Despite the assertion by Miller and Rao, the evidence to support a simple transfusion over erythrocytapheresis early in the course of ACS is lacking. To our knowledge, no randomized control trial exists comparing simple transfusion therapy with erythrocytaphere-
sis for ACS. Further, the potential benefits versus risks of repeated simple transfusions in this patient population should be evaluated carefully. Of 5 patients, 4 had a positive fluid balance prior to their neurologic event, 3 with subsequent hypertension and reversible posterior leukoencephalopathy syndrome.

In regard to our definition of silent cerebral infarct, we defined a silent infarct as a lesion consistent with infarction on magnetic resonance imaging without evidence of a focal neurologic finding lasting longer than 24 hours. This definition is based on the one used by a standard neurologic textbook that defines a stroke as a “sudden occurrence of a nonconvulsive, focal neurologic deficit” and distinguishes strokes from reversible transient ischemic attacks based upon duration of symptoms lasting less than 24 hours. Additionally, our definition of silent cerebral infarct is one that we have used previously. In our case series, none of the 3 patients determined to have a silent cerebral infarct had evidence of a focal neurologic deficit persisting longer than 24 hours. Patient 1 had a headache (a nonfocal neurologic symptom); patient 2 had general-
ized and multifocal seizures and transient, mild right-arm weakness and left-eye deviation lasting less than one hour (focal findings resolved in one hour); and patient 3 had evidence of diffuse deconditioning (nonfocal) after being intubated for several months. All patients had normal neurologic examination after being examined by a pediatric neurologist.

Regardless of the definition of silent cerebral infarcts, children with sickle cell anemia and ACS have a high incidence of cerebral infarcts, placing them at increased risk for further neurologic morbidity and associated cognitive impairment. In the setting of severe ACS following erythrocytapheresis, we recommend consideration be given for assessment of occult neurologic morbidity.

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References

To the editor:

Rituximab-associated immune myelopathy

Rose et al recently reported a case of agranulocytosis following autologous transplantation for diffuse large B-cell lymphoma after in vivo purging with rituximab. Agranulocytosis developed on day 122 after transplantation as a result of trilineage engraftment; the bone marrow (BM) was hypocellular with little maturation of the myeloid series, cytogenetic analysis demonstrated del(20)(q11.2), and tests for infectious agents or antineutrophil antibodies were negative. The patient proved refractory to granulocyte/granulocyte-macrophage colony-stimulating factor (G/GM-CSF) and eventu-
ally responded to cyclosporine, leading the authors to deduce an autoimmune destruction of myeloid precursors.

Rituximab administration before transplantation does not compromise peripheral blood (PB) progenitor cell harvest; nevertheless, although prompt engraftment is the norm, there are reports of transient neutropenia after transplantation, albeit without increased infections. Rose et al are right in proposing an autoimmune mechanism; in this context, data on the immunophenotypic profile of that patient’s lymphocytes would have been very helpful. As we have shown, neutropenia in rituximab-treated lymphoma patients may be considered as one end of a spectrum of immunohematologic sequelae due to autoimmune myelopathy, often associated with rituximab-induced T-cell large granular lymphocyte (T-LGL) proliferation (CD3+ CD8+ CD57+ CD28-, CD8+ > > CD4+).3 4

We have followed-up 34 rituximab (± chemotherapy)-treated lymphoma patients. Based on PB morphology and flow cytometry findings, patients were assigned to 4 groups: (1) 11 patients with PB T-LGL lymphocytosis and profound neutropenia of 1 to 5 months duration (10/11) or thrombocytopenia (1/11); in 8 patients neutropenia developed after transplantation (autologous, 4; allo-
gegenic, 4), a median of 75 days after transplantation (range, 40-135 days), after prompt engraftment; at onset of cytopenias, only 1 of 4 patients who underwent allotransplantation had evidence of chronic graft-versus-host disease (135 days after hematopoietic cell trans-
plantation); (2) 4 patients with neutropenia without T-LGL lympho-
cytosis; (3) 2 patients with PB T-LGL lymphocytosis without cytopenias; and (4) 17 patients with neither PB cytopenias nor T-LGL lymphocytosis. In all cases, tests for hepatitis B/C, HIV, cytomegalovirus, and Epstein-Barr virus were negative. BM biopsy examination revealed in most cases mild to moderate depression of the myeloid series with a left shift. With a median follow-up of 13 months (range, 1-23 months), patients with neutropenia did not have increased infections. Furthermore, contrasting the patient described by Rose et al, neutrophil count promptly increased with G-CSF; nevertheless, G-CSF discontinuation was usually associated with a rapid decline in neutrophil count.

Activated and neoplastic T-LGLs express and secrete large amounts of Fas and Fas ligand; thus, T-LGL- associated neutrope-
ia may result from apoptosis of mature neutrophils through CD95 (Fas) triggering; T-LGLs could also mediate cytokine/chemokine myelosuppression independently of Fas/Fas ligand interactions. Possible causes for neutropenia in the 4 patients without T-LGL lymphocytosis could be (1) autoantibody production in a context of a new immune repertoire developing after rituximab-induced B-cell depletion, as reported in 3 rituximab-treated lymphoma
patients who developed agranulocytosis and tested positive for antineutrophil antibodies;\(^7\) and (2) tumor necrosis factor (TNF)–mediated myelosuppression, in a setting of rituximab-induced TNF-\(\alpha\) release.\(^8\)

Finally, detection of del(20)(q11.2) is evidence for secondary myelodysplastic syndrome related to high-dose therapy (HDT)\(^9\); nevertheless, as previously shown, one cannot exclude the possibility of stem cell damage resulting from prior conventional dose chemotherapy and actually unrelated to HDT.\(^1\)

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References


To the editor:

Vagaries of genetic association studies in myocardial infarction

Those who follow publications on genetic association studies are aware that none of the single nucleotide polymorphisms (SNPs) of genes encoding proteins involved in hemostasis and thrombosis have been consistently associated with an increased or decreased risk of such complex and multifactorial diseases as myocardial infarction or stroke.\(^1\) Studies on the same gene SNPs have often given discrepant results, so that only 16% of initially identified associations was subsequently replicated.\(^2\) Typically, a few large studies (those including 1000 cases or more) found weak associations or no association at all, with strong associations found by several small studies.\(^3\) This situation is epitomized by 2 recent studies, those by Butt et al\(^4\) and by the Atherosclerosis Thrombosis and Vascular Biology Italian Study Group\(^5\) on the role of SNPs of coagulation factor genes such as 20210G>A factor II, 1691G>A factor V, and 185G>T factor XIII-A. In 1210 Italian patients who survived a first myocardial infarction at an age younger than 45 years compared with an equal number of matched controls, none of these SNPs nor 6 additional SNPs of genes encoding proteins involved in coagulation, platelet function, and fibrinolysis were associated.\(^3\) In contrast, in 500 Canadians from Newfoundland, 20210G>A factor II was significantly more prevalent in patients with myocardial infarction than in controls (Table 1). Prevalence of mutant 1691G>A factor V (generally known as factor V Leiden) and of 185G>T factor XIII-A was not significantly different in cases and controls, but the prevalence of 185G>T factor V was significantly higher when a subgroup of 46 patients who developed myocardial infarction at an age of 50 years or younger was analyzed (Table 1).\(^4\) Furthermore, Butt et al\(^4\) claim that their study gives evidence of strong gene-gene interaction, the prevalence of combined carriership of 20210G>A factor II and 185G>T factor

Table 1. Frequency of genotypes of single nucleotide polymorphisms of coagulation factor genes and relative risk of myocardial infarction (as measured by odds ratios) in Italians (aged 45 years or younger) and in Canadians (aged 50 years or older)

<table>
<thead>
<tr>
<th>Polymorphism and gene</th>
<th>Cases, (n = 1210)</th>
<th>Controls, (n = 1210)</th>
<th>Odds ratio</th>
<th>Cases, (n = 500)</th>
<th>Controls, (n = 500)</th>
<th>Odds ratio</th>
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<td>20210G&gt;A, factor II</td>
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<tr>
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<td>(NS)</td>
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<td>5.6* ((P = .04))</td>
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<td>0.8* (NS)</td>
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</table>

\(^{0/0}\) indicates genotypes characterized by the presence of 2 wild-type alleles (values are percentages); \(^{0/1}\), the presence of 1 wild-type and 1 mutant allele; \(^{1/1}\), the presence of 2 mutant alleles, and NS, not statistically significant.

*The odds ratios obtained in the subgroup of 46 patients 50 years or younger.