Clinical Reasoning:

Left hemiparesis, ataxia, and optic neuritis in a child previously treated for pineoblastoma

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SECTION 1

A 13-year-old girl presented acutely with an episode of headache and signs of elevated intracranial pressure from a pineal gland tumor causing obstructive hydrocephalus. After an endoscopic third ventriculostomy and pineal gland biopsy, she was diagnosed with pineoblastoma. She was treated with surgical resection, craniospinal radiotherapy, and subsequent chemotherapy. Brain MRIs were performed every 3 months after surgery and remained stable with no new lesions or signs of residual tumor. However, a follow-up brain MRI performed 6 months after chemotherapy showed some small white matter nonenhancing lesions in supratentorial subcortical areas and within the cord at C7. She had no neurologic symptoms at that time and the white matter lesions improved over the next 3 months.

However, 10 months later, she developed acute weakness of her left arm and leg and blurry vision. Her neurologic examination confirmed left optic neuritis and moderate left hemiparesis. Routine laborato-

ries did not show any abnormalities. A new brain MRI showed new and enhancing lesions in the brain and spinal cord, including cerebellar hemispheres, left cerebellar peduncle, subcortical white matter, left optic nerve, and multilevel (thoracic and lumbar) intramedullary spinal cord lesions (figure, A and B). Some of them were round and had a complete ring-enhancing pattern. Additional MRI sequences such as diffusion-weighted imaging and perfusion-weighted imaging did not clarify the nature of the lesions (normal apparent diffusion coefficient [ADC] values and slightly increased perfusion in enhancing areas). Spectroscopy was normal. Magnetic resonance angiography demonstrated no flow-limiting stenosis. The patient and her family declined a lumbar puncture. She was empirically treated with high-dose IV steroids and her examination results returned to normal after 6–8 weeks.

Question for consideration:

1. What is your differential diagnosis regarding her second neurologic presentation?

GO TO SECTION 2

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(A) Brain MRI (T2 and T1+ gadolinium) after the second neurologic presentation. Many enhancing areas of signal abnormality are present in subcortical white matter, both cerebellar hemispheres, left medial cerebellar peduncle, lateral recesses of fourth ventricle, and left optic nerve. (B) Spinal cord MRI (T2 and T1+ gadolinium) at the same time. Multilevel (thoracic and lumbar) intramedullary spinal cord lesions at T3, T11-T12, lower cord, and conus. (C) Follow-up brain MRI (T2 and T1+ gadolinium) after a clinical relapse 4 months later. New enhancing region along the ventral aspect of the right hemi-pons and foci of nodular enhancement within the cerebellar vermis can be seen. Note improvement of the previous lesions.

SECTION 2

Pineoblastomas correspond to WHO grade IV tumors, being highly malignant and infiltrative, with a significant potential for dissemination. Although craniospinal irradiation has been shown to prevent leptomeningeal recurrence, pineoblastomas are known to have a poor prognosis.¹ Pineoblastomas tend to recur on the surfaces of the neural tissue rather than in the parenchyma and all the lesions identified in the patient were far from the pineal gland, although there are case reports of brain metastasis related to the manipulation of a pineoblastoma after stereotactic or endoscopic biopsy.² In this case, tumor recurrence was considered after the first MRI showing white matter changes, but the subsequent improvement without specific treatment is not expected in a malignant condition. Moreover, the pineoblastoma surgery was performed more than a year before the appearance of lesions on MRI, making it much less likely that the procedure caused dissemination of the malignancy.

On the other hand, radiation to the brain is known to produce late delayed changes in the white matter (from several months to years after exposure) and subsequent administration of chemotherapy may increase the risk of cerebral injury. A variety of patterns of radiation-induced injury have been described. The brain and spinal cord MRIs were not suggestive of radionecrosis, lacking signs of low ADC signal and hypoperfusion. Magnetic resonance spectroscopy did not show a decrease in NAA as is typically seen.³ Another form of delayed radiotoxicity called radiation-induced enhancement usually occurs

within the periventricular white matter and has different patterns of enhancement, although its clinical course and MRI findings are usually progressive and irreversible. Despite the fact that some cases of improvement or fluctuation have been reported, a complete resolution of the lesions is not expected.⁴

Considering that chemotherapeutic drugs administered to the patient might be potentially toxic to the brain and spinal cord, the possibility of chemotherapy-related neurotoxicity was also taken into consideration. However, in this setting neurotoxicity usually develops a few weeks after the chemotherapy and progresses, while the patient's symptoms started months after the end of the chemotherapy, rendering a toxic mechanism unlikely.⁵

Four months later, the patient developed 2 episodes of subacute left-sided weakness lasting more than a week. The second episode occurred during an upper respiratory infection. A new brain MRI showed several new enhancing lesions affecting the right pons, midbrain, and cerebellar vermis, with improvement of the previous lesions (figure, C), without new lesions in the spinal cord. A lumbar puncture was performed and showed 8 leukocytes (90% lymphocytes), normal protein and glucose levels, negative cultures, and 10 unique oligoclonal bands (OCBs) with elevated immunoglobulin G (IgG) index. Cytology was negative for malignant cells in the CSF. The patient improved with steroids but did not return to her baseline.

Question for consideration:

1. How has your differential diagnosis changed and what further investigations should be done?

GO TO SECTION 3

SECTION 3

This patient presented with relapsing-remitting symptoms due to brain, optic nerve, and spinal cord involvement. Follow-up MRIs have shown enhancing and nonenhancing white matter lesions in different areas of the CNS. Her differential diagnosis is broad⁶:

- Although neurologic symptoms can be the first presentation of some autoimmune systemic disorders, the patient did not have features suggestive of systemic lupus erythematosus, Behçet syndrome, or scleroderma. Extensive workup included negative autoantibodies (antinuclear antibodies, ds-DNA, antineutrophil cytoplasmic antibodies, anticardiolipin, smooth muscle antibodies, antiphospholipid, anti-Ro, anti-La, anti-aquaporin-4) and normal results for erythrocyte sedimentation rate, C-reactive protein, thyroid-stimulating hormone, C3, and C4. There was no evidence for sarcoidosis on complete neuro-ophthalmologic examination, 24-hour urine calcium levels, or serum or CSF angiotensin-converting enzyme. Sjögren syndrome was ruled out as the patient had no typical symptoms and autoantibodies were also negative.
- CNS vasculitis is known to produce fluctuating symptoms in a relapsing-remitting manner due to vascular compromise. However, this entity does not explain the optic nerve and spinal cord involvement of this patient and there were no features suggestive of CNS angiitis on the magnetic resonance angiography. Additionally, rapid progression is expected without immunosuppressive medications.
- CSF analysis was not compatible with a CNS infection. Infections such as tuberculosis, herpesvirus, or neurocysticercosis would not have improved without antimicrobial therapy. Even considering the possibility of an immunocompromised state related to the previous chemotherapy, atypical infections (such as fungal or toxoplasma) can be reasonably ruled out.
- CNS lymphomas can affect the brain, spinal cord, and optic nerves and MRI findings commonly improve with steroids. However, these neoplasms usually affect basal ganglia and leptomeninges, while posterior fossa involvement is very uncommon. On MRI, lymphomas can present as ring-enhancing lesions, but usually have low ADC values and decreased NAA, whereas the CSF often reveals an elevated protein concentration and a lymphocytic pleocytosis, features that were not present in the patient.
- Other causes of demyelination in children such as leukodystrophies (symmetric and progressive course) and mitochondrial diseases (multisystem involvement) are very unlikely.
- The patient did not meet criteria for a diagnosis of neuromyelitis optica and aquaporin-4 antibodies were negative.

Questions for consideration:

1. Could the development of multiple sclerosis (MS) be related to previous brain radiotherapy?
2. Would you recommend starting any long-term therapeutics?

GO TO SECTION 4

SECTION 4

The diagnosis of MS in both children and adults rests on the evidence of inflammatory demyelination in different regions of the CNS occurring over time. Considering the clinical course and the neuroimaging, the patient's presentation was typical of relapsing-remitting MS. The MRI showed more than 2 T2 lesions in many locations commonly affected in patients with MS (periventricular, juxtacortical, brainstem, and spinal cord), with clinically silent enhancing and nonenhancing lesions. Once autoimmune, infectious, and space-occupying lesions had been ruled out, this patient met the most current criteria for a diagnosis of pediatric MS.⁷ Furthermore, detection of OCBs and elevated IgG index in the CSF are characteristic features of MS, and an improvement with steroids is expected. Although both circumstances are not specific for MS, they support the diagnosis.⁸

This case brings to light an interesting question of whether or not radiotherapy puts a patient at risk for later developing MS. It has been reported that brain radiotoxicity is higher in patients with MS. The underlying mechanism remains unclear. It has been suggested that patients with MS could have more difficulty in repairing radiation-induced demyelination of the CNS, which makes them more vulnerable to brain radiotoxicity.⁹ On the other hand, radiotherapy could induce changes in the blood-brain barrier that may allow immune-mediated effects on the irradiated brain.¹⁰ This case conceivably represents an example of either new demyelinating disease triggered by preceding brain radiotherapy or preexisting disease brought to the clinical surface after radiotherapy.

Based on the fact that relapsing-remitting MS is a chronic disease and new relapses are expected, the patient was started on a first-line disease-modifying therapy (subcutaneous interferon- β -1a). She has not shown clinical or MRI evidence of disease activity during the first 6 months on this treatment. The most recent examination of the patient is consistent with sequelae of previous left optic neuritis and mild left hemiparesis.

AUTHOR CONTRIBUTIONS

Sara Vila-Bedmar, MD: drafting/revising the manuscript and design, acquisition of data, analysis and interpretation. Bardia Nourbakhsh, MD: critical revision of the manuscript. Susan Anzalone, MD: acquisition of data, analysis and interpretation. Emmanuelle Waubant, MD,

PhD: study concept and design, critical revision of the manuscript for important intellectual content, and supervision.

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