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Case Report

CASE REPORT

Successful eradication of leptomeningeal plasma cell disease

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Abstract

Plasma cell leukaemia (PCL) is a rare and aggressive form of malignant monoclonal gammopathy characterized by the presence of high levels of plasma cells in peripheral blood. Central nervous system involvement of PCL has no established treatment and an extremely poor prognosis. We here present a 59-year-old male patient diagnosed with PCL, initially treated with induction chemotherapy followed by autologous peripheral blood hematopoietic stem cell transplantation. After achieving a partial response, he relapsed and presented with leptomeningeal disease. He was then successfully treated with dexamethasone, pomalidomide, and an intrathecal combination of methotrexate, methylprednisolone and cytarabine. This cleared his cerebrospinal fluid from plasma cells achieving a durable partial response.

INTRODUCTION

Primary plasma cell leukaemia (PCL) is a rare and aggressive plasma cell dyscrasia with distinct biologic, clinical and laboratory features, and a poor prognosis. It is defined by the presence of >2 × 10^9/L plasma cells in peripheral blood or plasmacytosis accounting for >20% of the total white cell count, not arising from a pre-existing multiple myeloma (MM). The clinical course is aggressive with short remissions and reduced survival [1]. Although rare, neurological complications of PCL occur and may be due to spinal myeloma, skull or intracranial myeloma, or cranial nerve involvement [2]. We here present a 59-year-old male patient diagnosed with PCL, initially treated with induction chemotherapy and autologous peripheral blood hematopoietic stem cell transplantation (auto-HSCT). After achieving a partial response, he developed neurological symptoms and was diagnosed with leptomeningeal PCL. He was then given a combination of immunomodulatory drugs (IMiDs) and intrathecal (IT) chemotherapy which cleared his cerebrospinal fluid (CSF) from plasma cells giving a stable disease.

CASE REPORT

A 59-year-old man presented to the emergency department with a history of perspiration at night, decreased appetite with a possible mild weight loss, pain in the back, and a general fatigue. The symptoms had progressed over the last weeks. He

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had no significant past medical history. On the physical examination he was pale and in reduced general condition, notably without splenomegaly or palpable glandular nodes. The initial laboratory tests are given in Table 1 (Diagnosis). A peripheral blood smear revealed dysplastic plasma cells and his bone marrow was dominated by small and heterogeneous plasmacytoid cells, accounting for 50% of the total nucleated cells (Fig. 1). Moreover, immunophenotypic characterization of the bone marrow aspiration using flow cytometry showed CD28+, CD38+, CD56−, CD119−, CD138+ cells and the polymerase chain reaction (PCR) for clonality revealed monoclonal B-cells. A computer tomography (CT) scan revealed an osteolytic lesion in the third lumbar vertebrae (L3). Based on the above he was diagnosed with primary PCL and was treated with 4 cycles of bortezomib (1.3 mg/m^2), cyclophosphamide (900 mg/m^2), and dexamethasone (20 mg day 1, 2, 4, 5, 8, 9, 11 and 12); the VCD regimen [3]. A reduced dose of cyclophosphamide (450 mg/m^2) was given because of liver- and renal failure. He improved clinically and biochemically and was followed in the out-patient clinic. Furthermore, stem cells were mobilized by high dose cyclophosphamide (2000 mg/m^2), plerixafor (20 mg) and G-CSF (480 µg for 5 days), and he was given high dose melphalan (200 mg/m^2) with support from CD34+ stem cells infusion, without complications. Post-transplant maintenance therapy with bortezomib (1.3 mg/m^2) was given every second week [4].

Bortezomib was discontinued after 14 months because of neuropathy, recognized as a common side effect [4]. However, 10 days later he was admitted to the medical department with a significantly reduced general condition and he did not manage to eat or drink properly. A severe expressive aphasia, ataxic gait and objectively reduced strength in both legs were also present. The laboratory tests are given in Table 1 (Relapse). A peripheral blood smear showed 28% plasmacytoid cells, and magnetic resonance imaging (MRI) of the skull, brain and spinal cord indicated leptomeningeal disease (Figs 2 and 3). His CSF was rich in cells with leucocyte cell count of 520 × 10^6/L (reference: <3 × 10^6/L), 95% being mononuclear. Immunophenotypic characterization demonstrated 70% of the nucleated cells to be plasma cells positive for CD38 and CD138. Based on the MRI and CSF findings, the diagnosis of leptomeningeal PCL was established.

Systemic treatment with dexamethasone (40 mg, Days 1, 8, 15, 22, etc.) and pomalidomide (3 mg Days 1–21) was prescribed, and an IT combination of methotrexate (15 mg), methylprednisolone (10 mg) and cytarabine (40 mg) was started in parallel. The patient had a good clinical response, a gradual reduction of plasma cells in the CSF until eradication, and a decrease in serum lambda light chain levels (Fig. 4). He received a total of 11 cycles of IT treatment. A minor ataxia in both arms was persistent, but no other significant clinical manifestations. Unfortunately the patient relapsed with a rapid progression of his PCL within a month after the last IT treatment, about three months after the diagnosis of leptomeningeal PCL. He died shortly thereafter with an overall survival of 20 months from PCL diagnosis, hence, the progression free intervals (PFS) 1 and 2 were 17 and 3 months, respectively.

DISCUSSION

Invasion of the CNS in PCL is rare and thought to be a result of a haematogenous spread [5–7]. The neurological manifestations are highly variable including cerebral symptoms, cranial neuropathy and spinal cord or nerve root affection [2, 8]. Most patients diagnosed have Salmon–Durie stage III disease [2], and the median interval between diagnosis of PCL and leptomeningeal PCL is reported to be ~12–15 months [2, 8]. Typical CSF findings are increased cell counts and elevated protein levels. MRI typically demonstrates leptomeningeal metastasis with cranial or spinal leptomeningeal contrast enhancement, and leptomeningeal-based mass lesions [2]. Our patient presented with typical clinical features, and both radiological- and biochemical CSF findings consistent with diagnosis. CNS disease is currently not stated as organ dysfunction by The International Myeloma Working Group (IMWG) criteria [9], mainly because of its rarity. However, in our opinion CNS disease is a clear indication for treatment in plasma cell disorders.

The prognosis of PCL involving the CNS is extremely poor with an overall survival ranging from 2 to 6 months [8, 10, 11]. Although there are currently no well-established treatment of leptomeningeal PCL, novel agents in CNS myeloma treatment are described [12], and pomalidomide and dexamethasone are described effective in a few case reports [13, 14]. Moreover, long-term survival is described in some patients treated with the combination of CNS radiotherapy, multi-dosing intrathecal chemotherapy, and IMiD-containing therapy [8, 15]. In addition, pomalidomide have shown a high penetration of the blood–brain-barrier in murine models and significant anti-tumour activity in the CNS [16], and the anti-tumour effect is described

Table 1: The table gives the laboratory tests at diagnosis, relapse and after treatment

	References	Diagnosis	Relapse	After treatment
Haemoglobin	13.4–17.0 g/dL	7.1	9.0	8.8
Leucocyte count	4.3–10.7 × 10^9/L	11.7	5.1	4.8
Platelet count	145–348 × 10^9/L	60	39	85
Creatinine	45–90 µmol/L	205	144	124
Calcium	2.20–2.55 mmol/L	2.45	2.32	2.22
Albumin	39–48 g/L	27	40	42
Ionized calcium	1.13–1.28 mmol/L	1.45	1.26	1.21
Sedimentation rate	<21	12	–	–
IgG	6.0–15.3 g/L	3.17	0.81	1.78
IgA	0.8–4.0 g/L	0.28	0.26	<0.25
IgM	0.3–2.3 g/L	<0.18	0.19	0.19
Kappa light chains	6.7–22.40 mg/L	6.26	0.72	1.72
Lambda light chains	8.3–27.0 mg/L	192	492	475
Ratio K/L light chains	0.31–1.65	0.001	<0.001	<0.001
Beta-2-microglobulin	<2.0 mg/L	11.5	–	–

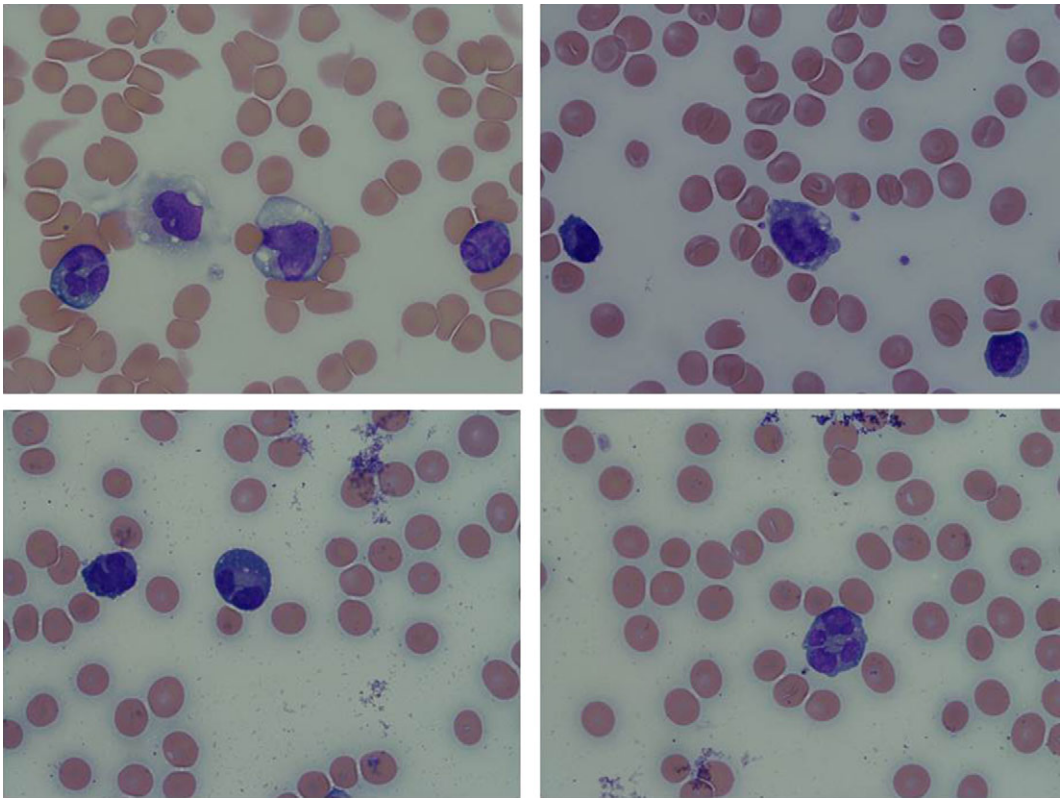

Figure 1: Plasma cell leukaemia. Peripheral blood smear (May–Grünwald–Giemsa staining) from the patient at diagnosis. The peripheral blood smear is characterized by the presence plasma cells, including binucleated cells and cells with clover shaped nucleuses. Notably, some plasma cells have a lymphoplasmacytoid appearance including vacuolization.

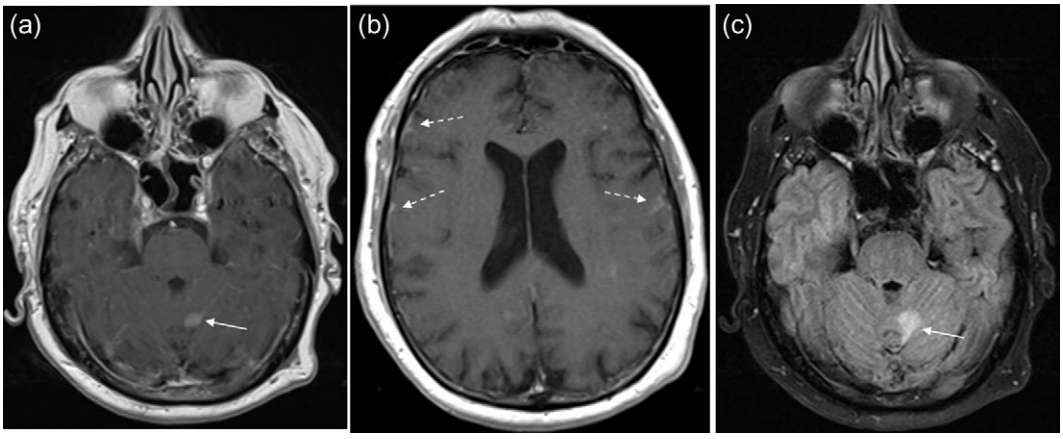

Figure 2: Leptomeningeal infiltration (cerebral). Nodular contrast enhancement medially in the left cerebellum (arrow) and diffuse contrast enhancement on the cerebral surface (stippled arrows) on contrast enhanced axial T1-weighted images (**a**, **b**) with corresponding high signal intensity in cerebellum (arrow) on axial FLAIR image (**c**) in the patient with leptomeningeal PCL.

superior compared to thalidomide [17]. We therefore chose to treat our patient with a combination of systemic dexamethasone and pomalidomide, and an IT combination of methotrexate, methylprednisolone and cytarabine. Using other novel therapeutics was also considered. However, the general condition of the patient, together with the sign of bone marrow failure and risk of severe side effects, especially neuropathy, restricted the use of utterly therapy. Other proteasome inhibitors such as carfilzomib and ixazomib are less neurotoxic than bortezomib [18]. Extramedullary disease is often an exclusion criterion for entering clinical trials, and the potential role of novel therapeutics in CNS disease therefore remains elusive. In contrast, the new proteasome inhibitor marizomib is currently under investigation in relapsed-refractory MM and malignant glioma [19], making it an interesting agent in CNS disease. Cases with encouraging results have been published [20],

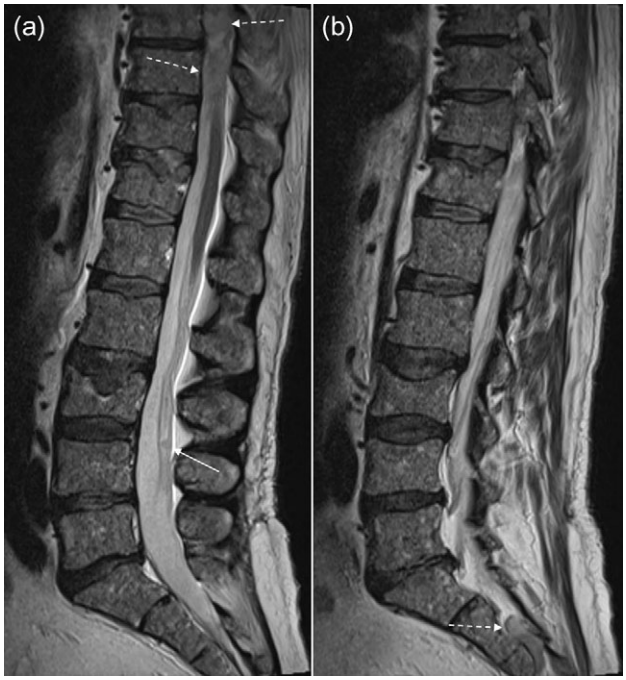

Figure 3: Leptomeningeal infiltration (spinal). Small nodular lesion in cauda equina at level L3/L4 (arrow) and more confluent lesions behind Th9–Th10 and S2–S3 (stippled arrows) on sagittal T2-weighted images near the midline (**a**) and laterally (**b**) in the patient with leptomeningeal PCL.

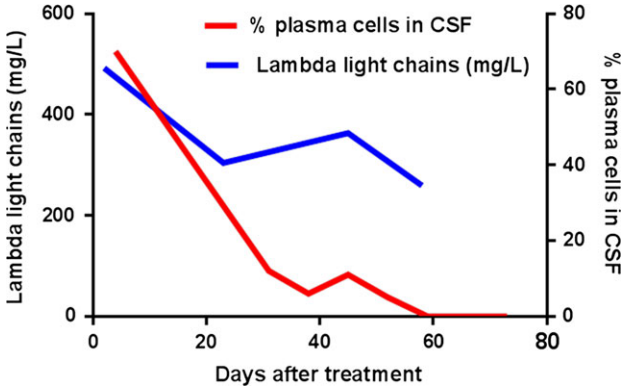

Figure 4: Treatment effect. The figure demonstrates the development of plasma cell in CSF (red graph) and the lambda light chain levels (mg/L) in serum (blue graph) during the treatment courses with intrathecal chemotherapeutics and pomalidomide and dexamethasone. The *x*-axis gives the days after treatment onset.

emphasizing further exploring of marizomib in patients with CNS disease.

Monoclonal antibodies, in particular elotuzumab and daratumumab, are also emerging as therapeutic alternatives in MM. Clinical trials regarding PCL or CNS disease do not exist, but a recent case report describes promising results regarding daratumumab and CNS disease [21], supporting further investigation of immunotherapy in aggressive plasma cell diseases [22]. CNS radiotherapy has proven beneficially as consolidation therapy in lymphoproliferative CNS disease and was considered for our patient. Unfortunately, the PCL relapsed and the patient died before radiotherapy was applied.

CONCLUSION

Treatment of PCL involving the CNS should be systematically further investigated in clinical trials to reveal the optimal combination of drugs, administration and duration. However, the present case report illustrates the potential to treat these patients with a combination of CNS radiotherapy, IMiDs and intrathecal chemotherapy, with the potential of durable responses.

CONFLICT OF INTEREST STATEMENT

No conflicts of interests.

FUNDING

No funding.

ETHICAL APPROVAL

No approval is required.

CONSENT

The patient gave written consent for publication of this case report.

GUARANTOR

Håkon Reikvam.

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