Acta Neurol. Belg., 2010, **110**, 325-333

Primary diffuse leptomeningeal gliomatosis: an autopsy case and review of the literature

J. Somja[1], M. Boly[2], B. Sadzot[2], G. Moonen[2] and M. Deprez[1]
Departments of [1]Neuropathology and [2]Neurology, CHU Sart Tilman, University of Liege, Belgium

Abstract

We report a case of primary diffuse leptomeningeal gliomatosis (PDLG) in a 76-year-old male presenting with confusion, dysarthria, diplopia, lumbal pain and headaches of recent onset. Neurological examination revealed nuchal rigidity and bilateral sixth cranial nerve palsy. The cerebrospinal fluid showed a marked hyperproteinorachia (4711 mg/L) and mild cytorachia (5-10 leucocytes/mm³) with a few atypical lymphoid cells. On admission, brain CT scan and MRI demonstrated diffuse and nodular leptomeningeal contrast enhancement predominant at the skull base and several osteolytic lesions in the right parietal bone. Extensive serological studies for infectious, autoimmune or neoplastic diseases were negative. The work-up diagnosis was neurosarcoidosis or multiple meningeal and osseous metastases of an unknown primary cancer. Surgical biopsy of the right parietal bone lesion showed only fibrous tissue with no evidence of tumour or inflammation. The patient was treated with high dose corticosteroids but its neurological status progressively worsened and he died of aspiration pneumonia 35 days after admission. Post-mortem examination revealed a PDLG, a rare fatal tumour with about 60 cases reported. PDGL is characterized by the diffusion of neoplastic glial cells throughout the leptomeninges without evidence of a primary intra-parenchymal lesion. Recognition of this rare brain tumour is important as recent reports suggest that radiotherapy and chemotherapy can improve patient survival.

Key words: Primary diffuse leptomeningeal gliomatosis; leptomeninges; brain tumour; glioma; subacute meningitis.

Introduction

Primary diffuse leptomeningeal gliomatosis (PDLG) is a rare neoplastic condition in which glioma cells extend diffusely throughout the leptomeninges in the absence of a primary intra-parenchymal lesion. This condition must be distinguished from the more common secondary leptomeningeal gliomatosis which refers to the neoplastic invasion of leptomeninges by a primary parenchymal glioma (Debono *et al*., 2006). In the literature, we found 66 cases reported among which 39 cases were confirmed by autopsy (Felix, 2009; Ko *et al*., 2009).

Due to the lack of specificity and variability of clinical presentation, the clinical diagnosis of these tumours poses a difficult challenge and encompasses the differential diagnosis of chronic/subacute meningitis of neoplastic, infectious and auto-immune etiology. CSF findings are non specific and a MRI guided surgical biopsy of the pathological meninges is required to confirm the diagnosis.

PDLG has a poor prognosis but recent reports suggest that treatments combining radiation and chemotherapy can improve survival (Baborie *et al*., 2001; Beauchesne *et al*., 1998; Jicha *et al*., 2009; Michotte *et al*., 2009).

Here we report a case of PDLG occurring in a 76-year-old male who presented with signs of subacute meningitis and bilateral sixth cranial nerve palsy. Serological testing, CSF findings and surgical biopsy of a cranial osteolytic lesion were inconclusive and the diagnosis was made at post-mortem examination.

Case report

A 76-year-old man with a previous history of chronic obstructive pulmonary disease, pulmonary sarcoidosis and alcoholism was admitted for horizontal diplopia, dysarthria, lumbal pain and headaches of recent onset (3-6 weeks). His wife described memory deficit, aggressive behavior and disorientation starting two years ago with a progressive onset and gradually worsening. At the time of admission, neurological examination revealed nuchal rigidity, bilateral sixth cranial nerve palsy,

and confusion. The patient was not febrile and blood chemistry only showed an elevated C-reactive protein (CRP) at 62.2 mg/L (N = 6). The tumour markers CEA, CA 15.3, CA 19.9, CA 125, NSE, Alpha-fetoprotein and PSA were negative. An extensive screening for autoimmune disease was performed and test results were negative. Anti-Yo was also tested for paraneoplastic diseases and was negative. Infectious serology showed no immunisation for HIV, Hepatitis A, B and C virus, Herpes Simplex virus, Cytomegalovirus, Epstein-Barr virus, adenovirus, Cocksackia/Echovirus, *Brucella*, *Listeria monocytogenes*, *Borrelia burgdorferi*, *Tropheryma Whippelei*, *Treponema*, *Histoplasma*, *Toxoplasma Gondii*, *Candida*, *Cryptococcus*, Cysticercosis. The patient had a past immunisation for Varicella Zoster virus (IGg+ IgM-).

The lumbar punctures showed an elevated opening pressure and CSF examination repeatedly demonstrated a markedly elevated protein content (ranging from 2477 mg/L to 4711 mg/L) and hypoglycorachia (0.28 g/L). CSF cytology showed a mild cytorachia with 5 to 10 leucocytes/mm^3 including a few atypical large lymphocytes and monocytes (CD 45 and CD68 positive on immunocytochemistry) (Fig. 1a). CSF aerobic and anaerobic cultures, cryptococcal antigens, fungal and mycobacterial cultures were negative as well as PCR for *Borrelia Burgdorferi* and *Toxoplasma Gondii*. Cerebrospinal fluid angiotensin converting enzyme activity levels were within normal range.

At the time of admission, the brain CT scan without contrast only showed moderate ventricular dilatation and periventricular leukoencephalopathy. Two brain MRI performed at 1 and 3 weeks post-admission revealed diffuse and nodular gadolinium enhancement of the leptomeninges, with three dural based nodules located in the left posterior fossa, the clivus and the left temporal fossa (Fig. 1b). Several cranial osteolytic lesions and nonspecific white matter lesions were also described (Fig. 1c).

A surgical biopsy of the right parietal bone lesion was performed but histology showed only fibrous tissue with no evidence of inflammation or neoplasm.

The search for a primary tumour outside the neuraxis was negative and included a chest radiography and a CT-Scan of the abdomen and pelvis. Because of the lack of evidence for infection or cancer, the previous history of pulmonary sarcoidosis and the brain imaging features, neurosarcoidosis was suspected and the patient was put on high doses of corticosteroids. In spite of this treatment, the patient's neurological status rapidly worsened and he died of aspiration pneumonia 35 days after admission. A complete autopsy was performed.

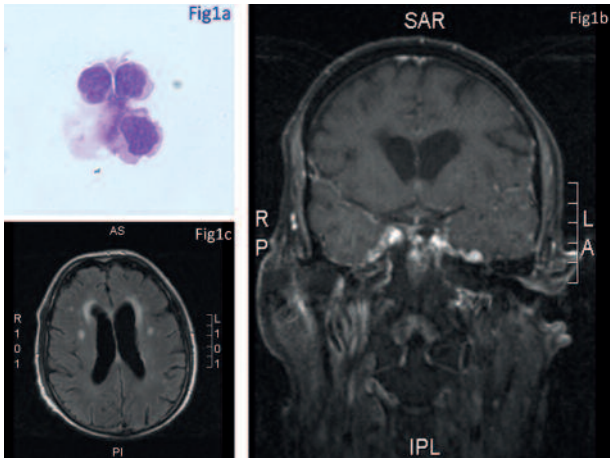

FIG. 1. — a. CSF cytology showed a few atypical large lymphocytes and monocytes; b. Brain MRI, T1 sequence with gadolinium: diffuse and nodular contrast enhancement of the meninges predominates at the skull basis, in the left posterior fossa, clivus and left temporal fossa; c. Brain MRI, FLAIR sequence: abnormal (non specific) signals are detected in the peri-ventricular white matter and in the centrum semi-ovale.

Pathological findings

The general autopsy confirmed a massive pulmonary inhalation. No distant neoplasia was found. There was no lesion of sarcoidosis in the lungs or elsewhere. Unfortunately, none of the osteolytic lesions was sampled for histology.

The brain weighed 1460 g with a moderate diffuse swelling. Examination of the dura mater confirmed the presence of three 4-20 mm reddish nodules adherent to the arachnoid in the left temporal fossa, clivus and both cerebellar fossae (Fig. 2a). The leptomeninges showed a few floconnous whitish opacities (Fig. 2b). There was no gross abnormality of the Willis' circle and cranial nerves. On serial coronal sections, several 5-10 mm areas of grayish discoloration were seen in the periventricular white matter and the corpus callosum. In addition, a 8 mm intraparenchymal nodule was found within the temporal cortex of the right rolandic operculum (Fig. 2c).

Microscopic examination revealed neoplastic cells extending throughout the subarachnoid space and invading the dura mater in the three nodules described macroscopically (Fig. 3a-b). Tumour cells were also found on the ependymal surface of the ventricular cavities, suggesting cerebrospinal fluid dissemination. At the base of the brain, the tumour massively infiltrated the cranial nerves. At high magnification, tumour cells were non cohesive, showing scant cytoplasm, ovoid hyperchromatic nuclei and numerous

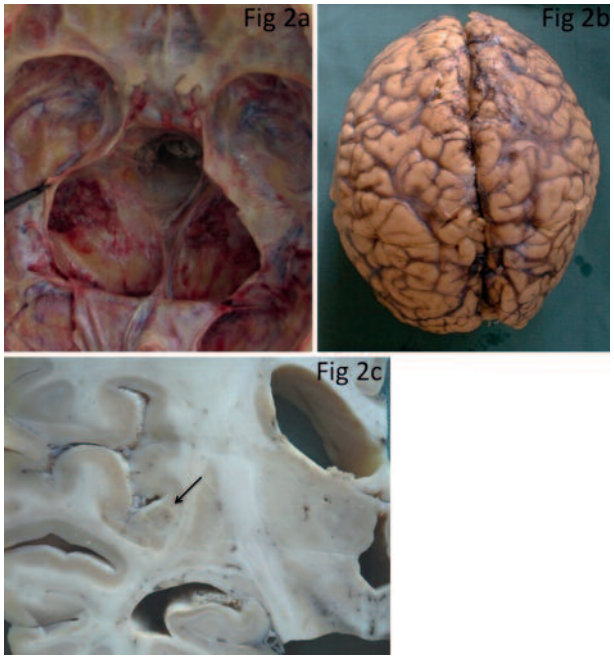

FIG. 2. — Macroscopic findings at autopsy. Several reddish nodules were scattered on the dura of the skull base (2a). The leptomeninges showed a few flocculent whitish opacities (2b). On coronal sections, a 8mm intra-parenchymal nodule (arrow) was found within the temporal cortex of the right Rolandic operculum (2c).

mitotic figures (Fig. 3c). There was no tumour necrosis. Interestingly, there was a small area of secondary parenchymal invasion in the right rolandic cortex, where astroglial tumour cells assumed a more protoplasmic appearance and were associated with marked endothelial hyperplasia (Fig. 3d). Immunohistochemistry showed that the tumour cells were positive for GFAP (glial fibrillary acidic protein), protein S-100, Sox-2, CD56 (N-CAM) and 40% of them showed a positive nuclear staining for p53 protein (Fig. 3e). They were negative for NeuN, Neurofilament, Synaptophysin, NSE and EGFR. Ki-67 labelling showed a proliferative index of 15%. Fluorescence In Situ Hybridisation (FISH) studies on chromosomes 1, 7, 19 and 10 were inconclusive probably due to fixation artefacts. The cerebral cortex showed a severe oedema and superficial gliosis. The white matter lesions corresponded to non-inflammatory glial scars of microinfarcts.

The final diagnosis was PDLG with histological features of glioblastoma (WHO grade IV) with focal secondary invasion of the brain parenchyma. The parenchymal invasion was probably a late event in the tumour progression as it could not be identified retrospectively on the brain MRIs.

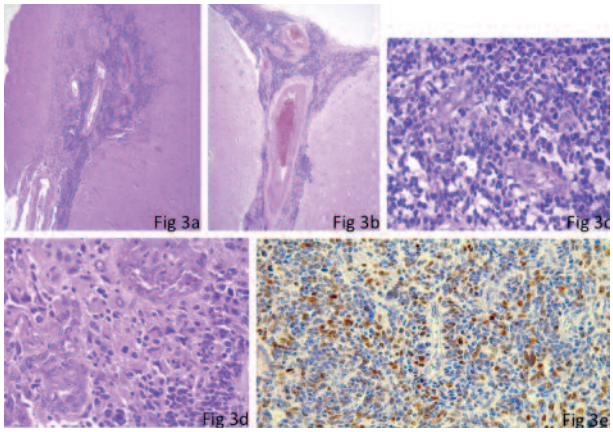

FIG. 3. — a-b. Neoplastic cells extend throughout the subarachnoid space (H&E, a OM ×2 and b OM ×5); c-d. At higher magnification, tumour cells were non cohesive and showed scant cytoplasm, ovoid hyperchromatic nuclei and numerous mitotic figures (c). A small area of secondary parenchymal invasion was seen in the right rolandic cortex, where astroglial tumour cells assumed a more protoplasmic appearance and were associated with marked endothelial hyperplasia (d), H&E, OM ×40; e. Immunohistochemistry showed that 40% of tumour cells are positive for P53 (OM ×40).

Discussion

PDLG was originally defined by Cooper and Kernohan as a "rare neoplastic condition in which glial tumor cells extend diffusely throughout the leptomeninges without forming any intra-axial lesions" (Cooper & Kernohan, 1951; Goncalves *et al*., 2008). The diagnosis of PDLG was then based on three criteria: no tumour attachment to the neural parenchyma, no evidence of intra-axial neoplasia, leptomeningeal encapsulation around the tumour.

Two anatomo-clinical patterns of PDLG have been reported: nodular and/or diffuse. The nodular form is described as "a solitary or focal leptomeningeal gliomatosis, defined by limited tumour masses in cranial or spinal leptomeninges" (Debono *et al*., 2006; Dietrich *et al*., 1993) and the diffuse form is "a diffuse extension outside the nervous parenchyma of glial tumour cells over a wide area of the CNS" (Debono *et al*., 2006; Myers *et al*., 1990). Histopathology of PDLG includes astrocytoma of various grades, glioblastoma, ependymoblastoma, oligodendroglioma, primitive neuroectodermal tumor and gliosarcoma (Debono *et al*., 2006; Fayet *et al*., 1994; Watanabe *et al*., 2008).

However, since then, several cases of PDLG have been described for which serial magnetic resonance imaging showed the late appearance of secondary brain parenchymal infiltration (Ashworth & Gordon, 1994; Davila *et al*., 1993; Riva *et al*., 2005). In the

WHO classification of tumours, PDLG is thus now defined as "a neoplasm, although largely leptomeningeal, associated with a parenchymal component small enough to be considered as an ingrowth from the meningeal lesion" (Kleihues & Sobin, 2000; Louis *et al*., 2007).

PDLG has been proposed to arise from heterotopic glial cell nests located into the leptomeninges that undergo neoplastic transformation followed by rapid and widespread leptomeningeal dissemination. Glial heterotopias are defined as nests or linear arrays of glioneuronal tissue in the meninges. Such heterotopic nests have been found in the subarachnoid space in about 1% of unselected necropsies (Goncalves *et al*., 2008). A higher incidence was observed (25%) in patients with congenital abnormalities of the central nervous system (Goncalves *et al*., 2008). The etiology of heterotopic glial nests is unknown but it is probably related to an abnormal migration of glio-neuronal precursor during antenatal development (Debono *et al*., 2006; Goncalves *et al*., 2008). In the patient that we report, as in the vast majority of published cases, we did not find heterotopic glial nests or arrays in the meninges, although these were not specifically and extensively searched for.

The genetic background of PDLG is still unknown. Some authors have reported DNA multiploidy and a correlation between leptomeningeal dissemination and mutations of p53 and PTEN. However, mutations of those genes are not specific of PDLG (Debono *et al*., 2006; Yomo *et al*., 2007). In our case, FISH analysis was not contributive probably due to fixation artefacts. However, the finding of p53 expression by immuno-histochemistry is consistent with a possible mutation of the TP53 gene.

PDLG occurs within a wide age range from one to 80 years and there is no gender predilection (Debono *et al*., 2006; Yomo *et al*., 2007). Mean age at presentation is 34 years and 18 cases have been described in children aged from 2 to 17 years (Debono *et al*., 2006; Felix, 2009).

The clinical presentation is variable, depending on the preferential location of the lesions (Debono *et al*., 2006). The most common manifestation is increased intracranial pressure often complicated by hydrocephalus, meningism, headaches and bilateral papilledema. Increased intracranial pressure is thought to result from an impaired absorption of CSF, variably caused by increased CSF protein content, subarachnoid haemorrhage, infiltration into a basal cistern and tumour compression of a venous plexus (Kobayashi *et al*., 1996; Riva *et al*., 2005). Cranial nerve palsy is also common and may be caused by intracranial hypertension or direct invasion of peripheral nerve by tumour cells in the subarachnoid space. Spinal root involvement, epilepsy, confusion, mental status change, back pain and tetraparesis have also been described (Goncalves *et al*., 2008; Ko *et al*., 2009; Yomo *et al*., 2007). Focal signs seem related to focal vascular involvement following tumour extension along the Virchow-Robin spaces (Jicha *et al*., 2009).

Blood chemistry and cell counts are most often normal. An inflammatory syndrome, as was present in our case, has been occasionally reported (Goncalves *et al*., 2008). CSF analysis usually shows an increase of the protein content and a normal or low glucose value that can mislead to a diagnosis of tuberculosis or fungal meningitis (Goncalves *et al*., 2008; Yomo *et al*., 2007). Repeated lumbar punctures often fail to find malignant cells probably because of their adhesive nature with a meshwork of cell processes holding the cells together (Ko *et al*., 2009). When atypical cells are seen, GFAP staining should be performed to differentiate PDGL from chronic aseptic meningitis or leptomeningeal carcinomatosis (Bilic *et al*., 2005; Ishige *et al*., 2007).

CT scan findings are non-specific. Ventricular dilatation is seen in 50% of patients (Debono *et al*., 2006). Improved imaging techniques and particularly gadolinium-enhanced MRI has made the diagnosis of PDLG more common during the patient's life (Jicha *et al*., 2009). In most case MRI with gadolinium demonstrates enhancement of the leptomeninges (especially around the brainstem, cerebellum and the spinal cord) and of the periventricular regions. Ventricular enlargement and effacement of the cortical sulci is also often seen (Corsten *et al*., 2001; Debono *et al*., 2006; Ishige *et al*., 2007; Riva *et al*., 2005). FLAIR (Fluid Attenuated Inversion Recovery) sequence can be useful as it shows diffuse high intensities in the subarachnoid space similar to FLAIR images of acute subarachnoid haemorrhage (Yomo *et al*., 2007). In this context, the absence of an intra-parenchymal component should raise the possibility of PDLG. In some cases, brain MRI can be negative and the diagnosis relies then entirely on the post-mortem examination, which should always be performed in both definite and suspected cases (Davila *et al*., 1993; Riva *et al*., 2005).

Due to the lack of specificity of clinical presentation, CSF and imaging findings, PDLG is often misdiagnosed. The differential diagnoses include, secondary meningeal gliomatosis, metastatic carcinomatous meningitis and infectious or autoimmune meningitis (Debono *et al*., 2006; Fayet *et al*., 1994; Watanabe *et al*., 2008). Among infectious meningitis, tuberculosis is often suggested because of the

Table 1

Case	Age	Sex	Treatment	Time between first symptoms and death
(Armao *et al*., 2000)	8	M	Non oncologic	5 years
(Ashworth & Gordon, 1994)	69	F	Unknow	6 weeks
(Bae *et al*., 2000)	18	F	Non oncologic	Unknow
(Bailey & Robitaille 1985)	53	M	Non oncologic	84 days
(Baborie *et al*., 2001)	71	M	Non oncologic	7 months
(Beauchesne *et al*., 1998)	17	M	Corticospinal RT, CT (MTX it and SFOP 91)	23 months
(Bhrany *et al*., 1974)	46	F	Non oncologic	2 months
(Bilic *et al*., 2005)	19	M	Craniospinal RT	13 months
(Blumenkopf *et al*., 1986)	48	M	RT	Alive at time of report
(Bohner *et al*., 2005)	25	M	CT (VCR-CBDCA)	3 months
(Bourne *et al*., 2006)	2	M	CT (CDDP, VRC, CPM, VP16 as induction ; thiotepa and CBDCA for 6 months; sequential VP16, CPM, TMZ and isoretinoin as maintenance.	Alive at time of report
(Carpentier *et al*., 1994)	44	F	CT (MTX it)	5 months
(Chen *et al*., 1995)	17	F	RT, CT ((PCZ-CCNU-VCR)	Unknow
(Corsten *et al*., 2001)	44	M	RT	Unknow
(Davila *et al*., 1993)	38	M	RT, CT (MTX it)	3 months
(Debono *et al*., 2006)	50	M	Non oncologic	7 months
(Dietrich *et al*., 1993)	63	F	Non oncologic	40 days
(Fayet *et al*., 1994)	53	F	Non oncologic	6 months
(Fayet *et al*., 1994)	55	F	Unknow	40 days
(Franceschi *et al*., 2005)	40	F	CT (TMZ-CBDCA-VP16-BCNU)	17 months
(Giordana *et al*., 1995)	49	F	CT (MTX it-AraC it)	5 months
(Goncalves *et al*., 2008)	13	M	CT (TMZ, CDDP, VP16)	Unknow
(Havlik *et al*., 2001)	28	F	Non oncologic	1 day
(Heye *et al*., 1990)	43	M	Non oncologic	4 months
(Ho *et al*., 1981)	55	M	Non oncologic	3 months
(Ishige *et al*., 2007)	45	M	CT (MTX it-ADR-VCR- ACNU-PCZ)	18 months
(Janisch *et al*., 1991)	22	F	Unknow	78 months
(Jicha *et al*., 2009)	24	M	CT (TMZ-BCNU)	13 months
(Jicha *et al*., 2009)	19	M	RT, CT(TMZ)	11 months
(Jicha *et al*., 2009)	16	M	RT,CT(TMZ)	41 months(Alive at time of report)
(Jicha *et al*., 2009)	14	M	Craniospinal RT, CT (TMZ)	7 months
(Kastenbauer *et al*., 2000)	28	M	Non oncologic	5 months
(Kitahara *et al*., 1985)	15	F	RT, CT (ACNU It)	3 years 6 months
(Ko *et al*., 2009)	24	M	Non oncologic	6 months
(Kobayashi *et al*., 1996)	60	M	RT, CT	11 months
(Korein *et al*. 1957)	17	M	Non oncologic	18months
(Leproux *et al*., 1993)	13	F	RT	Unknow
(Michotte *et al*., 2009)	60	M	RT, CT(TMZ)	2 years (Alive at time of report)
(Ng & Poon, 1999)	6	F	Non oncologic	65 days

(Olivera-Leal *et al*., 1997)	24	F	Non oncologic	4 months
(Ozkul *et al*., 2007)	25	F	Non oncologic	15 months
(Park *et al*., 1996)	21	F	RT, CT (PCZ-CCNU-VCR)	5 months
(Paulino *et al*., 1999)	9	F	RT, CT (VP16/CBDCA/VCR/CCNU), Topotecan it	Alive at time of report
(Pingi *et al*., 1995)	19	M	Unknow	50 days
(Pradat *et al*., 1999)	35	M	Cranial RT, MTX it	40 days
(Pradat *et al*., 1999)	44	M	Cranial RT, MTX it	1 months
(Radhakrishnan *et al*., 1994)	12	F	Non oncologic	3 months
(Ramsay *et al*., 1990)	34	M	RT	7 months
(Rees *et al*., 2001)	34	F	Non oncologic	3 months one week
(Rees *et al*., 2001)	28	M	Non oncologic	4 months one week
(Rees *et al*., 2001)	51	M	CT(MTX it-CMP-ADR-5-FU)	6 weeks and two days
(Riva *et al*., 2005)	62	F	Non oncologic	3 weeks
(Rogers *et al*., 1995)	21	M	RT	4 years 2 months
(Sell *et al*., 2000)	62	M	RT, CT (MTX it)	4 months
(Singh *et al*., 2009)	20	M	CT (MTX it)	110 months
(Sumi & Leffman, 1968)	61	M	Non oncologic	3 months
(Trivedi *et al*., 2000)	80	M	Unknow	10 weeks
(Tsui *et al*., 2001)	23	F	Non oncologic	47 days
(Verslegers *et al*., 1998)	7	M	Unknow	8 months
(Wacker *et al*., 1992)	1	F	RT CT (6 thioguanine-CCNU-PCZ-dibromodulcitol)	5 months
(Wada *et al*., 1986)	17	F	Non oncologic	3 months
(Watanabe *et al*., 2008)	48	F	Craniospinal RT, CT (ACNU-INF)	11 months
(Whelan *et al*., 1987)	42	F	Non oncologic	38 days
(Whelan *et al*., 1987)	11	M	Non oncologic	5 months
(Whelan *et al*., 1987)	12	F	Non oncologic	4 months
(Yomo *et al*., 2007)	52	M	Craniospinal RT, CT(MCNU-INF)	3 months
Our case	76	M	Non oncologic	8 weeks

RT: Radiotherapy; CT: Chemotherapy; it: intrathecal injection; MTX: Methotrexate; AraC: Cytarabine; PCZ: Procarbazine; CBDCA: Carboplatine; VCR: Vincristine; ACNU: Nimustine; BCNU: Carmustine; CCNU: Lomustine; MCNU: Ranimustine; VP16: Etoposide; INF: Interferon; CDDP: Cisplatin; CPM: Cyclophosphamide; TMZ: Temozolomide; SFOP 91 protocol: VCR/BCNU/Methylprednisolone/PCZ/Hydroxyurea/CDDP/AraC/CPM.

combined finding of raised protein and low glucose level, with mild pleiocytosis.

Surgical meningeal biopsy is the most efficient investigation for primary tumoural involvement of the leptomeninges and can provide an ante-mortem diagnosis of PDLG enabling specific treatment (Yomo *et al*., 2007). Biopsy should be guided by MRI and performed in a contrast enhancing area (Beauchesne *et al*., 1998; Debono *et al*., 2006). Biopsy material may be normal or inconclusive even if the biopsy samples affected leptomeninges (Yomo *et al*., 2007). Non-diagnostic leptomeningeal biopsies in PDLG may be explained by the predilection of leptomeningeal gliomatosis to involve the skull base more than the cerebral convexity where biopsies are usually performed (Dietrich *et al*., 1993; Ko *et al*., 2009; Yomo *et al*., 2007). In other cases, biopsy reveals a glioma or a non-specific inflammatory reaction (Yomo *et al*. 2007). Although rare, extraneuraxic metastatic lesions have been described in PDLG

(Debono *et al*., 2006; Ko *et al*., 2009; Myers *et al*., 1990; Pingi *et al*., 1995; Schatzki *et al*., 1977). They appear in the bone and are usually more osteoblastic than osteolytic (Debono *et al*., 2006). In the patient reported here, surgical biopsy of meninges was not performed due to the poor general condition of the patient. A diagnostic biopsy was rather performed on an osteolytic lesion of the parietal bone but it was not conclusive. This bone lesion was not re-evaluated at autopsy, unfortunately.

The prognosis is generally poor, although quite variable with a survival ranging from 1 day to more than 9 years. In the adult, median survival without oncologic treatment is 4 months but increases to 15,6 months for patients treated by radiotherapy and/or chemotherapy (see Table 1). Children have a median survival of 4 months without oncologic treatment but radiotherapy and/or chemotherapy improves survival with a median value of 23 months (Table 1). It is of note that rare patients, with histologically proven PDGL, have been reported to survive more than 110 months without aggressive treatment suggesting than long survival without aggressive therapy is possible (Singh *et al*., 2009).

Given the rarity of PDLG, the development of an effective treatment has been limited. The general symptomatic treatment includes ventricular drainage, steroids and antiepileptic therapy (Singh *et al*., 2009). However, peritoneal seeding of the tumour has been described as a complication of ventriculo-peritoneal shunt (Bilic *et al*., 2005). Specific therapy consists of whole CNS irradiation and/or chemotherapy (systemic and/or intrathecal or intraventricular) (Baborie *et al*., 2001; Beauchesne *et al*., 1998; Felix, 2009; Jicha *et al*., 2009; Singh *et al*., 2009). Cisplatin was mostly used in the published reports (Felix, 2009). More recently, temozolomide has shown promising results but this needs to be confirmed by longer follow-up studies and larger cohort (Franceschi *et al*., 2005; Goncalves *et al*., 2008; Yomo *et al*., 2007). Interestingly, oligodendroglial types of PDGL seem to have a better prognosis and cases of primary diffuse oligodendroglioma gliomatosis with combined loss of 1p/19q chromosomes may show a better response to chemotherapy (Michotte *et al*., 2009).

In conclusion, PDLG is a rare type of primary central nervous system tumour that enters the differential diagnoses of chronic/subacute meningitis. MRI guided biopsy of pathological leptomeninges is the most useful diagnostic tool. Untreated, PDLG has an extremely poor prognosis but survival can be markedly improved by early combined radio- and chemotherapy.

Acknowledgements

Dr. J. Somja is a research assistant for the Belgian FNRS (grant n° 7.4625.09).

REFERENCES

Armao DM, Stone J, Castillo M, Mitchell KM, Bouldin TW, Suzuki K. Diffuse leptomeningeal oligodendrogliomatosis: radiologic/pathologic correlation. AJNR Am J Neuroradiol. 2000;21:1122-6.

Ashworth B, Gordon A. 1994. Leptomeningeal gliomatosis. J Neurol Neurosurg Psychiatry 57:471-3.

Baborie A, Dunn EM, Bridges LR, Bamford JM. Primary diffuse leptomeningeal gliomatosis predominantly affecting the spinal cord: case report and review of the literature. J Neurol Neurosurg Psychiatry. 2001; 70:256-8.

Bae JY, Choi BO, SunWoo IN, Kim DI, Cho SH, Kim TS. Diffuse cerebrospinal gliomatosis with extensive leptomeningeal spread. Yonsei Med J. 2000;41: 517-21.

Bailey P, Robitaille Y. Primary diffuse leptomeningeal gliomatosis. Can J Neurol Sci. 1985;12:278-81.

Beauchesne P, Pialat J, Duthel R, Barral FG, Clavreul G. *et al*. Aggressive treatment with complete remission in primary diffuse leptomeningeal gliomatosis – a case report. J Neurooncol. 1998;37:161-7.

Bhrany D, Murphy MG, Horenstein S, Silbert SW. Diffuse periventricular and meningeal glioma. Acta Neuropathol. 1974;30:243-9.

Bilic M, Welsh CT, Rumboldt Z, Hoda RS. Disseminated primary diffuse leptomeningeal gliomatosis: a case report with liquid based and conventional smear cytology. Cytojournal. 2005;2:16.

Blumenkopf B, Gutierrez J, Bennett W. Primary leptomeningeal gliomatosis and "numb, clumsy hands": a case report. Neurosurgery. 1986;18:363-6.

Bohner G, Masuhr F, Distl R, Katchanov J, Klingebiel R. *et al*. Pilocytic astrocytoma presenting as primary diffuse leptomeningeal gliomatosis: report of a unique case and review of the literature. Acta Neuropathol. 2005;110:306-11.

Bourne TD, Mandell JW, Matsumoto JA, Jane JA Jr., Lopes MB. Primary disseminated leptomeningeal oligodendroglioma with 1p deletion. Case report. J Neurosurg. 2006;105:465-9.

Carpentier AF, Sanson M, Kujas M, Giroud M, Poisson M, Delattre JY. [Primary meningeal gliomatosis]. Rev Neurol (Paris). 1994;150:232-5.

Chen R, Macdonald DR, Ramsay DA. Primary diffuse leptomeningeal oligodendroglioma. Case report. J Neurosurg. 1995;83:724-8.

Cooper IS, Kernohan JW. Heterotopic glial nests in the subarachnoid space; histopathologic characteristics, mode of origin and relation to meningeal gliomas. J Neuropathol Exp Neurol. 1951;10:16-29.

Corsten LA, Raja AI, Wagner FC Jr. Primary diffuse leptomeningeal gliomatosis. Br J Neurosurg. 2001;15:62-6.

Davila G, Duyckaerts C, Lazareth JP, Poisson M, Delattre JY. Diffuse primary leptomeningeal gliomatosis. J Neurooncol. 1993;15:45-9.

Debono B, Derrey S, Rabehenoina C, Proust F, Freger P, Laquerriere A. Primary diffuse multinodular leptomeningeal gliomatosis: case report and review of the literature. Surg Neurol. 2006;65:273-82; discussion 82.

Dietrich PY, Aapro MS, Rieder A, Pizzolato GP. Primary diffuse leptomeningeal gliomatosis (PDLG): a neoplastic cause of chronic meningitis. J Neurooncol. 1993;15:275-83.

Fayet G, Bertout-Lemercier C, Gugenheim M, Auffray E, Jardel-Bouissiere J. *et al*. [Leptomeningeal gliomatosis. 2 clinicopathological cases]. Rev Neurol (Paris). 1994;150:700-3.

Felix FH. Primary diffuse leptomeningeal gliomatosis: a rare disease in pediatric patients. J Pediatr (Rio J). 2009;85:277-9; author reply 9-80.

Franceschi E, Cavallo G, Scopece L, Esposti RD, Paioli G. *et al*. Temozolomide-induced partial response in a patient with primary diffuse leptomeningeal gliomatosis. J Neurooncol. 2005;73:261-4.

Giordana MT, Bradac GB, Pagni CA, Marino S, Attanasio A. Primary diffuse leptomeningeal gliomatosis with anaplastic features. Acta Neurochir (Wien). 1995;132:154-9.

Goncalves AL, Masruha MR, Carrete Jr H, Stavale JN, Silva NS, Vilanova LC. Primary diffuse leptomeningeal gliomatosis. Arq Neuropsiquiatr. 2008; 66:85-7.

Havlik DM, Becher MW, Nolte KB. Sudden death due to primary diffuse leptomeningeal gliomatosis. J Forensic Sci. 2001;46:392-5.

Heye N, Iglesias JR, Tonsen K, Graef G, Maier-Hauff K. Primary leptomeningeal gliomatosis with predominant involvement of the spinal cord. Acta Neurochir (Wien). 1990;102:145-8.

Ho KL, Hoschner JA, Wolfe DE. Primary leptomeningeal gliomatosis: symptoms suggestive of meningitis. Arch Neurol. 1981;38:662-6.

Ishige S, Iwadate Y, Ishikura H, Saeki N. Primary diffuse leptomeningeal gliomatosis followed with serial magnetic resonance images. Neuropathology. 2007;27:290-4.

Janisch W, Engel U, Leonhardt T. [Diffuse primary leptomeningeal gliomatosis]. Zentralbl Pathol. 1991; 137:523-30.

Jicha GA, Glantz J, Clarke MJ, Lehwald LM, Russo DP. *et al*. Primary diffuse leptomeningeal gliomatosis. Eur Neurol. 2009;62:16-22.

Kastenbauer S, Danek A, Klein W, Yousry TA, Bise K. *et al*. Primary diffuse leptomeningeal gliomatosis: unusual MRI with non-enhancing nodular lesions on the cerebellar surface and spinal leptomeningeal enhancement. J Neurol Neurosurg Psychiatry. 2000;69:385-8.

Kitahara M, Katakura R, Wada T, Namiki T, Suzuki J. Diffuse form of primary leptomeningeal gliomatosis. Case report. J Neurosurg. 1985;63:283-7.

Kleihues P, Sobin LH. World Health Organization classification of tumors. Cancer. 2000; 88:2887.

Ko MW, Turkeltaub PE, Lee EB, Gonatas NK, Volpe NJ. *et al*. Primary diffuse leptomeningeal gliomatosis mimicking a chronic inflammatory meningitis. J Neurol Sci. 2009;278:127-31.

Kobayashi M, Hara K, Nakatsukasa M, Murase I, Toya S. Primary spinal leptomeningeal gliomatosis presenting visual disturbance as the initial symptom: case report. Acta Neurochir (Wien). 1996;138:480-1.

Korein J, Feigin I, Shapiro MF. Oligodendrogliomatosis with intracranial hypertension. Neurology. 1957;7: 589-94.

Leproux F, Melanson D, Mercier C, Michaud J, Ethier R. Leptomeningeal gliomatosis: MR findings. J Comput Assist Tomogr. 1993;17:317-20.

Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, *et al*. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol. 2007;114:97-109.

Michotte A, Chaskis C, Sadones J, Veld PI, Neyns B. Primary leptomeningeal anaplastic oligodendroglioma with a 1p36-19q13 deletion: report of a unique case successfully treated with Temozolomide. J Neurol Sci. 2009;287:267-70.

Myers T, Egelhoff J, Myers M. Glioblastoma multiforme presenting as osteoblastic metastatic disease: case report and review of the literature. AJNR Am J Neuroradiol. 1990;11:802-3.

Ng HK, Poon WS. Diffuse leptomeningeal gliomatosis with oligodendroglioma. Pathology. 1999;31:59-63.

Olivera-Leal IR, Gomez-Viera N, Gonzalez-Espinosa L, Borrajero-Martinez I, Alvarez-Santana R, Cubero-Rego D. [Primary diffuse leptomeningeal gliomatosis. Presentation of one case]. Rev Neurol. 1997; 25:1419-21.

Ozkul A, Meteoglu I, Tataroglu C, Akyol A. Primary diffuse leptomeningeal oligodendrogliomatosis causing sudden death. J Neurooncol. 2007;81: 75-9.

Park JS, van den Noort S, Kim RC, Walot I, Licht H. Primary diffuse leptomeningeal gliomatosis with signs of increased intracranial pressure and progressive meningeal enhancement on MRI. J Neuroimaging. 1996;6:250-4.

Paulino AC, Thomas C, Slomiany DJ, Suarez CR. Diffuse malignant leptomeningeal gliomatosis in a child: a case report and review of the literature. Am J Clin Oncol. 1999;22:243-6.

Pingi A, Trasimeni G, Di Biasi C, Gualdi G, Piazza G. *et al*. Diffuse leptomeningeal gliomatosis with osteoblastic metastases and no evidence of intraaxial lesions. AJNR Am J Neuroradiol. 1995;16: 1018-20.

Pradat PF, Hoang-Xuan K, Cornu P, Mokhtari K, Martin-Duverneuil N. *et al*. Treatment of meningeal gliomatosis. J Neurooncol. 1999;44:163-8.

Radhakrishnan VV, Saraswathy A, Rout D. Diffuse form of primary leptomeningeal gliomatosis — a

case report. Indian J Pathol Microbiol. 1994;37 Suppl:S51-3.
Ramsay DA, Goshko V, Nag S. Primary spinal leptomeningeal astrocytoma. Acta Neuropathol. 1990;80:338-41.
Rees JH, Balakas N, Agathonikou A, Hain SF, Giovanonni G. *et al*. Primary diffuse leptomeningeal gliomatosis simulating tuberculous meningitis. J Neurol Neurosurg Psychiatry. 2001;70:120-2.
Riva M, Bacigaluppi S, Galli C, Citterio A, Collice M. Primary leptomeningeal gliomatosis: case report and review of the literature. Neurol Sci. 2005;26: 129-34.
Rogers LR, Estes ML, Rosenbloom SA, Harrold L. Primary leptomeningeal oligodendroglioma: case report. Neurosurgery. 1995;36:166-8; discussion 9.
Schatzki SC, Mc IG, Lowis S. Diffuse osteoblastic metastases from an intracranial glioma. AJR Am J Roentgenol. 1977;128:321-3.
Sell M, Mitrovics T, Sander BC. Primary nodular meningeal glioma mimicking metastatic tumor of the cerebellum with diffuse infra- and supratentorial leptomeningeal spread. Clin Neuropathol. 2000;19:126-30.
Singh A, Kesavadas C, Radhakrishnan M, Santhosh K, Nair M, *et al*. Primary diffuse leptomeningeal gliomatosis. J Neuroradiol. 2009;36:52-6.
Sumi SM, Leffman H. Primary intracranial leptomeningeal glioma with persistant hypoglycorrhachia. J Neurol Neurosurg Psychiatry. 1968;31: 190-4.
Trivedi RA, Nichols P, Coley S, Cadoux-Hudson TA, Donaghy M. Leptomeningeal glioblastoma presenting with multiple cranial neuropathies and confusion. Clin Neurol Neurosurg. 2000;102: 223-6.
Tsui EY, Loo KT, Mok CK, Yuen MK, Cheung YK. Primary multifocal leptomeningeal gliomatosis. Eur J Radiol. 2001;37:5-7.
Verslegers I, Demaerel P, Van Calenbergh F, Sciot R. Primary multifocal leptomeningeal gliomatosis. Pediatr Radiol. 1998;28:580-2.
Wacker MR, Cogen PH, Etzell JE, Daneshvar L, Davis RL, Prados MD. Diffuse leptomeningeal involvement by a ganglioglioma in a child. Case report. J Neurosurg. 1992;77:302-6.
Wada C, Kurata A, Hirose R, Tazaki Y, Kan S. *et al*. Primary leptomeningeal ependymoblastoma. Case report. J Neurosurg. 1986;64:968-73.
Watanabe Y, Hotta T, Yoshioka H, Itou Y, Taniyama K, Sugiyama K. Primary diffuse leptomeningeal gliosarcomatosis. J Neurooncol. 2008;86:207-10.
Whelan HT, Sung JH, Mastri AR. Diffuse leptomeningeal gliomatosis: report of three cases. Clin Neuropathol. 1987;6:164-8.
Yomo S, Tada T, Hirayama S, Tachibana N, Otani M. *et al*. A case report and review of the literature. J Neurooncol. 2007;81:209-16.

M. Deprez,
Laboratory of Neuropathology,
B35, C.H.U, University of Liege,
4000 Liege (Belgium).
E-mail: Manuel.Deprez@ulg.ac.be