

Primary diffuse leptomeningeal gliomatosis: An autopsy case report

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Abstract

Primary diffuse leptomeningeal gliomatosis (PDLG) is a rare condition, characterized by infiltration of the meninges by glial cells without evidence of the primary tumor in the brain or spinal cord parenchyma. Glioma arising primarily from the leptomeninges is extremely rare and often diagnosed only in post mortem examination and the diagnosis may be missed in meningeal biopsy. We describe a young female who presented with symptoms of raised intracranial pressure with imaging evidence of diffuse leptomeningeal enhancement in whom autopsy confirmed the diagnosis of PDLG. Our case illustrates the diagnostic difficulties in making the pre-mortem diagnosis even with multiple cerebrospinal fluid cytologies and leptomeningeal biopsy.

Key Words

Chronic meningitis, leptomeningeal gliomatosis, meningeal biopsy, neoplastic meningitis

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Introduction

Primary diffuse leptomeningeal gliomatosis (PDLG) is a rare, fatal disease characterized by infiltration of the meninges by glial cells without evidence of primary tumor in the brain or spinal cord parenchyma.^[1,2] This condition was first described by Moore in 1954. Primary leptomeningeal glioma can be in the form of a solitary tumor or a diffuse tumor involving intracranial or spinal cord leptomeninges. The typical signs and symptoms are indicative of increased intracranial pressure, cranial neuropathies, and seizures. Due to the non-specific nature of clinical presentation, ante mortem diagnosis poses a challenge to the clinician. About one-third of all the cases were diagnosed only on post mortem studies.

Case Report

A 22-year-old lady, presented with headache, vomiting, double vision, swaying while walking and tremor of left upper

limb since 20 days. There was no history of fever, seizures, altered sensorium, and focal weakness and the past history was unremarkable. General and systemic examinations were normal. Neurological examination revealed bilateral papilledema, left sixth nerve paresis with action tremor and signs of cerebellar dysfunction in left upper limb. There were no meningeal signs. Rest of the examination was normal.

Magnetic resonance imaging (MRI) brain showed diffuse, thick leptomeningeal enhancement [Figure 1a] with few nodular

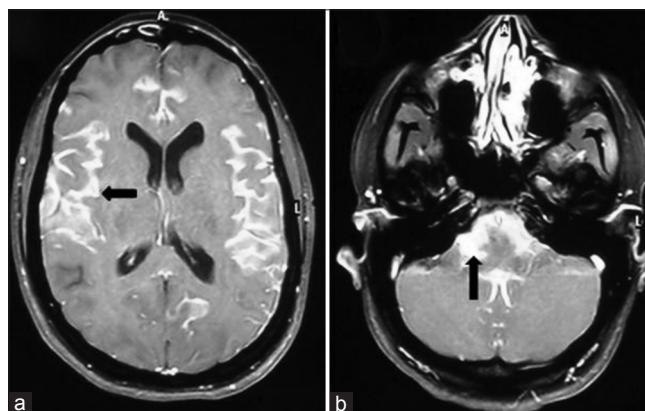


Figure 1: (a) T1 weighted axial magnetic resonance imaging brain with gadolinium contrast showing diffuse, thick leptomeningeal enhancement (black arrow) with normal brain parenchyma and ventricles and (b) thick nodular leptomeningeal enhancement in cerebellomedullary cistern (black arrow)

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enhancing meningeal lesions in right cerebellomedullary cistern [Figure 1b]. The brain parenchyma and ventricles were normal.

Lumbar punctures were performed four times during the course of illness [Table 1]. All the cerebrospinal fluid (CSF) samples showed elevated protein (up to 1.2 g/dl) and normal glucose levels. Though all the lumbar punctures were atraumatic, all CSF samples showed red blood cells (RBCs) (200-2,000/dl). There were few (0-100/dl) white blood cells. Smears and cultures for acid fast bacilli including DNA polymerase chain reaction for mycobacterium tuberculosis were negative. Gram stain, aerobic, and anaerobic cultures, fungal stains and fungal cultures were also negative on repeated testing. Large volumes of CSF analyzed with cytopspin did not show any evidence of malignant cells. CSF angiotensin converting enzyme levels were normal. Complete hemogram, liver, and renal function tests were normal. Serological markers for vasculitis were negative. Mantoux test was non-reactive. Contrast enhanced computed tomography scans of chest and abdomens were normal. HIV and HBsAg serology were negative.

A diagnosis of chronic meningitis with raised intracranial pressure was considered. Possible etiological considerations were infectious (tuberculous or fungal), non-infectious inflammatory (sarcoidosis or other vasculitides) or neoplastic (primary meningeal or secondary carcinomatous) meningitis.

A meningeal with brain biopsy was obtained from left temporal region. Histopathology showed normal brain tissue with lymph mononuclear infiltrate in one of the dural vessels with vessel wall destruction without any granulomas or fungal elements.

She was empirically treated with anti-tuberculous drugs and there was no improvement. Short course of steroids were given. She continued to deteriorate, became comatose and succumbed to the illness after about 8 weeks from the onset of her symptoms. A partial autopsy (confined to brain) was carried out after obtaining consent from her parents.

Pathological findings

On opening the dura, the temporal lobe was seen herniating out which corresponded to the biopsy site. The brain weighted

Table 1: Results of lumbar punctures

CSF parameter	Day 10	Day 25	Day 27	Day 30
Protein (mg/dl)	64	1200	1270	832
Glucose (mg/dl)	40	87	110	107
WBC (cells/mm ³)	40	Nil	100	Nil
Differential count (%)	90 L 10 N		100 L	
RBC (cells/mm ³)	Present	200	800	2000
Gram stain	Negative	Negative	Negative	Negative
AFB stain	NA	Negative	Negative	Negative
India ink preparation	NA	Negative	Negative	Negative
Cryptococcal antigen agglutination test	NA	Negative	Negative	Negative
ADA (normal<0 IU/L)	NA	11 IU/L	NA	NA

L=Lymphocytes, N=Neutrophils, NA=Not available, RBC=Red blood cell, AFB=Acid fast bacilli, IU=International units, CSF=Cerebrospinal fluid

1,200 g on fixing for 4 weeks and there was evidence of cerebral edema. The base of the brain showed a whitish material plastering over the superior surface of cerebellum and entrapping the vessels of circle of Willis and lower cranial nerves [Figure 2]. Multiple coronal sections of the brain showed normal cortex and white matter. There was no evidence of a mass lesion. Sections from the cortical and basal meninges revealed a cellular lesion with fibrillary background. The cells showed marked pleomorphism with giant cells and brisk mitotic activity. Focal area showed necrosis and microvascular proliferation [Figure 3]. The cells showed strong expression of glial fibrillary acidic protein (GFAP), vimentin and S-100 whereas CD99, LCA and synaptophysin were negative. Epidermal growth factor (EGFR) was positive and p53 showed nuclear positivity in almost 60% of tumor cells [Figure 4]. The tumor was restricted to leptomeninges and multiple sections through parenchyma did not reveal any microscopic focus of tumor. In view of the morphologic and immunohistochemical features, a diagnosis of primary leptomenigeal gliomatosis was made and graded as glioblastoma (WHO grade IV) in view of presence of mitosis, necrosis, and microvascular proliferation.

Discussion

Leptomeningeal gliomatosis is uncommon, but should be considered in patients presenting with neurological symptoms suggestive of meningitis or raised intracranial pressure and leptomenigeal enhancement on MRI especially, if they do not respond to conventional treatment. The differential diagnosis is extensive and includes, infectious, inflammatory, granulomatous, and neoplastic conditions. This condition may be commonly mistaken for tuberculous meningitis especially, in endemic areas.^[3] It is challenging to have an ante mortem diagnosis as PDLG can have varying and non-specific clinical features, time course, and progression of the illness. According to Cooper and Kernohan,^[1] the definite diagnosis of PDLG is based on the following criteria: No apparent attachment of extra medullary meningeal tumor to the neural parenchyma, no evidence of primary neoplasia within the neuraxis, and the existence of distinct leptomenigeal encapsulation around the tumor.

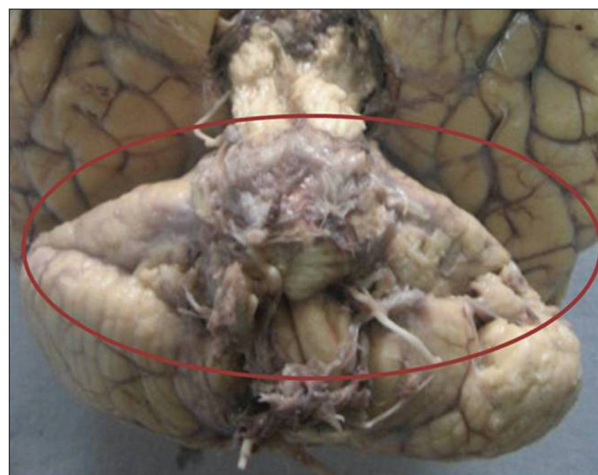


Figure 2: The base of the brain seen to be plastered by thick whitish exudative material encasing the vessels of circle of Willis and basal cranial nerves

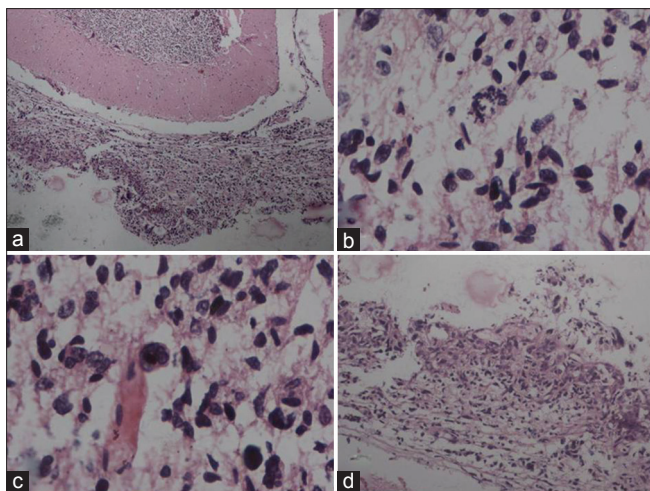


Figure 3: (a) Tumor cells seen over the surface of cerebellum (H and E, $\times 40$) (b, c) Tumor cells showing pleomorphism, atypical mitosis, giant cells and fibrillary background (H and E, $\times 400$) (d) Foci of microvascular proliferation (H and E, $\times 200$)

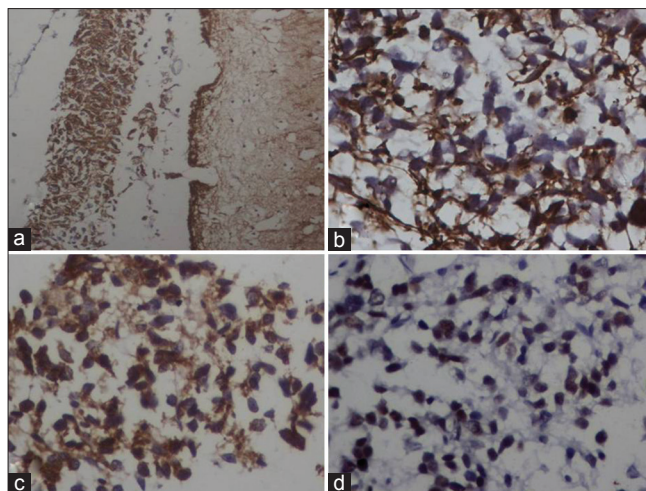


Figure 4: Immunohistochemical profile of tumor with cytoplasmic positivity for glial fibrillary acidic protein (GFAP) (a) Vimentin (b) epidermal growth factor (EGFR) (c) GFAP $\times 40$, Vim, EGFR HRP $\times 200$ (d) P53 showing nuclear positivity in almost all the tumor nuclei. (p53 $\times 200$)

The clinical manifestations of PDLG are non-specific and those of raised intracranial pressure, which is seen in about 80% of the cases at presentation, cranial nerve palsies (35%), seizures (29%) being the most common.^[4] Though focal neurological deficits have been described, cerebellar signs at presentation have not been reported previously. Our patient had clinical features suggestive of raised intracranial pressure with sixth nerve palsy, bilateral papilloedema and asymmetric cerebellar deficits probably due to the location of a focal nodular enhancing lesion in cerebello-medullary cistern encasing the inferior cerebellar peduncle. Presence of nodular non-enhancing lesions over the cerebellum without any related clinical involvement had been previously reported.^[5] Common neuroradiological findings in PDLG include ventriculomegaly with diffuse or focal leptomeningeal contrast enhancement. The spinal cord may be predominantly involved.^[6,7] Our patient showed similar, though non-specific features like diffuse and thick cranial leptomeningeal enhancement with few nodular extra medullary enhancing lesions in cerebello-medullary cistern.

CSF analysis in PDLG may reveal decreased or normal glucose, elevated protein, and pleocytosis. Our patient had lymphocytic pleocytosis and all the samples showed plenty of RBC. This is the second case to our knowledge to report consistent presence of CSF RBCs.^[8] CSF cytology is usually unremarkable in PDLG. Cytologies were positive in 5 of 45 reported cases, only once in the first sample examined.^[2] CSF cytology for malignant cells was negative in our patient and it is suggested to do GFAP staining in CSF cytospin to detect cells of glial origin.^[9] The negative CSF cytology could be related to the inability of glioma cells to detach from the primary focus, because of a desmoplastic reaction limiting the dissemination of tumor cells.

Surgical biopsy should be performed in areas with contrast enhancement in MRI. In a review of 24 published autopsy proven cases of PDLG, 16 patients underwent ante mortem biopsy of which histology missed the diagnosis in 5 cases.^[3] We performed a meningeal with brain biopsy near the temporal lobe where there was thick meningeal enhancement. However, the biopsy did not show any

tumor cells. Difficulty of obtaining a positive CSF cytology and diagnostic leptomeningeal biopsy has also been highlighted previously and consideration of multi-site or repeat leptomeningeal biopsy has been emphasized.^[10] There are three cases published in literature where the initial leptomeningeal biopsy was non-diagnostic but a repeat biopsy was useful.^[2,6,11] One possible explanation for non-diagnostic leptomeningeal biopsies in PDLG may be the predilection for the leptomeningeal involvement to be the most prominent at the skull base, compared to the cerebral hemispheres, where biopsies are commonly performed and also due to the presence of skip lesions.

Based on the definition of PDLG, a post mortem morphological study of the entire neuraxis should be required to confirm the diagnosis. The morphologic subtype of PDLG is usually a high-grade astrocytoma, oligodendroglioma or gliosarcoma. A single case of pilocytic astrocytoma presenting as PDLG has been reported.

Other tumors, which can have primary leptomeningeal distribution includes ependyoblastoma, primary neuroectodermal tumor (PNET), melanocytoma, and lymphoma. Immunohistochemistry and morphology helps in identifying the particular subtype. Positivity for GFAP, vimentin and S-100 helped in diagnosis of glioblastoma in the present case. Some of the PNETs can also show glial differentiation however, negativity for CD99 and synaptophysin ruled out the possibility of PNET.

A molecular and genetic basis in the biology of different grades of glioblastoma has been well-established. EGFR amplification is the hallmark of primary glioblastoma multi-forme (GBM) whereas the secondary GBMs are characterized by mutations of P53 gene. The present case showed immunohistochemical expression of both P53 and EGFR though we did not have fluorescence *in situ* hybridization analysis. Loss of P53 and phosphatase and tensin homolog gene tumor suppressor gene has been described in PDLG earlier. Other

genetic attribute to PDLG has been described in the form of Neurofibromatosis 1 (NF1) mutations by King *et al.* They have reported PDLG in a 12 year old child involving central and spinal meninges. Presence of additional mutations in addition to neurofibromin is shown to give rise to more malignant tumors in the NF1 patients.

In high-grade gliomatosis, prognosis remains poor. Mean survival time after diagnosis is 4 months. Only few cases have been reported to respond to chemotherapy and craniospinal irradiation.^[11,12]

Conclusion

Leptomeningeal gliomatosis should be suspected in cases of unexplained subacute or chronic meningeal processes. On the basis of the lack of specificity concerning symptoms and CSF data, PDLG is often misinterpreted as being of infectious or autoimmune origin with tuberculous meningitis being considered as the most common clinical diagnosis. Meningeal biopsy may be inconclusive. Prognosis is universally poor. Review of previous case reports and detailed analysis of our case suggests a need for high-suspicion of PDLG in the presence of raised intra cranial pressure early in the clinical course with marked leptomenigeal enhancement on imaging. Presence of CSF RBC may be the clue in few cases.

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