Acute ischemic stroke in the setting of neurosarcoidosis

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Introduction

Sarcoidosis is a systemic granulomatous disease of unknown etiology that most commonly affects the lungs and lymph nodes but can involve nearly any organ. When the central nervous system is affected, a condition known as neurosarcoidosis [1], it often presents with cranial neuropathies [2]. Among its less common but severe complications, acute ischemic stroke can occur due to mechanisms such as granulomatous vasculitis, vascular compression, or systemic hypercoagulability [3]. The overlap of symptoms with other neurological conditions, combined with its rarity, makes diagnosing stroke in neurosarcoidosis particularly challenging. Early identification and targeted treatment are crucial to minimizing long-term disability.

Case History/examination

A 59-year-old Caucasian man with a history of hypertension, polycythemia, central retinal artery occlusion, and optic neuritis presented with worsening painless right visual impairment and bilateral lower extremity (LE) weakness. His visual loss, which began a year ago, persisted despite a 5-day course of IV Solu-Medrol and 6 months of oral steroids. Additionally, he reported progressive weakness in both legs over 3 months, requiring increasing mobility aids, and new-onset urinary and fecal incontinence. On examination, his visual acuity was limited to "counting fingers" bilaterally, with proximal LE strength at 2/5 and distal LE strength at 3/5, alongside hyperreflexia.

Differential diagnosis, investigations and treatment

Subacute progressive extremities weakness with painless visual loss strongly suggests inflammatory and demyelinating disorders such as neuromyelitis optica spectrum disorder (NMOSD) or multiple sclerosis (MS), as well as autoimmune and paraneoplastic syndromes like systemic lupus erythematosus (SLE), sarcoidosis, or paraneoplastic neurological disorders. Other considerations include vascular causes (e.g., Susac syndrome, ischemic optic neuropathy), infectious etiologies (e.g., neurosyphilis, HIV), metabolic and toxic causes (e.g., vitamin B12 deficiency, methanol toxicity), and mitochondrial disorders (e.g., mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes, MELAS) Investigations included MRI of the brain and spine with contrast to evaluate for demyelination, CSF analysis for oligoclonal bands and inflammatory markers, serological tests for aquaporin-4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG) antibodies and autoimmune panels (ANA, dsDNA, ACE, paraneoplastic antibodies)

Cerebrospinal fluid analysis revealed significantly elevated protein and decreased glucose levels, no white blood cells, positive oligoclonal bands, mild elevation in lactate dehydrogenase, and negative CSF cultures for various pathogens. Serum ACE levels were within normal limits, ESR levels were not elevated, ANA, dsDNA were negative and screening tests for HIV, syphilis, tuberculosis, and Coccidioides were negative. Anti- AQP4 and anti-MOG antibodies were also negative.

MRI Brain with and without contrast [Figure 1,2] showed leptomeningeal enhancements within the intraorbital portion of the right optic nerve, in the left hypothalamic region, along the left superior cerebellar

hemisphere, along the surface of the cervicomedullary junction, and along the anterior surface of the pons, without evidence of abnormal enhancement in the brain parenchyma. MRI C-T-L spine with and without contrast [Figure 3,4] revealed multifocal nodular leptomeningeal enhancements along the surface of the cervical cord, thoracic cord, and along the cauda equina nerve roots, with suspected intramedullary enhancement associated with leptomeningeal enhancing lesions at the C6, C7, T1, T4, T7-8, T11, and T12 levels.

The patient was treated with 5 days of IVIG at 0.4 g/kg/day due to a diagnosis of possible neurosarcoidosis, but his clinical status remained unchanged after treatment. He was discharged to a rehabilitation facility.

Conclusion and Results (Outcome and follow-up)

Six weeks later, the patient presented to the hospital with the acute onset of left facial droop and worsening left-sided weakness. His vison by that time had progressed to almost complete visual loss. Neurological examination during this admission "hand motion" perception in both eyes, left facial droop, decreased left facial sensations, and spasticity in the left upper extremity (UE), with 0/5 power proximally and 1/5 distally, along with 3+ reflexes and a positive Hoffman sign. The right UE exhibited normal tone and 4/5 power. The left LE demonstrated increased tone compared to the right LE, and both LE weakness had progressed to grade 0 (no discernible contractions). Deep tendon reflexes were brisk bilaterally, with an absent ankle jerk and a negative Babinski sign. Sensations were absent in the bilateral LE and left UE. Code stroke was activated.

Non-contrast CT of the head and CT angiography of the head and neck showed no significant vessel occlusion, and the patient was not a candidate for IV thrombolysis due to being outside the treatment window. Stroke workup revealed an HbA1c of 5.1, and the lipid profile was normal. Cardiac telemetry showed no abnormal rhythm, and a transthoracic echocardiogram revealed normal left ventricular ejection fraction without evidence of a right-to-left shunt. MRI of the brain confirmed a new ischemic stroke with restricted diffusion in the right posterior limb of the internal capsule and adjacent thalamus. Additionally, new periventricular enhancement was observed in the right inferior lentiform nucleus, alongside unchanged corticomedullary junction T2 hyperintensities and nodular leptomeningeal enhancement at the brain base and brainstem, raising concerns for disease progression [Figure 5]. MRI of the cervical, thoracic, and lumbar spine remained stable with multiple areas of nodular leptomeningeal enhancement consistent with prior imaging.

As part of the workup for a potential diagnosis of neurosarcoidosis, a CT of the chest [Figure 6] revealed mediastinal lymphadenopathy and right hilar lymphadenopathy, raising the possibility of neoplastic disease or secondary sarcoidosis. Following a pulmonology consultation, bronchoscopy and endobronchial ultrasound-guided biopsy were performed, which showed reactive bronchial cells mixed with inflammatory cells, including histiocytes, but no definitive granulomas. Negative cytology did not entirely rule out malignancy or granulomatous disease. Additional testing, including an interferon-γ release assay for tuberculosis and an acid-fast bacilli (AFB) stain, was negative.

The patient was started on aspirin and a statin as a secondary prevention measure for this likely small vessel stroke. He was also started on high-dose methylprednisolone therapy (1 g/day), which led to improvements in vision, with return of color perceptions but still "hand motion" in acuity after two doses. A five-days course was completed. Upon discharge to an inpatient rehabilitation facility, the patient was prescribed prednisone 50 mg twice daily and mycophenolate mofetil 500 mg twice daily.

At the 3-month follow-up, there was subjectively increased leg strength, but no further improvement in vision. The patient continued to require a wheelchair for ambulation and experienced persistent loss of bowel and bladder function. MRI of the brain showed interval resolution of medullary involvement but revealed new leptomeningeal enhancement along the cavernous sinus. Consequently, a TNF-alpha inhibitor was initiated, with plans for follow-up in one month.

Discussion

We present a case of acute ischemic stroke associated with neurosarcoidosis [4]. The stroke's location pointed to a small-vessel disease mechanism. Although the patient had risk factors such as hypertension and poly-

cythemia, the close proximity of the ischemic lesions to areas of previous leptomeningeal enhancement on MRI supports the hypothesis that the ischemic events were secondary to neurosarcoidosis.

Over the past decade, numerous case reports have described acute ischemic stroke as a rare but important complication of neurosarcoidosis [5,6]. Small-vessel vasculitis is the most common ischemic subtype in these cases, with pontine perforating vessels and lenticulostriate arteries frequently affected. These infarcts tend to be small, often involving the basal ganglia, thalamus, and brainstem [8], while rostral supratentorial vessels are less frequently involved [5]. Post-mortem studies indicate that granulomatous vasculitis primarily targets small vessels, particularly perforating arteries [3,8]. Veins, especially in the periventricular region, may also be involved [9]. Histological findings often show granulomas extending along Virchow-Robin spaces in a perivascular distribution, suggesting mechanisms such as vessel compression or direct arterial wall involvement as contributors to ischemia [10,11].

The mechanisms underlying stroke in neurosarcoidosis are diverse and multifactorial. While large-vessel strokes are rare, they may result from inflammation-induced thrombosis, characterized by non-circumferential vessel wall involvement, or compression from adjacent granulomatous lesions [7]. A Moyamoya-like vasculopathy, unilateral or bilateral, has also been reported [12]. Cardioembolic strokes secondary to cardiac sarcoidosis are less frequent [13]. Hemorrhagic lesions, although uncommon, are clinically significant and may arise from inflammatory vascular damage or anticoagulant use. In some cases, extensive thrombosis involving dual sinuses causes venous outflow obstruction, further contributing to ischemic or hemorrhagic complications. These findings underscore the complex interplay of vascular and inflammatory processes in stroke associated with neurosarcoidosis.

The treatment of ischemic stroke in neurosarcoidosis consists of two key components: managing the stroke itself and addressing the underlying sarcoidosis. For stroke management, antiplatelet monotherapy [14] and lipid-lowering agents [15] are commonly employed for secondary stroke prevention. In treating the inflammation associated with neurosarcoidosis, glucocorticoids remain the first-line therapy, often yielding rapid improvements [16]. Severe cases may require pulse-dose intravenous methylprednisolone (1000 mg daily for 3–5 days), followed by maintenance therapy with oral prednisone (60–80 mg daily). To reduce the risk of stroke recurrence, long-term maintenance with steroid-sparing immunosuppressants is often necessary [17, 18]. Monotherapy with agents such as methotrexate or mycophenolate mofetil has generally been insufficient to achieve remission, with most patients requiring at least two lines of immunosuppression. TNF-alpha inhibitors, particularly infliximab, have demonstrated the highest efficacy in achieving remission. However, infliximab use is associated with challenges, including side effects such as chondritis, infusion reactions related to anti-drug antibodies, and potential drug discontinuation. Relapses have also been reported in patients tapered off infliximab, underscoring the complexity of treatment.

Key clinical message Neurosarcoidosis can present as ischemic stroke through small-vessel vasculitis, requiring early recognition and targeted immunosuppressive therapy to prevent severe disability.

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Patient Consent Statement

Informed consent was obtained from all individual patients included in the study. The patients provided written consent for the use of their clinical data and any associated images for research and publication purposes. Patient confidentiality has been maintained in accordance with applicable ethical guidelines, and no identifying information is included in the manuscript.

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Figure 1a and 1b: Coronal view of T1-weighted MRI of the brain with contrast demonstrates subtle asymmetric volume loss in the intraorbital portion of the left optic nerve, as well as

subtle abnormal enhancement within the intraorbital portion of the right optic nerve [1a]. There is also subtle abnormal leptomeningeal enhancement in the left hypothalamic region, as well as along the surface of the cervicomedullary junction [1b].

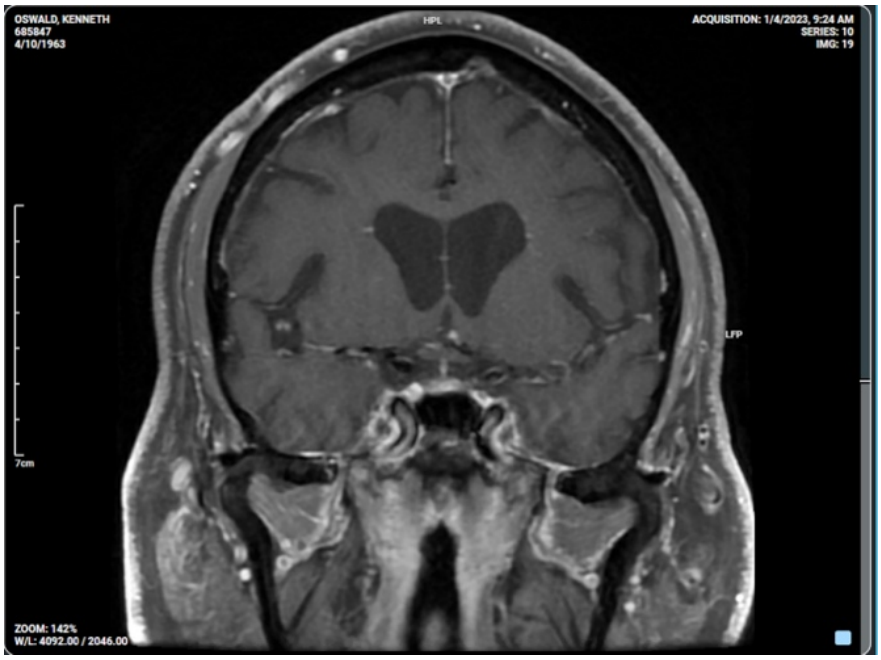
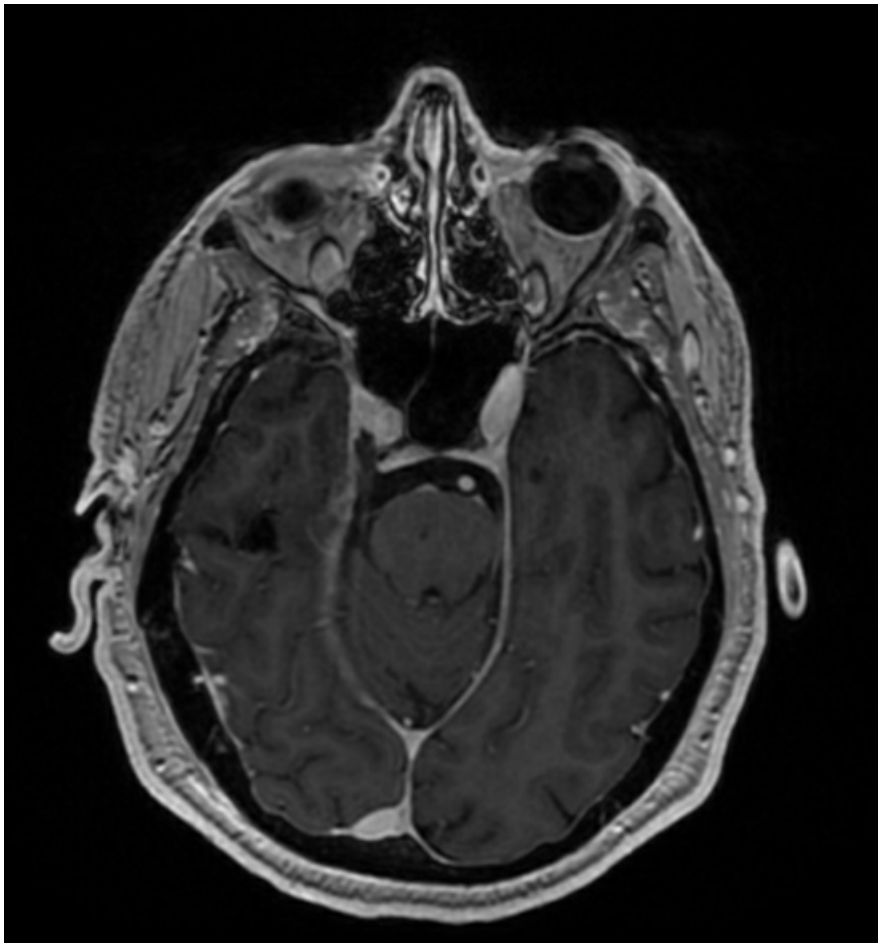


Figure 1c and 1d: Axial view of T1-weighted MRI of the brain with contrast demonstrating subtle abnormal leptomeningeal enhancement along the left superior cerebellar hemisphere [1c] and the anterior surface of the pons [1d].



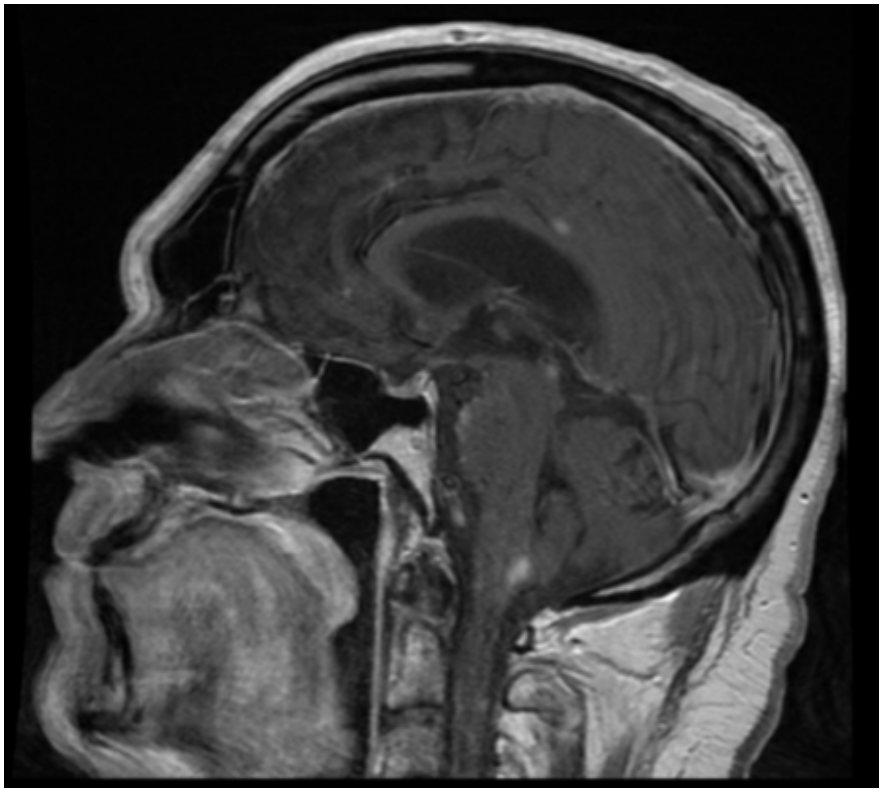


Figure 2a-c: Sagittal [2a] and axial views [2b] of T1-weighted MRI of the brain with contrast showing contrast enhancement at the right medial pericallosal, tectal, anterior pontine, and posterior cervicomedullary junctions, as well as at the left superior cerebellum [2c].

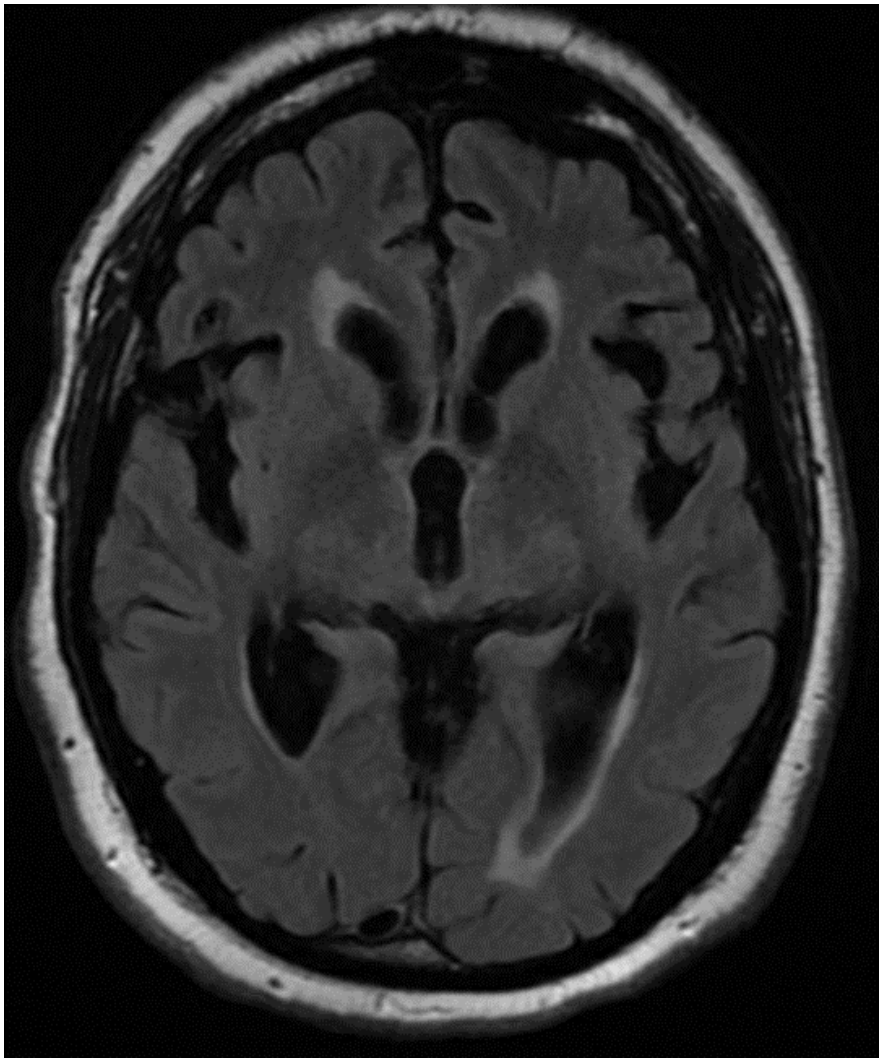


Figure 2d: Axial FLAIR sequence MRI of the brain showing mild dilation of the third ventricle and nonspecific white matter hyperintensities in the subcortical areas.

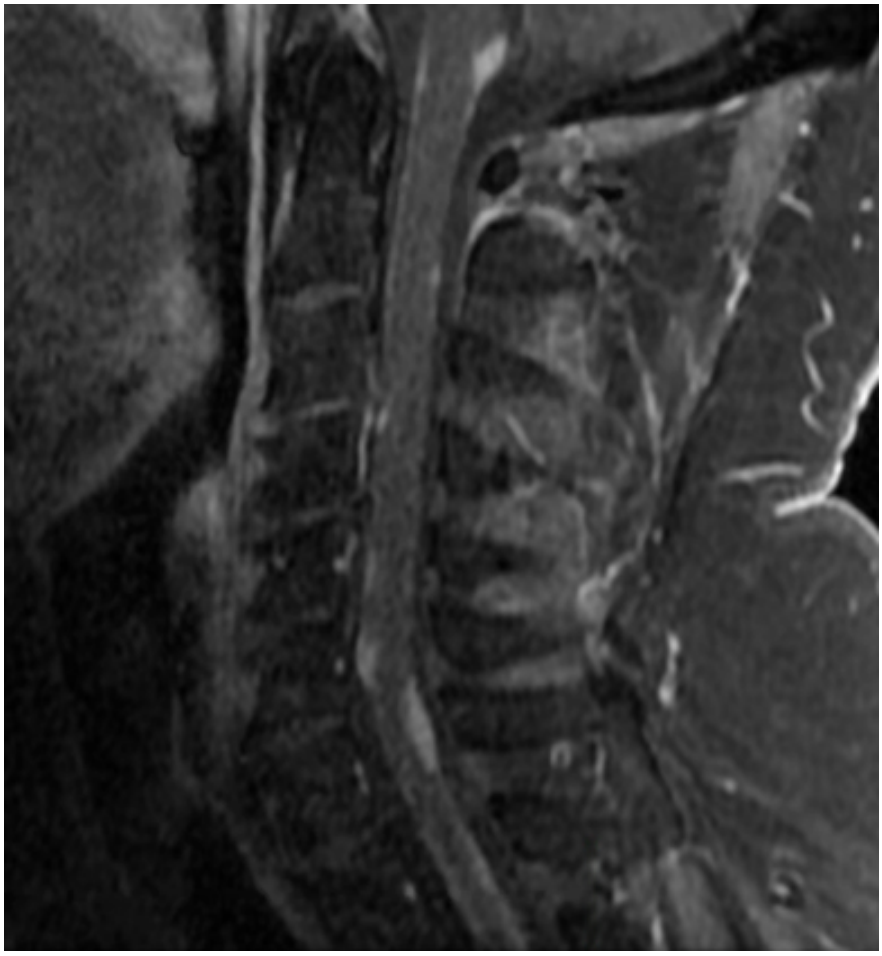


Figure 3a-c: Sagittal [3a] and axial T1 sequence MRI of the C-spine with contrast showing enhancement in the right cervicomedullary junction[3b], as well as right anterior C6 and posterior C6-C7 spinal cord levels[3c].

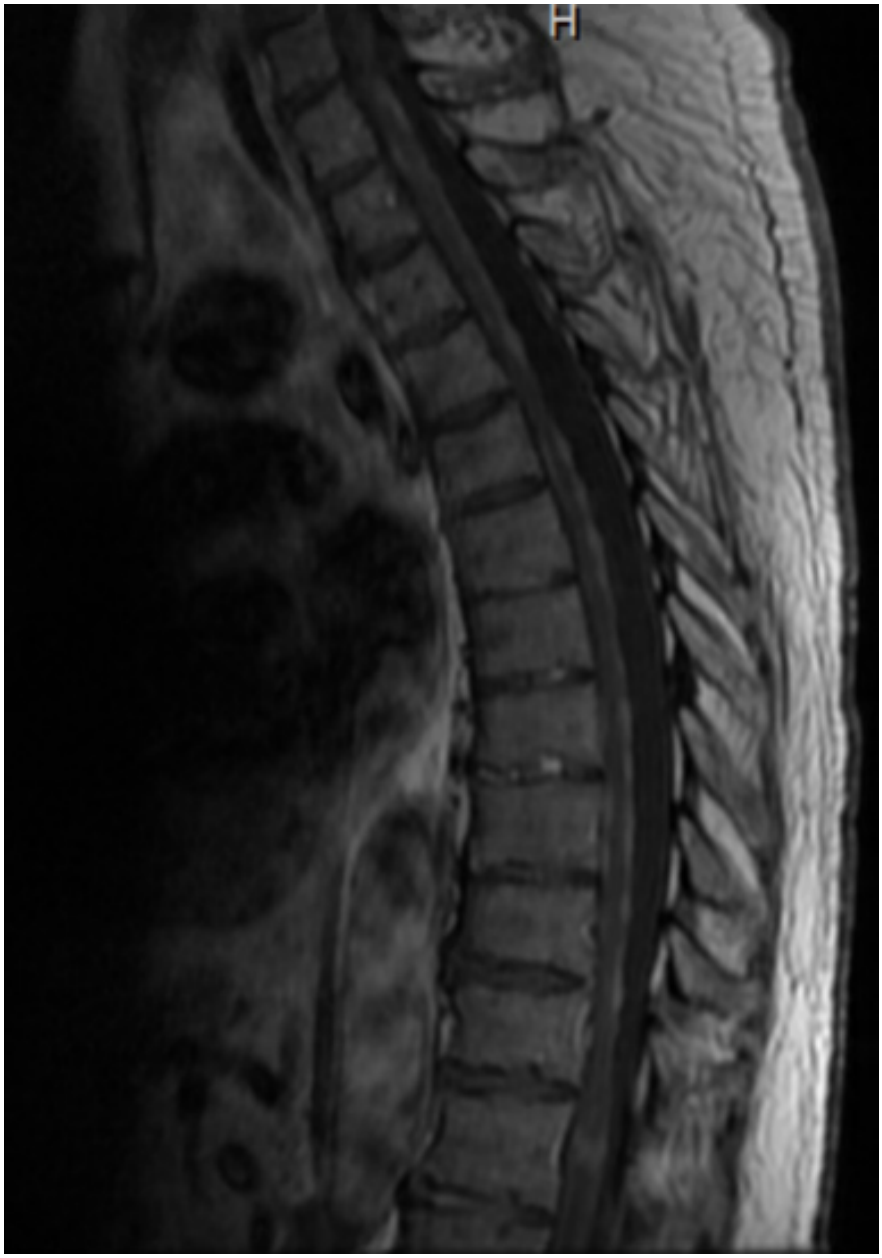


Figure 4a and 4b : T1-weighted image with contrast in sagittal view showing patchy contrast enhancements at T3-12 levels [4a] and multifocal nodular leptomeningeal enhancement along the spinal cord and cauda equina nerve roots [4b].

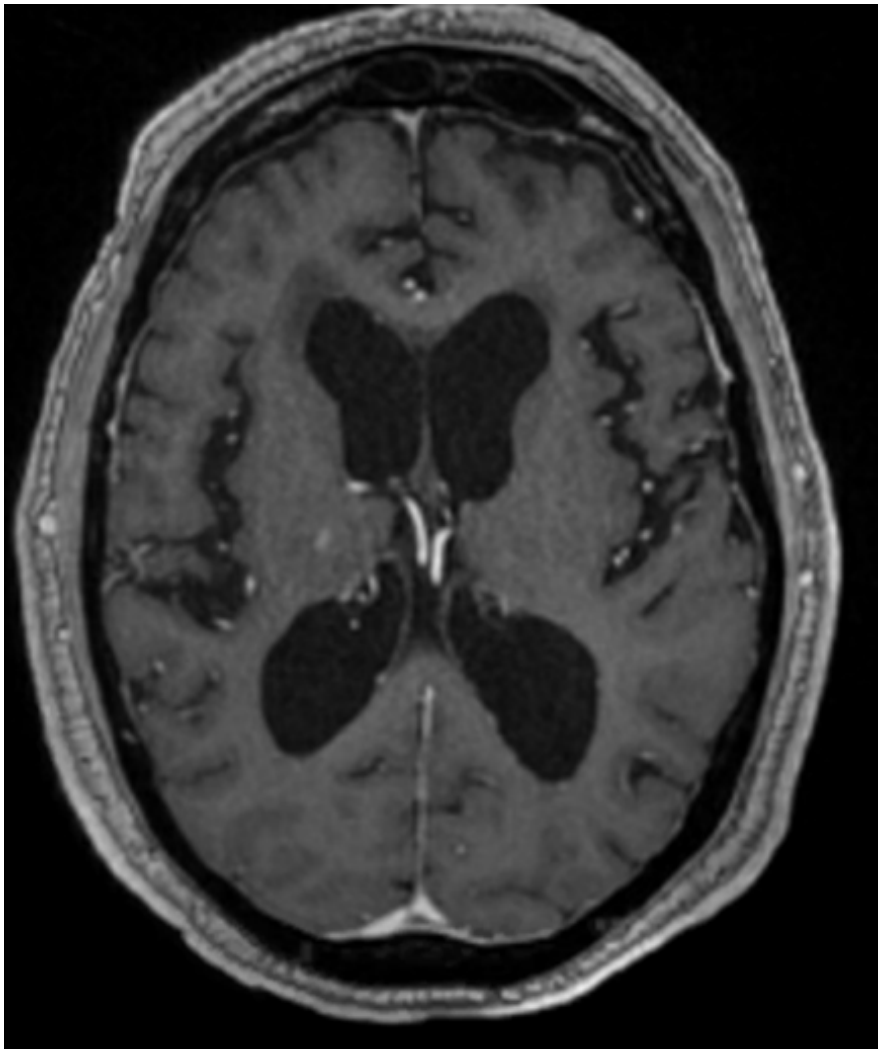


Figure 5a-c: DWI [5a], ADC [5b], and T2-FLAIR [5c] sequences without contrast revealed restricted diffusion in the posterior limb of the internal capsule. There was a faintly increased ADC signal and very faint contrast enhancement observed on the T1-weighted image with contrast.

Figure 5d-f: T1-weighted image with contrast in axial showing faint enhancement of right oculomotor nerve[5d] and right midbrain [5e] as well as sagittal [5f] views.

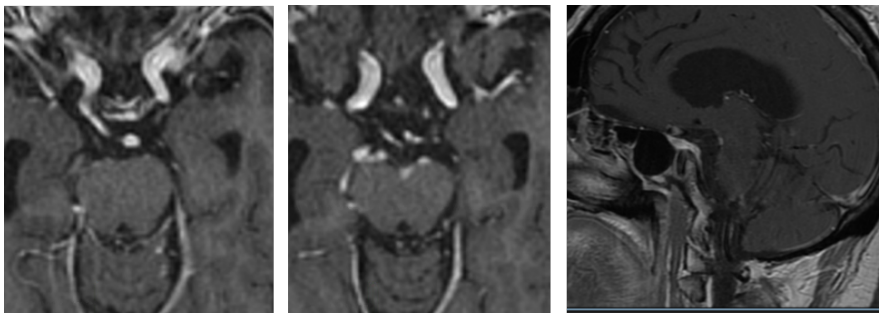


Figure 6: CT chest with contrast in axial view demonstrated Mediastinal lymphadenopathy and right hilar lymphadenopathy.