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Clinical Neuropathological Conference

Clinical Neuropathology Conference: "It's Getting on My Nerves"

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Case Presentation: Dr. Cathy Meng Fei Li

A 64-year-old man with type 2 diabetes mellitus, hypertension, and bipolar disorder presented with a 4-month history of constant, progressive sensorimotor dysfunction of his left arm, accompanied by a 2-month history of sensorimotor dysfunction of the legs and urinary retention. He described persistent numbness in the left C7–T1 distribution, followed by a gradual loss of function in his left hand. Shortly thereafter, he noticed patchy numbness in his left foot and right anterior thigh, with progressive right greater than left leg weakness. He also reported burning pain in his left arm and thighs that was worse at night, and a 30 lb weight loss over the prior 3 weeks. Review of systems was otherwise negative.

When he initially presented to an outside hospital, he was started on duloxetine for neuropathic pain. His home medications were bupropion, losartan-hydrochlorothiazide, metformin, omeprazole, and clonazepam. He was an active smoker with a 35-pack-year smoking history.

Neurological examination demonstrated atrophy of the left forearm, left intrinsic hand muscles, and right quadriceps. He had flaccid 1/5 distal left arm weakness, 4/5 proximal right leg weakness, and 2/5 bilateral distal leg weakness (Table 1). He had reduced sensation to pinprick in the left hand and forearm, worse on the medial aspect; vibration sense was reduced up to the fifth metacarpophalangeal joint in the left hand. Sensation to pinprick was also reduced on the dorsolateral aspect of his right calf and dorsum of his right foot; vibration sense was reduced up to the right medial malleolus. Reflexes were slightly reduced in the left arm (1+), absent in the right patella, and absent in both ankles. Plantar responses were down-going bilaterally. He had a Foley catheter in situ, and he was able to walk 6 meters using a 4-wheel walker.

Initial investigations at the outside hospital demonstrated normal complete blood count, liver enzymes, kidney function, and electrolytes. His HbA1c was 6.1% and vitamin B12 levels were 189 pmol/L. He had a normal erythrocyte sedimentation rate and C-reactive protein. MRI cervical and lumbar spine without contrast demonstrated multilevel degenerative changes with severe foraminal stenosis on the left (C2–C3, C3–C4, and C6–C7), moderate-to-severe neural foraminal stenosis at C7–T1 bilaterally, and moderate neural foraminal narrowing at L5–S1 on the right. The MRI brain demonstrated two nonspecific foci of white matter changes.

Discussion: Dr. Alexandra Muccilli

This gentleman with vascular risk factors and a smoking history presents with progressive bilateral asymmetric sensorimotor symptoms with associated neuropathic pain and sphincteric dysfunction on a background of a 30 lb weight loss. The neurological examination suggests a lower motor neuron (LMN) localization, likely a polyradiculopathy given the predominant motor involvement. The depressed reflexes could be accounted for by his longstanding history of diabetes. A process involving both the central and peripheral nervous system is not excluded, but the non-pyramidal pattern of weakness makes this less likely. MRI of the cervical and lumbar spine was done without gadolinium and shows multilevel foraminal stenoses, but these changes certainly do not account for his clinical picture.

Etiology, of course, is influenced by localization. This is likely an axonal process but electrophysiologic studies are necessary for confirmation and notably to ensure this is not an atypical chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Given the significant smoking history and recent weight loss, an axonal polyradiculopathy secondary to leptomeningeal carcinomatosis is at the top of the differential diagnosis. Other possibilities include vasculitic, inflammatory or granulomatous diseases, and atypical infections.

Next steps in the diagnostic work-up include repeat MRI of the complete spine and brain with gadolinium as well as electrodiagnostic testing. Verification of HIV status has important implications and should be sent with the initial serum work-up in addition to serum angiotensin converting enzyme (ACE) and lactate dehydrogenase (LDH). Cerebrospinal fluid (CSF) should be sent for basic studies, IgG index, and oligoclonal bands, in addition to testing for atypical infections and repeat high-volume cytology with adjunct flow cytometry. Unfortunately, a single CSF cytologic analysis is relatively

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Table 1: Medical Research Council (MRC) grading of upper and lower extremities

	Shoulder Abd.	Shoulder ER	Elbow Ext.	Elbow Flex.	Wrist Ext.	Wrist Flex.	Finger Ext.	Finger Abd.	FPL	APB	FDP (M)	FDP (U)
Right	4+	4+	5	5	5	5	5	5	5	5	5	5
Left	2	2	4	4+	4+	2	1	1	1	1	1	0
	Hip Flex.	Hip Abd.	Hip Add.	Knee Flex.		Knee Ext.	Ankle DF	Ankle Inv.		Ankle Ev.		Ankle PF
Right	4	4	5	4		4+	2	1		4–		4
Left	5	5	5	5		5	2	2–		1		2

APB = abductor pollicis brevis; Abd. = abduction; Add. = adduction; DF = dorsiflexion; ER = external rotation; Ev. = eversion; Ext. = extension; Flex. = flexion; FPL = flexor pollicis longus; FDP = flexor digitorum profundus; Inv. = inversion; (M) = median; PF = plantarflexion; (U) = ulnar.
A detailed motor examination demonstrates severe 1/5 distal left arm weakness bilaterally, moderate 4/5 proximal right arm weakness, and severe 2/5 bilateral distal leg weakness.

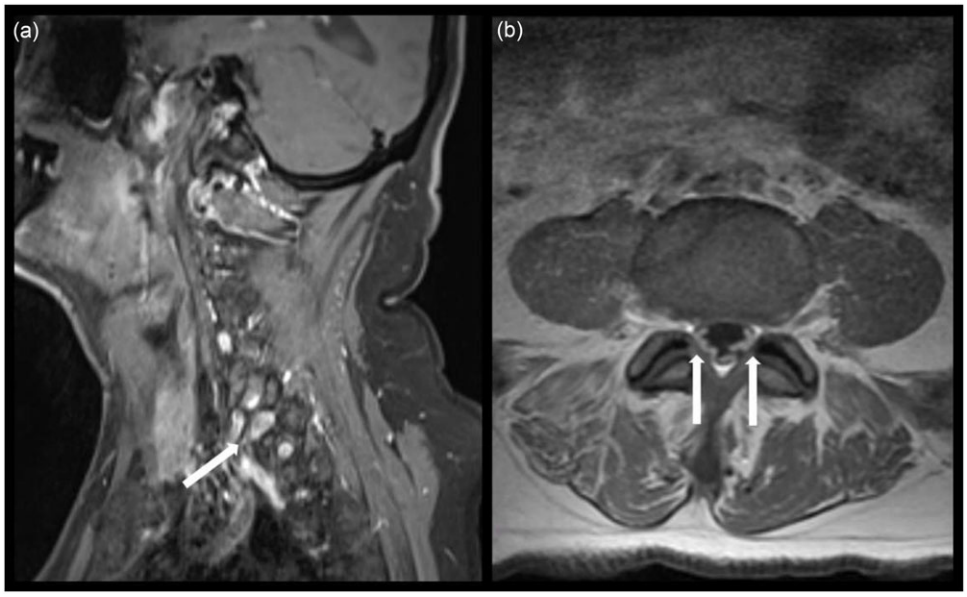

Figure 1: MRI with gadolinium during the initial hospitalization. ***a***) Sagittal T1-weighted post-gadolinium image demonstrates abnormal nerve root enhancement at left C8. ***b***) Axial T1-weighted post-gadolinium image demonstrates smooth, diffuse thickening, and enhancement of the cauda equina.

insensitive. The sensitivity improves with large volume and serial sampling but may be reduced by exposure to corticosteroids and delays in processing. Finally, a computed tomography (CT) of the chest, abdomen, and pelvis should be performed to look for an underlying malignancy or evidence of systemic involvement from an inflammatory, granulomatous, or infectious process.

Course in Hospital

The patient was transferred from the outside hospital to our center. A lumbar puncture was completed and CSF analysis demonstrated glucose of 2.8 mmol/L (serum glucose was 5.8 mmol/L), protein of 2407 mg/L, 183 nucleated cells (100% lymphocytes), and 735 red blood cells in Tube 1 (compared to 94 nucleated cells and 83 red blood cells in Tube 4). CSF flow cytometry demonstrated 99% T-cell predominance and was reviewed with the on-call hematologist. CSF cytology was indeterminant with abundant lymphocytes of variable sizes. CSF cultures were negative. Polymerase chain reactions for herpes simplex virus, varicella-zoster virus, and enterovirus were negative in the CSF.

Serologies for Lyme, arbovirus, HIV, leptospirosis, and hepatitis B and C were negative. Venereal disease research laboratory, serum protein electrophoresis, and ganglioside-monosialic acid antibodies were also negative. LDH was normal. CT scans of the thorax, abdomen, and pelvis with contrast were unremarkable. Gallium scan was normal.

Neuroimaging: Dr. Sachin Pandey

MRI complete spine with gadolinium was performed. In the cervical region, there was abnormal nerve root enhancement at the left C7–T1, and this was best visualized at the C8 level (Fig. 1a). In the lumbar region, there was smooth, diffuse thickening, and enhancement of the cauda equina (Fig. 1b). There was no intrinsic cord signal change noted.

MRI brain was subsequently performed, which demonstrated faint nodular enhancement of the internal auditory canal and two nonspecific foci of white matter changes.

Nerve Conduction Studies/Electromyography (NCS/EMG): Dr. Christen Shoesmith

The patient was initially referred for NCS/EMG studies prior to the results of the lumbar puncture with a question of possible multifocal acquired demyelinating sensory and motor variant of CIDP.

The studies demonstrated reduced motor and sensory amplitudes in the left median and ulnar distributions with relative sparing of the right arm motor and sensory nerves. In the legs,

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Table 2: Results of nerve conduction studies and electromyography

Motor conduction studies					Sensory conduction studies		
	Distal latency	Conduction velocity (m/s)	Amplitude (mV)	Temporal dispersion		Conduction velocity (m/s)	Amplitude (mV)
R Median	N	N	N	—	R Radial	N	N
R Ulnar	N	Elbow (41)	N	—	R Ulnar	N	N
L Median	N	Forearm (42)	↓ (5.4)	—	L Radial	N	N
L Ulnar	N	↓ Forearm (36) ↓ Elbow (31) ↓ Arm (24)	↓ (3.4)	Forearm	L Ulnar L Median	N N	↓ ↓
R Tibial	N	N	N	—	R Sural	N	N
R Peroneal	N	N	↓ (1.7)	—	L Sural	N	½ of R Sural
L Tibial	N	N	↓ (5.7)	—			
L Peroneal	N	N	↓ (3.6)	—			

Electromyography				
	Fibs	PSW	Motor Units	Recruitment
L Deltoid	++	++	Large	↓
L Biceps brachiae	++	++	Large	↓
L Triceps	++	++	Large	↓
L Extensor digitorum communis (EDC)	++	++	N/A	No units recruited
L Flexor carpi radialis (FCR)	++	++	N/A	No units recruited
L Pronator teres	++	++	N/A	No units recruited
L Mid-thoracic paraspinals	-	-	N	N
L Vastus medialis	-	-	N	N
L Tibialis anterior	++	++	Large	↓
L Gastrocnemius	++	++	N/A	No units recruited
L Biceps femoris	-	-	N	N

Fibs = fibrillations; L = left; N/A = not able to be assessed; N = normal; PSW = positive sharp waves; R = right.
These studies demonstrated reduced motor and sensory amplitudes in the left median and ulnar nerves, with relative sparing of the same nerves on the right. In the legs, there was asymmetrical reduction in motor amplitudes that was worse on the left, with relative reduction of the left sural sensory amplitude. Although there was possible demyelinating features in left ulnar nerve (slow conduction velocity across all three segments), the studies were mostly consistent with a multifocal, predominantly axonal process. EMG demonstrated evidence for acute and chronic denervation in multiple muscles on the left, which are innervated by multiple nerves and spinal roots.

there was asymmetrical reduction in the motor amplitudes and the left sural sensory amplitude was half of the right-sided amplitude. The only nerve with possible demyelinating findings was in the left ulnar motor nerve conduction study, which had slowed conduction velocities across three segments and temporal dispersion in the forearm segment. Overall, the NCS demonstrated a multifocal, predominately axonal process with minimal evidence for demyelination (Table 2).

Needle EMG demonstrated evidence for acute and chronic denervation in multiple muscles in the left arm and the left legs, which are innervated by multiple nerves and multiple spinal roots (Table 2).

The electrodiagnostic conclusion of the electrophysiology is an asymmetric axonal predominant sensorimotor polyneuropathy. Although a single nerve demonstrated some evidence of demyelination, most of the evidence point toward a predominately axonal process. These results cannot exclusively be explained by a polyradiculopathy due to the reduction in sensory amplitudes and are not consistent with an acquired demyelinating disease. These results would be consistent with multifocal involvement of peripheral nerves or in a pathological process non-homogeneously affecting both spinal roots and post-ganglionic nerves.

Treatment and Course: Dr. Li

This 64-year-old man presented with subacute, progressive, painful, and asymmetric axonal sensorimotor polyneuropathy. His CSF pleocytosis suggested an infectious, inflammatory, and/or neoplastic process. As such, our differential diagnoses included Lyme, leptospirosis, HIV, West Nile virus (WNV), vasculitis, neurolymphomatosis, and neurosarcoidosis. Initial investigations did not reveal any evidence of infection, malignancy, or vasculitis; therefore, neurosarcoidosis was a leading consideration. Neurosarcoidosis can be classified into possible, probable, and definite. Probable and definite neurosarcoidosis requires pathological confirmation of granulomatous inflammation outside and within the nervous system, respectively. In the absence of any tissue to suggest granulomatous inflammation, this was considered as possible neurosarcoidosis. He was started on prednisone 50 mg daily and methotrexate 25 mg once weekly, with a plan to taper the

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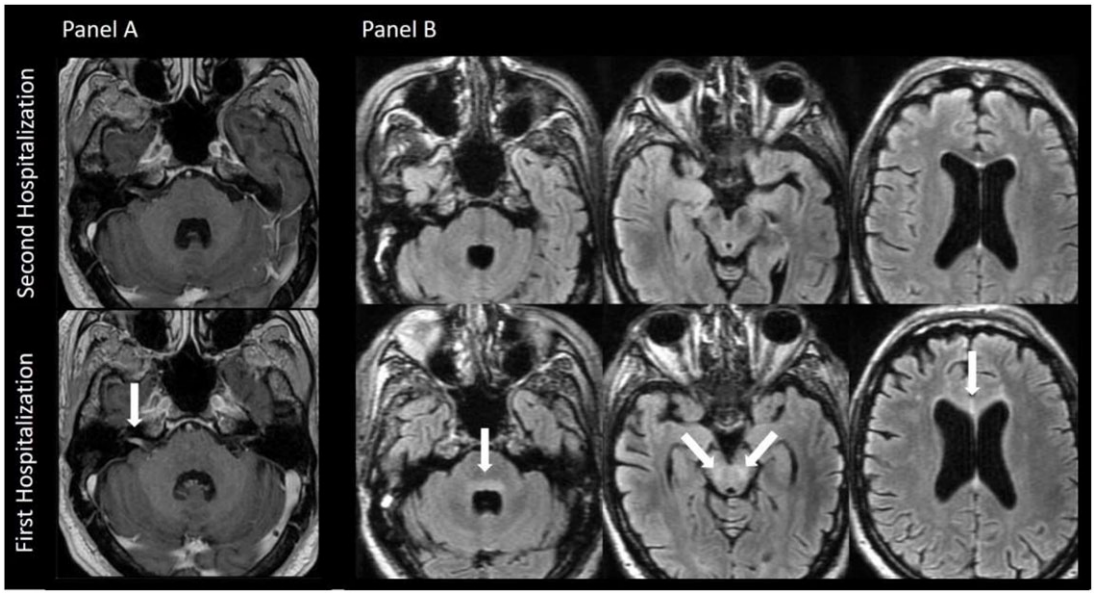

Figure 2: MRI brain with gadolinium during the first and second hospitalizations (four months apart). Panel ***a***) Axial 3D T1-weighted post-gadolinium images of the brain from the first and second hospitalizations demonstrate interval enlargement of abnormal enhancement in the right internal auditory canal. Panel ***b***) Axial 3D T2-weighted FLAIR images of the brain from the first and second hospitalizations demonstrate several new areas of relatively symmetric abnormal signal hyperintensity involving the periventricular dorsal pons, the cerebral peduncles bilaterally, and the corpus callosum.

prednisone as an outpatient. Three months after discharge, he demonstrated marked improvement and was able to ambulate independently with a narrow-based gait. Residual deficits included 1/5 strength in his left finger flexors, abductor pollicis brevis, extensor pollicis longus, 4/5 strength in the remainder of his left arm, and 4/5 strength in bilateral ankle dorsiflexors. He had ongoing reduced sensation to pinprick in the left C8–T1 distributions. He continued his prednisone taper.

One month later, the patient endorsed worsening fatigue, reduced appetite, and an additional 20 lb weight loss over 3 weeks. He also described new-onset headaches that would wake him up from sleep. On reassessment, he had right facial weakness in a LMN pattern, worsening weakness of his left arm, reduced vibration sense up to the distal tibial tuberosity bilaterally, and new upper motor neuron signs. He also had a broad-based gait with mild right leg circumduction.

Given his decline, he was readmitted to hospital. He was on prednisone 20 mg daily at that time. A repeat lumbar puncture demonstrated low glucose of 1.8 (normal 2.2–3.9), elevated protein 2740 mg/L, and worsening pleocytosis (147 nucleated cells and 1 red cell in Tube 4) with lymphocytic predominance. CSF cultures were negative. CSF cytology was indeterminant with abundant mixed population of lymphocytes. CSF flow cytometry revealed 5% B-cells and 62% T-cells; results were reviewed with the hematologist on-call and felt to be consistent with reactive lymphocytes.

Neuroimaging: Dr. Sachin Pandey

Repeat MRI scans were performed and compared to 4 months earlier. There was interval enlargement of the abnormal enhancement in the internal auditory canals, particularly on the right (Fig. 2a). As well, there were several new areas of abnormal T2 hyperintensities in the brain, predominantly and symmetrically involving the periventricular dorsal pons, the cerebral peduncles, and corpus callosum (Fig. 2b).

Final Discussion: Dr. Muccilli

A clinical response to corticosteroids is unfortunately not discriminating and can be seen with inflammatory, infectious, and neoplastic processes. The CSF remains inflammatory and now with evidence of hypoglycorrhachia, which is also a nonspecific finding. Hypoglycorrhachia can be associated with neurosarcoidosis, neurolymphomatosis, and other malignancies, as well as atypical bacterial and fungal infections. In addition to persistent leptomeningeal enhancement, repeat imaging now shows evidence of periventricular and callosal fluid attenuated inversion recovery (FLAIR) hyperintensities. Given these MRI findings, lymphoma with both central and peripheral nervous system involvement remains at the top of the differential diagnosis.

It is critical to continue with high-volume CSF cytology sampling and adjunct flow cytometry, ideally off steroids. In the absence of a clear diagnosis, early consideration of biopsy is warranted. Given high suspicion for lymphoma vs. neurosarcoidosis, a positron-emission tomography/computed tomography (PET/CT) scan should be obtained and may reveal a biopsy target not seen on the initial pan-CT. Consideration should also be given to hematology consultation and bone marrow biopsy. Finally, a spinal leptomeningeal biopsy could be pursued if a tissue diagnosis cannot otherwise be made.

Course in Hospital: Dr. Li

A third lumbar puncture demonstrated low-normal glucose of 2.3 (normal 2.2–3.9), elevated protein 1922 mg/L, and worsening pleocytosis (193 nucleated cells and 0 red cells in Tube 4) with lymphocytic predominance. CSF flow cytometry revealed 40% B-lymphocytes and CSF cytology revealed a highly cellular sample with some larger atypical lymphocytes, both appearing suspicious for a B-cell lymphoproliferative neoplasm.

A PET/CT scan was performed, which demonstrated a hypermetabolic 2.2 cm right cervical lymph node and extensive

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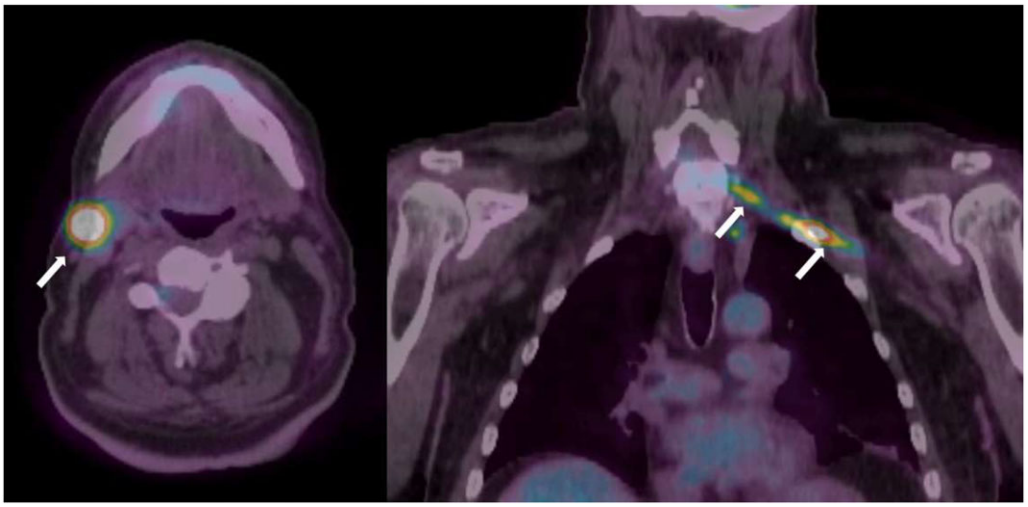

Figure 3: Fusion PET/CT scan of whole body. There was increased 18FDG uptake in right cervical lymph node (2.2 cm) and extensive FDG uptake along the C7–T1 nerve roots extending into the left brachial plexus.

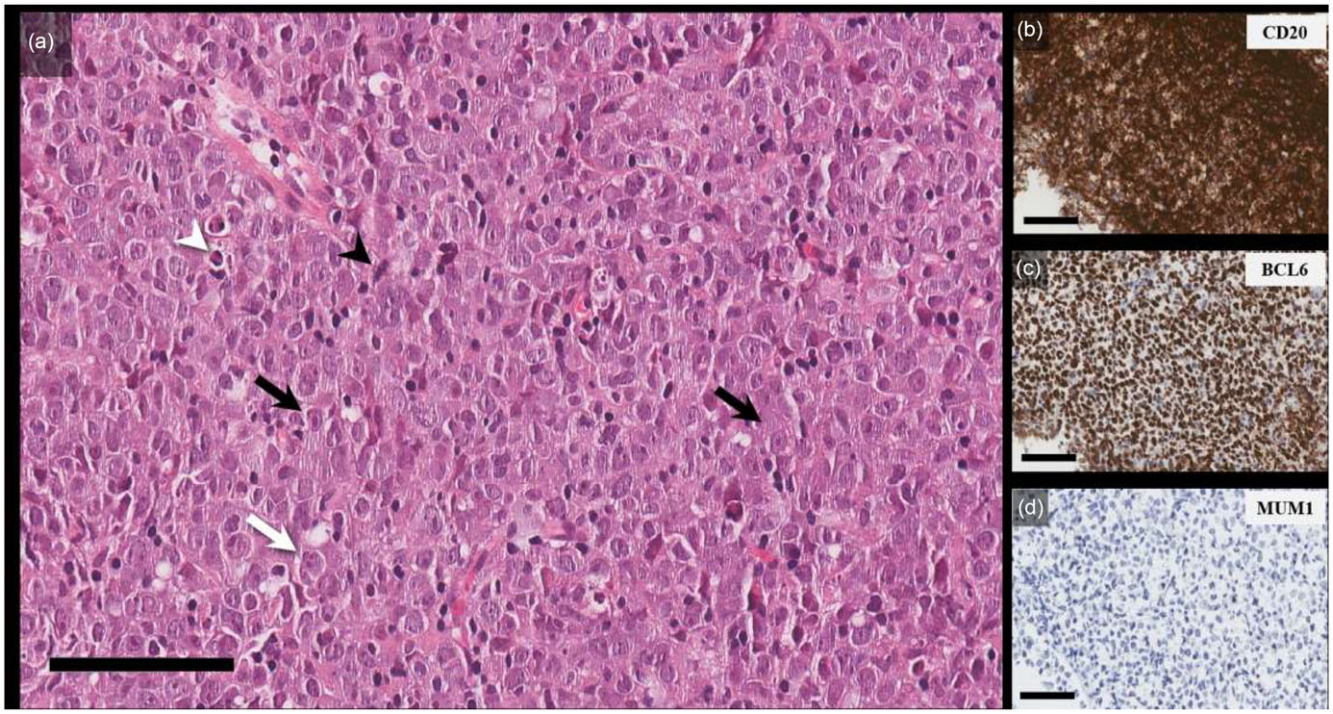

Figure 4: Pathology results of the cervical lymph node biopsy. Photomicrographs demonstrate the diffusely infiltrative architecture of the lymphoma, whereby the presence of atypical lymphocytes has effaced the normal lymph node architecture. ***a***) Lesional cells display immunoblastic (black arrow) and centroblastic (white arrow) morphologies. Mitoses (black arrowhead) and apoptotic cells (white arrowhead) are present (H&E, bar = 100um). ***b***) Immunohistochemical studies reveal expression patterns of a diffuse large B-cell lymphoma with germinal center B-cell like immunophenotype with CD20 expression (immunoperoxidase, DAKO monoclonal anti-CD20, clone L26, bar = 100um). ***c***) BCL6 expression (immunoperoxidase, DAKO monoclonal anti-BCL6, clone PG-B6p, bar = 100um). ***d***) Absence of MUM1 expression (immunoperoxidase, DAKO monoclonal anti-MUM1, clone MUM1p, bar = 100um in Panel D).

FDG uptake along the C7–T1 nerve roots extending into the brachial plexus (Fig. 3). The culprit lymph node was biopsied.

Pathology: Dr. Robert Hammond & Dr. Shervin Pejhan

The architecture of the biopsied lymph node was effaced by a diffuse, hypercellular, and mitotically active lesion of atypical mononuclear cells. Immunohistochemical studies revealed expression of B-cell markers (such as CD20) and BCL6, and the absence of CD10 and MUM1 (Fig. 4).

The pathological diagnosis was diffuse large B-cell lymphoma (DLBCL). The specific immunophenotype was germinal center B-cell-like. No MYC rearrangement was present.

Treatment and Management: Dr. Cheryl Foster

The patient was treated with R-CHOMP (rituximab, cyclophosphamide, vincristine, doxorubicin, prednisone and high-dose methotrexate) for four cycles and received one dose of intrathecal methotrexate. He tolerated therapy well.

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Interim PET imaging identified a complete metabolic response (Deauville 1). MR head and spine identified subsequent improvement of the leptomeningeal and cauda equina enhancement. He also underwent a repeat lumbar puncture, and CSF results were normal.

He proceeded to autologous stem cell transplant with filgrastim mobilization and 10.7 x10^6 CD34-positive stem cells were collected. He subsequently underwent autologous stem cell transplant with rituximab, thiotepa, busulfan, and melphalan conditioning and is currently recovering from transplant.

Clinical Updates: Dr. Seth Climans

Within 2 days of starting high-dose intravenous methotrexate, his neuropathic pain disappeared completely and he was able to stop his neuropathic pain medications. He had gradual improvement in his sensation and his strength, especially in his proximal muscles. His walking has significantly improved.

Comment: Dr. Muccilli

This challenging case highlights the importance of maintaining a broad differential diagnosis early on with rigorous diagnostic testing prior to pursuing empiric treatment. From a clinical standpoint, neuroinflammatory disorders may present quite similarly to neoplastic and atypical infectious processes; response to corticosteroids can be seen with all three. Repeat CSF analysis with high volumes sent for cytology and paired flow cytometry specimens prior to initiation of steroids increases the sensitivity of testing. This is also the case for numerous infectious causes of chronic meningitis. Each of the plausible etiologies of this patient's presentation has a distinct management strategy and outcomes are often associated with early-directed treatment. As a result, if a diagnosis cannot be made via noninvasive testing, early consideration of biopsy is warranted.

Review of Topic: Dr. Li

Overall, our patient's initial presentation was most consistent with DLBCL with neurolymphomatosis, which is caused by direct neural infiltration of lymphoid cells due to a primary hematological malignancy. Approximately 90% of neurolymphomatosis occurs in the setting of non-Hodgkin's lymphoma (typically a B-cell lymphoma), and the remaining 10% in leukemia.[1]

Primary neurolymphomatosis is defined as the initial presentation of non-Hodgkin's lymphoma, whereas secondary neurolymphomatosis represents relapse or progression of previously diagnosed non-Hodgkin's lymphoma. Primary neurolymphomatosis occurs in 25% of patients, highlighting the importance of early recognition and diagnosis.[1,2] Unfortunately, the clinical manifestations of NHL in the peripheral nervous system can be highly variable. The most common presentation is painful involvement of roots or nerves, which comprises 30%–40% of patients with neurolymphomatosis. Other presentations include cranial neuropathy (20%), mononeuropathy (15%), and painless multifocal neuropathy (20%–30%).[3]

Nodular enhancement or nerve root enlargement is seen on MRI in 80% of patients.[1] CSF studies typically demonstrate increased protein and nucleated cells; hypoglycorrhachia is seen in 11% of patients.[1] Overall, the neuroimaging and CSF findings are nonspecific and can support a wide range of peripheral nerve disorders, including inflammatory, infectious, neoplastic, and rarely, paraneoplastic causes of neuropathy. The classic finding of neurolymphomatosis on NCS is an asymmetric, non-length dependent axonal neuropathy[4]; in contrast, paraneoplastic causes of neuropathy tend to be symmetrical and demyelinating.[5] A PET scan shows increased metabolic activity in 84% of neurolymphomatosis (usually linear uptake along the nerves) and can identify the affected nerve(s) for biopsy.[1,6] Increased metabolic activity in other sites, in addition to peripheral nerves, was also observed in 35% of patients.[6]

CSF flow cytometry is more sensitive than CSF cytology in diagnosing occult CNS malignancies (13% vs. 4.5%), although the diagnostic yield in both cases is very low.[7] The majority of patients required three lumbar punctures before tumoral cells were reliably identified.[8] Targeted biopsies of an affected nerve, identified on MRI or PET, demonstrated neural infiltration by malignant cells and were diagnostic in 88% of patients with neurolymphomatosis.[1] Peripheral nerves were the most common site of nerve biopsy (79% of cases); other biopsy targets included cranial nerves (11%), spinal nerve root (5%), and brachial plexus (5%).[1] In general, targeted proximal nerve biopsies, either fascicular or cutaneous, have a greater diagnostic yield than non-targeted distal cutaneous nerve biopsies (74–85% vs. 20–50%).[9,10] Although nerve biopsies carry a theoretical risk of permanent nerve damage, recent studies revealed that most adverse effects associated with a targeted proximal nerve approach were mild or self-limited.[9,10] Overall, the possible risks of nerve injury must be carefully balanced against the benefits of nerve biopsy as a key diagnostic tool.

Clinicians should also be aware of critical blind spots when relying on a pan-CT and/or testicular ultrasound as their standard malignancy screening tools; specifically, the cervical lymph nodes are not captured. A thorough lymph node examination should always be performed and CT neck should be considered as a more sensitive assessment of cervical lymphadenopathy.

Non-Hodgkin's lymphoma requires systemic chemotherapy using the R-CHOP protocol (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). With nervous system involvement, high-dose methotrexate is added.[11] Intrathecal methotrexate can be considered in patients with leptomeningeal disease.[1,12] Chemotherapy followed by autologous stem cell transplant is also associated with increased survival.[13] Similar to primary CNS lymphoma, neurolymphomatosis responds to corticosteroids, but its symptomatic response is short-lived and may contribute to diagnostic delays.[3] Elevated LDH, more than 1 extranodal site of disease, and the presence of B symptoms are independent factors of CNS relapse.[14,15]

With treatment, the median survival in patients with primary neurolymphomatosis was 11.5 years, which is significantly longer than the median survival of 2.1 years in patients with secondary neurolymphomatosis.[13] Early treatment portends better prognosis and serial PET scans can reflect response to treatment.[1,2]

Learning Points

- Consider three lumbar punctures before starting empiric steroids.
- Consider early tissue biopsy (e.g. affected sites identified on PET scan, targeted proximal nerve biopsy of affected nerve, leptomeningeal biopsy, spinal leptomeningeal biopsy, or bone marrow biopsy) in discussion with appropriate services.
- Consider CT neck to assess for cervical lymphadenopathy.

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Critical review of the article: (all authors).

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