CASE REPORT

Posterior reversible encephalopathy syndrome in a postpartum woman with acute lymphoblastic leukaemia after intrathecal methotrexate

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SUMMARY

Posterior reversible encephalopathy syndrome (PRES) is the most common neurological complication occurring in children undergoing induction chemotherapy for acute lymphoblastic leukaemia (ALL) but is increasingly recognised to occur in adults as well. Here, we report a woman who presented with B-cell ALL (B-ALL) at the time of delivery and developed PRES 1 day after receiving intrathecal (IT) methotrexate (MTX) that rapidly resolved. She subsequently received IT MTX without recurrence of neurological symptoms. This case represents the first case of PRES in a postpartum B-ALL patient receiving IT MTX, demonstrates that re-treatment with MTX in this case could be done safely and highlights the risk of PRES in adults treated for B-ALL.

BACKGROUND

This is a unique case of posterior reversible encephalopathy syndrome (PRES) in a patient with multiple risk factors for developing PRES that occurred shortly after administering IT MTX, who was re-exposed to IT MTX later in her treatment course without developing neurological symptoms. This case illustrates the complexity of PRES in haematological malignancy patients and prompted a review of literature of PRES in such patients.

CASE PRESENTATION

A 21-year-old woman presented to an outside hospital at 36 weeks gestation with severe epistaxis. She was reportedly found to have leucocytosis and thrombocytopenia (initial lab values not available) with circulating lymphoblasts compatible with B-cell acute lymphoblastic leukaemia (B-ALL). Because of the significant abnormalities noted in her white blood cells (WBC) and platelets, 15 days prior to beginning induction chemotherapy, she underwent an induction of labour and gave birth to an apparently normal girl with a normal blood counts. The method of induction was unavailable for review. She was transported to our facility for further management. Her blood pressure on admission was 123/69 mm Hg. On the day of her admission (day -4 from induction) her labs revealed a WBC 28.400/ μ L (absolute neutrophil count 15.400/ μ L, absolute lymphocyte count 3.100/ μ L, absolute lymphoblast count 4.300/ μ L), haemoglobin 8.0 g/dL, platelet count 12×10^9 /L.

Lactate dehydrogenase (LDH) was 7464 U/L, uric acid 7.7 mg/dL, phosphorus 5.3 mg/dL and creatinine 0.7 mg/dL. A bone marrow biopsy identified a high-grade B-cell leukaemia with a c-myc rearrangement. Flow cytometry showed expression of monotypic lambda, dim CD19, dim CD20, CD22, CD79a, CD9, CD10, CD38, dim CD45 and bright human leukocyte antigen-antigen D related. The cells were negative for CD34, TdT, MPO, CD3, CD66c, CD13, CD33, CD15, CD16 and CD117. Fluorescent in situ hybridisation revealed an Immunoglobulin Heavy Chain-MYC gene fusion t(8;14), biallelic loss of CDKN2A locus, three copies of RUNX1 and three copies of PBX1.

TREATMENT

She began induction chemotherapy with cyclophosphamide, vincristine, doxorubicin and dexamethasone (hyper-CVAD) as well as intrathecal (IT) methotrexate (MTX). She received cyclophosphamide on days 1, 2 and 3. On day 2, she received her first dose of IT MTX. Cerebral spinal fluid (CSF) evaluation was positive for leukaemic cells by cytology and flow cytometry. At the end of day 3, during her last infusion of cyclophosphamide, she developed visual hallucinations and had a generalised tonic-clonic seizure. For her seizure, she received intravenous lorazepam and phenytoin and was then maintained long term on levetiracetam. Her blood pressure at the time of the seizure was 169/104 mm Hg; amlodipine was started and she remained normotensive the remainder of her hospitalisation. MRI showed patchy cortical T2 hyperintensity along bilateral cerebral convexities, the right caudate nucleus and the left basal ganglia in the bilateral cerebellar hemispheres compatible with PRES (see [figure 1](#)). Her symptoms quickly resolved and a repeat MRI on day 8 of induction therapy showed near normalisation of the original MRI findings.

OUTCOME AND FOLLOW-UP

She was safely discharged on day 19 after her induction, and a day-24 bone marrow biopsy showed a complete remission. Given her young age, the treatment was changed to the CALGB 10403 protocol for young adults for consolidation and maintenance, which she received closer to her home during the course of which she received high-dose intravenous MTX without

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Figure 1 Brain MRI T2 signal findings at the time of development of posterior reversible encephalopathy syndrome with patchy T2 hyperintensity of bilateral cerebellar hemispheres (left) and 5 days later (right) showing near complete resolution of bilateral cerebellar lobe lesions.

apparent complication but had IT treatments with cytarabine only. Eight months after initial presentation, she developed central nervous system (CNS) relapse of her disease. She was treated with several doses of IT MTX combined with cytarabine without adverse consequences and underwent reinduction with hyper-CVAD cycles 1A and 1B. She remained on levetiracetam throughout this period. Unfortunately, 11 months after diagnosis, she died suddenly just prior to her scheduled myeloablative matched sibling donor allogeneic peripheral blood stem cell transplant. An autopsy was performed and showed a large pulmonary embolus.

DISCUSSION

It has been 20 years since PRES was first described¹ and it has become increasingly reported in the literature. PRES is a condition characterised by headaches, visual disturbances, abnormal mental status, seizures, nausea and vomiting. MRI findings typically show symmetric T2 high signal intensities caused by subcortical oedema, most commonly in the occipital and parietal lobes bilaterally.¹

Despite 20 years of research, the exact mechanism of PRES remains uncertain and there are four proposed hypotheses for its pathogenesis: the vasogenic theory, the cytotoxic theory, the immunogenic theory and the neuropeptide theory.² In all of these, the predominant pathophysiology is that of failed brain vasculature autoregulation and cerebral oedema. The vasogenic theory, first adduced by Hinchey *et al* in their original description of PRES, posits that rapid development of hypertension leads to the inability of the brain vasculature to autoregulate and a breakdown of the blood–brain barrier leading to extravasation of plasma and subsequent oedema. In contrast, the cytotoxic, immunogenic and neuropeptide theories propose that endothelial dysfunction/injury leads to release of cytokines, increased permeability and oedema.²

Our case of a young postpartum patient with ALL who developed PRES during induction chemotherapy is unique because the potential inciting factor could be one of several previously implicated in the development of PRES or, perhaps, the interplay of many. First, her blood pressure began to rise 2 days prior to initiation of induction chemotherapy, and sudden rises in blood pressure are well documented in PRES, although hypertension can also be a manifestation of PRES as well.¹ Preeclampsia/eclampsia is a well-known risk factor for PRES.³ Though she delivered 19 days prior to developing PRES, eclamptic episodes are not limited to the prenatal period and episodes of PRES have been reported as many as 12 days after delivery.⁴ There are reports in childhood malignancies that suggest tumour lysis syndrome (TLS) may cause PRES. Though our patient did have an elevated LDH and uric acid, she was receiving intravenous fluids for TLS prophylaxis.⁵ Furthermore, there is a single report describing a patient presenting with PRES as the initial feature of lymphoma, suggesting that even the malignancy itself can have neurological effects.⁶ Our patient's CSF analysis was positive for CNS involvement of her ALL. Finally, cytotoxic chemotherapy is a known risk factor for PRES and the hyper-CVAD regimen contains several medications that have been reported as the cause of PRES, including cyclophosphamide, vincristine, cytarabine and methotrexate. Our patient developed PRES after receiving cyclophosphamide for 3 days and 1 day after IT MTX.

On review of the literature, there have been 34 cases of PRES described in adults with haematological malignancies, including lymphoma, myeloma and leukaemia (table 1). Of those, only six had the diagnosis of ALL and two had been exposed to intrathecal methotrexate. Expanding this further, there are five cases of patients with lymphoma who developed PRES and had exposure to IT MTX, four of which also had recent exposure to cyclophosphamide. Two of the cases

Table 1 PRES in 34 adults with haematological malignancies

Age	53.5 (18–79)
Type of malignancy (34)	Lymphoma 13/34 (38%) Acute Myeloid Leukemia (AML) 7/34 (20.5%) ALL 6/34 (17.5%) Myeloma 8/34 (24%)
Chemotherapy exposed	Anthracycline 15/34 (44%) Steroids (pred/dex) 12/34 (35%) Cyclophosphamide 11/34 (32%) Vincristine 11/34 (32%) Intrathecal therapy 8/34 (25%) IT methotrexate 6/8 IT cytarabine 3/8 Cytarabine 7/34 (20.5%) Etoposide 7/34 (20.5%) Bortezomib 6/34 (17.5%) Rituximab 5/34 (15%) HD-MTX, thalidomide 3/34 (1%) Ifosfamide, platinum 2/34 (0.6%) L-asparaginase, mitoxantrone, pembrolizumab 1/34 (0.3%)
Re-exposure to chemotherapy	Yes 12/34 (35%) Withheld potential offending agent 6/12 Rituximab 1/6 Methotrexate 2/6 Bortezomib 1/6 Thalidomide 1/6 Pembrolizumab 1/6 No/no comment 22/34 (65%)

See online supplementary references in supporting information file S1.

ALL, acute lymphoblastic leukaemia; HD-MTX, high-dose methotrexate; IT, intrathecal; PRES, posterior reversible encephalopathy syndrome.

specifically name IT MTX as the causative agent.^{7 8} A third names IT chemotherapy in general and the patient had previously received IT MTX but more recently IT cytarabine.⁹ PRES has also been reported in a patient with rheumatoid arthritis who was only on oral MTX.¹⁰

This case indicates that the precise aetiology of PRES in patients with ALL or lymphoma can be difficult to ascertain because they typically receive multiple chemotherapy agents

over a short period. Further complicating this was the added risk factor of a postpartum woman, which is a known risk factor for PRES. Clinicians must weigh the risks and the benefits of re-exposure to a potential inciting agent. Our patient was subsequently treated with the potentially causative drugs cyclophosphamide and both intravenously and IT MTX without subsequent neurological complications. PRES is the single most common neurological complication reported during treatment of childhood ALL (3.9% of patients) but is increasingly now reported in adults.¹¹ Though apparently common in childhood haematological malignancies, uneventful re-exposure to implicated agents is less commonly reported among adults. To our knowledge, this is the first case of PRES reported in a recently postpartum adult undergoing induction therapy for ALL as well as the first example of uneventful re-exposure of an adult to intrathecal methotrexate after PRES that was closely temporally associated with previous administration of the same drug.

Contributors CAM analysed and interpreted the data, wrote a draft and made revisions of the manuscript and approved of the submitted version. AS analysed and interpreted the data, revised the manuscript and approved of the submitted version.

Competing interests None declared.

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Learning points

- The aetiology of posterior reversible encephalopathy syndrome (PRES) is broad with multiple contributing factors.
- PRES in haematological malignancy does not preclude cautious repeat challenging with a possibly inciting drug.
- Further documentation and reporting of cases of PRES is indicated to broaden experience and provide further insights for PRES in patients with cancer.

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