Plasma Cell Meningitis: A Rare Neurological Complication of Multiple Myeloma Requiring a High Index of Suspicion

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Abstract-

Purpose: Plasma cell meningitis is an uncommon neurologic complication of multiple myeloma with a very poor prognosis (median overall survival of 3 months).

Case Report: We describe a previously heavy treated 54-year-old caucasian female with Bence Jones multiple myeloma who developed, shortly after a good partial response to a third line therapy, a plasma cell meningitis. Intrathecal chemotherapy was give with achievement of a complete response and improvement of her neurologic status, being alive after more than 6 months of follow-up.

Conclusion: A high index of suspicion is necessary to diagnose this rae entity since treatment initiation may provide symptomatic relief and improve the quality of life.

Key Words: multiple myeloma, neurological symptoms, plasma cell meningitis, meningeal myelomatosis, cerebrospinal fluid, cytology, immunophenotyping

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INTRODUCTION

Multiple myeloma (MM) is a cancer of differentiated clonal B-cells frequently accompanied by monoclonal protein production and either diffuse osteoporosis or lytic bone lesions. It accounts for approximately 1% of all malignant diseases and 10% of hematologic malignancies. The clinical manifestations of MM are the direct consequence of marrow or other organ infiltration by plasma cells, production of monoclonal protein in blood or urine, and immune deficiency. Among the many possible complications, neurologic symptoms are quite common in patients with MM. Neurologic complications include spinal cord compression by a soft-tissue plasmocytoma or bone fragments of a fractured vertebral body; metabolic encephalopathy secondary to hypercalcemia or uremia; peripheral neuropathies in the context of amyloidosis or treatment toxicities; hyperviscosity symptoms; and more rarely direct invasion of the central nervous system by clonal plasma cells as intracerebral plasmacytomas or as plasma cell meningitis (PCM)[1].

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CASE REPORT

A 54-year-old female patient was diagnosed in 2007 with a Bence Jones kappa light chain MM, Durie-Salmon stage IIIA, International Scoring System-II (marrow plasmacytosis — 86%; Hb-6,8 mg/dL; 24h urine kappa light chain- 12g/dL; b2microglobulin-3,3mg/dL; albumin-3,2g/dL; disseminated lytic lesions and back pain).

Treatment was started with thalidomide 200mg/day and dexamethasone 40mg days 1-4, 9-12 and 17-20 for 3 cycles with a partial response followed by tandem consolidation with high-dose chemotherapy with melphalan 200/m^2, with autologous hematopoietic stem cell support. This treatment enabled a stringent complete response in 2008 (negative urine kappa light chain and serum and urine immunofixation; normal free light chain ratio). Maintenance treatment was given with thalidomide 100mg/day.

Ten months later, in 2009, while still on maintenance, the patient relapsed (66% marrow plasmocytosis and abnormal free light chain ratio). Salvage treatment

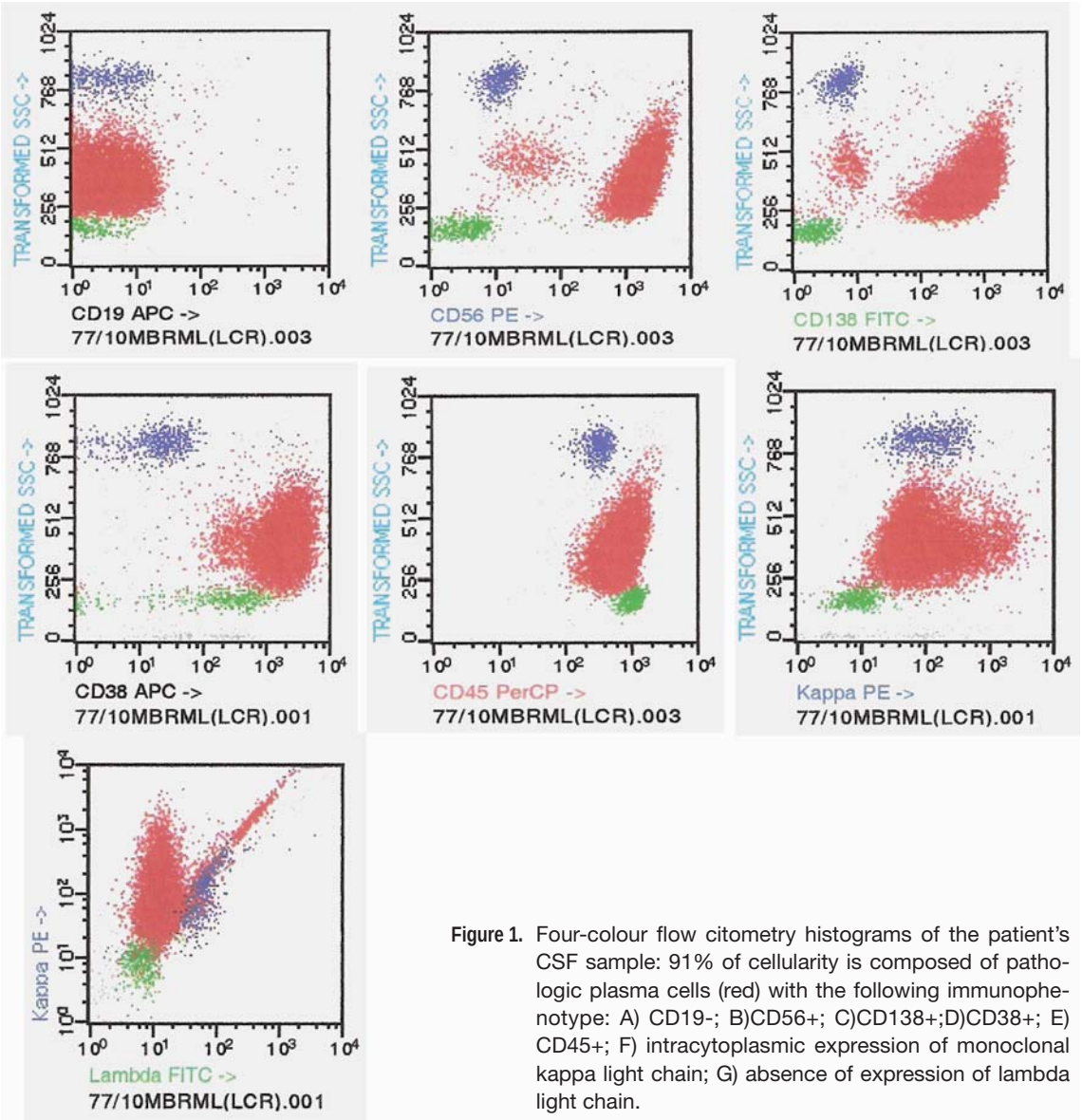

Figure 1. Four-colour flow citometry histograms of the patient's CSF sample: 91% of cellularity is composed of pathologic plasma cells (red) with the following immunophenotype: A) CD19-; B)CD56+; C)CD138+;D)CD38+; E) CD45+; F) intracytoplasmic expression of monoclonal kappa light chain; G) absence of expression of lambda light chain.

was started with bortezomib 1,3mg/m^2 and dexamethasone 20mg on days 1,4,8 and 11 for 4 cycles without response so a second salvage regimen was instituted with D-PACE (dexamethasone 40mg/day; cisplatin 10mg/m^2/day; doxorubicin 10mg/m^2/day; cyclophsphamide 400mg/m^2/day; etoposide 40mg/m^2/day from days 1 to 4 for 6 cycles), which resulted in a good partial response. A month after her last course she was admitted following a sudden onset of mental confusion, psicomotor agitation, holocranial headache, slurred speech and leg weakness. No meningeal signs were present and fundoscopy was normal. Neuro-imaging studies including cranial MRI ruled out ischemic or hemorrhagic lesions and no other alterations were detectable. Cerebrospinal fluid (CSF) analysis had elevated LDH (189U/L), proteinorrachia (247mg/dL), hypoglycorrhachia (11mg/dL), and a high count of plasma cells. Flow citometry analysis of CSF demonstrated 91% of cells with immunophenotyping expression of clonal plasma cells (Figure 1). The diagnosis of plasma cell meningitis was established and treatment with daily intrathecal chemotherapy with methotrexate 12mg, dexamethasone 20mg and cytosine arabinoside 50mg was initiated and radiotherapy was planned. There was a complete clearing of the CSF pleocytosis after 6 administrations with improvement of her neurologic status.

DISCUSSION

Infiltration of meninges with malignant cells is a well recognized complication of many hematological neoplasms in adults[2] if left untreated, such as acute myeloid leukemia (20%), acute lymphoblastic leukemia (33%), non-Hodgkin lymphoma (22%)[3] and primary CNS lymphoma (12,5-42%)[4,5], but meningeal involvement in multiple myeloma is exceedingly rare (1% prevalence)[6]. Direct invasion from contiguous involved bone when lytic lesions erodes the skull and dura-mater or hematogenous spread as in plasma cell leukaemia[7] could be the mechanisms responsible for involvement of CNS by MM. It appears that PCM is more frequently associated with plasma cell leukemia. Our patient did not have clonal plasma cells circulating in her blood. However she had had lytic bone lesions so at first we could have hypotesized that CNS invasion occurred by infiltration of contiguous structures although there are cases reported without circulating plasma cells but whose hematogeneous infiltration occurred via lymphocytes progenitors of myeloma cells[8]. In the case reported here meningeal infiltration of plasma cells might have occurred during her relapse or earlier and grown slowly during the course of the disease because most of the drugs used to treat MM do not cross the blood-brain barrier, even high dose melphalan and bortezomib[9].

It is known that thalidomide has the property to upregulate adhesion molecules in the bone marrow environment. A mechanism of resistance to this drug is the appearance of myeloma cells that are not sensitive to the increased expression of these adhesion molecules and therefore are more prone to dislodge from the bone marrow and colonize extramedullary sites as plasmacytomas[10]. Although a case of CNS involvement has been reported in this circumstance[11], no meningeal infiltration occured and as far as we know there are no reports showing increased susceptibility to meningeal invasion after thalidomide treatment.

The spectrum of neurological symptoms presented by our patient was compatible with meningeal disease as already reported in the literature[12]. Cerebral MRI at first may be negative like in our case[13].

Lumbar puncture is crucial for diagnosis with cytomorphological analysis of CSF showing plasma cells. Other conditions both infectious and non-infectious can be accompanied by the presence of plasma cells in CSF[14], but if they occur in a MM patient, it strongly supports the diagnosis of PCM. However, the definitive diagnosis is by proving the monoclonality of the cells[15].

PCM has a dismal prognosis with a 6-month neurological disease progression-free survival rate of 7%. Intrathecal chemotherapy with or without cranial irradiation is the standard modality of treatment. Good clinical responses can be attained but they are not long lasting[16,17]. particularly in patients with end-stage multiple myeloma like the one described here. Our patient however is free of disease for almost a year.

The apparent rarity of plasma cell meningitis proba-

bly stems from underdiagnosis (advanced stage MM with misinterpretation of the neurological symptoms) much more than from underreporting, since most cases are diagnosed ante-mortem[6,18].

In summary, meningeal involvement should be sought in a patient with multiple myeloma presenting with neurological symptoms when other possible causes like medullary compression, hyperviscosity or metabolic derangements are excluded. Even if meningeal signs are absent, fundoscopy and cranial MRI scan are normal, it is of utmost importance to have a CSF analysis to exclude this rare but potentially treatable complication although with a bad prognosis.

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