Spinal Cord Lesions in Patients with Cancer

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ABSTRACT
Patients with cancer are prone to unique disease processes different from those that occur in the general population. Spinal cord lesions in patients with cancer may reflect neoplastic, infectious, ischemic, hemorrhagic, metabolic, and toxic etiologies. As treatments become more efficient in different cancers, subsequent early and late cancer and treatment complications may also become more frequent. The purpose of this article is to review common spinal cord lesions in patients with cancer with an emphasis on imaging and clinical clues that can narrow the differential diagnosis.

Learning Objective: List 5 imaging findings that differentiate neoplastic and non-neoplastic sources of spinal pathology in patients with known malignancies.

INTRODUCTION
Spinal cord lesions are uncommonly encountered in clinical practice. The differential diagnosis is limited, and recall of common entities is facilitated by mnemonics such as HEALSME (Hemangioblastoma, Ependymoma, Astrocytoma, Arteriovenous malformation, Lymphoma, Syringohydromyelia, Sarcoidosis, Metabolic, Metastasis, Multiple sclerosis, and Edema). The distribution of spinal cord lesions in a cancer population, however, is different from that in the general population and is less well-described. The incidence of new cancer diagnoses is estimated to increase by 45% to 2.3 million in 2030, with dramatic and disproportionate increases of 67% in the elderly and 99% in minorities. In 2013, the number of new primary central nervous system cancers in the United States is estimated to be 69,720 or 12% higher than the mean annual number between 2005 and 2009. Proper recognition, diagnosis, and treatment of spinal cord lesions in patients with cancer are growing challenges for health care providers. Although the categories (tumor, infection, metabolic, vascular, and so forth) may appear similar to those in patients without cancer, different pathologies are often observed in patients with cancer due to unique tumor conditions, treatments, and vulnerabilities. The purpose of this article is to summarize spinal cord lesions that may occur in patients with cancer, with an emphasis on differential points to assist in making the proper diagnosis.

Malignant
Spinal cord invasion by leptomeningeal metastasis. Increased survival for patients with cancer has been associated with an increased detection of leptomeningeal metastasis.
This is probably due to 2 main factors: First, in the past, many patients would have died of their primary cancers because the treatments were less effective; therefore, many did not have the opportunity to develop leptomeningeal metastases. Second, continued technologic advances have yielded high sensitivity to modern imaging methods that was not previously available. Breast and lung cancer account for the largest numbers of patients with leptomeningeal metastases, which are usually seen in patients with late stage cancer in the setting of widely disseminated disease.

Primary CNS cancers that also commonly metastasize to the leptomeninges include medulloblastoma, ependymoma, and glioblastoma. Lower extremity weakness and paresthesias are the most common presenting symptoms, with simultaneous presentation of symptoms localized to separate spinal levels being highly suggestive of leptomeningeal metastasis. CSF analysis remains the criterion standard for diagnosis, though multiple CSF samplings may be necessary, with accuracy described as only 54% after 1 sampling and 90% after 3 samplings. MR imaging remains critical for disease management and has a growing role for diagnosis, though it may be more sensitive for detecting leptomeningeal metastases from solid tumors than from hematopoietic malignancies.

MR imaging in leptomeningeal disease reveals focal or diffuse nodular and/or plaquelike enhancement along the surface of the spinal cord and subarachnoid space on contrast T1-weighted images. Tumor nodules may also be visualized along the surface of the cauda equina or on nerve roots. On T1-weighted images, the CSF demonstrates slightly hypointense signal intensity, which can blur the distinction between CSF and the cord. The leptomeningeal metastases may cause T2 hyperintense reactive changes and vasogenic edema in the spinal cord or may directly invade the spinal cord (Fig 1).

**Direct Spinal Cord Metastasis**

Spinal cord metastases are rare. The most common presentation is a solitary lesion in the cervical or thoracic cord. Lung and breast cancer again account for the most common primaries to metastasize to the cord. Similar to leptomeningeal disease, the growing incidence of spinal cord metastases is probably associated with improvement in systemic control of disease. The route of spread is often hematogenous via arterial supply or direct extension from the leptomeninges. Radiation therapy and corticosteroids are the mainstay of palliative care after diagnosis of intramedullary metastasis, which carries a dismal prognosis of 65% mortality in 6 months. Clinical findings are often nonspecific; weakness is the most common presenting symptom.

MR imaging of a spinal cord metastasis usually shows a well-circumscribed expansile lesion with avid homogeneous enhancement on contrast T1-weighted images and extensive hyperintense edema on T2-weighted images (Fig 2). Cystic features and hemorrhage are uncommon (Fig 3) and help to distinguish metastases from primary neoplasms such as ependymomas. The rim sign (more intense peripheral enhancement) and flame sign (ill-defined flame-shaped enhancing tail at the superior and/or inferior margin) were also recently described as specific for metastasis. Lymphoma and post-transplant lymphoproliferative disorders may also cause spinal cord lesions (Figs 4 and 5).

**Nonmalignant**

**Vascular: infarct.** Cancer is widely considered a hypercoagulable state, with prophylactic anticoagulation advocated for some patients with cancer. Spinal cord infarction is most commonly seen in the upper thoracic and thoracolumbar cord because the blood supply to these areas is less redundant compared with other regions of the cord. Patients usually report the acute onset of severe pain, followed within hours by motor and sensory impairment and incontinence. By admission, most patients are paraplegic and
functional outcomes remain poor. Suspension based on clinical presentation is often crucial to a prompt work-up; diagnosis can be confirmed with MR imaging.

MR imaging typically demonstrates spinal cord enlargement with T2 hyperintense and T1 hypointense changes. T2 hyperintense changes may also be present within the adjacent vertebral body, indicative of vertebral infarction. Diffusion restriction on diffusion-weighted imaging sequences and a lack of contrast enhancement in the acute phase are critical to the imaging diagnosis (Fig 6).

**Hemorrhage**

Hematomyelia or spinal cord hemorrhage is a rare cause of myelopathy, but patients with cancer have unique risk factors that may increase the incidence of spontaneous spinal cord hemorrhage. Patients with cancer are often maintained on anticoagulation for prophylaxis or for long-term treatment of a previous thrombosis. Patients on thrombotic prophylaxis may have up to a 22.5% increase in absolute risk of bleeding complications compared with untreated controls. Primary spinal cord tumors, metastasis, and previous radiation therapy also increase the risk of hemorrhage.

MR imaging findings in hematomyelia depend on the timing of imaging and the stage of the blood products. T1 hyperintense signal intensity is highly suggestive of hemorrhage. Lesions are commonly expansile and contain mixed blood products manifest by T2 hyperintense signal intensity and central or peripheral hypointense signal intensity (Fig 7). Susceptibility artifacts with signal-intensity dropout may be visible on gradient echo sequences, with blooming due to the paramagnetic effect of blood products. Diffusion-weighted images should be interpreted with caution, because the blood products may appear hyperintense and mimic acute infarction.

**Infection**

Spinal cord infection or myelitis is uncommon compared with other spinal infections that may involve the vertebrae, intervertebral disk, epidural space, meninges, or subarachnoid space. Patients with cancer are often immunocompromised or immunosuppressed by cancer treatments and are prone to infection from unusual causes such as fungi, as well as more common bacterial, viral, and parasitic etiologies. Spread is usually hematogenous, but contiguous extension from adjacent diskitis/osteomyelitis or meningitis may also occur.

MR imaging usually demonstrates enlargement of the spinal cord. While this finding is nonspecific and can mimic tumor, skip areas between regions of spinal cord

![Fig 2. Spinal cord metastasis from lung carcinoid. Sagittal and axial T2-weighted (A and B) and contrast T1-weighted (C and D) images show an expansile spinal cord metastasis at the T8 level. Isolated spinal cord metastasis is less common than direct invasion from overlying leptomeningeal metastases.](image1)

![Fig 3. Hemorrhagic spinal cord metastasis. Sagittal and axial T2-weighted (A and B) and contrast T1-weighted (C and D) images show a large expansile intramedullary metastasis in the cervical and thoracic cord. There is mild heterogeneous enhancement near the central T2 hypointense acute blood products. This child had widely disseminated stage IV high-risk metastatic neuroblastoma.](image2)
enlargement should strongly suggest an infectious rather than neoplastic etiology. Extensive T2 hyperintense edema may be present. Nodular enhancement can also mimic a neoplastic process, but enhancement is variable because diffuse, peripheral, and heterogeneous patterns may occur (Figs 8 and 9).

**Autoimmune**

**Paraneoplastic syndrome.** A paraneoplastic syndrome is a constellation of signs and symptoms that result from the presence of cancer within the body but are not the direct result of the tumor or a tumor metastasis. Several mecha-
nisms of paraneoplastic syndrome have been well described in the literature, but an immune-mediated response is most commonly implicated in paraneoplastic neurologic syndromes. Several autoantibodies have been identified; these may have a diagnostic role, though failure to detect an autoantibody does not exclude the diagnosis. The best studied antibodies include anti-Hu, anti-Yo, anti-Ri, and anti-Ma2, which precipitate a T-cell-mediated response.

Fig 7. Treatment-related hemorrhage. Sagittal T2-weighted (A) and contrast T1-weighted (B) images illustrate an expansile nonenhancing spinal cord lesion in the cervical and thoracic cord with T2 hypointense acute blood products. A sagittal image (C) from FDG PET/CT shows a striking decrease in metabolic activity at the lesion levels (compare with normal avid activity in the cerebellum and upper cervical cord). Postmortem examination revealed organizing necrosis and hemorrhage with underlying vacuolating and necrotic myelopathy in the anterior, lateral, and posterior columns. There was no tumor or infection. The patient underwent multiple courses of chemotherapy and radiation therapy for desmoplastic small round cell tumor of the parotid gland. Sclerotic hypointense bone metastases are present in C6 and T2.

Fig 8. Herpes simplex myelitis. Axial (A) and sagittal (B) T2-weighted images and contrast sagittal T1-weighted image (C) show a T2 hyperintense enhancing spinal cord lesion in the dorsal right cord at the C1–C2 level. This patient had undergone chemotherapy for chronic lymphocytic leukemia and developed leg weakness, paresthesias, and Lhermitte’s phenomenon. The patient was found to have disseminated herpes zoster infection, and improved with acyclovir.

Fig 9. Fungal leptomeningitis. Axial T2-weighted (A) and contrast axial (B) and sagittal (C) T1-weighted images reveal nodular intradural extramedullary nodular enhancing lesions. Mild T2 hyperintense spinal cord edema is present in A.
that attacks the nervous system, neuromuscular junction, and connective tissue.\textsuperscript{22,24} Clinical manifestations of paraneoplastic neurologic syndromes, accordingly, include cerebellar degeneration, brain stem encephalitis, myelopathy, and peripheral nerve palsy.\textsuperscript{22}

Paraneoplastic neurologic syndromes occur in \textless 1\% of patients with cancer but account for approximately 10\% of all nonmetastatic neurologic complications.\textsuperscript{24,25} Paraneoplastic syndromes are most commonly associated with small cell lung cancer, breast cancer, lymphoma, plasmacytoma, and gynecologic cancers. Symptoms may present before any cancer diagnosis in more than half of patients.\textsuperscript{24} Diagnosis of the primary neoplasm, however, is critical to appropriate treatment. Stabilization or, rarely, improvement in symptoms requires a 2-pronged approach, with treatment of the primary malignancy as well as immunosuppressive therapy.\textsuperscript{22,24} Disabilities are usually permanent and severe.

Spinal cord lesions from paraneoplastic neurologic syndromes often show nonspecific features. Symmetric elongated T2 hyperintensity with or without associated enhancement after contrast administration is usually found along white matter tracts or central gray matter (Fig 10).\textsuperscript{23,25} The MR imaging findings may occasionally appear normal, or the abnormal imaging findings may lag behind clinical manifestations.

**Metabolic**

**Vitamin B\textsubscript{12} deficiency.** Vitamin B\textsubscript{12} is an important component of blood cell biology, along with folic acid and ferritin. Active vitamin B\textsubscript{12} or holotranscobalamin only comprises 20\% of the total serum vitamin B\textsubscript{12}, with the remainder comprising inactive holohaptocorrin. Vitamin B\textsubscript{12} levels are affected by many different medications and chemotherapy agents\textsuperscript{26,27} and may decrease with different tumors such as acute leukemia.\textsuperscript{28} With limited storage capacity as a water-soluble vitamin, deficiency may lead to subacute combined degeneration with myelopathy of the cervical and upper thoracic cord. Demyelination and axonal loss in the dorsal and lateral cord manifest with paresthesias of the hands and feet, loss of proprioception and vibration sense, sensory ataxia, spasticity, and lower extremity weakness. A quarter of patients may present with Lhermitte’s sign, transient and self-limited electric shock-like sensations due to sensory axon damage in the dorsal columns. Lhermitte’s sign may occur with spinal cord tumors, bone marrow transplantation, chemotherapy, and radiation therapy as well as noncancer conditions such as multiple sclerosis.\textsuperscript{29}

MR imaging demonstrates T2 hyperintensity throughout the dorsal spinal cord that is symmetric and columnar, without associated expansion or abnormal enhancement (Fig 11). MR imaging findings often normalize with treatment.

**Treatment-Related**

**Radiation-induced damage and necrosis.** An increased incidence in radiation-induced damage of the spinal cord is anticipated due to the growing use of radiation therapy, despite advances in image-guided radiation therapy techniques. Radiation-induced changes may be classified as acute complications, early delayed complications, or late complications according to the interval between radiation therapy and the onset of injury.\textsuperscript{30} While the first 2 categories are reversible, the latter that usually develops ≥3 months after treatment is often progressive and irreversible.\textsuperscript{31}

Radiation-induced complications are poorly understood, and there is no consensus threshold dose above which radiation damage becomes much more likely.\textsuperscript{32,33} It is generally accepted, however, that radiation dose per fraction, interfraction interval, and total radiation dose are impor-
Fig 11. Chemotherapy-related myelitis mimicking subacute combined degeneration in breast cancer. Sagittal (A) and axial (B) T2-weighted images show small symmetric T2 hyperintense lesions in the dorsal columns of the mid- to distal thoracic cord. There is loss of the normal hypointense margin of the dorsal cord on the sagittal image, without expansion or enhancement. The patient had undergone multiple chemotherapy regimens (including ABI-007, bevacizumab, and capecitabine). Although the dorsal column distribution is typical for subacute combined degeneration from vitamin B₁₂ deficiency, she had normal vitamin B₁₂ and folic acid levels and no evidence of human immunodeficiency virus to suggest human immunodeficiency virus-associated vacuolar myelopathy.

Fig 12. Radiation therapy–induced changes. Axial T2-weighted (A) and contrast axial (B) and sagittal (C) T1-weighted images reveal a punctate enhancing lesion in the ventral right spinal cord at the C3 level 6 months after undergoing image-guided radiation therapy for a C3 chordoma. Note T1 hyperintense marrow changes in C2–C4 and a residual T2 hypointense enhancing chordoma in the right C2–3 neural foramen on the axial images. The patient remained asymptomatic from this new cord lesion, which spontaneously resolved in 7 months.

Fig 13. Radiation therapy–induced changes. Axial (A) and sagittal (B) T2-weighted and contrast sagittal (C) T1-weighted images show numerous T2 hyperintense nonenhancing lesions throughout the spinal cord. This child had undergone craniospinal radiation (2340 cGy, posterior fossa boost to 5580 cGy) for standard risk medulloblastoma 7 years ago. He had only mild symptoms of imbalance. The spinal cord lesions remained stable for >6 months, although the medulloblastoma progressed with diffuse leptomeningeal metastases.
Clinical manifestations of radiation damage to the spinal cord (e.g., acute weakness and sphincter dysfunction) can mimic those of spinal cord compression; a thorough understanding of a patient’s malignancy and radiation therapy histories and a high index of suspicion are important for guiding appropriate work-up and treatment.

MR imaging findings in acute spinal cord necrosis include an expansile ring-enhancing mass with edema and mass effect, which can be easily mistaken for tumor recurrence. T1 and T2 hyperintense postradiation therapy changes in the marrow of the adjacent vertebral bodies and posterior elements can be a clue to diagnosis (Figs 12 and 13). Up to half of patients who undergo spinal radiation therapy may develop chronic spinal cord atrophy within the radiation field.

CONCLUSIONS
Although rare, spinal cord lesions in patients with cancer may become more common with increasing cancer diagnoses and increasingly effective cancer treatments. The spectrum of spinal cord lesions in patients with cancer is broad and may differ in frequency compared with patients without cancer. Proper recognition of characteristic imaging features and key clinical signs and symptoms is necessary for determining the proper diagnosis and directing management and subsequent laboratory and/or pathologic investigations.

REFERENCES
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