


SHORT REPORT

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Management of radiation-induced proctitis using submucosal endoscopic injections of autologous adipose-derived stromal vascular fraction: a case report

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Abstract

Background Standard approaches to the treatment of chronic post-radiation proctitis are associated with a high risk of complications and a high percentage of unsatisfactory results due to the reduced regenerative potential of irradiated tissues. Regenerative surgery techniques using the stromal-vascular cell fraction (SVF) based on the patient's autologous adipose tissue are a promising direction for study.

Clinical case description A 76-year-old patient suffering from chronic post-radiation erosive-ulcerative proctitis, grade 4 according to RTOG–EORTC, complicated by recurrent profuse rectal bleeding, underwent local autotransplantation of SVF into the submucosal layer of the rectum and pararectal connective tissue. The follow-up colonoscopies 1 and 6 months after the surgery and histological examination showed the complete epithelialization of ulcerative defects and a decrease in proctitis activity. There were no bleeding episodes during the 12-month postoperative observation period.

Conclusion The proangiogenic, wound-healing, and anti-apoptotic effects of the SVF cell suspension provided reduction of inflammation activity, epithelialization of ulcers, and elimination of defecation-associated hemorrhage, following the SVF injection into the submucosal layer of the rectal wall and pararectal connective tissue in a patient with post-radiation proctitis with ulcers and recurrent bleeding.

Keywords Regenerative surgery, Stromal-vascular fraction, Chronic post-radiation proctitis, Mesenchymal stromal cells

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Introduction

The incidence of chronic post-radiation proctitis reaches 47% among patients who underwent radiation therapy due to pelvic malignancies [1, 2]. These disorders have a chronic relapsing course and represent a serious problem for modern clinical practice. The existing algorithms of post-radiation proctitis treatment involve 3 basic therapy components: drug therapy, endoscopic approaches, and surgery [3–6].

The traditional conservative therapy for proctitis-associated hemorrhage from the mucosal ulcers includes systemic and local application of amino salicylates and glucocorticoids, and a treatment with formalin, with the efficiency of up to 75% [7, 8]. An alternative approach of the conservative therapy for hemorrhages due to radiation-induced proctitis is the use of hyperbaric oxygenation, resulting in 32% efficiency [9]. However, these approaches are directed at symptoms and do not affect the pathogenesis of post-radiation complications. Endoscopic argon plasma and radiofrequency coagulation are 80–90% effective when applied in a stepwise manner, with the procedures repeated every 4 weeks. The risk of complications, such as hemorrhage, rectal wall necrosis and perforation are 10% for these techniques [10].

Surgery is usually reserved for patients with highly significant and debilitating bleeding, stricture, or fistula (see below) due to very high morbidity and mortality rates. The ideal surgical approach, in particular the question of simple diversion versus formal resection, remains unclear [3, 11].

The techniques of regenerative surgery appear thus most preferable due to their direct effect on the pathogenetic mechanisms of post-radiation pathological changes [12]. Currently, autotransplantation of biomaterials derived from the autologous adipose tissue harvested by liposuction is one of the basic instruments of regenerative surgery. Their regenerative potential is based upon the biological effects of the stromal-vascular fraction (SVF), which contains multipotent mesenchymal stem cells and other bioactive components. SVF realizes proangiogenic, wound-healing, antifibrotic, antiapoptotic and immunomodulating effects via the paracrine mechanism [12–14]. Application of autologous SVF derived from the adipose tissue appears the most promising technology for treating post-radiation lesions of the rectum from the viewpoint of safety and efficiency [14].

Materials and methods

Patient A., 76-year-old, received 2 courses of proton therapy to the pelvic region with the total radiation equivalent dose of 90.6 Gr ($\alpha/\beta=1.5$) in September, 2022 due to prostate adenocarcinoma. In February, 2023 the patient noted discharge of bright red blood from the

rectum during defecation. The patient received 5-aminosalicylic acid therapy systemically and locally, strictly followed the nutrition and lifestyle recommendations, however, the bloody discharge of varying intensity from the rectum was still present. The patient was urgently hospitalized three times with profuse rectal hemorrhage. Endoscopic hemostasis was performed, including argon plasma coagulation. Hemostatic therapy and transfusion of blood components were also performed. The last hospital admission took place in May, 2023, with the reduction in the hemoglobin level to 60 g/L. In June, 2023 the patient had an outpatient consultation at the FRCC of the FMBA of Russia. Colonoscopy revealed restricted ulcerative proctitis in the middle and upper ampullary region of the rectum with multiple ulcerative lesions at the posterior semicircle of the rectum with diameters of 7–14 mm, covered with fibrin, bleeding upon contact (Fig. 1A, B). Biopsy showed chronic proctitis of the high activity grade (Fig. 1C). The complex clinical and instrumental examination of the patient did not provide data indicating the oncological process's progression (relapse or metastases).

The oncological consultation was held. The patient was diagnosed with chronic post-radiation erosive-ulcerative proctitis, class 4 according to RTOG–EORTC, complicated by relapsing hemorrhages, against the background of the primary disease, prostate cancer stage cT3N0M0, after the radiation (proton) therapy with the total radiation equivalent dose of 90.6 Gy in September, 2022. The therapy administered for 5 months in the framework of clinical recommendations did not result in a positive effect, the risk of the profuse rectal hemorrhage relapse was still high. A decision was made about injection autotransplantation of the adipose-derived stromal-vascular fraction into the submucosal layer of the rectum and pararectal subcutaneous tissue.

The adipose tissue was harvested in the aseptic conditions of the operating room, using a Ø2.0 mm cannula with 16 Ø0.75 mm holes by syringe liposuction with the preliminary Klein's solution infiltration of the hypogastric and mesogastric adipose tissue through the skin punctures of Ø1.5 mm. After the completion of the lipoaspiration the skin punctures were sutured. The harvested lipoaspirate with the volume of 300 mL was transferred in the aseptic conditions to the Laboratory of Cell Technologies of the FRCC of the FMBA of Russia, where it was refabricated to obtain a purified SVF cell suspension. In the laboratory conditions of a laminar flow hood the obtained adipose tissue was placed in sterile 50 mL test tubes and washed 5 times with the buffer solution. The washed adipose tissue underwent an enzymatic treatment with the equal volume of collagenase type 1 (activity of 300 U/mL). The mixture was incubated for 2 h at 37 °C. Upon the incubation, the mixture was centrifuged

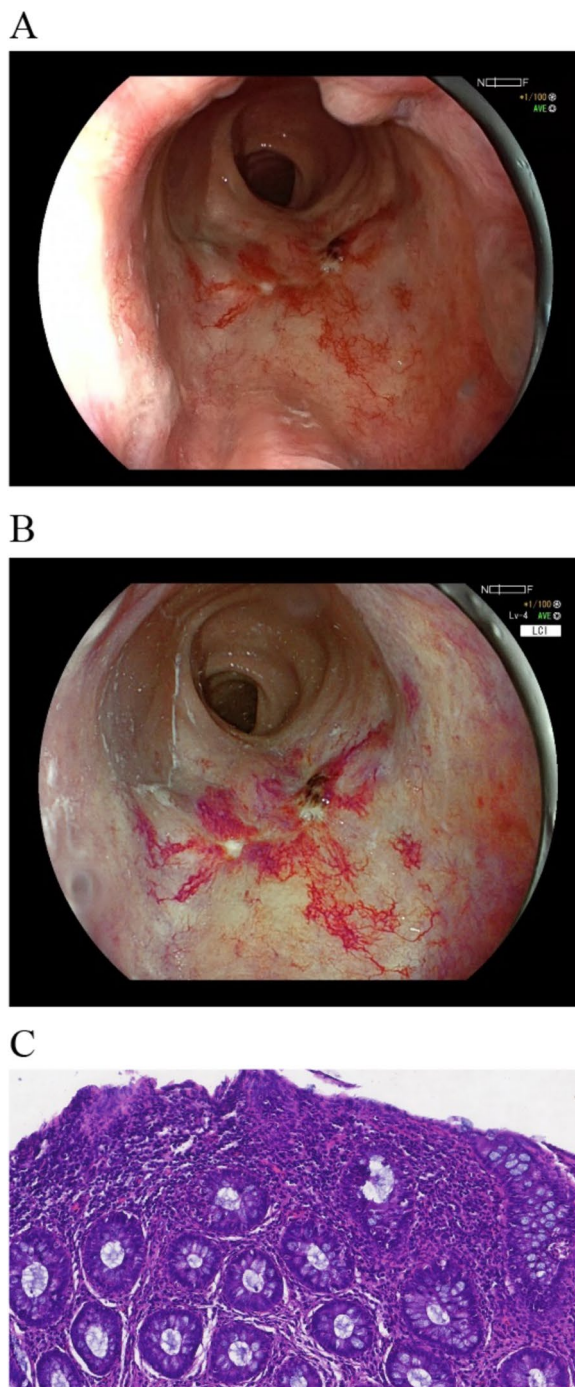


Fig. 1 Ulcerative colitis with numerous ulcerous defects at the posterior semicircle of the rectum with the diameters of 7–14 mm, covered with fibrin, bleeding upon contact. Endoscopic picture of the rectum prior to surgery in the white light (**A**) and with narrow-band imaging (**B**). High activity chronic proctitis with desquamation of the epithelium and pronounced lympho-leukocyte infiltration. Hematoxylin–eosin stain (**C**)

at 500 g for 5 min, then the fatty fraction on top was collected and removed. The cell precipitate was resuspended in the buffer solution, and the obtained mixture was centrifuged again at 500 g for 5 min. The supernatant was removed, and the cell precipitate was disseminated in the buffer solution.

The SVF cell composition was analyzed as described in the Supplementary materials.

The prepared SVF cell suspension was transferred into two 10 mL syringes in the aseptic conditions, packed in the same conditions and transported to the operating room. Using the visual control by colonoscopy, periulcer injections into the submucosal layer of the rectum were performed over the whole circumference of the rectal ampulla with the formation of papules (Fig. 2) and in a diffuse manner in the pararectal subcutaneous tissue. An endoscopic injector with the length of 280 cm and the needle diameter of 0.7 mm was used for the submucosal and pararectal injections.

The successful SVF administration was achieved due to the precision injection using endoscopic visualization and an endoscopic injector with the diameter of as small as 0.7 mm. This technique allows gentle administration of the bioproduct into the tissues with fibrosis.

Results

Cell composition of SVF

As shown by flow cytometry of SVF, the obtained cells had the following phenotypic composition: CD29+ 5.56%; CD44+ 9.7%; CD90+ 10.2%; CD105+ 8.09% (these 4 markers are characteristic of mesenchymal stromal cells); CD34+ 10.4%; CD45+ 11.8% (these two markers are characteristic of hematopoietic cells) (Fig. 1S). Stromal cells derived from SVF after culturing in the standard conditions (3d passage) demonstrated the ability to differentiate into adipocytes, chondrocytes and osteoblasts, characteristic of MSC (Fig. 2S).

Clinical observations

The postoperative period was uneventful, the patient was discharged on the 3rd day.

The control colonoscopy in 1 month post-surgery showed the complete epithelization of ulcerous defects of the rectum and the positive dynamics of the proctitis course (Fig. 3A, B).

Six months post-surgery, the endoscopic picture of proctitis remission, as well as the absence of hyperemia and mucosal lesions were noted during colonoscopy. When examining in the narrow-band mode, neoangiogenesis of the rectal wall was observed (Fig. 4A). The

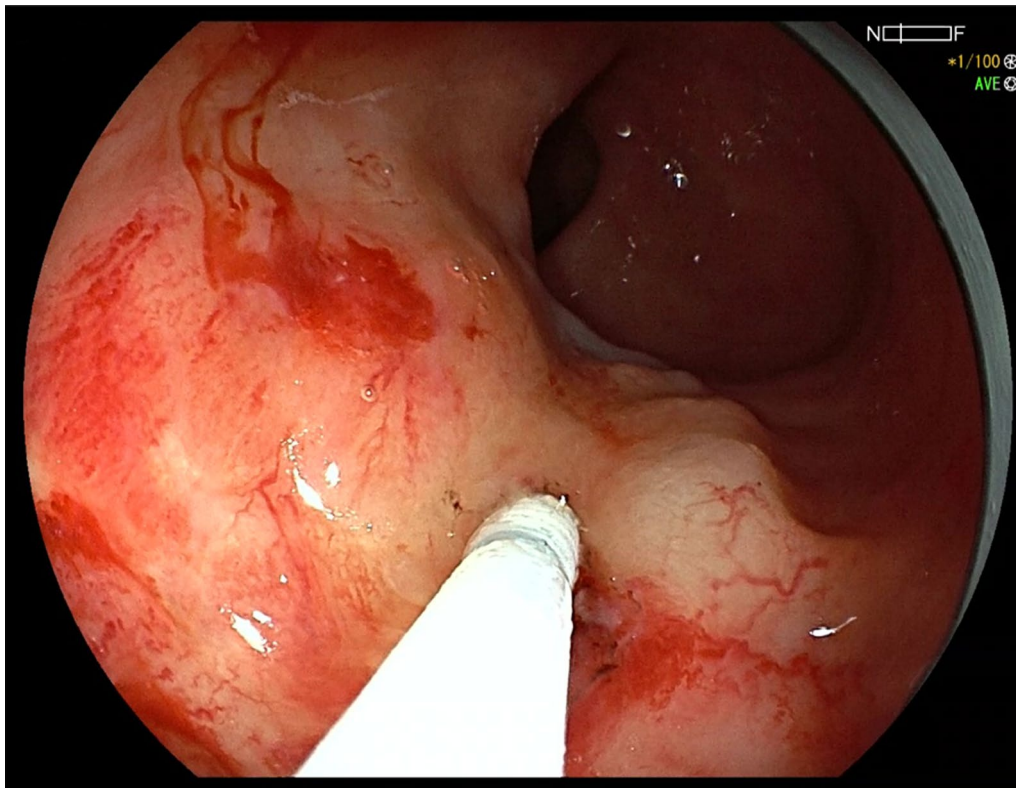


Fig. 2 Periulcer injections of the SVF cell suspension with the formation of papules

histological study of the rectal mucosa showed chronic moderately expressed catarrhal proctitis of the minimum activity (Fig. 4B). No signs of rectal bleeding were noted for 12 months. Laboratory studies found no signs of chronic anemia. Thus, stable remission of post-radiation proctitis was achieved in the patient against the background of the performed regenerative therapy based on local autologous SVF injections.

Discussion

The histological changes observed in radiation-induced proctitis include lesions and atrophy of the mucosa, caused by infiltration of inflammatory cells during the acute stage, as well as ischemia and fibrosis due to “swelling” of endothelial cells and development of endarteritis during the subacute and chronic stages. The deficit of the tissues’ regenerative potential after radiation therapy prioritizes the search for any approaches to the stimulation of regeneration in the radiation-affected rectum.

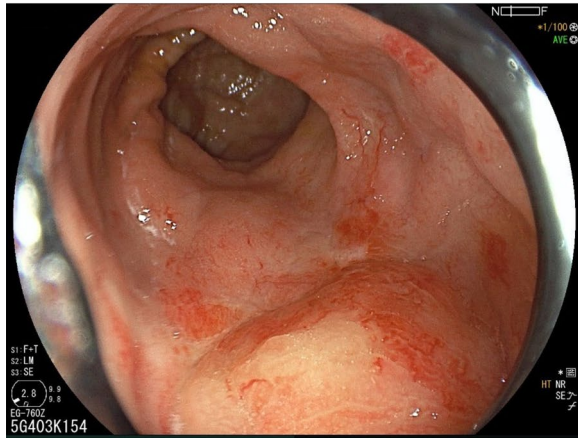
To date, a fairly large set of data has been accumulated on the regenerative effects of allogeneic MSC and their exosomal preparations in various diseases [15]. In our previous studies, we demonstrated the regenerative action of conditioned medium derived from allogeneic

MSC in the treatment of chronic hard-to-heal wounds [16].

MSC launch immune modulation, neovascularization and are characterized by pronounced antifibrotic properties [17]. MSC affect antigen-presenting cells by altering the cytokine profiles of T-cells, NK-cells and dendritic cells from the proinflammatory phenotypes to tolerant ones. MSC have an immunosuppressive effect on dendritic cells, reducing the secretion of tumor necrosis factor- α , interferon- γ , costimulatory molecules (CD 80 and CD 86). They also act on T-cells, inhibiting differentiation and proliferation, and on T-regulatory cells to activate the secretion of transforming growth factor- β , interleukin-10 and prostaglandin E2. MSC are multipotent cells which can differentiate into neural, adipose, bone and epithelial cells, and also may migrate to damaged tissues and participate in the regeneration. MSC demonstrate low immunogenicity, low levels of the main histocompatibility complex (MHC) I and absence of MHC II and costimulatory molecules and are therefore considered adequate candidates for allogeneic cell therapy [18].

The safety and efficiency of allogeneic MSC and their derivatives in the therapy of post-radiation proctitis in humans is still to be studied. However, the

A



B

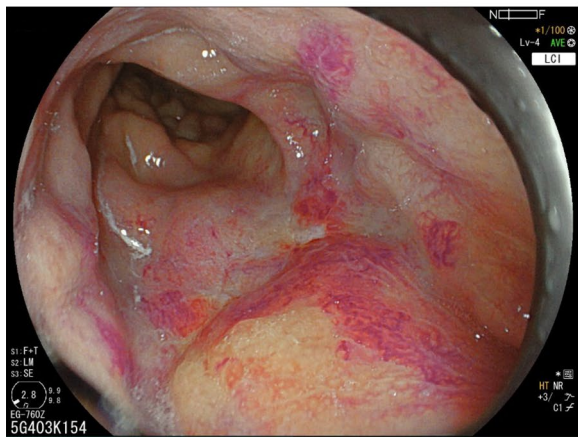
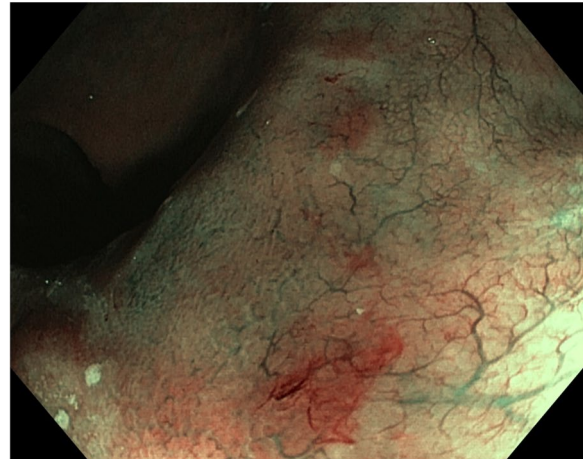


Fig. 3 Endoscopic picture of the rectum 1 month post-surgery in the white light (A) and with narrow-band imaging (B). The complete epithelization of ulcerous defects of the rectum, positive dynamics of the proctitis course

preclinical testing using animal models of ulcerative proctitis (including radiation-induced proctitis) has demonstrated the efficiency of both bone-marrow and adipose-derived MSC [18]. A few Phase IB/IIA studies have been conducted on the MSC treatment of the rectum affected by Crohn's disease and ulcerative colitis. At the Cleveland Clinic (USA), 18 patients with Crohn's disease complicated by perianal fistulae were treated, and the complete clinically and radiologically confirmed healing was observed in 15 patients (83%) [19]. A group of researchers from the Leiden University (Netherlands) published successful treatment results for 13 patients with refractory ulcerative colitis [20]. At the Luigi Sacco University Hospital, University of Milan (Italy), 3 patients with complicated refractory perianal

A



B

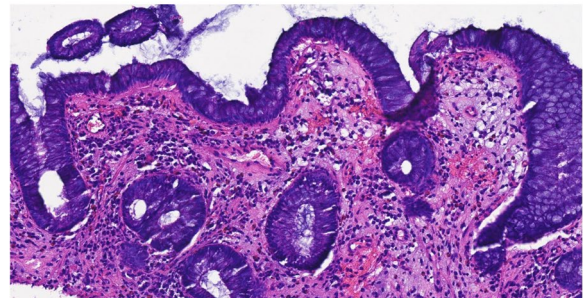


Fig. 4 Narrow-band imaging colonoscopy 6 months post-surgery. Neoangiogenesis in the rectal wall (A). Chronic moderately expressed catarrhal proctitis with the minimum activity and weakly expressed lympho-leukocyte infiltration. Restoration of the surface epithelium. Hematoxylin–eosin stain (B)

fistulae due to Crohn's disease were successfully treated [21]. The researchers from the Asan Medical Center (Seoul, Korea) have accumulated the largest experience, from 2014 to 2022 they treated 65 patients with Crohn's disease-associated perianal fistulae with the closure rates of 66.2%, 73.8% and 75.4% for 1, 2 and 3 years, respectively [22].

Due to the difficulties with the regulations and production of allogeneic MSC and their derivates, adipose-derived autologous preparations, such as SVE, present a safe alternative for regenerative therapy. According to different data, they contain from 10 to 20% of MSC [23]. Our data testify that SVF contains no less than 10% of MSC, if judging from the number of CD44+ and CD90+ cells (Fig. 1S). The experience of Russian coloproctologists has demonstrated that adipose-derived autologous SVF is safe and efficient in the treatment of post-radiation lesions, including proctitis and rectovaginal fistulae [12].

The procedure we applied here implies the use of a purified cell suspension—SVF. We used the enzymatic method of SVF extraction, which is advantageous in respect to non-enzymatic approaches in the total cell yield per adipose tissue volume unit [24]. However, the practical application of the enzymatic method is possible only with the special equipment, expendables, trained laboratory personnel and conditions for timely aseptic transportation of the adipose tissue and prepared bio-material. These limitations hinder the wide spread of this technique making it applicable only in the conditions of big clinics. The oncological safety of autologous adipose-derived bioproducts has been proven by a number of studies [25, 26] and should not be a limiting factor for the technique implementation.

In this study, the patient had a 5-month long therapy of post-radiation proctitis, complicated with hemorrhage, using the traditional protocols, which involved local and systemic administration of 5-aminosalicylic acid preparations, without any positive effect. In spite of the traditional treatment, the patient's condition worsened. After the SVF treatment, we observed the stable remission of the clinical symptoms, and regression of the proctitis signs according to the histological study. Thus, the treatment of this patient prior to the SVF administration may be considered a rescue experiment, in which no active component was applied.

Conclusion

The presented clinical observation demonstrates the safety and potential efficiency of local injections of the autologous stromal vascular fraction in the treatment of post-radiation proctitis.

To date, only little experience has been accumulated in the injection autotransplantation of adipose-derived SVF for post-radiation lesions. So far, such techniques have been applied only in the framework of Phase IB/IIA studies, that does not allow for their wide recommendation. However, in our opinion, the SVF application is justified in certain cases of severe post-radiation proctitis, accompanied by the development of life-threatening complications or those essentially impairing the patient's quality of life.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13287-024-04017-3>.

Additional file 1.

Acknowledgements

The authors declare that they have not used Artificial Intelligence in this study.

Author contributions

AVS, VIS, DVS, SMK performed the surgical and laboratory parts of therapy. AVS, VIS contributed to the overall concept, search-analytical work, data analysis and discussion, and writing the manuscript. MAK, SMK, VAK contributed to writing the manuscript. YVI contributed to the overall concept, patient treatment supervision and discussion of results, and editing the text. VRS, FGZ, VPB contributed to the discussion of results and editing the text. VPB, VSV provided scientific consultation on the methodology. AVT provided the entire project supervision.

Funding

The study was performed in the framework of the State Assignment of the FMBA of Russia, in the framework of the research project "Regenerative Therapy of Socially Significant Diseases".

Availability of data and materials

No data were used in this study.

Declarations

Ethics approval and consent to participate

The study was approved by the Local Ethical Committee of the FRCC of the FMBA of Russia "Radiation-induced proctitis treatment using submucosal endoscopic injections of autologous adipose-derived Stromal Vascular Fraction" (protocol No. 5 of May 24, 2022). The patient had signed the informed consent about the participation in the study.

Consent for publication

The patient had signed the informed consent about the publication of the study results.

Competing interests

The authors declare that they have no competing interests.

Received: 24 July 2024 Accepted: 25 October 2024

Published online: 09 November 2024

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