

Remarkable effects of infliximab on severe radiation-induced side effects in a patient with uterine cervical cancer: a case report

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Abstract

Pelvic radiotherapy is a powerful treatment for a broad range of cancers, including gynecological, prostate, rectal, and anal cancers. Despite improvements in the delivery of ionizing beams, damage to non-cancerous tissue can cause long-term effects that are potentially severe, affecting quality of life and daily function. There is an urgent need for new strategies to treat and reverse the side effects of pelvic radiotherapy without compromising the antitumor effect. A woman with severe radiation-induced intestinal side effects was treated with the tumor necrosis factor-alpha inhibitor infliximab with a dose of 3 mg/kg every 4 to 6 weeks. With infliximab treatment, a remarkable improvement in her bowel health was observed. The patient's late bowel toxicity was reduced from Grade 2 to Grade 0 (RTOG/EORTC Late Radiation Morbidity Scale). Although it is necessary to proceed cautiously because of the risk of serious side effects from immunosuppressants, our case suggests that infliximab can be used to treat symptoms of chronic bowel dysfunction after radiotherapy.

Keywords

Radiotherapy, pelvic cancer, side effect, infliximab, case report, tumor necrosis factor-alpha, immunosuppressant

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Introduction

Radiotherapy is curative in several types of cancer, particularly in locally advanced uterine cervical, vaginal, vulvar, anal, and head-and-neck cancers. Radiotherapy is

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also frequently used as an adjuvant therapy in other malignancies to improve local control, progression-free survival, and overall survival. Moreover, radiotherapy is a useful palliative treatment that can relieve symptoms such as pain and bleeding. However, this potent therapy is not without side effects. The long-term side effects of pelvic radiotherapy are collectively termed manifestations of “pelvic radiation disease,” and the impact of the disease is substantial.¹ At least 80% of irradiated pelvic cancer survivors develop long-term bowel dysfunction because of radiation damage to the intestines.^{2,3} Among these patients, 60% live with deleterious effects on the urinary tract, 50% experience effects on the lymphatic system (lymphedema), and almost all patients experience symptoms that affect sexuality and fertility.⁴ These long-term effects have severe consequences on quality of life and daily function.^{5,6}

There is an urgent need for new strategies to treat and reverse the side effects of pelvic radiotherapy without compromising its antitumor effect. In this brief clinical report, we present a patient with severe radiation-induced intestinal side effects (Grade 2, according to the RTOG/EORTC Late Radiation Morbidity Scale)⁷ and discuss her remarkable improvement after treatment with infliximab (Remicade), a tumor necrosis factor-alpha (TNF- α) inhibitor.

Case description

The patient was born in the early 1950s and subsequently diagnosed with uterine cervical cancer FIGO stage IVA in 1992 with tumor growth to the bladder. She participated in a clinical trial and received three cycles of neoadjuvant chemotherapy (platinol, bleomycin, vincristine), followed by full-dose pelvic radiotherapy. The patient received two-dimensional radiotherapy from two opposite directions (anterior/posterior) with a total dose of 55 Gy (25×2.2 Gy).

With this two-dimensional technique, this means the bladder and rectum also received 2.2/55 Gy (EQD₂ α/β 3 57.2 Gy). The patient also completed two brachytherapy sessions (2×7 Gy). The calculated dose to the bladder and rectum from brachytherapy was 11.2 Gy.

A complete clinical and radiological response was obtained, and the patient was recurrence-free at her first visit to our institution in 2012, 20 years after she completed pelvic radiotherapy.

Unfortunately, during follow-up after her cancer treatment, she developed severe treatment-related side effects. The primary effects were severe radiation cystitis, a vesicovaginal fistula, and chronic obstruction of the left ureter with progressive renal failure of that kidney. In 2006, she underwent surgery with a Bricker conduit and left-sided nephrectomy. Moreover, she suffered from diarrhea, frequent defecation, and imperative defecation urges with numerous occurrences of fecal incontinence.

Her symptoms deteriorated and eventually ruled her daily life and well-being. She started to develop weakness in her legs that progressively worsened. Eventually, she became wheelchair-dependent for longer distances, although she was able to walk short distances. In 1993, she was diagnosed with bilateral lower extremity lymphedema and started using compression garments. Starting in 2012, she had to wear compression garments throughout all waking hours, and she regularly consulted physiotherapists sub-specialized in lymphedema care. Her sexual life was non-existent, mainly because of her physical impairments associated with intestinal and urinary tract dysfunction and lymphedema. In 2012, her intestinal health further deteriorated, and her physician at the Department of Oncology recommended a colostomy. However, around this time, an experienced nurse at her oncological outpatient clinic advised her to consider conservative approaches before undergoing extensive

procedures, such as a colostomy, prompting her to contact our cancer rehabilitation team.

For 5 years, we provided the patient with advanced counseling and medication. In addition to patient-centered education, coaching, and support regarding symptoms, we primarily treated the patient with over-the-counter medications such as bulks (*e.g.*, sterculia gum), antidiarrheals (loperamide), and generous doses of dimethicone to reduce excessive intestinal gas. Furthermore, we tried several specific treatments (*e.g.*, tinctura opii, intermittent antibiotics for bacterial overgrowth, bile acid absorbents, pancreatic enzymes because of her relative pancreatic insufficiency, probiotics, and anticholinergic drugs for intestinal spasms/sub-ileus). Our efforts significantly improved the patient's symptoms, quality of life, working ability, and social life. However, her chronic radiation-induced bowel symptoms limited her daily life, and we continuously sought new strategies to relieve and potentially reverse them.

Immunomodulatory drugs, such as TNF- α inhibitors, are commonly used, and they have displayed significant effects against erosive rheumatoid arthritis, fulminant ulcerative colitis, and Crohn's disease.^{8,9} Bower *et al.* presented their research on inflammatory-induced fatigue after radiotherapy mediated by TNF- α , a cytokine involved in inflammation and infection.¹⁰ We therefore hypothesized that TNF- α inhibitors would ameliorate, or even reverse, at least some of the radiation-induced bowel symptoms. Despite searching databases and consulting with gastroenterology and rheumatology specialists, we found no prior studies or case reports that provided support for our hypothesis.

The side effects of infliximab are primarily acute allergic (anaphylactic) reactions and exacerbation of latent infections. Cervical cancer is caused by persistent human papillomavirus¹¹ modified by immunological factors in the host.

Consequently, we were hesitant to treat a patient who had a verified virus-induced cancer with an immunosuppressant. However, because this patient was treated 25 years ago with complete remission and no tumor recurrence, we decided to treat her with infliximab after her approval.

She received her first treatment with infliximab 3 mg/kg in September 2017, a second treatment 2 weeks later, and a third treatment 4 weeks later according to protocols for erosive rheumatoid arthritis and fulminant inflammatory bowel diseases (weeks 0, 2, and 6). Shortly after the first treatment, she reported improvement of her intestinal symptoms. By the third treatment, her bowel habits had changed from 30 to 40 episodes of diarrhea daily, including at nighttime, to one or two normal defecations on a good day and six or seven defecations on a bad day. She stated she had not felt this healthy in many years, and she experienced no side effects related to infliximab. According to the treatment protocols for inflammatory bowel disease, we planned maintenance treatment with infliximab every eighth week. However, when she came for her first maintenance treatment in early January 2018, her symptoms had intensified in the last 2 weeks, and she was again experiencing 30 to 40 episodes of diarrhea per day, including at nighttime. The day after her planned treatment in week 8, she again reported remarkable improvement with restored well-being, undisturbed sleep, and one or two normal defecations daily. We found that by shortening the maintenance treatment intervals to 4 to 6 weeks, we could sustain her improved bowel health. Before infliximab treatment, the patient experienced Grade 2 late bowel toxicity according to the RTOG/EORTC Late Radiation Morbidity Scale.⁷ Following infliximab treatment, the patient's bowel symptoms improved, and they did not qualify for any toxicity grading.

During a routine check-up in September 2020, after 36 total treatments, the patient disclosed that she had a pressure sore because of being confined to a wheelchair. Due to this disclosure, we opted to pause the treatment for safety reasons. During a telephone follow-up in December 2020, the patient said that her bowel symptoms had remained mild despite discontinuing infliximab. At the time, she was receiving treatment for her pressure ulcer at another clinic, and it had almost healed. Unfortunately, in December 2020, the function in her remaining kidney deteriorated (for unknown reasons), and she eventually died from kidney failure in August 2021. Our last telephone follow-up was in July 2021, and she had no problems with diarrhea at that time. Other than continuous clinical interviews during treatments and between treatments over the telephone, she completed questionnaires focusing on her intestinal health at repeated intervals. We also regularly collected routine blood samples and occasionally analyzed fecal calprotectin levels to evaluate inflammation and the gut–blood barrier (with normal values).

According to institutional guidelines, this case report was approved by the head of the Department of Oncology, Sahlgrenska University Hospital (Gothenburg, Sweden). Patient details are de-identified, and per institutional guidelines, consent was not required for this case report. The reporting of this study conforms to the CARE guidelines.¹²

Discussion

We observed a remarkably positive effect of infliximab in a cervical cancer survivor with severe pelvic radiation disease. We do not know if this is an exceptional case, as we have not identified earlier studies or case reports that attempted to treat radiation-induced bowel symptoms with infliximab. However, our own studies in a mouse

model of pelvic radiotherapy^{13–15} and biopsies from pelvic cancer survivors with chronic bowel dysfunction¹⁶ suggest the presence of chronic low-grade inflammation in the radiation-exposed intestinal mucosa. Infliximab could improve low-grade inflammation, although we have no data supporting this hypothesis and it is unknown whether the inflammation was related to the patient's symptoms. Taken together, this case has raised many questions that we hope to be able to answer within the near future:

1. Could TNF- α inhibitors, such as infliximab, alleviate radiation-induced bowel symptoms or even prevent the progression to chronic bowel dysfunction in pelvic radiation disease?
2. If this is proven, then when is the optimal time point to introduce the treatment? A remarkable effect was observed in this patient despite being treated more than 25 years after radiotherapy.
3. How long should the treatment continue?
4. What are the underlying mechanisms of action?
5. Does treatment with infliximab also ameliorate radiation-induced symptoms in other organs?

Other important questions include whether other biologicals developed to treat inflammatory bowel disease, such as vedolizumab, would be equally or more effective, whether treatment with immunosuppressants would compromise the cancer prognosis, and whether a previous virus-induced cancer poses a greater risk than other cancers. In addition, it will be crucial to determine which additional factors should be contraindications or prompt the discontinuation of treatment.

In gynecological patients, the most distal part of the bowels receives extremely high radiation doses despite current radiation techniques that ensure more precise delivery.

Additionally, the radiation oncologist can use modern high-precision radiotherapy to increase the dose to the tumor, thereby reducing the tissue-sparing effect.¹⁷ In combination with increased cancer survival rates and life expectancies, these factors ensure that gastrointestinal toxicity following radiotherapy remains a relevant challenge.¹⁸ Our case report suggests that infliximab can potentially serve as a therapeutic agent for chronic bowel dysfunction after radiotherapy. However, because of the powerful biological effects of infliximab, caution is required. We are currently designing a pilot study that after ethical approval will include a small number of pelvic cancer survivors with chronic and severe bowel issues. If we find that infliximab reduces their symptoms, we plan to conduct a controlled trial that we hope will lead to a much-anticipated breakthrough in the treatment of pelvic radiation disease.

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Author contributions

K.B.: Conceptualization, clinical management, and writing of the original draft; C.B.: Funding acquisition, writing – review and editing; A.T.: Writing – review and editing.

Data availability statement

Not applicable.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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