worsening in his general condition, as well as painful hepatomegaly. Analysis showed bilirubin 3.7 mg/dL (normal values up to 1) LDH 638 U/L (normal values up to 460); chest X-ray revealed diffuse alveolar-interstitial infiltrates. The BAL performed ruled out *Pneumocystis carinii*, HSV, RSV, CMV, Legionella, BARR or fungal infection. The echocardiogram showed no abnormalities. Saline restriction measures were taken and diuresis was stimulated but the patient's condition did not improve.

On day +28 he was transferred to the intensive care unit. One day later, adenovirus was isolated in BAL, so i.v ribavirin was administered along with assisted ventilation; 48 hours later the fever disappeared and a marked improvement was observed in breathing and liver function. Total resolution occurred on day +37. The ribavirin dosage administered was 15 mg/Kg every 6 hours for 8 days. A further BAL was carried out on day +46 which was negative for adenovirus. The leukocytic graft reached 1,000 leukocytes with 500 granulocytes on day +29, fell to 200 on day +36 which required G-CSF and remained at < 500 granulocytes up to day +48.

Although adenovirus may remain present in tonsillar and other lymphoid tissue for prolonged periods, if isolated from a BAL done under optimal conditions in which no other pathogens can be found, this can be considered diagnostic of acute adenovirus. To date, the efficacy of intravenous ribavirin has been demonstrated in adenovirus infections such as cystitis,[3-5] nephritis,[6] gastroenteritis,[7] pneumonitis,[8] and disseminated adenovirus infection.[9] The dosage employed by most authors varied between 15 and 30 mg/kg/d divided in three doses. In our case, following Wulffraat *et al.*,[8] we administered a dosage of 15 mg/kg/6 h (a total dosage of 60 mg/kg/d), which led to rapid clinical improvement and clearance of adenovirus infection. This did, however, have a negative affect on the leukocytic graft which, fortunately, was reversible. The hematologic effects of ribavirin have been investigated in Rhesus monkeys. Mild normocytic anemia or severe anemia occurred when ribavirin was administered at dosages of up to 30 or 50 mg/kg/day, respectively; however, no significant effects were observed on white blood cells.[10]

Like other authors, we consider that intravenous ribavirin is an effective treatment for adenovirus infection, but believe it is necessary to determine the exact dosage at which toxic effects are avoided but efficacy is maintained.

Key words

Autologous bone marrow transplantation, adenovirus pneumonitis, ribavirin

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References

1. Shields AF, Hackman RC, Fife KH, Corey L, Meyers JD. Adenovirus infection in patients undergoing bone marrow transplantation. N Engl J Med 1985; 312:529.
2. Wasserman R, August CS, Plotkin SA. Viral infections in pediatric bone marrow transplant patients. Pediatr Infect Dis J 1988; 7:109.
3. Cassano WF. Intravenous ribavirin therapy for adenovirus cystitis after allogeneic bone marrow transplantation. Bone Marrow Transplant 1991; 7:247.
4. Murphy GF, Wood DP, McRoberts JW, Hensleee-Downey PJ. Adenovirus-associated hemorrhagic cystitis treated with intravenous ribavirin. J Urol 1993; 149:565.
5. Jurado M, Navarro JM, Hernández J, Molina MA, De Pablos JM. Adenovirus associated haemorrhagic cystitis after bone marrow transplantation successfully treated with intravenous ribavirin [letter]. Bone Marrow Transplant 1995; 15:651.
6. Liles WC, Cushing H, Holt S, Bryan C, Hackman RC. Severe adenoviral nephritis following bone marrow transplantation: successful treatment with intravenous ribavirin. Bone Marrow Transplant 1993; 12:409.
7. Kapelushnik J, Or R, Delukina M, Nagler A, Livni N, Engelhard D. Intravenous ribavirin therapy for adenovirus gastroenteritis after bone marrow transplantation. J Pediatr Gastroenterol Nutr 1995; 21:110.
8. Wulffraat N, Geelen S, van Dijken P, Graeff-Meeder B, Kuis W, Boven K. Recovery from adenovirus pneumonia in a severe combined immunodeficiency patient treated with intravenous ribavirin [letter]. Transplantation 1995; 59:927.
9. Mc Carthy AJ, Bergin M, De Silva LM, Stevens M. Intravenous ribavirin therapy for disseminated adenovirus infection. Pediatr Infect Dis J 1995; 14:1003-4.
10. Canonico PG, Kastello MD, Cosgriff TM, et al. Hematological and bone marrow effects of ribavirin in Rhesus monkeys. Toxicol Appl Pharmacol 1984; 74:163.

Portal and mesenteric venous thrombosis in a patient heterozygous for the 20210 A allele of the prothrombin gene

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We give the first description of portal and mesenteric venous thrombosis associated with the 20210 A allele of the prothrombin gene in a 48-year-old woman after splenectomy.

Recently, the 20210 A mutation of the prothrombin gene has been described in patients who have had venous thromboses in unusual sites, such as the superior sagittal sinus and in the Budd-Chiari syndrome.[1,2] Mesenteric thrombosis in patients with idiopathic thrombocytopenic purpura (ITP) undergoing splenectomy is uncommon. The usually transient post-splenectomy thrombocytosis has a not well defined effect on the development of thromboembolism.

However, this condition can be a predisposing risk factor for thrombosis in chronic myeloproliferative disorders and hemolytic anemias.[3] Moreover, genetic abnormalities such as inherited deficiencies of antithrombin III, protein C and protein S and factor V Leiden, have been associated with portal thrombosis.[4,5] To our knowledge we give the first description of a patient with venous portal and mesenteric thrombosis who is heterozygous for the 20210 A allele of the prothrombin gene.

A forty-eight year old woman was admitted to our hospital on May 19, 1997, complaining of diffuse abdominal pain for ten days, and fever for two days prior to admission. She had no history of thrombotic events. The patient had been diagnosed in June 1996 as having ITP. She was refractory to steroids so she had undergone a splenectomy on April 23, 1997 without any acute complications.

The patient was conscious when admitted to hospital. Her temperature was 37°C and blood pressure was 130/80 mmHg. Lungs and heart were normal. Abdominal examination revealed no remarkable abnormalities. Routine laboratory findings were normal, except for an increased platelet count (838,000/mm^3). Ultrasonography of the upper and lower abdomen showed an abnormal liquid collection (about 150 mL) in a perivesical location and the pouch of Douglas. A computed tomography scan showed abnormal hypodensity of the superior mesenteric vein with no contrast filling of mesenteric and portal vein districts. An arteriography was also performed which revealed mild stenosis of the superior mesenteric artery, 2-3 centimeters from its origin with no contrast filling of the mesenteric vein. Furthermore, there was an apparent lack of contrast filling in the superior portal vein, supporting the possibility of another thrombus in this location.

The patient started anticoagulation therapy with non-fractionated heparin; her symptoms improved. Ten days after, an echo Doppler scan showed partial recovery of portal vein patency. The patient was discharged with optimal INR levels.

Factor V Leiden or deficiencies of antithrombin III, protein C or protein S were excluded. Antiphospholipid antibodies and lupus like anticoagulant were not observed. Analysis of the prothrombin gene was performed as described elsewhere,[6] showing the presence of heterozygosity for the 20210 A mutation. This is the first reported clinical observation of a patient with portal and mesenteric venous thrombosis associated with a 20210 A genotype of the prothrombin gene. The combined presence of two predisposing factors for the development of venous thrombosis (recent surgery and thrombocytosis) could increase thrombin formation which, for a subject with the 20210 A mutation (with higher plasma thrombin levels),[7] could trigger clot formation in unusual locations.

This mutation has been considered as a mild risk factor for venous thrombosis. Its prevalence is about 2% in healthy controls and 6% in unselected consecutive patients with venous thrombosis. However, our case and two recent reports of this mutation being found in patients with venous thrombosis in unusual locations, suggest that the 20210 A allele of the prothrombin gene could have a similar clinical penetrance to other inherited deficiencies. This seems to indicate the need for systematic screening for this mutation, as well as for other thrombosis risk factors in all cases of mesenteric and portal vein thrombosis.

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Key words

Prothrombin 20210 A, portal thrombosis, splenectomy.

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References

1. Bloem BR, van Putten MJAM, v. d. Meer FJM, van Hilten JJ, Bertina RM. Superior sagittal sinus venous thrombosis in a patient heterozygous for the novel 20210 allele of the prothrombin gene. Thromb Haemostas 1998; 79:235.
2. Bucciarelli P, Franchi F, Alatri A, Bettini P, Moia P. Budd-Chiari syndrome in a patient heterozygous for the G20210A mutation of the prothrombin gene. Thromb Haemostas 1998; 79:445-6.
3. Stewart GW, Amess JAL, Eber SW, et al. Thromboembolic disease after splenectomy for hereditary stomatocytosis. Br J Haematol 1996; 93:303-10.
4. Sas G, Blasko G, Petro I, Griffin JH. A protein S deficient family with portal vein thrombosis. Thromb Haemostas 1985; 54:724.
5. Denninger MH, Helley D, Valla D, Guillin MC. Prospective evaluation of the prevalence of factor V Leiden mutation in portal or hepatic thrombosis. Thromb Haemostas 1997; 78:1297-8.
6. Corral J, Gonzalez-Conejero R, Lozano ML, Rivera J, Heras I, Vicente V. The venous thrombosis risk factor 20210 A allele of the prothrombin gene is not a major risk factor for arterial thrombotic disease. Br J Haematol 1997; 99:304-7.
7. Poort SR, Roosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood 1996; 88:3698-703.