Cryoglobulinemia Presenting as Acute Polyneuropathy
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Abstract
A 48 years male presented with acute axonal neuropathy and palpable purpura over bilateral lower limb, RA factor, and cryoglobulins were present in the serum. Nerve biopsy revealed myelinated fibre loss, axonal degeneration and necrotizing vasculitis of epineural vessels.

INTRODUCTION
Cryoglobulinemia is a condition characterized by presence of serum protein that reversibly precipitates in the cold. Frequency of peripheral neuropathy range form 10-57% in patients of cryoglobulinemia; and 46-54% of them are associated with hepatitis-C co-infections. Renal involvement at presentation is present in 25% of cases and ultimately in 50% of cases.

CASE REPORT
We report a patient of essential mixed cryoglobulinemic acute axonal polynueopathy who was HCV negative.

A 48 year old man presented with bilateral painful distal lower limb weakness, pitting pedal edema and palpable purpuric rashes over both lower limbs. Patient was apparently asymptomatic 3 days back when he developed acute onset painful distal weakness in form of bilateral foot drop with history of moderate grade continuous fever, arthralgias, 15 days prior to weakness. On 4th day of hospital stay; we noticed purpuric spots which were associated with severe pain in distal part of lower limb. At that time patient was afebrile. There was no past history of Raynaud’s phenomenon, hematuria, bony pain, jaundice, rash on face, mouth ulcer, arthritis, oliguria or abdominal mass. Examination revealed afebrile patient, with stable vitals having bilateral pitting pedal edema and (1-2 mm) palpable purpura below knee. There was no icterus or lymphadenopathy. These rashes became confluent on 6th day of hospital stay. CNS examination revealed decreased tone in bilateral lower limbs, power was grade 0/5 in dorsiflexors, 1/5 in planter flexors, knee joint 3/5 in flexors and extensors, and hip joint 4/5. Deep tendon reflexes diminished in upper limb, bilateral knee, however it was absent over bilateral ankle. Plantars were bilateral down going. Sensory examination revealed 50-75% sensory loss all modality below knee and autonomic nerve. Bilateral fundus examination was normal, other cranial nerve examination and autonomic nervous system examination did not reveal any abnormality. Abdominal and lymphoreticular system examination were normal. Urine examination showed albumin in traces (24 hour urinary protein 400 mg), 10-12 RBCs (patient was catheterized). Investigations showed urine albumin 2+, sugar nil, RBCs 10-12, hemoglobin 9 gm/dl, TLC 8000/mm³ with normal differential platelet count 2.2 lac/mm³, BT, CT and PT were normal, blood urea 20 mg/dl, blood sugar 84 mg/dl, serum creatinine 0.8 mg/dl, serum sodium 133 mEq/L, potassium 4 mEq/L, alkaline phosphatase 339 IU/L. GBP - normocytic normochromic, ESR – 40 mm in first hour. HCV Ag and Ab and HBsAg were negative, RA factors, anti dsDNA was mildly positive by ELISA(50 IU/ml using varel elisa kit from Germany) and ANA were positive, anti smooth muscle antibody was negative. LFT and lipid profile were normal. Myeloma profile, M peak, BJ proteins were absent, serum cryoglobulins were present after 24 hours of incubation. Chest X-ray, USG for abdomen was normal.

Fig. 1 : Palpable Purpuric Spot over lower.
NCV study showed markedly diminished CMAP amplitude over bilateral tibial nerve with normal conduction velocity and distal latency and non generation of CMAP observed over bilateral CPN. SNAP could not be generated in bilateral sural nerve. EMG showed chronic active denervation. Upper limb nerve conduction study showed normal latency, amplitude, and conduction velocity in median and ulnar nerves, however,”F” wave generation was persisting with “F” mean latency 34.1 ms in upper limb. Nerve biopsy showed vasculitis of small size artery in epineurium with non uniform pattern of myelinated fibre loss. Patient was diagnosed as a case of Type II essential mixed cryoglobulinemia leading to acute axonal sensory motor polyneuropathy mainly involving the lower limbs, with negative hepatitis C viral marker. Patient was treated with oral prednisolone 1 mg/kg. The skin rash and pain in lower limbs disappeared, but the power in LL did not show much improvement. Follow up for one and half year did not showed much improvement in power or fresh palpable purpura, there was no evidence of S.L.E according to ACR criteria.

**DISCUSSION**

Cryoglobulinemia is a condition characterized by trace of serum proteins that reversibly precipitative on cold.

According to molecular composition cryoglobulinemias are classified into three types. Type 1 isolated monoclonal IgG that are associated with myeloma microglobulinemia and other lymphoproliferative disorders, type 2 mixture of monoclonal IgM with anti rheumatoid factor activity and polyclonal IgG, type 3 are polyclonal IgM and IgG immunoglobulins. Type 2 and Type 3 are classically referred to as mixed cryoglobulinemia.4 CG may be idiopathic (Essential mixed CG) or secondary to other disease such as lymphoproliferative disorders, collagen vascular disease and chronic infection (HCV). According to different reports the frequency of peripheral neuropathy in mixed CG ranged from 10-57%. PN usually occur in type 2 and type 3 CG rather than type 1 and only clinically present as a mono neuropathy, multiple mononeuropathy are polyneuropathy. Most of the time it present as a painful sensory motor neuropathy.6 Other clinical features are arthalgias, and recurrent purpura of lower limbs although, the condition is uncommon in India. Malti et al reported cerebellar disease with mixed CG. Few cases of multiple myeloma and systemic sclerosis with CG are also reported.4 The pathogenesis is deposition of cryoglobulins immune complex in small and medium sized arterioles and occlusion of vasa nervosum which result in ischemic axonal damage, other mechanism is there is direct necrotizing vasculitis of epineurial vessels.2 Most of the cases reported are associated with HCV co-infection2 or secondary to collagen vascular disease like SLE, our patient had only 2 criteria among ARA criteria for SLE (for SLE 4 or more than 4 is criteria should be there), anti smooth muscle antibody was negative and anti Ds DNA titer was mildly positive (50 IU/ml using ELISA method, however follow up of patients is needed to see any evidence of SLE. Electro diagnostic studies show axonal changes with denervation particularly in distal leg muscles.4 In most cases the sural nerve biopsy showed myelinated fibre loss and axonal degeneration.6 Thus, the case demonstration is not only the difficult diagnostic process but also has the problem of adequate and effective therapy. Since the usual immunosuppressive treatment such as methotrexate, high dose cortisosteroids and intermittent intravenous pulse cyclophosphamide therapy fails. But plasmapheresis and interferon alpha have shown better outcome.2 Our patient presented with fever, arthralgia palpable purpura, sensory motor axonal polyneuropathy involving mainly LL, however hepatitis C viral marker was negative. Nerve biopsy showed mild to moderate dense perivascular cuffs of lymphocytes, fibre dropout with endoneural fibrosis and K-pal stain for myelin revealed involvement of al fascicles with pockets of large and small myelinated fibre loss.

We diagnosed the case as essential mixed Cryoglobulinemia presenting as acute sensorimotor axonal polyneuropathy mainly involving the lower limbs. In conclusion; we present a rare case of essential mixed Cryoglobulinemia with peripheral neuropathy not related to hepatitis C virus co-infection and search for cryoglobulins prove useful in substantial number of undiagnosed peripheral neuropathy.

**REFERENCES**