

# Demyelinating Pseudotumours Presenting as Space Occupying Lesions Mimicking Brain Tumours- A Histopathologic Assessment of Seven Cases

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## ABSTRACT

Demyelinating lesions which present as solitary contrast-enhancing masses pose a diagnostic challenge for both radiologists and surgical neuropathologists and can mimic a number of intracranial space occupying lesions either neoplastic/inflammatory. Herein, a series of seven cases with particular emphasis on histopathological and immunohistochemical characterisation of these lesions was presented. The seven cases of Tumefactive Demyelinating Lesions (TDLs) diagnosed on histopathology include three males and four females with age ranging from 10 to 58 years (median-25 years) chiefly presenting with focal neurological deficits. Radiologically, the lesions were predominantly localised in the temporo-parietal region. Histologically, the lesions were well-demarcated, hypercellular with infiltration by foamy macrophages and reactive astrocytes. In addition, Creutzfeldt astrocytes and granular mitoses were seen. Additional special stains for myelin (Luxol fast blue), demonstrated focal, sharply marginated loss of myelin, and Immunohistochemistry (IHC) with Neurofilament (NF) for axons showed relative preservation of axons in areas of myelin loss. IHC with Glial Fibrillary Acidic Protein (GFAP) highlighted the fibrillary processes of the reactive astrocytes and the cytoplasm of the Creutzfeldt cells. Knowledge of the characteristic features such as well-demarcated lesions with histological characterisation by large number of macrophages, including Creutzfeldt astrocytes, granular mitoses and perivascular inflammation should raise index of suspicion and prompt pathologist to do additional myelin stains and IHC to confirm demyelination and preservation of intact axons thereby, differentiating from neoplasms and other non-neoplastic inflammatory lesions.

**Keywords:** Creutzfeldt cells, Glioma, Mass effect, Perivascular lymphocytes, Tumefactive multiple sclerosis

## INTRODUCTION

Multiple sclerosis (MS) is a multifocal autoimmune inflammatory disorder of the CNS characterised by demyelination and progressive neurodegeneration. TDL is a variant of MS and mimics a number of intracranial space occupying lesions either neoplastic/inflammatory clinically and imageologically [1,2]. TDLs presenting as contrast-enhancing solitary lesions may pose a great diagnostic challenge to the clinician, radiologists and the surgical neuropathologists [2,3]. Many of these lesions respond to steroids, hence a high index of suspicion and early diagnosis is crucial to avoid aggressive treatment [4]. There are only very few case reports and few case series reported [5-8]. The series describe seven cases with particular emphasis on histopathological and immunohistochemical characterisation of these lesions.

## CASE SERIES

The demographic data, presenting clinical features and imageological data of seven cases histopathologically diagnosed as TDLs from January 2005 to December 2012 in the Department of Pathology, Nizams Institute of Medical Sciences, Hyderabad were obtained from medical records. The slides were reviewed with Haematoxylin and Eosin (H&E) along with special stain Luxol<sup>®</sup> Fast Blue-Periodic Acid Schiff (LFB-PAS) stains. Immunohistochemistry (IHC) was performed with Glial Fibrillary Acidic Protein (GFAP) (Biogenex, California), NF (Biogenex, California) and CD68 (Biogenex, California). The morphological features evaluated include circumscription of the lesion from adjacent brain parenchyma, hypercellularity, axonal loss, demyelination, presence of macrophages, perivascular inflammatory cell aggregates,

reactive gliosis, presence of gemistocytes, mitoses, areas of necrosis and haemorrhage.

The seven cases during the study period include three males and four females with age ranging from 10 to 58 years (median-25 years). All the patients presented with focal neurological deficits. In addition two patients had headache, one had fever and aphasia [Table/Fig-1]. There was no history of remitting and relapsing illness or any immunosuppression. On MRI, the lesions were located in temporo-parietal region in three, parietal in two and multiple in two cases [Table/Fig-2].

Intraoperative smears were available in three cases. The smears showed macrophages with variable number of reactive astrocytes [Table/Fig-3]. Few perivascular lymphocytes were seen in one case. Diagnosis of reactive gliosis and infarct were made in one case each. In the case where perivascular lymphocytes were seen, a possibility of demyelination was suggested.

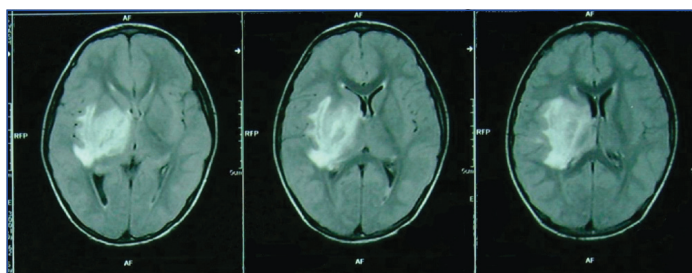
On histology, the lesions were typically demarcated from adjacent brain parenchyma. The lesions were hypercellular with infiltration by foamy macrophages [Table/Fig-4a,b] along with perivascular lymphocytic infiltration seen in all cases [Table/Fig-4c,d]. Amidst, the macrophages were evenly distributed reactive astrocytes with eosinophilic cytoplasm and multipolar processes [Table/Fig-4e]. IHC with GFAP highlighted the fibrillary processes of the reactive astrocytes and the cytoplasm of the Creutzfeldt cell [Table/Fig-4f]. The macrophages had distinct cell borders, foamy/pale granular cytoplasm and small dense nuclei [Table/Fig-5]. There were large astrocytic cells with abundant glassy cytoplasm and multiple micronuclei (Creutzfeldt cells) in four biopsies [Table/Fig-5]. There were large astrocytic cells with abundant glassy cytoplasm and multiple micronuclei (Creutzfeldt cells) in four biopsies [Table/Fig-6]. LFB-PAS stain showed sharply defined area of demyelination



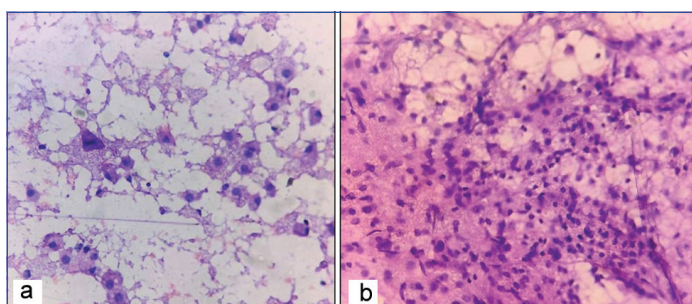
Serial No.	Age/Gender	Clinical features	Location in MRI	MRI features	Pre-operative diagnosis
1.	33/M	Weakness left upper limb and lower limb since three months	Right temporo-parietal	Suggestive of demyelination	Tumefactive demyelination
2.	25/F	Headache Weakness right upper limb since 20 days	Left parietal	Intracranial Space occupying Lesion with perilesional oedema	Glioma
3.	17/M	Fever, aphasia Weakness left upper limb and lower limb	Multiple lesions	Demyelination Lymphoma	Lymphoma
4.	26/F	Headache Weakness left upper limb and lower limb	Right temporo-parietal	Heterogenous	Glioma
5.	10/M	Weakness right upper limb and lower limb	Multiple	Suggestive of Glioma Tumefactive demyelination	?Tumefactive demyelination ? Glioma
6.	58/F	Weakness left lower limb since two months	Right temporo-parietal	Suggestive of right temporo- parietal lesion	Glioma
7.	26/F	Weakness right upper limb and lower limb since one month	Left parietal	Suggestive of left parietal lesion	?Glioma

[Table/Fig-1]: Description of the cases.

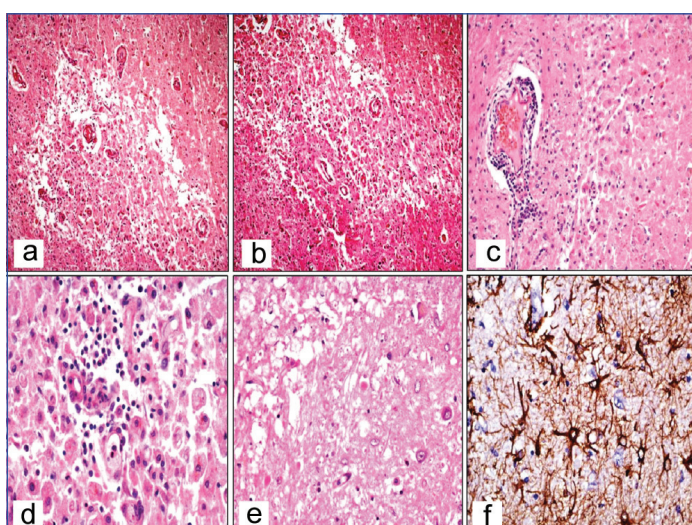
MRI: Magnetic resonance imaging



[Table/Fig-2]: MRI image showing hyperintense lesion involving the right capsuloganglionic (Case 7).

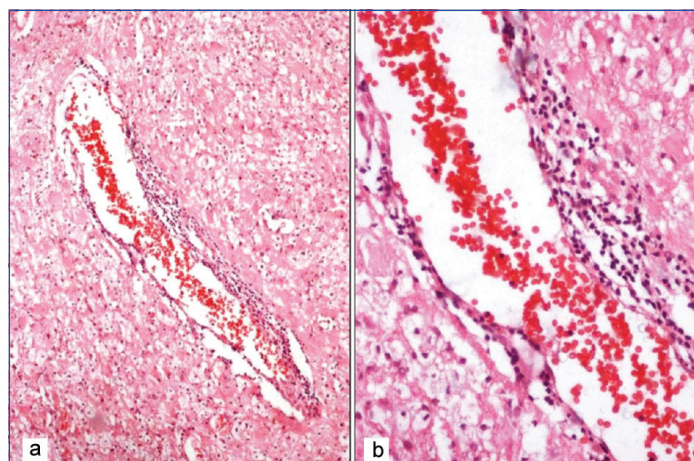


[Table/Fig-3]: Rapid H and E smears of squash images showing a) Numerous foamy macrophages (200 x); b) Lymphocytic collection; (200x).

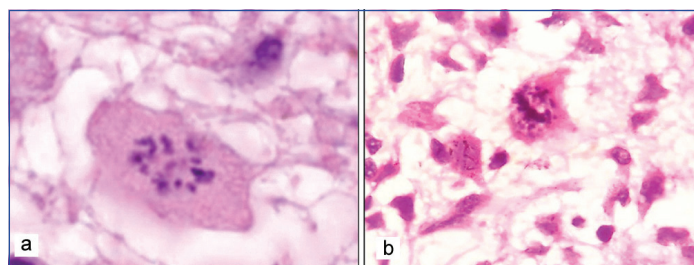


[Table/Fig-4]: (a,b) Hypercellular lesion with infiltration by foamy macrophages (H and E, 40x); (c,d) Distinct perivascular inflammatory infiltrate (H&amp;E, 40x and 400x); e) Reactive Astrocytes with eosinophilic cytoplasm (H&amp;E, 100 x); f) Reactive Astrocytes show intense GFAP positivity (IHC,100x).

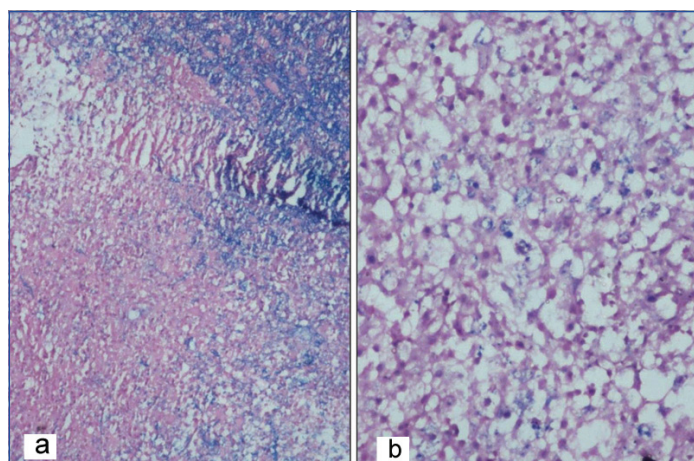
and some PAS positive granular material within the macrophages [Table/Fig-7]. IHC with Cluster of Differentiation (CD68) delineated the macrophages and the margin of lesion. The preserved axons were highlighted by IHC with NF [Table/Fig-8].



[Table/Fig-5]: Case 5 showing collection of foamy macrophages with abundant glassy cytoplasm with perivascular lymphocytic collection (H&amp;E) a) 200x, b) 400x.



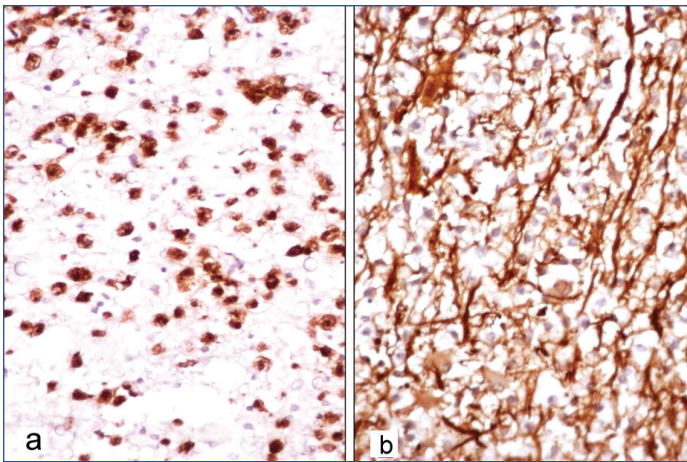
[Table/Fig-6]: a) Large astrocytic cells with abundant glassy cytoplasm and multiple micronuclei (Creutzfeldt cells); b) Granular mitosis; (H&amp;E, 400x).



[Table/Fig-7]: a) LFB-PAS stain showing loss of myelin with distinct boundaries from adjacent myelinated white matter (LFB-PAS stain, 100 x); b) Accumulation of degraded myelin within histiocytes (LFB-PAS stain, 400x).

The provisional differential diagnoses with various histopathological and immunohistochemical findings are summarised in [Table/Fig-9].





**[Table/Fig-8]:** a) Positivity for CD68 in histiocytes (IHC, 100 x); b) Intact axons shown by neurofilament immunostain (IHC, 400 x).

perilesional vasogenic oedema, relatively low cerebral blood volume, central necrosis, cystic change, incomplete or open ring contrast enhancement, variable involvement of grey matter and vessel-like structures traversing through the center of the lesion [14], hence clinically and radiologically may mimic primary and secondary brain tumour, brain abscess, tuberculous abscess, or other inflammatory disorders. Certain features on MRI like open ring enhancement, peripheral restriction on diffusion weighted imaging, vascular enhancement were suggested as useful parameters for differentiating TDLs from tumour [3,5]. In this series, diagnoses of TDL was suspected in two cases. Glioma was the pre-operative diagnosis in majority (5/7) of the cases. A possibility of lymphoma was considered in one case. In most of the reported series, the preoperative diagnosis was glioma [4,6]. The lesions in this series were solitary in five and multiple in two cases. Elevation of glutamate/ glutamine peaks on Magnetic Resonance Spectroscopy (MRS) can be helpful in differentiating TDL from tumours [5,15].

S. No.	Squash findings	Squash Dx	Histoapthology findings					LFB-PAS	CD 68	NF	GF-AP In RA	Final Dx
			FM	PLI	RA and CZ cells	Granular mitosis	Provisional Dx					
Case 1	Not done	-	+	+	-	-	Inflammatory Infarct TDL	DM +	+	Preservation of axons	Not done	CNS Demyelination
Case 2	Reactive astrocytes	Reactive gliosis	+	+	+	+	Glioma Lymphoma TDL	DM +	+	Preservation of axons	+	Demyelinating Pseudotumour
Case 3	Not done	-	+	+	-	-	Inflammatory Infarct TDL	DM +	+	Preservation of axons	Not done	Demyelinating Pseudotumour
Case 4	Not done	-	+	+	+	+	Glioma TDL	DM +	+	Preservation of axons	+	Tumefactive demyelinatinglesion
Case 5	Perivascular lymphocytes with FM	TDL	+	+	+	+	Glioma TDL	DM +	+	Preservation of axons	+	Demyelinating Pseudotumour
Case 6	Reactive astrocytes	Infarct	+	+	+	+	Glioma TDL	DM +	+	Preservation of axons	+	Demyelinating Pseudotumour
Case 7	Not done	-	+	+	-	-	Inflammatory Infarct TDL	DM +	+	Preservation of axons	Not done	Demyelinating Pseudotumour

**[Table/Fig-9]:** Summary of histopathological features with special stains and IHC results.

FM: Foamy macrophages; PLI: Perivascular lymphocytes; RA: Reactive astrocytes; CZ: Cruetzfeldt cells; LFB-PAS: Luxol fast blue-Periodic acid schiff stain; NF: Neurofilament; GFAP: Glial fibrillary acidic Protein; DM: Demyeliantion; TDL: Tumefactive demyelination; CNS: Central nervous system; Dx: Diagnosis; (+)- present, (-) absent

## DISCUSSION

Acute demyelinating disorders such as MS and Acute Demyelinating Encephalomyelitis (ADEM) presenting as TDL poses diagnostic problem as they closely mimic primary brain tumours. Subset of patients present typically with large solitary white matter lesions greater than 2 cm with perilesional oedema associated with mass effect and contrast enhancement masquerading an intracranial neoplasm. The prevalence of TDL is estimated to be 1-3/1000 with incidence estimated at 0.3 cases per 100000 population [9]. They may occur in isolation or more commonly in established MS. Atypical clinical or radiological manifestation in an established MS can suggest concurrent neoplasms owing to similar clinical presentations [10,11]. These lesions typically showing perilesional oedema with ring enhancement in MR imaging which clinically and radiologically may mimic primary and secondary brain tumour, brain abscess, tuberculous abscess, or other inflammatory disorders.

The usual clinical manifestations of TDL are related to mass effect and are variable, depending on lesion location and size, and include headache, cognitive changes, mental confusion, aphasia and apraxia, neurological deficits, seizures [12,13]. All the patients presented with monophasic illness and had no association with previous diagnosis of MS and presented with focal neurological deficits and few cases along with headache and aphasia. TDLs on MRI show large white matter lesions with ill-defined borders,

Patients with clinically monophasic solitary lesion or atypical ring enhancing lesions and mass effect may require biopsy to establish diagnosis [13,16,17]. The diagnosis on TDL on pre-operative squash smear can be difficult. The main differential diagnoses includes infarct, inflammatory lesions, xanthomatous lesions and CNS lymphomas treated with corticosteroids [18]. Diagnosis was suggested in only one out of three cases in this series. Hence, a clinicoradiological correlation is necessary and pathologist at best can confirm abnormal tissue in smears.

Histopathological findings of a sharply demarcated white matter lesion with macrophage infiltration, reactive astrocytes and perivascular lymphocytic aggregates point towards a non-neoplastic pathology and should prompt the pathologist to do additional stains for myelin and IHC for axons and CD68. The preservation of intact axons together with demyelination confirms the diagnosis of TDLs. The distribution of macrophages and reactive astrocytes also gives a clue to the diagnosis [7,15]. The lymphocytic infiltrate in the perivascular area varies with the activity of the disease and the perivascular inflammation can be seen within and outside the lesional area [7]. The aggregates of macrophages, the bizarre nuclei of the reactive astrocytes and granular mitosis lead to a mistaken diagnosis of glioma especially oligodendroglioma and astrocytoma. Foamy macrophages can occur in a few gliomas like pleomorphic xanthoastrocytoma, lipidized glioblastoma and others but the age, location, imageology and pattern of distribution of macrophages

within the lesion along with demyelination and IHC with CD68 help in the differential diagnosis [7,8]. The presence of macrophages and reactive astrocytes also raises the possibility of infarct but the location and preservation of intact axons help in making the diagnosis. Both axons and myelin are lost in infarct. Infarct usually involves the cortex and hence, may show red neurons (hypoxic) and thick capillaries. Progressive Multifocal Leukoencephalopathy (PML) can also show presence of macrophages with areas of demyelination but a prior history of immunosuppression and presence of ground glass inclusions in oligodendroglial nuclei which can be confirmed on IHC, differentiates it from TDL [8]. Multiple lesions, treated with corticosteroids with a diagnosis of lymphoma have large number of macrophages posing problems on histology. The enhancing pattern on imageology favour a lymphoma and presence of demyelination and younger age favour TDL.

## CONCLUSION(S)

A detailed neurological history, examination and radiological findings are essentially important in dealing with patients presenting as space occupying single/multiple white matter lesions. The particular attention to prior episodes of transient neurological dysfunction for which the patient may not have sought medical attention may be very helpful specifying features more characteristic to demyelinating disease. There are specific histopathological findings which can be helpful in arriving at a conclusive diagnosis, provided there is a high index of suspicion to have to consider a demyelinating lesion leading to in-addition routine histopathological protocols for special staining for myelin and axons.

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