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Case Report

Unusual coexistence between lupus nephritis and neurofibromatosis 1: a case report and review of previous cases

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ABSTRACT

The association of Neurofibromatosis 1 (NF 1), an autosomal dominant genetic disease with autoimmune diseases like systemic lupus erythematosus is rare, five case reports are there in medical literature showing such association. Here we have documented a case of Lupus nephritis associated with Neurofibromatosis 1 diagnosed in the same setting, in a 24 years old female patient presented with oliguria, hypertension, anasarca, cafe-au-lait spots, palmer freckling, subcutaneous nodules, alopecia areata and positive family history for NF 1.

Keywords: Systemic lupus erythematosus, Lupus nephritis, Neurofibromatosis 1, Neurofibromin

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is an autoimmune connective tissue disease causing inflammation and tissue damage via both a type II and a type III hypersensitivity reaction by autoantibody response to nuclear and cytoplasmic antigens.[1] The disease occurs more commonly in women in child-bearing ages and has an unpredictable relapsing and remitting course.[2] Lupus nephritis is serious manifestations Of Systemic Lupus Erythematosus (SLE). It may histologically found in patients with SLE, even without clinical manifestations of frank renal disease. The symptoms of lupus nephritis usually include hypertension, proteinuria even renal failure.[3]

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder at chromosome 17q that commonly is presented with cutaneous findings, mostly café-au-lait spots and axillary freckling, skeletal dysplasias, and the growth of both benign and malignant nervous system tumours, most commonly benign neurofibromas. It is common in 1.0 to 10.4 cases of 10000 populations.[4]

So far five cases have been reported in literature showing association between Neurofibromatosis and SLE. Here we are going to report a case of Lupus nephritis with neurofibromatosis 1 in a 24 years old female patient.

CASE REPORT

A 24 years old female patient was presented with swelling of whole body starting from face for 2 weeks, associated with decreased urine output on background of previously diagnosed Systemic Lupus Erythematosus (SLE) characterized by orthopnea, paroxysmal nocturnal dyspnea, alopecia areata, multiple small joints pain and swelling for 3 years. The patient was on tacrolimus, azathioprine, prednisolone therapy. She also had complained of blackish spots on her face, neck regions and also in both palms for last 14 years. Moreover she

had swellings at right forearm and left arm for these she had not sought any medical advice. She had no significant past medical or surgical history beside this. Her father had clinical history of blackish spots, skin nodules, pain with bluish discolouration of extremities on exposure to cold and was diagnosed as neurofibromatosis 1.

On general examination, blood pressure was 154/108, heart rate 110/minutes, pallor was present, bipedal pitting oedema positive associated with facial puffiness (anasarca). Café-au-lait spots over face (Figure 1A), forehead and neck region with bilateral palmer freckling (Figure 1D) were evident. Subcutaneous nodules were present over right forearm and left arm (Figure 1C, 1B). Also there were alopecia areata (Figure 1A).

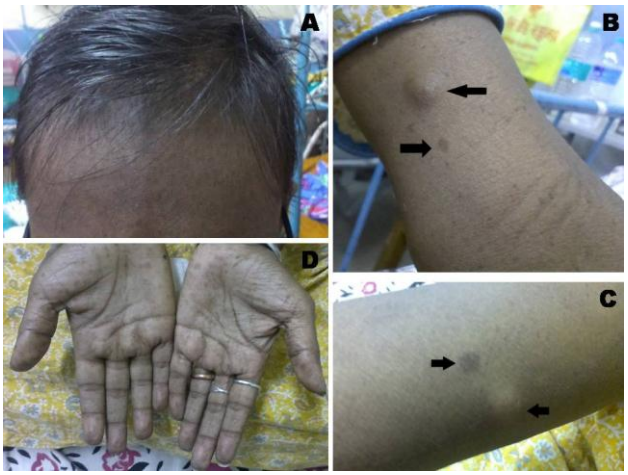

Figure 1: A - Patient's fore head showing alopecia areata and cafe-au-lait spots. B - Left arm showing subcutaneous nodule and cafe-au-lait spot. C - Right forearm showing subcutaneous nodule and cafe-au-lait spot. D - Palmer freckling.

On systemic examination, fine bi-basal crepitations were found on chest auscultation. Ascites was present. Other systemic examinations were normal.

Hb - 8.7g%, TLC - 11000/cu.mm, platelets - 2.7 lakhs/cu-mm. Serum electrolytes were normal. No abnormal finding was detected in liver and kidney function tests (urea and creatinine were normal). ESR - 67 mm/hour (normal 0-15), serum C_3 was 0.498 g/L (normal 0.83-1.77) and C_4 was 0.068 g/L (normal 0.12-0.40). CRP value was normal. Her SLE was diagnosed on the basis of positive titres of Anti-nuclear antibodies, Anti-dsDNA, Anti-phospholipid antibodies. Urine routine and microscopic examination showed high protein (4+) and 5-7 RBCs/hpf, red cells cast present.

Renal biopsy was taken and stained in PAS, silver and trichrome and showed increased mesangeal cells and matrix; diffuse segmental endocapillary proliferations; Wire-loop lesions and hyaline thrombi; double contours and spikes and pinhole lesions on basement membrane (Figure 2). Stains for antibodies, antibody light chains and complements revealed IgG (+2), IgM (+1), C_3 (+3) along the capillary wall; C_{1q} (+4) along the capillary wall and over tubular basement membrane as well.

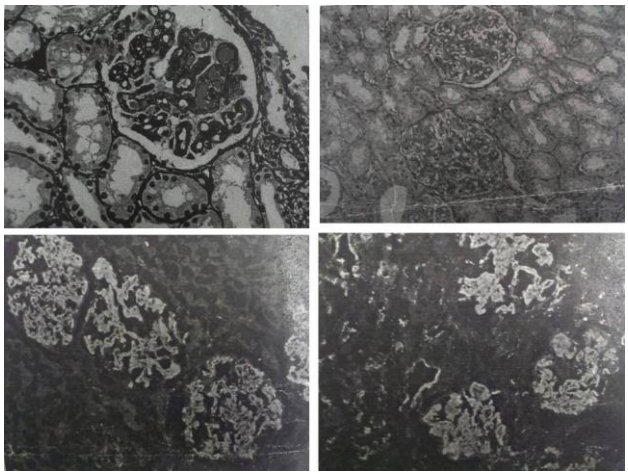

Figure 2: Renal biopsy (PAS, silver and trichrome stain) showing increased mesangeal cells and matrix; diffuse segmental endocapillary proliferations; wire-loop lesions and hyaline thrombi; double contours and spikes and pinhole lesions on basement membrane.

DISCUSSION

Here the patient discussed above has SLE in terms of 2012 SLICC SLE criteria,[5] showing:

1. Patient having multiple small joint pain and swelling,
2. Alopecia areata,
3. RBC casts in urine,
4. Anti-nuclear antibodies are positive,
5. Anti-dsDNA antibodies are positive,
6. Anti-phospholipid antibodies are positive, and
7. Low serum complements level.

Renal biopsy findings as mentioned above revealed membranoproliferative pattern of glomerular injury with membranous nephropathy suggestive of lupus nephritis class IV-A/class V.[6]

The diagnosis of Neurofibromatosis 1 has been done on Nation Institutes of Health criteria (NIH), 1987,[7] with the following history and clinical features:

1. Father had history of Neurofibromatosis 1,
2. Multiple café-au-lait spots (Figure 1),

3. Two neurofibromas, one in the right forearm and another in the left arm (Figure 1C, 1B).

Now her palmer freckling (Figure 1D) does not meet the diagnostic criteria as stated in NIH, as axillary and inguinal frecklings are included there. But studies have shown palmer freckling can also be associated with neurofibromatosis 1.[8]

If we search medical literature, the coexistence of SLE and NF1 is very much rare.[9-13] In 1975, Bitnun and Bassan[9] reported the 1st case in a 26 years old male, and also[10] in a 16 years old female who initially developed SLE and subsequently were diagnosed as having neurofibromatosis 1. In another report Riccardi[11] showed a 35 years old female patient was first diagnosed as having SLE, and then 2 years later, she developed nodular subcutaneous neurofibromas as reported in biopsy. The authors of both the above mentioned reports hypothesized that such presentation might either be coincidental or perhaps be related to viral infections. Corominas et al. examined a 32 years old female patient who developed SLE 5 years after Neurofibromatosis 1 and concluded as a matter of mere coincidence.[12] Akyüz et al. also demonstrated a 9 years old girl, who initially developed Neurofibromatosis 1, followed by SLE.[13]

In the reported case the patient developed lupus nephritis with history of SLE for last 3 years on background of NF 1 from the age of 10 years. Now in the question of possible explanation of such rare coexistence, it can be hypothesized that as NF 1 is a disease by inactivation of the NF1 tumour suppressor gene, encoding neurofibromin,[14-16] deficiency of the protein may be responsible for causing autoimmune diseases like SLE.[13] Neurofibromin inhibits proliferation of some cells like myeloid cells, astrocytes, melanocytes[17] but functions as a positive regulator of lymphocyte proliferation .[18] This protein downregulates Ras activity in T cells,[17] incidence of lymphoproliferative disorder has been demonstrated by Ingram et al.[19] due to Ras activation in T cells for neurofibromin abscence in mice.

So, the uniqueness of the case is that the patient already developed lupus nephritis at the time of diagnosing NF 1, featured with cafe-au-lait spots, palmer freckling, subcutaneous nodules.

CONCLUSION

From this rising incidences we can conclude that clinicians should be aware of such rare association, early diagnosis accredits for patient's wellbeing and more studies are necessary to come up with the exact pathophysiology, prognosis and management.

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