



Hereditary hemorrhagic telangiectasia associated with inherited thrombophilia

Nasledna hemoragijska teleangiektazija udružena sa naslednom trombofilijom

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Abstract

Introduction. Hereditary hemorrhagic telangiectasia and inherited thrombophilia are genetic disorders with quite opposite clinical manifestation. The main characteristic for hereditary hemorrhagic telangiectasia is recurrent bleeding, while the main characteristic for hereditary thrombophilia is thrombosis. The association between hereditary hemorrhagic telangiectasia and inherited thrombophilia in the same patient is rare. **Case report.** We presented a 32-year-old female with recurrent gastrointestinal hemorrhage and epistaxes, during a 9-year period. Hereditary hemorrhagic telangiectasia was established according to “Curaçao” criteria. Three of four criteria have been present: spontaneous recurrent epistaxis, multiple telangiectasias (nose) and visceral lesions (gastric angiodysplasias, jejunal telangiectasias, arterio-venous jejunal fistula). Pulmonary thromboembolism was the first manifestation of thrombophilia; the diagnosis was confirmed by genetic testing. Therapy of hemorrhage with tranexamic acid (anti-fibrinolytic agent; its use increases risk of thrombosis) was unsuccessful. Remission was achieved by thalidomide. The initial therapy for pulmonary thromboembolism included aspirin (that have an increased risk of bleeding), but aspirin had to be discontinued because of massive hematemesis. Unfortunately, a year later, anticoagulant therapy combined with the proton pump inhibitors, were introduced, because of a new thrombosis. One month after, the patient was still on this therapy, without new episodes of bleeding and thromboembolic events. **Conclusion.** Hereditary hemorrhagic telangiectasia and inherited thrombophilia could be unrecognized for years, partly due to the lower degree of clinical suspicion. Early diagnosis and the appropriate choice of therapy are essential for reducing serious consequences and to improve quality of life.

Key words:
telangiectasia, hereditary hemorrhagic; thrombophilia;
comorbidity; diagnosis; treatment outcome.

Apstrakt

Uvod. Nasledna hemoragijska teleangiektazija i nasledna trombofilija su genetski poremećaji sa potpuno suprotnim kliničkim manifestacijama. Glavna karakteristika nasledne hemoragijske teleangiektazije su ponavljana krvarenja, a glavna karakteristika nasledne trombofilije je tromboza. Udruženost oba poremećaja kod istog bolesnika retko se sreće. **Prikaz bolesnika.** Prikazali smo bolesnicu staru 32 godine, koja je tokom devet godina imala ponavljana gastrointestinalna krvarenja i epistakse. Dijagnoza nasledne hemoragijske teleangiektazije postavljena je prema „Curaçao“ kriterijumima. Kod bolesnice su postojala tri, od četiri kriterijuma: spontane, ponavljane epistakse, multiple teleangiektazije (u nosu) i visceralne lezije (angiodisplastične promene u želucu, teleangiektazije i arterio-venska fistula u jejunumu). Prva manifestacija trombofilije bila je plućna tromboembolija, a dijagnoza je potvrđena genetskim testiranjem. Jednomesečna terapija krvarenja traneksamičnom kiselinom (anti-fibrinolitički agens čije korišćenje povećava rizik od tromboze) bila je neuspešna, pa je remisija postignuta talidomidom. Plućna tromboembolija inicijalno je lečena aspirinom (koji je lek sa povišenim rizikom od krvarenja), ali lečenje je prekinuto zbog masivne hematemeze. Godinu dana kasnije, zbog pojave novih tromboza, započeta je antikoagulantna terapija u kombinaciji sa blokatorima protonске pumpe. Tokom mesec dana terapije nije bilo novih epizoda krvarenja, niti tromboze. **Zaključak.** Nasledna hemoragijska teleangiektazija i nasledna trombofilija mogu biti neprepoznate godinama, delom i zbog toga što se na ove bolesti retko misli. Rana dijagnoza i izbor adekvatne terapije su od ključnog značaja za smanjivanje broja ozbiljnih posledica i poboljšanje kvaliteta života.

Ključne reči:
teleangiektazija, nasledna, hemoragijska; trombofilija;
komorbiditet; dijagnoza; lečenje, ishod.

Introduction

Hereditary hemorrhagic telangiectasia (HHT) or Rendu-Osler-Weber disease is an autosomal dominant disorder of angiogenesis, presented by mucocutaneous and visceral telangiectasias and arteriovenous malformations in the lungs, liver, gastrointestinal tract, spinal cord, and the brain. Visceral arteriovenous malformations may cause serious, and sometimes lifethreatening complications, such as brain abscesses, strokes and hemorrhages¹⁻³. The prevalence for HHT is of 1.5–2.0 /10,000 persons⁴. Clinical diagnosis is based on the “Curaçao” criteria⁵, while genetic testing is indicated in asymptomatic patients with positive family history and in the patients with clinical suspected disease^{6,7}.

Inherited thrombophilia is a genetic disorder caused by the lack of natural inhibitors of coagulation (antithrombin, protein C, protein S), or by gene mutations for factor V Leiden, prothrombin G20210A and methylene tetrahydrofolate reductase C667T^{8,9}. It represents a hypercoagulable state, leading to venous and arterial thrombosis. The most frequent clinical manifestations are deep vein thrombosis and pulmonary embolism^{10,11}.

We presented a patient, suffered from HHT associated with inherited thrombophilia. In the current literature, we found only two similar cases so far^{12,13}.

Case report

A 32-year-old female was admitted to our Clinic for the first time in January 2009, because of recurrent gastrointestinal hemorrhage (melena and hematemesis) and the consequent hypochromic anemia. Her previous medical history included purulent meningitis in 1996 and repeated episodes of epistaxis, bloody stools, hematemesis, metrorrhagia and hematuria, and Henoch Schonlein purpura between 2001 and 2006. Gastroenterological examination performed in 2004 in other institution revealed angiodysplasia in gastric mucosa without the signs of active bleeding. In July 2005, after cessation of pregnancy due to sepsis, the patient had a grand-mall seizure, but computed tomography (CT) brain scan was normal. On admission, the patient was pale, with normal coagulation status, but with low levels of hemoglobin [61 g/L – the normal range (NR) is 120–160 g/L], mean corpuscular volume – MCV [67 fL, NR 80–100 fL], serum iron (5 µmol/L, NR 9–30.4 µmol/L), and ferritin (31 µg/L, NR 50–200 µg/L). During the one month hospitalization, the patient had seven episodes of melena, hematemesis and epistaxis, resulted in severe hypochromic anemia (hemoglobin 60 g/L), which required blood transfusions. Frequently, gastrointestinal hemorrhage was followed by the grand-mall seizure. Gastric angiodysplasia without active bleeding was found by repeated endoscopy, and it was treated by argon plasma coagulation. Thoracic and brain CT, as well as abdominal ultrasound, gynecological and otorhinolaryngological examination were all normal. The patient was discharged in stable condition and recommended therapy included proton pump inhibitors and iron preparations.

The next hospitalization followed a week after discharge, due to abundant hematemesis, which was repeated seven

times in the hospital. Abdominal CT angiography revealed arteriovenous fistula between the I and II jejunal arteries and the I and II jejunal vein, in the jejunal wall distal to the ligament Treitz (Figure 1). The patient underwent jejunal resection in length of 70 cm and jejunojejunal anastomosis. Upon discharge, the patient continued to take proton pump inhibitors and iron preparations. In the following 16 months the patient had two episodes of appearance of blood in the stool lasting for 7 days each.

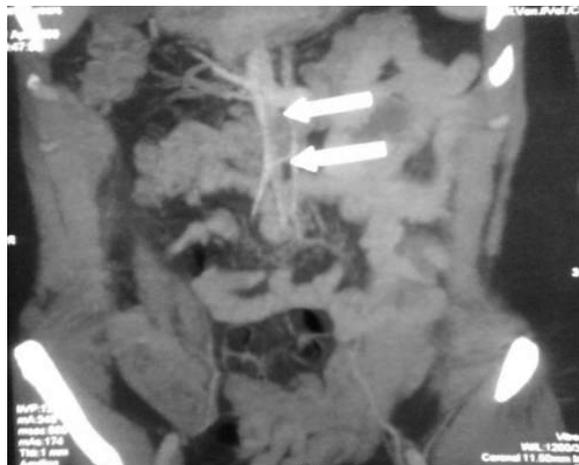


Fig. 1 – Abdominal computed tomography (CT) angiography: arteriovenous fistula between the I and II jejunal arteries and the I and II jejunal vein.

In September 2010 the patient was readmitted to our Clinic because of hematemesis and severe hypochromic anemia (hemoglobin 65 g/L). No sign of bleeding was found endoscopically, but selective angiography of visceral abdominal blood vessels revealed the presence of multiple telangiectatic lesions in jejunal mucosa (Figure 2). Pulmonary and brain arteriovenous malformations were excluded by thoracic CT, cerebral magnetic resonance imaging (MRI) and cerebral angiography. The patient was considered to have HHT, and was commenced on tranexamic acid at a daily dose of 3 g. Bleeding tendency was not decreased and the therapy was discontinued after one month. After that, thalidomide therapy was initiated (100 mg twice daily), which stopped bleeding. The patient continued with the same therapy after discharge, but unfortunately not regularly.

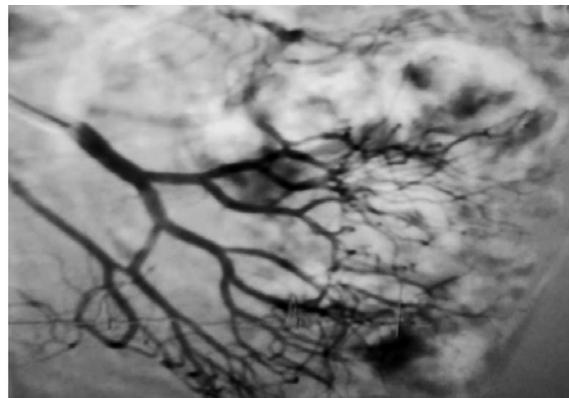


Fig. 2 – Selective angiography of visceral abdominal blood vessels: multiple telangiectatic lesions in jejunal mucosa.

In November 2011 the patient was hospitalized again because of hematemesis, anemia (hemoglobin 60 g/L), and diminished breath sounds over the right lung base. CT angiography of the chest diagnosed pulmonary thromboembolism (Figure 3). DNA analysis confirmed the diagnosis of hereditary thrombophilia. The patient was found to be a homozygous carrier for methylene tetrahydrofolate reductase C667T gene mutation. In spite of bleeding tendency, we started with antiplatelet therapy after discharge with aspirin (100 mg twice weekly) and thalidomide 100 mg daily.

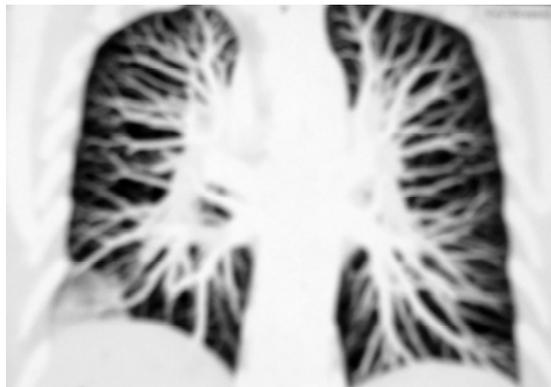


Fig. 3 – Computed tomography (CT) angiography of the chest: pulmonary thromboembolism.

In the next twenty months there were no episodes of bleeding. However, the patient stopped taking thalidomide therapy, which resulted in gastrointestinal hemorrhage and epistaxis, 1.5 months after the cessation of the therapy. This was the reason for new hospitalization in July 2013. During that hospitalization, the patient had hematemesis and melena every two or three days. External carotid angiography revealed numerous telangiectasia in the posterior part of the middle concha and in the nasopharynx (Figure 4).



Fig. 4 – External carotid angiography: numerous telangiectasia in the posterior part of the middle concha and in the nasopharynx.

A low hemoglobin level (60 g/L) was the only biochemical disturbances. Clinical course was complicated with biliary colic and cholecystectomy was necessary. The initial therapy included aspirin and thalidomide, but aspirin had to be discontinued after one month because of massive hematemesis. After discharge,

the patient had an episode of hematemesis (2014) with hemoglobin level of 82 g/L and an episode of epistaxis (March 2015). The patient was admitted to the hospital in March 2015 because of neck pain. Color duplex scan of the neck blood vessels detected thrombosis of external jugular veins bilaterally. Lung scanning showed small perfusion scan defects, possibly due to pulmonary thromboembolism. It was decided to start anticoagulant therapy (dabigatran etexilate tbl, 110 mg/12 h), combined with the proton pump inhibitors. One month after, in April 2015, the patient was still on this therapy, without new episodes of bleeding and thromboembolic events.

Discussion

Hereditary thrombophilia and HHT are disorders with quite different clinical manifestation. The main characteristic for HHT is recurrent bleeding, most frequently from the nose and gastrointestinal tract. Epistaxis, from mild to severe, is usually the first manifestation in preschool children, although it may appear later, after thirty years of life. It is present in almost 90% of patients^{1,6,14}. Gastrointestinal hemorrhage with chronic anemia is present in 15–30% of patients with HHT, and frequency increases with age. The first appearance is usually between forty and fifty years of life. The causes of bleeding are mucosal telangiectasias, angiodyplasias, or arteriovenous malformations^{15–18}.

In the presented patient, epistaxis and gastrointestinal bleeding started in her 24-year. Unfortunately, the disease had been unrecognized for almost 9 years. The diagnosis was established according to the “Curaçao” criteria. Three of four criteria were present: spontaneous recurrent epistaxis, multiple telangiectasias (nose), and visceral lesions: gastric angiodyplasias, jejunal telangiectasias, arterio-venous jejunal fistula. Some other authors have reported on a long diagnostic delay in patients with HHT^{19,20}. Interestingly, in the study of Pierucci et al.¹⁹ diagnostic delay was 25.7 years.

Some studies demonstrated that patients with HHT are under “increased risk for both events: bleeding and clotting”. Increased levels of coagulant factors V, VIII, and von Willebrand factor in HHT, result in enhance thrombotic risk in those patients^{21,22}.

We did not find such abnormalities in the presented patient.

The main characteristic for thrombophilia is thrombosis, which may occur in different sites^{23,24}. Some authors pointed on increased risk for deep venous thrombosis and vascular gestational abnormalities in the patients with inherited thrombophilia^{8,25,26}. In light of that, pregnancy loss in the presented patient in her 28, might be a complication due to thrombophilic gene mutation. However, the diagnosis was established 6 years later by finding the signs for pulmonary thromboembolism on chest CT angiography and by genetic testing.

Although patients with HHT may have increased risk for thrombosis, reports on the association between HHT and inherited thrombophilia in the same patient have been rare^{12,13}. There is a dilemma regarding the treatment of these patients, because of the opposite clinical manifestations of both diseases. Tranexamic acid, an antifibrinolytic agent, reduces epistaxis,

and to a lesser extent gastrointestinal bleeding, but caution is needed because of possible thrombotic events^{14, 17, 27, 28}. Wechalekar and Parapia¹³ successfully treated their patient, who had HHT associated with inherited thrombophilia, with tranexamic acid for 3 years. In the presented patient one month therapy with tranexamic acid was unsuccessful. Remission was achieved by thalidomide. In a few recent studies, the use of thalidomide, as inhibitor of angiogenesis, has been recommended for the treatment of gastrointestinal bleeding in HHT^{2, 17}. Another problem in the presented patient was the therapy of pulmonary thromboembolism. Acetylsalicylic acid (aspirin) was stopped after 20 months because of gastrointestinal hemorrhage. A year later, anticoagulant therapy combined with the proton pump inhibitors, was introduced, because of a new thrombosis. We have no other experience with such patients, but the results of the other authors suggest that the “long time anticoagulant therapy in patients with HHT is possible”^{13, 29}. Wechalekar and Parapia¹³ reported the second patient with HHT and predominant thrombosis who was on oral anticoagulant for 5 years, without bleeding or new thrombosis¹³. Bianca et al.¹² suggest that antio-

agulant therapy is indicated in pregnant women with HHT and inherited thrombophilia, but obligatory hematological and clinical monitoring are required.

Conclusion

The association between HHT and inherited thrombophilia is a rare disorder. It could be unrecognized for years, partly due to the lower degree of clinical suspicion. The early diagnosis and appropriate choice of therapy are essential to reduce serious consequences and to improve quality of life.

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R E F E R E N C E S

- Duffau P, Lazarro E, Viillard JF. Hereditary hemorrhagic telangiectasia. *Rev Med Interne* 2014; 35(1): 21–7. (French)
- Kapur KN, Morin JK, Letarte M. Endoglin: A critical mediator of cardiovascular health. *Vasc Health Risk Manag* 2013; 9:195–206.
- Soubrier F, Chung WK, Machado R, Grunig E, Aldred M, Geraci M, et al. Genetics and genomics of pulmonary arterial hypertension. *J Am Coll Cardiol* 2013; 62(25 Suppl): D13–21.
- Grosse SD, Boulet SL, Grant AM, Hulihan MM, Faughnan ME. The use of US health insurance data for surveillance of rare disorders: Hereditary hemorrhagic telangiectasia. *Genet Med* 2014; 16(1): 33–9.
- Shovlin CL, Guttmacher AE, Buscarini E, Faughnan ME, Hyland RH, Westermann CJ, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). *Am J Med Genet* 2000; 91(1): 66–7.
- Gonani FS, Shovlin CL. Hereditary haemorrhagic telangiectasia: A clinical and scientific review. *Eur J Hum Gen* 2009; 17(7): 860–71.
- Botella LM, Albiñana V, Ojeda-Fernandez L, Recio-Poveda L, Bernabèu C. Research on potential biomarkers in hereditary hemorrhagic telangiectasia. *Front Genet* 2015; 6: 115.
- Rambaldi MP, Mecacci F, Guaschino S, Paidas MJ. Inherited and acquired thrombophilias. *Reprod Sci* 2014; 21(2): 167–82.
- Schellong SM. Importance of thrombophilia screening. *Internist (Berl)* 2014; 55(5): 529–30; 532–4, 536. (German)
- Pomero F, Ageno W, Serraino C, Borretta V, Gianni M, Fenoglio L, et al. The role of inherited thrombophilia in patients with isolated pulmonary embolism: A systematic review and a meta-analysis of the literature. *Thromb Res* 2014; 134(1): 84–9.
- Martinelli I, De Stefano V, Mannucci PM. Inherited risk factors for venous thromboembolism. *Nat Rev Cardiol* 2014; 11(3): 140–56.
- Bianca S, Cutuli N, Bianca M, Barrano B, Cataliotti A, Barone C, et al. Hereditary haemorrhagic telangiectasia and genetic thrombophilia. *Eur J Hum Genet* 2010; 18(4): 405–6.
- Wechalekar A, Parapia L. Hereditary haemorrhagic telangiectasia with protein S deficiency in a family: A case report. *Eur J Haematol* 2000; 64(1): 59–60.
- Zarrabietia R, Albiñana V, Salcedo M, Señaris-Gonzalez B, Fernandez-Forcelledo J, Botella L. A review on clinical management and pharmacological therapy on hereditary haemorrhagic telangiectasia (HHT). *Curr Vasc Pharmacol* 2010; 8(4): 473–81.
- Kjeldsen AD, Kjeldsen J. Gastrointestinal bleeding in patients with hereditary hemorrhagic telangiectasia. *Am J Gastroenterol* 2000; 95(2): 415–8.
- Ha M, Kim YJ, Kwon KA, Hahn KB, Kim M, Kim DK, et al. Gastric angiodysplasia in a hereditary hemorrhagic telangiectasia type 2 patient. *World J Gastroenterol* 2012; 18(15): 1840–4.
- Kamath N, Bhatia S, Singh H, Shetty A, Shetty S. Hereditary hemorrhagic telangiectasia. *N Am J Med Sci* 2015; 7(3): 125–8.
- Amanzada A, Töppler GJ, Cameron S, Schwörer H, Ramadori G. A case report of a patient with hereditary hemorrhagic telangiectasia treated successively with thalidomide and bevacizumab. *Case Rep Oncol* 2010; 3(3): 463–70.
- Pierucci P, Lenato GM, Suppressa P, Lastella P, Triggiani V, Valerio R, et al. A long diagnostic delay in patients with hereditary haemorrhagic telangiectasia: A questionnaire-based retrospective study. *Orphanet J Rare Dis* 2012; 7: 33.
- Sabbà C. A rare and misdiagnosed bleeding disorder: Hereditary hemorrhagic telangiectasia. *J Thromb Haemost* 2005; 3(10): 2201–10.
- Shovlin CL. Hereditary haemorrhagic telangiectasia: Pathophysiology, diagnosis and treatment. *Blood Rev* 2010; 24(6): 203–19.
- Dittus C, Streeiff M, Ansell J. Bleeding and clotting in hereditary hemorrhagic telangiectasia. *World J Clin Cases* 2015; 3(4): 330–7.
- Cruz-Amy M, Hunter-Mellado R. Factor V Leiden thrombophilia: presentation of three patients and a literature review. *Bol Asoc Med P R* 2006; 98(3): 213–21.
- Martinelli I, Passamonti SM, Bucciarelli P. Thrombophilic states. *Handb Clin Neurol* 2014; 120: 1061–71.
- Kupfermanc MJ, Eldor A, Steinman N, Many A, Bar-Am A, Jaffa A, et al. Increased frequency of genetic thrombophilia in women with complications of pregnancy. *N Engl J Med* 1999; 340(1): 9–13.

26. *Bleker SM, Coppens M, Middeldorp S.* Sex, thrombosis and inherited thrombophilia. *Blood Rev* 2014; 28(3): 123–33.
27. *Zaffar N, Ravichakaravarthy T, Faughnan ME, Shebata N.* The use of anti-fibrinolytic agents in patients with HHT: A retrospective survey. *Ann Hematol* 2015; 94(1): 145–52.
28. *Gaillard S, Dupuis-Girod S, Boutitie F, Rivière S, Morinière S, Hatron PY, et al.* Tranexamic acid for epistaxis in hereditary hemorrhagic telangiectasia patients: a European cross-over controlled trial in a rare disease. *J Thromb Haemost* 2014; 12(9): 1494–502.
29. *Edwards CP, Shebata N, Faughnan ME.* Hereditary hemorrhagic telangiectasia patients can tolerate anticoagulation. *Ann Hematol* 2012; 91(12): 1959–68.

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