macrophages, these last often engaged in hemophagocytosis.\(^1,2\) The central nervous system (CNS) is variably involved, with symptoms that range from irritability, bulging fontanel, and neck stiffness to seizures, cranial nerve palsies, ataxia, psychomotor retardation, and coma. Markedly different presenting pictures are not described in the available series.\(^1,5\)

Adult onset of familial HLH, never reported before, is the most prominent feature in this family. Their presenting features were different, with a prominent CNS involvement\(^6\) in one case and a diagnosis of non-Hodgkin lymphoma (NHL) in the other. Remarkably, in both cases the final diagnosis was delayed by about 3 years from the onset of symptoms; both achieved an adequate disease control when treated and did not show disease reactivation for more than one year after the diagnosis. Given the limited potential for antiviral defense in patients with \(PRF1\) mutations,\(^10\) the prolonged absence of clinical manifestations due to macrophage activation following common viral infections in these subjects is unexpected. In case 2 the diagnosis of NHL led to polychemotherapy followed by autologous BMT. Her prolonged remission is also unexpected, as an autologous BMT consolidation has no potential to restore the genetically determined immune deficiency of the patient. We have previously observed in one HLH patient, after acute graft rejection, an 18-month disease-free interval before overt disease reactivation (M.A. and F.L., unpublished observation, 1998). The mechanism by which massive immune suppression associated with the pre-BMT conditioning regimen may result in a prolonged disease control remains to be elucidated.

Even in the presence of quite different clinical presentations, both patients carried the same mutations. The Trp374Stop mutation has been previously reported in 9 patients always as a homozygous mutation. All these patients showed a homogeneous phenotype with a severe clinical course and an early age of onset, within the first months of life in 8 of 9 cases, with the ninth presenting at 39 months. This mutation was always found in subjects of Turkish origin; historical data are available that may support the hypothesis of migration of the mutation from Turkey to southern Italy in ancient times. Further research will clarify whether this mutation originated in the same haplotype both in the Italian and Turkish population.

We confirm that Trp374Stop appears to be the most frequently reported mutation in HLH and suggest that Ala91Val (which we found also in 4 other Italian patients; Clementi et al, in preparation) may be an “Italian mutation.” Thus the knowledge of the ethnic background of HLH patients may usefully address mutation analysis. In our patients the genotype Trp374Stop/Ala91Val results in an atypical presentation and milder clinical course, which is possibly attributed to the latter mutation. Identification of patients with milder clinical course and Ala91Val/Ala91Val genotype will confirm this hypothesis; whether they indeed share the usual HLH phenotype remains to be demonstrated.

The presence of patients with atypical presentation makes differential diagnosis in hemophagocytic syndromes more difficult. We suggest that HLH is included in the differential diagnosis of such patients not only in infants and children but also in adults. In the attempt to facilitate the diagnostic approach, we have recently proposed a flow chart, which includes testing for perforin expression, to improve the procedure.\(^11\)

**References**


To the editor:

**Transcription of AML1/ETO in bone marrow and cord blood of individuals without acute myelogenous leukemia**

The translocation t(8;21), AML1/ETO, represents a frequent aberration in de novo acute myelogenous leukemia (AML) and is detectable in up to 40% of AML FAB M2.\(^1\) In constitutively transgenic mice, AML1/ETO abrogates fetal hematopoiesis, but in inducible transgenic mice AML1/ETO is not leukemogenic per se.\(^2,3\) AML1/ETO is detectable in stem cells of patients in complete continuous remission (CCR) and only an increasing transcript number indicates a forthcoming clinical relapse.\(^5,6\) We investigated...
whether AML1/ETO transcripts are also present in bone marrow (BM) aspirates of 18 adults (22 to 76 years old) without neoplasia, 4 adults (25 to 76 years old) with hematopoietic neoplasia (non-Hodgkin lymphoma [NHL], myelodysplasia syndrome [MDS]), and 156 cord blood (CB) samples from healthy newborns. The samples were investigated by 3 independent laboratories in Goettingen, Vienna, and Hannover.

Of 22 adult bone marrow samples, 6 (27%) were AML1/ETO-positive (Figure 1), of which 2 derived from patients with NHL. Of all samples, 2 exhibited neoplastic cells (NHL, MDS), of which 3 out of 6 were comparable to patients with CCR. Assuming similar transcriptional levels, the number of AML1/ETO-positive cells in half of all positive healthy newborns may resemble that of patients with AML in CCR.

We postulate that positive cells are either generated by permanent mutagenesis or are derived from aberrant hematopoietic stem cells. Since the gene fusion AML1/ETO is prone to be induced by radiation in vitro, an ongoing generation in all age groups by external mutagens may explain our observations. In this model it seems unlikely that AML1/ETO-positive cells have a survival advantage; otherwise, a much higher incidence in the elderly should be expected, though our observations may be influenced by the better cDNA quality of the cord blood samples.

On the other hand, the t(8;21) may be generated in early hematopoiesis. Positive cells will then permanently derive from a positive stem cell pool but only few positive individuals may attract secondary genetic alterations and progress to AML. The latter mechanism is supported by the recent report of Wiemels et al on the detection of AML1/ETO in neonatal blood spots of children who developed a corresponding AML with more than 10 years latency. Jörg Basecke, Lukas Cepek, Christine Mannhalter, Jurgen Krauter, Stefanie Hildenhagen, Guenter Brittlinger, Lorenz Trumper, and Frank Griesinger

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References


To the editor:

Tumor necrosis factor α (TNF-α) promoter polymorphisms and liver abnormalities of homozygotes for the 845G>A (C282Y) hereditary hemochromatosis mutation

Although many opinions have been offered regarding the penetrance of hemochromatosis in homozygotes for the 845G>A (C282Y) HFE mutation, a controlled study has shown that very few of these individuals develop clinical disease. Clearly, the homozygous state is a necessary but not sufficient condition for the development of the clinical disease. Finding the other factors that may play a significant role is of great importance, particularly if population screening for hemochromatosis is to be carried out. The studies of Fargion et al suggesting that polymorphisms in the tumor necrosis factor alpha (TNF-α) promoter may be such modifiers of the hemochromatosis phenotype were, therefore, of special interest. In
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