Prikaz slučaja nasljedne hemoragijske telangiektazije s teškom anemijom

Case report of hereditary hemorrhagic telangiectasia with severe anemia

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Sažetak

Nasljedna hemoragijska telangiektazija (engl. *hereditary hemorrhagic telangiectasia*, HHT) ili Osler-Rendu-Weberova bolest genetički je uvjetovana sustavna bolest s autosomno dominantnim načinom nasljeđivanja. Patofiziološki mehanizam uključuje poremećaj na razini kapilara kože i sluznica, ali i kapilarne povezanosti arterija i vena drugih organa. Zbog rijetke pojavnosti ove bolesti često se prava dijagnoza ne postavlja na vrijeme, a zbog organske nespecifičnosti brojni su simptomi koji se često razlikuju u populaciji oboljelih. U ovom je radu prikazan slučaj pedesetdvogodišnje bolesnice koja se dugi niz godina liječila s pogrešnom dijagnozom sideropenične anemije, a nasljedna hemoragijska telangiektazija dijagnosticirana je tek prije sedam godina. Svakodnevna obilna krvarenja iz nosa u bolesnice dovela su do razvoja izrazite sideropenične anemije (vrijednosti koncentracije hemoglobina od 30 g/L i serumskog željeza 1 µmol/L) koja se kao nalaz u HHT rijetko opisuje u literaturi. Kako bi se nadoknadio gubitak krvi te time regulirala anemija, posljednje dvije godine bolesnica mjesečno prima transfuzije deplazmirane krvi. Kako se radi o izrazito progresivnoj bolesti koja traje cijeli život, sustavno smo prikazali razvoj simptoma i komplikacija bolesti, nalaze relevantnih laboratorijskih analiza i slikovnih pretraga te primjenu postupaka liječenja koje su bolesnicu doživotno vezale za učestalo ambulantno liječenje.

Ključne riječi: arteriovenska malformacija, prikaz slučaja, sideropenična anemija, nasljedna hemoragijska telangiektazija

Abstract

Hereditary hemorrhagic telangiectasia, also called Osler-Rendu-Weber disease, is a systemic autosomally dominant inherited disease which affects most small blood vessels of the skin and mucosa. Abnormal communication between arteries and veins is also present in visceral organs. This rare condition is often not duly recognized and, because of its nonspecific symptoms which vary among affected population, it is usually misdiagnosed. This article presents a case of a 52-year-old female patient with an illness that had been misdiagnosed as sideropenic anemia for years; hereditary hemorrhagic telangiectasia was diagnosed only seven years ago. The patient's everyday nosebleeds led to severe iron deficiency anemia (hemoglobin values 30 g/L and serum iron concentration 1 µmol/L) which is rarely associated with HHT. The patient has been given blood transfusions on monthly bases for the last two years in order to restore blood loss and treat anemia. As hereditary hemorrhagic telangiectasia is a progressive lifelong disease, we presented history of the development of symptoms and complications, results of relevant laboratory tests and imaging methods, as well as the therapeutic procedures which made the patient dependent on medical outpatient treatment for life.

Key words: arteriovenous malformation, case report, iron-deficiency anemia, hereditary hemorrhagic telangiectasia

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Uvod

Nasljedna hemoragijska telangiektazija (engl. *hereditary hemorrhagic telangiectasia*, HHT) ili Osler-Rendu-Weberova bolest je autosomno dominantno nasljedna bolest krvožilnog sustava. Najčešće se očituje na razini kapilarnih

Introduction

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Rendu-Weber disease, is an autosomally dominant inherited vascular disorder. The main characteristics of the disease are abnormal capillary connections between

spletova arteriola i vena, ali i na razini komunikacije većih krvnih žila. Poremećaji kapilara očituju se u obliku telangiektazija koje su najizraženije na koži i sluznicama. Telangiektazije su abnormalne komunikacije arterija i vena na kapilarnoj razini koje se očituju kao žarišna proširenja postkapilarnih venula, a koje često rezultiraju krvarenjem kapilarne mreže u međustanični prostor tkiva. Abnormalnosti većih krvnih žila mogu dovesti do po život opasnih arteriovenskih malformacija, najčešće u plućima, jetrima, mozgu i probavnom sustavu (1). Sitne telangiektazije u većini slučajeva predstavljaju samo estetski problem, za razliku od arteriovenskih malformacija koje mogu dovesti do kroničnog gubitka krvi, hipoksije i embolije. HHT je prvi puta opisana 1865. godine, a sve do nedavno smatralo se da je pojavnost ove bolesti u populaciji 1:100.000. Noviji podatci pokazuju da je pojavnost bolesti ipak znatno veća, 1:5000–8000 stanovnika, no zbog općih nespecifičnih simptoma često ostaje neprepoznata (1). Dijagnoza HHT postavlja se prema kriterijima Curacao postavljenim 1999. godine kako bi se olakšao i unaprijedio pristup oboljelima od HHT (2). Kriteriji su postavljeni na temelju četiri glavna klinička entiteta: spontane ponavljajuće epistakse (krvarenje iz nosa), mukokutane telangiektazije (poremećaji povezanosti krvnih žila na razini kapilara koji su najizraženiji u koži i sluznicama), visceralne arteriovenske malformacije (poremećaj komunikacije većih arterija i vena jetara, pluća, probavnog sustava i mozga) i postojanje bolesti kod srodnika po prvoj liniji koji upućuje na autosomno dominantno nasljeđivanje. Definitivna dijagnoza za HHT postavlja se u slučaju prisutnosti tri od četiri opisana kriterija, sumnja na HHT u slučaju potvrđivanja dva kriterija, te mala vjerojatnost za postojanje HHT ukoliko postoje manje od dva kriterija (2).

Mehanizam nastanka poremećaja krvnih žila razjašnjen je otkrićem dvaju gena uključenih u angiogenezu. Transkripti tih gena su proteini uključeni u popravak i obnavljanje oštećenja krvnih žila koja nastaju kao posljedica pojačanog protoka krvi, nastajanja tromba, lokalnih upalnih procesa i sličnih procesa. Prva opisana mutacija pronađena je na 9. kromosomu u genu za endoglin (gen *ENG*) (3). Drugi gen povezan s nastankom HHT je gen za aktivin-receptoru sličnu kinazu 1 (gen *ACVRL1*) smješten na 12. kromosomu (4). S obzirom na zahvaćeni gen, HHT se dijeli u dva podtipa, HHT1 u slučaju mutacije gena za endoglin i HHT2 kod mutacije gena za aktivin-receptoru sličnu kinazu 1. Rezultati novijih studija upućuju na povezanost mutacije još dva gena s nastankom HHT, gena *MADH4* čija je mutacija povezana sa združenim sindromom mladenačke polipoze i HHT te još neidentificirani gen HHT3 na 5. kromosomu (5).

S obzirom na nespecifične simptome te nekarakterističnu kliničku sliku blažih oblika bolesti, HHT se često pogrješno dijagnosticira kao, primjerice, sideropenična anemija ili idiopatska telangiektazija koje se pojavljuju mnogo češ-

arterioles and venules of the skin and mucosa which present as telangiectases. Telangiectases are abnormal arteriovenous communications of capillary origin also described as focal dilatations of postcapillary venules which often cause small capillary bleedings. Apart from small blood vessels, abnormalities can also affect communication between larger arteries and veins, which can lead to life threatening arteriovenous malformations. These malformations can be found in the lungs, liver, brain and digestive system (1). Small telangiectases represent mainly cosmetic problem as opposed to arteriovenous malformations which can cause severe blood loss, hypoxemia and embolism. HHT was first described in 1865 and until recently it was considered an extremely rare disease with incidence of 1 in 100,000. However, new studies show that HHT incidence is more frequent and estimated at 1 in 5,000–8,000. The main reason for misdiagnosis is its wide variety of symptoms (1). Diagnosis of HHT is based on four main clinical features called Curacao criteria which were established in 1999 to improve and facilitate admission of individuals with HHT (2). These features are as follows: spontaneous recurrent epistaxis (nosebleeds), mucocutaneous telangiectases (abnormal capillary connections that mostly appear on the skin and mucosa), visceral arteriovenous malformations (inadequate connection between arteries and veins in the liver, lungs, digestive system and brain) and an affected first degree relative as indication of autosomal dominant inheritance. Definite diagnosis of HHT is made if three of the four mentioned criteria are present. HHT can be suspected if there are two positive criteria and, in case that only one criteria is present, HHT is considered to be unlikely (2).

The occurrence of blood vessel disorder is linked to two recently identified genes involved in angiogenesis. Protein transcripts of these genes participate significantly in recovery and regeneration process of impaired blood vessels which arise as a result of increased blood circulation, formation of thrombus, local inflammations and similar processes. The first described mutation was established on chromosome 9 in gene encoding for endoglin (*ENG* gene) (3). The second gene linked to HHT is located on chromosome 12 and identified as gene for activin-receptor-like kinase 1 (*ACVRL1* gene) (4). According to affected gene, HHT is divided into two clinically indistinguishable forms: HHT1 caused by mutations in *ENG* gene and HHT2 in case of mutations in *ACVRL1* gene. Results of newer studies indicate two additional genes associated with HHT, *MADH4* gene, mutated in a combined syndrome of juvenile polyposis and HHT, and an unidentified HHT3 gene related to chromosome 5 (5).

Considering great variety of symptoms and clinical manifestations especially in less serious cases, HHT is often misdiagnosed for one of more common diseases like iron deficiency anemia or idiopathic telangiectasia (6). Since

će (6). Kako u Republici Hrvatskoj još ne postoji mogućnost analize genskih mutacija karakterističnih za ovu bolest, izrazito je važno prepoznati pojedinačne simptome i povezati ih u jedinstveni klinički oblik HHT. Pogrješna dijagnoza odgađa primjerenu terapiju, a s obzirom na progresivni tijek bolesti, povećava vjerojatnost pojave kroničnih komplikacija koje mogu ostati neprepoznate do uznapredovanih stadija.

U radu je prikazan slučaj bolesnice kojoj je dijagnosticirana HHT nakon što je desetak godina bezuspješno liječena prema pogrješnoj dijagnozi. Cilj je prikaza ukazati ne samo na postojanje ove rijetke i kronične bolesti već i na brojne komplikacije kojima je popraćena, te na ispravno tumačenje karakterističnih laboratorijskih nalaza.

Prikaz bolesnice

Bolesnica ženskog spola, rođena 1955. godine liječi se u Hematološkoj poliklinickoj službi Klinike za unutrašnje bolesti Kliničkoga bolničkog centra Rijeka s dijagnozom nasljedne hemoragijske telangiektazije (Osler-Rendu-Weberove bolesti). Fizikalni pregled otkriva pokazatelje teške anemije: opću sliku slabosti i malaksalosti, krhku i rijetku kosu, izrazito bljedilo kože i sluznica. Prisutne su mjestimične telangiektazije, najizraženije u području usta i nosa. Bolesnica svakodnevno ima obilna krvarenja iz nosa, a nerijetko se javlja i krvarenje iz ždrijela. Bolesnica je izrazito mršava te je razvidan stalan polagani gubitak tjelesne mase.

Prilikom redovitog dolaska u ambulantu vrijednosti koncentracije hemoglobina kreću se od 26 g/L do 60 g/L, a broj eritrocita oko $2{,}5 \times 10^{12}$/L, hematokrit 0,210 L/L, a MCV (engl. *mean corpuscular volume*) 75 fL. Nakon transfuzije krvi hemoglobin poraste najviše do 90 g/L, a broj eritrocita do $3{,}1 \times 10^{12}$/L. Zbog čestih transfuzija, RDW (engl. *red blood cell distribution width*) zadržava vrijednosti oko 20%, što pokazuje izrazitu anizocitozu kao odraz različitih eritrocitnih populacija. Iako oralne i intravenske preparate željeza bolesnica prima redovito, koncentracija serumskog željeza uvijek se kreće oko 1 µmol/L i praćena je povišenim vrijednostima nezasićenog kapaciteta vezivanja željeza u krvnoj plazmi (UIBC) (60 µmol/L), normalnim vrijednostima ukupnog kapaciteta vezivanja željeza u krvnoj plazmi (TIBC) (61 µmol/L), te koncentracijom feritina oko donje granice referentnog intervala (10 µg/L).

Od 2005. godine do danas bolesnica mjesečno regulira anemiju transfuzijama deplazmirane krvi uz prethodnu pripremu kortikosteroidima koji suprimiraju moguću imunološku reakciju primatelja na antigene iz krvi darivatelja. Preparate ljudskog rekombinantnog eritropoetina i željeza te antagoniste H2-receptora za zaštitu želučane sluznice kao i multivitaminske koktele bolesnica prima prema potrebi uz obvezno mirovanje i redovite kontrole.

specific genetic testing is not available in Croatia, it is of great importance to recognize individual symptoms and associate them into the unique clinical entity of HHT. Wrong diagnosis postpones appropriate therapeutic measures and, regarding the progressiveness of HHT, increases the possibility of chronic complications which can remain unrecognized till advanced stages of the disease.

This report describes a case of a female patient who has been diagnosed with HHT after she was unsuccessfully treated with misdiagnosis for approximately ten years. Major goal of this case report was not only to remind readers of this rare chronic disease but also to point out many complications that may accompany it, and describe how to correctly interpret laboratory test results.

Case report

A female patient, born in 1955, has been treated for hereditary hemorrhagic telangiectasia (Osler-Rendu-Weber disease) in the Outpatient Division of Hematology, Department of Internal Medicine, Rijeka Clinical Hospital Center. Physical examination revealed signs of severe anemia: fatigue and weariness, weak and sparse hair, extremely pale skin and mucosa. Capillary telangiectases were also present, mostly on lips and nose. The patient suffered from massive nosebleeds on daily basis and also on few occasions from bleedings in the larynx. The patient was very slim and case history revealed slow but constant body weight loss.

When she presented for her regular follow-up in the outpatient clinic, her hemoglobin levels varied between 26 g/L and 60 g/L, erythrocyte count was around 2.5×10^{12}/L, hematocrit 0.210 L/L and MCV (*mean corpuscular volume*) 75 fL. After blood transfusion, hemoglobin levels rose up to 90 g/L at most and erythrocyte count to 3.1×10^{12}/L. Due to frequent blood transfusions, RDW (*red blood cell distribution width*) was around 20%, which indicated significant anisocytosis resulting from the presence of different erythrocyte populations. Although oral and intravenous iron therapy was applied regularly, serum iron concentration was invariably low (1 µmol/L) accompanied by high levels of unsaturated serum iron binding capacity (UIBC) (60 µmol/L), normal total serum iron binding capacity levels (TIBC) (61 µmol/L) and ferritin levels nearing the lower reference interval value (10 µg/L).

Since 2005, the patient has been receiving transfusions of deplasmatized blood monthly with previous corticosteroid treatment which prevents possible immune reaction against donor's blood antigens. When needed, the patient is also given human recombinant erythropoietin and iron therapy as well as multivitamins and histamine H2 receptor antagonist for protection of gastric mucosa, and required to rest and present for regular checkups.

Jedan od kriterija za postavljanje dijagnoze HHT je postojanje bolesti u krvnog srodnika po prvoj liniji. Utvrditi postojanje bolesti kod roditelja nije moguće s obzirom da su preminuli prije postavljanja dijagnoze u bolesnice. Iz obiteljske anamneze doznaje se kako je otac preminuo od tuberkuloze pluća. Majka je bila anemična i često umorna, što može upućivati na anemiju uzrokovanu nasljednom hemoragijskom telangiektazijom. Brat i sestra bolesnice pokazuju simptome slične njezinima, ali u blažem obliku. Za razliku od sestre kod koje nema potrebe za transfuzioloških liječenjem, brat bolesnice povremeno prima transfuzije krvi.

Povijest tijeka bolesti

S obzirom na kasno postavljenu dijagnozu, pojavu simptoma i komplikacija te liječenje, vremenski tijek bolesti može se podijeliti u četiri razdoblja kako je prikazano u tablici 1. Osim nalaza tipičnih za HHT, u bolesnice se tijekom razvoja bolesti i liječenja pojavljuju i nekarakteristični simptomi.

Zbog simptoma anemije bolesnica se prvi puta 1990. godine upućuje u Hematološku poliklиničku službu Klinike za unutrašnje bolesti Kliničkoga bolničkog centra Rijeka. S obzirom na tada učinjene laboratorijske nalaze i status bolesnici je postavljena dijagnoza teške sideropenične anemije te je započeto liječenje preparatima željeza. U oskudnoj medicinskoj dokumentaciji iz tog vremena u anamnezi stoji preboljena tuberkuloza pluća 1986. godine. S dijagnozom sideropenične anemije bolesnica je liječena desetak godina, a nadomjesno liječenje preparatima željeza provođeno je cijelo vrijeme praćenja bolesti i nije znatno popravljalo status željeza i anemiju.

One of the criteria for HHT diagnosis is presence of the disease in first-degree relatives. It was not possible to determine the disease in the patient's parents as they died before she was correctly diagnosed. Family history revealed that the patient's father died of pulmonary tuberculosis. The patient's mother was anemic and often tired, which could indicate anemia caused by hereditary hemorrhagic telangiectasia. The patient's brother and sister show similar symptoms but in a milder form. As opposed to sister who does not need blood transfusions, her brother occasionally receives blood transfusions.

Case history

Regarding late determination of the diagnosis, appearance of symptoms and complications and therapeutic approach, the course of disease could be divided into four time periods as presented in Table 1. During development of the disease and therapy, the patient showed some non-typical signs apart from findings typical for HHT.

Due to symptoms of anemia in 1990, the patient was referred to the Outpatient Division of Hematology, Department of Internal Medicine, Rijeka Clinical Hospital Center. According to performed laboratory tests, the patient was diagnosed with severe iron deficiency anemia and started with iron therapy. In scarce medical documentation and anamnesis from that time, the patient was known to have had tuberculosis in 1986. She was treated and monitored for years with the diagnosis of iron deficiency anemia, and was taking iron substitutes during that period. However, this therapy did not improve iron status or diagnosed anemia.

Tablica 1. Prikaz tijeka bolesti s obzirom na koncentraciju hemoglobina, broj eritrocita, hematokrit, koncentraciju serumskog željeza te transfuzije deplazmirane krvi. Tumačenje znakova: N - vrijednost unutar referentnog intervala, ↓ – snižene vrijednosti s obzirom na referentni interval

Table 1. Disease course overview according to blood hemoglobin concentration, erythrocyte count, hematocrit, serum iron concentration and deplasmatized blood transfusions. Symbol interpretation: N – value within reference interval, ↓ – low value according to reference interval.

Period (years)	Hemoglobin (g/L)	Erythrocyte count	Hematocrit	Serum iron concentration	Deplasmatized blood transfusion
1990-1997	95-110	N	N	↓↓	-
1997-2003	70-100	N	N	↓↓	1 per year
2003-2005	45-95	N	↓	↓↓↓	4 per year
2005-today	25-80	↓↓	↓↓↓	↓↓↓	1 per month

Sedam godina kasnije (1997. godine), kada je bolesnica ponovno detaljno obrađena zbog teške sideropenične anemije, u statusu stoji gubitak tjelesne mase, povremene epistakse, te sve oskudnije menstruacije. Pregled pulmologa upućivao je na inaktivnu tuberkulozu pluća, a nalaz ginekologa bio je uredan. Za razliku od irigografije i rektoskopije koje su pokazale uredan nalaz, ezofagogastroduodenoskopija pokazala je prisutnost dobro ograničenih petehija na više mjesta u želucu. Test prisutnosti okultnog krvarenja u stolici iz tri uzastopna uzorka dao je pozitivan nalaz. U bolesnice su 2000. godine otkriveni polipi glasnica zbog čega je upućena na operacijski zahvat u Klinički bolnički centar Zagreb gdje se, s obzirom na učinjene pretrage tijekom pripreme za zahvat, dijagnoza sideropenične anemije stavlja pod sumnju. Na temelju zadovoljenja kriterija za postavljanje dijagnoze HHT, odnosno Osler-Rendu-Weberove bolesti, bolesnici je utvrđena nova dijagnoza. U razdoblju od 1997. do 2003. godine bolesnica dolazi na redovite kontrolne preglede kada je ispitivana prisutnost okultnog krvarenja koje nije potvrđeno, stanje u probavnom sustavu pratilo se kolonoskopijom i ezofagogastroduodenoskopijom. Slikovne pretrage, osim proširenja petehija sa sluznice želuca na sluznicu dvanaesnika, nisu pokazale promjenu stanja bolesnice niti značajan napredak bolesti tijekom promatranog vremena.

U tom razdoblju bolesti koncentracija hemoglobina kreće se od 70 g/L do 100 g/L uz normalan broj eritrocita (oko $3,5 \times 10^9$/L), relativan postotak retikulocita iznad gornje granice referentnog intervala (3,8%) i snižene vrijednosti MCV, oko 67 fL. Vrijednosti koncentracije željeza u serumu kretale su se od 0,7 µmol/L do 11,3 µmol/L, vrijednosti UIBC bile su povišene uz istovremeno nepromijenjenu vrijednost TIBC. Vrijednosti pokazatelja zgrušavanja i hemostaze su tijekom cijeloga razdoblja praćenja bolesnice bile unutar granica referentnih intervala. Pojedini laboratorijski pokazatelji varirali su ovisno o primljenim preparatima željeza i transfuzijama deplazmirane krvi koje bolesnica u tom razdoblju prima prosječno jednom godišnje.

Sljedeće razdoblje bolesti obilježeno je pogoršanjem općeg stanja organizma. Godine 2003. bolesnica je hospitalizirana na Hematološkom odjelu Klinike za unutrašnje bolesti KBC-a Rijeka. Imala je obilne epistakse koje se pojavljuju svakodnevno. Nakon otpusta iz bolnice ambulantne kontrole postale su učestalije, u prosjeku jednom u tri mjeseca, a pri svakom kontrolnom pregledu bolesnica prima i transfuzije deplazmirane krvi uz prethodnu pripremu kortikosteroidima. U tom su se razdoblju vrijednosti koncentracije hemoglobina kretale od oko 45 g/L po dolasku do oko 95 g/L nakon transfuzije deplazmirane krvi. Broj eritrocita bio je unutar referentnog intervala, ali je vrijednost hematokrita u prosjeku bila niska, oko 0,250 L/L. Vrijednost koncentracije željeza bila je oko 1,5 µmol/L, TIBC se kretao prema gornjoj vrijednosti referentnog intervala, oko 73 µmol/L. U tom se razdoblju pojavljuje

She was again thoroughly examined seven years later. The examination revealed loss of body weight, occasional nosebleeds and fewer menstrual bleedings. Pulmonary examination showed inactive tuberculosis, and gynecological report indicated no abnormalities. As opposed to irigography and rectoscopy findings which were normal, esophagogastroduodenoscopy revealed well restricted petechial bleeding in several parts of the stomach. Test for occult bleeding was positive from three consecutive stool samples. In 2000, she was found to have vocal cord polyps and was referred to the Zagreb Clinical Hospital Center for surgery. During preoperative examination, diagnosis of severe iron deficiency anemia was questioned and shortly afterwards the diagnosis of HHT or Osler-Rendu-Weber disease was made according to diagnostic criteria. In that period (1997 – 2003) the patient presented for her regular follow-ups and was checked for occult bleeding which was negative. The condition of the digestive tract was monitored using colonoscopy and esophagogastroduodenoscopy. However, these imaging tests, apart from expansion of petechial bleeding from stomach to duodenum, did not reveal any changes in the patient's condition or the progress of the disease during that time.

During the period stated above, hemoglobin concentration varied from 70 g/L to 100 g/L and erythrocyte count was normal (about 3.5×10^{12}/L), relative reticulocyte percentage exceeded the upper reference interval limit (3.8%) and MCV was low, around 67 fL. Serum iron concentrations showed values from 0.7 µmol/L to 11.3 µmol/L, UIBC level was high, with a constant TIBC level. Results of laboratory coagulation and hemostasis tests were within reference intervals during the entire period of observation. Some parameters varied depending on iron replacement therapy and deplasmatized blood transfusions which were during that period administered once a year.

The period in the course of disease that followed was marked with severe general status. In 2003 patient was hospitalized at the Division of Hematology, Department of Internal Medicine, Rijeka Clinical Hospital Center. She experienced massive epistaxis on a daily basis. After discharge from hospital, the patient was monitored more often than before, approximately once every three months, and during each checkup she was given deplasmatized blood transfusions after previous corticosteroid treatment. On arrival to the outpatient treatment, the patient's hemoglobin levels were around 45 g/L and around 95 g/L after transfusion of deplasmatized blood. Although erythrocyte count was within the reference interval, hematocrit values were low, usually around 0.250 L/L. Serum iron concentration was around 1.5 µmol/L, TIBC level was near the upper reference interval value, 73 µmol/L. At that time, the patient's ferritin levels were found to be low (7 µg/L). Positive occult blood test indicated bleedi-

nalaz snižene vrijednosti feritina (7 μg/L). Pozitivan test okultnog krvarenja upućuje na krvarenje u probavnom sustavu dok su pretrage zgrušavanja bile i dalje uredne. Bolesnici je također učinjena višeslojna kompjutorizirana tomografija (MSCT) mozga koja je pokazala na malom dijelu patološki promijenjene krvožilne strukture u smislu kapilarnih telangiektazija, što odgovara dijagnozi. MSCT prsnog koša pokazao je ostatke upale, vjerojatno preboljene tuberkuloze pluća. U srednjem režnju desnoga plućnog krila dokazana je poveznica između plućne arterije i vene, tj. arteriovenska malformacija, što je značajka dijagnosticirane HHT.
Značajke posljednjeg razdoblja bolesti (od 2005. godine do danas) izrazito su niske vrijednosti hemoglobina i redovito transfuzijsko liječenje kao što je prethodno opisano.

Rasprava

Rezultat vrlo niske koncentracije hemoglobina u laboratoriju treba uvijek pobuditi dodatnu pažnju prilikom procjene nalaza. Vrijednosti od 26 g/L najprije će pobuditi sumnju u predanalitičku pogrješku, npr. nepravilno vađenje, uzorak razrijeđen infuzijskom otopinom ili postojanje mikrougruška koji je onemogućio ispravnu analizu. Međutim, isključi li se predanalitička pogrješka, osim što se rečene vrijednosti mogu očekivati u bolesnika s obilnim krvarenjem uz akutnu ugroženost životnih funkcija, moguć je takav nalaz i u bolesnika s kroničnim bolestima, upravo kao što je opisani slučaj bolesnice s nasljednom hemoragijskom telangiektazijom.
Ograničenja prikaza ovog slučaja proizlaze iz nedostatne medicinske dokumentacije. S obzirom kako se bolesnica liječila u više zdravstvenih ustanova tijekom dugog niza godina, a medicinska dokumentacija nije sustavno objedinjena, pojedinim nalazima nije moguće ući u trag.
Izrazita anemija, kakva je prisutna kod prikazane bolesnice, nije karakterističan nalaz za HHT te je svega dvadesetak takvih slučajeva dosad zabilježeno u literaturi (7). Anemija se navodi najčešće kao posljedica kroničnog krvarenja u probavni sustav, a rjeđe obilnih epistaksi (7). U prikazane bolesnice epistakse se počinju pojavljivati u kasnijoj životnoj dobi (oko tridesete godine života), što je u 90% slučajeva prva manifestacija HHT koja se uobičajeno pojavljuje oko dvadesete godine života (8). Međutim, krvarenja iz nosa kod bolesnice s godinama postaju obilnija i učestalija te se sada javljaju svakodnevno. Iz povijesti bolesti vidljivo je i jače krvarenje iz ždrijela, a ezofagogastroduodenoskopija kod bolesnice osim petehijalnih krvarenja sluznice želuca i dvanaesnika nikada nije sa sigurnošću dokazala značajnije krvarenje karakteristično za HHT. Iako je test na okultno krvarenje u nekoliko navrata bio pozitivan, bolesnici s obilnim epistaksama često progutaju velike količine krvi koje daju pozitivan test na okultno krvarenje (9). Kronična, po život opasna anemija

ng in digestive tract and coagulation test values were still within normal range. During examination the patient was subjected to imaging tests. Multislice computed tomography (MSCT) of the brain showed restricted areas of vascular pathological structures that could be associated to capillary telangiectases which were consistent with diagnosis. MSCT of the chest revealed inflammation residues, probably pulmonary tuberculosis. The examination also showed a shunt between a branch of the pulmonary artery and pulmonary vein in the right middle lung lobe, which indicated the presence of arteriovenous malformation characteristic for HHT diagnosis.
The features that marked the latest period in the course of disease (since 2005) are extremely low hemoglobin levels and regular deplasmatized blood transfusions as described previously.

Discussion

Low blood hemoglobin concentration should always be considered with great attention when evaluating laboratory test results. Hemoglobin concentration of 26 g/L may well imply a preanalytical error such as incorrect specimen collection, sample dilution with intravenous infusion liquid or the presence of microclots which prevented accurate analysis. However, with the preanalytical error excluded, low hemoglobin concentrations can be expected not only in patients with massive bleeding and acute threat to vital functions but also in patients with chronic diseases like the one described above, i.e. in a patient with hereditary hemorrhagic telangiectasia.
Limitations of this case report arise from scarce medical documentation. As the patient was treated in several medical institutions during a long period and her medical documentation was not complete, some test results could not be traced.
Severe anemia, like the one present in the reported patient, is not a characteristical finding in HHT and until now only 20 similar cases have been reported in literature (7). Anemia is most often the consequence of chronic gastrointestinal bleeding and in some cases of massive epistaxis (7). The reported patient experienced her first epistaxis around the age of 30, somewhat later than specified in the literature which describes epistaxis as a first clinical manifestation of the disease in more than 90% of cases that occurs before the age of 20 (8). However, our patient's nosebleeds became over the years ever more intense and frequent so that nowadays they occur on a daily basis. The case history states bleedings in the larynx on a few occasions, while esophagogastroduodenoscopy, apart from petechial bleeding in the stomach and duodenum, did not reveal with certainty any significant bleeding typical for HHT.

uz izrazito snižene vrijednosti serumskog željeza i feritina kod prikazane bolesnice vjerojatno su posljedica čestih epistaksi. Za razliku od koncentracije željeza i feritina koje su u suglasnosti s literaturnim podatcima, vrijednosti ukupnog kapaciteta vezivanja željeza u plazmi bolesnice nisu povišene kao što bi se moglo očekivati (10). Laboratorijski rezultati pokazatelja zgrušavanja u prikazane bolesnice tijekom čitavog tijeka bolesti ne pokazuju patološke vrijednosti i broj trombocita je normalan, što je suglasno s objavljenim podatcima koji ukazuju kako osobe oboljele od HHT imaju normalnu funkciju trombocita i urednu koagulaciju (11).

Osim pojave kožnih i sluzničkih telangiektazija, bolest uključuje i abnormalne poveznice između većih arterija i vena – arteriovenske malformacije. Organi koji su najčešće pogođeni ovakvim abnormalnostima su pluća, jetra, mozak i probavni sustav (12). Kompjutoriziranom tomografijom prsnog koša u bolesnice dokazana je plućna arteriovenska malformacija, međutim bez izraženih plućnih simptoma. Najčešće visceralne manifestacije bolesti uključuju upravo pojavu plućnih arteriovenskih malformacija (30%). Također se procjenjuje da 60–70% svih plućnih arteriovenskih malformacija nastaje kod oboljelih od HHT (13). Bolesnici su često bez izraženih simptoma, ali pokazuju znakove zaduhe i umora koji mogu biti i posljedica anemije. MSCT prsnog koša u prikazane bolesnice osim arteriovenskih malformacija otkriva i tragove preboljene tuberkuloze pluća. Povezanost tuberkuloze pluća i plućnih arteriovenskih malformacija rijetko se navodi u literaturi, no takvi su slučajevi ipak opisani (14,15). Međutim, postoje opisani slučajevi i pogrješno dijagnosticirane tuberkuloze pluća za koje je kasnije utvrđeno kako se radi o arteriovenskoj malformaciji u bolesnika s HHT (16). Jedna od značajki tuberkuloze jest angiogeneza u upalnom tkivu u svrhu pojačane opskrbe krvlju, a novostvorene krvne žile slabije su kvalitete, što dovodi do nastanka malformacija (14). U slučaju prikazane bolesnice moguće je da je tuberkuloza pluća dodatno potakla stvaranje abnormalnih arteriovenskih poveznica. S druge strane, abnormanosti na razini kapilara, kakve su prisutne u bolesnice, mogu biti podloga za brži razvoj infekcije poput tuberkuloze od kojih bi se inače zdravi organizam uspješno obranio. Slikovnom pretragom kakva je kompjutorizirana tomografija ne može se sa sigurnošću utvrditi vremenski slijed patoloških događanja u plućima.

Kompjutorizirana tomografija mozga bolesnice pokazuje manje vaskularne promjene koje također odgovaraju HHT, no zahvaćenost mozga promjenama karakterističnima za bolest nalazi se u malom (< 10%) postotku bolesnika (17). Vaskularne promjene u mozgu mogu dovesti do akutnih neuroloških komplikacija kao npr. ishemijskog infarkta mozga ili moždanog apscesa. Osim vaskularnih razloga komplikacije nastaju i kao posljedica arteriovenskih poveznica u plućima koje su uzrok slabijeg filtriranja krvi

Although occult blood test showed to be occasionally positive, patients who suffer from heavy epistaxes usually swallow considerably large amounts of blood which can result in positive fecal occult blood testing (9). Chronic, life threatening anemia in the reported patient, with extremely low concentrations of serum iron and ferritin, are probably due to recurrent nosebleeds. Unlike serum iron and ferritin concentrations, which are consistent with published data, total serum iron binding capacity values were not as high as expected (10). Results of laboratory hemostasis tests as well as the thrombocyte count were normal during the whole period of the patient's follow-up. These findings are in accordance with published data which indicate that HHT patients have unimpaired coagulation and normal thrombocyte function (11).

Besides mucocutaneous telangiectases, HHT is also manifested through formation of a direct communication between larger arteries and veins which are called arteriovenous malformations. These arteriovenous malformations mainly occur in the lungs, liver, brain and digestive tract (12). MSCT of the patient's chest detected pulmonary arteriovenous malformation, yet without any pulmonary symptoms. The most common visceral manifestation of HHT is pulmonary arteriovenous malformation (30%). It is also estimated that 60–70% of all pulmonary arteriovenous malformations develop in patients with HHT (13). Patients are often asymptomatic and usually experience only dyspnea and weariness which can also be due to anemia. Besides arteriovenous malformations, MSCT of the chest revealed residues of pulmonary tuberculosis. Association between pulmonary tuberculosis and arteriovenous malformations has been poorly described in literature but some cases have been reported (14,15). There is evidence of some misdiagnosed tuberculosis that was only later discovered to be an arteriovenous malformation within HHT (16). One of the features of tuberculosis is intensive angiogenesis in inflammatory mass occurring in order to increase blood supply. As new blood vessels are of poor quality, they are likely to give rise to arteriovenous malformations (14). In case of the described patient there is a possibility that pulmonary tuberculosis, as an inflammatory process, stimulated the development of arteriovenous malformation. On the other hand, capillary abnormalities which were found in our patient can be the basis for easy onset of infection such as tuberculosis against which an otherwise healthy organism would defend. Imaging procedures like MSCT cannot determine the exact order of pathological events in the lungs.

MSCT of the patient's brain showed minor vascular abnormality, which is consistent with the diagnosis even though cerebral vascular malformations are associated with HHT in low percentage (< 10%) of patients (17). Vascular cerebral abnormalities can lead to acute complications such as ischemic attack or brain abscess. Apart from vas-

na razini kapilara, što pospješuje stvaranje tromba. Dospiju li u sistemsku cirkulaciju, trombi mogu zapriječiti krvne žile vitalnih organa te upravo iz tog razloga, čak i u slučaju najblažih plućnih simptoma, bolesnici mogu podleći akutnim neurološkim komplikacijama (17,18).

Liječenje HHT je simptomatsko s obzirom kako se radi o nasljednoj bolesti. Jedini pravi lijek bila bi genska terapija koja je za sada nedostupna. U liječenju i praćenju tijeka bolesti u razvijenim zdravstvenim sustavima moguća je potpora centara za HHT gdje se provodi i gensko testiranje na mutacije koje su dokazano povezane s bolešću (3-5). Sukladno današnjim mogućnostima liječenje se temelji na zaustavljanju akutnog krvarenja iz nosa te preventivnim mjerama. Nažalost, svi su pristupi liječenu epistaksi najčešće kratkotrajnog učinka. Osim zaustavljanja krvarenja, oboljeli od HHT imaju potrebu za stalnim transfuzijama krvi koje ovise o jačini krvarenja. Opisana bolesnica je od primanja transfuzije krvi jednom godišnje kroz razdoblje od deset godina razvila potrebu za transfuzijom krvi jednom mjesečno uz primjenu ljudskoga rekombinantnog eritropoetina. Oboljeli također obvezno primaju preparate željeza, što ovisi o stupnju sideropenije.

Nasljedna hemoragijska telangiektazija je za bolesnika izrazito iscrpljujuća bolest progresivnog tijeka. Osim samom bolešću, pacijenti su pogođeni i dugotrajnom iscrpljujućom terapijom, stalnim kontrolama, a često i pogrešnom dijagnozom. Prikazom ovog slučaja namjera nam je bila upozoriti na mogućnost relativno rijetkih kroničnih stanja koja znatno utječu na laboratorijske nalaze, a koji mogu među prvim znacima ukazati na postojanje bolesti te potrebu pažljivog postavljanja dijagnoze, posebice sa sindromom anemije čija etiopatogeneza može biti vrlo složena i različita.

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cular causes, complications often arise as a result of arteriovenous shunts in the lungs, the main reason of deficient capillary blood filtration that facilitates formation of a thrombus. When in system circulation, the thrombus can obstruct blood vessels of vital organs and, even in the presence of the mildest pulmonary symptoms, patients can experience acute neurological complications (17,18).

As HHT is a genetic disorder, therapeutic efforts remain symptomatic. The only effective treatment would probably be gene therapy which is presently not available. HHT centers in health systems of developed countries support treatment and monitoring of the disease and also provide genetic testing for mutations that have been proven to be connected with HHT (3-5). According to current possibilities, treatment of the disease is based on the management of acute nasal bleeding and preventive measures. Unfortunately, therapeutic aproaches to nosebleeds are often short-termed. Besides management of epistaxes, HHT patients have constant need for blood transfusions which depend on bleeding intensity. At the beginning of treatment, the reported patient was given blood transfusions once a year and during a ten year period she developed the need for blood transfusions on monthly basis together with human recombinant erythropoietin. HHT patients also take iron substitutes whose dosage depends on the severity of sideropenia.

Hereditary hemorrhagic telangiectasia is a progressive and extremely debilitating disease. Patients are also exhausted by long lasting treatments, constant monitoring and often wrong initial diagnosis. By reporting this case we wanted to draw attention to the possibility of the rare but chronic disorder that can have significant effect on laboratory test results which in that case might be the first sign of the disease. Also, our intention was to remind of the importance of careful diagnosing and medical decision making, particularly in the case of anemia due to its considerable variety and complexity.

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