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.[4] Erythroblasts with peripheral chromatin condensation are sufficiently characteristic for a provisional diagnosis of B 19 infection to be made on the histology[5] 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.[6]

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 exapanded 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?

Gianmaria Sitar, Carlo L. Balduini,* Luigi Manenti,* Alessandro Castello,° Dario Balanzin,* Edoardo Ascari**

**Institute of Internal Medicine and Oncology and °Institute of Pathology, University of Pavia, IRCCS Policlinico S. Matteo, Pavia, Italy*

Key words

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Correspondence

Gianmaria Sitar, MD, Istituto di Medicina Interna e Oncologia Medica, IRCCS Policlinico S. Matteo, 27100 Pavia, Italy. Phone: international +39-0382-502567 – Fax: international + 39-0382-526223.

References

1. Brown KE, Young NS, Lin JM. Molecular, cellular and clinical aspects of parvovirus B19 infection. Crit Rev Oncol Hematol 1994; 16:1-31.
2. Dimitrov DS, Blumenthal R. Photoinactivation and kinetics of membrane fusion mediated by the human immunodeficiency virus type 1 envelope glycoprotein. J Virol 1994; 68:1956-61.
3. Gentilomi G, Zerbini M, Musiani M. In situ detection of B19 DNA in bone marrow of immunodeficient patients using a digoxigenin-labelled probe. Mol Cell Probes 1993; 7:19-24.
4. Atkinson J, Hrisinko MA, Weil SC. Erythroleukemia: a review of 15 cases meeting 1985 FAB criteria and survey of the literature. Blood Rev 1993; 6:204-14.
5. Kurtzman GJ, Ozawa K, Cohen BJ, Hanson G, Oseas R, Young NS. Chronic bone marrow failure due to persistent B19 parvovirus infection. N Engl J Med 1987; 317:287-94.
6. Heegaard ED, Myhre J, Hornsleth A, Gundestrup M, Boye H. Parvovirus B19 infections in patients with chronic anemia. Haematologica 1997; 82:402-5.

Pulmonary thromboembolism in thalassemia intermedia patients

Sir,

We[1] and others[2] 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.[2] However, TI also predisposes to thrombotic events, similar to the life-long hypercoagulable state that exists in TM patients.[2,3] 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

Table 1. Clinical details of the patients.

	Patient #1	*Patient #2*
Age (years)/Sex	51/Female	46/Female
Genotype	IVS1nt6/?	β039/αααα
Splenectomy	yes	yes
Cholecystectomy	yes	yes
Chelation therapy	no	irregularly
Blood transfusions	rare	rare
Hb (g/dL)	9.0	8.0
WBC (x10^9/L)(% normoblasts)	90.0 (90%)	22.9 (63%)
Platelets (x10^9/L)	650	580
PO_2 (mm Hg)	59	66
PCO_2 (mm Hg)	38	35
Ventilation/Perfusion scan		
Ventilation	normal	normal
Perfusion	4 segmental defects	bilateral lower lobe defects
Abdominal ultrasound	normal	normal
Other imaging studies	doppler of legs normal	venography normal

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

	Normal values	*Patient #1*	*Patient #2*
Antithrombin III activity	84-112%	100%	102%
Protein C activity	60-160%	70%	74%
Free protein S Antigen	74-126%	78%	80%
APC-resistance (ratio)	> 2.0	2.2	2.4
Factor V Leiden mutation	negative	ND	negative
Anticardiolipin Ab	negative	negative	negative

ND, not done.

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.[4] 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.[5]

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,[6,7] as demonstrated by the ability of thalassemic erythrocytes to support the prothrombinase complex generating thrombin.[7,8] It is interesting to note that the highest rates of thrombin generation were found in TI erythrocytes.[6] This was attributed to the lack of dilution of pathologic erythrocytes by normal transfused erythrocytes as occurred in TM patients.[6] 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.[9] Flow cytometry has also demonstrated the presence of a similar magnitude of circulating activated platelets in TI patients to that observed in TM patients.[10]

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.[2] 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.

Shmuel Gillis, Maria Domenica Cappellini, Ada Goldfarb, Laura Ciceri, Gemino Fiorelli, Eliezer A. Rachmilewitz

Department of Hematology, Hadassah University Hospital, Jerusalem, Israel, and the Hereditary Anemia Center, Maggiore Hospital IRCCS, University of Milan, Italy

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Correspondence

S. Gillis, M.D., Department of Hematology, Hadassah University Hospital, Ein Kerem, PO Box 12,000, Jerusalem, Israel 91120. Phone: international +972-2-6776744 – Fax: international +972-2-6423067 – E-mail: sgillis@md2.huji.ac.il

References

1. Michaeli J, Mittelman M, Grisaru D, Rachmilewitz EA. Thromboembolic complications in β-thalassemia major. Acta Haematol 1992; 82:71-4.
2. Pignatti BC, Carnelli V, Caruso V, et al. Thromboembolic events in β-thalassemia major: an Italian multicentre study. Acta Haematol 1998; 99:76-9.
3. Cappellini MD, Coppola R, Bottasso B, et al. Hypercoagulability in patients with thalassemia intermedia. In: Beuzard Y, Lubin B, Rose J, eds. Sickle cell disease and thalassemias: new trends in therapy. Colloque INSERM/John Libbey Eurotext Ldt., 1995; 234:467-8.
4. Sonakul D, Fucharoen S. Pulmonary thromboembolism in thalassemic patients. Southeast Asian J Tropic Med Pub Hlth 1992; 23(Suppl 2):25-8.
5. Grisaru D, Rachmilewitz EA, Mosseri M, et al. Cardiopulmonary assessment in beta-thalassemia major. Chest 1992; 98:1138-42.
6. Borenstain-Ben Yashar V, Barenholz Y, Hy-Am E, Rachmilewitz EA, Eldor A. Phosphatidylserine in the outer leaflet of red blood cells from β-thalassemia patients may explain the chronic hypercoagulable state and thrombotic episodes. Am J Hematol 1993; 44:63-5.
7. Helley D, Eldor A, Girot R, et al. Increased procoagulant activity of red blood cells from patients with homozygous sickle cell disease and β-thalassemia. Thromb Haemost 1996; 76:322-7.
8. Cappellini MD, Coppola R, Robbiolo L, et al. Procoagulant activity of erythrocytes in thalassemia intermedia [abstract]. Blood 1996; 88:(Suppl 1):38a.
9. Eldor A, Lellouche F, Goldfarb A, et al. In vivo platelet activation in β-thalassemia major reflected by increased platelet-thromboxane urinary metabolites. Blood 1991; 77:1749-53.
10. Ruf A, Pick M, Deutsch V, et al. In-vivo platelet activation correlates with red cell anionic phospholipid exposure in patients with β-thalassemia major. Br J Haematol 1997; 98:51-6.