Unusual presentation of more common disease/injury

T cell acute lymphoblastic leukaemia presenting with sudden onset right oculomotor nerve palsy with normal neuroradiography and cerebrospinal fluid studies

Vijaya Raj Bhatt,¹ Muniba Naqi,¹ Rajiv Bartaula,¹ Srujitha Murukutla,¹ Sulagna Misra,¹ Muhammad Popalzai,² Kavitha Paramanathan,² Qun Dai²

¹Department Of Medicine, Staten Island University Hospital, Staten Island, New York, USA;

²Division Of Hematology/Oncology, Department of Medicine, Sanford R Nalitt Institute for Cancer and Blood Related Diseases, Staten Island University Hospital, Staten Island, New York, USA

Correspondence to Dr Srujitha Murukutla, srujitha.murukutla@gmail.com

Summary

Leptomeningeal disease presenting with neurological dysfunction is not uncommon in leukaemia. However, it is often accompanied by abnormalities in cerebrospinal fluid (CSF) studies and/or neuroradiography. Here, the authors describe a case of a young patient presenting with sudden onset right oculomotor nerve palsy with normal neuroradiography and CSF studies, who was subsequently diagnosed to have T cell acute lymphoblastic leukaemia (T-ALL). This case highlights that neurological manifestations can be the initial presenting feature of T-ALL and can occur suddenly despite normal neuroradiography and initial CSF studies.

BACKGROUND

T cell acute lymphoblastic leukaemia (T-ALL), originating from developing T-cells in the thymus,¹ accounts for about 25% of adult ALL.¹⁻³ The presence of $\geq 25\%$ lymphoblasts of T cell lineage in the bone marrow establishes diagnosis of the disease.⁴ T-lymphoid-affiliated antigens include cytoplasmic cluster differentiation (CD)3, CD1a, CD2, surface CD3, CD4, CD5, CD8, CD62L, CD57 and surface α/β and β/γ ⁵; presence of these cell markers identifies the T cell lineage of the blasts.

Leptomeningeal disease presenting with neurological dysfunction is not uncommon in leukaemia.³⁻⁵ However, it is usually accompanied by abnormalities in cerebrospinal fluid (CSF) studies and/or neuroradiography.^{3-5,6} Here, we describe a young patient presenting with sudden onset right oculomotor nerve palsy found to have T-ALL, but no abnormalities on neuroradiography or CSF studies.

CASE PRESENTATION

A 28-year-old lady, without significant medical or surgical history, presented to the emergency department with a 4-day history of frontal headache, worse in the morning, associated with nausea and a few episodes of vomiting. She had a 1-day history of drooping right eyelid. Additional symptoms included pain over both hand joints for several weeks before presentation and a documented elevated rheumatoid factor performed a week before her presentation. She denied fever, chills, sweating, morning stiffness, oral ulcer, photosensitivity, weight loss or trauma. She smoked approximately three cigarettes a day but denied alcohol or illicit drug use.

Upon evaluation, she had a pulse of 81/min, blood pressure of 114/58, respiratory rate of 18 and temperature of 36.9°C. Neurological examination revealed right third nerve

palsy with otherwise unremarkable neurological examination. Physical examination was otherwise unremarkable.

INVESTIGATIONS

Laboratory studies included: white blood cell (WBC) 18 000/ μ l, haemoglobin 12.8 g/dl and platelet count 189 000/ μ l. Peripheral blood smear revealed atypical lymphocytes and immature cells, so the slides were sent to haematopathologist for further evaluation. Rheumatoid factor and erythrocyte sedimentation rate were 73 IU/ml and 1 mm/h, respectively. Values of glucose, electrolytes, bicarbonate, lactate, coagulation profile and renal and liver function tests were all within normal limits.

TREATMENT

The patient was admitted to the hospital to rule out a possible central nervous system (CNS) space occupying lesion, vasculitis, infection or stroke. She was started on intravenous morphine and metoclopramide as needed for symptom control. An urgent MRI brain with and without intravenous gadolinium, and magnetic resonance venography brain were unremarkable. Magnetic resonance angiography of the brain was within normal limits with the exception of a 1 mm laterally directed aneurysm in the left cavernous carotid artery. An urgent neurosurgical consult concluded that the patient's condition was not related to the aneurysm because of its location. An urgent spinal tap was done; CSF examination showed: WBC 0/ μ l, red blood cell 0/ μ l, glucose 53 mg/dl and protein 37.4 mg/dl. CSF Gram stain, India ink, culture, herpes simplex virus (HSV), ELISA and PCR and cytology were all negative. In addition, chest x-ray, CT orbit non-contrast, urine and blood cultures were negative. Lyme antibodies, antineutrophil cytoplasmic antibody, antinuclear antibody, anti-SSA

and anti-SSB antibodies, rapid plasma reagin, as well as cytomegalovirus, HSV and hepatitis serologies were negative as well.

OUTCOME AND FOLLOW-UP

Peripheral blood smear was reviewed by haemato-pathologist and haematology-oncology consultant; it revealed: 36% blasts, 33% neutrophils, 20% lymphocytes and 4% atypical lymphocytes. A bone marrow aspiration and biopsy was performed. Bone marrow studies showed hypercellular marrow with 70–80% blasts without Auer rods or azurophilic granules. Megakaryocytes, myeloid and erythroid series were decreased. Immunohistochemical studies showed blasts positive for CD3, CD43 and terminal deoxynucleotidyl transferase (TdT) (nuclear). Many of the cells were positive for CD4 and CD7. There was no significant expression of any of the following markers: CD2, CD34, CD79a, PAX-5, CD117 and myeloperoxidase. Cytogenetic studies revealed normal karyotype, 46, XX. PCR for BCR-ABL translocation was negative. Thus, a diagnosis of T-ALL with CNS involvement was established and the patient was started on hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone (as a part of hyper-CVAD chemotherapy) and intrathecal chemotherapy with methotrexate. A repeat CSF sample was obtained before intrathecal methotrexate; CSF analysis revealed no white count and normal chemistry and cytology. The patient tolerated her first course of chemotherapy and intrathecal treatment. She was subsequently transferred to tertiary care cancer centre for further management. At the other centre, the patient was continued on hyper-CVAD and intrathecal chemotherapy. The patient also received whole brain radiation. After the completion of whole brain radiation and four cycles of chemotherapy, she went into remission and her left eye ptosis resolved.

DISCUSSION

CNS involvement at presentation occurs in nearly 10% of patients diagnosed with T-ALL.^{3–5} The median age at presentation is 29 years. Although CNS involvement is more common in males and Philadelphia-chromosome negative ALL, there is no difference between ALL patients with and without CNS leukaemia with regard to sex, age, Philadelphia positivity, hepatomegaly, splenomegaly, or lymph node enlargement. On the other hand, patients with CNS leukaemia are more likely to have a higher white count compared with those without and also more likely to have a mediastinal mass on radiographic imaging.⁵

The disease pathology in CNS leukaemia can involve the entire nervous system; however, involvement of cerebral hemispheres, cranial nerves or spinal cords and associated nerve roots is more frequent. The most common clinical symptoms are the result of intracranial hypertension (eg, headache, nausea, vomiting and change in mental status), cranial nerve palsies (particularly facial and oculomotor nerve palsies), spinal cord dysfunction and radicular pain.⁷ The neurological manifestations of the patient discussed here, oculomotor palsy and clinical symptoms suggestive of intracranial hypertension, are typical of CNS leukaemia. However, few patients present with such unequivocal symptoms.⁹ CNS involvement in ALL is characterised

by the presence of significant neurological dysfunction, unequivocal blasts in the CSF, or abnormal neuroradiography.^{3–6} While gadolinium enhanced MRI is more sensitive than contrast enhanced CT scans, nearly two thirds of patients with positive CSF cytology will have meningeal enhancement on CT scan.⁷ It is not uncommon to find neurologic manifestations and/or abnormalities on neuroradiographic imaging with a normal initial CSF cytology.^{7–8} However, the patient discussed herein had neurologic deficits without any abnormality in both CSF and neuroradiography (MRI). This finding is very rare.

CSF abnormalities in CNS leukaemia are usually discovered during a routine diagnostic evaluation of CSF. Traditionally, a positive CSF cytology requires the presence of at least 5 leucocytes/ μ l of CSF and the unequivocal presence of leukemic blast cells in a centrifuged specimen.⁷ However, nearly one-third of CSF with positive cytology can have <4 leucocytes/ μ l. Furthermore, initial CSF cytology may be normal with subsequent CSF sampling showing the aforementioned cytological findings. In one study, the first CSF analysis was positive in only 64% of patients with CNS leukaemia. In other words, 36% of patients with CNS leukaemia had normal CSF cytology initially and required two or three lumbar punctures and CSF analyses before results showed abnormal cytology.⁸ Lastly, it may be difficult to distinguish blast cells from reactive lymphocytes with morphology alone. In such cases, flow cytometry¹² or surface marker analysis can be useful.⁹

Notably, in the case presented here, the CSF chemistry was completely unremarkable. However, CSF cytology can be falsely negative in several settings including a small volume spinal tap or if there is a delay in processing the sample.¹³ Therefore, it is possible that the negative CSF cytology in this patient is a false negative and repeat lumbar puncture may have revealed abnormal findings.

Learning points

- Sudden onset focal neurological deficit can herald the presence of T-ALL.
- The possibility of CNS leukaemia cannot be refuted based on normal initial CSF studies or neuroradiography.
- Lymphocytosis can be the only clue to the diagnosis of ALL and mandates early investigation in the absence of alternate explanation.

Competing interests None.

Patient consent Obtained.

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