization of anti-dsDNA antibodies and complements levels.

Both prolonged lymphopenia and receiving CYC, as in our reported case, have been considered as association with development of PML in patients with SLE as reviewed by Molloy et al. (7, 13)

Unfortunately, PML carries a high mortality rate due to lack of effective treatment. Several treatments have been tried in non-HIV patients includingCidofovir, Mirtazapine, Pembrolizumab and Nivolumab, yet no convincing evidence of effectiveness was proven.(14)Therefore, in non-HIV patients, the median survival rate is three months.However, low JCV burden (50 to 100 copies/mL) in CSF samples of HIV patients is considered a good prognostic factor with longer survival time than those with higher burden. (15)

Table 1:- Laboratory investigations during first hospital admission.

Lab	Result	Normal range
WBC	3.1x 10^9/L	4.0 - 11.0 x 10^9/L
Hgb	10.0 g/dL	11.5-16.5 g/dL
Platelet	249x 10^9/L	150-450x 10^9/L
Neutro Auto#	2.36 x 10^9/L	2-7.5 x 10^9/L
Lymph Auto#	0.43 x 10^9/L	1.5-4 x 10^9/L
C4 Complement	0.11 g/L	0.1-0.4 g/L
C3 Complement	0.53 g/L	0.9-1.8 g/L
Anti-dsDNA (ELISA)	907.77IU/mL	Less than 200 IU/mL
CRP	10.4 mg/L	0 - 5 mg/L
ESR	90 mm/hr	0-20 mm/hr
Lupus Anticoag	Not detected	negative
PC Ratio	56.54 mg/mmol	Less than 20 mg/mmol
ACA IgM	13.07 MPL unit	Less than 12.5 MPL unit
ACA IgA	3.41 APL unit	Less than 12 APL unit
ACA IgG	3.51 GPL unit	Less than 15 GPL unit
BGP IgA	4.49SAU	Less than 20 SAU
BGP IgG	1.69SGU	Less than 20 SGU
BGP IgM	1.37SMU	Less than 20 SMU
CSF WBC count	0 per CMM	Less than 3 per CMM
CSF RBC count	0 per CMM	0
CSF TP	0.48	0.15-0.45 g/L
CSF Glucose	4.5	2.2-3.9 mmol/L

Table 2:- Laboratory investigations during second hospitalization.

Lab	Result	Normal range
WBC	7.2 x 10^9/L	4-11x 10^9/L
Hgb	11.3 g/dL	11.5-16.5 g/dL
Platelet	337 x 10^9/L	150-450 x 10^9/L
Neutro Auto#	4.92 x 10^9/L	2-7.5 x 10^9/L
Lymph Auto#	1.44 x 10^9/L	1.5-4 x 10^9/L
C4 Complement	0.55 g/L	0.1-0.4 g/L
C3 Complement	1.61 g/L	0.9-1.8 g/L
Anti-dsDNA (ELISA)	135.45 IU/mL	Less than 200 IU/mL
CRP	66 mg/L	Less than 5 mg/L
ESR	21 mm/hr	0-20 mm/hr
CSF WBC count	12 per CMM	Less than 3 per CMM
CSF RBC count	4080 per CMM	0
CSF TP	0.60 g/L	0.15-0.45 g/L
CSF Glucose	2.7 mmol/L	2.2-3.9 mmol/L
Meningitis/encephalitis panel multiplex PCR	Negative	Negative

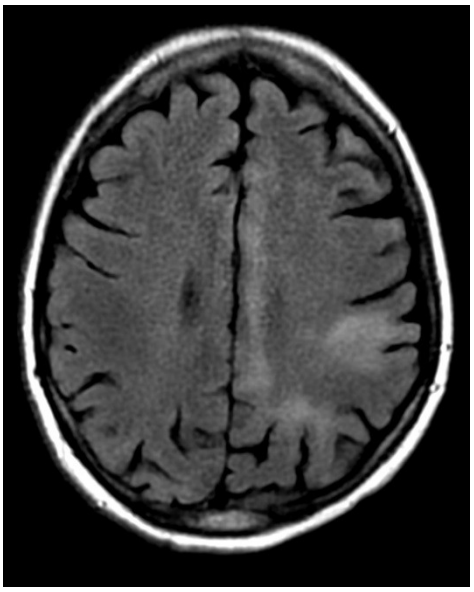

Figure 1:-First brain MRI showed subcortical left parietal white matter lesion.

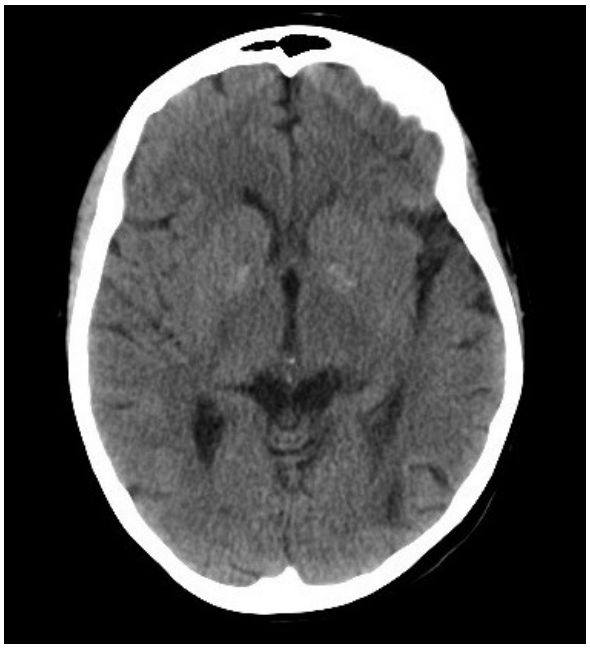

Figure 2:- Brain CT showed faint SLE related vasculitis/vasculopathy of the intracranial vessels

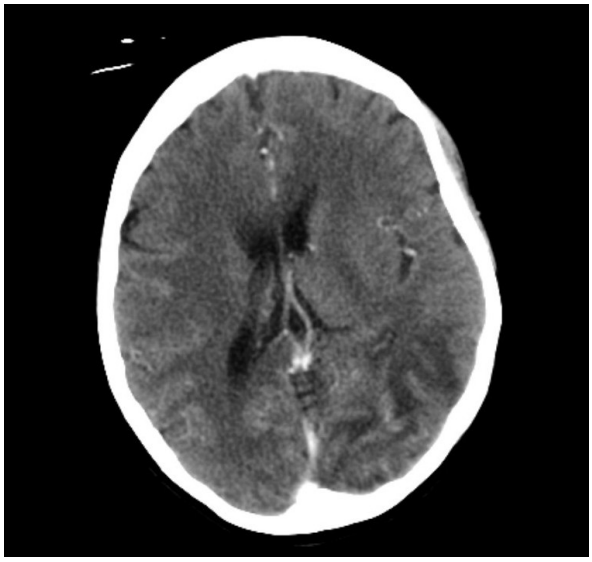

Figure 3:- Brain CT shows scattered hypodensities involving cortical and subcortical white matter of both frontal lobes, both parietal, occipital & posterior temporal lobes.

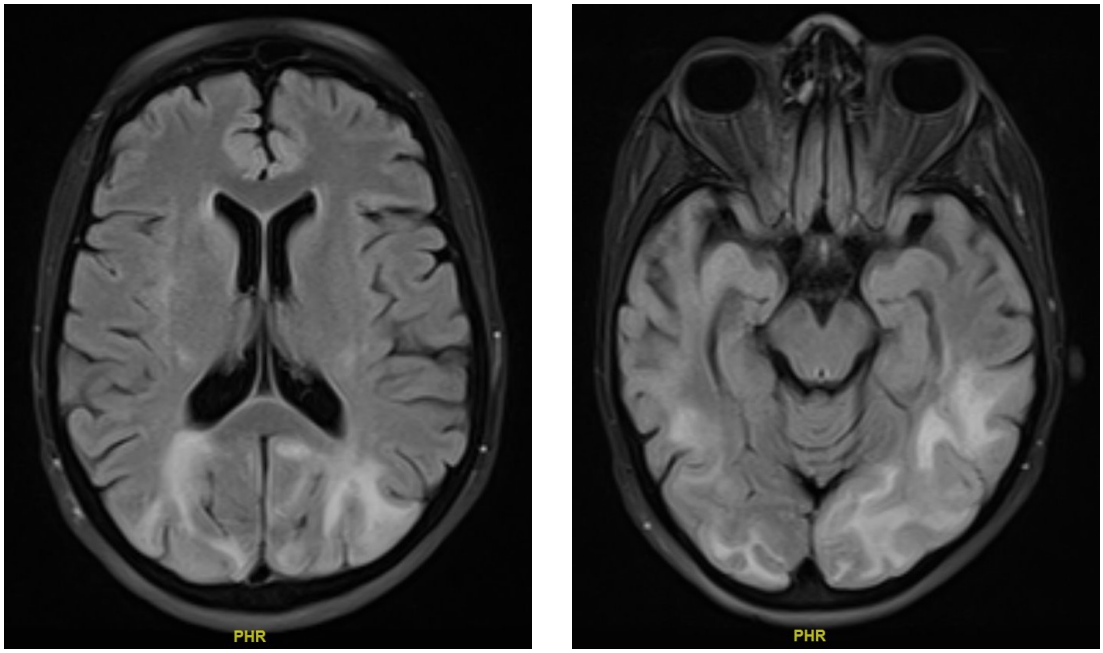

Figure 4:- Brain MRI images show multifocal patchy cortical/subcortical edema at the bilateral parieto-occipital and frontal lobes as well as at the body of corpus callosum and bilateral cerebellum sides in keeping with PRES.

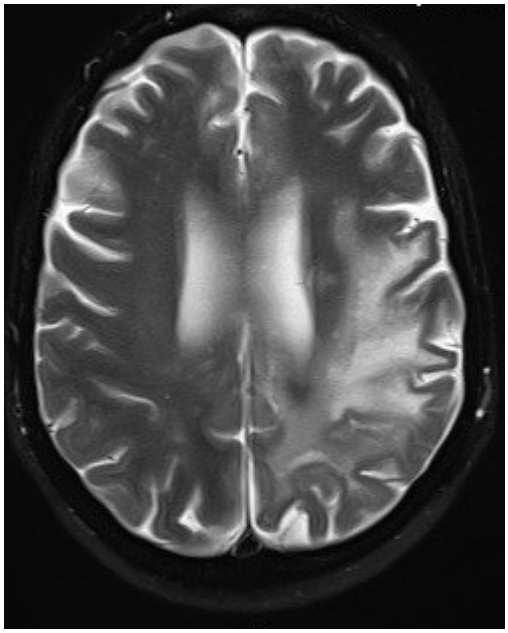

Figure 5:- Brain MRI imgaing shows SLE related cerebritis and resolution of previously seen PRES related changes

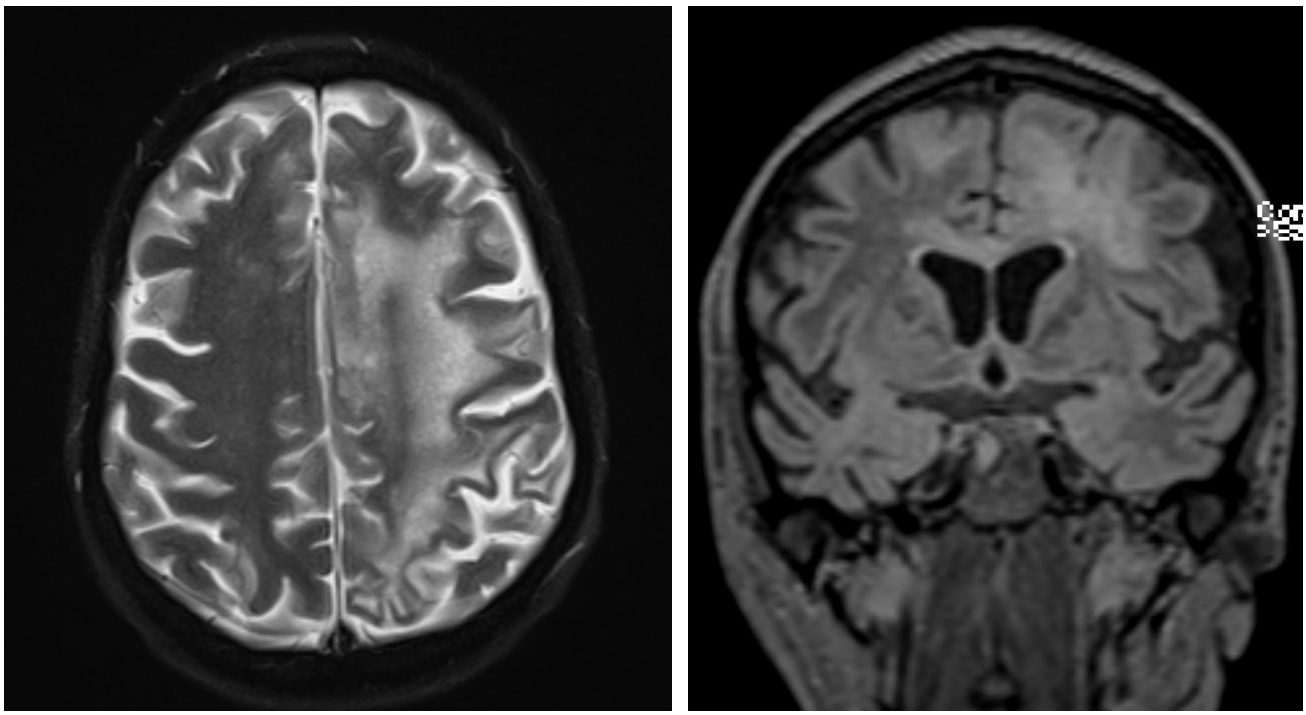

Figure 6:- Brain MRI imaging showed left subcortical frontoparietal white matter high T2/flair signal intensity lesions crossing the corpus callosum into the right frontal lobe with some restricted diffusions peripherally without significant enhancement

Conclusion:-

Neurological manifestations in SLE patients are wide and have broad differential diagnoses. Although PML development in SLE patients is rare, rheumatologists should keep such a rare devastating disease in their differential diagnoses as its management is totally different than that of NPSLE.

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