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Neurologic complications of lymphoid cancer can be challenging to recognize and treat. The nervous system can be affected directly by hematogenous or local spread of lymphoma. Indirect neurologic effects of lymphoma include paraneoplastic syndromes and vascular complications. Lymphoma treatments can also cause neurologic complications. Early identification and treatment are crucial to stabilize or reverse neurologic deficits, prevent further nervous system injury, and to optimize overall oncologic therapy. This article provides an overview of different neurologic complications of lymphoma and its treatments, in addition to presentation of case studies that emphasize commonly encountered clinical scenarios.

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Abstract:
Neurologic complications of lymphoid cancer can be challenging to recognize and treat. The nervous system can be affected directly by hematogenous or local spread of lymphoma. Indirect neurologic effects of lymphoma include paraneoplastic syndromes and vascular complications. Lymphoma treatments can also cause neurologic complications. Early identification and treatment are crucial to stabilize or reverse neurologic deficits, prevent further nervous system injury, and to optimize overall oncologic therapy. This article provides an overview of different neurologic complications of lymphoma and its treatments, in addition to presentation of case studies that emphasize commonly encountered clinical scenarios.

Neurologic complications in lymphoid cancers can manifest in several ways;

1) Direct complications: involvement of the central or peripheral nervous system by lymphoma
2) Indirect complications: paraneoplastic syndromes, vascular complications
3) Treatment associated complications.

Depending on the specific cause, patients can present with mild, self-limiting symptoms, or severe, disabling and irreversible neurologic deficits that can be fatal. As immunotherapies are being increasingly used in patients with lymphoma, there has been an increase in referral of lymphoma patients for neurologic symptoms and signs. Given that various conditions can lead to the same clinical presentation, it can be quite challenging to determine the exact etiology. Differentiation between presentations is necessary to guide treatment.

In this review, we will discuss an overview of neurologic complications from Hodgkin and non-Hodgkin lymphoma, describe some cases and highlight practical issues encountered in the recognition and management of these complications. We will not discuss primary central nervous system lymphoma as it is beyond the scope of this review.

Direct complications:

Central Nervous System (CNS) Involvement:

Non-Hodgkin lymphoma (NHL) can rarely involve the CNS concurrently at the time of initial diagnosis or at the time of relapse. The median time to development of CNS relapse is less than a year and can occur as isolated CNS disease or in conjunction with systemic relapse of disease. The overall incidence of CNS involvement is 2-7% and while several risk factors including histologic subtype (Burkitt's lymphoma, lymphoblastic lymphoma) have been identified, the CNS international prognostic index (IPI) composed of variables such as older age, poor performance status, advanced stage (III/IV) disease, ≥1 extranodal sites, elevated serum lactate dehydrogenase, and involvement of specific organs such as the adrenal glands and kidneys can help stratify patients at risk.[1] Primary testicular lymphomas are associated with a high incidence of CNS relapse.[2] Biomarkers including, double-hit lymphomas characterized by *MYC* and *BCL2* and/or *BCL6* rearrangements and activated B-cell (ABC) like diffuse large B-cell lymphomas (DLBCL) that are associated with poor prognosis also increase risk of CNS involvement.[3,4] Risk of CNS relapse with Hodgkin lymphoma is rare with an incidence of <0.5% and Epstein Barr virus may be seen in association.[5,6] CNS involvement from systemic NHL or HL may include the

brain, spinal cord, eye, leptomeninges (includes subarachnoid space and cerebrospinal fluid (CSF)) and dura in isolation or in combinations. Contrast-enhanced MRI of the brain and spine, CSF studies and/or brain biopsy are typically recommended for diagnosis. Ophthalmologic evaluation including a slit-lamp examination is recommended for those with symptoms concerning for intraocular involvement. High-dose methotrexate-based chemotherapy followed by thiotepa-based autologous transplant in patients with secondary CNS DLBCL (SCNSL) was associated with a complete response rate of 63% and a 2-year event-free survival of 51% and this should be considered in the appropriate transplant-eligible patient.[7] Targeted agents such as ibrutinib and lenalidomide have demonstrated response rates of 60-75% in patients with SCNSL, although these responses are not durable and the median progression-free survival is approximately 6 months.[8,9] Whenever possible and if available, we recommend consideration of enrollment of patients in clinical trials. CD19 directed CAR T cell therapy, which has improved outcomes of patients with relapsed and refractory DLBCL, is promising treatment in SCNSL with responses observed in 4 out of 8 patients treated with tisagenleucleucel in a case series. Clinical trials are ongoing.[10]

Peripheral Nervous System (PNS) involvement:

NHL can involve the peripheral nerves and plexi either by direct invasion or infiltration. Neurolymphomatosis can cause a painful peripheral neuropathy or radiculopathy. Occasionally, patients may present with mononeuropathies of the sciatic, radial or median nerves, or even cranial nerves leading to radicular pain, paresthesias and weakness in legs or arms, or diplopia and facial weakness, respectively. Diagnosis can be made by MRI of the involved area and FDG-PET which typically shows increased uptake. Treatment involves focal radiation or systemic chemotherapy. Given this is a rare complication, it is important to consider in the differential diagnosis other unrelated causes of neuropathies such as medications, vitamin or nutrient deficiencies, metabolic and autoimmune conditions and in patients with a history of NHL or HL, paraneoplastic causes or chemotherapy-induced neuropathy as discussed below.

Case 1:

A 25-year-old man presented with fatigue with abdominal and bone pain, evaluation of which led to the diagnosis of a high-grade DLBCL with *MYC* and *BCL2* rearrangements. Upon

completion of treatment with 6 cycles of R-EPOCH and prophylactic intrathecal methotrexate, he developed severe pain in his right shoulder and left leg associated with numbness of his left foot. Over the next month, his symptoms progressed, and he developed worsening pain and weakness in the right arm as well as bilateral foot drop. He was then diagnosed with Parsonage-Turner Syndrome, an idiopathic brachial plexopathy, and started on methylprednisolone which did not help. Subsequently, MRI of the brachial plexus showed increased enhancement and FDG-PET scan showed increased uptake in the right brachial plexus and bilateral sciatic nerves (Figure 1). Finally, he was diagnosed with neurolymphomatosis. He responded to treatment with high-dose methotrexate and cytarabine and made a full recovery.

Case 1 highlights the fact that any patient with a history of any aggressive cancer, including lymphomas, presenting with new onset neurologic symptoms or signs, or change in quality, severity or frequency of existing symptoms, must be subject to a thorough evaluation to identify the etiology and rule out malignant involvement of the nervous system. Asymmetric neurological symptoms and signs are typically not due to chemotherapy-induced neuropathy.

Indirect Complications

Spinal cord compression:

Spinal cord compression can cause severe and permanent neurologic deficits, and must be diagnosed and treated emergently to reverse symptoms and prevent devastating sequelae. Epidural lesions caused by lymphoma involvement of the vertebral bodies of the spine or paravertebral lymph nodes can lead to spinal cord compression (Figure 2). In a retrospective study of 131 patients with primary bone lymphoma, one third of the patients had involvement of the spine leading to cord compression in half of them.[11] The majority of patients present with back pain, although neurologic symptoms including paralysis, sensory loss, and bladder/bowel dysfunction can evolve rapidly. Delayed diagnosis and treatment can result in permanent neurologic deficits. Diagnosis is typically made with MRI spine. Dexamethasone can improve neurologic symptoms and signs until definitive treatment including chemotherapy and/or radiation can be instituted. Occasionally, patients may need neurosurgical intervention to maintain stability of the spine.

Paraneoplastic Syndromes (PNS):

Classic PNS are rare complications of lymphomas, and in fact, PNS are associated with unique presentations with a higher incidence in HL compared to NHL.[12,13] Unlike the case with solid tumors, onconeural antibodies are rarely identified, with exceptions, such as paraneoplastic cerebellar degeneration (PCD) and limbic encephalitis (LE) more commonly observed in HL rather than NHL (Table 1). PCD presents with progressive symptoms of vertigo, truncal and limb ataxia, dysarthria, diplopia and nystagmus. MRI may initially be normal and cerebellar atrophy occurs over time. Anti-Tr antibodies are found in serum and CSF of patients.[14] PCD from HL has a slightly better prognosis compared to PCD secondary to solid tumors and improvement has been reported in patients <40 years of age upon treatment of the underlying HL. Paraneoplastic LE, Ophelia syndrome, presents with confusion, memory loss, hallucinations and behavioral problems.[15] Brain MRI may be unremarkable or associated with abnormalities in the bilateral medial temporal lobes, hippocampus and amygdala. This rare syndrome is associated with an anti-mGLU5 (metabotropic glutamate receptor type 5) antibody. Often, patients have a full recovery upon treatment of the underlying HL. Paraneoplastic sensorimotor neuropathies or neuronopathies or conditions resembling Guillain Barre syndrome or, more commonly, chronic inflammatory demyelinating polyradiculopathy (CIDP) present in patients with NHL with a subacute course and absence of onconeural antibodies. Sensory neuronopathies generally have a poor prognosis. Dermatomyositis is also observed in NHL and the presence of a p155 antibody is highly suggestive of an underlying malignancy.[16] Outside of the classic syndrome of PCD, it can be challenging to make the diagnosis of PNS in lymphoma, especially when there is no associated onconeural antibody. Suspicion for PNS should trigger a diagnostic evaluation as they typically present before lymphoma diagnosis, followed by prompt treatment of the same. In the absence of co-existent lymphoma, corticosteroids, intravenous immunoglobulin, plasma exchange, cyclophosphamide and rituximab are treatment options based on the specific type of PNS.

Vascular complications:

Primary angiitis of the CNS (PACNS) is a rare, non-infectious, granulomatous condition affecting the cerebral blood vessels. This can be seen in association with HL either immediately before or after diagnosis. As the histopathologic picture resembles an autoimmune condition and

due to its association with lymphoma, it is often considered as a PNS, although it could be related to varicella-zoster viral infection.[17] Patients present with headaches, confusion, seizures, or focal deficits. Rarely, this can involve the spinal cord causing transverse myelitis. MRI often shows infarcts or leptomeningeal enhancement, cerebral angiography may demonstrate beading suggestive of vasculitis, and CSF may demonstrate pleocytosis, but these are non-specific findings. Brain biopsy is necessary for confirmation and occasionally may also show Aβ amyloid angiopathy.[18] Patients typically recover with corticosteroids and treatment for HL.

Intravascular lymphoma (IVL) is an aggressive extranodal NHL involving the small vessel lumen, particularly capillaries. Although any organ can be involved, the CNS is the most common, occurring in 42% of IVL cases, followed by the skin.[19] Patients typically present with stroke-like symptoms, fever, fatigue and skin rashes. Brain MRI typically demonstrates infarcts that are not specific for any vascular territory and this finding should alert the clinician to this diagnosis. Often skin and bone marrow biopsy are enough, but occasionally brain biopsy can be required for histopathologic confirmation. Treatment options include high-dose methotrexate and cytarabine in addition to R-CHOP.[20] Relapse risk is high and prognosis is poor. The CNS is less likely to be involved in the hemaphagocytosis variant of IVL seen in Asian patients.

Paraprotein-associated neuropathies:

Peripheral neuropathy is the most common neurologic complication of paraproteinemias including lymphoplasmacytic lymphoma with IgM (Waldenström's macroglobulinemia), monoclonal gammopathy of unknown significance (MGUS), multiple myeloma, amyloid light chain amyloidosis, and POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes) syndrome. The majority of these polyneuropathies are associated with IgM paraprotein, up to 70% of which are associated with anti-myelin-associated glycoprotein (MAG) antibody.[21,22] The peripheral neuropathy may present as a distal large fiber sensory neuropathy, multiple mononeuropathies, or painful length-dependent sensory, motor or sensorimotor neuropathy that may be associated with autonomic dysfunction. POEMS syndrome may present with chronic inflammatory demyelinating polyradiculopathy (CIDP). Patients may present with progressive symmetric paresthesias, sensory impairment, pain, weakness, and often tremor. Electrophysiologic studies can confirm neuropathy. High titers of anti-MAG antibodies

can be detected in serum in untreated patients. Nerve biopsy may be necessary. Treatment of the underlying disease with rituximab monotherapy or in combination with chemotherapy may result in improvement of symptoms and reduction or normalization of anti-MAG antibody titers.[23] Corticosteroids, intravenous immunoglobulin, and plasma exchange have been tried with varying success in patients with CIDP.

Treatment Related Complications:

Neurologic complications can result from the various treatments for NHL and HL including chemotherapy, radiation, autologous stem cell transplant, allogeneic stem cell transplant, targeted therapies and immunotherapies. Neurologic side effects from traditional chemotherapy are common non-hematologic dose-limiting toxicities in oncology.[24] With the advent of targeted and immunotherapies, specific targeting of tumors can occur which may lead to reduction in off-target side effects such as myelosuppression. However, some newer therapies have unique neurotoxicities and their early recognition is critical. It is important to note that *treatment related neurotoxicity is a diagnosis of exclusion* and other etiologies should be considered first. Comprehensive diagnostic evaluation is warranted including ruling out nervous system involvement by lymphoma as described above. Conditions such as headaches, strokes, peripheral neuropathies, and Guillain-Barre syndrome, all of which occur in patients without cancer, may develop in lymphoma patients and it is necessary to determine whether these were triggered by the lymphoma, its treatment, or are completely unrelated. Several factors can affect the incidence and severity of neurotoxicity. These include age, dose of drug and route of administration, concurrent renal or liver dysfunction, combined modality treatments, and pre-exiting neurologic conditions. For example, an older adult >60 years of age is at a higher risk of long-term neurocognitive decline from combination intravenous methotrexate and whole brain radiation compared to younger patients.[25] Underlying conditions can predispose patients to early or exaggerated side-effects depending on the type of treatment involved. For example, a patient with an inherited motor and sensory neuropathy such as Charcot-Marie-Tooth disease is at a higher risk of chemotherapy-induced peripheral neuropathy from anti-microtubule drugs like vincristine.[26] A patient with a history of seizure disorder may be at a higher risk of seizures from treatment with high-dose busulfan or CD19 CAR T Cell therapy. For this reason, a detailed neurologic history and baseline neurologic examination are essential prior to starting treatment.

Lymphoma treatment can affect any part of the nervous system including the central and the peripheral nervous system (Table 2). Neurotoxicity in the CNS can manifest with non-specific, non-localizing symptoms and signs such as headaches, confusion, seizure, or loss of consciousness which, in turn, can be manifestations of different underlying neurologic conditions such as meningitis, encephalitis, cerebral infarction, or intracerebral hemorrhage. Localizing or focal deficits such as weakness, aphasia, visual loss or seizures or can also be observed with these underlying neurological conditions. Patients with a myelopathy may present with Lhermitte's sign which is an electric shock-like sensation throughout the spine, limbs and occasionally trunk, triggered by bending the neck. Peripheral nervous system toxicity can present as a sensory or motor neuropathy, ascending polyradiculopathy like Guillain Barre syndrome, myasthenia gravis from involvement of the neuromuscular junction or myositis. In general, diagnosing neurologic complications of lymphoma treatment is challenging as the same set of symptoms and signs may result from direct complications from lymphoma, or indirect (infectious, vascular) complications of lymphoma or a paraneoplastic syndrome. Once a treatment-related neurotoxicity is recognized, the determination needs to be made whether the treatment should be discontinued or whether the side effect is dose-dependent and dose adjustment can be made. Below are common therapeutics used to treat lymphoid cancers that have a propensity to cause neurologic complications.

Immunotherapies:

Immune checkpoint inhibitors are approved treatments for HL (pembrolizumab, nivolumab) and primary mediastinal B cell lymphoma (pembrolizumab). The incidence of immune-related neurologic toxicities from anti-PD1 antibodies is 6%.[27,28] Headache and peripheral sensory neuropathy are more common manifestations, although patients treated with these therapies can develop a wide range of neurologic symptoms (Table 3). Immune-mediated encephalitis can present with acute onset of confusion, depressed level of consciousness, or personality change. Hypophysitis may also occur as a complication with acute onset of headaches, fatigue and generalized weakness, in addition to endocrine abnormalities. Cerebellar toxicity can present with ataxia, nystagmus and vertigo. Symptoms typically occur acutely or subacutely within 3 months of initiation of treatment but can occur as early as after the 1st dose of treatment.[29] Brain

MRI and CSF should be obtained to rule out malignant spread, infection and toxic-metabolic causes of altered mental status. Therapy should be discontinued in patients with grade 2 or higher neurotoxicity and corticosteroids should be instituted rapidly to prevent fatal outcomes. Empiric antibiotic or antiviral coverage for encephalitis should be considered until an infectious etiology is excluded.[27] Checkpoint inhibitors can also lead to polyradiculopathy or a Guillain-Barre syndrome with facial diplegia, dysphagia, sensory loss, paresthesias, weakness, and areflexia. CSF can demonstrate a cytoalbuminologic dissociation (high protein with few cells) and demyelinating polyneuropathy is detected on nerve conduction study. Corticosteroids and intravenous immunoglobulin are advised. Plasma exchange may also be considered for severe cases. Recovery may be full or incomplete, in the latter case patients are left with residual neurologic deficits. Myositis can involve various muscle groups and typically causes proximal limb weakness, muscle pain, dysarthria, dysphagia, ptosis, diplopia and occasionally dyspnea from diaphragmatic weakness.[30,31] Serum creatine kinase is elevated and muscle biopsy may be needed for diagnosis, typically demonstrating necrotic and inflammatory changes. Corticosteroids and immune checkpoint discontinuation may allow for complete recovery although prolonged morbidity and fatal cases have been described.[31] Approximately 60% of patients with myasthenia are found to have acetylcholine receptor antibodies and despite aggressive treatment with pyridostigmine, corticosteroids, IVIG and plasmapheresis, this condition can be fatal in up to a third of patients.[32] Myasthenia gravis and myositis can occasionally occur at the same time and both can overlap with myocarditis. For this reason, when one of these conditions is suspected, evaluation for the others is recommended.[33] The risk of retreatment with an immune checkpoint inhibitor is not well defined and such a strategy should be considered on a case by case basis taking into account the severity/grade of the neurotoxicity, degree of recovery, any residual neurologic deficits, and the status of the lymphoma including alternative options.

Case 2.

A 66-year-old man with systemic and CNS DLBCL was treated with RCHOP and high-dose methotrexate followed by an autologous stem-cell transplant. Three months post-transplant, his lymphoma relapsed in the ethmoid sinus. He underwent CD-19 directed CAR T cell therapy and on post-infusion day 2, he developed headaches and mild aphasia followed by confusion. A non-

contrast head CT was unremarkable, and an EEG did not show an epileptiform discharges. He responded to corticosteroid therapy and was discharged home in 9 days. He remained in remission more than a year later.

Chimeric Antigen Receptor (CAR) T-cell therapy directed toward CD19 is approved for relapsed/refractory DLBCL, mantle cell lymphoma and B-cell acute lymphoblastic leukemia, and can cause immune effector cell associated neurologic syndrome (ICANS) in association with cytokine-release syndrome (CRS).[34] Acute encephalopathy with delirium and aphasia are frequently observed within the first 7 days of infusion, as in Case 2.[35] Other symptoms may include headaches, hallucinations, tremors, and myoclonus. Often symptoms peak and then resolve within the next few days to weeks.[36] Rarely, the syndrome can rapidly progress to generalized seizures, coma and death. Brain MRI is typically unremarkable although occasionally T2/FLAIR hyperintensity without restricted diffusion in deep brain regions is observed and in rare cases, cerebral edema has been reported.[37] Most patients are treated with and respond to corticosteroids.[38] Anti-IL6 receptor antibody, tocilizumab approved for use in CRS, is not effective in ICANS and in fact may be associated with worsening neurotoxicity.[39,40] There is preclinical evidence that the IL1 receptor antagonist, anakinra, prevents neurotoxicity and clinical trials are ongoing.[41] For all patients scheduled for CAR T-cell therapy a baseline neurologic examination and ICANS grading scale should be completed on admission with frequent monitoring during the hospital course.

Monoclonal Antibodies:

Brentuximab vedotin is a CD30-specific antibody drug conjugate approved for relapsed/refractory HL and anaplastic large cell lymphoma (ALCL) and its most common neurologic side effect is peripheral neuropathy. A sensory neuropathy characterized by numbness, paresthesias and burning pain is common, observed in 40-69% of patients, although patients can also present with a motor neuropathy.[42,43] The majority of patients present with a grade 2 neuropathy, but some develop severe symptoms requiring temporary or permanent discontinuation of the drug. In case of a temporary hold, it is advised that brentuximab vedotin be restarted at a lower dose once symptoms are grade 1 or less. Severe pain from peripheral neuropathy can be managed using gabapentin, pregabalin or duloxetine. These drugs are not

typically recommended in the absence of pain as they do not help with alleviating numbness, tingling or paresthesias. Physical therapy may be helpful in patients with weakness from a motor neuropathy. It is noteworthy that many patients receiving brentuximab vedotin may have had prior exposure to other drugs associated with peripheral nerve toxicity such as vinca alkaloids and cisplatin and this prior exposure may increase risk of neurotoxicity. In most cases, symptoms resolve after completion of treatment.

Rituximab, an anti-CD20 antibody and *Alemtuzumab,* an anti-CD52 antibody can rarely cause reactivation of latent JC virus infection leading to progressive multifocal leukoencephalopathy (PML). Many patients present with altered mental status, although some may have motor deficits, aphasia, or visual loss. Diagnosis is made by MRI and confirmed by CSF PCR for JC virus or brain biopsy.[44,45] There is no standard treatment for PML and most cases are fatal. Mefloquine, mirtazapine, cytarabine have been tried. In a series of 8 PML patients, immune checkpoint blockade with pembrolizumab resulted in clinical improvement or stabilization as well as a reduction in CSF JC viral load in 5 out of 8 patients and is a promising therapy for this devastating neurologic complication.[46] Case reports have indicated benefit from interleukin-2 and interleukin-7. Treatment with N-803, an interleukin-15 superagonist resulted in a response in one patient with PML.[47]

Polatuzumab vedotin is an anti-CD79B monoclonal antibody conjugated to the microtubule disrupting agent, monomethyl auristatin E, and is implicated in peripheral sensory neuropathy in 44-67% of patients treated with this agent.[48,49] The majority of patients report a grade 1/2 neuropathy including paresthesias which typically resolves, although higher grade neuropathy requiring treatment discontinuation has been reported.

Small molecule inhibitors

Ibrutinib, a first-in-class BTK inhibitor is associated bleeding and, rarely, intracerebral hemorrhage.[50,51] Patients may present with headaches or focal neurologic deficits. If minimally symptomatic, then the drug can be restarted at a lower dose after resolution of hemorrhage and symptoms.

Lenalidomide, pomalidomide and thalidomide, which are immunomodulatory drugs, can cause a length-dependent axonal sensory neuropathy, typically several months after starting therapy.[52] Nerve conduction studies are typically abnormal. Most patients report mild symptoms and do not require any treatment.

Case 3.

A 69-year-old woman with a history of DLBCL treated with RCHOP presented with diplopia 3 months after completion of therapy. On neurologic examination she had a left abducens nerve (cranial nerve VI) palsy. Brain MRI with contrast did not demonstrate any abnormal leptomeningeal enhancement, infarct or hemorrhage. Over the next week, her symptoms worsened. CSF studies did not reveal malignancy or other abnormality. After 10 days, the symptoms stabilized and over the next 2 months, her diplopia resolved.

Vinca alkaloids:

Vincristine causes a dose-limiting, axonal, sensory and motor neuropathy and its incidence in patients with lymphomas is higher than when used in other cancers.[53] Often patients present with paresthesias, wrist drop or foot drop.[54] Muscle cramps may be an initial sign of an impending neuropathy. Paresthesias can occur during treatment, but it is not uncommon for patients to develop symptoms months after completion of treatment as seen in our case. Cranial neuropathies (as in case 3) including involvement of the facial nerve (facial weakness), oculomotor and abducens nerves (diplopia, ptosis), optic nerve (visual loss), auditory nerve (hearing impairment), recurrent laryngeal nerve (dysphagia) have been reported. Autonomic neuropathy presenting with orthostatic hypotension, constipation and abdominal pain from ileus, and erectile dysfunction can occur. In general, the severity of the neuropathy increases with cumulative vincristine dosing and a dose-limit of 1.4 mg/m^2 with a maximum dose of 2 mg per cycle is recommended.[55] Concurrent administration of vincristine with the anti-fungal agents, voriconazole and itraconazole is associated with enhanced neurotoxicity.[56] Physical therapy is often necessary for recovery from motor neuropathies and severe cases may not have a complete recovery. Gabapentin for prophylaxis or treatment is not beneficial.

Case 4

A 74-year-old man with prior history of DLBCL treated with R-CHOP presented with progressive confusion and right sided weakness. Brain MRI demonstrated a contrast-enhancing lesion in the corpus callosum with extension into the left parietal region. A biopsy of the enhancing lesion confirmed a diagnosis of DLBCL. No other sites of disease were identified, and he was diagnosed with isolated CNS relapse. He was treated with HD-MTX, rituximab and temozolomide for 4 cycles and he achieved a complete radiographic response. Three years later, he presented with progressive memory loss, urinary incontinence and gait ataxia. Brain MRI demonstrated periventricular whiter matter T2/FLAIR hyperintensities (Figure 3). Evaluation for toxic and metabolic causes of his symptoms was negative. He was diagnosed with MTX induced leukoencephalopathy.

Antimetabolites:

High-dose methotrexate (HD-MTX) as well as *intrathecal (IT) MTX* can cause an acute as well as subacute encephalopathy.[57,58] Acute encephalopathy is usually reversible. Subacute or chronic encephalopathy as seen in case 4, is typically progressive, irreversible and associated with high morbidity and mortality. It is a diagnosis of exclusion and as described in case 4, other causes must be excluded. The risk is higher with older age and when combined with whole brain radiation therapy.[59]

Cytarabine arabinoside (AraC) in high doses can result in an acute cerebellar syndrome characterized by incoordination, ataxia, gait imbalance, dysarthria and nystagmus.[60] Risk factors include pre-existing liver or renal dysfunction, older age and history of prior neurologic deficits. Typically, the cerebellar deficits resolve within 2 weeks of discontinuation of drug, although rarely the syndrome can be permanent with cerebellar atrophy over time.

Case 5.

A 24-year-old man presented with stage IVB DLBCL and completed 6 cycles of RCHOP with FDG-PET after treatment showing resolution of all disease except in the mediastinum. After a biopsy of this residual FDG-positive confirmed DLBCL, he received treatment with salvage chemotherapy with minimal response, followed by mediastinal involved field radiation therapy (IFRT) to a dose of 40 Gy plus 6 Gy boost, to which he had a complete response (CR).

Subsequently, he underwent autologous stem-cell transplant (SCT) followed by RIC allogeneic SCT. He remained in CR for 16 months when he presented with 3 weeks of new right leg weakness, erectile dysfunction, and urinary hesitancy. Brain MRI was unremarkable, but spine MRI demonstrated spinal cord expansion and edema with multifocal enhancement within the prior RT portal from T5-T9, demarcated by fatty marrow replacement between T5-T9 vertebral bodies (Figure 4). Diagnostic evaluation including CSF studies was negative for malignancy, infection, autoimmune or inflammatory conditions or demyelination. He was diagnosed with radiation-induced myelitis. He was treated with high-dose dexamethasone to which he had minimal response. Treatment with bevacizumab led to complete resolution of the lesion, and after intensive physical therapy, he regained neurologic function.

Radiation

Ionizing radiation to the brain or spinal cord can cause acute, subacute or delayed adverse effects.[58] Acute brain toxicity from radiation is typically due to cerebral edema and/or raised intracranial pressure and resolves with corticosteroids. Subacute effects due to radiation necrosis occur weeks to months after radiation and usually present with headache, lethargy and focal neurologic deficits. Rarely, radiation myelopathy can result from focal radiation delivered to the mediastinum for HL and NHL as in case 5.[61] Spine MRI typically shows contrast enhancement within the spinal cord and symptoms may resolve with corticosteroids. Bevacizumab has been used to treat radiation necrosis as described in our case.[62] Delayed neurotoxicity typically presents years after treatment. It can present as radiation induced vasculopathy resulting strokes or hemorrhage, or as brain atrophy and leukoencephalopathy. Older age and concurrent HD-MTX use increase this risk.[63]

In conclusion, patients with lymphoma are at high risk of neurologic complications from direct or indirect effects, including treatment-related toxicities. With an increasing number of FDA approved treatments for lymphoma, awareness of rare side effects that can lead to significant neurologic morbidity or even mortality, is important. Consideration of a broad differential diagnosis for new onset or exacerbation of existing neurologic symptoms is advisable along with early intervention and involvement of appropriate neurological specialists.

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Figure Legends:

Figure 1. MRI brain and FDG-PET scan of a patient with neurolymphomatosis. A) An axial T1 weighted image post-gadolinium contrast shows enhancement of the right brachial plexus, B) FDG-PET scan shows increase in FDG uptake in the right brachial plexus.

Figure 2. MRI of the cervical and thoracic spine of a patient with epidural spinal cord compression. A sagittal T2 image shows epidural involvement by non-Hodgkin lymphoma with compression of the underlying spinal cord.

Figure 3. MRI brain of a patient with leukoencephalopathy from high-dose methotrexate use. An axial T2 FLAIR image shows periventricular hyperintense signal reflecting leukoencephalopathy.

Figure 4. MRI of the cervical and thoracic spine of a patient with radiation induced myelopathy. A) Axial T1 weighted image post-gadolinium contrast shows enhancement within the spinal cord. B) Sagittal T2 image shows a signal change throughout his prior radiation portal from T5-T9, demarcated by fatty marrow replacement between T5-T9 vertebral bodies.

Table 1. Paraneoplastic neurologic syndromes associated with lymphomas.

Syndrome/Presentation	**Antibody**	**Type of lymphoma**	**Prognosis/ Recovery**
Cerebellar Degeneration	Anti-Tr	HL	Improvement possible
Limbic Encephalitis (Ophelia Syndrome)	Anti-mGLU5 Anti-Ma2	HL HL, NHL	Full recovery possible
Myelopathy	None	HL, NHL	Improvement possible
Opsoclonus-myoclonus	None	NHL	improvement unlikely
Stiff-person syndrome	None, may have co-existing anti-GAD65	HL	Improvement possible
Sensorimotor neuronopathy	None	HL	Improvement rarely noted
Myasthenia gravis	AChR	HL, NHL	Improvement expected, prognosis dependent on prognosis of lymphoma
Dermatomyositis	p155	NHL	Improvement possible but poor

			prognosis

*HL: Hodgkin lymphoma, NHL: Non-Hodgkin lymphoma

Table 2. Neurologic complications of radiotherapy, chemotherapy and novel agents used in treatment of lymphomas.

Neurologic Presentation	**Offending Agent**
Acute Encephalopathy	High-dose Methotrexate (IV, IT) Ifosfamide Busulfan Cytarabine Immune checkpoint inhibitors CD19 directed CAR T cell therapy Whole brain radiation
Chronic Encephalopathy	High-dose Methotrexate Whole brain radiation
Progressive multifocal leukoencephalopathy (PML)	Rituximab Alemtuzumab Brentuximab vedotin
Aseptic meningitis	Methotrexate (IT) Cytarabine (IT) Immune checkpoint inhibitors
Intracranial hemorrhage	Ibrutinib
Cerebellar Syndrome	High-dose cytarabine
Seizures	High-dose busulfan High-dose etoposide CD19 directed CAR T cell therapy
Aphasia	CD19 directed CAR T cell therapy
Myelopathy	Thiotepa (IT)

	Cytarabine (IT) Immune checkpoint inhibitors Radiation
Peripheral Neuropathy	Vincristine Vinblastine Carboplatin Thalidomide Lenalidomide Pomalidomide Brentuximab vedotin Polatuzumab vedotin Checkpoint inhibitors Alemtuzumab
Guillain-Barre syndrome	Checkpoint inhibitors Alemtuzumab
Myositis	Checkpoint inhibitors Brentuximab vedotin
Myasthenia gravis	Checkpoint inhibitors

Table 3. Neurologic adverse events associated with immune checkpoint inhibitors

Toxicity	Presentation	Evaluation	Recovery
Encephalitis	Confusion, depressed level of consciousness, behavioral changes	Brain MRI, LP	Most recover with early treatment; high morbidity/mortality with delayed diagnosis
Aseptic meningitis	Headache, neck stiffness, photophobia, nausea, vomiting	Brain and Spine MRI, LP	Most recover completely
Hypophysitis	Headache, fatigue, endocrine dysfunction	Brain MRI, LP, hormone levels	Permanent damage to pituitary in most; replacement hormone therapy necessary
Cerebellar toxicity	Ataxia, nystagmus, vertigo	Brain MRI, LP	Most recover
Transverse myelitis	Back pain, weakness/paralysis, sensory loss, bladder/bowel dysfunction	Spine MRI, LP	Most recover
Cranial and peripheral neuropathy	Facial palsy, trigeminal neuralgia, paresthesias, sensory loss, weakness, autonomic symptoms	Brain MRI and LP (if cranial nerve involvement), EMG/NCS	Most recover
Guillain Barre Syndrome	Ascending sensory loss, weakness, areflexia, facial diplegia, dysphagia, autonomic dysfunction	Spine MRI, LP, EMG/NCS	Variable prognosis; mortality associated with respiratory muscle involvement
Myasthenia gravis	Muscle weakness, diplopia, ptosis	Serum for AChR antibodies, EMG	Fatal in 1/3rd patients
Myositis	Proximal muscle weakness, pain, dysphagia, ptosis,	CK, aldolase, EMG, consider muscle biopsy	Most patients recover completely

	diplopia, dyspnea		

*LP: lumbar puncture, NCS: nerve conduction studies, EMG: electromyography, AChR: acetyl choline receptor, CK: creatine kinase

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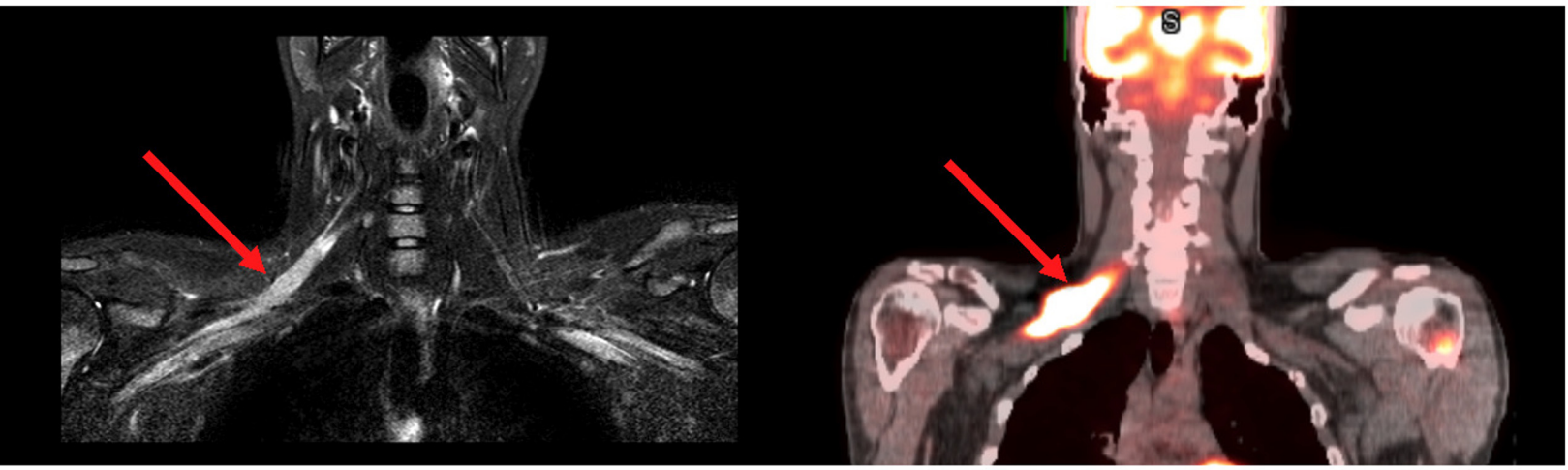
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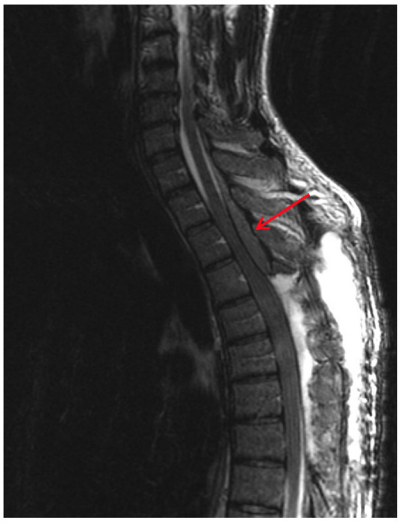

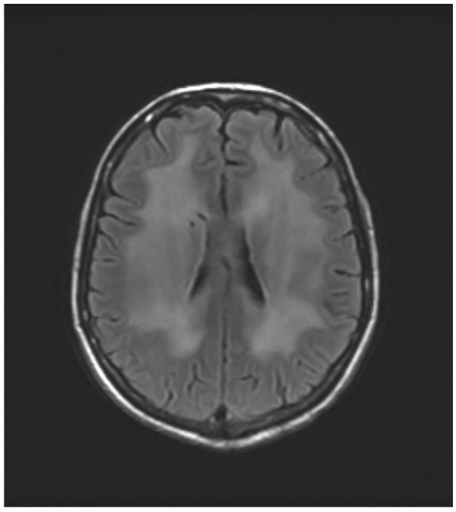

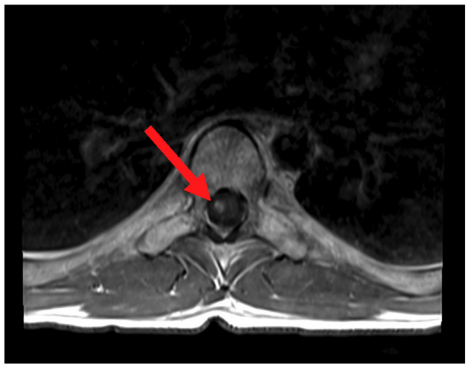

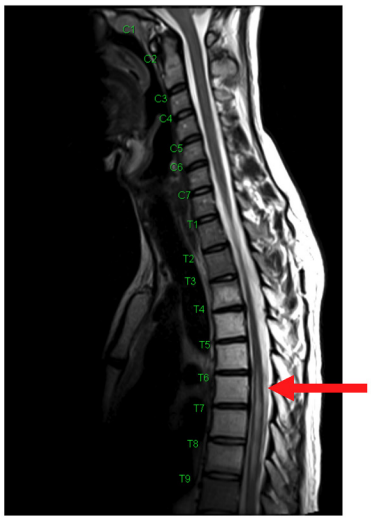
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