G102 Acute Pancreatitis in a 2½-Year-Old Child: A Fatal Therapeutic Complication of Polyethylene Glycol (PEG)-L-Asparaginase

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The goal of this presentation is to present to the forensic community a case report and review of an unusual cause of acute pancreatitis. The authors discuss therapeutic effects and complications of the administration of PEG-asparaginase as a chemotherapeutic agent.

This presentation will impact the forensic community and/or humanity by heightening awareness in the forensic community of an unusual cause of acute pancreatitis, stressing the importance of gathering health history in a patient diagnosed with acute pancreatitis, and informing the medical community of this possible complication of the use of PEGasparaginase and to raise the index of suspicion so that preventative measures may be applied.

This presentation consists of a case study of a female toddler who died suddenly from acute pancreatitis, a complication of chemotherapeutic intervention for Acute Lymphoblastic Leukemia (ALL). The authors review the pathogenesis, incidence, and diagnostic workup of PEG-Lasparaginase-induced acute pancreatitis.

A 2 ½-year-old white female was diagnosed with ALL after the onset of easy bruising, nosebleeds, and lower leg (shin) pain. Induction therapy consisted of an antineoplastic and palliative regimen of vincristine, dexamethasone, pegaspargase (PEG), cytarabine, and methotrexate. Remission was induced as the blast counts, which initially ranged from 10 to 14% on peripheral smear, became essentially absent. The therapy was complicated by hypertension and sinus bradycardia, which prompted treatment with enalapril, an angiotensin-converting enzyme inhibitor. The symptoms resolved by discharge. For approximately one week thereafter, the patient's blood count remained free of leukemic cells. Approximately two weeks post induction chemotherapy, the patient developed abdominal pain without fever. The patient's mother attributed two episodes of vomiting to dexamethasone prescribed to the patient. On the morning of death her mother administered an over-the-counter oral stomach remedy and reported that the toddler had difficulty breathing. The emergency medical service was notified and transported the patient to the hospital where, despite aggressive resuscitation attempts she was pronounced dead in the emergency department.

Due to the sudden and clinically unexpected nature of the patient's death while in apparent remission, an autopsy was requested by the local coroner. At autopsy the body was that of a normal but pale female child with no congenital anomalies. Internal examination exhibited hemorrhagic ascites with petechiae of the small bowel mesentery and omentum. The pancreatic tail was enlarged and violaceous. Microscopical examination revealed multifocal necrosis, hemorrhage, and acute inflammatory cellular infiltrates in the pancreatic parenchyma. Inflammation extended to the peripancreatic fat, small intestine and appendiceal wall. Other findings included hepatic steatosis and a focal intraluminal thrombus in a pulmonary artery of the right lower lobe. Histopathological examination of the postmortem bone marrow confirmed the presence of all three hematopoietic cell lines, but severe autolytic change precluded unequivocal recognition of blasts. No gallstones, structural anomalies of the gastrointestinal tract, or other risk factors for pancreatitis were noted. The cause of death was ascribed to acute hemorrhagic pancreatitis with the contributing factor of ALL, status post chemotherapeutic intervention (PEG-aspargase).

Asparaginase is an enzyme manufactured by certain bacteria, plants and animals. *Escherichia coli* bacteria supply asparaginase used for medical purposes. Asparaginase catalyzes the hydrolysis of the amino acid, asparagine, to aspartic acid. Neoplastic cells, especially those of ALL, have low levels of asparagine synthetase. For this reason they fail to produce sufficient asparagine to survive and require an exogenous source of the amino acid. Asparaginase, a chemotherapeutic agent for ALL, eliminates exogenous asparagine by hydrolyzing serum asparagine into nonfunctional aspartic acid and ammonia. Asparagine is needed by ALL cells to build proteins for cellular structure and enzymes. Documented complications of asparaginase include allergic reactions, chemical hepatotoxicity, thrombogenic coagulopathies, hyperglycemia, and acute pancreatitis. Clinical acute pancreatitis is noted in about 1% of patients receiving asparaginase, and rarely results in death.

Asparaginase is used in several forms in conjunction with other chemotherapeutic agents to combat ALL. The L-asparaginase form produced by *E. coli* has been reported to have a lower rate of acute pancreatitis than that of asparaginase alone. In an effort to reduce the incidence of immunogenicity, polyethylene glycol (PEG) is added to L-asparaginase.

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PEG-asparaginase therapy is a known cause of acute pancreatitis in the absence of other risk factors. The implications for the patient can be serious: in rare instances significant morbidity and, as this case study demonstrates, even mortality may occur. Acute pancreatitis must be considered in the differential diagnosis of gastrointestinal symptoms in the leukemic patient treated with PEG-asparaginase.

Fatal Acute Pancreatitis, PEG-asparaginase, Acute Lymphoblastic Leukemia

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