Posterior Reversible Encephalopathy Syndrome Secondary to Asparaginase Associated Pancreatitis in Two Pediatric Patients with Acute Leukemia

Amanda Scheuermann[1], Paul Harker-Murray[2], and Lauren Pommert[3]

[1]Medical College of Wisconsin
[2]Midwest Children's Cancer Center
[3]Cincinnati Children's Hospital Medical Center

January 28, 2021

Abstract

Asparaginase, a critical component of current pediatric acute leukemia treatment protocols, is associated with a number of serious side effects, one of which is pancreatitis. Pancreatitis can result in significant morbidity and mortality from necrosis, pseudocyst formation, hemorrhage, systemic inflammation, intestinal perforation and sepsis. Another rare complication of pancreatitis is posterior reversible encephalopathy syndrome (PRES), likely mediated by systemic inflammation secondary to pancreatic autodigestion and pro-inflammatory cytokine-mediated vascular endothelial damage. Here we review this association in the literature and report two pediatric patients with leukemia who developed PRES secondary to asparaginase-associated pancreatitis.

Introduction:

Improved survival of pediatric acute lymphoblastic leukemia (ALL) is partially attributed to therapy intensification with the addition of asparaginase to multi-agent chemotherapy backbones in the late 1960's (1-4). Asparaginase depletes serum asparagine through deamination into aspartic acid and ammonia resulting in leukemic cell death through inhibition of protein synthesis (5). There are four commercially available formulations of asparaginase: native *Escherichia coli*L-Asparaginase, polyethylene glycol (PEG)-Asparaginase, *Erwinia*asparaginase, and calaspargase pegol-mknl (6, 7). The major side effects of asparaginase preparations include allergic reactions, hypercoagulability, liver dysfunction and pancreatitis. Asparaginase-associated pancreatitis is seen in 8% of children and young adults treated on current ALL protocols (8). Most cases resolve with supportive treatment; however, severe complications including necrosis, pseudocyst formation, hemorrhage, systemic inflammatory response syndrome (SIRS), sepsis, and intestinal perforation are associated with significant morbidity and mortality (8-10). In the adult literature, posterior reversible encephalopathy syndrome (PRES) has also been described as a complication of pancreatitis. PRES is a rare condition of the central nervous system characterized by acute neurological changes including headache, altered mental status, seizures, vision changes, and is associated with specific magnetic resonance imaging (MRI) abnormalities typically in the posterior cerebral gray and white matter reflecting vasogenic edema (11). PRES resolves with supportive care and removal of the causative agent. While hypertension, sepsis, immunosuppressive agents, and cytotoxic drugs are known risk factors for the development of PRES (11, 12), it has not yet been associated with asparaginase-associated pancreatitis. Here we report two pediatric patients with acute leukemia who developed PRES in the setting of asparaginase-associated pancreatitis during induction therapy.

Case Presentations:

Patient 1: A 13-year-old Hispanic male with mixed phenotype acute lymphoblastic leukemia (MPAL) receiving induction therapy with prednisone, vincristine, pegaspargase, and daunorubicin was admitted on day 20 with grade 3 pancreatitis associated with 30% pancreatic gland necrosis on CT imaging and peak lipase of 7,290 U/L. One week after admission, he developed acute bilateral visual loss followed by a generalized tonic clonic seizure. Labs were notable for hyponatremia (131 meq/L), hypochloridemia (90 mmol/L), and hyperglycemia (322 mg/dL). Systolic blood pressures (SBPs) preceding the event ranged from 110-130s. Brain MRI demonstrated vasogenic edema in bilateral parietal-occipital lobes compatible with PRES (Figure 1). He returned to his neurologic baseline, did not have repeat seizures after initiation of maintenance levetiracetam and was discharged after a three week hospitalization. He was minimal residual disease (MRD) negative at the end of induction and continued treatment per AALL1131 (NCT02883049), currently in maintenance cycle 4. Asparaginase was omitted from subsequent therapy; however, he developed recurrent, grade 3 pancreatitis in maintenance cycle 1, day 38 attributed to the combination of underlying pancreatic damage, steroids and 6-mercaptopurine.

Patient 2: A 9-year-old African American female with NCI-standard risk B-ALL receiving induction therapy with dexamethasone, vincristine, and pegaspargase was admitted in shock on day 29 secondary to grade 4 pancreatitis associated with 75% pancreatic necrosis and large abdominal ascites on CT imaging and peak lipase of 3,984 U/L. One week after admission, she had a complex partial seizure. Her electrolytes were within normal ranges and SBPs preceding the event ranged from 110-130s. Brain MRI demonstrated abnormal signal involving the frontal, parietal, temporal and occipital regions with subcortical vasogenic edema consistent with PRES (Figure 1). She continued to have sub-clinical seizures despite multiple anti-epileptic drugs (AEDs) which ultimately resolved with a versed drip. Her course was complicated by endocrine and exocrine pancreatic insufficiency requiring insulin and pancreatic enzyme replacement, hypertriglyceridemia, and multiple pancreatic pseudocysts (largest measuring 13 x 12 x 16 cm) necessitating cyst-gastrostomy tube placement, and multiple GI hemorrhages with hemodynamic instability which ultimately required splenic artery embolization and temporary stent placement. She was discharged after a two month hospitalization and slowly returned to her cognitive baseline. She was MRD negative at the end of induction and has continued treatment per AALL0932 (NCT01190930), currently in cycle 1 of maintenance therapy. Asparaginase was omitted from subsequent therapy and she has not had recurrent pancreatitis.

Discussion:

While asparaginase is an essential chemotherapeutic agent used in the treatment of pediatric ALL, it carries the risk for severe side effects including pancreatitis which is associated with a 2% overall mortality rate (13). In general, acute pancreatitis results from activation of trypsin which leads to pancreatic autodigestion (14). Although the pathophysiology behind asparaginase-associated pancreatitis is not fully understood, it may be related to hypertriglyceridemia which is a known risk factor for the development of pancreatitis (15) and one of the common side effects of asparaginase (16, 17), especially in patients receiving concomitant steroids (9, 18). Hydrolysis of triglycerides by pancreatic lipase causes release of fatty acids that result in acinar cell injury, activation of trypsinogen, and ultimately, pancreatitis (9, 17). 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 (8, 9, 19). Additionally, genome wide association studies have identified multiple genetic polymorphisms associated with pancreatitis in children with ALL including *RGS6* , *ULK2, CPA2, PRSS1* (10, 19, 20)

PRES is an underappreciated complication of pancreatitis. In the adult literature, there are case reports of PRES in the setting of pancreatitis, though the etiology of pancreatitis differs and includes: alcoholism, gallstones, pregnancy, biliary manipulation, malignancy and acute intermittent porphyria (Table 1) (12, 21-32). Three cases are reported in the pediatric literature, none of which are related to asparaginase (Table 1) (33-35). A summary of all reported cases of PRES and pancreatitis are detailed in Table 1.

The pathophysiology of PRES is not fully understood but is related to disordered cerebral autoregulation and endothelial dysfunction, previously attributed to acute rise in blood pressure (34, 36). It is now recognized

that direct endothelial activation and dysfunction are the common pathway shared by all clinical conditions resulting in PRES (34, 37, 38). This endothelial damage can be caused directly by immunosuppressant and cytotoxic drugs, steroids, voriconazole, sepsis, autoimmune diseases or by abrupt rise in blood pressure which exceeds the threshold of cerebral blood flow autoregulation and results in altered perfusion, blood–brain barrier disruption, and vasogenic edema (34, 37, 39-41). Pancreatic irritation can also lead to vascular endothelial damage through overwhelming systemic production of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6) (42-44). These cytokines activate the vascular endothelium resulting in leakage of the capillary veins, migration and activation of leukocytes into tissues, and release of proteolytic enzymes and oxygen radicals that further damage vascular endothelial cells (45, 46). Additionally, there are *in vitro* data suggesting antithrombin III (ATIII) has a role in reversing TNF-mediated endothelial cell permeability (47) and that reduction in ATIII, a common side effect of asparaginase therapy, may further contribute to endothelial injury and increased permeability in the setting of systemic inflammation.

Conclusion:

Our experience and review of the literature reveals that pancreatitis, a side effect of asparaginase chemotherapy, may contribute to the development of PRES through pro-inflammatory cytokine-mediated vascular endothelial damage, though further research is needed to better understand the pathophysiology. It is helpful to be aware of the association between asparaginase-associated pancreatitis and PRES and may be prudent to correct electrolyte derangements, maintain age appropriate blood pressures, and be cognizant of concomitant medications in an effort to mitigate this risk.

References:

1. Pession A, Valsecchi MG, Masera G, Kamps WA, Magyarosy E, Rizzari C, et al. Long-term results of a randomized trial on extended use of high dose L-asparaginase for standard risk childhood acute lymphoblastic leukemia. J Clin Oncol. 2005;23(28):7161-7.

2. Silverman LB, Gelber RD, Dalton VK, Asselin BL, Barr RD, Clavell LA, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91-01. Blood. 2001;97(5):1211-8.

3. Amylon MD, Shuster J, Pullen J, Berard C, Link MP, Wharam M, et al. Intensive high-dose asparaginase consolidation improves survival for pediatric patients with T cell acute lymphoblastic leukemia and advanced stage lymphoblastic lymphoma: a Pediatric Oncology Group study. Leukemia. 1999;13(3):335-42.

4. Clavell LA, Gelber RD, Cohen HJ, Hitchcock-Bryan S, Cassady JR, Tarbell NJ, et al. Four-agent induction and intensive asparaginase therapy for treatment of childhood acute lymphoblastic leukemia. N Engl J Med. 1986;315(11):657-63.

5. Muller JH BJ. Use of L-asparaginase in childhood ALL. Crit Rev Oncol Hematol. 1998;28(2):97-113.

6. Avramis VI, Panosyan EH. Pharmacokinetic/pharmacodynamic relationships of asparaginase formulations: the past, the present and recommendations for the future. Clin Pharmacokinet. 2005;44(4):367-93.

7. Li RJ, Jin R, Liu C, Cao X, Manning ML, Di XM, et al. FDA Approval Summary: Calaspargase Pegol-mknl For Treatment of Acute Lymphoblastic Leukemia in Children and Young Adults. Clin Cancer Res. 2020;26(2):328-31.

8. Rank CU, Wolthers BO, Grell K, Albertsen BK, Frandsen TL, Overgaard UM, et al. Asparaginase-Associated Pancreatitis in Acute Lymphoblastic Leukemia: Results From the NOPHO ALL2008 Treatment of Patients 1-45 Years of Age. J Clin Oncol. 2020;38(2):145-54.

9. Raja RA, Schmiegelow K, Frandsen TL. Asparaginase-associated pancreatitis in children. Br J Haematol. 2012;159(1):18-27.

10. Wolthers BO, Frandsen TL, Abrahamsson J, Albertsen BK, Helt LR, Heyman M, et al. Asparaginase-associated pancreatitis: a study on phenotype and genotype in the NOPHO ALL2008 protocol. Leukemia. 2017;31(2):325-32.

11. Fischer M, Schmutzhard E. Posterior reversible encephalopathy syndrome. J Neurol. 2017;264(8):1608-16.

12. Luo J, Zhan YJ, Hu ZP. Posterior reversible encephalopathy syndrome in a woman with pancreatitis. Chin Med J (Engl). 2019;132(18):2265-7.

13. Wolthers BO, Frandsen TL, Baruchel A, Attarbaschi A, Barzilai S, Colombini A, et al. Asparaginase-associated pancreatitis in childhood acute lymphoblastic leukaemia: an observational Ponte di Legno Toxicity Working Group study. Lancet Oncol. 2017;18(9):1238-48.

14. Frossard JL, Steer ML, Pastor CM. Acute pancreatitis. Lancet. 2008;371(9607):143-52.

15. Yadav D, Pitchumoni CS. Issues in hyperlipidemic pancreatitis. J Clin Gastroenterol. 2003;36(1):54-62.

16. Cohen H, Bielorai B, Harats D, Toren A, Pinhas-Hamiel O. Conservative treatment of L-asparaginase-associated lipid abnormalities in children with acute lymphoblastic leukemia. Pediatr Blood Cancer. 2010;54(5):703-6.

17. Parsons SK, Skapek SX, Neufeld EJ, Kuhlman C, Young ML, Donnelly M, et al. Asparaginase-associated lipid abnormalities in children with acute lymphoblastic leukemia. Blood. 1997;89(6):1886-95.

18. Salvador C, Meister B, Crazzolara R, Kropshofer G. Management of hypertriglyceridemia in children with acute lymphoblastic leukemia under persistent therapy with glucocorticoids and L-asparaginase during induction chemotherapy. Pediatr Blood Cancer. 2012;59(4):771.

19. Liu C, Yang W, Devidas M, Cheng C, Pei D, Smith C, et al. Clinical and Genetic Risk Factors for Acute Pancreatitis in Patients With Acute Lymphoblastic Leukemia. J Clin Oncol. 2016;34(18):2133-40.

20. Wolthers BO, Frandsen TL, Patel CJ, Abaji R, Attarbaschi A, Barzilai S, et al. Trypsin-encoding PRSS1-PRSS2 variations influence the risk of asparaginase-associated pancreatitis in children with acute lymphoblastic leukemia: a Ponte di Legno toxicity working group report. Haematologica. 2019;104(3):556-63.

21. Larmour K, Lewis G, Benson G, Hanko J. The challenges of antiphospholipid syndrome: experience from diagnosis to self-care. BMJ Case Rep. 2014;2014.

22. Kur JK, Esdaile JM. Posterior reversible encephalopathy syndrome–an underrecognized manifestation of systemic lupus erythematosus. J Rheumatol. 2006;33(11):2178-83.

23. Ishikawa H, Natsume N, Matsui K, Tsuda H. Acute alcohol withdrawal accompanied by posterior reversible encephalopathy syndrome. Psychiatry Clin Neurosci. 2013;67(3):189.

24. Ali SM, Shaikh NA, Aftab Z, Latif E, Sameer M, Khan MB, et al. Peripartum Severe Acute Pancreatitis with Rare Complications: Case Report and Review of Literature. Case Rep Surg. 2020;2020:5785413.

25. Magno Pereira V, Marote Correia L, Rodrigues T, Serrao Faria G. Acute Pancreatitis and Posterior Reversible Encephalopathy Syndrome: A Case Report. Acta Med Port. 2016;29(9):567-71.

26. Murphy T, Al-Sharief K, Sethi V, Ranger GS. Posterior Reversible Encephalopathy Syndrome (PRES) After Acute Pancreatitis. West J Emerg Med. 2015;16(7):1173-4.

27. Hagemann G, Ugur T, Witte OW, Fitzek C. Recurrent posterior reversible encephalopathy syndrome (PRES). J Hum Hypertens. 2004;18(4):287-9.

28. Baek HS, Lee SJ. A case of posterior reversible encephalopathy syndrome associated with acute pancreatitis and chronic alcoholism. Gen Hosp Psychiatry. 2015;37(2):192 e3-5.

29. Shen FC, Hsieh CH, Huang CR, Lui CC, Tai WC, Chuang YC. Acute intermittent porphyria presenting as acute pancreatitis and posterior reversible encephalopathy syndrome. Acta Neurol Taiwan. 2008;17(3):177-83.

30. Pinotti E XR, Famuaro S, Sandini M, Montuori M, Fumagalli L, et al. Posterior reversible encephalopathy syndrome (PRES) associated with acute pancreatitis. Open Journal of Clinical and Medical Case Reports. 2018;4(8):1-6.

31. Bonavia LJ, Jackson J, Jurevics R. Posterior reversible encephalopathy syndrome in acute pancreatitis: a rare stroke mimic. BMJ Case Rep. 2020;13(9).

32. Compagnone C, Bellantonio D, Pavan F, Tagliaferri F, Barbagallo M, Fanelli G. Posterior reversible encephalopathy syndrome in acute pancreatitis. Minerva Anestesiol. 2016;82(11):1236-7.

33. Yamada A, Atsumi M, Tashiro A, Hiraiwa T, Ueda N. Recurrent posterior reversible encephalopathy syndrome in nephrotic syndrome: case report and review of the literature. Clin Nephrol. 2012;78(5):406-11.

34. Sigurta A, Terzi V, Regna-Gladin C, Fumagalli R. Posterior Reversible Encephalopathy Syndrome Complicating Traumatic Pancreatitis: A Pediatric Case Report. Medicine (Baltimore). 2016;95(22):e3758.

35. Nishimoto M, Koh H, Bingo M, Yoshida M, Nanno S, Hayashi Y, et al. Posterior reversible encephalopathy syndrome following acute pancreatitis during chemotherapy for acute monocytic leukemia. Rinsho Ketsueki. 2014;55(5):552-7.

36. Granata G, Greco A, Iannella G, Granata M, Manno A, Savastano E, et al. Posterior reversible encephalopathy syndrome–Insight into pathogenesis, clinical variants and treatment approaches. Autoimmun Rev. 2015;14(9):830-6.

37. Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. Lancet Neurol. 2015;14(9):914-25.

38. Marra A, Vargas M, Striano P, Del Guercio L, Buonanno P, Servillo G. Posterior reversible encephalopathy syndrome: the endothelial hypotheses. Med Hypotheses. 2014;82(5):619-22.

39. Parikh NS, Schweitzer AD, Young RJ, Giambrone AE, Lyo J, Karimi S, et al. Corticosteroid therapy and severity of vasogenic edema in posterior reversible encephalopathy syndrome. J Neurol Sci. 2017;380:11-5.

40. Singhal AB, Topcuoglu MA. Glucocorticoid-associated worsening in reversible cerebral vasoconstriction syndrome. Neurology. 2017;88(3):228-36.

41. Amanati A, Lotfi M, Manen RV, Faghihi MA, Yavarian M, Zekavat O, et al. Potential voriconazole associated posterior reversible leukoencephalopathy in children with malignancies: Report of two cases. J Oncol Pharm Pract. 2020:1078155220941590.

42. Bone RC. Toward a theory regarding the pathogenesis of the systemic inflammatory response syndrome: what we do and do not know about cytokine regulation. Crit Care Med. 1996;24(1):163-72.

43. Montravers P, Chollet-Martin S, Marmuse JP, Gougerot-Pocidalo MA, Desmonts JM. Lymphatic release of cytokines during acute lung injury complicating severe pancreatitis. Am J Respir Crit Care Med. 1995;152(5 Pt 1):1527-33.

44. Castell JV, Gomez-Lechon MJ, David M, Andus T, Geiger T, Trullenque R, et al. Interleukin-6 is the major regulator of acute phase protein synthesis in adult human hepatocytes. FEBS Lett. 1989;242(2):237-9.

45. Osman MO, Jensen SL. Acute pancreatitis: the pathophysiological role of cytokines and integrins. New trends for treatment? Dig Surg. 1999;16(5):347-62.

46. Farkas G, Marton J, Nagy Z, Mandi Y, Takacs T, Deli MA, et al. Experimental acute pancreatitis results in increased blood-brain barrier permeability in the rat: a potential role for tumor necrosis factor and interleukin 6. Neurosci Lett. 1998;242(3):147-50.

47. Friedl J, Puhlmann M, Bartlett DL, Libutti SK, Turner EN, Gnant MF, et al. Induction of permeability across endothelial cell monolayers by tumor necrosis factor (TNF) occurs via a tissue factor-dependent mechanism: relationship between the procoagulant and permeability effects of TNF. Blood. 2002;100(4):1334-9.

Legends:

Table 1: Reported cases of simultaneous pancreatitis and PRES in the pediatric and adult literature

Figure 1: MRI at seizure onset for Patient 1 (A) showing vasogenic edema in the bilateral parieto-occipital lobes and along the margins of the superior frontal gyri, and for Patient 2 (B) showing vasogenic edema in the frontal, parietal, temporal and occipital cortices. The abnormal signal enhancement and pattern of distribution in both of these images are consistent with a diagnosis of PRES.

Hosted file

`Pancreatitis_PRES table_Final.pdf` available at https://authorea.com/users/392228/articles/506208-posterior-reversible-encephalopathy-syndrome-secondary-to-asparaginase-associated-pancreatitis-in-two-pediatric-patients-with-acute-leukemia

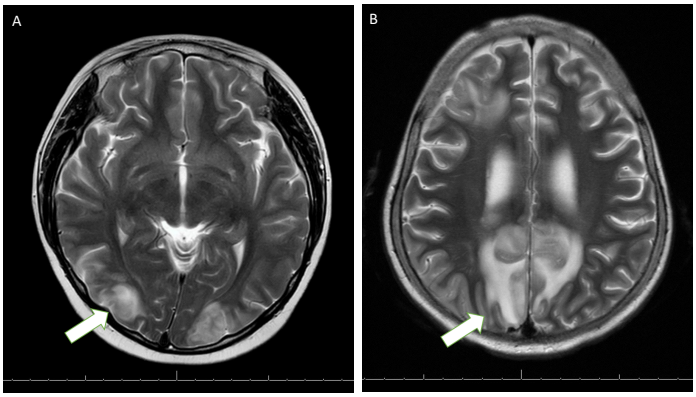

Figure 1: MRI at seizure onset for Patient 1 (A) showing vasogenic edema in the bilateral parieto-occipital lobes and along the margins of the superior frontal gyri, and for Patient 2 (B) showing vasogenic edema in the frontal, parietal, temporal and occipital cortices. The abnormal signal enhancement and pattern of distribution in both of these images are consistent with a diagnosis of PRES.