Differentiating Juvenile Myelomonocytic Leukemia From Infectious Disease

To The Editor:

Two recent articles in Blood1,2 review the findings and outcome of juvenile myelomonocytic leukemia (JMML). Both omit an important aspect of JMML: its differentiation from infectious disease. Several disseminated microbial infections of infancy can result in persistent fever, failure to thrive, hepatosplenomegaly, skin lesions, anemia, thrombocytopenia, and myelomonocytosis, including Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpes virus-6 (HHV-6), histoplasma, mycobacteria, and toxoplasma. Thorough investigation for infection is needed in infants with these findings to avoid erroneous diagnosis and mistaken interventions.

Herrod et al3 reported two infants with persistent EBV infection and findings consistent with JMML, including increased numbers of F and i cells and abnormal granulocyte-macrophage colony formation in vitro. Both recovered without treatment and remained well. This raises the possibility that some of the long-term survivors reported by Niemeyer et al and Arico et al had similar infections rather than leukemia. Neonatal CMV and HHV-6 infections can also mimic JMML,4,5 Might erroneous diagnosis account for the better prognosis reported for patients with JMML who are less than 6 months old?6

The excellent reviews of Niemeyer et al and Arico et al suggest that JMML represents a group of diseases rather than a single entity. Careful investigation for microbial associations, including more recently identified herpesviruses, might contribute to understanding pathogenesis as well as to diagnosis and management.

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References

syndrome, because their clinical and biological similarities suggest that they are spectrums of the same disease. We believe that the broad agreement on nomenclature will facilitate cooperative treatment trials and hasten research on the pathogenesis of JMML.

As addressed by Dr Pinkel, the clinical and morphological picture of JMML can be mimicked by a variety of infectious organisms. In addition, granulocyte-macrophage colony-stimulating factor hypersensitivity of myeloid progenitor cells, thought to play a central role in the pathogenesis of JMML, has been noted in vitro in children with viral infections. A basic tenet for the definition of myeloid leukemias is the demonstration of the clonal origin from a malignant hematopoietic progenitor cell. The clonal nature is often inferred by evidence of a chromosomal abnormality or an activating mutation of a proto-oncogene. In this respect about half of the children with JMML have evidence of a clonal disorder; 35% are known to have a chromosomal abnormality, and 15% to have a point mutation of the Nras or Kras oncogene in their hematopoietic cells. More recently, the study of X-chromosome inactivation patterns showed evidence for monoclonal origin of mononuclear cells in all female JMML patients analyzed. In the absence of a marker of clonality, the establishment of the diagnosis JMML and firm exclusion of an infectious origin can be difficult.

To address this issue in our retrospective study we collected data on the serology for cytomegalovirus (CMV; n = 56), herpes virus type I (HSV; n = 27), and Epstein-Barr virus (EBV; n = 51) from the time of diagnosis. Thirty-eight percent of children were positive for CMV, 44% for HSV, and 47% for EBV. The prevalences of antibodies to these viruses were similar to those observed in normal infant populations in Western Europe.

There were no significant differences in age at diagnosis or length of survival between JMML patients with or without previous or recent CMV, HSV, or EBV infection. Dr Pinkel raises the concern that some of our long-term survivors might have had infections rather than leukemia. Of the seven patients with a survival of more than 5 years without bone marrow transplantation, four have succumbed to their disease (Table 7 in Niemeyer et al). Of the three remaining patients, one girl currently alive with disease 6.5 years after diagnosis is known to have an Nras point mutation (A. Biondi, personal communication). Another patient had monosomy 7 in his bone marrow cells documented twice within 6 months after diagnosis, whereas a normal karyotype was found 4 and 9 years later. He had no evidence of disease when seen last 9.6 years after diagnosis. The patient with the longest survival, currently 13 years after diagnosis, had no marker of clonality. His smears and clinical data were thoroughly reviewed, but it cannot be excluded that he suffered from an infection rather than from leukemia. Viral studies from the time of the diagnosis were not available.

We agree with Dr Pinkel that a careful investigation for an infectious cause is mandatory in all children suspected as suffering from JMML. Until the chromosomal and molecular abnormalities of the majority of JMML patients with so-called “normal karyotype” have been unraveled, the diagnosis of JMML will have to be based on a number of clinical and laboratory features (Table 1). The suggestive clinical features, the minimal laboratory criteria, and the criteria requested for definite diagnosis may prove to be a guideline in establishing the diagnosis of JMML.

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REFERENCES


Hereditary Hyperferritinemia-Cataract Syndrome: Two Novel Mutations in the L-Ferritin Iron-Responsive Element

To the Editor:

Cazzola et al. recently reported two kindreds with hereditary hyperferritinemia cataract syndrome (HHCS) associated with novel point mutations within a regulatory stem-loop motif in the L-ferritin mRNA termed the iron-responsive element (IRE). Affected individuals showed a characteristic clinical phenotype of elevated serum ferritin concentration and cataract developing early in life. The proposed pathogenesis of this disorder is that nucleotide substitutions within the IRE disrupt its specific interaction with the cytoplasmic iron regulatory protein (IRP). Failure of optimal IRP-IRE binding in turn leads to failure of suppression of L-ferritin translation.

There are now increasing numbers of reports that describe the genotype-phenotype relationship in kindreds with naturally occurring IRE mutations, and as Cazzola et al. report, the phenotype varies with the position of the mutation in the IRE. These descriptions now provide clinical data that support the structural model of the IRE-IRP interaction deduced from in vitro binding studies using artificially created IRE mutants.2-4

We have identified two further kindreds with HHCS and novel mutations in the L-ferritin IRE that further support this model.

Kindred 1. The 51-year-old male proband of English origin developed visual symptoms in his mid-thirties from cataracts, but was otherwise asymptomatic. Investigations revealed a serum ferritin of 1,389 µg/L but normal transferrin saturation. Similar abnormalities were noted in the proband’s sister, and liver biopsy specimens from both these individuals showed no iron overload. Sequencing of genomic DNA from the proband showed a heterozygous point mutation that corresponded to a $\text{C} \rightarrow \text{U}$ substitution in the L-ferritin mRNA.

Kindred 2. The 42-year-old female proband of English origin was investigated for anemia detected at one of her regular blood transfusion sessions. Although her red cell indices and transferrin saturation were consistent with mild iron deficiency, her serum ferritin was elevated at 1,020 µg/L. The proband herself had had previous surgical extraction of cataracts, and there were premature cataracts in 8 other family members. The son of the proband required cataract extraction at 5 years old. Hyperferritinemia was confirmed only in family members with cataract. Analysis of genomic DNA also showed a heterozygous point mutation that corresponded to a $+39 \text{C} \rightarrow \text{U}$ substitution in the L-ferritin mRNA. This substitution created an $\text{Mse I}$ restriction site within the amplified sequence, and restriction digests from additional family members confirmed that the substitution segregated with the hyperferritinemia-cataract phenotype.

The nucleotide substitutions detected in kindreds 1 and 2 lie in the apical loop and upper stem of the IRE, respectively (Fig 1). We note that in both kindreds individuals display a severe phenotype, and this is consistent with the observations of Cazzola et al that mutations near the apex of the IRE result in higher serum ferritin concentrations and denser cataracts. These results also comply with data from in vitro binding studies; nucleotide substitutions in the apical loop of the IRE dramatically reduce IRP affinity, consistent with its putative role as the IRP binding site.2,3 Individuals from kindred 1 with a naturally occurring mutation at this site are therefore expected to have a severe defect in L-ferritin regulation. In the case of kindred 2, artificially created nucleotide substitutions in the IRE upper stem exert a profound effect on IRP binding in vitro, but only if complementary base pairing in the stem is disrupted.4 Pairing of nucleotides may facilitate IRE-IRP binding by maintaining an optimum secondary structure of the IRE. The