CASE REPORT

Initial presentation of CNS-restricted acute lymphoblastic B cell leukaemia as peripheral polyneuropathy

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SUMMARY

We report a case of a 58-year-old woman who presented with a 1-month course of progressive lower and upper extremity weakness in addition to binocular diplopia. Diagnostic lumbar puncture revealed atypical lymphoid cells with 28% blasts. Immunophenotype was consistent with B cell acute lymphoblastic leukaemia (B-ALL). Further work up showed no systemic involvement but extensive thoracolumbar-sacral leptomeningeal disease. The patient was treated with several courses of intrathecal and systemic chemotherapy followed by craniospinal irradiation for consolidation. There was initial steady improvement in neurological symptoms and leptomeningeal disease, the latter being ascertained through radiological studies and cerebrospinal fluid examination. After 10 months of response, the patient relapsed with central nervous system (CNS) and systemic disease. B-ALL is a rare precursor lymphoid neoplasm that generally presents with systemic disease. While CNS involvement is not uncommon, isolated involvement of this compartment without systemic disease is exceedingly rare.

BACKGROUND

Central nervous system (CNS) involvement with malignant cells is a well-recognised complication of haematological neoplasms.¹ Lymphoid malignancies such as acute lymphoblastic leukaemia (ALL) and high-grade lymphomas not uncommonly involve the CNS. B cell acute lymphoblastic leukaemia (B-ALL) is a relatively rare malignancy that occurs most frequently in childhood and in young adults. Most patients present with features of blood and bone marrow involvement in B-ALL, and additional CNS involvement is seen in <10% of patients.² Mass lesions including extranodal involvement are uncommon in B-ALL and more characteristic of B cell lymphoblastic lymphoma. CNS involvement by mature lymphoid neoplasms is observed in 8% and 3% of patients with aggressive and indolent systemic non-Hodgkin's lymphoma (NHL), respectively.³ Primary CNS lymphoma, in the absence of systemic disease, is even rarer, representing 1–2% of NHL. A solitary intracranial mass is the initial presentation in 60–70% of these patients, while solely leptomeningeal involvement is seen in only 5–7%.^{3,4}

CASE PRESENTATION

A 58-year-old woman presented for evaluation following a 1-month course of progressive lower and

upper extremity weakness. Her medical history was significant for Graves' disease status post iodine ablation, rotator cuff arthritis and low back pain. Her medications at that time included alprazolam and levothyroxine in addition to cyclobenzaprine, naproxen and hydrocodone for pain as needed. There was no family history of cardiovascular or neurological diseases. Family history was significant for the patient's mother, who died from leukaemic transformation of polycythaemia vera. The patient denied alcohol or tobacco consumption.

She initially presented to her primary care provider, reporting of bilateral lower extremity weakness with preservation of sensation and reflexes. There was no history of trauma. Additionally, she reported right-hand paraesthesia involving the second and third digits radiating medially to her entire arm. Electromyography evaluation at that time showed mild peripheral neuropathy, primarily axonal, with motor involvement. She had chronic right lumbosacral polyradiculopathy and right ulnar neuropathy. Spine MRI showed diffuse degenerative disease with L3/L4 spondylolisthesis and L1 compression. Given worsening of her lower extremity symptoms, the patient underwent decompressive right L3–L4 transforaminal lumbar interbody fusion with right iliac crest bone grafting. She was treated with steroids perioperatively and regained lower extremity strength. No changes were observed regarding her upper extremity symptoms.

One month following her surgery, her motor symptoms recurred in upper and lower extremities, now accompanied by binocular diplopia. Contrasting with initial presentation, there was areflexia and sensory loss distally in the lower extremities, with preserved vibratory sensation. There was evidence of neither genital nor saddle anaesthesia. She denied bladder and bowel function impairment. With concern for worsening of her disease, she was referred to our centre for further evaluation.

INVESTIGATIONS

Initial investigation aimed to assess metabolic, infectious, autoimmune and malignant causes of the patient's peripheral polyneuropathy (table 1). Laboratory evaluation showed neither iron nor vitamin deficiencies. Electrolyte and liver panels were within normal limits. Thyroid function was well-controlled and there was no indication of

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Table 1 Differential diagnosis of the patient's peripheral polyneuropathy presentation

Metabolic	Infectious	Autoimmune	Malignant
Vitamin B ₁₂ deficiency	Lyme disease	Connective tissue disease	Metastatic disease
Thyroid dysfunction	Syphilis	Multiple sclerosis	Primary CNS neoplasia
Diabetic neuropathy	HIV, HTLV, CMV	Guillain-Barré syndrome	Leukaemia/lymphoma with CNS involvement
CMV, cytomegalovirus; CNS, central nervous system; HTLV, the human T-lymphotropic virus.			

diabetes. C reactive protein level was normal, however, the erythrocyte sedimentation rate was elevated at 81 mm/h. Autoimmune and paraneoplastic panels were negative. Additionally, negative serologies for lyme-syphilis, HIV, human T cell lymphotropic virus and cytomegalovirus infections were documented. Serum protein electrophoresis showed no monoclonal protein.

Cerebrospinal fluid (CSF) analysis showed clear fluid with 227 nucleated cells and 96% atypical lymphocytes (figure 1). Glucose was undetectable and protein was elevated at 74 mg/dL. IgG concentration was 11.1 mg/dL and albumin 51.8 mg/dL with an IgG/albumin ratio of 0.52. There were four oligoclonal bands detected. Immunophenotyping by flow cytometry showed 28% lymphoblasts expressing CD34 (partial), CD19, CD45 (dim), CD13 (partial), terminal deoxy- nucleotidyl transferase enzyme (nTdt), cCD22 and cCD79a. The blasts did not express: CD10, CD3, cMPO, cCD3. Overall, the immunophenotype was consistent with pre-B-ALL.

Complete blood count showed haemoglobin of 12.5 g/dL, platelets $318 \times 10^9/L$, leucocytes $4.6 \times 10^9/L$ and absolute neutrophil count of $2.71 \times 10^9/L$. The white cell count differential was unremarkable, with no evidence of circulating immature cells. Bone marrow biopsy revealed a normocellular marrow with normal trilineage haematopoiesis without leukaemic involvement. Positron emission tomography-CT (PET-CT) demonstrated increased activity in the spinal canal in thoracolumbar and sacral regions, consistent with leptomeningeal disease

Figure 1 Atypical lymphocytes on cerebrospinal fluid cytology.

(figure 2). There was no evidence for extra CNS or systemic involvement with disease. Limited cytogenetic studies were possible on the CSF sample. Rearrangements of BCR-ABL and MLL genes were excluded by fluorescence in situ hybridisation studies.

TREATMENT

The patient initially received two cycles of a Hyper-CVAD (Hyperfractionated Cyclophosphamide, Vincristine, Doxorubicin and Dexamethasone) multiagent chemotherapy regimen, which included intrathecal administration of cytarabine and methotrexate. She tolerated chemotherapy well and there was an initial clinical response with clearing of the CSF lymphoblasts. Concurrently, MRI of the spine revealed improvement of leptomeningeal enhancement along the cervical and thoracic cord, however, with persistent thickening of the cauda equina.

The patient subsequently received a cycle of systemic high-dose methotrexate chemotherapy. After the aforementioned treatments, which included 10 intrathecal chemotherapy treatments, the CSF was rendered clear of malignant lymphoblasts. Given the persistent residual leptomeningeal enhancement in the thoracic spine and cauda equina, the patient underwent cranio spinal irradiation as consolidation treatment for her initial response. PET-CT, after radiotherapy, indicated no evidence of fludeoxyglucose-avid residual leukaemic involvement and MRI of the spine showed additional improvement. Despite strong recommendations to consider allogeneic stem cell transplantation, the patient declined this option for personal reasons.

OUTCOME AND FOLLOW-UP

The patient returned 4 months later reporting worsening upper extremity weakness and progression of ocular symptoms. MRI of the head revealed no intracranial findings. On the other hand, MRI of the spine showed new enhancement within the right C4–C5 neural foramen and right lateral thecal sac. Furthermore, CSF was again positive for B-ALL. Staging studies continued to indicate CNS-restricted disease. The patient received systemic fludarabine and dexamethasone, in addition to intrathecal cytarabine infusions. CSF cytology became negative for blasts but minimal residual disease remained detectable by flow cytometry. The symptoms continued to slowly improve. A second cycle of fludarabine and dexamethasone was planned in order to maintain response but the patient refused, primarily due to logistical challenges. Monthly intrathecal treatments with liposomal cytarabine and oral dexamethasone continued for palliative purposes. Peripheral blood and bone marrow continued to be negative.

After another 4 months of clinical response, the patient presented for evaluation of right eye proptosis and right shoulder pain. MRI of the spine demonstrated stable thoracic and lumbar spine disease with interval growth of a contrast enhancing mass along the right C5 nerve root. Diffuse leptomeningeal enhancement was again confirmed with CSF showing B-ALL blasts. MRI of the brain demonstrated enhancement of the right medial rectus muscle but no intraparenchymal masses. Biopsy of the extraocular muscles confirmed involvement of B-ALL. The symptoms were attributed to progression of the CNS-restricted disease, now with systemic involvement. Treatment options are being actively discussed with the patient.

DISCUSSION

Acute lymphoblastic B cell leukaemia/lymphoma is a rare precursor lymphoid neoplasm with the majority of cases occurring in children and young adults.⁵

Figure 2 Positron emission tomography-CT demonstrated increased activity in the spinal canal in the thoracolumbar and sacral regions, consistent with leptomeningeal disease.

Among the spectrum of adult ALL, primary-CNS involvement at diagnosis, generally concurrent with systemic involvement, is seen in 5–10% of cases.² CNS presentation in adult ALL is more commonly seen in the setting of relapsed disease, hence, the strong emphasis on CNS prophylaxis as part of most treatment regimens.^{5 6} A large study showed hyperleucocytosis, mediastinal mass and T cell immunophenotype to be associated with CNS involvement.⁶ Furthermore, survival of adult patients with ALL without CNS involvement at presentation was significantly superior to that of patients with such involvement, however, some patients achieved durable disease remissions with intensive induction and postremission chemoradiation therapy with or without allogeneic stem cell transplantation.

The diagnostic assessment of this condition is still a matter of debate. CSF examination remains the most useful test in the diagnosis of ALL CNS involvement. It indirectly detects abnormalities in fluid content, and allows direct morphological examination with conventional cytology and flow cytometry. In regard to neuroimaging, MRI has been shown to be superior to CT, but has a high rate of false negatives, thus, should not be used as a stand-alone diagnostic tool.⁷

Our patient had a very unique presentation of primary CNS disease in the form of leptomeningeal and CSF involvement, without evidence of systemic involvement, even when the latter was assessed by sensitive flow cytometry techniques. Given the rarity of this particular presentation of B-ALL, the treatment approach was challenging. The case illustrates that while it was possible to sterilise the CSF of leukaemic cells, using a multi-modality approach that included systemic and intrathecal chemotherapy as well as craniospinal radiation, the benefit was short-lived and was complicated by systemic relapse. Whether consolidation with allogeneic stem cell transplantation at the time of clinical remission would have resulted in a durable response remains an open question.

Learning points

- ▶ Peripheral polyneuropathy may be a presenting feature of malignant involvement of the central nervous system (CNS) by haematological neoplasms.
- ▶ CNS-restricted involvement by B cell acute lymphoblastic leukaemia is not common at initial presentation and may precede systemic involvement by the disease.
- ▶ Optimal treatment of the aforementioned condition remains to be determined.

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Competing interests None declared.

Patient consent Obtained.

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REFERENCES

- 1 Sham RL, Phatak PD, Kouides PA, *et al.* Hematologic neoplasia and the central nervous system. *Am J Hematol* 1999;62:234–8.
- 2 Pui CH. Central nervous system disease in acute lymphoblastic leukemia: prophylaxis and treatment. *Hematology Am Soc Hematol Educ Program* 2006:142–6.
- 3 Rubenstein J, Ferreri AJ, Pittaluga S. Primary lymphoma of the central nervous system: epidemiology, pathology and current approaches to diagnosis, prognosis and treatment. *Leuk Lymphoma* 2008;49(Suppl 1):43–51.
- 4 Lachance DH, O'Neill BP, Macdonald DR, *et al.* Primary leptomeningeal lymphoma: report of 9 cases, diagnosis with immunocytochemical analysis, and review of the literature. *Neurology* 1991;41:95–95.
- 5 Inaba H, Greaves M, Mullighan CG. Acute lymphoblastic leukaemia. *Lancet* 2013;381:1943–55.
- 6 Lazarus HM, Richards SM, Chopra R, *et al.* Central nervous system involvement in adult acute lymphoblastic leukemia at diagnosis: results from the international ALL trial MRC UKALL XII /ECOG E2993. *Blood* 2006;108:465–72.
- 7 Del Principe MI, Maurillo L, Buccisano F, *et al.* Central nervous system involvement in adult acute lymphoblastic leukemia: diagnostic tools, prophylaxis, and therapy. *Mediterr J Hematol Infect Dis* 2014;6:e2014075.

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