

Short reports

Congenital acute T lymphoblastic leukaemia: report of a case with immunohistochemical and molecular characterisation

Jianguo Tao, Elsa Valderrama, Leonard Kahn

Abstract

A newborn infant with congenital T cell lymphoblastic leukaemia presented with hepatosplenomegaly and pancytopenia at birth and died on the 21st day of multi-organ failure. Biopsy and necropsy examination showed extensive atypical lymphoid infiltrates in the lungs, liver, spleen, kidneys, lymph nodes, and bone marrow. Immunohistochemically, the lymphoid cells were TdT+, CD3+, CD45RO+, and CD10-, CD79a-, CD20-. Genotypic analysis using polymerase chain reaction showed T cell receptor γ chain gene rearrangement and absence of immunoglobulin heavy chain gene rearrangement. This appears to be the first documented case of congenital T cell lymphoblastic leukaemia. The case had unusual histological and immunogenotypic features, disseminated early, and pursued a highly aggressive course. Consideration of the diagnosis is of paramount importance. The immunophenotypic studies and molecular characterisation of such congenital leukaemias are critical in arriving at a definite diagnosis.

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Congenital leukaemia refers to leukaemia occurred at birth or immediately after and is usually acute myeloid leukaemia, either acute monocytic (M5) or myelomonocytic leukaemia (M4).^{1,2} Congenital acute lymphoblastic leukaemia (ALL) is rare, most often of B cell lineage, and with a worse prognosis than childhood ALL.³ A literature search failed to reveal any reports of congenital T cell lymphoblastic leukaemia (T-ALL), although this is a well documented entity in the older children.⁴ This communication documents a case of acute congenital T lymphoblastic leukaemia in a 21 day old female infant who presented with hepatosplenomegaly and pancytopenia at birth and died on day 21 from multiorgan failure. A necropsy examination was performed and the histopathological, immunohistochemical, and immunogenotypic features are presented here.

Case report

A 3900 g girl was born at 38 weeks gestation to a 28 year old mother (gravida 2, para 1). Caesarean section had been performed at another hospital because of severe polyhydramnios and hepatosplenomegaly, diagnosed by routine ultrasound examination. Multiple petechiae were noted on the infant's back at birth. Laboratory evaluation showed thrombocytopenia, anemia, and pancytopenia, refractory to transfusion. The infant also developed severe jaundice. She was intubated and transferred to Schneider Children's Hospital (SCH) of Long Island Jewish Medical Center on her 12th day.

Admission laboratory data revealed white cell count of 6.9×10^9 /litre, with 10% neutrophils, 74% lymphocytes, 5% monocytes, and 10% atypical lymphocytes. The packed cell volume was 29% and the platelet count 7×10^9 /litre. A peripheral blood smear revealed a few atypical lymphocytes but no leukaemic process. Pertinent negative results included Epstein-Barr virus and parvovirus B19 serology. Viral and bacterial cultures were negative. Chromosome analysis, chest x ray, and cranial ultrasound were normal. No mediastinal mass was discerned. A genetic or metabolic storage disease, viral disease, and bacterial sepsis were considered in the differential diagnosis.

The patient remained stable after admission to SCH until her 18th day of life, when she developed marked abdominal distension, respiratory distress with metabolic acidosis, hypotension, and bradycardia. She died from multiple organ failure on the 21st day of life. A liver biopsy was performed immediately after death, and a necropsy was performed.

Methods

HISTOLOGICAL EXAMINATION AND IMMUNOHISTOCHEMICAL ANALYSIS

Representative tissue was submitted in formalin for routine processing. After embedding in paraffin, haematoxylin and eosin stained sections were prepared.

Immunostains were performed on formalin fixed, paraffin embedded tissue sections using a peroxidase labelled detection system with antibodies to CD3, CD20, CD10, CD79a, CD45RO (Dako), and TdT (Supertechs)

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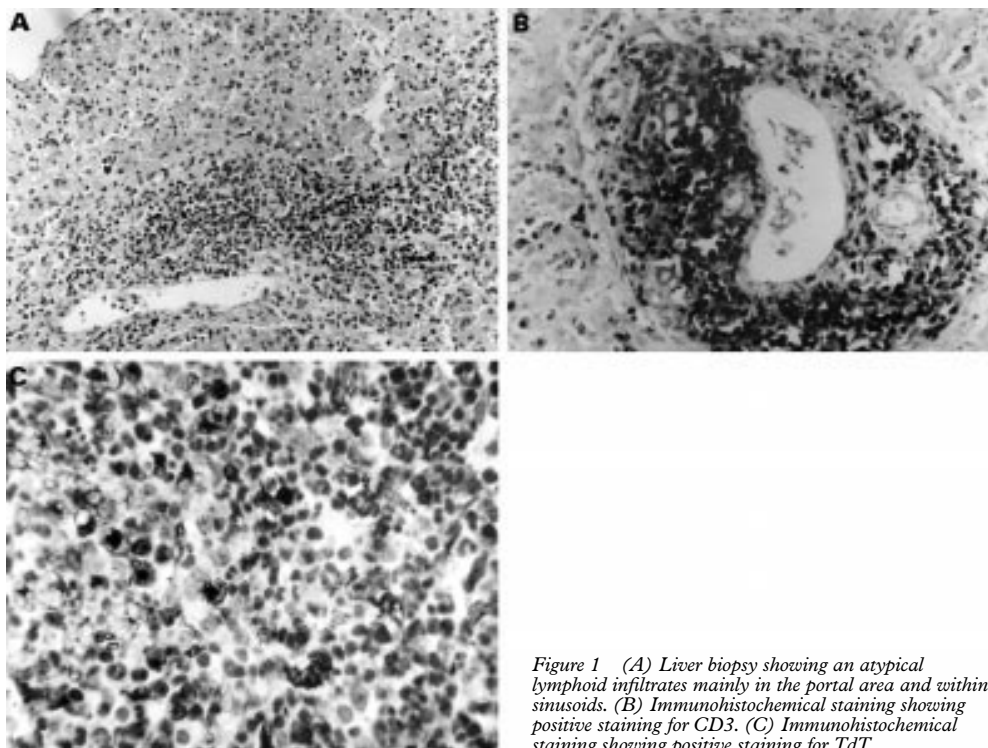


Figure 1 (A) Liver biopsy showing an atypical lymphoid infiltrates mainly in the portal area and within sinusoids. (B) Immunohistochemical staining showing positive staining for CD3. (C) Immunohistochemical staining showing positive staining for TdT.

following deparaffination and rehydration, according to the DAB protocol (Ventana Medical System). Appropriate control tissue confirmed the sensitivity and specificity of the stains.

DNA EXTRACTION AND PCR AMPLIFICATION

Genomic DNA was extracted from cryopreserved tissue using a salting out procedure.⁵ Briefly, DNA was isolated with a saturated sodium chloride solution after sodium dodecyl sulphate/proteinase K lysis of the tissue. Polymerase chain reaction (PCR) amplification and primers/probes for immunoglobulin heavy chain and T cell receptor gamma chain were performed as described previously.⁵ Briefly, the presence of IgG heavy chain gene rearrangements was detected with PCR using a primer of the heavy chain joining gene region on an automated heat block (DNA Thermal-Cycler, Perkin-Elmer Cetus). T cell receptor γ chain gene was probed by PCR using a primer specific for the TCR γ gene. Reaction products were fractionated in agarose and visualised under ultraviolet light by ethidium bromide fluorescence. Specificity of the products was confirmed by hybridisation with an internal ³²P labelled oligonucleotide.

Results

Microscopic examination of the liver biopsy showed marked congestion and extensive necrosis of hepatocytes. An atypical lymphocyte infiltrate was seen, mainly in the periportal area and within sinusoids. The infiltrate consisted of small to medium sized lymphoid cells with hyperchromatic irregular nuclei, scant amphophilic cytoplasm, and indistinct nucleoli (fig 1A).

Immunophenotyping of liver tissue showed that the lymphoid infiltrates were T cell positive (CD3+ and CD45RO+) and B cell

negative (CD20- and CD10-) confirming the T cell origin of the lymphoid infiltrates (fig 1B).

The expression of TdT and CD79a, markers of immature B and T cells, was investigated to distinguish between T cell lymphoblastic leukaemia/lymphoma and B cell lymphoma. The immunostaining showed TdT+ (fig 1C) and CD79a-, indicating a diagnosis of T cell lymphoblastic leukaemia/lymphoma.

The necropsy examination revealed generalised organomegaly with similar atypical lymphoid infiltrates in the liver, spleen, kidneys, lungs, lymph nodes, and bone marrow. Sections from bone marrow showed that 50% of the cells were atypical lymphoid cells indicating a leukaemic process.^{6,7} Immunohistochemically, the neoplastic infiltrates in the liver, kidneys, spleen, lungs, and bone marrow showed an identical staining pattern to those in the liver biopsy, indicating the spread of neoplastic cells to all these organs. Immunostains for herpes virus and cytomegalovirus were negative. No mediastinal mass was seen, and the sections from the thymus were unremarkable.

The clonality and cell lineage of the lymphoid infiltrate in the liver were investigated by PCR. PCR for the immunoglobulin heavy chain gene rearrangements showed no distinct bands identified. PCR for the T cell receptor γ chain gene showed two distinct bands, indicating the presence of a clonal T cell population and proof of T cell origin of this leukaemia.

Discussion

Acute leukaemia in the newborn is rare. The diagnostic criteria for congenital leukaemia include proliferation of immature leucocytes, infiltration of these cells into extrahaematopoietic tissue, absence of diseases that can cause

leukaemoid or leucoerythroblastic reactions such as congenital infection, and absence of chromosomal disorders that may be associated with unstable haematopoiesis, such as trisomy 21.⁸ The present case fulfilled all these criteria.

Most congenital leukaemias are of monocytic origin,⁹ but the existence of a small number of cases with lymphoid⁹ or mixed phenotypes has been reported.^{3,9} In the present case, the morphology of the lymphoid infiltrates was compatible with a diagnosis of lymphoblastic leukaemia. The expression of TdT and T cell markers, demonstrated by immunohistochemical staining, proved a lymphoblastic, T cell origin of the lesion, confirmed to be a neoplastic process by PCR that showed a T cell receptor gene rearrangement. Thus this case represents a rare congenital lymphoblastic leukaemia of T cell phenotype. A thorough search of the literature suggests that this is the first reported case of congenital T cell lymphoblastic leukaemia.

The case had clinical features common to other form of congenital leukaemias, namely hepatosplenomegaly, petechiae, and respiratory distress because of pulmonary involvement.¹⁰ The lesion pursued an aggressive clinical course and caused the infant's death before a definite diagnosis could be made and treatment begun. The clinical and biological characteristics of the present congenital

leukaemia differed from those normally encountered in older children. The unusual manifestation of pancytopenia, lack of thymic involvement, and absence of a leukaemic process increased the difficulty in arriving at a diagnosis. Suspicion or consideration of congenital T cell lymphoblastic leukaemia is of paramount importance. An early biopsy and its immunophenotypic and molecular analysis are essential in establishing a diagnosis of congenital leukaemia.

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