Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/poamed

Case report

Minimally invasive surgical techniques for hemostasis in Osler–Weber–Rendu disease

Mihail Tuşaliu [a,b], *Viorel Zainea* [a,b], *Cristina-Maria Goanță* [a], *Andreea Sorică* [a,*]

[a] *University of Medicine and Pharmacy ''Carol Davila'', Bucharest, Romania*
[b] *Institute of Phonoaudiology and Functional ENT Surgery ''Prof Dr D. Hociota'', Bucharest, Romania*

ARTICLE INFO

Article history:
Received 9 July 2014
Accepted 17 March 2015
Available online 20 April 2015

Keywords:
HHT disease
Argon plasma coagulation
Epistaxis

ABSTRACT

Introduction: Osler–Weber–Rendu disease, also called ''hereditary hemorrhagic telangiectasia'' (HHT), is an autosomal dominant genetic disorder characterized by the appearance of small disseminated vascular malformations in the skin, mucous membranes and organs (lungs, brain, liver) with repeated bleeding tendency. Most common symptom is epistaxis.

Argon plasma coagulation (APC) is an on-contact electrosurgical monopolar thermal procedure used for achieving hemostasis. The principle of this method consists in transferring energy to a target tissue via plasma, the fourth fundamental state of matter. To achieve coagulation, argon (an inert, non-toxic gas) is delivered through a probe and ionized by a discharge current elective high voltage. Electrical energy is transferred to the tissue through the argon plasma.

Aim: The authors present a clinical case of a HHT where a minimally invasive surgical technique based on APC proved to be effective for controlling repeated bleeding of nasal origin.

Case study: We present the case of P.L. patient, aged 71, from rural environment, presented to the emergency room of our clinic for active bilateral anterior epistaxis. The patient reports a long history of the pathology, starting approximately 23 years ago and characterized by the existence of frequent episodes of recurrent epistaxis.

Results and discussion: Immediate and late postoperative results are presented and compared. The APC proved to be effective both in the short and long term, in increasing bleeding-free interval, and in decreasing the frequency and intensity of episodes of nasal bleeding origin.

Conclusions: The presented clinical case with favorable outcome highlights the role of a modern surgical technology – APC – effective in achieving nose hemostasis. In the presented case, APC has brought many advantages in achieving hemostasis: non-contact coagulation with minimal tissue penetration and destruction, a safe method with minimal complications, decreased risk of perforation.

* *Correspondence to*: University of Medicine and Pharmacy ''Carol Davila'', 1 Mai Bld. 22, District 6, Bucharest 062631, Romania. Tel.: +40 723 003 513.
E-mail address: andreea.sorica@gmail.com (A. Sorică).

http://dx.doi.org/10.1016/j.poamed.2015.03.012

1. Introduction

HHT (hereditary hemorrhagic telangiectasia, hemorrhagic angiomatosis) is a rare hereditary, acquired, autosomal dominant affection[1] characterized by malformations of blood vessels in the skin, mucous membranes and of some organs, such as lungs, liver, brain, with bleeding tendency. Prevalence of HHT in Europe is 1 to 5 000–8 000 inhabitants.[2–5]

Pathophysiological basis of this condition is the defective transforming growth factor β (TGF-β) receptor.[3,6,7] TGF-β is a protein involved in cellular differentiation and proliferation. In the capillary endothelium two receptors – proteins for TGF-β are found: endoglin and activin receptor-like kinase (ALK) type 1.[8] Altered expression of these proteins leads to disturbances in the function of TGF-β that determine changes in angiogenesis and endothelial proliferation and differentiation disorders: degeneration of endothelial cells and synthesis of poor quality connective tissue that causes occurrence of thin-walled blood vessels, dilated capillaries and veins (telangiectasia). In larger vessels these disturbances cause arteriovenous malformations (torturous vessels characterized by the presence of both arterial and venous components).[9]

Diagnosis of HHT is made following the Curaçao criteria (1999):

- nose bleeds – spontaneous and recurrent;
- telangiectasia – with multiple locations (nasal, facial, oral cavity, pharynx, on the fingers);
- visceral lesions (arteriovenous malformations of the lung, brain, liver, gastro-intestinal);
- family history – first degree relative with hereditary telangiectasia.

The positive diagnosis of HHT requires the presence of at least three of these criteria. The meeting of two criteria makes the diagnosis possible.[10]

Most commonly, HHT begins during puberty and adolescence, in the second or third decade of life, but there are cases of onset in childhood.[11] It affects men and women in similar proportions.

Epistaxis is the most common symptom (90%). Nasal bleeding episodes are repetitive, most commonly occur daily, but may have a rare frequency, up to an episode per month.

The severity of epistaxis episodes can be quantified considering blood loss and transfusion requirements during life:

- mild epistaxis – several episodes a week that do not require blood transfusion (third part of cases);
- moderate epistaxis – one or two episodes per day, with a need for transfusions of less than 10 times during lifetime (third part of cases);
- severe epistaxis – episodes lasting longer than 30 min, which require more than 10 times lifetime transfusions (third part of cases).[12]

2. Aim

The authors present a clinical case of a HHT where a minimally invasive surgical technique based on APC proved to be effective for controlling repeated bleeding of nasal origin.

3. Case study

We present the case of P.L. patient, aged 71, from rural environment, presented to the emergency room of our clinic for active bilateral anterior epistaxis. The patient reports along history of the pathology, starting approximately 23 years ago and characterized by the existence of frequent episodes of recurrent epistaxis. Initially, the bleeding had unilateral character, occurring alternately in the nasal fosse and later became bilateral and repeated at an average interval of two weeks.

In terms of family history, the patient describes the presence of repeated bleeding nasal origin of the mother, without being able to specify the exact diagnosis.

Patient medical history includes: hypertension, coronary heart disease, single kidney renal function, osteoporosis, and chronic anemia syndrome. The patient is in treatment for hypertension and was administered over time various iron based supplements to correct anemia syndrome.

Regarding hemostasis maneuvers, they were generally local and consisted of:

- bleeding has stopped spontaneously or by digital nasal compression;
- local treatment of pituitary anesthetic – vasoconstrict or solution;
- bipolar electrocoagulation of bleeding points – one session five years ago, followed by increasing interval between bleedings up to two months.

Ear, nose and throat (ENT) clinical examination and naso-pharyngeal-laryngeal video-fibroscopic exam shows: nasal septum with pituitary diffuse bleeding; multiple telangiectasias on endonasal mucosa, the nasal septum and the inferior and middle nasal concha; hematic clots in the nasal vestibule and nasal bilateral fosse; multiple telangiectasias in the lining of the mouth, palate, tongue and sublingual region. The multiple telangiectasias are found also on the skin of the face, lips and hands of the patient. The patient's skin had a generalized pale appearance (Figs. 1–4).

Biological samples reveal an anemic syndrome: serum iron 35 μg/dL (50–175 μg/dL), erythrocytes $3.02 \times 10^3/\mu L$ ($3.8–5.4 \times 10^3/\mu L$), hemoglobin 9.8 g/dL (12–16 g/dL), hematocrit 29.9% (36%–47%), MCV 99 fL (80–95 fL).

In terms of therapeutic management, the patient received emergency treatment, symptomatic treatment of nasal bleeding origin and a palliative treatment, with destruction of hemorrhagic lesions. In emergency has been performed nasal toilet, clots aspiration, local inspection, bilateral topical application cotton pads soaked in a solution of naphazoline and lidocaine (1%) diluted (1:1) with saline solution, local compression. Hemostatic and antibiotic treatment was administered i.v.

3.1. *Palliative therapy*

Considering the long history of nasal bleeding origin of the patient, which led to the installation of a syndrome of chronic anemic and ineffective long-term hemostasis means other local and general, it was considered appropriate to use a

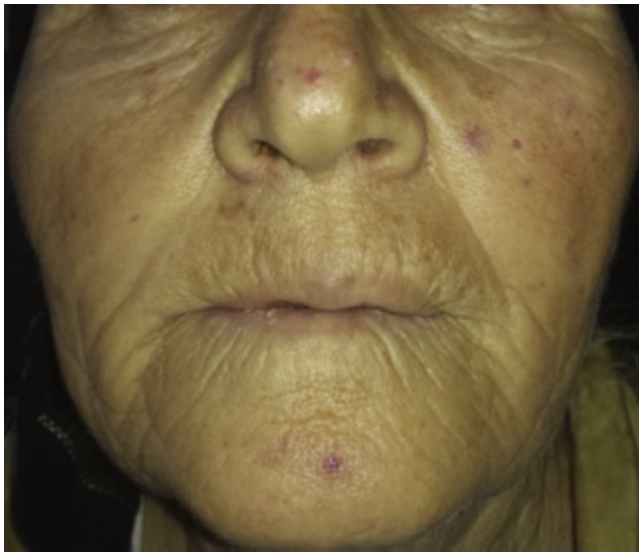

Fig. 1 – Telangiectasia of the face.

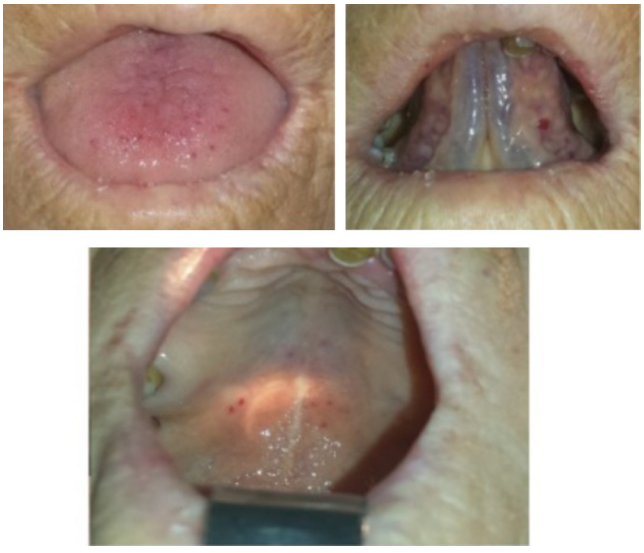

Fig. 2 – Oropharyngeal telangiectasia.

minimally invasive surgical hemostasis technologies based APC. We used argon plasma mucosal nasal septum and inferior nasal turbinates and bilateral average. The surgery was performed under general anesthesia with endotracheal intubation under endoscopic control using optical rod 0° (Fig. 5).

The tip of the probe was conducted close to hemorrhagic areas and maintained throughout the procedure to 2–5 mm.

Argon plasma probe was directed along the pituitary, close to the telangiectasias. The application of argon plasma at the same level on both sides of the nasal septum was avoided, to prevent necrosis by suppressing septal cartilage vascularization. The method has proved useful in achieving hemostasis, and the mucosa was covered with crust of tissue coagulation in the argon plasma application areas. At the end of the procedure nasal packing was not required.

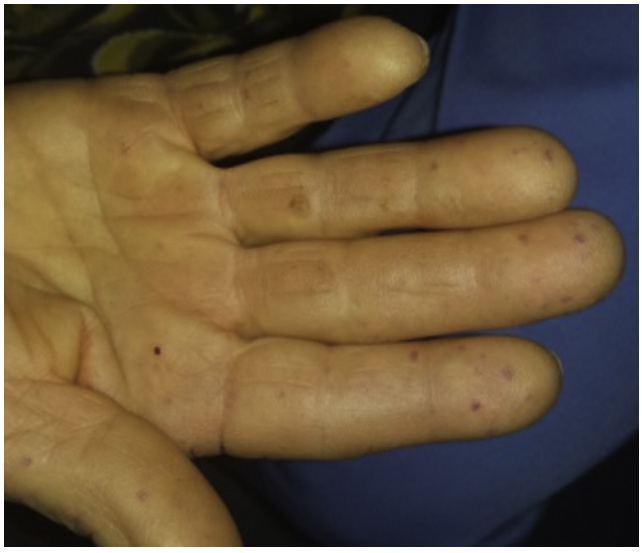

Fig. 3 – Telangiectasia of the fingers.

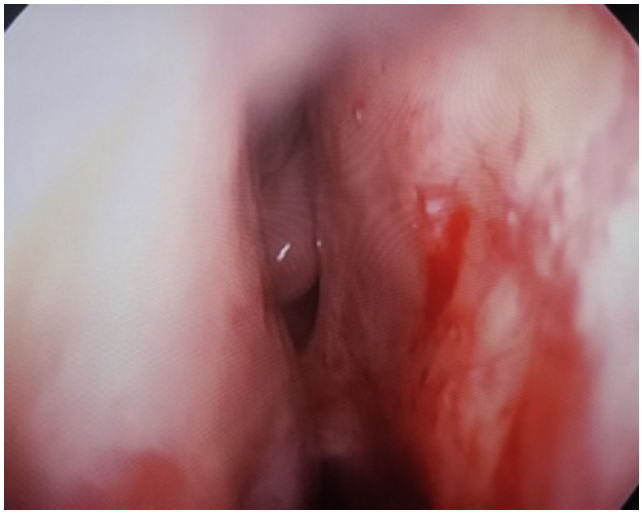

Fig. 4 – Nasal endoscopic view of pituitary telangiectasia.

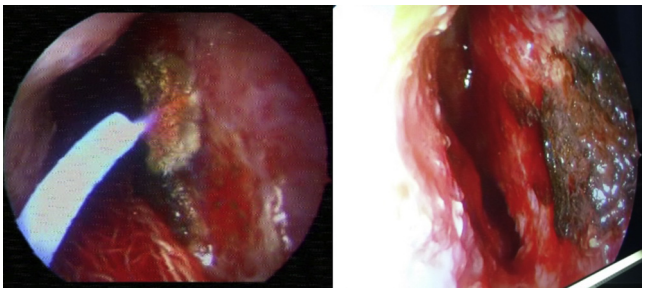

Fig. 5 – APC used for nasal hemostasis.

4. Results

Patient evolution was favorable. During hospitalization nose bleeding did not occur.

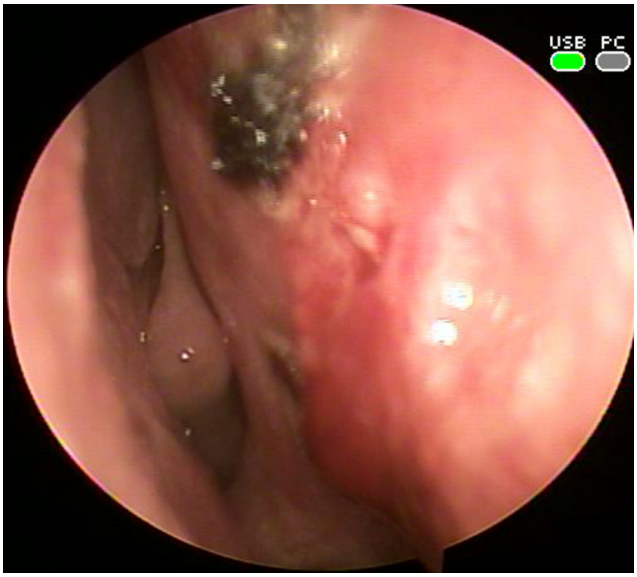

Fig. 6 – Postoperative endoscopic view of nasal mucosa.

Medical examination 3 weeks after surgery showed favorable local evolution, undergoing surgical healing of nasal mucosa, covered by crusts and shells, without active bleeding areas. The patient has been free of epistaxis during this time (Fig. 6).

At 6 months after operation, the patient's general condition was good, with partial improvement of anemic syndrome. The patient reported in this interval a single episode of bleeding with nasal origin, of reduced quantity, that stopped by minimum local hemostasis maneuvering: instillations of vasoconstrictor substances and digital compression.

5. Discussion

HHT is a rare genetic disorder characterized by the presence of multiple telangiectasias, occurring with a frequency of 75%–80%,[9,13,14] characteristic on the nasal and lingual and pharyngeal mucosa, in the conjunctiva, at the level of digestive tract, on the lips, the nose and the skin of the fingers. They are benign lesions described as pulsating red dots or of the size of a match head, that partially disappear with digital pressure.[15] In most patients, telangiectasia appears after the first episode of epistaxis, often before the age of 40.[16] Telangiectasias number increases over time.[14]

Viscerallesions involving arteriovenous malformations are found less frequently in the HHT. We can identify arteriovenous malformation in the lungs (15%–30% of patients, involving dyspnea, exercise intolerance, cyanosis, hypoxemia, secondary polycythemia),[17,18] the central nervous system (13%–50% of patients associating migraine, focal symptoms, seizures, increased frequency of stroke and cerebral abscess compared to spur population),[19] in the liver (involving the right abdominal flank pain, jaundice, bleeding from esophageal varices, signs of heart failure related to hepatic arteriovenous shunt).[9]

Complications associated with HHT may include iron deficiency anemia (in chronic nasal or gastro intestinal bleeding), lungs bleeding, esophageal varices and portal hypertension with liver cirrhosis, congestive heart failure, ischemic or hemorrhagic stroke, brain abscess (due to poor pulmonary vascular function).[20]

Differential diagnosis is made with CREST syndrome, dermatomyositis with cutaneous manifestations, essential telangiectasia, rosacea, and scleroderma.

Therapeutic approach takes into account the severity of recurrent epistaxis in HHT. Cases with recurrent mild epistaxis benefit local hemostatic treatment (topical vasoconstrictors, nasal plugging, humidified inspired air).

In cases of moderate or severe epistaxis, with significant blood loss, associated with chronic iron deficiency anemia, therapeutic approach includes, besides usual local maneuvers, also systemic medication and surgical maneuvers.

Drug treatment usually includes hemostatic substances and iron supplements. In selected cases hormone therapy with estrogen,[21] antifibrinolytic therapy (aminocaproic acid) associated with haemostatic treatment,[22] Thalomid,[23] and N-acetylcysteine[24] orinterferonalfa proved to be useful.[25,26] In cases with significant blood loss blood transfusion is needed.

Hemostatic surgical techniques for epistaxis in HHT include bleeding points electrocautery, laser photocoagulation with Nd:YAG, APC, endovascular embolization, and septal dermoplastia.[27–29]

APC is a non-contact electro surgical monopolar thermal procedure used for achieving hemostasis.[30] The principle of the method consists in transferring energy to a target tissue via plasma, the fourth fundamental state of matter, together with solid, liquid and gas. Plasma can be obtained by ionization of a gas and has electrical conductivity, the property of conducting electricity.

To achieve coagulation, argon (an inert, non-toxic gas) is delivered through a probe (plastic tube that associates an electrical conductor wire) and ionized by a discharge current elective high voltage (6 kV) at the probe tip. Argon plasma is thus formed. Argon ions follow the path of minimum electrical resistance, heading toward the nearest tissue with minimal electrical resistance (blood). Coagulation occurs both linear and tangential. Electrical energy is transferred to the tissue through the argon plasma, not being necessary direct contact between the probe and the targeted tissue. The distance between the probe tip and the tissue can be 2–10 mm. For optimal effect, it is necessary to emit a maximum concentration of argon between the probe tip and the targeted tissue. In that tissue, coagulation and tissue devitalization effect spread at a depth of 2–3 mm. Due to the conductive characteristics of argon, fulguration generated by argon flow is homogenized and smoothed.

In the presented case, APC has brought many advantages in achieving hemostasis: non-contact coagulation with minimal tissue penetration and destruction, a safe method with minimal complications, decreased risk of perforation – something to note given the age. The results proved to be effective both in the short and long term, in increasing bleeding-free interval, and in decreasing the frequency and intensity of episodes of nasal bleeding origin.

6. Conclusions

Clinical case presented with favorable evolution highlights the role of a modern minimally invasive surgical technology – APC – in achieving effective hemostasis of epistaxis in HHT.

Conflict of interest

None declared.

REFERENCES

1. Grover S, Grewal RS, Verma R, Sahni H, Muralidhar R, Sinha P. Osler–Weber–Rendu syndrome: a case report with familial clustering. *Indian J Dermatol Venereol Leprol.* 2009;75(1):100–101.
2. Adler DG, Leighton JA, Davila RE, et al. ASGE guideline: the role of endoscopy in acute non-variceal upper-GI hemorrhage. *Gastrointest Endosc.* 2004;60(4):497–504.
3. Zucco L, Zhang Q, Kuliszewski MA, et al. Circulating angiogenic cell dysfunction in patients with hereditary hemorrhagic telangiectasia. *PLOS ONE.* 2014;9(2):e89927. http://dx.doi.org/10.1371/journal.pone.0089927.
4. Kjeldsen AD, Oxhøj H, Andersen PE, Elle B, Jacobsen JP, Vase P. Pulmonary arteriovenous malformations: screening procedures and pulmonary angiography in patients with hereditary hemorrhagic telangiectasia. *Chest.* 1999;116(2):432–439.
5. Dakeishi M, Shioya T, Wada Y, et al. Genetic epidemiology of hereditary hemorrhagic telangiectasia in a local community in the northern part of Japan. *Hum Mutat.* 2002;19(2):140–148.
6. Shovlin CL, Letarte M. Hereditary haemorrhagic telangiectasia and pulmonary arteriovenous malformations: issues in clinical management and review of pathogenic mechanisms. *Thorax.* 1999;54(8):714–729.
7. Choi EJ, Chen W, Jun K, Arthur HM, Young WL, Su H. Novel brain arteriovenous malformation mouse models for type 1 hereditary hemorrhagic telangiectasia. *PLOS ONE.* 2014;9(2):e88511. http://dx.doi.org/10.1371/journal.pone.0088511.
8. McDonald J, Bayrak-Toydemir P, Pyeritz RE. Hereditary hemorrhagic telangiectasia: an overview of diagnosis, management, and pathogenesis. *Genet Med.* 2011;13(7):607–616.
9. Lessnau KD, Lanza J, Thirumala RRD, Izaguirre DE, Lopez Rowe V. *Osler–Weber–Rendu Disease.* 2014 http://emedicine.medscape.com/article/2048472-overview. Accessed 03.03.15.
10. Shovlin CL, Guttmacher AE, Buscarini E, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu–Osler–Weber syndrome). *Am J Med Genet.* 2000;91(1):66–67.
11. Urushihara M, Furukawa S, Ota A, Iwai A, Matsumura K, Hamada Y. Hemorrhagic telangiectasia with thrombocytopenia in a newborn infant. *Pediatr Int.* 2000;42(6):693–695.
12. Rebeiz EE, Bryan DJ, Ehrlichman RJ, Shapshay SM. Surgical management of life-threatening epistaxis in Osler–Weber–Rendu disease. *Ann Plast Surg.* 1995;35(2):208–213.
13. Govani FS, Shovlin CL. Hereditary haemorrhagic telangiectasia: a clinical and scientific review. *Eur J Hum Genet.* 2009;17(7):860–871.
14. Dupuis-Girod S, Bailly S, Plauchu H. Hereditary hemorrhagic telangiectasia (HHT): from molecular biology to patient care. *J Thromb Haemost.* 2010;8(7):1447–1456.
15. Schoen FJ, Cotran RS, Vinay K, Collins T. *Robbins Pathologic Basis of Disease.* 5th ed. Philadelphia: WB Saunders; 1994:509.
16. Berg J, Porteous M, Reinhardt D, et al. Hereditary haemorrhagic telangiectasia: a questionnaire based study to delineate the different phenotypes caused by endoglin and ALK1 mutations. *J Med Genet.* 2003;40(8):585–590.
17. Lacombe P, Lagrange C, Beauchet A, El Hajjam M, Chinet T, Pelage JP. Diffuse pulmonary arteriovenous malformations in hereditary hemorrhagic telangiectasia: long-term results of embolization according to the extent of lung involvement. *Chest.* 2009;135(4):1031–1037.
18. Jakobi P, Weiner Z, Best L, Itskovitz-Eldor J. Hereditary hemorrhagic telangiectasia with pulmonary arteriovenous malformations. *Obstet Gynecol.* 2001;97(5 Pt 2):813–814.
19. McDonald MJ, Brophy BP, Kneebone C. Rendu–Osler–Weber syndrome: a current perspective on cerebral manifestations. *J Clin Neurosci.* 1998;5(3):345–350.
20. Khalid SK, Pershbacher J, Makan M, Barzilai B, Goodenberger D. Worsening of nose bleeding heralds high cardiac output state in hereditary hemorrhagic telangiectasia. *Am J Med.* 2009;122(8):779.e1–779.e9.
21. Yaniv E, Preis M, Hadar T, Shvero J, Haddad M. Antiestrogen therapy for hereditary hemorrhagic telangiectasia: a double-blind placebo-controlled clinical trial. *Laryngoscope.* 2009;119(2):284–288.
22. Isaacs E. Aminocaproic acid. In: *Pediatric Drug Dosage Handbook.* 8th ed. Ottawa, Canada: Winnipeg Health Sciences Center and CSHP; 1998:161.
23. Franchini M, Frattini F, Crestani S, Bonfanti C. Novel treatments for epistaxis in hereditary hemorrhagic telangiectasia: a systematic review of the clinical experience with thalidomide. *J Thromb Thrombolysis.* 2013;36(3):355–357.
24. de Gussem EM, Snijder RJ, Disch FJ, Zanen P, Westermann CJ, Mager JJ. The effect of N-acetylcysteine on epistaxis and quality of life in patients with HHT: a pilot study. *Rhinology.* 2009;47(1):85–88.
25. Massoud OI, Youssef WI, Mullen KD. Resolution of hereditary hemorrhagic telangiectasia and anemia with prolonged alpha-interferon therapy for chronic hepatitis C. *J Clin Gastroenterol.* 2004;38(4):377–379.
26. Wheatley-Price P, Shovlin C, Chao D. Interferon for metastatic renal cell cancer causing regression of hereditary hemorrhagic telangiectasia. *J Clin Gastroenterol.* 2005;39(4):344–345.
27. Harvey RJ, Kanagalingam J, Lund VJ. The impact of septodermoplasty and potassium-titanyl-phosphate (KTP) laser therapy in the treatment of hereditary hemorrhagic telangiectasia-related epistaxis. *Am J Rhinol.* 2008;22(2):182–187.
28. Layton KF, Kallmes DF, Gray LA, Cloft HJ. Endovascular treatment of epistaxis in patients with hereditary hemorrhagic telangiectasia. *AJNR Am J Neuroradiol.* 2007;28(5):885–888.
29. Lesnik GT, Ross DA, Henderson KJ, Joe JK, Leder SB, White Jr RI. Septectomy and septal dermoplasty for the treatment of severe transfusion-dependent epistaxis in patients with hereditary hemorrhagic telangiectasia and septal perforation. *Am J Rhinol.* 2007;21(3):312–315.
30. Grund KE, Storek D, Farin G. Endoscopic argon plasma coagulation (APC) first clinical experiences in flexible endoscopy. *Endosc Surg Allied Technol.* 1994;2(1):42–46.