Neurolymphomatosis as a Presenting Feature of Primary Testicular Lymphoma

Sir,

Neurological symptoms due to the affection of the peripheral nervous system, which includes peripheral nerves, roots, plexus, and cranial nerves by the infiltration of malignant lymphoma are collectively termed as neurolymphomatosis (NL).[1,2] NL is a rare complication and is seen in 0.85–2.9% of non-Hodgkin's lymphoma.[1] Diffuse large B cell Lymphoma is mostly responsible for neurolymphomatosis. A high index of suspicion is required as the presenting symptoms of this condition are varied (plexopathy, mononeuritis multiplex, foot drop, radiculopathy, and cranial nerve palsies). These symptoms can proceed the actual diagnosis of lymphoma or occur subsequently in the form of relapse or recurrence of already known disease.[3]

Here authors describe a case of a 54-year-old gentleman who presented with 2 months history of right-sided lower motor neuron type facial weakness. He received oral steroids (prednisolone) in tapering dosages along with physiotherapy. Facial palsy partially improved. Two weeks later he developed left-sided facial weakness. Subsequently, he developed right eye mild ptosis and binocular diplopia at rest, as well on looking on either side. A week later he developed lower limb weakness in the form of difficulty in getting up from sitting position and buckling of knees and became wheelchair bound followed by dysphagia. General examination revealed a painless rubbery left testicular mass which according to the patient had noticed for 3 weeks and had regressed in size partially for 1 week. There was residual left l mn seventh nerve palsy, right partial third nerve palsy, and abducens palsy. There was a proximal weakness in hip and knee with some neck flexor and truncal weakness with generalized are flexia. The sensory loss was in S2,3,4 distribution. The plantar response was flexor. Clinically patient had multiple cranial nerve palsies of 2 months duration with partial response to steroids and recent development of areflexic paraparesis suggestive of polyradiculopathy which was rapidly progressing. Hence, possible etiologies considered were neoplastic/inflammatory/infective.

Biochemical tests were normal. Magnetic resonance imaging (MRI) brain with contrast revealed enhancement of bilateral seventh and eighth nerve complex enhancement and oculomotor nerve roots [Figure 1a and b].There was also epidural enhancement noted and enhancement of cauda equine nerve roots [Figure 1c]. Neurophysiology depicted F wave prolongation in lower limbs with normal snaps and cmap duration, amplitude, and velocity. CSF study revealed 540 cells predominantly lymphocytes with proteins of 306mg/dl and normal sugars. Cytology revealed large atypical cells with interspersed lymphocytes [Figure 2a]. Flow cytometry showed abnormal B cells

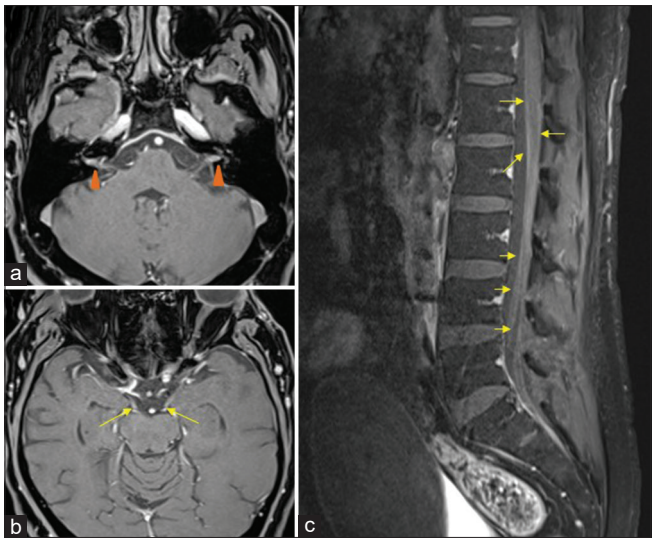

Figure 1: (a) 3D T1 postgadolinium contrast Magnetic resonance imaging MRI Axial sequence revealing enhancement of bilateral seventh and eight nerve complex (arrow heads). (b) Enhancement of bilateral oculomotor nerve roots after exiting from midbrain. (c) T1 Fat suppression Postcontrast MRI of Lumbosacral spine sagittal view showing epidural enhancement and subtle enhancement of cauda equine nerve roots (yellow arrows)

large in size with high side scatter along with CD45, CD19, and CD20 expression and lambda light chain clonality [Figure 3a-d].Whole body PET Scan revealed high uptake SUV max (Standard uptake value) in left testis, left sided retroperitoneal lymph nodes and left supraclavicular lymph node. CT Guided biopsy was done from the retroperitoneal lymph node revealed sheets of atypical lymphoid cells. IHC showing strong membranous diffuse expression of CD 20 [Figure 2b and c]. Also high Ki proliferative index suggestive of aggressive diffuse large B cell lymphoma. Patient initially received iv pulse methylprednisolone 1gram od for 3 days followed by oral steroids. On confirmation of lymphoma, patient was initiated on Rituximab and Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone regimen (R-CHOP) along with systemic and intrathecal methotrexate. After 3 cycles of chemotherapy ptosis resolved, facial weakness improved and dysphagia and motor weakness resolved. Patient was functionally independent. Follow-up PET CT at 3 months showed complete resolution of high uptake lesions in previous regions with no new lesion [Figure 4-d].

Diagnosis of NL is often difficult and delayed because of variability of presenting symptoms and wide differential diagnosis including viral, inflammatory or paraneoplastic neuropathy, cranial neuritis multiplex, leptomeningeal lymphomatosis, and nerve root compression.[4] Approximately 50% of the patients of central nervous system (CNS) metastases from NHL have progressive systemic lymphoma at the time of diagnosis of their CNS manifestation. The remaining 50% develop systemic disease within months.[5] Majority of NL cases exhibit multiple mononeuropathy patterns, whereas some

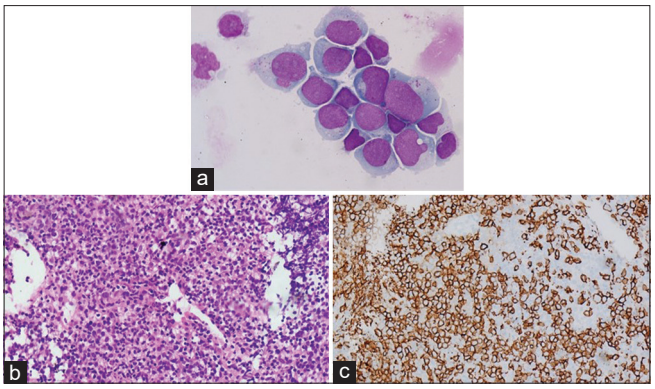

Figure 2: (a) CSF Cytospin smear microphotograph showing large atypical cells with interspersed lymphocytes. (b) H and E Staining showing sheets of atypical lymphoid cells. (c) Immunohistochemistry IHC Showing strong membranous diffuse expression of CD 20

cases show a symmetrical poly-neuropathy pattern, mimicking GuillainBarré syndrome, chronic inflammatory demyelinating polyneuropathy, and other types of neuropathy. Among the Non-Hodgkins lymphoma, Primary testicular lymphoma (PTL) is a rare extranodal lymphoma, accounting for 1% to 2% of all NHL and 4% of all extranodal NHLs.[6,7] Diffuse large B-cell lymphoma (DLBCL) constitute about 6590% of all PTL patients. Rapidly enlarging painless testis is the most common symptom with constitutional symptoms present in one-third of the patients. CNS dissemination is rare (4–5%); however, once it occurs usually it is regarded as a fatal complication of aggressive lymphomas,[8] with a median survival of 4–5 months.

MRI is the investigation of choice to demonstrate enlargement and nodularity of the peripheral nerves, brachial plexus, or the lumbosacral plexus. On STIR/T2-weighted images, infiltrated nerves, and roots appear hyperintense suggestive of lymphoma and peritumoral edema. Also enhancement of affected nerves, and occasionally enlargement is seen. Sensitivity and specificity ofFluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) CT for the initial staging of NHL are reported to be 97 and 100%.[9] PET CT may reveal high grade activity or hypermetabolic activity along the course of a nerve root or peripheral nerve favoring the diagnosis of neurolymphomatosis in patients with the appropriate clinical history and associated abnormal magnetic resonance findings.[10] Biopsy is the gold standard for confirming diagnosis and type of lymphoma. According to a review of 82 cases by Avila JD:[11] 38% patients presented with painful radiculopathy or neuropathy, 24% with mononeuropathy, 23% with cranial neuropathy, and 10% with mononeuropathy multiplex and 5% cases with painless neuropathy. CSF analysis showed malignant cells only in 18 (40%). MRI showed enlarged nerves, usually with contrast enhancement in 48 out of 58 patients (83%).FDG PET showed abnormal root, plexus, or nerve uptake in 55 (91%). Biopsies yielded diagnostic results in 39 of 43 patients (91%). A series by Baehring *et al*. found four main patterns of PNS involvement in NL: painful polyradiculopathy or neuropathy (31%), painless neuropathy (28%), cranial neuropathy (21%), and mononeuropathy (15%).[1] Our patient

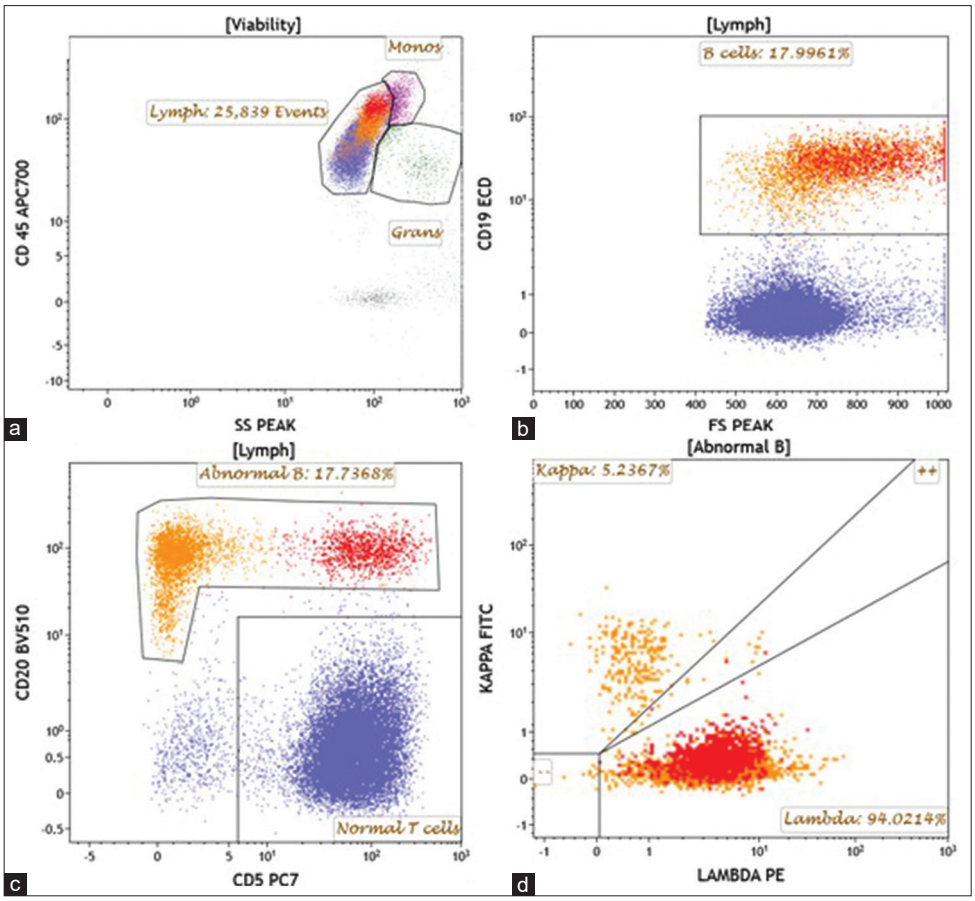

Figure 3: (a-d): CSF Flowcytometry scatter plot showing Abnormal B cells large in size and showing high side scatter along with CD45, CD19, and CD20 expression and lambda light chain clonality

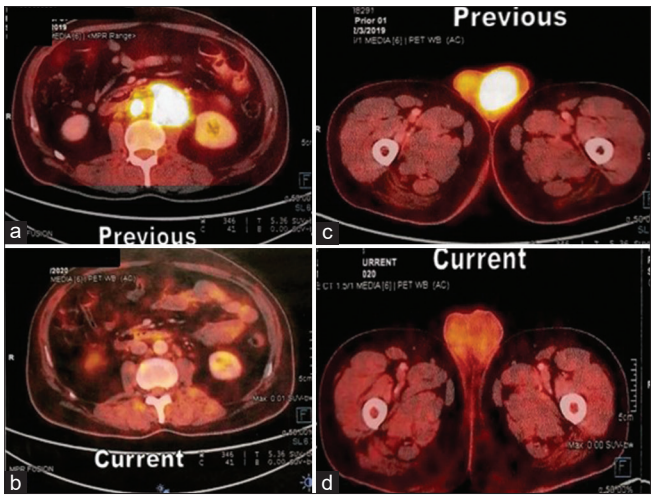

Figure 4: (a) PET CT Showing Increased uptake in left retroperitoneal lymph nodes. (b) Follow up PET CT Showing complete resolution of metabolic activity in previously seen lymph nodes. (c) PET CT Showing increased metabolic activity in left testis and hydrocele. (d) Follow-up PET CT Showing complete resolution of metabolic activity and hydrocele

presented with multiple cranial nerve involvement along with polyradiculopathy. CSF yielded malignant cells and PET CT revealed primary site of neoplasm in testis with metastasis to retroperitoneal lymph nodes with CT guided biopsy confirming the diagnosis of diffuse large B cell lymphoma.

The treatment of NL is similar to that of primary CNS lymphoma which includes systemic chemotherapy with or without intrathecal chemotherapy or radiotherapy. The median survival period of patients with primary NL is 20 months and that of patients with secondary NL is only 8 months.[2] For PTL, worse international prognostic index score (IPI, including age >60-year, ECOG performance ≥2, Ann Arbor stage III/IV, high LDH, more than one extranodal involvement,[12] B-symptoms and non-use of anthracyclines were significantly associated with shorter survival in multivariate analysis. Few studies promoted combined treatment for PTL regardless of stages, including radical orchiectomy, followed by anthracycline-based chemotherapy (CHOP) plus rituximab, intrathecal methotrexate CNS prophylaxis, and contralateral prophylactic testicular irradiation.[13] The response rate to combined treatment regimens in one series was 82%.[2] Prognosis becomes poor with late presentation and diagnosis, advanced stage, as well as the diagnosis of diffuse large-B-cell lymphomas. Radiotherapy is particularly useful in patients with significant neurologic dysfunction since it may rapidly improve or stabilize symptoms. Treatment with corticosteroids may initially result in a radiographic response and improved symptoms although

NL typically recurs or progresses as the malignancy progresses. Our case had a partial clinical response to steroids with complete clinical and hematological recovery post R-CHOP regimen and intrathecal and intravenous methotrexate regimen.

Neurolymphomatosis is clinically misleading yet potentially treatable disorder. Detailed clinical examination with prompt diagnosis using modern tools may help in early detection and treatment resulting in likelihood of a favorable outcome.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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