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Hormonal Therapy in Chronic Radiation Colitis

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Severe gastrointestinal bleeding is a rare complication of radiation therapy that requires frequent transfusions. This case report describes a patient with severe bleeding from radiation colitis after treatment of bladder cancer. During 5 months of therapy with multiple drugs, the patient needed 26 units of packed red cells. A subsequent hormone therapy consisting of an estrogen-progesterone combination significantly reduced the need for blood transfusions and hospitalization. We conclude that hormones might provide a promising new additional symptomatic therapy for bleeding radiogenic colitis. (Am J Gastroenterol 1998;93:2536–2538. © 1998 by Am. Coll. of Gastroenterology)

INTRODUCTION

Late gastrointestinal complications of radiation therapy may result from the treatment of a variety of malignancies in which the radiation beam passes through the gastrointestinal tract. The incidence of chronic radiation enterocolitis varies from 0.5% to 17% (1, 2). Bleeding is a rare complication in radiation enterocolitis (3, 4). The therapy is exclusively symptomatic and empirical (1, 3, 5). In severe cases of anemia, blood transfusions are required. Hormone therapy is a novel approach. To date, only few case reports, one placebo-controlled trial with a short follow-up period (6), and one long term follow-up study (7) have been published. The data indicate that estrogen-progesterone therapy is effective in controlling severe recurrent bleeding from gastrointestinal vascular malformations.

This case report describes a patient with severe recurrent bleeding due to late onset of radiation colitis. Treatment with estrogen-progesterone significantly reduced the need for blood transfusions and hospitalization.

CASE REPORT

A 72-yr-old man underwent superficial transurethral resection of a bladder carcinoma (T1 N0 M0). A colonoscopy was normal at that time.

Thirty-seven months later, a second transurethral resection was performed for relapse, followed by radiation therapy of the lymph nodes and the bladder (total 70.4 Gray, 1.8 Gray daily for 2 months) for histologically diagnosed invasion of lymph vessels.

Six months after radiation therapy, a CT scan revealed metastases in lung and liver.

One year after this diagnosis, the patient presented with frequent and urgent stools with frank blood of 3 months duration. On examination the patient was in good nutritional condition, but had been suffering from vertigo and dyspnea for several days. Blood pressure was 120/65 mm Hg and pulse was 82 beats/min. Rectal examination displayed cherry-red stool. The laboratory parameters reflected severe anemia with a hemoglobin of 6.3 g/dl (normal range 12–18 g/dl), hematocrit 19.3% (normal 36–53%), red blood cells 2.21×10^{12}/L (normal $3.8–5.5 \times 10^{12}$/L), reticulocytes 0.6% (normal 0.1–2.4%), mean corpuscular hemoglobin (MCH) 29.0 pg (normal 26–32 pg), iron 6.26 μmol/L (normal 6.6–28.3 μmol/L), and ferritin 22.9 μg/L (normal 24–371 μg/L). Platelets and coagulation parameters were normal.

Colonoscopy showed a pale mucosa, diffusely spread telangiectatic vessels, and hemorrhage throughout the rectum and the lower part of the sigmoid colon. Biopsies taken from the sigmoid colon during a colonoscopy performed because of diarrhea and occasional hematochezia 4 months before hospitalization had established mild mucosal edema and mild inflammatory infiltration as well as areas of hemorrhage. The epithelium showed mild reactive atypia. These morphological changes were not entirely specific but were consistent with radiation colitis.

On first admission to our ward, the patient was transfused with 4 units of packed red cells and treatment with loperamide (2–8 mg/day), mesalamine (3 g/day), prednisolone (10 mg/day), budesonide enemas (2 mg/day), and ferric-II-sulfate (210 mg/day) commenced.

During the subsequent 5 months, the patient suffered from constant hematochezia. In this period he was hospitalized five times and needed 22 erythrocyte concentrates, four of which were given for bleeding after a third transurethral resection of a local obstruction by the recurrent bladder tumor.

Subsequently, an estrogen-progesterone therapy was started (ethinyl estradiol 0.07 mg/day, norethisterone 1 mg/day—the dosage being approximated as close as possible to

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those in Ref. 6 and 7 with a preparation registered in Austria, Ovysmen *t.i.d.*). The patient left the hospital with a hemoglobin level of 11.8 g/dl. Apart from 2 units of packed red cells in the wk 6 after the beginning of hormone therapy, he did not receive any blood transfusions. Hematochezia almost stopped and the hemoglobin levels at the next three checks were 11.5, 10.8, and 11.0 g/dl. Concomitant medication comprised ferric-II-sulfate (210 mg/day) and loperamide (if required).

Mild gynecomastia was observed as a side effect.

The patient eventually died from multiple metastases of the lung and the liver 8 months after commencement of hormone therapy.

DISCUSSION

Late radiation injury may take years to develop. Most publications report a median of about 8–12 months before the lesions become apparent (1, 2, 8). Microscopically, the most marked changes of chronic radiation injury are found in the submucosa, whereas in acute disease the mucosa is mostly affected. In the presence of chronic radiation injury, the submucosa is characterized by atypical fibroblasts and collagen proliferation. Atypical vascular changes and telangiectatic vessels may occur (9).

No guidelines for the treatment of recurrent bleeding from chronic radiation enterocolitis are available to date. In cases of frank blood and ulcerations, frequent transfusions and subsequent surgical interventions are proposed (8).

Surgical and endoscopic treatment are often ineffective when the lesions are diffusely spread throughout the gastrointestinal tract.

More recent approaches to severe rectal hemorrhage in radiation colitis, *e.g.*, the neodymium:yttrium-aluminum-garnet (Nd:YAG) (10), the argon laser (11), and heat probe (12), induce a reduction in transfusion requirements in some cases. A few studies describe the use of hyperbaric oxygen (13, 14) and the local application of 4% formalin to the hemorrhagic mucosa (15).

In view of the extensive vascular abnormalities in our patient, laser coagulation was regarded as an inappropriate treatment (risk of perforation and rebleeding) (16). An argon beamer or hyperbaric oxygen treatment were not available in our hospital at that time.

Observations in epistaxis due to hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease) changing during women's hormonal cycles have prompted the use of systemic estrogens in the management of gastrointestinal bleeding caused by vascular malformations. Several studies report successful hormone therapy in vascular malformations of the gastrointestinal tract (6, 7, 17).

The precise mechanism of the action of hormone therapy (either estrogen *per se* or in combination with progesterone) on bleeding telangiectasias in the intestine is not clearly understood. A primary effect on blood coagulation may be a possible mechanism (18, 19). Electron-microscopic data imply that estrogens may restore the integrity of the endothelium in abnormal vessels (20, 21). Finally, stasis in the mesenteric microcirculation has been reported after intra-arterial injection of estrogen in animal models (22).

No significant influences of low dose estrogen-progestone combinations (ethinyl estradiol 0.03 mg/day, norethisterone 1 mg/day) on the hematopoietic system have been described in contraceptive therapy. Hemoglobin, red blood cell count, and platelets are not affected. Merely, the white blood cell count may rise slightly above normal (23–25). Only higher doses of norethisterone enanthate (200 mg at 60-day intervals) cause significant elevations in hemoglobin concentrations and red blood cell count (26).

For the first time we used a combination of estrogen and progesterone, in accordance with Van Cutsem (6, 7) in the treatment of gastrointestinal bleeding from late onset radiation colitis. After this therapy was started, we observed a significant reduction in blood loss and in the need for hospitalization.

The side effect of mild gynecomastia was easily tolerated by our patient. Recognized long term side effects of estrogen and/or progesterone in men with prostate cancer are the following: feminization, high risk for cardiovascular and thromboembolic complications, loss of libido, weight gain, retention of water, nausea, and headache (27, 28). There are no reports on long term treatment with estrogen-progesterone combinations in male patients such as the combination used in our patient.

This case documents a successful attempt to reduce repeated blood transfusions by hormone therapy in a patient with chronic radiation colitis. The reduced need for blood transfusions minimized the length of hospital stay and improved the patient's quality of life.

This case study is especially interesting in view of the fact that patients with radiation induced chronic enterocolitis are small in number and, as a rule, difficult to manage.

Our findings suggest that, because of the pathological similarities between radiation colitis and vascular malformations of the intestine, hormone therapy appears to be a suitable pharmacological alternative to expensive physical approaches in cases of bleeding from radiation colitis.

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REFERENCES

1. Gregor M. Strahlenschäden. In: Goebell H, ed. Gastroenterolgie. München: Urban & Schwarzenberg, 1992:700–3.
2. Kapadia CR. Radiation damage to the gut. In: Spiro HM, ed. Clinical gastroenterology. New York: McGraw-Hill, 1993:619–26.
3. Galland RB, Spencer J. The natural history of clinically established radiation enteritis. Lancet 1985;I:1257–8.
4. Bourne RG, Kearsley JH, Grove WD, et al. The relationship between early and late gastrointestinal complications of radiation therapy for carcinoma of the cervix. Int J Radiat Oncol Biol Phys 1983;9:1445–50.
5. Loiudice TA, Lang JA. Treatment of radiation enteritis: A comparison study. Am J Gastroenterol 1983;78:481–7.
6. Van Cutsem E, Rutgeerts P, Vantrappen G. Treatment of bleeding

gastrointestinal vascular malformations with oestrogen-progesterone. Lancet 1990;335:953–5.
7. Van Cutsem E, Rutgeerts P, Vantrappen G. Long-term effect of hormonal therapy for bleeding gastrointestinal vascular malformations. Eur J Gastroenterol Hepatol 1993;5:439–43.
8. Coia LR, Myerson RJ, Tepper JE. Late effects of radiation therapy on the gastrointestinal tract. Int J Radiat Oncol Biol Phys 1995;31:1213–36.
9. Berthrong M. Pathologic changes secondary to radiation. World J Surg 1986;10:155–70.
10. Alexander TJ, Dwyer RM. Endoscopic Nd:YAG laser treatment of severe radiation injury of the lower gastrointestinal tract: Long-term follow-up. Gastrointest Endosc 1988;34:407–11.
11. O'Connor JJ, Strickland KI, Burleson D. Argon laser treatment of radiation proctitis (letter to the editor). Gastrointest Endosc 1988;34: 489.
12. Fuentes D, Monserat R, Isern AM, et al. Colitis due to radiation: Endoscopic management with heat-probe. G-E-N. 1993;47:165–7.
13. Nakada T, Kubota Y, Sasagawa I, et al. Therapeutic experience of hyperbaric oxygenation in radiation colitis. Dis Colon Rectum 1993; 36:962–5.
14. Charneau J, Bouachour G, Person B, et al. Severe hemorrhagic radiation proctitis advancing to gradual cessation with hyperbaric oxygen. Dig Dis Sci 1991;36:373–5.
15. Seow-Choen F, Goh HS, Eu KW, et al. A simple and effective treatment for hemorrhagic radiation proctitis using formalin. Dis Colon Rectum 1993;36:135–8.
16. Hunter JG. Endoscopic laser applications in the gastrointestinal tract. Surg Clin North Am 1989;69:1147–66.
17. Harrison DF. Use of estrogen in treatment of familial hemorrhagic telangiectasia. Laryngoscope 1982;92:314–20.
18. Bronner MH, Pate MB, Cunningham JT, et al. Estrogen-progesterone therapy for bleeding gastrointestinal telangiectasias in chronic renal failure. Ann Intern Med 1986;105:371–4.
19. Daume E. Influence of modern low-dose oral contraceptives on hemostasis. Adv Contracept 1990;6(suppl):51–67.
20. Menefee MG, Flessa HC, Glueck HI, et al. Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease). Arch Otolaryngol 1975; 101:246–51.
21. Gelfand JA. Exploiting sex for therapeutic purposes (editorial). N Engl J Med 1983;308:1417–19.
22. Nagamine Y, Komatsu S, Suzuki J. New embolization method using estrogen: Effect of estrogen on microcirculation. Surg Neurol 1983; 20:269–75.
23. Taubert HD, Kuhl H. Einfluß von Ovulationshemmern auf laboranalytische Parameter. In: Taubert HD, Kuhl H, eds. Kontazeption mit Hormonen. Stuttgart: Thieme Verlag, 1995:320–31.
24. Loke DFM, Ng SA, Holck S, et al. Lipid and biochemical changes after low-dose contraception. Contraception 1992;46:227–41.
25. Mooji PNM, Thomas CMG, Doesburg WH, et al. The effect of oral contraceptives and multivitamin supplementation on serum ferritin and haematological parameters. Int J Clin Pharmacol Ther Toxicol 1992; 30:57–62.
26. Chaudhuri C, Dutta SK, Mukherjea M. Effect of norethisterone enanthate on the blood count and endometrial histology of Indian women. Contraception 1985;32:417–28.
27. Byar DP. Proceedings: The Veterans Administration Cooperative Urological Research Group studies of cancer of the prostate. Cancer 1973;32:1126–30.
28. Huggins C, Hodges CV: Studies of prostatic cancer: I: Effect of castration, estrogen and androgen injections on serum phosphatase in metastatic carcinoma of the prostate. Cancer Res 1941;1:293–7.