administration present simpler backgrounds upon which to evaluate the effect of the WBC count. In both cases, complications occurred with the development of marked WBC count elevations a few days after initiating the cytokine treatment in clinically well individuals. These cases suggest that an acute elevation in the polymorphonuclear leukocyte count can promote acute sickle cell complications. Alternatively or additionally, G-CSF–induced changes in granulocyte function, such as increased adhesiveness, might have played a major pathogenic role in the above cases since leukocyte adhesion appears to contribute to the pathophysiology of sickle cell vaso-occlusion.[7] Thus, in the absence of infection, dehydration, or other clinically important conditions, a large number of adherent polymorphonuclear leukocytes might have precipitated the fatal vaso-occlusive event described above.

The present case supports the concept that granulocytes play, or can play, an important role in acute complications of sickle cell disease. The importance of granulocyte number, versus functional characteristics, remains unknown, but understanding the role of granulocytes in acute sickle cell events might provide insights for new therapeutic intervention in this disease. Pending a better understanding of the pathophysiology of vaso-occlusion, patients with sickle cell disease should receive G-CSF with great caution.

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References

1. Pieters R-C, Rojer R-A, Saleh A-W, Saleh A-E-C, Duits A-J. Molgramostim to treat SS-sickle cell leg ulcers [letter]. Lancet. 1995;345:528.
2. Abboud M, Laver J, Blau C-A. Granulocytosis causing sickle-cell crisis. Lancet. 19986;351:959.
3. Platt O-S, Brambilla D-J, Rosse W-F, et al. Mortality in sickle cell disease. New Engl J Med. 1994;330:1639-1644.
4. Fadlon E, Vordermeier S, Pearson T-C, et al. Blood polymophonuclear leukocytes from the majority of sickle cell patients in the crisis phase of the disease show enhanced adhesion to vascular endothelium and increased expression of CD64. Blood. 1998;91:266-274.
5. Duits A, Schnog B, Lard L, Saleh A, Rojer R. Elevated IL-8 levels during sickle cell crisis. Eur J Haematol. 1998;61:302-305.
6. Graido-Gonzalez E, Doherty J, Bergreen E, Organ G, Telfer M, McMillen M. Plasma endothelin-1, cytokine, and prostaglandin E2 levels in sickle cell disease and acute vaso-occlusive crisis. Blood. 1998;92:2551-2555.
7. Hoglund M, Hakansson L, Venge P. Effects of in vivo administration of G-CSF on neutrophil functions in healthy volunteers. Eur J Haematol. 1997;58:195-202.

To the editor:

Acquired and inherited risk factors for splanchnic venous thrombosis

We read with great interest the paper of Janssen et al.[1] They reported an increased risk for Budd-Chiari syndrome (BCS) or portal vein thrombosis (PVT) among carriers of factor V Leiden or inherited protein C deficiency. Overall, in 58% of their patients a possible inherited or acquired cause of thrombophilia was found; in 14% of cases there was the coexistence of inherited or acquired risk factors. In particular, there was an associated overt chronic myeloproliferative disease (CMD) in 28 (21%) of 135 patients. The authors did not consider the patients as affected by a CMD who did not meet all the diagnostic criteria but in whom the presence of spontaneous endogenous erythoid colonies (EECs) was detected. Indeed, such approach has repeatedly been reported as a useful diagnostic tool for identifying a CMD at very early stages.[2]

The association of unusual or latent forms of CMD diagnosed by means of the EECs assay has been reported in a large number of patients with BCS or PVT.[3-6] Review of 51 published cases with BCS and 69 cases with portal and/or mesenteric vein thrombosis showed the presence of an overt CMD in 49% of the patients with BCS and 23% of the patients with portal/mesenteric vein thrombosis; the inclusion of patients with latent CMD as defined by the presence of EECs increased the diagnostic yield to 78% among patients with BCS and 48% among patients with portal/mesenteric vein thrombosis.[7] Therefore, we suggest that the exclusion of latent CMD as possible underlying cause of splanchnic vein thrombosis could have overestimated the role of inherited thrombophilia as a single risk factor for BCS or PVT. In our series of 11 patients with BCS and 45 patients with portal/mesenteric vein thrombosis, 14 (25%) of 56 had inherited thrombophilia (1 had antithrombin III deficiency; 2, protein C deficiency; 8, factor V Leiden mutation; and 3, prothrombin G20210A), in good agreement with the 23% reported by Janssen et al.[1] Among the 31 patients assayed for the presence of EECs, 18 (58%) were considered to be affected by CMD, in 4 cases in association with inherited thrombophilia. An overt polycythemia vera or primary thrombocythemia was present in 7 (22%) of 31 such patients, in 4 cases at the time of thrombosis. Three of the patients with EECs as the only sign of CMD at the time of thrombosis later developed an overt thrombocythemia. Thus, in 14 patients the presence of a CMD even at early stages should have been missed not applying the EECs assay at the time of thrombosis. Among the 13 patients with no detectable EECs, 4 had inherited thrombophilia (3, factor V Leiden mutation; 1, prothrombin G20210A) and 4 had an acquired cause of thrombosis (1 case each of antiphospholipid antibodies, puerperium, trauma, and surgery). Therefore among the 31 patients exhaustively investigated, 26 (84%) had an inherited or acquired cause of thrombophilia or both. This percentage is higher than that reported by Janssen et al[1] and reflects the improvement in detection of CMD as underlying cause of thrombosis, confirming that a thorough search for CMD is mandatory in evaluating patients with splanchnic venous thrombosis. Diagnostic yield of atypical or precocious forms of CMD can be substantially increased by the use of the EECs assay or novel additional assays such as the megakaryocyte expression of the thrombopoietin receptor (c-*mpl*), whose decrease has been recently reported as a hallmark of polycythemia vera.[8]

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References

1. Janssen HLA, Meinardi JR, Vleggaar FP, et al. Factor V Leiden mutation, prothrombin gene mutation, and deficiencies in coagulation inhibitors associated with Budd-Chiari syndrome and portal vein thrombosis: results of a case-control study. Blood. 2000;96:2364-2368.
2. Westwood NB, Pearson TC. Diagnostic applications of hematopoietic progenitor culture techniques in polycythaemias and thrombocythaemias. Leuk Lymphoma. 1996;22(suppl 1):95-103.

3. Valla D, Casadevall N, Lacombe C, et al. Primary myeloproliferative disorder and hepatic vein thrombosis. A prospective study of erythroid colony formation in vitro in 20 patients with Budd-Chiari syndrome. Ann Intern Med. 1985;103:329-334.
4. Valla D, Casadevall N, Huisse MG, et al. Etiology of portal vein thrombosis in adults: a prospective evaluation of primary myeloproliferative disorders. Gastroenterology. 1988;94:1063-1069.
5. Pagliuca A, Mufti GJ, Janossa-Tahernia M, et al. In vitro colony culture and chromosomal studies in hepatic and portal vein thrombosis. Possible evidence of an occult myeloproliferative state. Q J Med. 1990;76:981-989.
6. Teofili L, De Stefano V, Leone G, et al. Hematological causes of venous thrombosis in young people: high incidence of myeloproliferative disorders as underlying disease in patients with splanchnic vein thrombosis. Thromb Haemost. 1992;67:297-301.
7. De Stefano V, Teofili L, Leone G, Michiels JJ. Spontaneous erythroid colony formation as the clue to an underlying myeloproliferative disorder in patients with Budd-Chiari syndrome or portal vein thrombosis. Semin Thromb Hemost. 1997;23:411-418.
8. Tefferi A, Yoon S-Y, Li C-Y. Immunoistochemical staining for megakaryocyte *c-mpl* may complement morphologic distinction between polycythemia vera and secondary erythrocytosis. Blood. 2000;96:771-772.

Response:

Acquired and inherited risk factors for Budd-Chiari syndrome and portal vein thrombosis

De Stefano et al describe the role of diagnosing latent myeloproliferative disorder in Budd-Chiari syndrome (BCS) and mesenteric or portal vein thrombosis (PVT). Latent myeloproliferative disorder is diagnosed by growth of erythroid cells in the absence of erythropoietin, also referred to as spontaneous endogeneous erythroid colonies (EECs). The association between the presence of EECs and BCS or PVT is well known.[1,2] We agree with De Stefano et al that excluding EECs may lead to an underestimation of the number of patients with an acquired risk factor for thrombosis and, consequently, to an underestimation of those with a combination of acquired and inherited risk factors for thrombosis. EEC assays are technically demanding and not amenable to external quality assurance. As stated in our article, not all of the participating centers tested for the presence of EECs. Thus our data did not allow us to evaluate the relation between EECs and BCS or PVT. It should be emphasized that our study focused on the role of prothrombotic coagulation disorders rather than on myeloproliferative disorders. Risk estimates for coagulation abnormalities are not affected by the underrepresentation of EEC diagnoses.

In our opinion, several of the results presented by De Stefano et al necessitate a balanced interpretation. First, the presence of EECs alone is, using the current criteria, not sufficient to diagnose myeloproliferative disease.[3-5] Their presense is used merely as a confirmational criterion for this diagnosis. The prognostic significance of the presence of EECs as an indication for latent myeloproliferative disorder has not yet been elucidated. De Stefano et al reported that 3 of 14 patients with EEC developed an overt myeloproliferative disorder. Others have reported a lower incidence of manifest myeloproliferative disorders after long-term follow-up of patients with PVT.[6] Second, De Stefano et al describe the combined prevalence of myeloproliferative disorders in patients with different diseases (BCS, PVT, and mesenteric vein thrombosis). We did not study patients with isolated mesenteric vein thrombosis. Third, the presented review in which 78% of BCS patients and 48% of PVT patients exhibit a latent or overt myeloproliferative disorder results from data pooling of small-scale studies and early anecdotal reports of highly selected cases.[7] The expected publication bias of the reports collected in this review paper is exemplified by successive studies from the group of Valla who initially reported latent or overt myeloproliferative disorders in 75% of BCS patients but, after 15 years of follow-up, in 31% of their recently diagnosed patients.[1,8] Fourth, it is likely that the 31 patients exhaustively investigated by De Stefano et al are selected patients who were referred to a specialized hematology unit. It would be interesting to know the prevalence of, for example, liver cirrhosis and pancreatitis in the PVT population studied. In our opinion, the population studied by De Stefano et al is incomparable to our wider recruited population, for which we attempted to minimize patient selection.[9] Therefore, comparison of rates of acquired and/or inherited prothrombotic risk factors between their and our population does not seem appropriate.

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References

1. Valla D, Casadevall N, Lacombe C, et al. Primary myeloproliferative disorder and hepatic vein thrombosis: a prospective study of erythroid colony formation in vitro in 20 patients with Budd-Chiari syndrome. Ann Intern Med. 1985;103:329-334.
2. Valla D, Casadevall N, Huisse MG, et al. Etiology of portal vein thrombosis in adults: a prospective evaluation of primary myeloproliferative disorders. Gastroenterol. 1988;94:1063-1069.
3. Pearson TC, Messinezy M. The diagnostic criteria of polycythemia rubra vera. Leuk Lymphoma. 1996;22(suppl 1):87-94.
4. Murphy S, Peterson P, Iland H, et al. Experience of the Polycythemia Vera Study Group with essential thrombocythemia: a final report on diagnostic criteria, survival and leukemic transition by treatment. Semin Hematol. 1997;34:29-39.
5. Michiels JJ. Diagnostic criteria of the myeloproliferative disorders (MPD): essential thrombocythaemia, polycythaemia vera and chronic megakaryocytic granulocytic metaplasia. Neth J Med. 1997;51:57-64.
6. Cardin F, Graffeo M, McCormick PA, McIntyre N, Burroughs A. Adult "idiopathic" extrahepatic venous thrombosis: importance of putative "latent" myeloproliferative disorders and comparison with cases with known etiology. Dig Dis Sci. 1992;37:335-339.
7. De Stefano V, Teofili L, Leone G, Michiels JJ. Spontaneous erythroid colony formation as the clue to an underlying myeloproliferative disorder in patients with Budd-Chiari syndrome or portal vein thrombosis. Semin Thromb Hemost. 1997;67:297-301.
8. Denninger MH, Chait Y, Casadevall N, et al. Cause of portal or hepatic venous thrombosis in adults: the role of multiple concurrent factors. Hepatology. 2000; 31:587-591.
9. Janssen HL, Meinardi JR, Vleggaar FP, et al. Factor V leiden mutation, prothrombin gene mutation, and deficiencies in coagulation inhibitors associated with Budd-Chiari syndrome and portal vein thrombosis: results of a case-control study. Blood. 2000;96:2364-2368.

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