In contrast to myelocytic leukemias, leukostasis is a rare complication in patients with B-CLL or Richter syndrome. The leukostasis syndrome has been extensively investigated in a rat model of acute myelocytic leukemia. Physical characteristics of the tumor cells, such as cell size or hyperviscosity, as well as the activation of the complement system, contribute to the development of this syndrome. Patients with initially high or rapidly increasing tumor cell counts in the peripheral blood seem to be at higher risk for developing a leukostasis syndrome.

Severe infusion-related adverse events during first rituximab treatment in patients with very high numbers of circulating tumor cells (> 200.0 × 10⁶/L) have been reported to be life-threatening or fatal, with a characteristic symptom complex that included pulmonary toxicity, hypotension, and a rapid reduction of circulating leukocytes and platelets, which might not be explained by a cytokine release syndrome alone. The development of these symptoms shortly after application of rituximab argues for a causative role of this anti-CD20 antibody in mediating tumor cell agglutination in blood vessels producing the fatal complications. Rituximab can contribute to leukostasis either because of direct cross-linking tumor cells or by more complex effects as opsonization of tumor cells. By increasing the antigen concentration (either high numbers of CD20 expressing circulating tumor cells or augmented density of the CD20 antigen), a zone of equivalence can be reached, where immune complexes consisting of tumor cells and anti-CD20 antibodies are formed, resulting in tumor cell agglutination followed by vessel obstruction.

This case report provides the first evidence based on histopathologic findings that tumor cell agglutination could be responsible for severe infusion-related adverse events during rituximab treatment. Patients with very high blood tumor cell numbers have an increased risk of developing this serious complication. Rituximab therapy in such patients should therefore be initiated with caution, and tumor cell reduction (< 50.0 × 10⁶/L) prior to administration of rituximab is currently recommended because fractionated dosing schedules of rituximab, as in the case described here, obviously do not prevent this complication.

Volker Kunzmann, Thomas Ruediger, Michael Hallek, Hans-Konrad Mueller-Hermelink, and Martin Wilhelm

To the editor:

A novel, possibly functional, single nucleotide polymorphism in the coding region of the thrombin-activatable fibrinolysis inhibitor (TAFI) gene is also associated with TAFI levels

In a recent issue of Blood, Henry et al. reported the identification of several single nucleotide polymorphisms (SNPs) in the promoter and 3′ untranslated region of the thrombin-activatable fibrinolysis inhibitor (TAFI) gene. They also investigated the 505A/G SNP in the coding region of the TAFI gene resulting in an amino acid (aa) substitution, Thr147Ala. Henry et al. showed that plasma TAFI antigen (Ag) levels are strongly associated with all these SNPs that turned out to be in strong linkage disequilibrium. This association confirmed and extended preliminary reports on the association of TAFI plasma levels and SNPs in the TAFI gene promoter.

We identified another SNP, 1040C/T, in the coding region of the TAFI gene by comparing published sequences (GenBank no. NM_001872 and NM_016413). This SNP also results in an aa substitution (Thr325Ile). This SNP is of particular interest because it has been shown that the presence of an Ile325 residue has a positive influence on both TAFIa activity and stability in vitro resulting in increased antifibrinolytic activity. On the contrary, the Thr147Ala substitution has no effect on the functional properties of TAFI in vitro.

We determined in a group of 152 blood donors (mean age 45.8 years, SD 11.7, range 19-71 years, 94 males and 58 females) the genotype frequency and allele frequency of the 1040C/T SNP and correlated this with TAFI Ag levels. The 1040C/T SNP was significantly associated with TAFI Ag levels with the C/C genotype corresponding with the highest and the T/T genotype with the lowest TAFI Ag levels (Table 1). The 1040C/C genotype corresponds to Thr/Thr at position 325. Activated TAFI-Thr325 has a normal in vitro half-life of 8 minutes (at 37°C), whereas activated TAFI-Ile325 has a half-life of about 16 minutes and a 60% greater antifibrinolytic activity compared to TAFI-Thr325. The reduced antifibrinolytic activity of TAFI-Thr325 is very likely the result of the greater instability of this isoform. It is remarkable that the Thr325 allele, which is associated with increased TAFI Ag levels in vivo, encodes a TAFI isoform that is less stable after activation in vitro. At present, it is not known whether the substitution of Thr325Ile will make TAFI less susceptible to degradation by plasmin via an effect on the cleavage at Arg328.

To determine if the 1040C/T SNP is in linkage disequilibrium with the SNPs studied by Henry et al. we also determined the genotype and allele frequencies of the −438A/G TAFI promoter SNP and the 505A/G SNP in the coding region of the TAFI gene. The −438A/G and 505A/G SNP showed similar genotype distribution and allele distributions as described before (Table 1) and all 3 analyzed SNPs were in strong linkage disequilibrium (P < .001, χ² analysis). The −438G/G and the 505A/A genotype correspond to the highest TAFI Ag levels (Table 1), which is also in agreement with earlier observations.

References

To the editor:

Increased Lipoprotein(a) levels are not a steady prothrombotic defect

We have read the paper by Nowak-Göttl and coworkers on the meaning of combined prothrombotic defects for recurrence of venous thrombosis in childhood with great interest and congratulate the authors for their work. However, we would like to comment on their findings with regard to Lipoprotein(a) (Lp(a)). In their paper, the authors describe Lp(a) as the second most prevalent “prothrombotic defect” for recurrent and nonrecurrent venous thromboembolism (VTE) in childhood, using a cut-off of 300 mg/L (30 mg/dL).

We had the chance to examine Lp(a) concentrations in a small group of pediatric patients (n = 7) treated for acute lymphoblastic leukemia (ALL) or lymphoma on the ALL- or NHL-BFM (non-Hodgkin lymphoma–Berlin-Frankfurt-Muenster) trial 95, respectively. These 2 trials were used by Nowak-Göttl et al to study the incidence of increased Lp(a) and its possible relationship to the incidence of venous thrombosis in this setting. We found that Lp(a) was significantly decreased during therapy on the BFM trial 95 (Figure 1), with every patient showing reduction of Lp(a) concentration. A patient with an increased Lp(a) of 325 mg/L displayed a decrease to a nadir of 58 mg/L, only to end the first block of therapy with a level of 111 mg/L. Mean Lp(a) fell by 75% from 116.1 mg/L on day 8, to 28.9 mg/L on day 16 (P = 0.049, Figure 1). It is very likely that these changes in Lp(a) concentrations were due to the use of L-asparaginase, as described by other investigators in a different setting.2 Variation of Lp(a) levels with albumin concentrations has been described as well as with the state of thyroid function.3,6 Also, Lp(a) levels have repeatedly been linked to acute-phase responses.7-10 On the other hand, negative acute-phase characteristics occur.11,12 In vitro experiments show that Lp(a) messenger RNA (mRNA) expression can be positively regulated by interleukin-6 (IL-6), whereas it can be suppressed by transforming growth factor-β.13,14

Figure 1. Lp(a) levels can be unsteady: the course of Lp(a) concentration during L-asparaginase containing chemotherapy is displayed and a significant decrease can be seen.

Table 1. Association between TAFI genotypes and plasma TAFI Ag levels

<table>
<thead>
<tr>
<th>Allele</th>
<th>No.</th>
<th>Percentage</th>
<th>TAFI Ag (SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>505</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>75</td>
<td>49.3</td>
<td>0.934 (0.139)</td>
<td>.001</td>
</tr>
<tr>
<td>AG</td>
<td>69</td>
<td>45.4</td>
<td>1.000 (0.141)</td>
<td>.001</td>
</tr>
<tr>
<td>AA</td>
<td>8</td>
<td>5.3</td>
<td>1.029 (0.138)</td>
<td>.001</td>
</tr>
<tr>
<td>Allele G</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA/Thr</td>
<td>95</td>
<td>67.8</td>
<td>0.887 (0.137)</td>
<td>.002</td>
</tr>
<tr>
<td>AG</td>
<td>72</td>
<td>47.4</td>
<td>0.947 (0.136)</td>
<td>.002</td>
</tr>
<tr>
<td>GG</td>
<td>67</td>
<td>44.0</td>
<td>1.007 (0.140)</td>
<td>.002</td>
</tr>
</tbody>
</table>

*Test for trend.

References

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