Posterior Reversible Encephalopathy Syndrome in a Child with Acute Lymphoblastic Leukemia with Asparaginase-associated Pancreatitis

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Abstract

Posterior Reversible Encephalopathy Syndrome (PRES) is a neuroradiological condition characterized by headaches, altered mental status, visual disturbances, and seizures, often associated with hypertension, sepsis, or immunosuppressive therapies. Although PRES has been linked to pancreatitis in adults, its association with asparaginase-associated pancreatitis in paediatric patients remains rare. We present a case of a 10-year-old boy with T-cell acute lymphoblastic leukemia (ALL) who developed PRES following asparaginase-associated pancreatitis during consolidation chemotherapy. The patient presented with severe abdominal pain, nausea and vomiting 16 days after receiving asparaginase. Biochemically he has metabolic acidosis, and high pancreatic enzymes with serum amylase of 350 U/L and lipase of 952 U/L (normal <60). Imaging confirmed acute necrotizing haemorrhagic pancreatitis. Despite initial stabilization, five days later he developed delirium and altered mental status, prompting neuroimaging, which revealed bilateral parieto-occipital vasogenic oedema consistent with PRES. With conservative management, including blood pressure control and pain management, the patient achieved complete neurological recovery. This case highlights the importance of considering PRES in paediatric patients with neurological symptoms following asparaginase-associated pancreatitis, emphasizing timely diagnosis and management to prevent long-term sequelae.

Keywords: Leukemia; Chemotherapy; Child, Acute Pancreatitis; PRES.

Introduction

Posterior Reversible Encephalopathy Syndrome (PRES) is a neuroradiological diagnosis characterized by headache, altered level of consciousness, visual disturbances, and seizures.[1,2] While hypertension, sepsis, immunosuppressive agents, and cytotoxic drugs are known risk factors for the development of PRES,[3,4] it has been rarely reported to be associated with asparaginase-associated pancreatitis. Asparaginase-associated pancreatitis is seen in 8% of children and young adults treated on current acute lymphoblastic leukemia (ALL) protocols.[5]

While PRES has been described as a complication of pancreatitis in the adult literature, few cases have been reported in the pediatric population Table 2. Clinicians should maintain a high index of suspicion for this rare condition in patients who develop neurological symptoms following acute pancreatitis.[6]

We report a pediatric patient with acute leukemia who developed PRES in the setting of asparaginase-associated pancreatitis during consolidation therapy.

Case Report

We report a 10-year-old boy diagnosed with T-cell ALL (non-ETP-ALL) with aberrant expression of CD117 and cytogenetics 46XY, t(3;14)(q27;q22), del (9p21). The patient was initiated on chemotherapy with UKALL 2011 Protocol Regimen B (weeks 1-5 with Vincristine, Daunorubicin, Peg Asparaginase, Dexamethasone, and Intrathecal Methotrexate). Post-induction, he continued on consolidation with Regimen C (Vincristine, Cyclophosphamide, Cytarabine, Peg Asparaginase (Day 2 of week 8), and Intrathecal Methotrexate).

During week 10, the patient received Cyclophosphamide (day 1), with Cytarabine (day 2 onward 4 doses). On day 3, he developed severe abdominal pain, tachycardia, and tachypnea. He remained afebrile and normotensive with 100% SpO2 in room air. Abdominal examination revealed tenderness in the epigastric area. Blood gas analysis revealed metabolic acidosis, and serum blood glucose showed hyperglycemia. The patient was stabilized with hydration and pain management, and Tazocin was initiated.

His serum amylase and serum lipase levels were 350 U/L and 952 U/L, respectively (normal <60). Abdomen computed tomography (CT) revealed acute necrotizing hemorrhagic pancreatitis (Figure A), with necrosis predominantly in the body and tail, with partial involvement of the neck and significant peripancreatic fluid collection, and ascites.

The patient was transferred to the intensive care unit for continuous monitoring for possible inotropic support and mechanical ventilation because of anticipated decompensation. Antibiotics were upgraded to Meropenem and Vancomycin. The patient received fresh frozen plasma and cryoprecipitate, given a deranged coagulation profile with elevated d-dimers along with platelet transfusion. Granulocyte colony-stimulating factor

(G-CSF) and total parenteral nutrition were also initiated along with regular blood glucose monitoring. Simultaneously, he received treatment from the pain management team for the persistent abdominal pain.

Over the following 48 hours, the patient developed bilateral pleural effusion and was started on oxygen via high-flow nasal cannula. In the same evening, he had bradypnea (RR: 8/min) with decreased respiratory efforts and underwent elective endotracheal intubation for 4 days. Four days later, the patient was successfully extubated.

Within the next 72 hours, the patient became drowsy but was responsive to verbal commands. Subsequently, he developed delirium mixed type (hypoactive and hyperactive) and agitation. The CT brain [Figure 1 B and C] revealed bilateral hypodensities in the parietal and occipital lobes likely suggestive of vasogenic edema. A review of his vital signs over the preceding week showed fluctuations in the blood pressure with systolic BP ranging from 88-154 mm Hg and diastolic BP ranging from 44-88 mmHg. Table 1. His antihypertensive therapy was tailored to include Hydralazine, Lisinopril, and Amlodipine to achieve a target BP with 95th centile. Fundus examination revealed no disc edema. Magnetic Resonant Image of brain [Figure 1 D, E & F] revealed abnormal increased subcortical and white matter T2/FLAIR signal intensity in bilateral parieto-occipital lobes with multiple discrete patchy areas of cortical hyperintensities with acute diffusion restriction; favoring a diagnosis of posterior reversible encephalopathy syndrome (PRES).

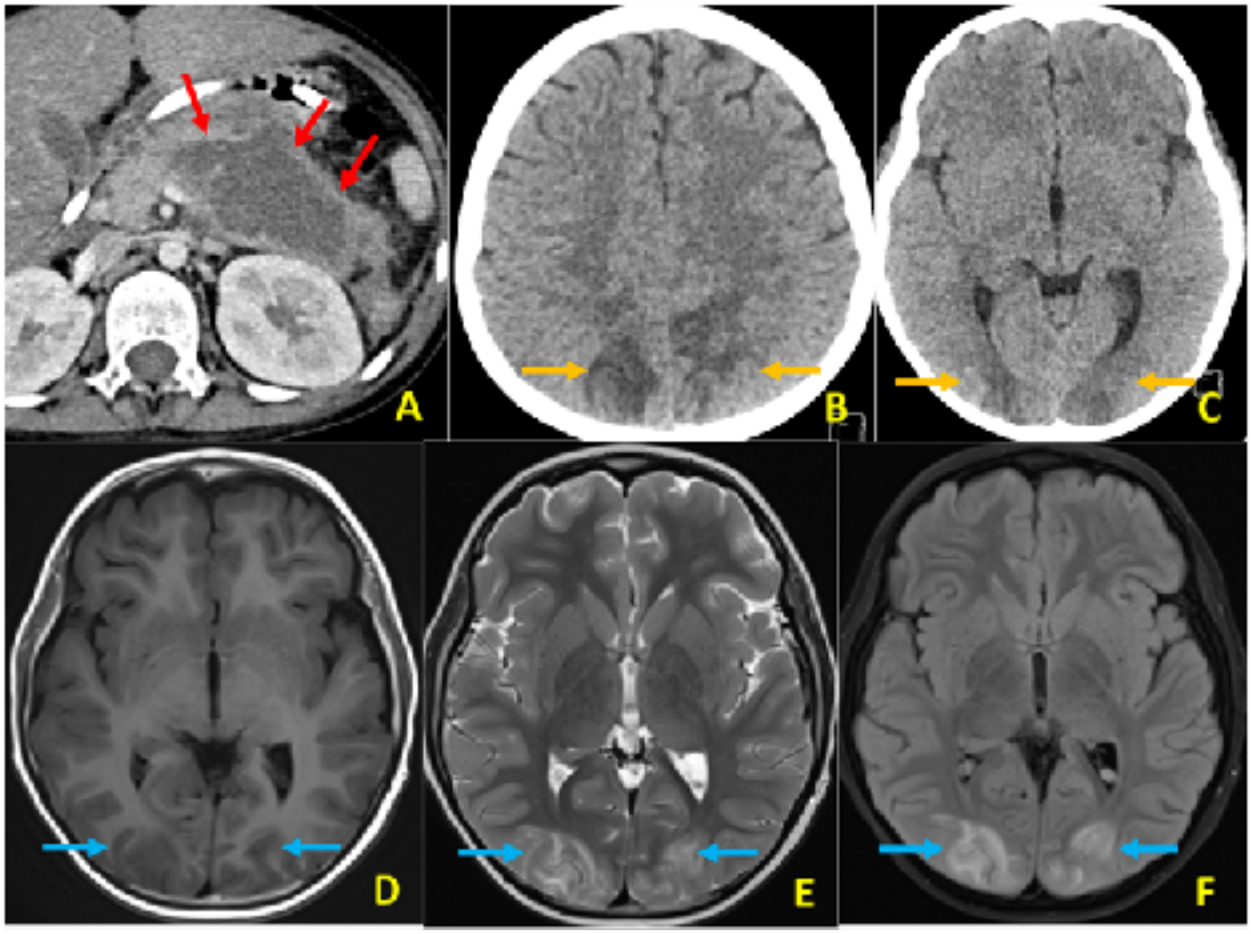

Figure 1: A) Axial contrast-enhanced CT at the pancreatic body level shows a large non-enhancing hypodense area in the pancreatic body and tail with peripancreatic fat stranding consistent with intrapancreatic necrosis (red arrows). B) C): Computerized tomography scan of brain showing Symmetrical bilateral posterior parietal and occipital hypodensity with preserved grey-white matter (yellow arrows). D), E), and F: T1W, T2W, and FLAIR selective MR images confirm the CT findings and reveal symmetrical vasogenic edema (blue arrows). Findings are consistent with posterior reversible encephalopathy syndrome (PRES).

Table 1: The patient's Blood Pressure Readings vs Pediatric Centile Ranges for his age and height.

	Systolic BP (mmHg)	**Diastolic BP (mmHg)**
Patient's BP Measurement	88 – 154	44 – 88
50th Percentile	102	55
90th Percentile	113	68
95th Percentile	116	72
99th Percentile	122	79

The patient was managed conservatively with blood pressure regulation and adequate pain management. He showed gradual improvement and complete recovery of his higher mental functions within the following week. He was subsequently continued on chemotherapy with complete omission of Peg Asparaginase. He is currently on maintenance chemotherapy week 56, and, remains in stable condition with no neurological sequelae.

Discussion

Posterior reversible encephalopathy syndrome (PRES) is an uncommon condition observed in the paediatric population.[1] This clinicoradiological condition manifests as visual disturbances, convulsions, headaches, and encephalopathy.[1,2] Hypertension, sepsis, immunosuppressive agents, and cytotoxic drugs have been linked to PRES.[1,2] The association of pancreatitis with PRES has been reported in the adult literature.[4,6-9]

Pereira et al. reported a patient with PRES and pancreatitis and documented eight such patients. Five of the eight patients were reported to have at least one comorbid condition in addition to pancreatitis that was associated with PRES. Furthermore, three out of eight patients, including their reported cases had alcoholism, which may have contributed to the pancreatitis and subsequent PRES.[6] All these patients were adults except a 13-year-old girl with nephrotic syndrome and pancreatitis with PRES. Amongst the other reported pediatric cases, Sigurta et al reported a 15-year-old patient with trauma-induced pancreatitis and PRES.[10]

Interestingly, Scheuermann et al. reported two pediatric patients with acute leukemia aged 9 and 13 years old who developed PRES in the setting of asparaginase-associated pancreatitis during induction therapy and suggested that pancreatitis, a side effect of asparaginase chemotherapy, may contribute to the development of PRES

through pro-inflammatory cytokine-mediated vascular endothelial damage.[5] Similar to our reported case, both patients developed pancreatitis, with the first experiencing it 20 days after asparaginase and the second patient after 29 days. Our patient developed pancreatitis 16 days after chemotherapy with asparaginase.

Mitsutaka et al reported an 18-year-old patient with leukemia with pancreatitis and PRES during consolidation chemotherapy.[11] Furthermore, Anastasopoulou, S. *et al* evaluated 52 acute lymphoblastic leukemia patients who fulfilled the clinical and radiological criteria of PRES and found that pancreatitis was reported in four patients two weeks before PRES, and noted that especially older children with T-cell ALL are prone to develop PRES.[12] In reviewing the literature, we found only 9 pediatric patients with PRES that were associated with acute pancreatitis (Table 2).

Table 2: Reported paediatric cases of PRES associated with pancreatitis

No	Author	Age	Gender	Aetiology of pancreatitis	Outcome
1	Scheuermann A. et al,[5]	13	Male	Asparaginase associated pancreatitis in Leukemia	Recovered with resolution of the neurological symptoms
2	Scheuermann A. et al,[5]	9	Female	Asparaginase associated pancreatitis in Leukemia	Recovered with resolution of the neurological symptoms
3	Sigurtà A. et al,[10]	15	Male	Blunt abdominal trauma associated pancreatitis	Recovered with resolution of the neurological symptoms
4	Nishimoto M. et al,[11]	18	Male	Methylprednisolone associated pancreatitis in Leukemia	Recovered with resolution of the neurological symptoms
5	Anastasopoulou, S. et al,[12]	Not documented	Not documented	Not documented	Not documented
6	Anastasopoulou, S. et al,[12]	Not documented	Not documented	Not documented	Not documented
7	Anastasopoulou, S. et al,[12]	Not documented	Not documented	Not documented	Not documented
8	Anastasopoulou, S. et al,[12]	Not documented	Not documented	Not documented	Not documented
9	Yamada A. et al,[14]	13	Female	Not documented	Recurrence of PRES in a child with Nephrotic syndrome

While asparaginase is an essential chemotherapeutic agent used in the treatment of paediatric ALL, it carries the risk for severe side effects, including pancreatitis, which is associated with a 2% overall mortality rate.[5] Risk factors for developing asparaginase-associated pancreatitis include older age, higher cumulative asparaginase dose, hypertriglyceridemia, and concomitant chemotherapeutic medications such as steroids, 6-mercaptopurine, and anthracyclines.[5] Similarly, our patient was on concomitant chemotherapy with these drugs during induction and consolidation therapy; adding to the risk of asparaginase-associated pancreatitis.

Pancreatitis causes hyperactivation of trypsinogen that results in the release of pro-inflammatory cytokines and chemokines, leading to endothelial dysfunction, including the cerebral vessels, which can lead to cytotoxic and vasogenic edema. Additionally, experimental models of pancreatitis showed that antithrombin III (ATIII) has a role in reversing TNF-mediated endothelial cell permeability and that reduction in ATIII, due to asparaginase side effects, may contribute to endothelial injury and increased vascular permeability in this proinflammatory status.[5,13]

Consistent with previously documented cases, our patient successfully recovered from pancreatitis, exhibiting a normal neurological examination at discharge and no lingering neurological symptoms.

Conclusion

To the best of our knowledge, the reported paediatric cases of asparaginase-associated pancreatitis with PRES are very limited. To conclude, pancreatitis emerges as a potential risk factor for PRES, prompting physicians to consider this factor when managing patients with acute pancreatitis; more so in leukemic patients with asparaginase-associated pancreatitis.

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