Int J Colorectal Dis (2004) 19:595–598
DOI 10.1007/s00384-004-0607-3

ORIGINAL ARTICLE

Eran Elinav
Shaden Salameh-Giryes
Zvi Ackerman
Neta Goldschmidt
Aviram Nissan
Tova Chajek-Shaul

Does any lower gastrointestinal bleeding in patients suffering from hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu) necessitate a full colonic visualization?

Accepted: 31 March 2004
Published online: 27 May 2004

E. Elinav · S. Salameh-Giryes · Z. Ackerman · N. Goldschmidt · A. Nissan · T. Chajek-Shaul (✉)
Department of Medicine,
Mount Scopus Hadassah Hospital,
P.O. Box 24035, Jerusalem 91240, Israel
e-mail: chajek@hadassah.org.il
Tel.: +972-2-5844521
Fax: +972-2-5812754

Abstract *Background:* Hereditary hemorrhagic telangiectasia (HHT) (the Osler–Weber–Rendu syndrome) is a rare autosomal dominant disease characterized by telangiectasias and arteriovenous malformations of the upper and lower respiratory tract, gastrointestinal tract, skin and central nervous system. Several previous reports have documented the appearance of a concomitant neoplasm in patients with this syndrome. *Aims:* To study the occurrence and the clinical characterization of colonic neoplasm in patients with HHT. *Methods:* We retrospectively reviewed the computerized database of the Hadassah University Hospitals (Jerusalem, Israel) for all patients with the diagnosis of HHT between January 1st, 1980 and July 30th, 2002. Cases of neoplasm were documented by review of medical charts and pathology reports. *Results:* Six of the 24 patients developed malignancy. Three of the cases had extra colonic malignancy (melanoma in two patients and adenocarcinoma of urinary bladder in one patient) and three patients had adenocarcinoma of the colon. An additional three patients developed multiple colonic polyps (one patient had melanoma and one patient had adenocarcinoma of urinary bladder). *Conclusions:* HHT may be associated with the development of colonic adenocarcinoma and polyps. Therefore, in patients with HHT who present with new-onset anemia or gastrointestinal bleeding a lower gastrointestinal tract evaluation should be performed, even if their blood loss is suspected to be a manifestation of gastrointestinal HHT.

Keywords Hereditary hemorrhagic telangiectasia · Colorectal cancer · Anemia · Gastrointestinal bleeding

Introduction

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant vascular dysplasia with incomplete penetrance, leading to telangiectasias and arteriovenous malformations of skin, mucosa, and viscera. Epistaxis and gastrointestinal bleeding are frequent complications of mucosal involvement. Visceral involvement includes that of the lung, liver, and brain. These lesions can result in spontaneous, at times life-threatening mucosal and internal bleeding, right-to-left pulmonary shunts, high output cardiac failure, brain abscess, cerebrovascular accidents, seizures, and rarely cirrhosis [1, 2]. The syndrome is caused by either a mutation in the endothelial TGF-β receptor endoglin (HHT1) [3], the activin receptor-like kinase 1 gene (*HHT2*) [4] or a third HHT variant, unlinked to either of these genes but no such gene has been identified yet (*HHT3*) [5, 6]. Treatment consists mainly of embolization or surgical ablation of the vascular malformations [1, 2].

HHT is presently regarded as a benign disorder. However, several case reports have suggested a possible association of the syndrome with malignancies including adenocarcinoma of the colon [7–15]. Other reports have pointed out a possible association between HHT and juvenile polyposis coli, a syndrome that by itself is believed

to predispose patients to a higher risk of colon cancer [16–24].

Other genetic syndromes that involve the gastrointestinal tract are associated with an increased risk for the development of neoplasms. These include the hamartoma syndromes Peutz-Jegher, Cowden, juvenile polyposis coli and the adenoma syndromes familial polyposis coli, Turcot, Gardner and hereditary non-polyposis coli [25–29].

In this paper we describe the occurrence of colonic neoplasm in patients with HHT. Therefore a prompt lower gastrointestinal tract evaluation should be performed in patients with HHT who present with new-onset anemia or gastrointestinal bleeding, even if their blood loss is suspected to be a manifestation of gastrointestinal HHT.

Methods

We retrospectively reviewed the computerized database of the Hadassah University Hospitals (Jerusalem, Israel) for all patients with the diagnosis of HHT between January 1st, 1980 and July 30th, 2002. A total of 27 patients were diagnosed as having HHT. All files were then reviewed for patients in whom the diagnosis of HHT was confirmed during their stay in the hospitals or during follow-up in the out-patient clinics. Only patients whose diagnosis fulfilled the diagnostic criteria described by Plauchu et al. [30], i.e., the presence of three of the four autosomal dominant modes of inheritance, telangiectasias, recurrent epistaxis, and visceral involvement were included in the study. A total of 24 patients (12 men and 12 women) were eligible, while three patients were excluded from the study after failing to meet these diagnostic criteria. One of the excluded patients also suffered from colonic adenocarcinoma. Senior pathologists at our institution confirmed the diagnoses of all of the neoplasm. None of the patients presented with neoplasm.

Results

Twenty-four patients, 12 males and 12 females, met the clinical diagnostic criteria for HHT. Mean follow-up period of the patients at our institution was 15 years. Patient characteristics are summarized in Table 1. Twenty-two patients were Jewish (12 patients were Ashkenazi Jews and ten patients were Non-Ashkenazi Jews. Seventeen patients (71%) suffered from the typical skin telangiectasias, while 18 patients (75%) suffered from recurrent epistaxis. In addition, 11 patients (46%) had HHT gastrointestinal involvement (manifested as lower and upper gastrointestinal bleeding), three patients (12%) had central nervous system involvement, and two patients (8%) had pulmonary involvement. Two patients had other systemic involvement, one with a spinal cord lesion and the other with high output cardiac failure due to arteriovenous malformations of the liver.

When comparing patients with and without a neoplasm, a higher but not significant incidence of skin, nasal, and pulmonary involvement was noted among the latter group. None of the rarer organ involvements (central nervous system, spinal cord, and liver) were noted among patients with a neoplasm, while it affected five patients without a neoplasm.

Table 1 Patient characteristics. HHT, hereditary hemorrhagic telangiectasia; CNS, central nervous system

	All	Cases with neoplasm	Cases without neoplasm
Number of patients	24	7	17
Gender (M/F)	12/12	5/2	7/10
HHT involvement (%)			
Epistaxis	18 (75)	4 (57)	14 (82)
Skin	17 (71)	4 (57)	13 (76)
Gastrointestinal	11 (46)	3 (43)	8 (47)
Pulmonary	2 (8)	0 (0)	2 (12)
CNS	3 (12)	0 (0)	3 (18)
Spinal cord	1 (4)	0 (0)	1 (6)
Liver	1 (4)	0 (0)	1 (6)

Table 2 Characteristics of the tumors observed in the study population

Type of neoplasm	Number of patients
Total number of tumors	9
Patients with a tumor	7
Colonic neoplasm	6
Multiple synchronous Villous adenomatous polyps	3
Colonic adenocarcinoma	3
Extracolonic neoplasm	3
Melanoma	2
Adenocarcinoma of urinary bladder	1

As depicted in Table 2, six of the 24 patients (25%) were diagnosed as having colonic neoplasm. Three were cases of colonic adenocarcinoma; an additional three had multiple (three or more) synchronous sessile adenomatous colonic polyps, at least one larger than 1 cm in greatest diameter. None of the patients suffered from juvenile polyposis coli. Three other neoplasms were of non-gastrointestinal origin, including two malignant melanomas and one urinary bladder transitional cell carcinoma.

Two patients suffered from two concurrent neoplasms. The earlier neoplasm in both these patients was multiple synchronous adenomatous colonic polyposis, while the second neoplasm was melanoma in one patient, and transitional cell carcinoma of the urinary bladder in the other.

The proportion of HHT intestinal involvement in patients with a colonic neoplasm (colonic adenocarcinoma and polyposis) was similar to that proportion in patients without a neoplasm (43% and 47%, respectively).

Table 3 Case reports in the medical literature of patients with hereditary hemorrhagic telangiectasia with neoplasm

Type of neoplasm	Reference	Patient age at diagnosis of neoplasm	Patient gender
Hepatocellular carcinoma	[7, 8]	79, 69	F, F
Multiple squamous cell skin carcinoma	[9]	65	M
Non-hodgkins lymphoma	[10]	60	F
Lymphoblastic leukemia	[11]	62	M
Multiple myeloma	[12]	62	M
Ovarian adenocarcinoma	[13]	74	F
Colonic adenocarcinoma	[14–16]	70, 77, 36	M, M, M

Discussion

This retrospective cohort study of patients with HHT suggests a possible association for developing neoplastic disease of the colon. A total of 29% of our patients, followed for an average of 15 years, developed both gastrointestinal and non-gastrointestinal tumors, including multiple colonic adenomatous polyps, colorectal adenocarcinoma, malignant melanoma, and transitional cell carcinoma of the urinary bladder. Our results demonstrate that six of 24 patients with HHT developed colonic neoplasm or polyposis. However, our patient population was relatively small, the patients with colonic neoplasm had either adenocarcinoma or multiple colon polyps and the SEER [31] data only include invasive cancer; we were therefore unable to calculate the standardized morbidity ratio.

HHT is believed to be a benign disorder, with possible complications such as hemorrhage, but without an established increased tendency for the development of cancer. However, several previously published reports have described patients with HHT who suffered from a concomitant neoplasm such as hepatocellular carcinoma [7, 8], squamous cell carcinoma of the skin [9], lymphoma [10], leukemia [11], multiple myeloma [12], ovarian adenocarcinoma [13], and adenocarcinoma of the colon [14–16] (Table 3), and has been suggested that a linkage exists between HHT and juvenile polyposis coli [16–24]. However, no clear-cut association between HHT and an increased incidence of cancer has been previously documented in the medical literature.

We found no linkage between gastrointestinal involvement in HHT and the increased risk of developing colonic neoplasm. In fact, during colonoscopy among the six patients suffering from a colonic neoplasm, the characteristic telangiectasias and arteriovenous malformations were reported in only three.

Some bias could arise from our study methodology, which was based on hospital admission diagnosis and therefore represents a sicker population of HHT and not necessarily a true association of neoplasm in the HHT population. The association of HHT with colonic neoplasm needs to be verified by a larger population-based approach. In addition, screening strategies should be constructed to better manage this unique patient population.

In the meanwhile, every episode of lower gastrointestinal bleeding and anemia in patients known to be suffering from HHT necessitates, in our opinion, a full visualization of the patient's colon, in order to rule out the possibility of a colonic malignancy. Regarding such bleeding as merely reflecting a gastrointestinal involvement in HHT might put the patient at risk for a delayed diagnosis of a potentially fully curable neoplastic disease.

References

1. Guttmacher AE, Marchuk DA, White RI (1995) Hereditary hemorrhagic telangiectasia—review. N Engl J Med 333:918–924
2. Shovlin CL, Letarte M (1999) Hereditary haemorrhagic telangiectasia and pulmonary arteriovenous malformations: issues in clinical management and review of pathogenic mechanisms. Thorax 54:714–729
3. McAllister KA, Grogg KM, Johnson DW et al (1994) Endoglin, a TGF-β binding protein of endothelial cells, is the gene for hereditary hemorrhagic telangiectasia type 1. Nat Genet 8:345–351
4. Johnson DW, Berg JN, Baldwin MA et al (1996) Mutations in the activin receptor-like kinase 1 gene in hereditary haemorrhagic telangiectasia type 2. Nat Genet 13:189–195
5. Piantanida M, Buscarini E, Dellavecchia C et al (1996) Hereditary haemorrhagic telangiectasia with extensive liver involvement is not caused by either HHT1 or HHT2. Med Genet 33:441–443
6. Wallace GMF, Shovlin CL (2000) A hereditary haemorrhagic telangiectasia family with pulmonary involvement is unlinked to the known HHT genes, endoglin and ALK-1. Thorax 55:685–690
7. Jameson CF (1989) Primary hepatocellular carcinoma in hereditary haemorrhagic telangiectasia: a case report and literature review. Histopathology 15:550–551
8. Sussman EB, Stephen MD, Sternberg MD (1975) Hereditary hemorrhagic telangiectasia—a case with hepatocellular carcinoma and acquired hepatocerebral degeneration. Arch Pathol 99:95–100

9. Breuninger H, Bogenschurz O, Konrad E et al (1997) Teleangiectasia haemorrhagica hereditaria (Osler–Weber–Rendu disease). Surgical therapy of malignant skin tumors. Hautarzt 48:496–499
10. Kato S, Ichiara K (1988) Hereditary hemorrhagic telangiectasia with malignant lymphoma. An autopsy case. Acta Pathol Jpn 38:383–391
11. Livandovskii IuA, Listratov Sia, Naumova GA (1975) Rare case of association of Rendu–Osler disease with lymphocytic leukemia. Klin Med (Mosk) 53:118–119
12. Patakfalvi A, Marton E (1974) Simultaneous occurrence of Osler–Weber disease and IgA myeloma with severe antibody deficiency syndrome. Orv Hetil 115:1287–1289
13. Gemke GR, Kaupasa MM, Rafalskii AA et al (1994) Association of Rendu–Osler disease, polyarthritis and ovarian cancer. Klin Med (Mosk) 72:65–66
14. Goldman K, De Pietro WP (1989) A case of adenocarcinoma of the colon in a patient with hereditary hemorrhagic telangiectasis. Cutis 43:371–372
15. Hisamura M, Akita K, Ide H (1994) A case of Rendu–Osler–Weber disease associated with simultaneous, multiple advanced cancers in the colon. Hokkaido Igaku Zasshi 69:1468–1475
16. Conte WJ, Rotter JI, Schwartz AG et al (1982) Hereditary generalized juvenile polyposis, arteriovenous malformations and colonic carcinoma (Abstract). Clin Res 30:93A
17. Baert AL, Casteels-Van Daele M, Broeckx J et al (1983) Generalized juvenile polyposis with pulmonary arteriovenous malformations and hypertrophic osteoarthropathy. Am J Roentgenol 141:661–662
18. Cox KL, Frates RC, Wong A et al (1980) Hereditary generalized juvenile polyposis associated with pulmonary arteriovenous malformation. Gastroenterology 78:1566–1570
19. Radin DR (1994) Hereditary generalized juvenile polyposis: association with arteriovenous malformations and risk of malignancy. Abdom Imaging 19:140–142
20. Prieto G, Polanco JS, Larrauri J et al (1990) Association of juvenile adenomatous polyposis with pulmonary arteriovenous malformation and hypertrophic osteoarthropathy. J Pediatr Gastroenterol Nutr 11:133–137
21. Gillespie JS, McIvor RA (2001) Hereditary hemorrhagic telangiectasia in association with generalized juvenile polyposis. Ulster Med J 70:145–148
22. Ballauff A, Koletzko S (1999) Hereditary hemorrhagic telangiectasia with juvenile polyposis-coincidence or linked autosomal dominant inheritance? Z Gastroenterol 37:385–388
23. Schumacher B, Frieling T, Borchard F et al (1994) Hereditary hemorrhagic telangiectasia associated with multiple pulmonary arteriovenous malformations and juvenile polyposis. Z Gastroenterol 32:105–108
24. Inoue S, Matsumoto T, Iida M et al (1999) Juvenile polyposis occurring in hereditary hemorrhagic telangiectasia. Am J Med Sci 317:59–62
25. Boardman LA, Thibodeau SN, Schaid DJ et al (1998) Increased risk for cancer in patients with the Peutz-Jeghers syndrome. Ann Intern Med 128:896–899
26. Giardiello FM, Welsh SB, Hamilton SR et al (1987) Increased risk of cancer in the Peutz-Jeghers syndrome. N Engl J Med 316:1511–1514
27. Lynch HT, Smyrk T, Lynch J (1996) Hereditary non-polyposis colorectal cancer (Lynch syndrome). An updated review. Cancer 78:1149–1167
28. Gilchrist DM (1997) Hereditary colon cancer. Can J Gastroenterol 11:421–423
29. Coburn MC, Pricolo VE, DeLuca FG et al (1995) Malignant potential in intestinal juvenile polyposis syndromes. Ann Surg Oncol 2:385–391
30. Plauchu H, De Chadarevian JP, Bideau A et al (1989) Age-related clinical profile of hereditary hemorrhagic telangiectasia in an epidemiologically recruited population. Am J Med Genet 32:291–297
31. SEER Program (1999) SEER cancer statistics review: 1990–1999. National Cancer Institute, Bethesda, MD. Seer cancer.gov