Case Report

Idiopathic CD4 lymphocytopenia with sensorimotor polyneuropathy

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Abstract

A, 21-years-old, male, presented with acute onset, gradually progressive, predominantly distal, symmetrical weakness of both upper and lower limbs with arreflexia. He had impaired sensations in glove and stocking distribution with distal gradient. He was found to have absolute CD4 + cell count of 188 cells/μL, absolute CD8 cell count, 532 cells/μL and CD4: CD8 ratio of 0.35. Electrophysiology revealed reduced to absent CMAP amplitude as well as SNAPs in various nerves of upper and lower limbs, along with normal conduction velocity and normal F wave latencies. Pattern evoked visual potentials were prolonged, on both sides, P100 being 130 ms, on right and 108 ms, on left side. In the follow up of 2 years, he showed spontaneous but gradual clinical improvement but his electrophysiological parameters as well as CD 4+ cells count did not show any significant improvement.

Key Words

Idiopathic CD4 lymphocytopenia, immune mediated neuropathy, neuropathy, optic neuropathy

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Introduction

Idiopathic CD4 + T cell lymphocytopenia (ICL) is a rare and clinically heterogeneous syndrome, characterized by a persistent decrease in CD4 + T cell lymphocytes in the absence of infection with HIV-1 or any other cause of immunodeficiency. Although commonly seen among middle aged individuals (43 ± 14 years), it has also been reported among children and adolescents.[1] Slight male predominance has been observed with a male:female ratio of 1.8:1.[2] Diagnostic criteria of ICL require that CD4 + T cell counts should be below 300 cells/μL or less than 20% of total lymphocytes, on more than one occasion, usually 2 or 3 months apart.[1] Furthermore, there should be no evidence of infection with human immunodeficiency virus (HIV)-1/2 or human T-cell lymphotropic 1/2 (HTLV-1/2); and lack of a defined immunodeficiency disease or therapy associated with depressed levels of CD4 + T cells. Transient CD4 lymphocytopenia has been reported in healthy HIV-negative individuals (0.4-4%) at any given time.[3] Patients suffering with ICL may be clinically asymptomatic or present with opportunistic infections, malignancies mostly hematological, or autoimmune disorders. Almost all reported cases with ICL with neurological manifestation are with opportunistic infections like cryptococcal meningitis or progressive multifocal leukoencephelopathy.[4,5] However, there are two reports with peripheral nervous system involvement; one with Guillain Barre Syndrome (GBS)[6] and another with subacute progressive motor axonal neuropathy.[7] The occurrence of sensorimotor polyneuropathy has not been reported previously with ICL. We report a case of ICL with sensorimotor polyneuropathy along with subclinical optic neuropathy.

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Case Report

A, 21-years-old, right handed, male who had no prior medical illness, presented to us, with gradually progressive weakness of both upper and lower limbs for the last 12 days along with decreased sensations of 10 days duration. He started with difficulty in wearing his slippers [footwear], thereafter experienced difficulty in getting up from squatting posture and climbing up the stairs over a period of 7 days. Simultaneously, he had difficulty in holding a glass of water, negotiating while dressing, breaking chapatti and holding a pen while writing. He had no difficulty in raising the arms above shoulders or combing hair. On tenth day, of the onset, he required assistance

of two persons in an attempt to walk. He was also experiencing decreased sensations in both hands and feet. He denied for any cranial musculature involvement, or any sphincter disturbance. He was non-vegetarian and occasional smoker. He had no promiscuity or drug abuse except being occasional alcoholic. He denied for any gastrointestinal illness or weight loss. He had no febrile illness or immunization, in the recent past.

The general physical as well as other systemic examinations were non-contributory. Detailed neurological examination revealed normal higher mental functions. All the cranial nerves were intact. Both the fundi were normal. There was no atrophy or any abnormal movements in any of the muscles. However, the muscle power, in upper limbs was 5/5[MRC scale of 5] at both shoulder and elbow and 3/5, on wrist extension and 4/5, on wrist flexion. Hand grip was weak, bilaterally. In the lower limbs, power was 4/5, at both hip and knees, 2/5 at dorsiflexion and 3/5 on plantar flexion. All deep tendon reflexes were absent, bilaterally. Both plantars were not elicitable. Touch, pain and temperature sensations were impaired in glove and stocking distribution with distal loss, in lower limbs being 70% compared to proximal loss in thighs of 10%, while, in upper limbs, loss was 70% in hands up to wrist. He also had impaired sensations by 20% over anterior aspect of trunk. Joint position and vibration sensations were impaired up to both ankles and wrists. Romberg's sign was positive.

His hemogram, biochemical profile for blood sugar, urea, creatinine, serum electrolytes, lipid and thyroid profile were normal. CSF examination, on 14 days into his illness, was normal and had not grown any bacterial or fungal growth. Roentgenogram of Chest, ECG and ultra sound examination of abdomen and MR brain were normal. C Reactive Protein, Antinuclear Antibody, Anti double stranded DNA, Cytoplasmic antineutrophil cytoplasmic antibodies, Perinuclear Anti-Neutrophil Cytoplasmic Antibodies, Rheumatoid factor, anti Ro, anti-La antibodies, were negative. Serology for hepatitis B, C, cytomegalovirus, Ebstein-Barr virus, herpes virus and toxoplasma were negative. Absolute lymphocyte count was 993/μL [normal, 1000-3000/μl] with CD3 cells accounting for 75% of the cells [normal, 57-85%], and CD4 cell accounting for 19% (normal, 29-61%). The absolute CD4 count was 188 cells/μL (normal, 440-1600 cells/μL). The absolute CD8 cell count was 532.00/μL [normal, 200.00-1100.00 cells/μL] with a CD4: CD8 ratio was 0.35 [normal, 0.70-3.50]. A repeat count after 6 weeks revealed that percentage of CD4 cells was still 19% while the CD3 cells accounted for 68% of the absolute lymphocyte count of 3036 cells/μL with an absolute CD4 count of 149 cells/μL. Serum immunoglobulin profile was IgG 876 mg/dl (normal, 800-1800 mg/dl), IgA 142 mg/dl (normal, 100-490 mg/dl), and IgM 76 mg/dl (normal, 60-280 mg/dl). ELISA for human immunodeficiency virus (HIV) was non-reactive on three occasions and on Western blot analysis, there was no viral specific band for HIV-1 or HIV-2. Serum vitamin B12 was 546 pg/ml [normal, 211-946 pg/ml].

Nerve conduction studies revealed the presence of normal distal motor latencies with decreased compound motor action potential amplitudes, normal conduction velocity and normal F wave latencies in both upper and lower limbs studied nerves [Table 1]. However, CMAP was not elicitable, in both common peroneal nerves. Sensory nerve action potentials were reduced in both median and sural nerves and were not recordable in both ulnar, dorsal ulnar cutaneous, superficial radial and superficial peroneal nerves. Needle EMG of deltoid, biceps, brachioradialis, flexor digitorum sublimus, First dorsal interossei, abductor pollicis brevis and abductor digiti minimi, quadriceps, medial gastrocnemius, tibialis anterior, extensor digitorum brevis was normal. Somatosensory evoked potentials, N20 and P 37, on stimulation of median and posterior tibial nerve, respectively, were normal on both sides. BAERs was normal on both sides. However, pattern Visual evoked potentials revealed, P100 being 130 ms, on right [normal, 104 ms] and 108 ms, on left side.

Patient was managed symptomatically along with physical rehabilitation regimes. After about 4 weeks of presentation, repeat electrophysiological evaluation revealed further reduction in CMAP amplitude of both median [Rt. 2.5 mV, Lt. 1.3 mV]; ulnar [Rt. 5.6 mV, Lt. 1.3 mV], posterior tibial [Rt. 0.2 mV, Lt. NR] nerves. However, the distal CMAP latency and velocity of all these nerves remained almost similar to the initial study. On further comparison with the initial study, the F wave latency showed prolongation; median [Rt. 25.7 ms, Lt. 26.6 ms], ulnar [Rt. 25.35 ms, Lt. 25.35 ms], posterior tibial [Rt. 49.35ms, Lt. NR] and SNAPs in both ulnar nerves became non elicitable while in other nerves there was no remarkable difference. In the follow-up of 2 years, he showed spontaneous

Table 1: Motor and sensory nerve conduction studies

Parameter	Median motor		Ulnar motor		Posterior tibial nerve		Median sensory		Ulnar sensory		Sural	
	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt
Distal latency in ms	3.55	3.10	2.70	3.15	3.65	3.85	2.50	2.25	2.95	2.45	2.40	1.80
Normal limit in ms	≤4.32		≤3.41		≤5.28		≤3.6		≤3.4		≤2.8	
Distal CMAP amp in mV/SNAP amp in μV	3.3	5.2	8.7	2.8	1.2	2.0	4.0	4.0	0.22	0.38	1.3	1.8
Proximal CMAP amp in mV	2.8	4.6	8.0	2.5	0.8	1.3						
Normal limitfor distal CMAP amp in mV/SNAP amp in μV	≥5.5		≥5.0		≥5.0		≥10.4		≥8.01		≥8.01	
NCV in m/s	65.6	54.5	61.9	62.5	45.1	47.6	52.0	57.8	52.0	56.5	50.0	50.0
Normal limit in m/s	≥50.24		≥52.34		≥40.61		≥36.7		≥36.96		≥39.01	
Minimum F wave latency in ms	22.3	23.90	22.7	23.0	42.7	45.5						
Normal limit in ms	≤29.41		≤28.49		≤54.71							

CMAP = Amplitude for motor nerves, SNAP amplitude for sensory nerves, CMAP of both common peroneal nerves were not recordable, SNAPS from both dorsal ulnar cutaneous, superficial radial and superficial peroneal nerves were not recordable, Rt = Right, Lt = Left

but gradual improvement. His electrophysiological parameters as well as CD 4+ cells count did not show any significant improvement.

Discussion

Transient depression in CD4+ cell counts, usually without inversion of the CD4: CD8 ratio, attributed to alteration of the cytokine and inflammatory response has been reported with opportunistic bacterial, viral (hepatitis B, Ebstein-Barr virus, and cytomegalovirus), parasitic, and fungal diseases.[8,9] Although infectious agent akin to HIV has always been speculated, the exact causative factor for ICL remains elusive. The pathogenesis of ICL also remains unknown but various postulations revolve around diminished generation of T-cell precursors, increased T-cell apoptosis, destruction of cells by anti CD4 T- cell antibodies and p56 Lck kinase alteration resultant in biochemical failure of the CD3-T-cell receptor pathway.[10] Various autoimmune disorders associated with ICL include Sjögren's syndrome, Systemic lupus erythematosus, idiopathic thrombocytopenic purpura, antiphospholipid antibody syndrome, Behçet's-like syndrome and vasculitis.[6] The treatment of ICL primarily revolves around prophylaxis and treatment of opportunistic infections. Experience with IL-2 therapy to increase CD 4 T cell count, in anecdotal reports, is promising. Use of other cytokines like IFN- gamma and IL-7 are also being investigated.[11]

Our patient was a case of ICL as per the diagnostic criteria[2] and had painless, predominantly distal, symmetrical sensorimotor polyneuropathy along with subclinical optic neuropathy, with low CD4: CD8 ratio but normal absolute CD 8 cell count and no evidence of opportunistic infection.

It has been observed that patients with a low CD8 count (<180 cells/mm3) are more likely to present with serious opportunistic infections than those with a higher CD8 count.[12] Normal absolute CD8 cell count, in our patient, might have shielded him from opportunistic infections, who, instead manifested with a possible immune mediated neuropathy involving both peripheral as well as optic nerves. The prolonged pattern evoked visual potentials are the signatures of demyelinating process but the peripheral neuropathy was in glove and stocking pattern suggestive of existent predominant axonal dysfunction. Tae Im Yi et al., encountered gradually progressive motor axonal neuropathy in a 10-year-old boy who had idiopathic CD4 + T-lymphocytopenia since the age of 5 years and postulated it to possible immune mediated mechanism.[7] Re´gent et al found one case of Guillain-Barre´ syndrome among their series of 40 patients with ICL.[6] Further details of their case were not provided.

The pattern of neuropathy in present case had some superficial similarity to acute motor and sensory axonal neuropathy (AMSAN), subtype of GBS[13] but differed in details, in particular, with optic nerve involvement, normal needle EMG examination, no cytoalbumin dissociation in CSF, no antecedent illness.

Since, ICL is rare, most of the complications or associations with ICL are being looked towards HIV induced CD+ cell lymohocytopeneia for the possible patho-mechanisms. In HIV infection, the neuropathy is not due to the viral invasion of nerves but due to vasculitis and/or immune mediated mechanism [Immune dysregulation and macrophage activation]. The activation of macrophages in the epineurium of peripheral nerves and dorsal nerve ganglia triggers the release of pro-inflammatory neurotoxic cytokines such as TNF-α, Interlukin (IL)-1and IL-6, thereby causing axonal damage.[14]

In the absence of any infectious, toxic or nutritional deficiency the most plausible mechanism of neuropathy, in our patient, could be an immune mediated neuropathy in the setting of an idiopathic CD4 lymphocytopenia. The exact mechanism of autoimmunity in ICL is not known. Perhaps there is lack of self-recognition in the setting of lymphopenia-induced T-cell proliferation[15,16] triggering the cascades of events as mentioned above. Demyelination observed in the optic nerves can also be attributed to immune dysregulation. Lack of pain and the needle EMG findings do not support the existence of vasculitis in our patient. Normal somatosensory evoked potentials in our patient also do not favor for preganglionic involvement.

Limitation of this study is lack of histopathological correlation due to refusal of the patient for nerve biopsy.

Thus, the present case is unique to have ICL with painless, symmetrical sensory motor neuropathy along with subclinical optic neuropathy. One must incorporate the evaluation of immune status in a patient with neuropathy, in whom initial work-up does not point towards an etiology.

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