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Case Report

Primary histiocytic sarcoma presenting as diffuse leptomeningeal disease: Case description and review of the literature

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Histiocytic sarcoma is a rare malignant neoplasm arising most commonly in lymph nodes, intestinal tract, skin and soft tissue. The incidence of primary CNS histiocytic sarcoma is even rarer with a total of just 27 cases reported in the literature so far. Herein we describe the first autopsy case of histiocytic sarcoma presenting as a diffuse leptomeningeal disease in absence of a CNS tumor-forming parenchymal lesion. The clinical, pathological and immunophenotypic features are described and an updated literature review on primary CNS histiocytic sarcoma is included.

Key words: brain, central nervous system, histiocytic sarcoma, malignant histiocytosis, meninges.

INTRODUCTION

Histiocytic sarcoma (HS) is a rare malignant neoplasm showing morphologic and immunophenotypic evidence of histiocytic differentiation.[1] There is a wide age range distribution from infant to elderly; however, most cases occur in adults with a male predominance. Histologically it is composed of a diffuse proliferation of large, round to ovoid pleomorphic cells. An extensive immunophenotypic work-up is essential before diagnosing HS. The most common sites of involvement are lymph nodes, intestinal tract, skin and soft tissue. Primary CNS HS is extremely rare and only 27 cases have been reported so far.[2–25] Of these, 26 were localized parenchymal or dural masses and only one case[2] in a 20-month-old boy was clinically confined to the leptomeninges. To the best of our knowledge this is the first reported autopsy case of primary HS diffusely involving the meninges. The tumor was mostly confined to the leptomeninges around the brain and the entire spinal cord up to the cauda equina, with only limited microscopical parenchymal involvement of the CNS. Clinical and radiological findings together with autopsy results are described. A review of the few reported cases of primary CNS HS is also included.

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CLINICAL SUMMARY

A 45-year-old woman was admitted to hospital for progressively severe headaches associated with episodes of vomiting, dizziness and unsteadiness, lasting for 1 month. On admission she was afebrile and her vital signs were normal. Neurological examination revealed deviation to the right of the oral rhyme, paraparetic deambulation, bilateral nystagmus, left seventh cranial nerve troncular paresis, normal reflexes and absence of motor deficits. She had no lymphadenopathy, splenomegaly, hepatomegaly or skin lesions. Blood tests showed no specific findings. Examinations for infections such as HIV, syphilis, toxoplasma, Epstein–Barr virus, hepatitis B and C viruses were all negative. Her past medical history was relevant only for a prolactin-secerning pituitary microadenoma; the patient had been on treatment with cabergoline for 10 years. CT scan and MRI (Fig. 1A.B) of the brain and spinal cord revealed prominent and diffuse thick leptomeningeal enhancement. The brain, the entire spinal cord up to the cauda equina and the nerve roots were covered with thick

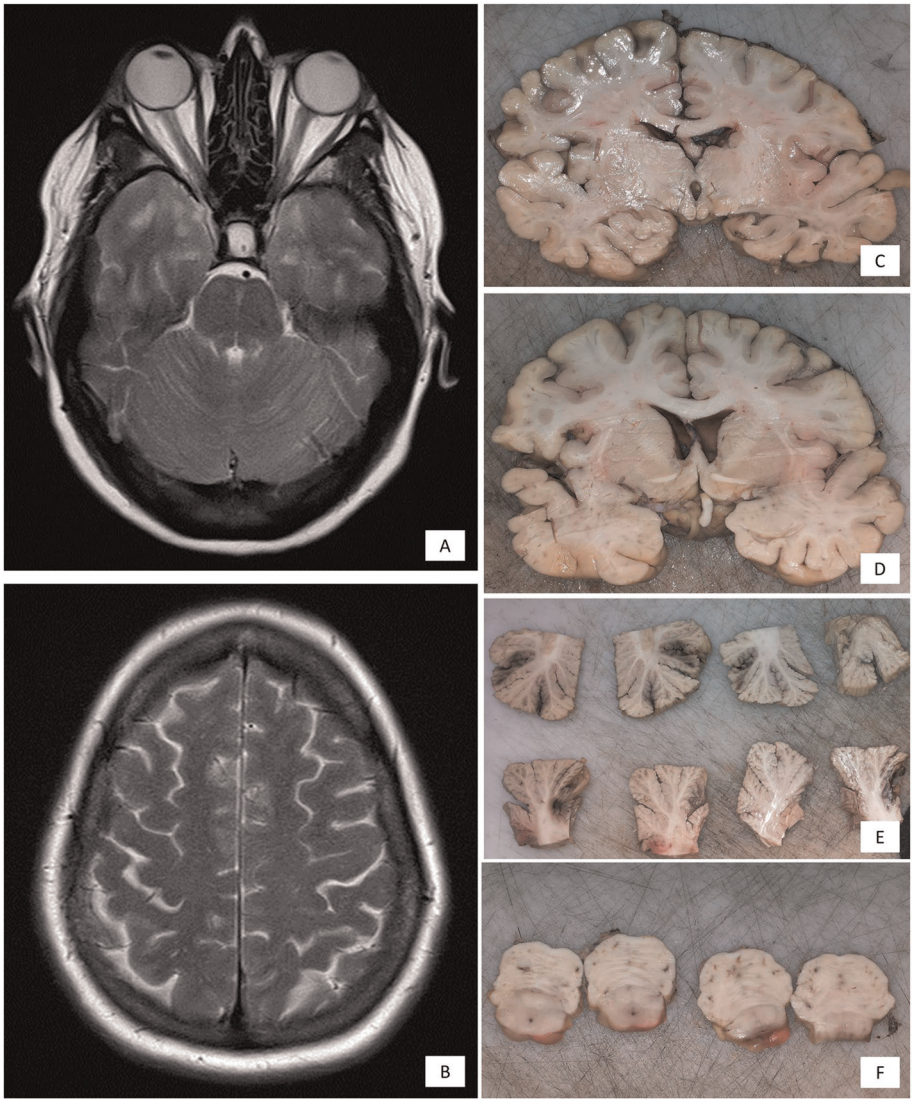

Fig. 1 (A, B) Magnetic resonance imaging demonstrating meningeal enhancement with no evidence of parenchymal lesions (axial T2 images). (C-F) On gross examination the brain is unremarkable.

enhancing tissue with an absence of parenchymal space-occupying lesions either in the brain or in the spinal cord. Multiple cultures of the CSF for bacteria, virus and fungi were all negative. Cytological examinations of CSF failed to detect neoplastic cells. Bone scan, chest X-ray, chest and abdominal CT scans were all unremarkable. Given the clinical presentation and the findings on imaging, the differential diagnoses included inflammatory and neoplastic lesions. The clinical conditions of the patient rapidly deteriorated; she developed multiple cranial nerve paralysis and endocranial hypertension. Four weeks after her admission, she had cardio-respiratory arrest and died.

PATHOLOGICAL FINDINGS

A complete autopsy was performed. Gross examination of the brain and spinal cord was unremarkable (Fig. 1). No abnormalities were found in the thoracic and abdominal organs. Histological examination and immunohistochemistry were performed on formalin-fixed, paraffin-embedded multiple sections from the nervous system. On histology (Fig. 2) the subarachnoid spaces of both the brain (Fig. 2A) and spinal cord (Fig. 2B,C) were filled with noncohesive, large pleomorphic cells, round to oval in shape with a quite abundant, eosinophilic cytoplasm (Fig. 2D). Few microscopical foci of brain parenchimal infiltration by noncohesive large cells were detectable (Fig. 2E,F). The cells were highly atypical with pleomorphic and irregularly folded nuclei (Fig. 2G,H). There were 10 mitoses/10 high-powered fields, some of which were atypical (Fig. 2H) and the proliferative index (Ki67) was about 20% (Fig. 2H, insert). The neoplastic cells represented the dominant cell population and rare neutrophils and lymphocytes were present in the background. The immunohistochemical results are summarized in Table 1. An extensive immunohistochemical panel was performed to characterize the atypical cells which were strongly positive for the histiocytic markers CD68PGM1 (Fig. 2D, inset),

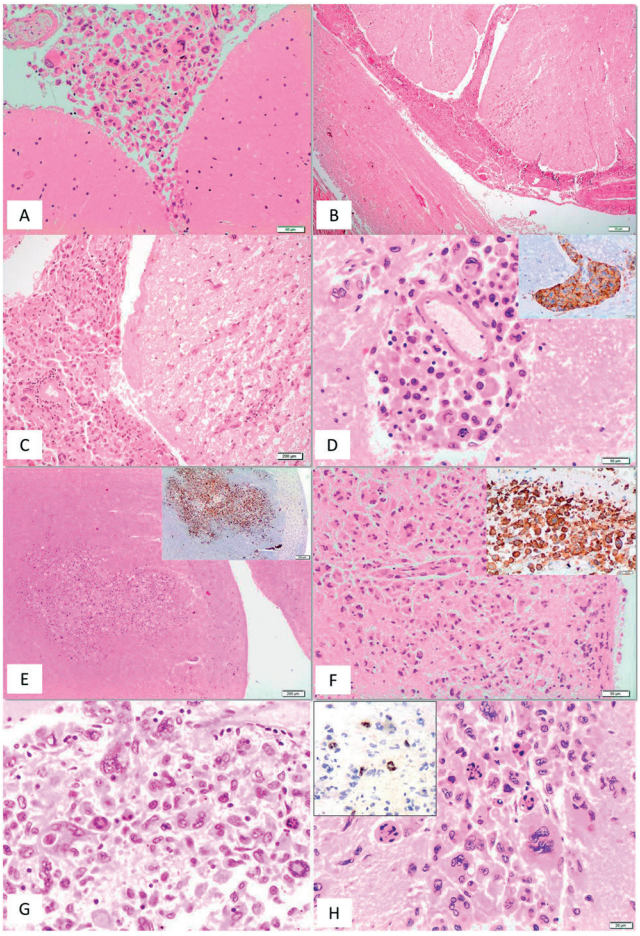

Fig. 2 (A) Cerebral subarachnoid space filled with noncohesive large, pleomorphic cells (HE stain 200×). (B) Spinal cord subarachnoid space filled with neoplastic cells (HE 40×). (C) A high-power view showing spinal cord subarachnoid space filled with large, pleomorphic cells and a focus of parenchymal infiltration (HE 200×). (D) A focus of perivascular neoplastic infiltration at high-power view. The cells are large with pleomorphic nuclei and abundant eosinophilic cytoplasms (HE stain 400×). Inset, the neoplastic cells are diffusely positive for CD68PGM1. (E) A focus of brain parenchyma infiltration by neoplastic cells at low power (HE stain 20×). Inset, immunohistochemistry highlights the neoplastic cells diffusely positive for CD163. (F) A focus of highly pleomorphic cells with irregular nuclei infiltrating brain parenchyma, at high-power view (HE stain 200×). Inset, diffuse positivity for CD163. (G) A high-power view showing highly atypical cells with pleomorphic and irregularly folded nuclei (HE stain 400×). (H) A high-power view showing pleomorphic nuclei and atypical mitoses (HE stain 400×). (H insert) Proliferative index (Ki67).

lysozyme and CD163 (Fig. 2F insert, 2F inset) and focally positive for CD4 and CD45. The tumor cells were negative for T-cell, B-cell, plasma-cell and NK-cell-associated markers (CD3, CD2, CD5, CD7, CD8, CD20, CD79alfa, PAX5, CD138, CD56, CD57, TIA-1, perforin, granzyme B). There was no staining for CD30, ALK-1 and CD15, ruling out anaplastic large cell lymphoma (ALCL) and Hodgkin's disease (HD). The cells were negative with myeloid markers (CD34, myeloperoxidase), follicular dendritic cell markers (CD21, CD23, CD35) and Langerhans cell marker (CD1a, langerin). In addition, no staining was found using epithelial markers such as low molecular weight and high molecular weight cytokeratins and epithelial membrane antigen excluding carcinoma and meningioma. Negative stainings for S100, HMB45, GFAP and Olig2 excluded melanoma and glioblastoma. Chromogranin and prolactin staining were negative. BRAF V600E staining was negative as well. A diagnosis of primary HS diffusely involving the leptomeninges of the brain and spinal cord was rendered. Histological evaluation of bone marrow did not show any evidence of neoplastic infiltration. Genetic assessment did not detect clonal IG and T-cell receptor (TCR) gene rearrangements.

Table 1 Immunohistochemical results

Immunohistochemistry	Clone (dilution)	Results
CD68	PGM1 (1:50)	+
CD163	10D6*	+
Lysozyme	BioGenex polyclonal (1:100)	+
CD4	SP35*	Focally +
CD45	2B11ePD7/26*	Focally +
CD3	2GV6*	–
CD2	LFA-2 (1:50)	–
CD5	SP19*	–
CD7	CD7-272 (1:50)	–
CD8	SP57*	–
CD20	L26*	–
CD79alfa	SP18*	–
PAX5	SP34*	–
CD138	B-A38*	–
CD56	123C3*	–
CD57	NK-1 (1:100)	–
TIA-1	2G9AI0F5 (1:100)	–
Perforin	MRQ-23*	–
Granzyme B	Polyclonal*	–
CD30	Ber-H2*	–
CD15	MMA*	–
CD34	QBend/10*	–
Myeloperoxidase	Dako polyclonal (1:4000)	–
CD21	EP3093*	–
CD23	SP23*	–
CD35	RLB25 (1:50)	–
CD1a	EP3622*	–
Langerin/CD207	Cell Marque 12D6 (1:150)	–
Cytokeratin AE1/AE3	AE1/AE3/PCK26*	–
Cytokeratin CAM5.2	CAM5.2*	–
Cytokeratin 34βE12	34βE12*	–
EMA	E29*	–
S100	Polyclonal*	–
Melanosoma	HMB45*	–
GFAP	EP/Y (1:200)	–
Olig2	211F1.1 (1:100)	–
Chromogranin	LK2H10*	–
Prolactin	Cell Marque polyclonal (1:150)	–
BRAF V600E	VE1 (1:50)	–

*Prediluted Ventana benchmark; +, positive; –, negative.

DISCUSSION

HS is an extremely rare malignant neoplasm, accounting for less than 1% of all hematolymphoid neoplasms.[26] According to the 2008 WHO classification of tumors of hematopoietic and lymphoid tissue, diagnosis of HS requires histological and immunohistochemical evidence of histiocytic differentiation.[1] In the 2016 revised WHO classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages, the term malignant histiocytosis is used to refer to HS.[27] Given the changes occurring in the classification of systemic lymphomas and histiocytic neoplasms over the past decade, the 2016 CNS WHO classification parallels the categories in the corresponding hematopoietic WHO classification.[28] By definition HS diagnosis relies on the expression of at least two of the histiocytic markers such as CD68PGM1, lysozyme and CD163. In particular CD163 is considered a more specific histiocytic marker compared with CD68PGM1 which can be positive in other entities such as in some carcinomas, melanoma, follicular dendritic cell neoplasms, some lymphomas and rarely in glioblastoma.[29] HS is a diagnosis of exclusion. Therefore an appropriate immunohistochemical panel is essential in order to rule out B- and T-cell lymphomas, especially anaplastic large cell lymphoma (ALCL), dendritic and Langerhans cell neoplasms, myeloid neoplasms, carcinoma, melanoma and glioblastoma. True histiocytic sarcoma, as defined by strict criteria, is a very rare neoplasm. It is nowadays well recognized that most cases previously reported as HS are now classified as non-Hodgkin's lymphomas, in particular ALCL and diffuse large B cell lymphoma (DLBCL), based on immunohistochemical and gene rearrangement studies.[11] HS is reported to arise in lymph nodes, and in extranodal sites (especially intestinal tract and skin) often presenting in a clinically advanced stage and with an aggressive clinical course.[1]

Primary CNS HS is very rare with a total of 28 cases, including the present case, reported so far in the literature.[2–25] The clinicopathological features of the cases are summarized in Table 2. The patients (15 male and 13 female) ranged in age from 17 months to 71 years and presented with different neurologic symptoms depending on the CNS site involved. Primary CNS HS should be suspected when facing rapidly evolving neurological symptoms. Twenty-six of these patients presented parenchymal or dural masses. Only two cases, including our case, were confined to leptomeninges; the case described by Torres *et al.* in a 20-month-old boy appeared clinically confined to leptomeninges. In our case post-mortem examination proved the predominant leptomeningeal involvement in absence of a tumor-forming parenchymal lesion.[2] Histologically all tumors showed morphological and immunohistochemical evidence of histiocytic differentiation. Twenty-one cases, including our case, were evaluated for CD163.[5–15,17,18,20–25] As already said, CD163 expression is limited to neoplasms of monocytic/histiocytic derivation and is more specific than other markers such as CD68PGM1.[29] An interesting feature identified in 15 out of 27 cases was the presence of a sometimes-prominent inflammatory infiltrate admixed with the tumor cells.[3–5,9,11–13,16,19,22,24,25] This feature is considered particularly common in HS involving the CNS when compared to HS occurring in other sites.[3] The presence of an intense inflammatory infiltrate can be somewhat misleading, masking the neoplastic cells, as described in the Almefty *et al.* case in which two biopsies suggestive of abscess were obtained prior to arrival at HS diagnosis.[16] CNS HS is an aggressive neoplasm with a grim prognosis. Owing to the small number of cases reported there are no standard treatment guidelines. Surgery, chemotherapy and radiotherapy are the common therapeutic modalities of choice. An interesting therapeutic option with a BRAF-inhibitor (vemurafenib) is reported[17] in a case of HS showing BRAF V600E mutation. BRAF mutations are known to be oncogenic in different neoplasms and are often detected in Langerhans cell histiocytosis and only rarely in other histiocytoses.[27]

CNS HS generally pursues an aggressive clinical course with survival ranging from 3 to 16 months. Among the cases reported to date there are only eight cases with longer survival.[5,11–13,19,20,22] A case with 3.5 years disease-free survival prior to mediastinal relapse is described by Cao.[5] The patient died 7 months after mediastinal recurrence. Bell described two cases of solitary meningeal lesions with a good outcome following surgical excision alone, at 24 months and 10 months.[11] The case reported by Wu followed an indolent course with the patient alive without disease 1.5 years after total tumor resection and radiotherapy.[12] Perez-Ruiz described a case with 42 months of disease-free survival following total tumor resection plus chemoradiotherapy.[13] Bai as well reported a case with 16 months of disease-free survival after complete tumor resection plus chemoradiotherapy.[19] Foster reported a 23-month recurrence-free pediatric case of HS following total tumor resection plus radiotherapy and chemotherapy.[20] Brown described a 60 months survival in a 23-year-old man alive with disease, who presented with primary CNS HS 7 years after achieving remission for precursor B-cell acute lymphoblastic leukemia (B-ALL).[22] The longer survival in the cases of Bell,[11] Wu,[12] Perez-Ruiz,[13] Bai[19] and Foster[20] may be a reflection of the circumscribed nature of the tumors and their complete surgical excision.

HS is generally associated with a poor prognosis; however, non-disseminated primary CNS HS completely removed can potentially have a good outcome.[20]

Table 2 Clinicopathological features of the cases

Ref.	Age/sex	Site	Size	Clinical presentation	Inflammatory background	Markers of histiocytic differentiation/ electron microscopy	Therapy	Outcome/ autopsy performed*
Torres *et al.* 1996[2]	20 months/M	Diffuse leptomeningeal involvement	NA	8 weeks of vomiting, lethargy, generalized muscle weakness, seizures	No	CD68, Lysozyme/ EM not performed	Systemic and intrathecal CT	DOD 3 months
Cheuk *et al.* 2001[3]	69/F	Parietal lobe lesion	1.5 cm	R lower limb weakness	Yes	CD68PGM1, Lysozyme/ EM performed	Partial tumor resection + RT + CT	DOD 8 months
	43/M	Intradural, extramedullary, T9 spinal cord lesion	1.7 cm	Back pain, bilateral lower limbs weakness	Yes	CD68PGM1, Lysozyme/ EM performed	Partial tumor resection + RT + CT	AWD 5 months
	11/M	Cerebellum, L occipital, R frontal lobe lesions	0.7–1 cm	Dizziness, dyplopia, fever	Yes	CD68PGM1, Lysozyme/ EM performed	Partial tumor resection	DOD 4 months
Sun *et al.* 2003[4]	13/M	L occipital lesion + meninges	1.1 cm	3 months of headaches, seizures, shoulder pain	Yes	CD68KP1, Lysozyme/ EM performed	No treatment	DOD 7 months
Cao *et al.* 2007[5]	53/F	R retroorbital lesion	3.1 cm	Visual impairment, unsteadiness, headache	Yes	CD68, CD163/ EM not performed	Partial tumor resection + RT	DOD 7 months
Toshkez *et al.* 2010[6]	71/F	Intramedullary spinal lesion	2.5 cm	1 month of back pain, progressive unilateral lower limb weakness	No	CD68, CD163/ EM not performed	Partial tumor resection + RT	DOD 5 months
Gentzler *et al.* 2011[25]	52/F	Parietal brain lesion	1.7 cm	Right upper extremity weakness and difficulty in walking in a patient with synchronous lung cancer	Yes	CD68, CD163/EM not performed	No therapy	DOD
Gomi *et al.* 2012[7]	17months/F	Cerebellar lesion	4.7 cm	2 weeks of progressive gait disturbance	No	CD68, CD163/ EM performed	Partial tumor resection + CT	AWD 16 months
Wang *et al.* 2012[8]	55/F	Multiple lesions of brain parenchyma	ND	2 months of progressive hypomnesia, difficulty in walking	No	CD68, CD163/ EM not performed	Partial tumor resection + RT	DOD 4 months
Devic *et al.* 2012[9]	43/F	Multiple lesions of brain parenchyma and spinal cord	ND	3 weeks of progressive ataxia, headache, altered general status	Yes	CD68, CD163/ EM not performed	CT	DOD 10 months
Gill-Samra *et al.* 2012[10]	38/F	Multiple cerebral supratentorial lesions	5 cm	1–2 months of headache, nausea, vomiting, dizziness	No	CD68KP1, CD163/ EM performed	RT + CT	DOD 0,3 months
Bell *et al.* 2012[11]	62/F		ND	1 month of general malaise, dizziness,	Yes	CD68, CD163, Lysozyme	Total tumor resection	ANED 24 months

(*Continues*)

Table 2 (continued)

Ref.	Age/sex	Site	Size	Clinical presentation	Inflammatory background	Markers of histiocytic differentiation/ electron microscopy	Therapy	Outcome/ autopsy performed*
		Meningeal solitary lesion of tentorium cerebelli		unsteadiness, headache and vomiting				
	34/M	Meningeal solitary lesion of the R frontal region	2 cm	8 weeks of R-sided scalp numbness + onset of cluster headaches	Yes	CD68, CD163, Lysozyme/ EM not performed	Total tumor resection	ANED 10 months
Wu *et al.* 2013[12]	50/M	R occipital/parietal lobe lesion	1.5 cm	Discovered during FU 4 years later RT for recurrent pineal hemangioma	Yes	CD68, CD163, lysozyme/ EM not performed	Total tumor resection + RT	ANED 18 months
Perez-Ruiz *et al.* 2013[13]	41/F	Temporal lobe parenchymal lesion attached to dura mater	2 cm	Headache, generalized weakness, chills	Yes	CD68PGM1, CD163/ EM not performed	Total tumor resection + RT + CT	ANED 42 months
Chalasani *et al.* 2013[14]	44/M	Two brain lesions	3.5 cm	T-ALL 16 years prior, 2 weeks of unsteadiness, loss of balance and L-sided weakness	No	CD68PGM1, CD163/ EM not performed	CT + RT	DOD 6.7 months
Laviv *et al.* 2013[15]	58/M	Brain lesion	6.5 cm	3 weeks of gait instability and memory difficulties, headaches and urinary incontinence	No	CD68, CD163/ EM not performed	Total tumor resection. No additional therapies for bad clinical conditions	DOD 4.2 months
Almefty *et al.* 2013[16]	16/M	L parietal lobe lesion	4.4 cm	2 months of headaches, emesis and altered sensorium	Yes	CD68/ EM not performed	2 drainage procedures for presumed abscess. HS confirmed histologically from a third craniotomy. RT	DOD 4 months
Idbaih *et al.* 2014[17]	40/M	L temporal lesion	ND	Memory impairment, R-sided paresthesia, neck pain	ND	CD68, CD163./ EM not performed. BRAF V600E mutation identified	BRAF inhibitor Vemurafenib	DOD 6 months
Moulignier *et al.* 2014[18]	63/F	Lesions of both trigeminal nerves and left pontic lesion	ND	2 months of face paraesthesia	No	CD68, CD163./ EM performed	CT	DOD 0,6 months
Bai *et al.* 2014[19]	52/M	Intra-axial lesion in the frontal lobe	ND	15 days of weakness of the L lower limb	Yes	CD68, Lysozyme	Complete tumor resection + CT + RT	ANED 16 months
Foster *et al.* 2015[20]	15/F	R frontal lobe lesion	5.8 cm	2 months of headache, vomiting,	No	CD68, CD163./ EM not performed	Complete surgical resection + RT + CT	ANED 23 months

(*Continues*)

Table 2 (continued)

Ref.	Age/sex	Site	Size	Clinical presentation	Inflammatory background	Markers of histiocytic differentiation/ electron microscopy	Therapy	Outcome/ autopsy performed*
				neurocognitive deterioration				
Chen *et al.* 2015[21]	61/M	Extra-axial cavernous sinus lesion	ND	Tongue paresthesia	No	CD68, CD163/ EM performed	CT + RT	ND
Brown *et al.* 2015[22]	23/M	L cerebellopontine lesion, 7 years after B-ALL	6 cm	Headache, L-sided diplopia, L facial numbness, loss of smell and taste	Yes	CD68, CD163/ EM not performed	CT + RT	AWPD 60 months
So *et al.* 2015[23]	59/M	Multiple brain and spinal cord lesions	ND	2 months history of right side weakness and numbness in L leg	No	CD68, CD163/ EM not performed	CT (diagnosis achieved at second biopsy)	DOD 2 months
Ueno *et al.* 2016[24]	65/M	Masses in frontal/ parietal lobes + spinal cord + meningeal dissemination	ND	3 months of progressive impaired consciousness and headache	Yes	CD68PGM1, CD163/ EM not performed	RT	ANED 11 months
Current case	45/F	Diffuse leptomeningeal involvement	NA	10 years history of pituitary adenoma; 1 month headache, vomiting, unsteadiness	No	CD68PGM1, CD163/ EM not performed	NO therapy	DOD 2 months*

ANED, alive with no evidence of disease; AWD, alive with disease; AWPD, alive with progressive disease; B-ALL, B-acute lymphoblastic leukemia; CT, chemotherapy; DOD, died of disease; EM, electron microscopy; F, female; FU, follow-up; L, left; M, male; ND, not defined; R, right; RT, radiotherapy; T-ALL, T- acute lymphoblastic leukemia.

Our case shows some similarities with the case described by Torres *et al.* in 1997 in a 20-month-old boy presenting with leptomeningeal HS who underwent a meningeal biopsy and chemotherapy and died 3 months later. Torres *et al.*'s case and our case were both confined to leptomeninges with no tumor-forming CNS lesions.[2] Due to the diffuse leptomeningeal involvement at presentation both cases followed an aggressive course. As far as we are concerned, our case is the first autopsy-reported HS mainly confined to the cerebral and spinal leptomeninges. In the present case radiological and post-mortem examinations showed no evidence of a mass within the spinal and brain parenchyma and no signs of dissemination outside the CNS.

Meningeal infiltration can be seen in several different scenarios. It can occur as a secondary complication of aggressive neoplasms (carcinomas, melanomas or systemic non-Hodgkin's lymphomas) in patients with no evidence of CNS involvement at initial presentation. In addition, leptomeningeal involvement can occur in patients with primary parenchymal brain lymphomas. By contrast primary leptomeningeal lymphoma is very rare, accounting for 7% of all primary CNS lymphomas (PCNSL) and is defined as the presence of lymphomatous infiltration of the meninges without systemic lymphoma or parenchymal CNS involvement.[30]

Presenting this case, our aim is to direct attention to such a rare entity as HS, which seldom occurs primarily in the CNS and can have such a tricky clinicopathological presentation of leptomeningeal involvement without a tumor-forming lesion.

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