Blood and Lymphatic Cancer: Targets and Therapy

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CASE REPORT

Leptomeningeal myelomatosis in previously treated high-risk kappa light chain multiple myeloma: case report and literature review

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Objective: To describe leptomeningeal myelomatosis (LM) in previously treated high-risk kappa light chain multiple myeloma (MM) and to review the literature.

Case report: A 71-year-old female with previously treated kappa light chain myeloma presented with right lumbosacral discomfort. Magnetic resonance imaging (MRI) of spine revealed multiple intradural masses involving the cauda equina, with mass effect on adjacent nerve roots. Brain MRI was unremarkable. Cerebrospinal fluid flow cytometry confirmed an abnormal population of plasma cells with kappa restriction; CD38, CD138, and CD56 were positive. She was originally diagnosed with kappa light chain myeloma 10 months earlier while hospitalized for anemia, thrombocytopenia, renal failure, and hypercalcemia. Bone marrow revealed plasma cell myeloma approaching 100% cellularity, with 92% plasma cells, atypical plasmacytoid cells with prominent nucleoli, and significant cytogenetic abnormalities: deleted 13, c-myc rearrangements, –X, +1. Treatments consisted of seven cycles of bortezomib with weekly dexamethasone. Her last dose had been 4 months earlier. After treatment, bone marrow demonstrated a complete remission with normal cytogenetics. Her clinical course had otherwise been indolent with a good hematologic response. After diagnosis of LM, therapy included focal external beam radiation to the cauda equina, weekly bortezomib and dexamethasone, intrathecal (IT) cytarabine liposomal every 2 weeks for five doses, and monthly IT cytarabine liposomal thereafter. The cerebrospinal fluid gradually cleared on serial lumbar punctures and follow-up MRI demonstrated near complete resolution of the intradural masses. Five months after diagnosis the patient is essentially asymptomatic.

Conclusion: The incidence of central nervous system (CNS) involvement in MM patients is 1%. LM is associated with cytogenetic abnormalities and plasmablastic morphology. It can occur with a seemingly low tumor burden. Novel agents such as bortezomib allow for prolonged survival in high-risk patients; however, with inadequate CNS penetration, complications such as LM may be inevitable.

Keywords: leptomeningeal myelomatosis, intrathecal, complete remission

Introduction

Leptomeningeal myelomatosis (LM), defined as the presence of monoclonal plasma cells in the cerebrospinal fluid (CSF), is so rare that many radiologists, pathologists, and oncologists will never see a case in their entire career. This was the first case of LM seen at our institution, a 634-bed tertiary care center where approximately 58 myeloma patients are seen per year. Unlike other hematologic malignancies such as acute lymphoblastic leukemia, which frequently invade the central nervous system (CNS), the incidence of CNS involvement in multiple myeloma (MM) patients is only 1% and can include intraparynchemal lesions, solitary cerebral plasmacytomas, or LM.[1] The incidence of LM alone has been estimated at <1% of MM patients.[2]

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In 2007, Nieuwenhuizen and Biesma published an international literature review of LM and found a total 109 previously reported patients of which 21 were pure light chain myeloma.[1] We found at least 47 cases since 2007, for an estimated total of 156 cases. Of the cases we found, only four were pure light chain (one kappa, two lambda, one unspecified).[2–16]

We present a case report of LM in previously treated kappa light chain MM. The patient had extremely high baseline kappa free light chains with a steep decline with initial treatment. Despite having a good hematologic response and achieving a complete remission, she developed LM 10 months after her original diagnosis. Our report and other case reports draw attention to LM's clinical and radiographic heterogeneity. Unfortunately, it can occur even after successful treatment with a seemingly low tumor burden. Furthermore it can occur in the setting of a complete remission (CR).[1] It is often associated with significant cytogenetic abnormalities and plasmablastic morphology.

Like other forms of leptomeningeal metastases, the overall prognosis is poor. Previously, median overall survival had been estimated at about 2 months (0.1–25 months).[1] However, since 2007, reported median overall survival has varied. In a 2008 report of a series of 14 patients, the median survival after diagnosis of LM was 4 months. A 2010 publication examining eleven cases reported a median overall survival of up to 6 months.[9]

Combining the Nieuwenhuizen and Biesma review and our search, 25 cases of pure light chain CNS myelomatosis have been previously reported, representing about 17% of the 156 cases of CNS myeloma.[1] Similarly, among patients with MM, up to 20% of cases are classified as light chain-only.[17] Our case illustrates common features of a rare disease. In this paper, we describe our patient's characteristics and relate them to the literature.

Case report

A 71-year-old woman, previously treated for kappa light chain MM presented with a 1-week history of right lumbosacral discomfort. On neurological exam, lower extremity strength was 5/5 throughout, except for reduced right hamstring strength, 4–5/5. Bilateral patellar reflexes were 2/4; bilateral achilles reflexes, 0/4. Lower extremity sensation was intact, except decreased pinprick on the right lateral foreleg and knee.

Magnetic resonance imaging (MRI) of the lumbar spine revealed multiple intradural masses involving the cauda equina which exerted mass effect on adjacent nerve roots (Figure 1A). The largest lesion was nearly 1.4 cm in the greatest dimension. Leptomeningeal enhancement was seen involving the distal thoracic cord as well, suspicious for additional metastatic disease. A known L4 plasmacytoma was present but did not exhibit extension beyond the vertebral body. Subsequent imaging of the entire neuroaxis (brain, cervical, and thoracic spine) revealed no additional intradural masses and no alternative primary lesion.

She subsequently underwent a large volume lumbar puncture and 30 mL of CSF was obtained. Cytological examination of the CSF confirmed the presence of numerous plasma cells with atypical morphology including plasmablastic and binucleate forms. No other malignant cells were identified (Figure 1B and C). CSF flow cytometry confirmed that about 90% of cells in the CSF were an abnormal population of plasma cells that showed CD38, CD138, and CD56 positivity with kappa restriction. This confirmed the diagnosis of leptomeningeal myelomatosis.

Past myeloma history and treatments

Ten months before diagnosis of LM, she was originally diagnosed with kappa light chain MM. Early in her hospitalization, her hemoglobin was 7.7 gm/dL; platelets were 23,000. Her calcium was elevated at 14 mg/dL. She was in acute renal failure with a creatinine of 5 mg/dL (glomerular filtration rate

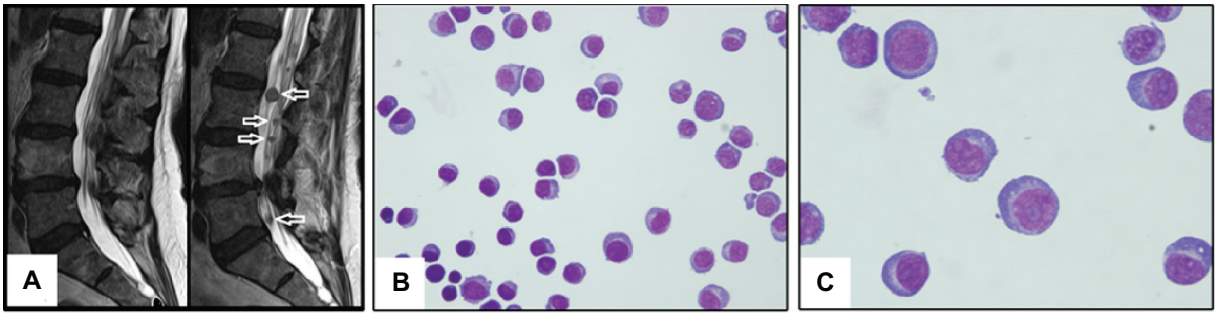

Figure 1 (**A**) Left: MRI obtained before onset of pain and neurological symptoms demonstrates no intradural lesions. Right: MRI obtained 4 months later and after onset of symptoms began reveals multiple intradural extramedullary lesions. (**B**) CSF contained numerous plasma cells, several with atypical morphology including plasmablastic features. (**C**) CSF plasma cells demonstrated plasmablastic morphology.
Abbreviations: CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

was 11 mL/min). Her lactate dehydrogenase (LDH) was elevated at 756 units/L.

At that time, her serum free light chain assay (SFLC) revealed a significantly elevated kappa light chain level of 5230 mg/dL. The lambda free light chain level was within normal limits at 0.12 mg/dL. The serum free light chain ratio (kappa:lambda) was >1000. The initial 24-hour urine immunofixation detected free kappa light chains. There was significant proteinuria: 16,812 mg in a 7590 mL sample.

Bone marrow evaluation revealed plasma cell myeloma approaching 100% cellularity, with 92% plasma cells demonstrating plasmablastic features, and significant cytogenetic abnormalities including an additional chromosome 1, a deleted 13q, and c-myc rearrangement (Figure 2A B and C). Because of the complex structural abnormalities of her chromosomes, the precise translocation of her c-myc rearrangement could not be determined.

She was classified as a Durie Salmon Stage IIIB kappa light chain MM. A beta-2 microglobulin for ISS staging was not checked at that time since it could not be accurately calculated in the setting of severe renal failure. Osseous survey was negative for lytic lesions.

While hospitalized, she received 4 days of pulse dexamethasone 40 mg daily. Once stabilized, she went home and proceeded with outpatient treatments consisting of a total of seven cycles of bortezomib (on day 1, 4, 8, and 11) with weekly dexamethasone.

After two cycles of therapy, 10 weeks after MM diagnosis, her laboratory parameters improved significantly. Kappa light chains normalized to 1.49 mg/dL – a 3-log reduction. Platelet count and creatinine also normalized; anemia improved to 10 g/dL. On 24-hour urine immunofixation, no free kappa or free lambda light chains were detected.

A repeat bone marrow evaluation 3.5 months after initiating MM treatment showed a good response: excellent trilineage maturation; marrow cellularity of 25% (Figure 3A and B); and 10% staining of plasma cells with CD138, kappa, and lambda – confirming a polyclonal (nonspecific), mild plasmacytosis. She was assessed to have a CR. Cytogenetics normalized with 46 XX (Figure 3C).

Six months after initial diagnosis, she experienced lower back and hip pains. MRI of lumbosacral spine showed a myelomatous L4 vertebral body lesion consistent with a plasmacytoma. Her lower back and hip pain resolved after the MRI and she did not require any specific therapy for the L4 plasmacytoma. Her seventh – and final – cycle was completed at 27 weeks, 4 months before she developed LM.

Prior to LM, her clinical course had been indolent with good hematologic and renal response. Figure 4A, B, C and D summarize laboratory parameters over time.

Our patient's LM treatments and clinical course

After LM diagnosis, our patient commenced weekly dexamethasone 40 mg/week and focal radiation to the cauda equina lesions. Her neurologic symptoms resolved after completion of radiation therapy. She then continued weekly dexamethasone along with weekly bortezomib and intrathecal cytarabine liposomal (every 2 weeks for five doses, followed by monthly maintenance dosing).

Due to ongoing anxiety and insomnia, dexamethasone was discontinued after a dose-reduction to 20 mg/week. It was later resumed at 20 mg/week without complications.

The CSF gradually cleared on serial lumbar punctures. On follow-up MRI (Figure 5), prior to the fifth dose of intrathecal (IT) cytarabine liposomal, the multinodular lesions of the cauda equina almost completely disappeared, with only minimal enhancement along the nerve roots. She continued to have a stable L4 plasmacytoma. Five months after diagnosis the patient was essentially asymptomatic.

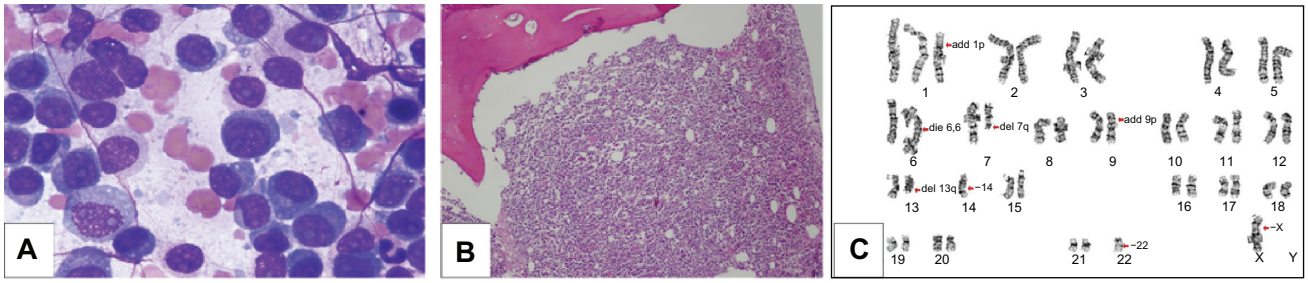

Figure 2 (**A**) Bone marrow aspirate revealed approximately 90% plasma cells, with many demonstrating plasmablastic features. (**B**) Bone marrow biopsy demonstrated plasma cell myeloma approaching 100% cellularity. (**C**) Bone marrow evaluation revealed significant cytogenetic abnormalities.

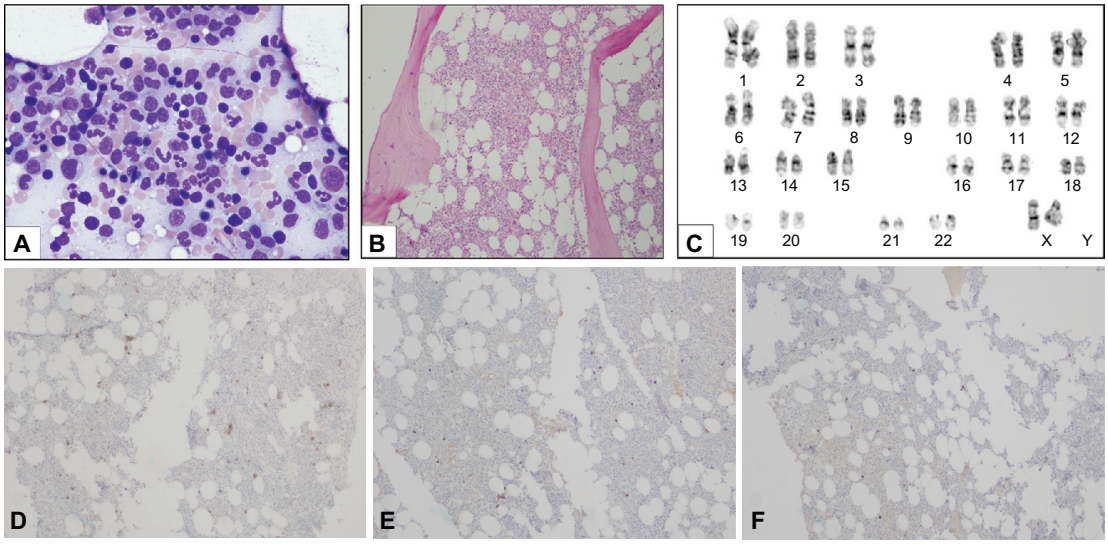

Figure 3 (**A**) After treatment, the repeat bone marrow aspirate identified approximately 10% plasma cells; (**B**) after treatment, the repeat bone marrow biopsy showed a good response to treatments with excellent trilineage maturation, a marrow cellularity of 25%; (**C**) after treatment, cytogenetics normalized, demonstrating 46XX. (**D**–**F**) Plasma cell immunohistochemical stains on the bone marrow biopsy after treatment. Approximately 10% of plasma cells stained with CD138, both kappa, and lambda, which confirmed a polyclonal and nonspecific mild plasmacytosis: (**D**) CD138 10X, (**E**) kappa 10X, (**F**) lambda 10X.

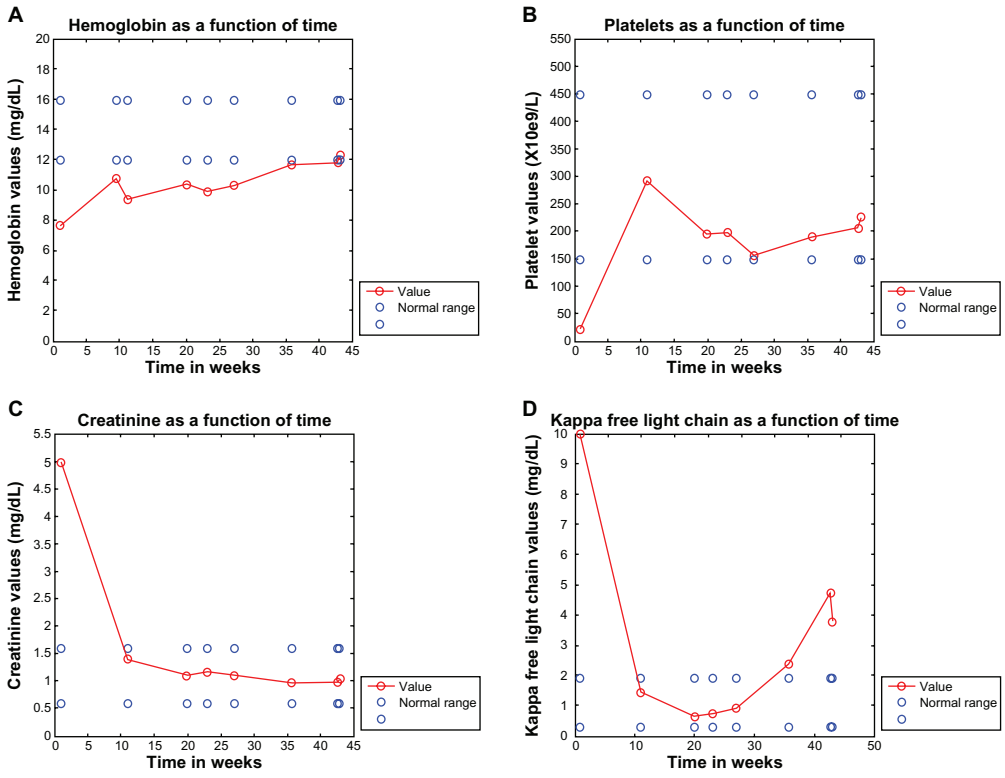

Figure 4 (**A**) Her hemoglobin improved from around 8 g/dL at baseline to around 10 g/dL after the first of two cycles, 10 weeks into treatment. It continued to improve after completion of treatment. At the time LM was diagnosed, hemoglobin had climbed to 12 g/dL. (**B**) After two cycles, her thrombocytopenia resolved from 23,000 at baseline to normal range and remained in the normal range during and after treatment. (**C**) After the first of 2 cycles of therapy, her creatinine dropped from 5 mg/dL at baseline to normal range and remained in the normal range. (**D**) As indicated on the graph, the first kappa free light chain value at week 1, the time of LM diagnosis was significantly elevated at 5230 mg/dL. After two cycles of treatment, at 11 weeks, the kappa light chains dropped steeply to 1.49 mg/dL – a 3 log reduction. The next measurements taken at weeks 20, 23, and 27 showed normal values. Her last dose of treatment was at week 27. The last few light chain values were obtained at weeks 36 and 43 when she was off treatment. Her kappa free light chains increased slightly after completion of treatment but were still only 2.39 mg/dL, 4.76 mg/dL, and 3.80 mg/dL, representing low volume disease. **Note:** The patient finished cycle 2 of therapy at week 10, and her seventh cycle was completed at week 27. On the graphs, time is in weeks, the blue bullets represent the reference range and the red bullets represent the patient's values.

Abbreviation: LM, leptomeningeal myelomatosis.

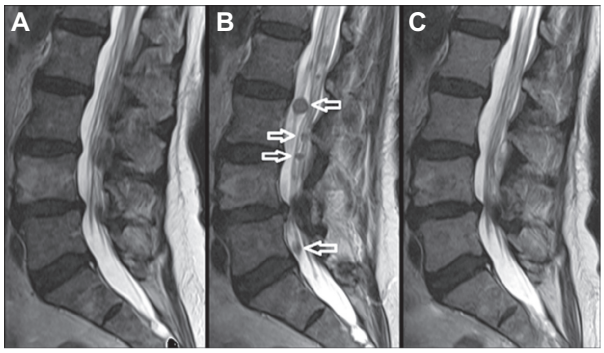

Figure 5 Comparison of T2 weighted MRIs obtained 4 months prior to diagnosis of LM, at the time of diagnosis, and 2 months later after treatment. (**A**) Four months prior to onset of pain and neurological symptoms no intradural lesions are seen. (**B**) At the time of diagnosis multiple intradural extramedullary lesions are present. (**C**) After treatment there is resolution of bulky lesions. Minimal residual enhancement was noted along the nerve roots on postcontrast images, likely representing residual disease.
Abbreviations: LM, leptomeningeal myelomatosis; MRI, magnetic resonance imaging.

Discussion

Pathogenesis

The precise pathogenesis of LM is unknown and meningeal seeding has been hypothesized to involve both hematogenous spread or extension from adjacent osseous lesions.[14] Our patient's known L4 plasmacytoma could have potentially been the source of spread to the nervous system. In low tumor burden MM patients, hematogenous spread of lymphoid precursors of myelomatous plasma cells has also been proposed.[9] Postmortem studies of LM cases have revealed arachnoid vein infiltration by myeloma cells with resulting destruction of the arachnoid trabeculae.[16,18]

Since most chemotherapeutic agents do not cross the blood–brain barrier (BBB), there is legitimate concern that current medications and novel agents used to treat MM patients may predispose these patients to both extramedullary spread and CNS invasion by malignant plasma cells.[11] It has been argued that leptomeningeal seeding does not necessarily represent progressive disease but coexistence of aggressive MM.[19] The prolongation of survival in myeloma patients may lead to a higher prevalence of LM involvement but the argument against this is that the interval between diagnosis of MM and LM is approximately 17.8 months[1] whereas the median survival gained with conventional chemotherapy is 24–36 months.[1,18] Most likely, the inherent biological features of aggressive myeloma predispose patients to leptomeningeal disease. The difficulty in diagnosing CNS involvement in low-volume systemic disease may represent underdocumentation of LM at the present time.[19] Whatever role loss of stromal dependency by myeloma cells plays in extramedullary spread remains to be elucidated.[20]

Radiographic findings

Our patient's radiographic findings emerged 4 months after undergoing MRI to investigate nonspecific lower back pain. Initial MRI showed no lesions involving the meninges, spinal cord, or cauda equina. The repeat MRI of the lumbar spine done after the patient developed renewed pain and neurologic symptoms revealed numerous enhancing intradural extramedullary masses in the cauda equina, consistent with metastatic disease described as "drop metastases". Linear areas of leptomeningeal enhancement were also noted covering the distal thoracic spinal cord, likely representing tiny granular tumor implants, also termed "sugar-coating" or intradural spread.[21] These abnormal findings can represent carcinomatous meningitis, arachnoiditis, sarcoidosis, or infectious processes in the appropriate clinical setting.[22]

Primary CNS tumors that have direct access to the subarachnoid space, such as glioblastoma, medulloblastoma, ependymoma, germinoma, choroid plexus carcinoma, teratoma, and pineoblastoma, are most likely to spread to the CSF and produce these patterns.[23] Other primary tumors, such as lung, breast, melanoma, colorectal, renal, and gastric carcinomas, may spread hematogenously to the brain paryncheme first and then subsequently seed to the CSF.[23,24] In the setting of drop metastases or other intradural metastases, the entire neuroaxis must be imaged in order to locate all potentially treatable lesions and to monitor treatment response. In this patient, the initial concern was for a primary CNS tumor or second primary peripheral neoplasm, given the rarity of leptomeningeal and parynchemal involvement in MM. This patient also had a known L4 plasmacytoma. No additional masses or abnormal enhancement were imaged. There are reports of direct dural penetration by myeloma of the skull resulting in leptomeningeal spread,[25] which theoretically may be duplicated in the spinal cord, but our patient's lesion was radiographically confined to the vertebral body, well away from the cortex.

This, as well as other cases, illustrate that radiographic findings in LM can be nonspecific, heterogeneous, and may raise concern for other pathologies. Given the rarity of LM, other pathologies are reasonable to investigate. In our patient the appearance of cauda equina lesions raised concern for a more proximal process, which was not found. Other unusual radiographic findings described in the literature include a myelomatous subdural effusion mimicking a subdural hematoma,[19] a dural plasmacytoma mimicking a meningioma,[26] leptomeningeal myelomatosis mimicking viral encephalitis,[27] or no radiographic findings, despite CSF confirmation of myeloma.[1]

CSF analysis

CSF sampling is required for a definitive diagnosis and for follow up of treatment. Our patient's diagnosis of LM was confirmed in the first large volume lumbar puncture (LP), which frequently is the case with LM. While other leptomeningeal metastases often require multiple CSF samplings, LM can often be diagnosed on the first LP, possibly because malignant plasma cells are less adherent to meningeal tissue.[19] Monoclonality of the plasma cells must be confirmed since plasma cells can be seen in the CSF in other infectious and noninfectious conditions. Because changes in BBB permeability allow passage of immunoglobulins into the CSF, evidence of a monoclonal M-component in the CSF cannot replace a cytologic diagnosis.[1,28]

High-risk features

Adverse features of aggressive myeloma associated with CNS myelomatosis have been described: high risk cytogenetics, plasmablastic morphology, extramedullary spread, plasma cell leukemia, and elevated LDH. These are considered predictors of poor survival due to drug resistance and loss of growth dependency on the bone marrow microenvironment.[19,28,29] While elevated LDH has been described in patients with LM,[19,29] our patient had a normal LDH at the time of her LM diagnosis. Hemoglobin, platelets, serum creatinine, total protein, and beta-2 microglobulin were also normal. Her earlier LDH at initial diagnosis with MM was significantly elevated at 756 units/L.

Cytogenetics

As in many previously reported cases of LM, our patient had a complex karyotype. The significant cytogenetic abnormalities associated with LM described in the literature include alterations of the p53 gene or c-myc rearrangements.[30] P53 deletions have been associated with metastatic behavior in MM.[1,19,30] Chromosome 13q deletions have been considered primary events in the pathogenesis of MM, while p53 gene abnormalities and c-myc rearrangements are thought to be secondary changes occurring with tumor progression.[30] Nieuwenhizen and Biesma's 2007 review of 109 cases of LM world-wide noted p53 deletions in 89% of cases.[1] They did not observe an association between CNS involvement and 13q deletions. Our patient had multiple karyotypic abnormalities at the time of her diagnosis: additional chromosome 1, loss of 13, a deletion of 13q, and c-myc rearrangement. However there were no p-53 aberrations or deletions. Duplication of all or part of 1q has been reported as a secondary aberration and associated with tumor progression and advanced disease.[31] Patients with a 13q deletion have significantly lower event free survival, overall survival, and CR duration.[32] Myc rearrangement has been implicated in leptomeningeal spread.[30] Our case is unique in that her cytogenetics normalized completely with her initial therapy with no evidence of the previously noted multiple chromosome abnormalities.

Elevated baseline serum free light chains

Our case also illustrates another unique feature associated with LM: extremely high baseline SFLC. Since there are so few cases of LM and the SFLC assay is relatively new, it is unlikely that this effect has been previously described with LM.

This case illustrates the prognostic significance of elevated baseline SFLC levels which drop rapidly with therapy.

Elevated baseline SFLC levels with a steep decline after induction therapy have been associated with poorer prognosis. This phenomenon was described by Van Rhee et al in 2007. High SFLC levels $>$ 75 mg/dL, and their rapid reduction with induction therapy, define an aggressive myeloma subtype with poor prognosis. This subgroup of patients had statistically significant inferiority in terms of event free survival and overall survival. It was also noted that higher percentages of patients with such elevated baseline SFLC were classified as ISS stage III, with elevated creatinine ($\geq$2 mg/dL), elevated LDH ($\geq$190 units/L), and bone marrow plasmacytosis $>$ 30%. Furthermore, a strong association between light chain only MM with high SFLC ($>$75 mg/dL) and cytogenetic abnormalities was described.[33]

Patients with significantly elevated baseline SFLC and a steep decrease in SFLC after induction treatment paradoxically have a significantly worse prognosis, despite higher response rates.[33] Our patient demonstrated this very rapid steep drop in SFLC. Such a steep decline in light chains should alert the clinician to anticipate an aggressive and possibly complicated clinical course. Whether there is a true association between high baseline SFLC with steep decline after therapy and risk of leptomeningeal invasion is still unknown. However, it is also important to mention that current research on the SFLC assay has shown imperfections in the assay including significant overestimation of SFLC concentrations.[34–36]

Treatment

The most effective treatment for LM remains unknown. Options include intrathecal chemotherapies, focal radiation for bulky disease, craniospinal irradiation, systemic therapies, and stem cell transplant. Cisplatin and etoposide do penetrate the CSF and have been used in combination with

other systemic agents that are not known to cross the BBB, including doxorubicin, cyclophosphamide, and melphalan. Responses to these agents have mostly been transient.[11] Vincristine and steroids have also been used.[1] Intrathecal therapy includes steroids, cytarabine arabinoside, cytarabine liposomal, methotrexate, and thiotepa. Among these standard treatments for neoplastic meningitis, only modest differences in efficacy and toxicity have been noted.[2]

Successful use of liposomal cytarabine in combination with cranial irradiation for LM has been described. This patient presented initially with a retro-orbital plasmacytoma with dural infiltration. A fronto-temportal craniotomy was performed. After failing three cycles of Cy-VAD (cyclophosphamide, vincristine, adriamycin, dexamethasone), two cycles of IT liposomal cytarabine were given with oral dexamethasone, followed by cranial irradiation (30 Gy). One month after completion of cranial irradiation, two more cycles of liposomal cytarabine were administered. Eighteen months later, the patient was alive with no mass noted on cranial MRI, no serum monoclonality, and only rare marrow plasma cells.[14,37]

A prospective study of 14 patients treated between 2000 and 2007 to assess treatment response to cytarabine liposomal was also reported by Chamberlain et al. All had received extensive prior chemotherapy and eleven had undergone transplantation. Induction therapy was three doses of 50 mg cytarabine liposomal IT every 14 days. Concurrent systemic therapy or involved field radiation therapy (XRT) was given when appropriate. Six patients (43%) had both partial neurologic responses and complete cytologic responses after induction and proceeded with maintenance therapy. Five patients (35%) had persistently positive CSF cytology (despite being neurologically stable) after induction therapy and were offered alternative therapy or supportive care. After initiating IT therapy, the median time to neurologic progression was 2.5 months and the median survival after diagnosis of LM was 4 months.[2]

Another case report of LM by Annibali et al in 2009 described treatment with systemic topotecan, temozolamide, and dexamethasone along with concurrent craniospinal irradiation. The patient's neurologic symptoms improved significantly, but lasted only 5 months before disease progression and death.[5] There is also a case report of a patient who developed LM after the fourth cycle of bertezomib, despite a good hematologic response.[1,38]

Likewise, the penetration into the CSF by thalidomide and lenalidomide has been considered insufficient.[1,11] However, a 2007 report by Katodritou et al described the first case of successful treatment of cavernous sinus extramedullary plasmacytoma with thalidomide/dexamethasone, followed by autologous transplantation.[20] Others report no benefit of thalidomide in the treatment of LM.[1,39]

Bendamustine may have penetration into the CSF based on a case report of significant regression of brain metastases from breast cancer.[40] In a separate report, Mourad et al described a patient with LM who was treated systemically with bendamustine and IT methotrexate/hydrocortisone. This patient had a normalization of CSF and neurologic improvement and was alive at 6 months after diagnosis of LM.[12]

Radiation therapy

Nieuwenhuizen and Biesma[1] described 72 patients whose treatments and survival information were previously reported. Those who received cranial irradiation had a significantly longer survival than those who did not receive cranial irradiation. For the cranial irradiation group, the median survival was 3 months vs 0.81 months for the noncranial irradiation group ($P = 0.004$).

Since leptomeningeal metastases necessitate treatment of the entire neuroaxis, craniospinal irradiation would be reasonable.[28] However, prophylactic cranial irradiation or craniospinal irradiation is controversial. While craniospinal irradiation treats the leptominenges, the CNS parenchyma, and the vertebral column, it is also associated with significant myelosuppression. This may preclude administration of further systemic chemotherapy when needed in the future. Focal radiation to bulky and symptomatic disease palliates symptoms, normalizes CSF flow in areas of blockage, and may be preferred treatment in certain patients.[41] Our patient had focal, bulky, symptomatic disease, and required urgent systemic and intrathecal treatments as well as focal XRT rather than craniospinal irradiation.

Review of the literature

Symptoms associated with leptomeningeal metastases of all types vary significantly depending on areas involved and include: cranial nerve palsies, mental status changes, weakness, confusion, headaches, lethargy, and disturbances of vision, gait, or speech.[1] Any new or unusual neurologic symptoms should raise suspicion for leptomeningeal involvement and should prompt a comprehensive evaluation of the CNS, including MRIs and lumbar puncture with CSF cytology analysis.

Presenting with limb weakness, our patient represents a common presentation of a rare disease. As in the majority of cases reported, she had stage III disease and high-risk features associated with LM including plasmablastic morphology and high-risk cytogenetics. Conversely, her extremely high baseline SFLC represents an aggressive myeloma subtype,

but this has not previously been considered characteristic of LM. Since the SFLC assay is relatively new, it was not utilized in earlier studies.

Recent observations by several authors have contributed significantly to the current understanding of this rare condition and can be summarized:

- While pure light chain LM is a rare, 19%, the majority are IgG (kappa/lambda) −34.8% and IgA (kappa/lambda) −22%[1]
- The median interval from diagnosis of MM to diagnosis of CNS myelomatosis is estimated to be around 17 months[1,9]
- 29.4% of patients were in a complete remission prior to presenting with LM[1]
- Intrathecal therapies used included methotrexate, steroids, and Ara-C[19]
- Systemic therapies used included: vincristine, doxorubicin, dexamethasone, bortezomib, thalidomide, cyclophosphomide, etoposide, cisplatin, semustine, teniposide, high-dose methotrexate, vindesine, melphalan, and prednisone.[9]
- The median overall survival reported by Qu et al was 6 months, much longer than that reported in other studies.[9] CNS myelomatosis was described in 11/625 myeloma patients, between 1993 and 2009. The longer median survival in this report may be due to the fact that some patients received cranial irradiation (CI) in addition to a wide variety of systemic therapies, including newer agents such as bortezomib, and IT therapy. Furthermore, one of the patients received an allogenic stem cell transplant which prolonged the patient's life by an additional 16 months. Qu et al described the following clinical scenarios:
  - Most had been treated with thalidomide prior to developing CNS myeloma.
  - Nine of the eleven patients received IT methotrexate and dexamethasone with or without cytarabine (one died soon after diagnosis and one refused further treatment).
  - Systemic therapies were administered to eight of the patients and included various combinations of: vincristine, doxorubicin, dexamethasone, bortezomib, thalidomide, cyclophosphomide, etoposide, cisplatin, semustine, teniposide, high-dose methotrexate, vindesine, melphalan, and prednisone.
  - Three patients lived >12 months and each had received IT methotrexate and dexamethasone with or without intrathecal cytosine arabinoside. Two of the three received CI in addition to systemic therapy and IT therapy. One of these two lived 34 months after systemic treatments with: bortezomib, thalidomide, dexamethasone, cyclophosphomide, etoposide, cisplatin, semustine, and teniposide; the other patient lived 32 months after receiving systemic therapy with: dexamethasone, cyclophosphamide, etoposide, cisplatin, and thalidomide. The remaining (third) patient presented with CNS involvement when originally diagnosed with MM and did not receive CI. This patient survived 16 months after treatment with allogenic stem cell transplant, IT therapy, and systemic treatment with VAD (vincristine, doxorubicin, dexamethasone).[9]
- In the largest single-institution case series, a total of 23 patients were described in two separate publications.[19,29]
  - The earlier publication focused on the unfavorable hematologic and cytogenetic features associated with LM: high-risk cytogenetics, plasmablastic morphology, plasmablastic leukemia, high LDH, and extramedullary involvement. The patients were rather homogeneous in their features and most had received intensive chemotherapy with intent for transplantation.[29]
  - The later report focused on the clinical course, radiographic findings, and CSF features of the patients. In all but two patients, the cytological diagnosis was obtained on the first LP.[19] At diagnosis of LM, three patients were in a CR, five had a near-CR, six had partial responses, and nine had progressive disease despite treatment.[19,29] The authors defined CR as negative serum and/or urine immunofixation with <5% bone marrow plasmacytosis (in the absence of new osteolytic lesions).[29]
  - For nine out of 18 patients who received high dose chemo and autologous stem cell transplant, the median time interval from original diagnosis to documentation of LM was 16.5 months (range 10–25 months). Conversely, for seven of those who developed LM during pre-transplant induction therapy, the median time interval from original diagnosis to documentation of CNS involvement was 11 months (range 4–22 months).[19]
  - All but one patient (who died 1 week after diagnosis) received IT chemotherapy with either IT methotrexate or IT cytosine arabinoside plus hydrocortisone.[19]
    - The number of IT treatments ranged from three to twelve depending on clinical improvement, condition, and sterilization of the CSF. Systemic chemotherapy was given to 18 of the patients: five received intermediate dose chemotherapy;

three were given salvage chemotherapy followed by allogenic stem cell transplant; six received high-dose chemotherapy and autologous stem cell transplant; two were given high-dose chemotherapy and autologous stem cell transplant followed with allogenic stem cell transplant; and two were administered high-dose chemo followed by allogenic stem cell transplant.[19]

While our patient's presentation was not unusual for LM, two particularly unique cases published by Pontikoglou et al demonstrate how presentations can vary dramatically in this heterogeneous condition. The first case describes a 64-year-old woman, previously successfully treated for MM (melphalan and prednisone), who presented with headaches and mental status changes 10 years after initial diagnosis. She was subsequently diagnosed with obstructive hydrocephalus and was successfully treated with cranial irradiation, IT chemotherapy (methotrexate and methylprednisolone), and six courses of VAD (vincristine, liposomal doxorubicin, dexamethasone). Twenty months later, she had no signs of relapse. The case is noteworthy because of the 10-year interval between diagnosis of MM and LM. Before their report, 7 years had previously been the longest reported time interval.[42] These isolated reports of prolonged intervals between diagnosis of MM and LM do not confirm that prolonged survival results in increased prevalence of LM.[43]

Pontikoglou et al describe a second case which is equally unusual: a 64-year-old woman presented with hypopituitarism, diabetes insipidus and a sellar mass. Original diagnosis of MM was 1 year before. These unusual symptoms occurred after her fifth cycle of vincristine, cyclophosphamide, melphalan, and prednisone. Cranial irradiation was administered, hormones were replaced, and systemic chemotherapy was later re-initiated. Her disease was resistant to both cranial radiotherapy and chemotherapy; she died from disease progression 2 years later.

Interestingly, the authors imply that her death resulted from systemic myeloma rather than LM when they state: "the patient died 2 years later, due to disease progression, but with no signs of deterioration in the CNS."

Conclusion

While LM is likely under-reported, the current literature suggests that the incidence of CNS involvement in MM is approximately 1%.[1,11] LM is associated with cytogenetic abnormalities and plasmablastic morphology. It can occur with a seemingly low tumor burden and even in the setting of a CR. It most often occurs in stage III disease.[1,43]

Novel agents such as bortezomib allow for prolonged survival in high-risk patients; however, with inadequate CNS penetration, complications such as LM may be inevitable. Our report and other case reports draw attention to LM's clinical and radiographic heterogeneity. This case demonstrates how LM can occur in the context of previous treatment and minimal volume disease. Our case is unique in that the patient had extremely high baseline serum free light chains which declined steeply after induction chemotherapy, representing an aggressive myeloma subtype. It remains unknown whether this is a risk factor for LM. Since there are so few cases of LM and the SFLC assay is relatively new, it is unlikely that this effect has been previously described with LM.

Further research of the biology, pathophysiology, and clinical course of LM will help clinicians to better understand how to approach it. With more cases reported, eventually multi-center trials may be designed to determine the best treatment modalities. With more case reports, the incidence and prevalence of this complication can be calculated more accurately. Additional understanding of the cytogenetic abnormalities associated with this condition may help clinicians identify patients at risk for LM.

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Disclosure

The authors report no conflicts of interest in relation to this paper.

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