Treatment of Oncological Post-surgical Wound Dehiscence with Autologous Skin Micrografts

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Abstract. *Background/Aim. The closure of postoperative wounds is essential in order to prevent surgical site infections or wound dehiscence, mainly in oncological patients. We aimed to demonstrate the efficacy of autologous micrografts in the management of wound dehiscence in an oncology patient undergoing decompressive spinal laminectomy. Case Report: A 57-year-old man with IgG multiple myeloma and medullary plasmocytoma C7-T3, was to undergo decompressive spinal laminectomy and vertebral fixation leading to a wound dehiscence with exposed instrumentation. Autologous micrografts were obtained by Rigenera protocol and directly applied to the dehisced wound. After 60 days of negative pressure wound therapy, we observed reduction of the diameter and depth of wound dehiscence, with a coverage of instrumentation, without complete re-epithelialization, that instead was reached by application of autologous micrografts after 70 days. Conclusion: The Rigenera protocol may be the solution for complex wounds in oncological and immune-compromised patients where other treatments are contraindicated.*

The closure and healing of postoperative wounds is essential for preventing potential complications such as surgical-site infections and the onset of wound dehiscence, and this aspect of surgery remains a great challenge for surgeons, patients and their relatives (1).

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This issue is certainly more pressing in patients affected by oncological diseases. In fact, while skin integrity is important for all patient, there is special consideration for oncological patients, who often have an increased risk of developing complications from non-healing wounds (2, 3). In addition, in 5-10% of oncology patients, adjuvant treatments such as chemotherapy but mainly radiotherapy, although needed to counteract neoplastic growth, significantly compromise local tissue vascularization, leading to the onset of complex wounds, such as fungating wounds or ulcerating tumors that arise from primary, secondary or recurrent malignant disease (4, 5). Regarding damage caused by radiotherapy and chemotherapy, while it is well known that all forms of radiation may damage the skin, the correlation between chemotherapy agents and complex wounds is still a matter of debate in the literature. Wound-healing complications can represent a long-term effect of radiotherapy, due to acute radiation inhibiting fibroblasts outgrowth, leading to a reduced deposition of collagen and wound strength with decreased angiogenesis (6). Although effective in the treatment of neoplastic diseases, chemotherapy is associated with many side-effects, including cutaneous or dermatological toxicities that may occur in various forms and occasionally may also cause dose-limiting toxicities (7).

Many others factors can delay wound healing in oncological patients, such as a high body mass index, moreover in obese women undergoing gynecological oncological interventions, an increased percentage of surgical dehiscence (8) or malnutrion, immunosuppressive disorders, diabetes, peripheral vascular disease and tobacco use were reported (9, 10). The incidence of post-surgical dehiscence in oncological patients is highly variable and dependent on the surgical site, for example, anastomotic dehiscence has an incidence of 8% following anterior rectal carcinoma resection (11), whereas port site hernias or dehiscence in robotic-assisted procedures in gynecological oncological patients is as low as 0-1.2% (12).

In general, surgical intervention in oncological patients is not without risk, and the benefits must be weighed against the mortality and morbidity profiles of the procedure. Adverse events (AEs) can be catastrophic in this fragile population, for whom quality of life is so paramount in their remaining time. The societal costs of these AEs for this palliative intervention is also an important consideration (13).

The aim of this study was to report a new promising clinical protocol, named the Rigenera protocol, in the management of post-surgical dehiscence affecting an oncological patient undergoing decompressive spinal laminectomy. The Rigenera protocol is based on the application of autologous micrografts directly to the dehisced wound and its efficacy was already shown in the management of leg ulcers and postoperative wound complications (14).

Case Report

A 57-year-old man with IgG multiple myeloma, already treated with chemotherapy, and medullary plasmocytoma C7-T3, 2 years earlier, was undergoing decompressive spinal laminectomy and vertebral fixation. A few days after surgery, there was a wound dehiscence with exposed instrumentation. One month after this intervention, the patient was treated with advanced dressings without benefit, and at the same time, the patient started chemotherapy again. Subsequently, 3 months after the laminectomy, the patient was treated with negative wound pressure therapy (NWPT) for 2 months to cover the bone. We observed a reduction of the diameter and depth of wound dehiscence accompanied by coverage of instrumentation but no complete re-epithelialization of the wound was evident (Figure 1a and b).

To better improve the wound-healing process, we treated the patient with autologous micrografts by the Rigenera protocol. The Rigenera protocol allows damaged tissues to regenerate, as already reported in previous studies (14, 15), and is based on the use of a Rigenera machine and Rigeneracons (Human Brain Wave, Turin, Italy). This method uses a biological disruptor that is able to disaggregate small pieces of human tissues and select a specific cell population, including progenitor cells that maintain the capacity to differentiate into several cell types and then regenerate damaged tissue. These progenitor cells allow for creation of autologous micrografts, ready to use alone or in combination with different biological scaffolds such as collagen.

In our case, we collected a small piece of skin from the internal surface of the left arm that was then cut into three pieces of almost 2 mm size. Each piece was disaggregated by Rigeneracons adding 1.2 ml of sterile saline solution for 2 min. We obtained 3.5 ml of cell suspension that was injected directly into all the wound edges and into a collagen dressing that was positioned over the wound floor. The wound was then dressed with hydrofiber and polyurethane foam. The patient was monitored weekly for 3 months.

As indicated in Figure 1c, as soon as 7 days from micrograft application, we observed a marked reduction of wound size which was more significant after 12, 35 and 48 days (Figure 1d-f, respectively). Finally, about 3 months after micrograft application, a beneficial outcome was achieved, we observed a good closure of the wound and re-epithelialization (Figure 1g).

This was the pivotal point for this patient as a quick reduction of the wound size was mandatory. In fact, the patient was to undergo new chemotherapy treatment for 1 month followed by bone marrow auto-graft. Hence we did not use a flap coverage as the risk of failure would be high and we did not use platelet-rich plasma (PRP) as the patient had been submitted to many chemotherapies, but we did need to reduce the wound surface as soon as possible to reduce risk of infection during chemotherapy and bone narrow grafting.

Note that the Rigenera protocol was successful and the patient started chemotherapy 21 days after micrograft application.

Discussion

In this report, we showed the effectiveness of autologous micrografts obtained through the Rigenera protocol in ameliorating the healing of postsurgical dehiscence in an oncological patient in whom classic advanced dressings, including NPWT, failed to reach an optimal outcome. These results are in accordance with other recent studies where it was reported that the Rigenera protocol improved the wound healing of complex wounds occurring as postoperative complications (14) and also of pathological scars (15). In addition, a recent article reported that micrografts obtained through the Rigenera protocol and applied to a leg lesion successfully repaired the lesion, promoting re-epithelialization and softness of the tissue (16). Furthermore, the Rigenera protocol has also been successfully applied in the field of dentistry, in the regeneration of both atrophic maxilla (17) and periodontal tissue (18), and in esthetic surgery where it promoted the engraftment of transplanted hair (19). The capacity of these micrografts to improve wound healing was also supported by *in vitro* results showing a high cell viability despite mechanical disaggregation that is performed to obtain them (16, 20). Additionally, these micrografts display a high regenerative potential, as indicated by increased positivity to mesenchymal stem cell markers such as CD90, CD73 and CD105 (20).

As reported in the literature, oncological patients frequently experience adverse events, whose high incidence should be considered by oncologists and surgeons in determining appropriate management and preventative strategies to reduce such risks (21). In fact, in oncological

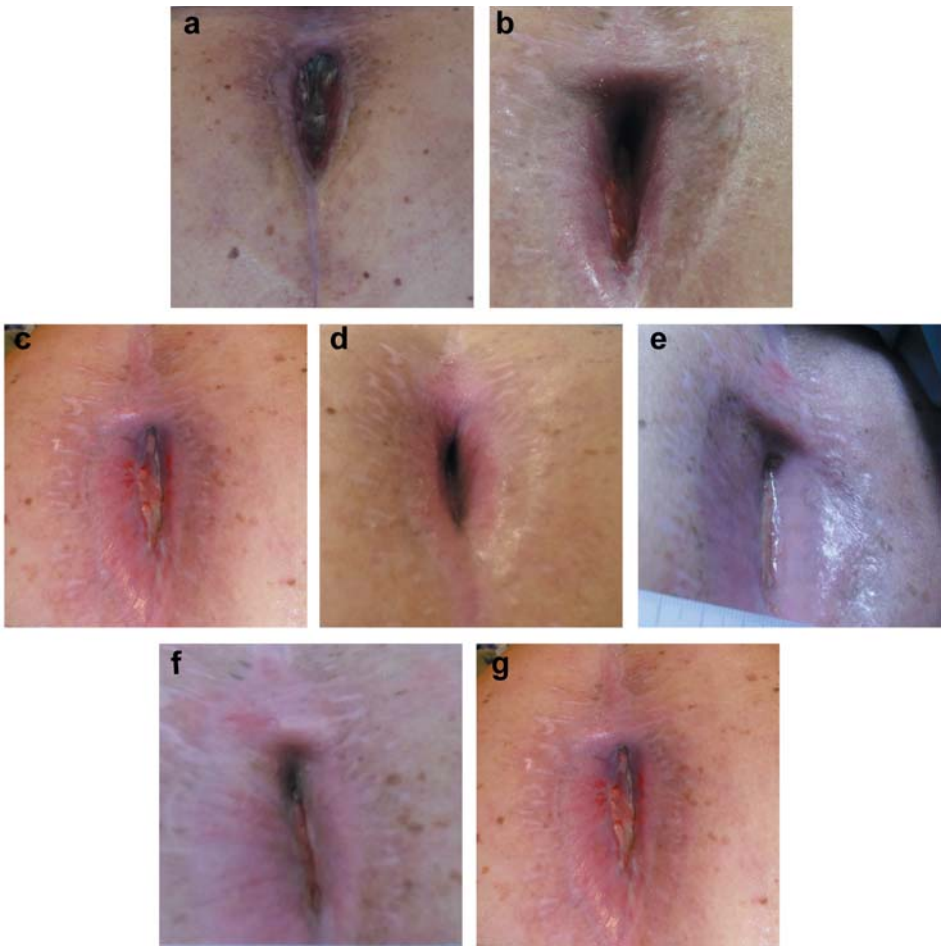

Figure 1. *Wound dehiscence was firstly treated with negative pressure wound therapy for 2 months and later with the Rigenera protocol for 75 days. Wound dehiscence before (a) and after (b) VAC therapy. Wound dehiscence at 7 (c), 12 (d), 35 (e), 48 (f) and 75 (g) days after treatment by the Rigenera protocol.*

patients undergoing surgical interventions for metastases, wound dehiscence occurs a few weeks after radiotherapy. In this case, some authors showed that the use of rotational and transpositional flaps significantly reduced the comorbidities associated with radiotherapy-induced wounds (22, 23).

Although several studies have been conducted to improve wound healing in oncological patients, to date the literature about wound management is still very poor. To address this issue, a retrospective study compared the healing pattern of patients with and without cancer, reporting that patients with cancer are less likely to have wounds that heal compared to patients without cancer, probably due to malnutrition or immunosuppression which can impair the wound-healing process. However, all healed wounds tended to heal at the same time (55 and 50 days for patients with cancer and those without cancer, respectively). Finally, as expected, patients with cancer had significantly more comorbidities which potentially affect wound healing than patients without cancer (24).

On the basis of these considerations, we believe that the Rigenera protocol offers a valid support to existing approaches for improving wound healing in patients with cancer who are more susceptible to developing wounds that are hard to heal. Among actual approaches, NPWT is certainly one of the most commonly used to treat wound complications, but although NPWT may improve wound healing, this therapy is usually contraindicated for necrotic and tumoral wounds because of its ability to promote proliferation of neoplastic cells, even when increasing drainage capacity and reducing the number of dressing changes (5, 25); on the contrary, there is no contraindication to its application over an oncologically safe resection site (26). Regarding our case, the use of NPWT for spinal wounds has been highlighted to promote wound healing and prevent surgical site infection but to date, as reported by a recent meta-analysis, there are limited randomized controlled trials to support the effectiveness of this treatment in spinal wound complications (27).

The current literature includes several studies investigating the molecular, cellular and clinical effects of compromised wound healing of irradiated wounds, as well as current and possible future therapeutic strategies, including special dressings, injection of multipotent cells, and topical administration of active substances (28). Among these, PRP represents an innovative and promising approach, mainly in the treatment of non-union defects, bone fractures, spinal fusion, bone implant and osteointegration, joint arthroplasty, and other conditions (29). The effect of PRP on tissue healing is a function of many variables, including platelet concentration, the volume of PRP delivered, the extent and type of injury, and the overall medical condition of the patient. However, PRP therapy can be inappropriate in cardiovascular patients due to elevated amounts of calcium chloride and bovine factor V used to activate clotting. To the best of our knowledge, there exist no contraindications in the literature for oncological patients, even if PRP also promotes angiogenesis in ischemic animal models of myocardial infarct and ischemic limb (30, 31). Another aspect is that in oncological patients, chemotherapy agents can make the blood toxic, leading to the use of homologous and not autologous PRP, with associated risks. From a clinical point of view, PRP and the Rigenera protocol seem to have very similar action in the improving wound-healing process, both providing an autologous system for tissue regeneration without excessive interference in the life of the patients. In this regard, we tried to identify some substantial differences between these two approaches; for example, the efficacy of PRP depends on platelet activation, which starts 10 min after clotting and most of the growth factors are secreted within 1 h. On the contrary, the micrografts obtained by the Rigenera protocol are ready to be applied to the injured tissue in a few minutes and *in vitro* data have reported that cell viability remains high even after 1 week of cell culture.

In addition, the use of PRP requires patients to undergo repeat applications in contrast to the Rigenera protocol which employs a single micro-graft application.

In conclusion, we suggest that the Rigenera protocol may be the solution for therapy of complex wounds, not only dehiscence, in all types of patients, but especially in oncological, cardiovascular, or immune-compromised ones in which other treatments are contraindicated.

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