View Point

Neurosarcoidosis: The Pan-Neurology Disease

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Abstract

Neurosarcoidosis (NS) is a protean illness with multiple clinical and radiological presentations giving it the moniker of "a chameleon" or the great mimic. NS can present as a wide spectrum of neurological syndromes localizing both to the central and peripheral nervous systems. The absence of a diagnostic serum test makes it difficult to diagnose with certainty and remains largely a histopathological diagnosis and one of exclusion. A high index of suspicion should be there in suspecting NS, and it should always be excluded among patients presenting with acute to subacute neurological deficits.

Keywords: ACE, granuloma, neurosarcoidosis, NS

Neurosarcoidosis (NS) is a protean illness with multiple clinical and radiological presentations giving it the moniker of "a chameleon" or the great mimic.[1] Sarcoidosis is an immune-mediated multi-system disorder that can involve any part of the neuroaxis. It is characterized by granulomatous inflammation of the affected region, with the presence of non- or minimally necrotizing granulomas.[2] The most common organs involved are the lungs (90%), eyes, and skin.[3] NS refers to the involvement of the nervous system (central, peripheral, or both) by sarcoidosis and reportedly occurs in 5–10% cases.[4] Neurologic symptoms are the presenting complaints in 50–70% of NS patients.[5] Approximately, 30% of patients have systemic disease at the time of NS presentation, whereas nearly 85% of patients eventually develop systemic manifestations.[5] Most individuals with systemic sarcoidosis who progress to NS develop neurologic symptoms within 2 years of symptom onset. Around 10–20% of sarcoidosis patients have neurologic impairment alone (isolated NS).[6] The diagnosis of NS is established on the basis of a recognizable clinical syndrome with supportive laboratory and imaging findings and the exclusion of other potential causes.[1] The common neurological presentations include cranial or peripheral neuropathy, pituitary/hypothalamic involvement, and central nervous system involvement through pachymeningitis, leptomeningitis, or vasculitis. The 2018 Consortium Consensus Criteria for the diagnosis of NS[7] require the presence of histopathological evidence of sarcoidosis to make a definite (biopsy from neural tissue) or probable (biopsy from extra-neural tissue) neurosarcoidosis.

No specific or sensitive serum tests exist for sarcoidosis till date, and the primary role of such testing is to exclude alternative etiologies. Serum angiotensin-converting enzyme (ACE) levels are increased in approximately 60% of pulmonary sarcoidosis patients, but are not sensitive or specific.[8] Chest X-ray may show evidence of mediastinal lymphadenopathy in 50% of patients at the time of NS presentation.[9] If normal, either a contrast-enhanced computed tomography (CECT) of the chest and abdomen or whole-body positron emission tomography (PET) can be done to look for metabolically active lymph nodes.[10] These can thereafter be biopsied to achieve a histopathological diagnosis of sarcoidosis. A cerebrospinal fluid (CSF) examination is done to look for evidence of intrathecal inflammation and rule out alternative pathologies. Most patients with NS have mild to moderate lymphocytic pleocytosis with increased protein. Occasionally, hypoglycorrhachia can be present (especially with leptomeningitis).[1] CSF ACE levels are neither sensitive nor specific for diagnosing NS.[11]

Neurosarcoidosis is usually responsive to treatment with corticosteroids, and the treatment aims to prevent or minimize organ damage caused by sarcoidosis-associated granulomatous inflammation.[1] The usual management plan involved pulse methylprednisolone therapy followed by a slow oral steroid taper with concomitant steroid-sparing immunosuppressants like azathioprine, mycophenolate mofetil, or methotrexate. More severe presentations can be treated with rituximab or cyclophosphamide. Infliximab (tumor necrosis factor alpha inhibitor) has been found beneficial in non-responders to conventional immunosuppressants.[12]

We describe the neurologic manifestations of this great mimic through a series of cases with different parts of the neuroaxis involved [Table 1].

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Table 1: Patient details

Sn. No.	Clinical Details	Investigations	Management
1	28/M, progressive left lower limb (proximal and distal) weakness with sensory loss x 1.5 months Weight loss Night sweats No spinal tenderness or deformity Power—3/5 in left lower limb on MRC scale DTRs—brisk in all four limbs Plantar-bilateral flexor Sensory—50% decrease of all sensory modalities below L2 on left side	MRI spine: [Figure 1] Complete blood count (CBC), liver and renal function tests (LFT/RFT), thyroid function tests (TFT), glycosylated hemoglobin, lipid profile, vitamin B12, and folate: normal Serum and urinary calcium: normal HIV, HBsAg, anti-HCV: negative S. NMO/MOG: neg ANA/ENA (by indirect immunofluorescence [IIF]): negative S. ACE: 42 mg/dl (normal ≤65 mg/dl) CSF – nil cells, protein: 80 mg/dl, sugar : 60 mg/dl (RBS-104 mg/dl) Gene Xpert for TB: negative VDRL: negative Malignant cytology: negative India Ink: negative OCB: negative Cultures: negative Whole-body PET: metabolically active right supraclavicular, mediastinal, celiac, and left para-aortic lymph nodes with discrete lung nodule in right upper lung lobe [Figure 2] EBUS guided transbronchial biopsy: Few discrete epitheloid cell granulomas with a cuff of chronic inflammation along with giant cells. No necrosis seen	Neurosarcodisosis presenting as *Non-compressive myelopathy* Pulse steroids followed by tapering oral steroids with methotrexate (25 mg/week). Complete symptom resolution at 6 month follow-up with repeat imaging showing near-complete resolution of spinal cord lesions
2	29/F, recurrent LMN type facial weakness (unilateral) x 4 years, responsive to steroids Last episode: 1 week back, left LMN facial weakness No constitutional symptoms Left LMN facial weakness with decreased taste sensation from the left side of the tongue No hyperacusis	MRI brain: [Supplementary Figure 1] CBC, LFT, RFT, TFT, B12, folate, glycosylated hemoglobin: normal Serum and urinary calcium: normal HIV, HBsAg, anti-HCV: negative ANA/ENA (by IIF): negative S. ACE: 41 mg/dl (normal ≤65 mg/dl) Whole-body PET: FDG avid conglomerated and discrete para-esophageal, bilateral upper paratracheal, prevascular, subcarinal, and bilateral hilar lymph nodes EBUS guided hilar lymph node biopsy: multiple tissue cores comprising numerous epitheloid cell granulomas with scant necrosis. Gene Xpert for AFB: negative	Neurosarcodisosis presenting as *cranial nerve palsy* Pulse steroids followed by tapering oral steroids with weight-based azathioprine. Improved completely and is free from subsequent relapses 3 years into the treatment
3	36/F, progressive lower limb weakness (distal followed by proximal) x 8 months Progressive upper limb weakness (proximal followed by distal) x 6 months No sensory loss, bowel or bladder involvement No wasting or fasciculation No cutaneous markers Bifacial weakness Power—3/5 in all four limbs on MRC scale Hand grip—50% bilaterally Normal reflexes Sensory—normal	CBC, LFT, RFT, TFT, B12, folate, glycosylated hemoglobin: normal CPK: 43 Serum and urinary calcium: normal HIV, HBsAg, anti-HCV: negative ANA/ENA (by IIF): negative NCS: normal EMG: myopathic pattern S. ACE: 40 mg/dl (normal ≤65 mg/dl) Muscle biopsy: maintained fascicular architecture with mild variation in fiber size, inflammation present, occasional granulomas seen in the endomysium and surrounding adipose tissue. MAC deposition in the endomysial blood vessels, with no necrosis. CD4 and CD20 negative[Supplementary Figure 2]	Neurosarcodisosis presenting as *Myopathy (fascioscapulo-humeral phenotype)* Pulse steroids followed by tapering oral steroids with weight-based azathioprine Improved to 5/5 power in all affected muscles at 3 months follow-up. She has symptom and relapse free at last follow-up, 2 years into treatment.
4	42/M, progressive right upper and lower limb weakness and numbness × 1.5 months with spastic dysarthria Spasticity of right upper and lower limbs Power—0/5 in right upper limb, 3/5 in right lower limb on MRC scale	MRI Brain: [Figure 3] CBC, LFT, RFT, TFT, B12, folate, glycosylated hemoglobin: normal Serum and urinary calcium: normal HIV, HBsAg, anti-HCV: negative ANA/ENA (by IIF): negative	Neurosarcodisosis presenting as *tumefactive demyelination* Plasma exchange with pulse steroids followed by tapering oral steroids with azathioprine. Improved to near baseline status

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Table 1: Contd...

Sn. No.	Clinical Details	Investigations	Management
	DTRs—brisk on the right side with extensor plantar 30% decreased sensations on right side	NMO/MOG: negative S. ACE: 32 mg/dl (normal ≤65 mg/dl) AFP, CEA, CA-125, CA-19-9: negative CSF—five cells (L100), protein: 112 mg/dl, sugar : 56 mg/dl (RBS-106 mg/dl) Gene Xpert for TB: negative VDRL: negative Malignant cytology: negative India Ink: negative OCB: negative Cultures: negative CT chest and abdomen: diffuse ground glass opacities with inter and intralobular septal thickening resulting in crazy paving appearance in bilateral lung fields along with peri-bronchial thickening EBUS guided transbronchial lung biopsy: respiratory mucosa lined tissue and lung parenchyma with ill formed epitheloid granuloma with scant central fibrinous necrosis. Giant cells containing Schaumann bodies present [Figure 4].	6 months into treatment and is symptom and relapse free 2 years into treatment. Pulse steroids followed by tapering oral steroids with weight-based azathioprine
5	51/M, progressively increasing binocular horizontal diplopia with right eye ptosis × 2 months Painful loss of vision from the right eye × 2 weeks Right eye visual acuity—6/60 Disc edema present in right eye Right eye pupil dilated with RAPD Right third, fourth, and sixth cranial nerve palsies	MRI Brain: [Supplementary Figure 3] CBC, LFT, RFT, TFT, B12, folate, and glycosylated hemoglobin: normal Serum and urinary calcium: normal HIV, HBsAg, anti-HCV: negative ANA/ENA (by IIF): negative NMO/MOG: negative S. ACE: 56 mg/dl (normal ≤65 mg/dl) CSF—five cells (L100), protein: 112 mg/dl, sugar : 56 mg/dl (RBS-106 mg/dl) Gene Xpert for TB: negative VDRL: negative Malignant cytology: negative India Ink: negative OCB: negative Cultures: negative Whole-body PET: FDG avid conglomerated and discrete para-esophageal, bilateral upper paratracheal, prevascular, subcarinal, and bilateral hilar lymph nodes EBUS guided hilar lymph node biopsy: multiple tissue cores comprising numerous epitheloid cell granulomas with scant necrosis. Gene Xpert for AFB: negative	Neurosarcodisosis presenting as *hypertrophic pachymeningits* Pulse steroids followed by tapering oral steroids with weight-based mycophenolate mofetil. Complete clinical and radiological resolution at 3 months treatment with no complaints or relapse at last follow-up.

*ACE=Angiotensin converting enzyme, AFB=Acid fast bacilli, AFP=alpha fetoprotein, ANA=anti-nuclear antibody, CEA=carcinoembryonic antigen, CSF=cerebrospinal fluid, CT=computed tomography, DTR=deep tendon reflexes, EBUS=endobronchial ultrasound, EMG=electromyography, ENA=extractable nuclear antigen, F=female, HBsAg=hepatitis B surface antigen, HCV=hepatitis C virus, HIV=human immunodeficiency virus, LMN=lower motor neuron, M=male, MAC=membrane attack complex, MOG=myelin oligodendrocyte glycoprotein, MRC=medical research council, MRI=magnetic resonance imaging, NCS=nerve conduction study, NMO=neuromyelitis optica, OCB=oligoclonal bands, PET=positron emission tomography, RAPD=relative afferent pupillary defect, RBS=random blood sugar, VDRL=venereal disease research laboratory

Myelopathy

Spinal cord involvement occurs in 20–25% of NS patients.[4] It can happen via the leptomeningeal or extra-dural spread, parenchymal infiltration, or extrinsic cord compression by the involvement of extraspinal tissues.[1] The characteristic imaging findings are leptomeningeal enhancement (nodular or linear) along with intraparenchymal T2 hyperintensity.[13] Four common patterns of involvement are seen: longitudinally extensive transverse myelitis (~50%, most common), short tumefactive, meningoradiculitis, and anterior myelitis with disc degeneration. The cervical and thoracic cord are most commonly involved. Clues to the diagnosis include the trident sign or subpial enhancement ≥ 2 spinal segments.[14] Our patient (case 1) had all characteristic findings: LETM with subpial gadolinium enhancement.

Cranial nerve palsies

They are among the most typical manifestations of NS and can occur because of granulomatous infiltration of the nuclei, fascicle, or cranial nerve.[1] Cranial nerve involvement can be isolated or multiple and usually follow a subacute course.

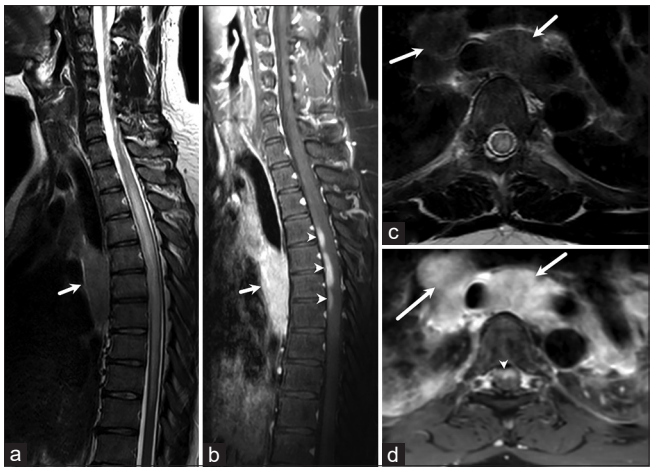

Figure 1: Sagittal (a) and axial (c) T2-WIs show long segment intramedullary hyperintensity and swelling of dorsal cord with enlarged isointense posterior mediastinal lymph nodes (arrows in a and c). Focal nodular enhancements (arrowheads in b and d) are seen in the ventral cord at D2–D4 levels with enhancing lymph nodes in the posterior mediastinum (arrows in b and d)

The most commonly involved nerves include facial, optic, and vestibulocochlear.[15] Facial nerve palsies which are recurrent or bilateral should raise suspicion for NS. Similarly, bilateral optic neuritis, perineuritis, or optic neuritis involving the optic chiasm should prompt consideration for NS (apart from neuromyelitis optica spectrum disorder and myelin oligodendrocyte glycoprotein-associated disorders). NS may also be associated with sellar/hypothalamic involvement due to their anatomical proximity to the optic chiasm.[16] MRI brain usually reveals contrast enhancement of the affected nerve with/without nearby leptomeningeal enhancement.[15] Our patient (case 2) revealed enhancement of the left facial nerve.

Myopathy

NS presenting as myopathy is among its rarer presentations and is seen in 10% cases. These can present in a subacute or chronic pattern and may have a concomitant neurogenic involvement. Our patient (case 3) presented had a subacute, inflammatory myositis type presentation but with normal creatinine phosphokinase (CPK) levels. The diagnosis of NS was established based on the muscle biopsy revealing non-caseating granulomas. The patient responded very well to treatment, and the case highlights the need to consider NS among the differentials in inflammatory myositis-like presentations, especially with normal or mildly elevated CPK values.[17]

Tumefactive demyelination

Parenchymal involvement leading to focal neurological deficits, seizures, or encephalopathy can be encountered in approximately 50% of NS patients. This occurs because of either meningeal spread or vascular involvement by the disease process.[1] The presentation as tumefactive demyelinating lesions is rare and seen in 5–10% cases.[1]

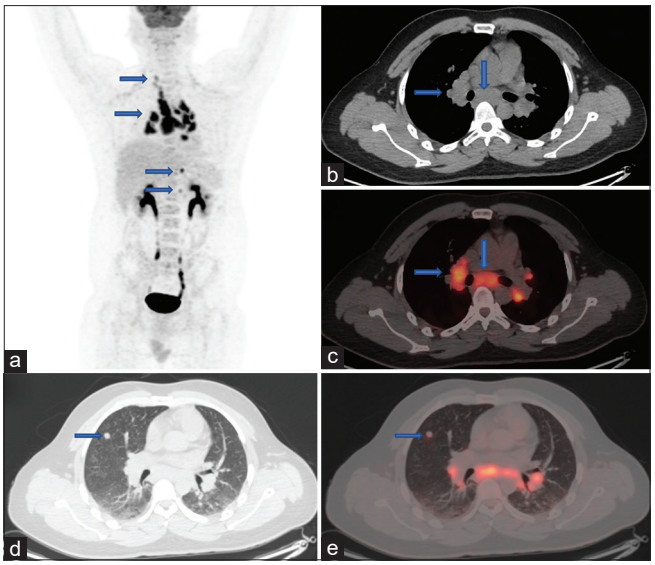

Figure 2: (a) Maximum intensity projection (MIP) image of a 29-year-old male with metabolically active lymph nodes (arrows) in the right supraclavicular, mediastinal, celiac, and left para-aortic locations. Axial CT image (b) of the same patient showing multiple enlarged mediastinal lymph nodes (arrows) with increased metabolic activity on axial fused PET-CT image (c). Axial CT image in lung window (d) showing a well-defined rounded nodule in right lung upper lobe (arrow) with increased metabolic activity on axial fused PET-CT image (e)

Our patient (case 4) was presented with progressive focal neurological deficits and was treated aggressively with pulse steroids along with plasma exchange with good functional recovery. Thereafter, he was continued on weight-based azathioprine and repeat imaging showed near-complete resolution of the demyelinating lesion.

Meningitis

NS can present as either lepto- or pachymeningitis, manifesting as a subacute syndrome of headache and focal neurologic deficits. Presentation as pachymeningitis is exceedingly rare, and other causes of hypertrophic pachymeningitis should be ruled out.[1] Our patient (case 5) was presented with an orbital apex syndrome because of hypertrophic pachymeningitis involving the cavernous sinus extending into the orbital apex through the superior orbital fissure.

NS can therefore present as a wide spectrum of neurological syndromes localizing both to the central and peripheral nervous systems. The absence of a diagnostic serum test makes it difficult to diagnose with certainty and remains largely a histopathological diagnosis and one of exclusion. None of our patients had an elevated serum ACE level or abnormalities of calcium (serum or urine testing), highlighting the need for a more specific and sensitive test to diagnose neurosarcoidosis non-invasively. Chest X-ray is a good screening tool that can reveal mediastinal lymphadenopathy but is not always present. Although increased interleukin (IL)-6, soluble IL-2 receptor levels, and CD4/CD8 ratio have been described in NS,[18] these tests are not yet widely available. All our patients were

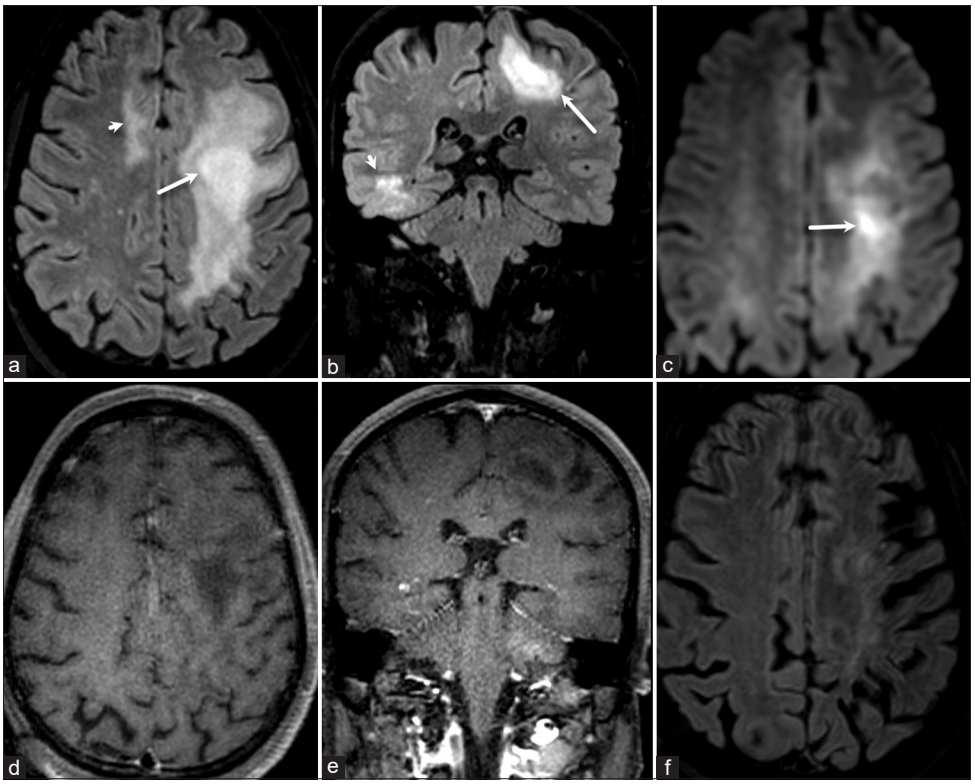

Figure 3: Axial (a) and coronal (b) FLAIR images show multiple lesions limited to the white matter in the left frontal, right frontal (short arrow in a), and right posterior temporal (short arrow in b) with a core of more hyperintensity in left frontal lesions (arrows in a and b). Focal diffusion restriction (arrow in c) is seen within the core of the left frontal lesion in the diffusion-weighted image (c). No enhancement is seen in post-contrast axial (d) and coronal (e) T1-Wis. Follow-up FLAIR image (f) done after a year shows complete resolution of lesions with atrophy

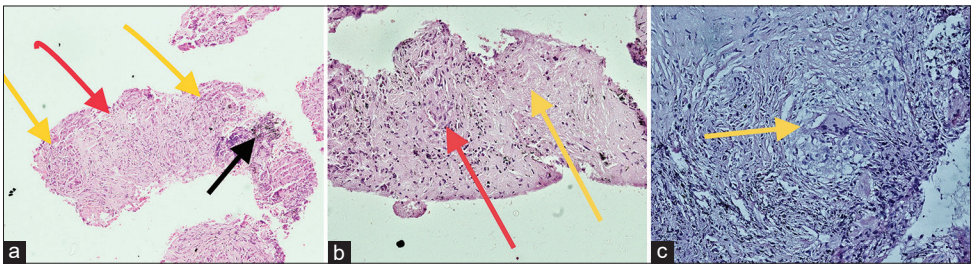

Figure 4: EBUS guided lymph node biopsy, (a) hematoxylin and eosin stain (10X) showing multiple epitheloid cell granulomas (yellow arrow) with scant necrosis (red arrow) and anthracotic pigment laden macrophages (black arrow). (b) On 40X resolution, hematoxylin and eosin stain showing multiple epitheloid cell granulomas (yellow arrow) with scant necrosis (red arrow). (c) Giant cells showing Schaumann bodies

diagnosed with NS histopathologically. Therefore, a high index of suspicion should be there in suspecting NS, and it should always be excluded among patients presenting with acute to subacute neurological deficits.

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Conflicts of interest

There are no conflicts of interest.

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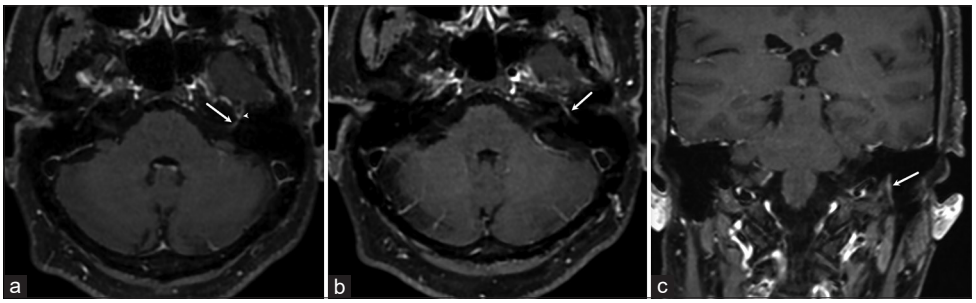
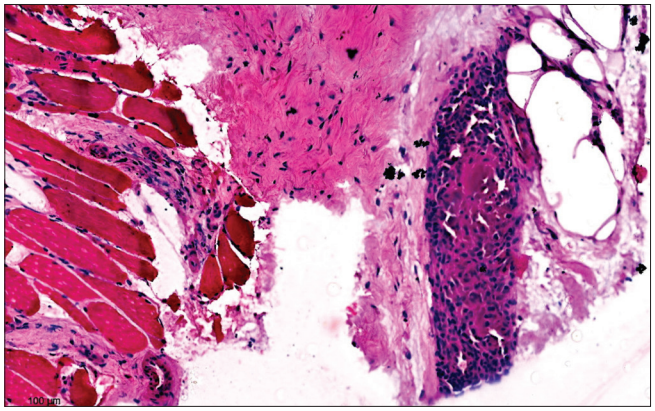
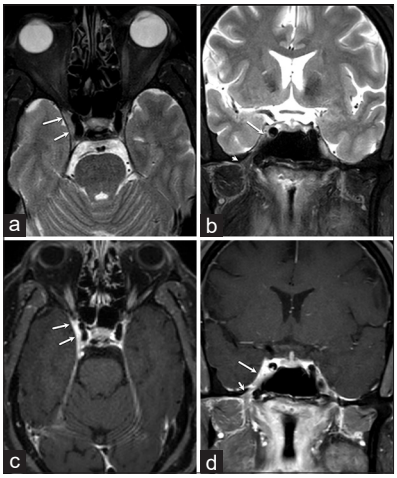
Supplementary Figures



Supplementary Figure 1: Axial (a, b) and coronal post-contrast T1-WIs show enhancement of intracanalicular segment (arrow in a), geniculate ganglion (arrowhead in a), tympanic segment (arrow in b), and mastoid segment (arrow in c) of left facial nerve suggesting of neuritis



Supplementary Figure 2: Muscle biopsy hematoxylin and eosin stain (40X) showing perineurial non-necrotizing epitheloid cell granuloma



Supplementary Figure 3: Axial (a) and coronal (b) T2-WI show thickening of the right cavernous sinus (arrows) extending anteriorly to the orbital apex and inferiorly along mandibular nerve through foramen ovale (short arrow in b dan d). The thickening is hyperintense on T2-WI and shows enhancement (arrows in c and d) on post-contrast axial (c) and coronal (d) T1-WIs