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Transient pancytopenia after non-A non-B non-C acute hepatitis preceding acute lymphoblastic leukemia

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ABSTRACT

Transient pancytopenia preceding childhood acute lymphoblastic leukemia (ALL) is an unfrequent but well-known event. The association of this preleukemic syndrome with hepatitis is extremely rare, with only two such cases having been published in the literature. We report the case of a 16-year-old boy who was diagnosed with B-cell type ALL that was preceded by transient pancytopenia with absent hemopoietic cells in the bone marrow following a seronegative hepatitis episode. The clinical, morphologic and immunophenotypic features of this patient are described and the literature on this preleukemic syndrome reviewed, with special emphasis being made on its differential diagnosis with hepatitis-associated aplastic anemia.

Key words: acute lymphoblastic leukemia, hepatitis, pancytopenia

Transient pancytopenia associated with bone marrow aplasia preceding acute lymphoblastic leukemia (ALL) is a rare event[1] usually affecting children and adolescents and showing a female predominance.[2-4] In such cases the aplastic episode lasts for only some days or a few weeks and is generally followed by complete recovery of the blood cell counts, with this rapid and spontaneous recovery being the distinctive feature from typical aplastic anemia. The ALL, usually of B-cell common type, occurs in most of such cases within 6 months from the onset of the marrow aplasia,[3,4] although longer time lapses have been reported.[2] On the other hand, the prior aplastic condition does not influence the outcome of these patients, whose evolution is similar to that of the remaining patients with B-ALL.[3] To the best of our knowledge, only two cases of ALL with previous aplasia in which the latter condition was preceded by non-A, non-B, non-C hepatitis have been reported.[6,7]

We describe the clinical, immunophenotypic, and pathological features of a patient with B-cell type ALL that was preceded by transient marrow aplasia following seronegative acute hepatitis, and review the literature on such an association.

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Case report

A 16-year-old boy was admitted in our institution in August 1995 after a two-week history of high fever, asthenia, jaundice and choluria. Physical examination revealed fever, jaundice and liver enlargement, whereas no lymphadenopathy or splenomegaly were observed. He had no previous history of exposure to myelotoxic agents. The peripheral blood hematological parameters were normal. Liver function tests revealed important hepatocellular damage (AST/ALT 850/1090 UI/L, normal value: 20-40 UI/L), whereas the coagulation tests were also abnormal (see Table 1 for detailed laboratory findings). Viral serologic studies, including hepatitis virus A, B and C, HIV, EBV, parvovirus B19 and CMV, were negative. Anti-nuclear, anti-LKM and anti-mitochondrial antibodies were also negative. The clinical diagnosis of seronegative acute hepatitis was established, and the patient was discharged. One month later he had to be readmitted because of pancytopenia (Table 1) and persistence of the liver function abnormalities. A bone marrow aspirate was markedly hypocellular, and a bone marrow biopsy showed disappearance of the hematopoietic cellularity and presence of diffuse reticulin fibrosis. A liver biopsy revealed changes consistent with acute hepatitis. The diagnosis of bone marrow aplasia secondary to seronegative hepatitis was made and supportive treatment and parenteral vitamin K subsequently instituted, which was followed by a progressive improvement of the patient's clinical condition and normalization of the analytical tests in a few weeks. In October 1995 a new bone marrow biopsy was normal.

In December 1995, the patient presented with a mass in the preauricular area of the right side of the face. Peripheral blood and liver function tests were normal. A biopsy of the tumor was performed, disclosing a lymph node diffusely infiltrated by a lymphoid proliferation consisting of intermediate size cells with scarce cytoplasm, round nuclei with small nucleoli, and fine disperse chromatin. The lymphoid cells spread out into the adjacent adipose tissue, and there were a high number of mitotic figures and tin-

Table 1. Main laboratory findings of the patient from presentation of hepatitis to the diagnosis of ALL.

Feature	Date 8/95	9/95	10/95	12/95
Liver function tests:				
*AST (UI/L)**	850	1128	37	40
ALT (UI/L)°	1090	2902	85	42
Bilirubin (mg/dL)	15	23	0.7	0.7
Prothrombin time (%)	75	24	100	100
Blood counts				
Hb (g/L)	120	80	150	135
WBC ($x10^9$/L)	4.5	0.3	5.6	11
Neutrophils ($x10^9$/L)	3.6		3.6	9.9
Lymphocytes ($x10^9$/L)	1.2		1.3	0.6
Platelets ($x10^9$/L)	150	13	161	144
Bone marrow				
Overall cellularity		decreased	normal	increased
Fibrosis		+	–	
Hemopoietic cells		decreased	normal	absent
Blast cells		absent	absent	60%

**normal range: 10 to 40; °normal range: 10 to 40.*

gible body macrophages. Occasional reactive follicles could be seen at the periphery of the lymph node. Immunologic studies demonstrated the tumor cells being positive for the CD45, CD45RA, TdT, CD19, CD10, and HLA-DR antigens, and negative for CD22, CD7, CD2, CD3, CD5, CD4, and CD8, whereas myeloid markers were also negative. Flow cytometry examination showed negativity for surface immunoglobulins. A bone marrow aspirate demonstrated 60% blast cells, whose immunophenotype study was consistent with the diagnosis of B-cell common ALL.

The patient was treated with an ALL-chemotherapy regimen, and complete remission was achieved in March 1996. In August 1996, an allogeneic bone marrow transplantation was performed, and the patient remains in complete remission at 20 months from transplantation.

Discussion

Aplastic anemia following viral hepatitis is a condition well recognized in the medical literature.[5] Thus, hepatitis-associated aplastic anemia is an uncommon but not exceedingly rare syndrome of bone marrow failure (2 to 5% of all cases of aplastic anemia in Western countries[5]) that usually affects boys and young men. Although the hepatitis is similar to typical viral hepatitis, most patients are negative for hepatitis A, B and C viruses. The severe pancytopenia generally appears after two to three months of the acute hepatitis. Since the prognosis of the aplastic anemia in these patients is poor, most authors recommend bone marrow transplantation, although some recent studies have shown response to immunosuppressive therapy, with this suggesting that immunologic mechanisms could mediate the post-seronegative hepatitis bone marrow aplasia. On the other hand, aplasia or hypoplasia preceding ALL is also a well-known situation, whose clinical and hematological features are indistinguishable from those of conventional aplastic anemia. In such patients the clinical symptoms derive from the anemia, thrombocytopenia and leukopenia, with infection being the most frequent complication. Occasionally, patients may present with lymphadenopathy, splenomegaly and hepatomegaly. This unfrequent preleukemic disorder has a spontaneous recovery and must be considered in the differential diagnosis of pancytopenia. In such cases ALL usually develops within 6 months of the onset of the pancytopenia, although it has been observed after longer time lapses.[2] The prognosis and evolution of ALL patients with preceding transient pancytopenia seem to be similar to that of other B-ALL patients.

Table 2. Characteristics of patients with ALL following hepatitis-associated pancytopenia.

Patient no. (ref.)	Age/sex	Time lapse pancytopenia-ALL	ALL type	Outcome
1 (6)	12/F	3 months	Common	Early death
2 (7)	3/M	1 month	Common	Early death
3*	16/M	3 months	Common	Remission at 20 months from BMT°

**Present case; °bone marrow transplantation.*

Only two cases of ALL preceded by post-seronegative hepatitis bone marrow aplasia have been reported (Table 2). The first patient was a 3-year old child who developed common ALL one month after post non-A non-B hepatitis transient bone marrow aplasia, and died from massive hemorrhage during induction chemotherapy.[6] The second one was a 12-year old girl who had ALL preceded for 3 months by hypoplastic anemia that followed non-A non-B hepatitis, and also died during the induction therapy.[7] Interestingly, as it occurred in the case herein reported, hepatitis A, B or C could not be demonstrated. In our patient the clinical features were similar to those of the above two patients, except for the fact that he attained a complete remission that persisted for more than 16 months after bone marrow transplantation. It is noteworthy that both in the second of the above two cases and in our patient during the pancytopenia phase the marrow biopsy showed an increase in the reticulin fibers, in addition to the absent hemopoietic cellularity. Since the presence of fibrosis argues against the diagnosis of aplastic anemia, its finding should alert the clinician about

the possibility of a pre-ALL aplasia.

With regard to the pathogenesis of pre-ALL aplasia, infection seems to play an important role.[8] Beside this, different studies have shown *in vitro* suppression of the hemopoietic progenitor cells from patients and normal donors by the CD8 lymphocytes of patients with aplastic anemia.[9] Finally, other investigators consider the hypoplastic anemia and the ALL in these patients as being the same process, since in some of these cases the same abnormal clone could be detected in the bone marrow during the hypoplastic episode and the subsequent ALL.[10] Unfortunately, in our patient marrow DNA was not obtained during the marrow aplasia episode to allow molecular studies. In this sense, since the cytogenetic or molecular events involved in the pathogenesis of the abnormal clone remain unknown, molecular studies should be performed during the aplastic phase in these cases in order to help clarifying the relationship between the aplastic episode and the subsequent ALL.

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