Case Report

Neuropsychiatric Lupus with Apla Syndrome and Auto-immune Haemolytic Anaemia in a Patient of Hansen's Disease — A Diagnostic and Therapeutic Challenge

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A 21-year-old gentleman of Hansen's disease on multi drug therapy presented with complaints of fever for 10 days and altered mental status for the last 5 days from the day of presentation. MRI brain which showed multiple infarcts in brain. He was evaluated with relevant investigations which were suggestive of Neuro Systemic Lupus Erythematosus with secondary Anti-phospholipid Syndrome and Auto-immune Haemolytic Anaemia. Immuno-suppressive therapy initiated with pulse dose of IV Corticosteroids but discontinued due to increasing TLC and new onset fever. Repeat Urine culture showed Candida tropicalis and he was started on IV Caspofungin. Then, Immuno-supressive therapy with IV Cyclophosphamide started. He had remarkable improvement in sensorium, his fever remitted and started to walk with help. He was discharged with oral steroids, warfarin and advice of IV Cyclophosphamide as per protocol.

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Hansen's disease is caused by slow-growing acid-fast rod-shaped bacilli Mycobacterium leprae. It is a chronic infectious disease that affects the skin, peripheral nerves, upper respiratory tract, eyes and lining of the nasal mucosa and the diagnosis is done clinically[1].

Systemic Lupus Erythematosus (SLE) is a multi-system auto-immune disorder with multi-factorial causes which influence the loss of immunological tolerance against self-antigens leading to the formation of pathologic auto antibodies that cause tissue damage through various mechanisms and affects females more than males[2].

Anti-phospholipid Syndrome (APS) is a multi-system autoimmune disorder characterised by persistent presence of anti-phospholipid antibodies directed against phospholipid-binding proteins and may present as venous and arterial thrombosis and or pregnancy loss. The most common sites of venous and arterial thrombosis are lower limbs and cerebral arterial circulation, respectively. The anti-phospholipid antibodies are anti-cardiolipin antibody IgG and IgM, anti-beta2-gp1 antibody IgG and IgM and Lupus anticoagulant. APS can be primary, without any previous underlying disease or secondary, having underlying disease[3].

Case Report

A 21-year-old gentleman with previous history of Hansen's disease on multidrug therapy of Dapsone, Rifampicin and Clofazimine from rural India presented to the Emergency Department with complaints of fever for 10 days and altered mental status of drowsiness and restlessness for 5 days from the day of presentation. Fever was insidious in onset, gradually progressive, intermittent and low grade in nature. He also developed altered mental status of drowsiness and restlessness for the last 5 days following which family admitted him.

On further inquiry, family also said that he had headache, occasional nausea and vomiting for the same duration and one episode of loss of consciousness 2 days back. He did not experience any episode of neck pain, photophobia, sore throat, chest pain, cough, palpitations, abdominal pain, yellowish discoloration of eyes and urine, reduced urinary output or leg pains.

On examination, he was conscious and alert but drowsy at times and was only obeying to simple commands. Pulse rate was 110 per minute, regular in rhythm, normal in volume, normal in character, all the peripheral pulses were palpable and there was no radio-radial or radio-femoral delay. Respiratory rate 22 per minute regular, thoraco-abdominal in nature and no accessory muscles of respirations were working. BP 90/60 mm Hg. Temperature 100°F. Pallor was present, there was no cyanosis, icterus, clubbing or oedema. No lymph node was palpable. Jugular vein pressure was not raised. Multiple hypopigmented patches of varying sizes along with multiple digital gangrene were present in both upper and lower limbs.

Editor's Comment :

- APLA syndrome is common in SLE patients.
- APLA syndrome can present as a very rare complication in patients with Hansen's disease.
- Hansen's disease can mimic as Lupus. There are multiple reports where Hansen's disease were misdiagnosed as Lupus initially. Biopsy should be done when there is any diagnostic dilemma.
- Hansen's disease may also act as a trigger to cause SLE.
- Active infections should always be ruled out for patients planned for therapeutic immunosuppression. Presence of active Urinary Tract Infection delayed the commencement of immunosuppressive drugs in our patient.

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On neurological examination, GCS was E4V2M6. He was only obeying simple commands. There was neck stiffness; Kernig's sign and Brudzinski's sign were absent. Cranial nerve examination was within normal limits. There was reduced power in all the 4 limbs which was suggestive of quadriparesis. Deep tendon reflexes were all exaggerated with ankle clonus. On superficial reflex, Babinski's sign was positive. Sensory examination only revealed decreased sensation in the hypopigmented areas of the body along with multiple digital gangrene in both upper and lower limbs.

All the relevant investigations for fever work up were sent. He was initiated on IV fluids, empirical IV Meropenem, IV Vancomycin with IV antiviral Acyclovir and pulse dose of IV Methylprednisolone prophylactically. He did not improve with for the following treatment and there was persistent fever. MRI brain was done which detected multiple thrombo-embolic stroke. CSF studies detected increased protein level. Dermatological consult was taken in view of Hansen's disease and patient was continued on multi drug therapy of Dapsone, Rifampicin and Clofazimine. Rheumatology consult was taken. Additional blood reports were suggestive of Systemic Lupus Erythematosus with probable secondary antiphospholipid syndrome but could not be initiated on immuno-suppressive therapy in view of persisting fever, increasing trend of Total Leukocyte Count and Catheter related Urinary Tract Infection with Candida tropicalis. IV Caspofungin was initiated and IV Methylprednisolone was stopped. His blood reports showed a decreasing trend of haemoglobin levels and direct Coombs' test was positive. He was then initiated on with oral corticosteroids, oral Hydroxychloroquine and IV Cyclophosphamide on day 17 of admission. His fever subsided and his general condition improved dramatically. He was discharged in a hemodynamically stable afebrile condition with oral steroids and warfarin. On follow-up after 14 days of discharge, he had remarkable improvement, was walking and eating with assistance and is planned for further Cyclophoshamide doses.

Other Reports

DAY 1 : INR 1.21; COVID 19 RTPCR, MPDA, Dengue NS1 and IgM/IgG, Scrub Typhus IgM, Leptospira IgM, HBsAg, ANTI-HCV, HIV 1 AND 2, Blood CS and Urine CS Negative; Urine RE Normal.

EEG BRAIN : suggestive of encephalopathic pattern.

MRI BRAIN : Multiple scattered T1 hypotense, T2/FLAIR hypertense intraparenchymal non-enhancing lesions of variable sizes showing intense diffusion restriction are seen in the bilateral basal ganglia, thalami, bilateral insular and fronto-parietal cortex, midbrain. Possible septic-embolic encephalitis or multiple cardioembolic infarct (Fig 1).

DAY 2 : Trans-esophageal Echo No Abnormality Detected; CSF Studies- Cell Count 3, Cell Type 100% Lymphocyte, Glucose 75 (Serum Glucose 142), Protein 110, TB Gene Xpert/ Gram Stain/AFB Stain/CNS Comprehensive Panel All Negative.

DAY 4 : ANA 3+ (1:180 titre in ELISA) (Fig 2)

DAY 7 : ANTI ds-DNA Positive (>200); Antibody to nRNP 2+, SMITH 1+, SS-A 3+, Ro-52 3+, Rib P-Protin 2+, AMA-M2 2+; c-ANCA Negative; p-ANCA 3+ (Atypical Pattern); SERUM C3 59; SERUM C4 10; RA Factor Negative; Serum ACE 19; URINE ACR 21.

DAY 10 : Blood CS Negative; Urine CS Candida Tropicalis growth.

DAY 11 : Lupus Anticoagulant Negative; Anti Cardiolipin Antibody IgM Reactive; Anti Phospholipid Antibody Negative; BETA2 GP1 Antibody Negative.

DAY 16 : Direct Coombs' Test Positive; Stool For Occult Blood Negative (Table 1).

Discussion

This patient of Hansen's disease on MDT and Systemic Lupus Erythematosus developed Secondary Anti-phospholipid syndrome with autoimmune haemolytic anaemia which was improved after administration of IV Corticosteroids and IV Cyclophosphamide.

The main differentials that required to be ruled out for this patient initially were Lucio phenomenon due to Hansen's disease and Acute Systemic Lupus

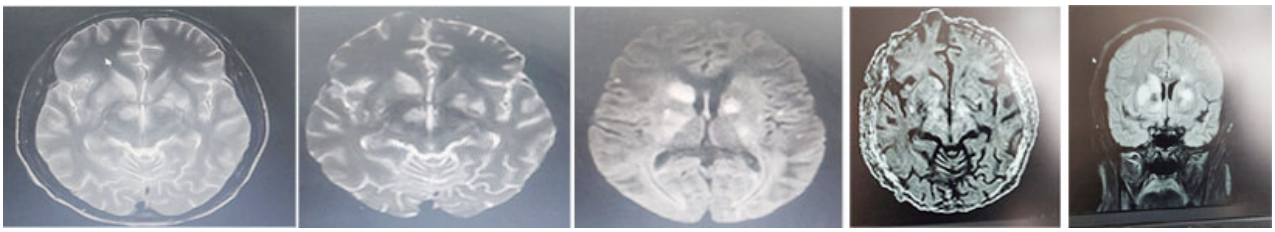

Fig 1 — MRI Brain : Multiple scattered T1 hypotense, T2/FLAIR hypertense intraparenchymal non-enhancing lesio

Table 1 — *Regular Blood Profile during Hospital stay*

Day of Admission	Day 1	Day 3	Day 7	Day 10	Day 14	Day 17	Day 21
Haemoglobin	9.5	9.3	9.8	8	7.6	8.5	9.1
TLC	19800 N81L7	12400 N84L12	21300 N84L5	17600 N71L11	15000 N70L15	7600 N62L33	11800 N84L11
Platelet	1.98	1.84	1.69	2.06	3.73	3.24	3.73
CRP / Procalcitonin		8.1/0.14			9.3/0.11		
Urea / Creatinine	57/0.9	72/0.8	45/0.6	32/0.7	30/0.6	39/0.5	36/0.6
Sodium / Potassium	136/4.4	135/4.2	126/4.1	133/3.3	127/4.2	130/4.1	126/4.2
Total / Unconjugated Bilirubin	0.8/0.6	0.6/0.5	1/0.7	1.4/0.9	1/0.7		0.6/0.5
Albumin / Globulin	2.7/3.3	2.6/3.2	1.9/2.3	2.5/2.4	2.7/2.8		2.9/3.1
SGOT / SGPT / ALP	175/65/80	66/71/44	36/38/51	29/38/74	27/28/830		25/40/87

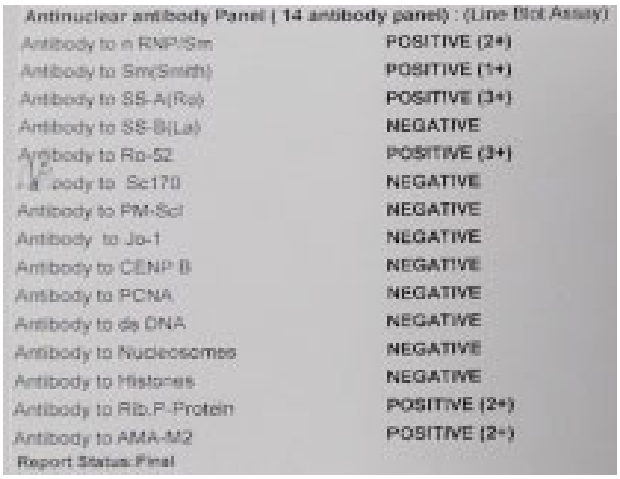

Fig 2 — 14 antibody ANA panel suggestive of Neuropsychiatric Lupus

Erythematosus flare up, apart from the definitive diagnosis of Secondary APS which was contributed by Hansen's disease and or SLE.

Diagnosis of APS is based on a combination of clinical features and diagnostic findings as per revised Sapporo APS Classification Criteria. Clinical criteria include (if any one present): vascular thrombosis and pregnancy morbidity. Laboratory criteria include (if any one present): IgG and or IgM cardiolipin antibody, IgG and or IgM anti beta2 glycoprotein and Lupus anticoagulant[4]. This patient had clinical criteria of vascular thrombosis and laboratory criteria of positive IgM anti cardiolipin antibody.

Hansen's disease is associated with secondary Anti-phospholipid syndrome- with previous documentations of case reports published previously as by Kaliyadan, *et al* in 2009 from India[5]. Previous studies of Hansen's disease associated APS has shown predominance of IgM subtype of antibodies of APS[6].

One of the most common causes of secondary APS is Systemic Lupus Erythematosus which is around 35 per cent of all APS patients[7]. APS is one of the main causes of thrombosis risk in patients of SLE with the presence of anti-phospholipid antibodies as they attach to negatively charged phospholipid surface that may induce platelet activation, interfere with coagulation inhibitors and antifibrinolytics and initiate formation of a thrombus[8].

Lucio phenomenon is an unusual presentation of Hansen's disease, a form of cutaneous vasculitis probably mediated by immune-complex deposition and present as large, sharply demarcated ulcerative lesions and thrombosis of bigger vessels and dermis and is treated by anti-leprotic medications, systemic glucocorticoids and other supportive medications[9].

Systemic Lupus Erythematosus flare up is defined as *a measurable increase in disease activity in one or more organ systems involving new or worse clinical signs and symptoms and/or laboratory measurements. It must be considered clinically significant by the assessor and usually there would be at least consideration of a change or an increase in treatment*[10].

Hansen's disease and SLE can mimic each other and having one can increase the risk of the occurrence of other disease[11]. Also, there have been case reports that a case of Hansen's disease has been misdiagnosed as SLE[12].

Auto-immune haemolytic anaemia in primary APLA syndrome is very rare. Co-existence of auto-immune haemolytic anaemia and primary APLA may define as a subgroup of patients who may later develop SLE[13].

Hence, we have been able to diagnose a patient of Systemic Lupus Erythematosus with Hansen's disease and secondary APLA syndrome and auto-immune haemolytic anaemia, which is very rare to come across.

Conclusion

Hence, we present a rare case of Neuropsychiatric Systemic Lupus Erythematosus with secondary Anti-Phospholipid Syndrome and auto-immune haemolytic anaemia in the background of Hansen's disease treated successfully with immuno-suppressive and anti-thrombotic therapy. It was a big challenge for coming to a diagnosis considering the presentation and even bigger challenge was the treatment course which was done judiciously.

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