

Case Report

Leptomeningeal dissemination of anaplastic medullary cone astrocytoma: an unexpected findings in a patient with leptomeningeal enhancement and clinical history of multiple myeloma

Linda Daffini¹, Francesca Pagani¹, Manuela Cominelli¹, Giovanni Lodoli², Andrea Tironi³, Pietro Luigi Poliani¹

¹ Department of Molecular and Translational Medicine, Pathology Unit, University of Brescia, Italy; ² Neuroradiology Unit, Spedali Civili of Brescia, Italy; ³ Pathology Unit, Spedali Civili of Brescia, Italy

Summary

We report a challenging autopsy case with an insidious clinical presentation with diffuse lepto- and pachymeningeal enhancement in a context of a complex clinical history. Clinical features, neuroradiological and anamnestic data were consistent with central nervous system (CNS) dissemination of a previously known lambda restricted multiple myeloma. Autoptic findings allowed to discard this hypothesis. Unexpectedly, CNS sampling revealed an atypical glial cell proliferation within the sacral meningeal layers. No primary intraparenchymal CNS glial lesion was found. Findings supported the final diagnosis of anaplastic astrocytoma IDH1-wild type of the medullary cone with diffuse leptomeningeal and cerebrospinal fluid (CSF) dissemination. This occurrence represents an extremely rare condition itself, further complicated by the clinical history of the patient that led to formulate the most probable diagnosis of localization of the primary known disease. This autopsy case underlines that patients previously diagnosed with a primary tumor are not only at risk of recurrences or progression of the original disease, but they must be always accurately checked for eventual onset of a second tumor, including rare conditions such as gliomatosis.

Key words: astrocytoma, leptomeningeal dissemination, multiple myeloma, spinal cord neoplasms, conus medullaris

Introduction

Diffuse leptomeningeal enhancement may be due to a variety of pathological conditions, including neoplastic processes such as carcinomatous meningitis or lymphomatous infiltration of the meninges. Central nervous system (CNS) involvement with leptomeningeal diffusion may be also a complication of multiple myeloma albeit occurs rarely with an incidence of less than 1% of cases ¹. Typically, myelomatous involvement of the CNS occurs in patients with a previous history of myeloma, rather than as a primary presentation. Contrast-enhanced MRI represents a useful tool in the diagnosis and staging of multiple myeloma with possible leptomeningeal manifestations. We herein report a case of a 68-year-old male patient with a previous diagnosis of indolent lambda restricted multiple myeloma hospitalized in our Institution due to progressive worsening of neurological symptoms. MRI of the brain and spinal cord revealed a diffuse leptomeningeal enhancement, interpreted as dissemination of

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Correspondence

Pietro Luigi Poliani
Pathology Unit, Department of Molecular and Translational Medicine, University of Brescia Medical School, p.le Spedali Civili 1, 25125, Brescia, Italy
Tel.: 030 3998 407
Fax: 030-3995-377
E-mail: luigi.poliani@unibs.it

Conflict of interest

The Authors declare no conflict of interest.

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multiple myeloma. General conditions declined rapidly and patient died. Autopsy was performed but no evidence of CNS involvement by multiple myeloma was found. A possible localization of a diffuse leptomeningeal mycosis consistent with the finding of severe pulmonary histoplasmosis was also discarded. Surprisingly, further CNS sampling revealed an atypical glial cell proliferation within the sacral meningeal layers consisting with anaplastic astrocytoma IDH1-wild type with diffuse lepto- and pachymeningeal spread. Our report represents a challenging autopsy case with insidious and aspecific clinical presentation in a context of a complex clinical history that cause a misleading clinical diagnosis.

Case report

A 68-year-old male patient presented at the emergency service for neurological deterioration with progressive worsening over the last two weeks and characterized by behavioral disturbances, memory disorders, postural instability and dysmetria. No history of trauma or seizure were reported. Clinical history revealed a previous diagnosis of lambda restricted multiple myeloma, clinically indolent. Anamnesis included also systemic hypertension with secondary dilated cardiomyopathy, type-2 diabetes mellitus with nephropathy and chronic multifactorial encephalopathy. CT scan and MRI of the brain and spine were negative for acute injury. Contrast enhancement was not used because of renal disease and risk of gadolinium induced nephrogenic systemic fibrosis. Metabolic or electrolyte imbalances were excluded. Hemoculture and serology for the main neurotropic viruses were negative. Peripheral blood smear was negative for acute hemopathies. Cerebrospinal fluid (CSF) chemical-physical and cultural analysis were negative. Due to rapid deterioration of neurological conditions and appearance of signs of intracranial hypertension contrast-enhancement MRI of brain and spine was then allowed. MRI showed a focal lesion, hypointense on T1-weighted and hyperintense on STIR images, in the anterior-superior L2 vertebral body corner, suggesting localization of multiple myeloma (Fig. 1, left and middle panels). Moreover, on T1 TSE fat saturated post-gadolinium sequences in sagittal plane MRI showed a diffuse leptomeningeal enhancement with thickened nerve roots along the cauda equina and medullary cone profile (Fig. 1, right panel). According to the clinical history, these findings were interpreted as leptomeningeal dissemination of multiple myeloma. General conditions declined rapidly and patient died few days later. Autopsy was performed.



Figure 1. MRI of the spinal cord revealed a focal lesion in the anterior-superior L2 vertebral body corner (hypointense on T1-weighted and hyperintense on STIR images; left and middle panels, respectively) consistent with localization of multiple myeloma. Post-gadolinium sequences in sagittal plane MRI showed diffuse leptomeningeal enhancement along the medullary cone profile and cauda equina (right panel) interpreted as leptomeningeal dissemination of multiple myeloma.

On gross examination, we observed diffuse thickening and congestion of the meningeal layers, more evident at sacral/caudal level. On sections, the brain showed no focal lesions and a mild dilatation of the lateral ventricles. Lung parenchyma exhibited congestion and increased consistency at lower lobes. Histological evaluation confirmed focal and minimal atypical plasma cells proliferation within the L2 vertebral body (Fig. 2A, left panel), as suggested by MRI. Neoplastic cells were immunoreactive for CD38 and lambda light chains (Fig. 2A, middle and right panels, respectively). Meningeal layers were extensively analysed with no evidence of myeloma on histological examination. Clinical suspect of central nervous system (CNS) dissemination of multiple myeloma was therefore discarded. Lung specimens highlighted a dense necrotic inflammatory infiltrate (Fig. 2B, left panel) with small intracytoplasmic inclusions in histiocytes that at high power field showed narrow-based budding with a tear drop appearance compatible with yeast. These inclusions stained positive for Periodic Acid-Schiff (PAS) (Fig. 2B, middle panel) and Grocott's Methenamine Silver (Fig. 2B, right panel), but not mucicarmine (not shown). Findings were consistent with *Histoplasma* infection. Based on a possible disseminated histoplasmosis, we analyzed liver, spleen, lymph

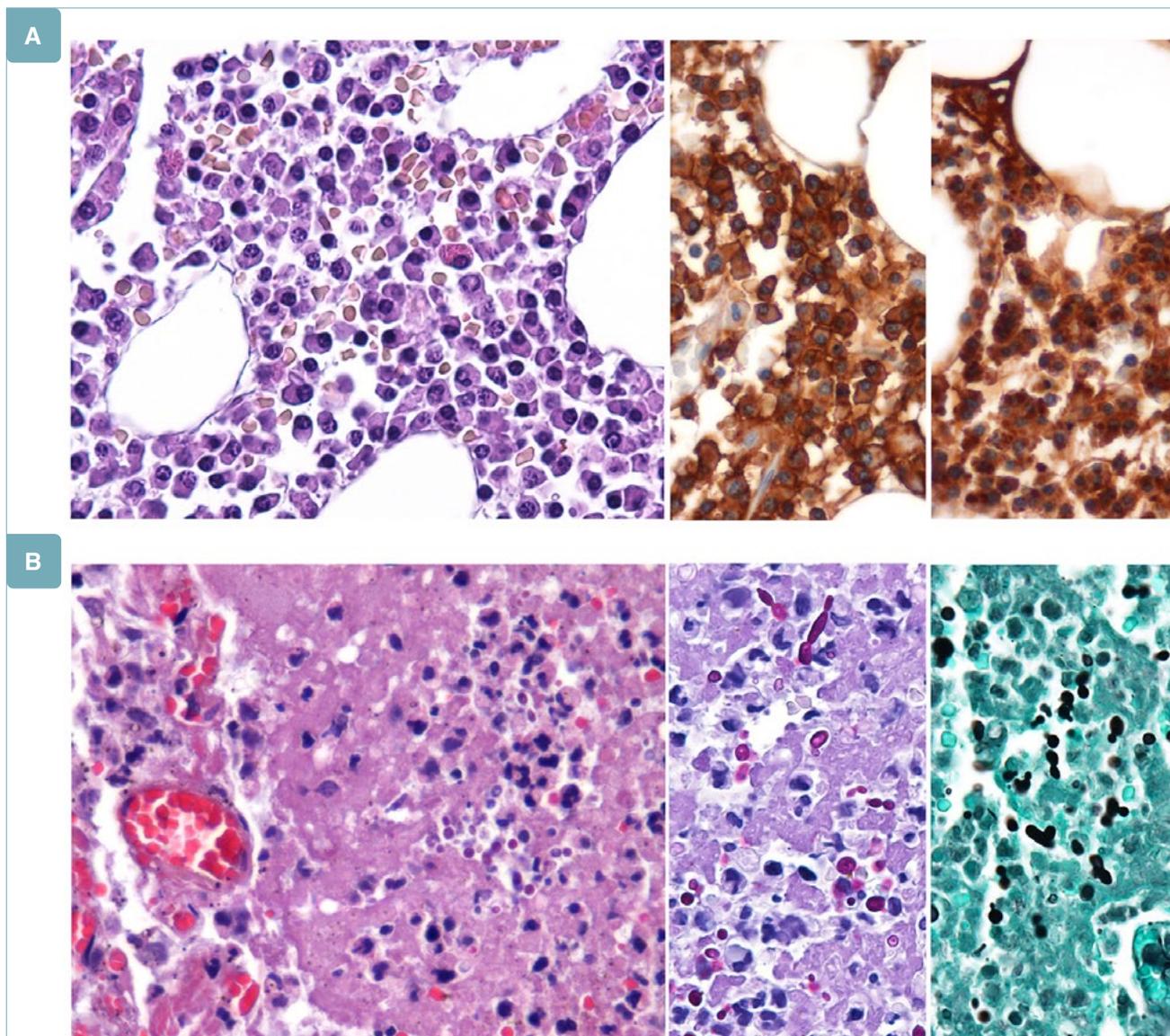


Figure 2. (A) Histological evaluation of the L2 vertebral body lesion confirmed the presence of atypical plasma cells consistent with multiple myeloma (left panel; H&E staining) and immunoreactive for CD38 and lambda light chains (middle and right panels, respectively). (B) Microphotographs from lung specimens showed a dense necrotic inflammatory infiltrate (left panel) with histiocytic intracytoplasmic inclusions positive for PAS and Grocott's Methenamine Silver (middle and right panels, respectively).

nodes, bone marrow, gastrointestinal mucosa, cerebral and meningeal specimens by both hematoxylin-eosin and special stains (PAS and Grocott), but no other *Histoplasma* related disease was found. Since the clinical picture was strongly suspicious for a CNS involvement, an extensive CNS sampling has been performed and additional CNS specimens were submitted for further examination. Indeed, we were able to highlight an atypical glial cell proliferation in the sacral meningeal layers

consisting of spindle-shaped tumor cells arranged in a perivascular pattern with scant cytoplasm and hyperchromatic elongated nuclei (Fig. 3A, left and middle panels). Mitotic activity was moderate (on average of 2 to 3 mitosis per 10 high power fields), microvascular proliferation absent. Rare necrotic foci were probably related to post-mortem tissue deterioration. Of note, we were able to highlight massive infiltration by neoplastic cells within the lower medullary profile and cauda

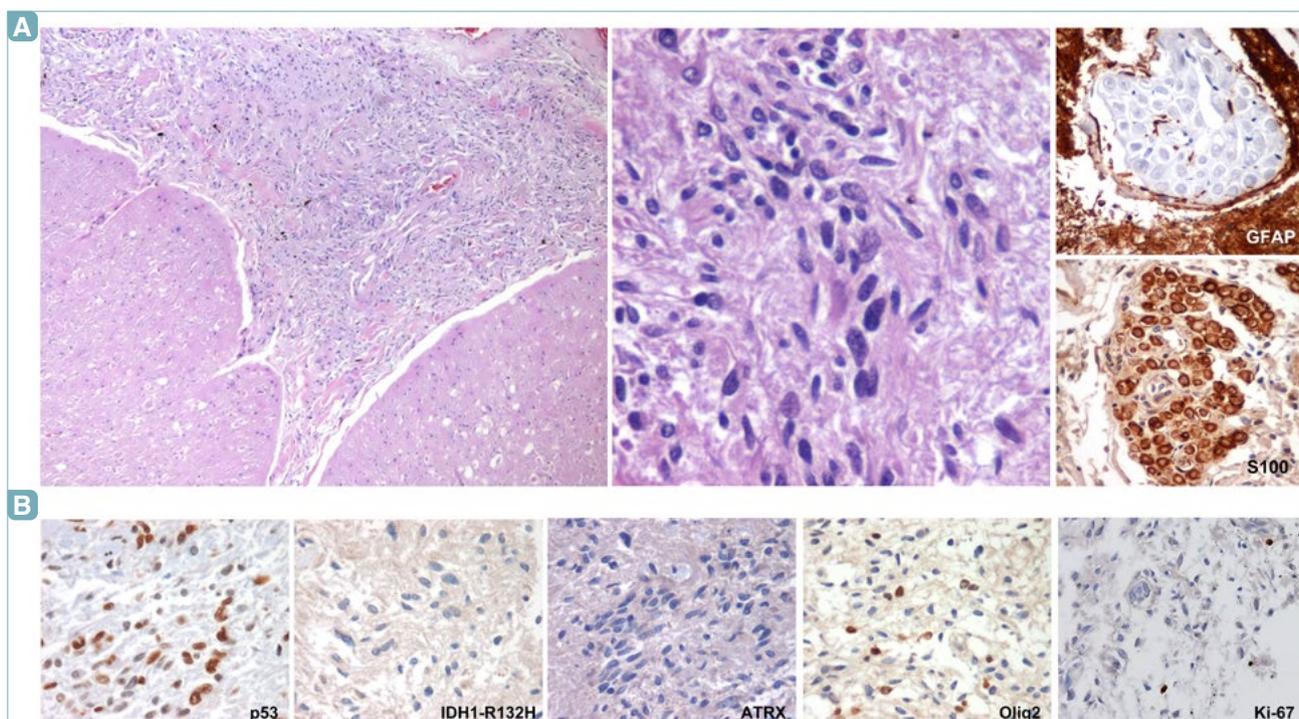


Figure 3. (A) A low-power image from histological analysis of lower sacral leptomeninges showed an uneven distribution of spindle-shaped glioma cells in a dense fibrillary background that at high-power displays hyperchromatic elongated nuclei with scant cytoplasm (left and middle panels, respectively). Neoplastic glial cells exhibit diffuse infiltration of the lower medullary and cauda equine spinal nerve roots highlighted by immunostaining for GFAP and S100 (right panels). (B) Glioma cells were immunoreactive for p53, negative for IDH1-R132H with loss of ATRX expression and moderate expression of OLIG2 in a subset of tumor cells. Ki67/Mib1 immunostain is also shown.

equine completely surrounding the spinal nerve roots, as highlighted by immunostaining for GFAP and S100 (Fig. 3A, right panels). Of note, additional brain sampling also highlighted leptomeningeal and CSF dissemination reaching the supra- and infra-tentorial regions. A single specimen from the periventricular brain area showed focal subependymal infiltration (not shown). Neoplastic cells were diffusely positive for GFAP with moderate expression of OLIG2 and loss of ATRX immunoreactivity. The large majority of neoplastic cells also stained for p53. Ki67 proliferative index was about 4% (Fig. 3B). EMA, S100, MART1 and CD38 were negative. Immunostains and molecular tests confirmed the absence of IDH1/2, BRAFv600e and H3.3-K27 mutations and no deletions on chromosome 1p and 19q were detected. Based on these findings the final diagnosis was: IDH1-wild type anaplastic astrocytoma of the medullary cone and cauda equina with leptomeningeal and CSF dissemination in a patient with pulmonary mycosis (coherent with histoplasmosis) and vertebral localization of multiple myeloma, lambda light chains-restricted.

Discussion

We report a challenging autopsy case with insidious and aspecific clinical presentation in a context of a complex clinical history. Clinical features, neuroradiological and anamnestic data were consistent with CNS dissemination of a previously known multiple myeloma. Autoptic findings allowed to discard this hypothesis. Due to dense inflammatory lung infiltrate diagnosed as histoplasmosis, the hypothesis of a possible systemic dissemination of *Histoplasma* was made, given the potential predisposing conditions of the patient (diabetes and multiple myeloma). Usually, T-cell immunity allows for an efficient recovery with a self-limited clinical course. However, immuno-compromised individuals due to underlying different conditions, such as AIDS, diabetes or patients receiving immunosuppressive medications, are at higher risk for developing more severe and progressive forms of infection². Patients with disseminated histoplasmosis exhibit frequent involvement of liver, spleen, lymph nodes, bone marrow, adrenal glands

and gastrointestinal tract. Of note, CNS involvement occurs only in 5 to 20% of cases, but appears to be more common in patients with underlying predisposing conditions³, as in our case. CNS presentation in symptomatic patients includes meningitis, cerebral vasculitis, focal brain lesions, diffuse encephalitis and involvement of the spinal cord. However, no other localizations, specifically meningeal, of *Histoplasma* related disease was found. Surprisingly, further examination of CNS samples revealed the presence of an anaplastic astrocytoma IDH1-wild type with leptomeningeal spread. We considered the diagnosis of *gliomatosis cerebri*, characterized by widespread infiltration with extensive involvement of multiple CNS regions, including spinal cord⁴. *Gliomatosis* was previously considered as a distinct nosological entity, but due to lack of a specific molecular signature is currently considered a peculiar pattern of astrocytoma growth with exceptional widespread involvement of the neuraxis⁵. It can be seen in any of the diffuse glioma subtypes, but is most common in anaplastic astrocytoma. The absence of the H3.3 K27M mutation and age of the patient also rule out the diagnosis of a possible rare diffuse midline glioma H3.3 K27M mutated⁶. Primary *de novo* forms with no obvious evidence of CNS mass lesions have been described⁶. The clinical and radiologic features are not specific and remains a challenging diagnosis with insidious clinical presentation typically with progressive neurologic symptoms. Of note, rarely *gliomatosis cerebri* has a major clinical presentation involving meningeal dissemination and this finding is commonly diagnosed later in the natural history of the disease and/or on autopsy examination^{5,7}. Alternative differential diagnosis may be considered, including leptomeningeal dissemination of glioneuronal tumors⁸ or the recently described diffuse leptomeningeal glioneuronal tumor (DLGNT)⁴. Nevertheless, we could not find any features related to a mixed glio-neuronal tumor or an oligodendroglial-like cytology. Moreover, we did not detect any deletions on either the short arm of chromosome 1 and the long arm of chromosome 19, usually associated to this entity⁴. In case of an unexplained leptomeningeal enhancement with the presence of neoplastic glial cells within the meninges, a primary diffuse leptomeningeal gliomatosis (PDLG) needs to be considered, albeit it represents an uncommon lesion with only few cases reported in the literature⁹. PDLG is characterized by glial infiltration of the meninges without evidence of a primary tumor within the brain or spinal cord parenchyma. However, for this diagnosis, a possible leptomeningeal dissemination from a primary unknown CNS lesion has to

be excluded. Secondary leptomeningeal *gliomatosis* represents a progressive leptomeningeal and subependymal spread of a known primary glioma. Pilocytic astrocytomas, as well as high grade gliomas in adults, with CNS spreading have been described¹⁰. Indeed, in light of the histological diagnosis, a revision of the MRI images was made highlighting on sagittal plane at vertebral level D12 an intradural nodule at the medullary cone and cauda equine junction. The lesion was iso-hypointense on T1 TSE sequences with no gadolinium enhancement (Fig. 4). The marked thickening of the surrounding leptomeninges make it difficult to clearly discern this lesion. In addition, the histological finding of CSF dissemination of neoplastic glial cells reaching the periventricular brain area with focal subependymal infiltration was coherent with a glial lesion originating from the medullary cone and cauda equina. It is worthful to point out that in our case the predisposition habit and a complex anamnesis were the first confounding factors for both clinician and pathologist suggesting alternative diagnoses. Only after a meticulous and specific histopathological approach, the diagnosis of IDH1-wild type anaplastic astrocytoma of the medullary cone and cauda equina with leptomeningeal and CSF dissemination was made.

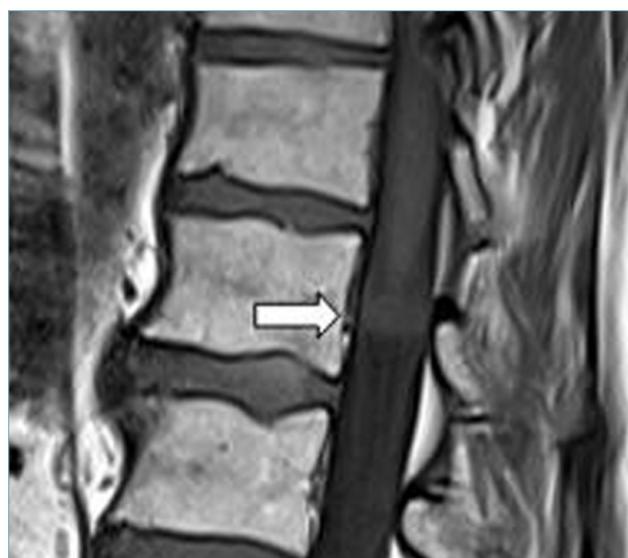


Figure 4. Revised MRI images highlighted an intradural nodule at the medullary cone and cauda equine junction at vertebral level D12, iso-hypointense on T1-TSE sequences with no gadolinium enhancement. Lesion was partially masked by the marked thickening of the surrounding leptomeninges.

Conclusions

Finally, it is useful to highlight that the onset of secondary cancers in patients with multiple myeloma should be considered. Of note, in 2012 the Food and Drug Administration issued a statement warning physicians of the increased risk for lenalidomide treatment for multiple myeloma to develop additional secondary malignancies¹¹. This statement did not mention glial tumors. However, cases of potential association between lenalidomide treatment and increased risk to develop primary high-grade gliomas have been described¹². In our case, after an accurate anamnestic collection, we assessed that patient was diagnosed with an indolent multiple myeloma without any necessary therapy, including lenalidomide. This challenging autopsy case underlines that patients previously diagnosed with a primary tumor are not only at risk of recurrences or progression of the original disease, but they must be always accurately checked for eventual onset of a second tumor, including gliomas.

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Authors' contributions

Conceptual design and critical revision of data: PLP, AT.; methodological expertise and performed most of the experiments: LD, FP, MC; clinical data revision and sample collection: GL, AT, LD; neuropathology, immunohistochemistry: FP, MC; manuscript preparation and critical revision: PLP, LD, AT. All authors contributed to data analysis/interpretation and approved the final version of this manuscript.

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