

Efficacy of Hyaluronic Acid in Radiation Proctitis: A Case Series

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ABSTRACT

Gastrointestinal toxicities of radiation might develop after exposure, thus leading to conditions such as abdominal pain, rectal bleeding, diarrhea, anemia, and weight loss. The development of drugs to reduce mucosal damage progression has been a focus on managing radiation proctitis. Radiation proctitis resulting from exposure to pelvic radiotherapies is effectively managed with topical administration on the anal mucosa. The clinical use of hyaluronic acid offers an innovative approach to managing radiation injury. Hyaluronic acid has multiple beneficial properties, such as regulating immune process to reduce inflammation and oxidative stress, supporting natural protective mechanism, promoting mucosa healing, and improving tissue hydration. Therefore, this case series introduces the idea that application of hyaluronic acid could potentially improve patients' clinical conditions.

Keywords: radiation proctitis, hyaluronic acid, enema.

INTRODUCTION

Pelvic radiotherapy is a commonly used treatment for gynecologic, urologic, and rectal cancers. However, this modality increases the risk of radiation injuries to large intestines, leading to radiation colitis and proctitis. These conditions often result in abdominal pain, rectal bleeding, diarrhea, anemia, and weight loss. Gastrointestinal complications can vary from anal pain, chronic abscess, fistula, and stricture to rectal malignancy. Patients who experience a new onset of hematochezia after previous radiation therapy are required to undergo a colonoscopy examination to assess mucosal damage of the rectum and colon.¹ The Vienna Rectoscopy

Score (VRS) is used to describe the endoscopic findings and the European Organization for Research and Treatment of Cancer (EORTC)/ Radiation Therapy Oncology Group (RTOG) to assess bowel toxicity and the effects of radiation.

Topical therapy, such as sucralfate enemas has been proven effective to treat rectal bleeding resulting from radiation proctitis.² Hyaluronic acid (HA) enemas have also shown promising potential for the clinical treatment of radiation proctitis. This is due to the functional properties of HA enemas that facilitate mucosa healing and provide a protective barrier.³ Therefore, we present 3 cases of radiation proctitis treated with hyaluronic acid (sodium hyaluronate) and their outcome.

CASE ILLUSTRATION

Patient 1

A 62-year-old female patient was admitted to the outpatient clinic with chronic constipation and nausea for one month. During the visit, the patient complained of epigastric pain and had a history of stage IB endometrial cancer. The patient had undergone radiotherapy one year earlier and had been diagnosed with type 2 diabetes ten years ago and was taking metformin 3 x 500 mg. The diagnostic procedures, including Esophagogastroduodenoscopy (EGD), showed grade B esophagitis and mild gastritis. Colonoscopy results showed swollen, hyperemic mucosa with multiple telangiectasia without active bleeding (VRS 2; EORTC/RTOG score 1). The patient was prescribed a daily self-administered sodium hyaluronate enema 2 x 60 cc for 28 days. On the follow-up visit, the symptoms had completely resolved, and the colonoscopy results showed an improvement in multiple telangiectasia appearance, without the signs of edema, ulcers, and stricture (VRS 1; EORTC/RTOG grade 0).

PATIENT 2

A 68-year-old female patient with a history of stage IVB endometrial cancer was referred for evaluation of hematochezia and abdominal pain. The patient had undergone radiotherapy with a total radiation dose of 50-60 Gy. Furthermore, the patient had a history of hypertension as well as type 2 diabetes and routinely takes amlodipine 1x10mg and metformin 2x500mg. Colonoscopy results showed multiple telangiectasia with no active bleeding along the rectosigmoid and swollen caecum mucosa (VRS 2; EORTC/RTOG score 2). After 28 days of daily self-administered sodium hyaluronate treatment, the follow-up visits for evaluation showed that symptoms had improved, including the colonoscopy result as presented in Figure 2 (VRS 1; EORTC/RTOG grade 1)

PATIENT 3

A 61-year-old female presented with a one-year history of symptoms including bloody mucus diarrhea, abdominal pain, and decreased appetite. The patient had previously experienced bloody diarrhea six years ago, which improved with the Argon Plasma Coagulation

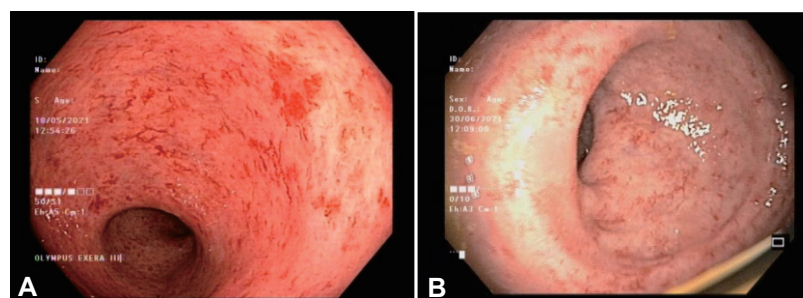


Figure 1. Hyperemic and edema appearance before treatment (a) and improvement in endoscopic findings after treatment (b).

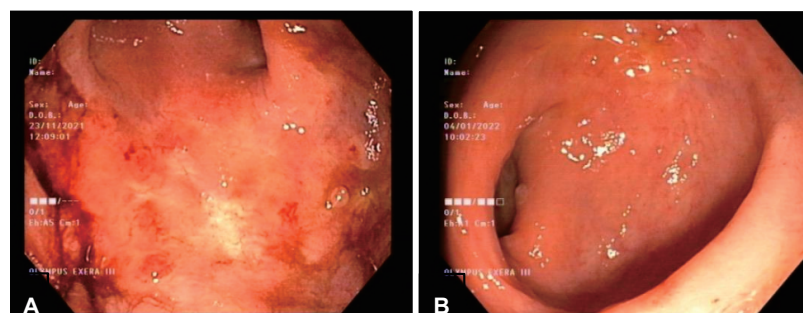


Figure 2. Multiple telangiectasia was detected before therapy (a) and completely resolved after therapy (b)

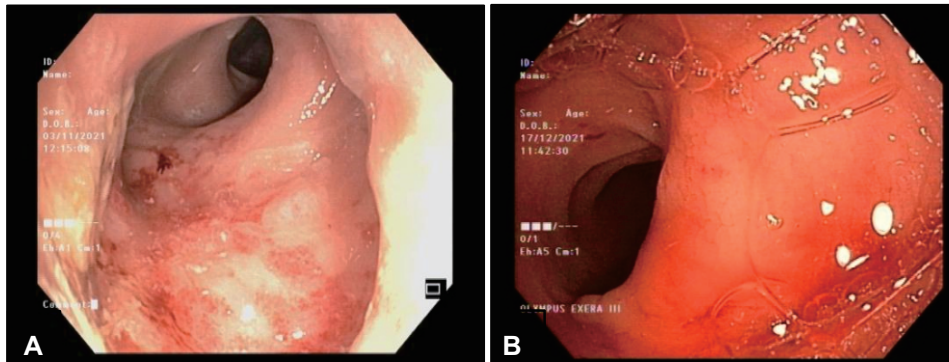


Figure 3. Colonoscopy findings of rectal mucosa before treatment (a) showed improvement in post-treatment examination (b).

(APC) procedure. The patient had undergone external and internal radiation therapy for endometrial cancer treatment nine years ago. The colonoscopy results showed multiple telangiectasia without active bleeding, congested mucosa, and hyperemic rectal mucosa (VRS 2; EORTC/RTOG grade 2). The hemoglobin level was normal (Hb 11,3 g/dL) and a prescription was given for the self-administration of sodium hyaluronate enema twice daily for 28 days. After the completion of the treatment, a repeated colonoscopy was performed, which showed mild hyperemic rectal mucosa, indicating mild radiation proctitis with improvement. The patient returned without any symptoms and the hemoglobin level remained normal (Hb 11,8 g/dL) (VRS 1; EORTC/RTOG grade 0).

DISCUSSION

Each year, more than 14 million new cases of cancer are reported worldwide. Among these cases, approximately half require radiation therapy for both curative and palliative purposes. Although radiation exposure in patients requiring radiotherapy can be beneficial for treating cancer, it also has side effects such as radiation proctitis or inflammation, particularly in cases of pelvic malignancies. Radiation proctitis is caused by direct damage to the mucosa from radiation exposure, which gradually leads to progressive epithelial atrophy and fibrosis with mucosal ischemia.^{4,5}

Radiation proctitis typically appears within three months or more after the initiation of radiation therapy. The risk factors associated with this condition include the radiation modality,

dose intensity, and the presence of IBD, HIV, or genetic predisposition.⁶ The risk of radiation proctitis increases with higher radiation doses, signifying that radiation therapy with doses below 45 Gy causes minimal side effects. Doses ranging from 45 to 70 Gy result in more complications, while those exceeding 70 Gy led to more significant and prolonged injuries. Based on previous reports, the incidence of radiation proctitis in patients receiving doses of 50 Gy or less is approximately 2%, while that of 80 Gy is 18%. Radiation therapy modalities have also been divided into two categories, namely, external beam and internal radiation (brachytherapy). Complications are more common in external radiation, with an incidence of radiation proctitis ranging from 2% to 39%.⁷⁻⁹ Meanwhile, in the case series, patient 1 had undergone radiation therapy with a total radiation dose of 50-60 Gy, which is considered relatively rare for causing radiation proctitis.

The symptoms that can arise in radiation proctitis include mucus rectal discharge, tenesmus, hematochezia, diarrhea, abdominal pain, rectal bleeding, and even iron deficiency anemia. The severity of these symptoms is classified using the EORTC/RTOG classifications.^{5,10} In the case series, all three patients exhibited abdominal pain, two had bloody or mucus-containing stools, and one patient experienced diarrhea. Other symptoms observed in the patients included decreased appetite, nausea, and chronic constipation. Moreover, there was variation in EORTC/RTOG scores, with patients 2 and 3 having symptom severity classified as grade 2. The remaining patient had grade 1 severity

and the laboratory results in the case series were limited. Patient 3, who came with bloody mucus diarrhea, initially had a hemoglobin level of 11.3 g/dL. After receiving an HA enema, the hemoglobin level slightly increased to 11.8 g/dL, and there was no recurrence of bloody mucus diarrhea symptoms.

Further evaluation such as an endoscopic examination was performed to diagnose the patient with radiation proctitis. This examination was used to show alterations in the rectal mucosa such as pale and friable mucosa, telangiectasia, mucosal edema, mucosal atrophy, ulceration, and, in severe cases, the presence of fistulas, strictures, or necrosis. These mucosal changes were assessed using the VRS, consisting of five parameters, namely congested mucosa, telangiectasia, ulceration, stricture, and necrosis. The VRS was highly correlated with the EORTC/RTOG scores and was used to assess clinical complications and mucosal changes during endoscopy.^{5,11} In the case series presented in this study, patients were diagnosed with radiation proctitis based on symptoms and colonoscopy findings. The colonoscopy results varied among the patients, with hyperemic, congested, and edematous rectal mucosa observed, including the presence of telangiectasia. All patients in the case series had colonoscopy findings with a VRS score of 2, indicating the absence of ulceration, strictures, or necrosis.

The management of radiation proctitis focuses on reducing and preventing the progression of mucosal damage. Therapeutic options for radiation proctitis can be divided into endoscopic or non-endoscopic/medication therapy. Endoscopic therapy includes APC, which destroys bleeding vessels and helps relieve rectal bleeding symptoms in radiation proctitis. Generally, medication therapy for radiation proctitis includes oxygen, oral/topical medications (such as 5-aminosalicylic acid (5-ASA), steroids, antioxidants), hormonal therapy, or antibiotics. One of the commonly used medications for radiation proctitis to promote healing and protect the rectal mucosa is sucralfate enema.^{5,10,12}

Hyaluronic acid is a mucopolysaccharide composed of N-acetyl glucosamine and glucuronic

acid, playing a significant role in the formation of the extracellular matrix. This compound has several functions, such as immunity enhancement, anti-inflammatory effects by suppressing proinflammatory cytokines, promotion of tissue healing, facilitation of regeneration of the mucosal epithelium, as well as the exhibition of mucoadhesive and mucoprotective properties to protect the mucosal epithelium. Due to its numerous benefits, hyaluronic acid is increasingly being used in the treatment of various diseases, particularly those associated with mucosal damage and inflammatory processes in different organs.¹³ A study by Riehl et al. in mice showed the radioprotective properties of intraperitoneally injected hyaluronic acid against post-radiotherapy intestinal epithelium, with the protective mechanism mediated by TLR-4 and COX-2. Other investigations have also indicated the benefits of hyaluronic acid in improving symptoms and complaints in the vaginal mucosa, nasal mucosa, and skin epithelium of post-radiotherapy patients.^{3,14} Fiorino et al. showed clinical improvement and endoscopic findings in patients with distal ulcerative colitis after receiving hyaluronic acid enemas for 28 days.³ Additionally, Ferini G et al. discovered that the administration of HA enemas during radiotherapy might be effective in reducing the severity of radiation proctitis.¹⁵ Previous studies supported the approach of hyaluronic application based on the histopathological similarity between rectal and vaginal mucosa. Vaginal ovules containing hyaluronic acid had been used to minimize vaginal toxicity. The results showed that hyaluronic acid promoted mucosa restoration, by improving tissue hydration, regulating inflammatory processes, and protecting against pathogens.¹⁶⁻¹⁷

In the case series presented in this study, all three patients were administered sodium hyaluronate/hyaluronic acid enemas twice a day for 28 days. After the treatment period, significant improvements were observed in symptoms such as diarrhea, bloody or mucus-filled stools, and abdominal pain. Patients 1 and 3 showed a significant response, reporting the absence of any complaints after the treatment. There was also improvement in the colonoscopy findings

compared to before treatment, as indicated by the reduction in EORTC/RTOG scores and VRS.

CONCLUSION

HA enemas are relatively effective in alleviating symptoms and prevent further mucosa damages in radiation proctitis. The benefits of HA enemas administration provide an information to consider HA enemas as initial therapeutic option for radiation proctitis.

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REFERENCES

- Williams HRT, Vlavianos P, Blake P, Dearnaley DP, Tait U, Andreyev HJN. The significance of rectal bleeding after pelvic radiotherapy. *Aliment Pharmacol Ther.* 2005;21(9):1085–90.
- Paquette IM, Vogel JD, Abbas MA, Feingold DL, Steele SR. The American society of colon and rectal surgeons clinical practice guidelines for the treatment of chronic radiation proctitis. *Dis Colon Rectum.* 2018;61(10):1135–40.
- Cosentino D, Piro F. Hyaluronic acid for treatment of the radiation therapy side effects: a systematic review. *Eur Rev Med Pharmacol Sci.* 2018;22(21):7562–72.
- Jaffray DA, Gospodarowicz MK. Radiation therapy for cancer. *Disease Control Priorities, Third Edition (Volume 3): Cancer.* 2015;3:239–47.
- Araujo IK, Muñoz-Guglielmetti D, Mollà M. Radiation-induced damage in the lower gastrointestinal tract: Clinical presentation, diagnostic tests and treatment options. *Best Practice & Research Clinical Gastroenterology.* 2020;48-49:101707.
- Ahmed M, Ahmed R. Radiation in gastroenterology. *Gastroenterology Research.* 2022;15(6):285–96.
- Do NL, Nagle D, Poylin VY. Radiation proctitis: current strategies in management. *Gastroenterology Research and Practice.* 2011;2011:1–9.
- Dahiya DS, Kichloo A, Tuma F, Albosta M, Wani F. Radiation proctitis and management strategies. *Clinical Endoscopy.* 2021.
- Jhingran A. Complications of radiation oncology. *Principles of Gynecologic Oncology Surgery.* 2018;318–29.
- Porouhan P, Farshchian N, Dayani M. Management of radiation-induced proctitis. *Journal of Family Medicine and Primary Care.* 2019;8(7):2173–8.
- Lee J, Hee Dong Han, Byung Soh Min, et al. The role of endoscopic evaluation for radiation proctitis in patients receiving intermediate-dose postoperative radiotherapy for rectal cancer. *Japanese Journal of Oncology.* 2018;48(11):988–94.
- Fuccio L, Guido A, Andreyev HJN. Management of intestinal complications in patients with pelvic radiation disease. *Clinical Gastroenterology and Hepatology.* 2012;10(12):1326-1334.e4.
- Motte CA, Kessler SP. The role of hyaluronan in innate defense responses of the intestine. *International Journal of Cell Biology.* 2015;2015:1–5.
- Riehl TE, Foster L, Stenson WF. Hyaluronic acid is radioprotective in the intestine through a tlr4 and cox-2-mediated mechanism. *American Journal of Physiology.* 2012;302(3):G309–16.
- Ferini G, Tripoli A, Umina V, et al. Radiation proctitis: The potential role of hyaluronic acid in the prevention and restoration of any damage to the rectal mucosa among prostate cancer patients submitted to curative external beam radiotherapy. *Gastroenterology Insights.* 2021;12(4):446–55.
- Delia P, Sansotta G, Pontoriero A, et al. Clinical evaluation of low-molecular-weight hyaluronic acid-based treatment on onset of acute side effects in women receiving adjuvant radiotherapy after cervical surgery: a randomized clinical trial. *Oncol Res Treat.* 2019;42(4):212–8.
- Laliscia C, Delishaj D, Fabrini MG, et al. Acute and late vaginal toxicity after adjuvant high-dose-rate vaginal brachytherapy in patients with intermediate risk endometrial cancer: is local therapy with hyaluronic acid of clinical benefit? *J Contemp Brachytherapy.* 2016;8(6):512.