A rare case report of neurolymphomatosis with NK-T-cell lymphoma

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Neurolymphomatosis (NL) is a rare neurological association in patients with non-Hodgkin's lymphoma.[1,2] It involves infiltration of peripheral nerves by lymphoma. The most common presentations of NL include painful polyneuropathy or radiculopathy, cranial neuropathy, painless polyneuropathy, and mononeuropathy or mononeuropathy multiplex.[1] It is important to distinguish neurolymphomatosis from other types of neuropathies, particularly treatable infectious and inflammatory causes such as CIDP. However, it is difficult to differentiate a cancer-related inflammatory vasculitis causing mononeuritis multiplex from infiltrative etiology without definitive histopathologic examination. In this report, we describe a rare case of non-Hodgkin's T-cell lymphoma (nasal NK–T cell lymphoma) presenting as neurolymphomatosis involving the brachial plexus and multiple peripheral nerves.

Case History

A 72-year-old male, with past medical history of diabetes mellitus, hypertension, and ischemic heart disease was treated for nasal NK-T cell lymphoma in November 2021 with excision surgery followed by radiation therapy. He had been in remission since then.

6 months later in June 2022, he presented with an acute painful left wrist drop. For which he received 30 mg of oral prednisolone which was tapered to 10 mg over the next 3 months. After the steroid taper, he developed a painful left foot drop followed by left shoulder pain with weakness and 15 days later, painful right wrist-drop. There was hyperalgesia to pin-prick in distribution of radial, superficial peroneal and sural nerves. Bilateral biceps and supinator deep tendon jerks (DTR) and left triceps DTRs were absent. Right triceps DTR and both knee jerks were normal. Both ankle DTRs were absent.

Electrophysiological studies revealed multiple mononeuropathies with severe axon loss in an asymmetric pattern. Needle electrode examination revealed severe axon loss in the muscles supplied by the affected nerves in upper and lower extremities as described in Table 3. In addition, there was involvement of proximal upper extremity muscles, severe in degree electrically which suggested involvement of upper trunk of brachial plexus on either side. (Refer table 2 and table 3)

Whole body PET-CT done 2 months into illness showed diffuse low grade increased metabolic activity in head of right humerus and left infraclavicular region. MRI spine with brachial plexus revealed T2 hyperintensity in left C6, C7, C8, D1 nerve roots. Divisions and cords of brachial plexus also showed mild thickening and hyperintensity bilaterally. Cerebrospinal fluid examination (CSF) revealed 7 cells (73% lymphocytes), protein 113, glucose 63 and no malignant cells. Inflammatory markers were elevated, erythrocyte sedimentation rate (ESR) was 24 and C-reactive protein (CRP) was 96.

He underwent biopsy of the left brachial plexus as it was the only area that showed increased metabolic activity on whole body-PET-CT which confirmed the diagnosis of neurolymphomatosis. Biopsy was suggestive of hypertrophied fascicles and prominent endoneurial lymphoid infiltration extending up to perineurium, lymphoid cells are small with dark nuclei and scanty cytoplasm. IHC was positive for CD3, CD8, CD56, Ki67 (figure A to H).

He was treated with intravenous immunoglobulins (2 gm/kg) over 5 days with minimal improvement in his neurological symptoms, his shoulder pain improved and he could feed himself with his right hand. He was offered palliative treatment in view of poor prognosis seen in neurolymphomatosis. He succumbed to the illness 3 months later.

Table 1: Muscle Strength assessment according to MRC grade:

		Right	Left			Right	Left
Shoulder	**Flexion**	**2**	**3**	**Hip**	**Flexion**	**4**	**4**
	Extension	**0**	**0**		**Extension**	**4**	**4**
	Abduction	**1**	**3**		**Abduction**	**4**	**4-**
	Adduction	**2**	**3**		**Adduction**	**4**	**4-**
Elbow	**Flexion**	**2**	**2**	**Knee**	**Flexion**	**4+**	**3**
	Extension	**2**	**2**		**Extension**	**4+**	**4-**
Wrist	**Flexion**	**4-**	**2**	**Ankle**	**Dorsiflexion**	**3**	**0**
	Extension	**2**	**1**		**Plantarflexion**	**4**	**1**
	Intrinsic hand muscles	**2**	**1**				

Table 2: Nerve conduction study

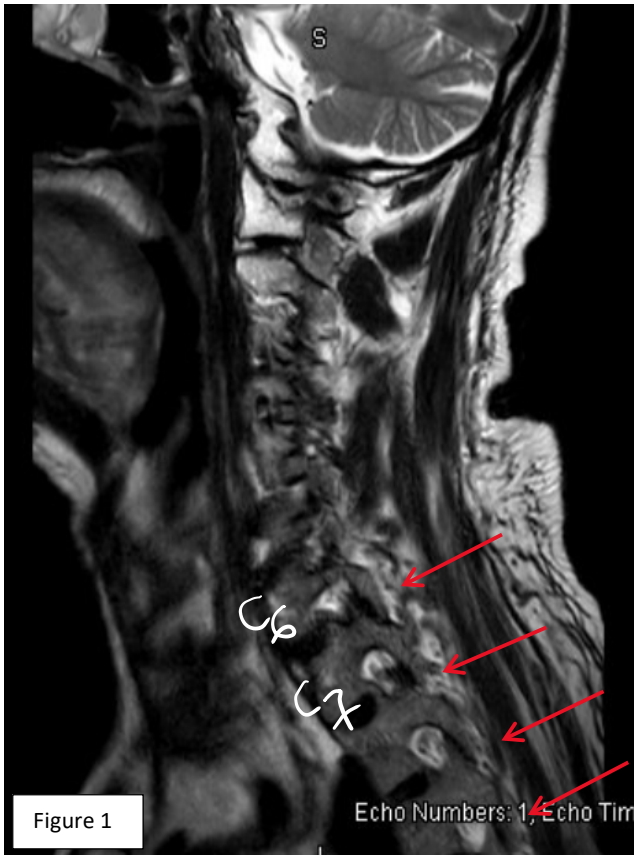
Nerve	Site	Latency (ms)		Amplitude (μV)		Conduction velocity (m/s)		F- latency	
		Right	Left	Right	Left	Right	Left	Right	Left
Sural sensory	Ankle	NR	NR	NR	NR	-	-	-	-
Superficial peroneal sensory	Dorsum of foot	4.4	NR	5	NR	-	-	-	-
Median sensory	Digit 2	3.3	3.2	17	10	-	-	-	-
Ulnar sensory	Digit 5	3.2	2.9	12	22	-	-	-	-
Radial sensory	Wrist	2.9	2.5	10	2	-	-	-	-
LABC	Forearm	NR	NR	NR	NR				
MABC	Forearm	NR	NR	NR	NR				
Peroneal motor	EDB	6.5	NR	1.7	NR	30	NR	73.1	
Tibial motor	Abductor hallucis	6.8	6.7	0.3	0.6	28	32	-	68.9
Median motor	APB	3.7	3.4	6.1	2.8	50	48	-	-
Ulnar motor	ADB	3.0	2.6	3.2	5	49	54	39.3	32.2
Radial motor	EIP	2.8	NR	6	NR	50	NR	32	NR

Abbreviations: LABC - Lateral antebrachial cutaneous sensory, MABC - Medial antebrachial cutaneous sensory

Table 3: Needle Electromyography study.

Muscle	Spontaneous activity	Recruitment	Duration	Amplitude	Polyphasia
Left deltoid	Nil	Severely reduced	Increased	Increased	Present
Left infraspinatus	Nil	Normal	Normal	Normal	No
Left biceps	Fibs +++	No motor units			
Left triceps	Fibs ++	Severely reduced	Increased	Increased	Present
Left FDI	Normal	Normal	Normal	Normal	No
Left EIP, EDC	Fibs ++	Severely reduced	Increased	Increased	Present
Right deltoid	Fibs +++	No motor units			
Right triceps	Fibs +++	No motor units			
Right FDI	Nil	Mildly reduced	Increased	Increased	No
Right EIP	Fibs ++	Moderately reduced	Increased	Increased	Present
Left TA	Fibs +++	No motor units			
Left MG	Fibs +++	No motor units			
Right TA	Fibs ++	Moderately reduced	Increased	Increased	Present
Right MG	Fibs ++	Moderately reduced	Increased	Increased	Present

FDI: first dorsal interossei, EIP: extensor indicis proprius, EDC: extensor digitorum communis, TA: tibialis anterior, MG: medial head of gastrocnemius, Fibs: fibrillation potentials



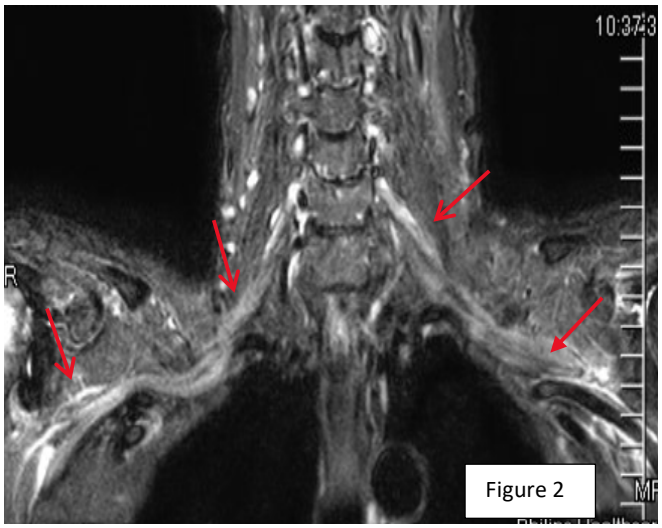


Figure 1: T2 weighted MRI cervical spine saggital section showing increased hyperintensity of left C6,C7,C8 and D1 exiting nerve roots.

Figure 2: Coronal STIR sequence of MRI suggestive of incresed thickeness of brachial plexus, cords and divisions on both sides.

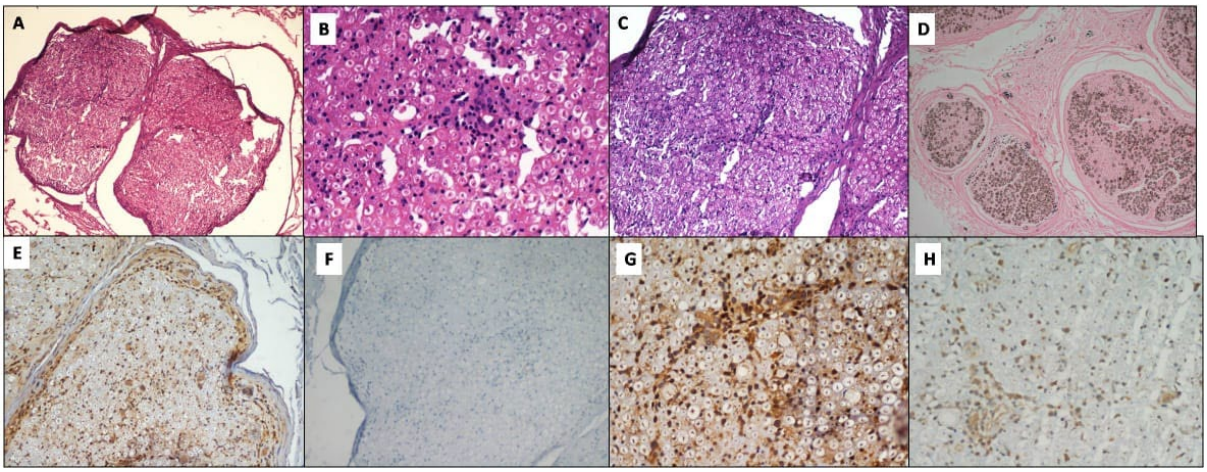


Figure 3: (A) The cross-section of the nerve showing endoneurium and perineurial thickening and (B&C) endoneurial lymphoid infiltrate. (D) Kapl stain showing non uniform involvement of the fascicles with multifocal fibre loss. Immunohistochemistry showing (E) positive CD3 in almost all lymphoid cells whereas (F) CD20 was negative. (G) The cells were positive for CD8 and (H) high proliferation index highlighted by Ki67

Discussion

Neurolymphomatosis is a rare entity. It is usually a manifestation of B-cell lymphoma. Our patient had nasal NK-T cell lymphoma, which itself is extremely rare. It has a rare association with neurolymphomatosis. In a series described by International Primary Central Nervous System Lymphoma Collaborative Group (IPCG) (Grisariu et al.), only one of 166 patients had NK cell lymphoma.[8] It affects the peripheral nervous system especially the spinal ganglia, nerve roots and nerve plexuses. it presents with progressive, severely painful sensori-motor peripheral neuropathy.[2] It can also present with cranial neuropathies.

Neurolymphomatosis can be confused with mononeuropathy, polyneuropathy, polyradiculopathies, Guillain-Barre syndrome, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), arachnoiditis, paraneoplastic neuropathy, leptomeningeal lymphomatosis, nerve root compression, vasculitic neuropathy, or secondary effects of chemotherapy or radiation.[3]

Our patient presented with asymmetric painful proximal and distal weakness in the upper extremities and left foot drop. Clinically the differentials considered were asymmetric CIDP and mononeuritis multiplex as his lymphoma was in remission and NK/T cell lymphoma is not commonly known to cause nerve infiltration. Autoimmune work up was unremarkable. He was treated empirically with steroids at an outside hospital. However, he did not improve. Since nerve conduction studies and needle electromyography were consistent with bi-brachial plexopathy, and whole-body PET-CT revealed increased uptake in the left infraclavicular area, an MRI brachial plexus was done. It showed T2/STIR hyperintensity in the brachial plexus on both sides (Figure 1,2). Hence, he underwent left brachial plexus biopsy to look for evidence of neurolymphomatosis. Biopsy was consistent with hypertrophied fascicles and prominent endoneurial lymphoid infiltration extending up to perineurium. Lymphoid cells were small with dark nuclei and scanty cytoplasm. Immuno-histochemistry was positive for CD3, CD8, CD56, Ki67. This confirmed the diagnosis of neurolymphomatosis and he was then offered palliative care.

MRI neurography and FDG-PET scan is helpful in diagnosis. The International Primary Central Nervous System Lymphoma Collaborative Group has stated that FDG PET and FDG PET/CT might be more sensitive than MRI in the diagnosis of neurolymphomatosis. NL has a characteristic appearance on 18F-FDG PET/CT. It generally presents as a linear or fusiform FDG-avid mass, following a neuronal path. Although, FDG activity can be variable (SUVmax range 1.5–17.0), NL is most often quite FDG-avid (average SUVmax 7.1).[4] CSF examination may show neoplastic cells, CSF protein may be elevated due to root involvement. Nerve biopsy is diagnostic.

Once diagnosed, the prognosis of neurolymphomatosis is poor, with a median survival of 10 months from initial diagnosis.[5] Our patient partially responded to IVIG with reduction in pain scores and was able to feed himself with his right hand due to some improvement in the strength in right shoulder abduction. This was probably more subjective improvement in pain scores than an actual objective improvement in strength. Strength improved very minimally, which may have been due to an inflammatory component that responded to IVIG. However, there was no further improvement and his strength remained more or less same. He succumbed to his illness 3 months after the diagnosis.

Neurolymphomatosis is treated similarly as CNS lymphoma with systemic and intrathecal methotrexate and radiotherapy.[1] In a case series by Alazawi et al., 3 patients were given high dose Methotrexate based chemotherapy and after salvage therapy with high-dose methotrexate regimen, one patient received autologous stem cell transplant. 2 out of 3 patients survived.[7] The prognosis is usually poor but high-dose methotrexate as well as high-dose chemotherapy and autologous stem cell transplant may be an effective way to treat NL.[7] There are few case reports demonstrating effectiveness of bendamustin in neurolymphomatosis.[6]

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