hybrid (myeloid-erythroid) blasts has been proposed to be a characteristic bone marrow feature in EL, but has not as yet been emphasized as a morphologic feature of the disease. Erythroblasts with peripheral chromatin condensation are sufficiently characteristic for a provisional diagnosis of B19 infection to be made on the histology and rare erythroblasts with this morphologic feature could be observed (Figure 1e). While we can firmly correlate the infectious phase of the disease to HPV B19, the association with the neoplastic phase is only hypothetical because of the absence of the virus in the marrow cells when searched for by in situ hybridization.

An alternative interpretation is that the patient had already subclinical EL which was unmasked by HPV B19 infection. If the virus hit compromised marrow, in which a shrunken compartment of normal hemopoiesis coexists with a still subclinical competing leukemia clone, pancytopenia may follow. Resolution of the virus infection might have given the normal marrow a chance to re-establish normal blood counts transiently, but EL finally expanded and took over. Since this is a case report it would be inappropriate to draw general conclusions. Nevertheless interesting speculation arise from this report: is there an association between HPV B19 and EL and can cell fusion play a role in the cytogenesis of giant multinucleated erythroblasts?

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Key words
Parvovirus B19 infection, erythroleukemia, cell fusion.

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References

Pulmonary thromboembolism in thalassemia intermedia patients

Sir,
We and others have reported thromboembolic phenomena in patients with β-thalassemia major (TM). Thalassemia intermedia (TI) patients have a phenotypically milder disease, not requiring regular blood transfusions. However, TI also predisposes to thrombotic events, similar to the life-long hypercoagulable state that exists in TM patients. It is unknown whether TI patients who suffer thrombotic events have other inherited or acquired predisposing risk factors. We report the cases of two TI patients with no other risk factors for thrombosis who suffered from potentially life-threatening pulmonary thromboembolism. Both patients presented with increasing dyspnea of recent onset. Investigations revealed bilateral pulmonary thromboembolism. Pertinent clinical details are summarized in Table 1. The results of a screen for hypercoagulable states are shown in Table 2.

These two patients with TI suffered from bilateral pulmonary thromboembolic disease with unusual features. No risk factors (other than thalassemia) were present. Furthermore, no source of emboli could be
detected, suggesting that the thrombi formed in situ in the pulmonary vasculature. Although not described in TI, multiple pulmonary thromboemboli have been found at post-mortem examinations in patients with TM and thalassemia-hemoglobin E disease. A cardiopulmonary assessment of 35 TM patients showed a high incidence of hypoxemia, pulmonary hypertension and right heart failure, suggesting recurrent thromboembolic damage to the pulmonary microvasculature.

Although of still uncertain pathogenesis, the hypercoagulable state in thalassemia is usually attributed to the abnormal exposure of phosphatidylserine at the outer surface of thalassemic erythrocytes, as demonstrated by the ability of thalassemic erythrocytes to support the prothrombinase complex generating thrombin. It is interesting to note that the highest rates of thrombin generation were found in TI erythrocytes. This was attributed to the lack of dilution of pathologic erythrocytes by normal transfused erythrocytes as occurred in TM patients. Another possible mechanism of hypercoagulability in thalassemia is in vivo platelet activation, triggered by accelerated thrombin generation. Increased platelet-thromboxane urinary metabolites were found in the urine of TM and TI patients, reflecting in vivo platelet activation. Flow cytometry has also demonstrated the presence of a similar magnitude of circulating activated platelets in TI patients to that observed in TM patients.

Taken together, these data suggest that the hypercoagulable state described in TM also exists in patients with TI. An unanswered question concerns the apparent rarity of clinically significant thrombotic events in TI patients. Since these patients do not require regular blood transfusions it is possible that they are followed less closely than TM patients and therefore some thrombotic events are not recognized. Recently, an Italian survey of thalassemia centers reported thromboembolic events in 9.6% (5 of 52) of TI patients, an incidence similar to that found in TM. However, these patients were not screened for other thrombophilias.

We conclude that TI is associated with thrombotic events independent of other thrombophilic risk factors. Clinicians involved in the treatment of TI patients should consider a thrombotic event in patients with a compatible clinical picture.

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**Table 2. Results of a hypercoagulability screen in both patients.**

<table>
<thead>
<tr>
<th></th>
<th>Normal values</th>
<th>Patient #1</th>
<th>Patient #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin III activity</td>
<td>84-112%</td>
<td>100%</td>
<td>102%</td>
</tr>
<tr>
<td>Protein C activity</td>
<td>60-160%</td>
<td>70%</td>
<td>74%</td>
</tr>
<tr>
<td>Free protein S Antigen</td>
<td>74-126%</td>
<td>78%</td>
<td>80%</td>
</tr>
<tr>
<td>APC-resistance (ratio)</td>
<td>&gt;2.0</td>
<td>2.2</td>
<td>2.4</td>
</tr>
<tr>
<td>Factor V Leiden mutation</td>
<td>negative</td>
<td>ND</td>
<td>negative</td>
</tr>
<tr>
<td>Anticardiolipin Ab</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
</tr>
</tbody>
</table>

ND, not done.

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**References**