for investigation of unexpected changes in patients with GD1 to confirm the cause when there are suggestive clinical features.

Thrombocytopenia is one of the most common features of GD1. The mechanism is a combination of hypersplenism and reduced normal hematopoiesis attributable to marrow infiltration.\(^5\) Thrombocytopenia may improve with specific treatment of Gaucher disease, such as enzyme therapy. In our patient, the platelet count was normalized with the emergence of JAK2 V617F and an increase in megakaryopoiesis. The patient would appear to have essential thrombocytopenia superimposed on Gaucher disease.

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Contribution: D.A. took care of the patient, conceived the concept, and wrote the manuscript; and C.W. reviewed bone marrow, collected and analyzed the data, and wrote the manuscript.

To the editor:

**Treatment of NLPHL**

The article on nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) by Drs Advani and Hoppe in *Blood* provides an excellent overview of this uncommon disease. However, their characterization of the outcome data available in the literature as supportive of continued use of radiation alone as the optimal treatment is somewhat incomplete and deserves careful re-examination.

It is important to remember that the large majority (≈80%) of patients with NLPHL present with stage I or II disease. Thus, the most relevant clinical evidence appropriately focuses on stage I and II disease. Additionally, the clinical course of NLPHL is indolent, and late relapses are regularly encountered, at least after radiation alone. For this reason, outcomes at ≥10 years from diagnosis are the most relevant.

As evidence of the effectiveness of radiation alone for limited stage NLPHL, Advani and Hoppe cite the pooled German Hodgkin Study Group data from the HD4 through HD12 studies,\(^1\) claiming that the freedom from treatment failure (FFTF) was 93% after radiation alone. It is true that the 50-month FFTF was 93%, but it is more relevant that the 10-year FFTF was ~75% and even more important that about one-half of the patients were treated with combined chemotherapy and radiation. Results for radiation alone are not provided in this paper.

My group at the British Columbia Cancer Agency recommends an alternative approach to NLPHL based on our observation that when one manages limited stage NLPHL using the same approach as for classical HL, results appear much improved compared with radiation alone.\(^2\) Using this approach for the 56 patients managed at our center over the last 20 years, we found a 10-year FFTF estimate of 98%. Readers might want to put the results cited by Advani and Hoppe into context using a level playing field analysis. Table 1 provides an excellent overview of this uncommon disease. However, their characterization of the outcome data available in the literature as supportive of continued use of radiation alone as the optimal treatment is somewhat incomplete and deserves careful re-examination.

Table 1. Ten-year FFTF after various approaches to treatment of NLPHL

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
<th>10-y FFTF estimate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I–II, A or B</td>
<td>IFRT or EFRT 48% or RT + ABVD type chemo 52%</td>
<td>75</td>
</tr>
<tr>
<td>IA</td>
<td>IFRT</td>
<td>94</td>
</tr>
<tr>
<td>IA, IIA</td>
<td>EFRT</td>
<td>84</td>
</tr>
<tr>
<td>IA</td>
<td>IFRT</td>
<td>77</td>
</tr>
<tr>
<td>IA</td>
<td>IFRT</td>
<td>83</td>
</tr>
<tr>
<td>IA, IIA</td>
<td>EFRT 76%</td>
<td>68</td>
</tr>
<tr>
<td>IFRT 24%</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>RT + chemo studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>RT + ABVD type chemo</td>
<td>94</td>
</tr>
<tr>
<td>IA, IIA</td>
<td>RT + ABVD type chemo 75% or ABVD alone (4 cycles) 25%</td>
<td>98</td>
</tr>
</tbody>
</table>

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References

The continued use of radiation alone for NLPHL is an accident of history and not the result of an evidence-based comparison. Clinicians should consider treating limited stage NLPHL the same as classical HL, especially given the available evidence that doing so appears to produce superior treatment outcomes.

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References


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To the editor:

Homogyosity by descent of a 3Mb chromosome 17 haplotype causes coinherence of Glanzmann thrombasthenia and primary ciliary dyskinesia

Glanzmann thromboasthenia (GT) is an autosomal recessively inherited bleeding diathesis, and mutations within the genes (ITGA2B and ITGB3) that code for subunits αIIbβ3 integrin have been shown to be responsible for this disorder.1

The GT clinical phenotype can be modulated by a series of factors, acquired as well as inherited.2

We now report the coinherence in 2 siblings of GT and primary ciliary dyskinesia (PCD). A 5-generation family history excluded consanguinity. Approval was obtained from the Ospedali Riuniti (Foggia, Italy) Institutional Review Board for these studies. Written informed consent was obtained from the parents in accordance with the Declaration of Helsinki.

The patients were a 9-year-old boy and his 6-year-old brother (Figure 1) who had mucocutaneous bleeding diathesis soon after birth. A diagnosis of GT was confirmed by complete platelet failure to aggregate in response to adenosine 5-diphosphate, epinephrine, collagen, and thrombin and lack of the αIIbβ3 platelet receptor in flow cytometry studies. In both patients, the presence of an opposite position of the internal organs (heart, stomach, spleen, liver, and gallbladder) and bronchiectasis allow for the diagnosis of PCD. In both of these patients, an atrial septal defect, a patent foramen ovale, and an ostium secundum (in the older and in the younger boy, respectively), was observed. In addition, sinus disease with recurrent infections gave rise to recurrent epistaxis, which needed the combined use of recombinant activated factor VII and antifibrinolytics, because of refractoriness to platelet transfusion due to the appearance of antibodies against platelet antigens. Both parents and the 14-year-old sister were asymptomatic.

Sequencing of ITGA2B and ITGB3 genes revealed the presence of a novel homozygous nonsense mutation within the ITGB3 gene (p.W264X, c.G33289A). Both parents were heterozygous, whereas the sister did not carry the mutation.

Clinical and instrumental information indicated the cosegregation of both diseases and suggested the contemporary inheritance of mutated alleles of different genes, raising the possibility of their linked germline transmission. Usually, because of crossing over, genes follow the expected inheritance patterns predicted by Mendel’s Theory of Independent Assortment, and their probability to be separated across generations depends on how far genes are.

PCD is inherited in an autosomal recessive manner and shows high locus heterogeneity, ~20 genes being known to be associated with the disease.3-10 One of them, CCDC103, is located in a 3Mb segment on the chromosome 17q, between the ITGA2B and ITGB3 genes. Thus, we explored whether the clinical phenotype observed in the family investigated might be ascribed to the inheritance of a chromosome 17q haplotype. In both patients, sequencing of the CCDC103 gene showed a homozygous missense mutation, p. H154P (c.A2826C), previously reported in families of Pakistan and German origin.7 Both parents and grandmothers were heterozygous, whereas the sister did not carry the mutation. To further confirm the pathogenetic role of a chromosome 17q haplotype inheritance, we analyzed informative gene polymorphisms. All alleles cosegregate (Figure 1), providing evidence of the existence of a 3Mb chromosome 17q haplotype, which carries both the ITGB3 p. W264X and the CCDC103 p.H154P gene mutation. The presence of an inherited haplotype and the absence of self-reported consanguinity strongly suggest a common ancestor and a founder effect of a rare haplotype.

To our knowledge, this paper is the first to describe coinherence of GT with PCD, a hereditary disease that affects GT clinical phenotype by modulating bleeding risk because of the presence of sinusitis, bronchiectasis, and malformations needing surgical approaches, as atrial septal defects.

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