G33 EBV (+) T-Cell Lymphoproliferative Disorder of Childhood Causing Sudden Death: A Case Report

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After attending this presentation, attendees will become familiar with this unusual disorder that can have a rapid course with high mortality such that medical examiner/coroners (ME/Cs) are involved in the investigation. Attendees will learn the value of special testing in autopsy cases, such as immunohistochemistry, EBER-ISH, and T-cell receptor gene rearrangement studies.

This presentation will impact the forensic science community by stressing the need for access by medical examiner/coroner's offices of good immunohistochemistry testing, in-situ hybridization testing, and gene rearrangement studies. Lack of access to these modern techniques can lead to many death investigations remaining unsolved, or misdiagnosed.

Systemic Epstein-Barr virus (EBV) positive T-cell Lymphoproliferative disorder (LPD) of childhood is a life-threatening illness of children that may be associated with chronic active EBV infection or following a primary acute EBV infection. This entity is most prevalent in Asia and rarely reported in the West. Common sites of involvement include the liver, spleen, lymph nodes, bone marrow, skin and lungs. It has a fulminant clinical course with development of hepatosplenomegaly, liver failure, lymphadenopathy, rapidly progressing to multiorgan failure. Other complications such as hemophagocytic syndrome and sepsis can occur. The prognosis in most cases is dismal with death resulting in days to weeks.

We present a case of a 3½-year-old, previously healthy, Hmong girl who presented with to a hospital ER with nausea and vomiting. Initial CBC revealed leukocytosis with an absolute neutrophilia and lymhocytosis. Over the next twenty-four hours, the decedent developed rapidly progressive hepatic failure, became lethargic and unresponsive. Her hematological parameters were as follows: Fibrinogen=152, PTT=41.8, PT=32.1, INR=3, D-dimers: 1869 (n<250ng/ml). Her liver function tests were markedly elevated AST: 4770, ALT: 5030, Ammonia:
421. Mushroom poisoning was strongly considered. Immunoassays for RSV, Influenza A & B, Adenovirus and Hepatitis A & B were negative. EBV serology showed antibodies to EBV (EBV VCA IgG: 1185 (Normal<100) and EBVNA IgG: 1392 (Normal <100). On day two of admission, a CT scan of the head showed cerebral edema with tonsilar herniation. Due to the extremely poor prognosis of the critically ill patient, care was ultimately withdrawn.

Significant findings at autopsy were cerebral edema with tonsilar herniation, hepatic necrosis, splenomegaly (96.9 grams) and massive mesenteric lymphadenopathy. Multiple matted mesenteric lymph nodes were noted; the largest measuring 3 cm in greatest dimension. Sections revealed homogenous tan-pink cut surfaces.

Microscopic examination of the liver showed moderate portal acute and chronic inflammation with hepatocellular necrosis. Sections of spleen showed atypical lymphoid cell infiltrates. Histological examination of an enlarged mesenteric lymph node revealed complete effacement of nodal architecture by medium to large, atypical lymphocytes with irregular nuclear contours and occasional nucleoli, and abundant mitoses. Immunohistochemical stains performed on the lymph node showed a predominant T-cell population (CD3+/CD5+ cells) with high proliferation index (MIB-1: 70-80%) and a small population of scattered B-cells (CD20+). EBV encoded RNA (EBER) was positive by in-situ hybridization (ISH) in the mesenteric lymph node and spleen. A T-cell receptor gene rearrangement study was performed confirming a clonal population of T-cells.

Neuropathologic examination performed after brain fixation revealed hypoxic encephalopathy with marked swelling and cerebellar tonsillar herniation. Alzheimer type II astrocytes were noted in globus pallidus, neostriatum, thalamus, medulla and cerebellar dentate nucleus consistent with hepatic encephalopathy.

In the work-up of sudden unexpected deaths in children and young adults with similar presentations, especially in Asians, EBV positive T- cell lymphoproliferative disorder should be considered. Since the clinical course is usually rapid and the mortality rate is high, medical examiner/coroners are often involved in investigating the cause of death. Antemortem EBV serology and relevant histological evaluation of liver, spleen, lymph nodes, and bone marrow aid in the initial diagnostic work- up. Immunohistochemistry, EBER-ISH & T-cell receptor gene rearrangement studies that can all be performed on paraffin embedded blocks are additional valuable tools in clinching the diagnosis.

Epstein-Barr Virus, T-cell Lymphoproliferative Disorder, EBER-ISH

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