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CASE REPORT

Treatment of complex recurrent fistula-in-ano by surgery combined to autologous bone marrow–derived mesenchymal stroma cells and platelet-rich plasma injection

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Abstract

Purpose We report a case of successful management of complex recurrent cryptoglandular fistula-in-ano by surgery combined with autologous bone marrow–derived mesenchymal stroma cells (MSCs) and platelet-rich plasma (PRP) injection.

Methods Clinical, radiological, and surgical data of the patient were reviewed, as well as the current literature on complex fistula-in-ano.

Results A 37-year-old man with a recurrent cryptoglandular perianal fistula was addressed to our department. Inflammatory bowel disease was excluded by clinical history, endoscopy, and blood tests. Physical examination and MRI showed an anterior external orifice on the midline, 5 cm from the anal verge, with an internal orifice on the same line. Surgery combined to injection of MSC-PRP solution was successfully performed. MSC-PRP solution was prepared while the patient was under general anesthesia: bone marrow MSCs were obtained by centrifugation of a tibial puncture specimen and PRP from a peripheral whole blood sample of the patient. There were no adverse events post-operatively. Clinical and MRI examination 4 months after treatment confirmed the absence of perianal fistula. More than 2 years after surgery, there has been no recurrence.

Conclusions Treatment of complex recurrent cryptoglandular fistula-in-ano by surgery combined to autologous bone marrow–derived MSCs and PRP injection seems safe in selected patients, allowing long-term healing. This procedure seems promising but further evaluation by clinical trials is warranted.

Keywords Fistula-in-ano · Perianal fistula · Mesenchymal stroma cells · Platelet-rich plasma

Introduction

Fistula-in-ano is a rare perianal disease with an incidence ranging from 1.1 to 2.2 per 10,000 population per year [1]. Perianal fistulas can significantly reduce quality of life of patients due to severe symptoms such as pain, embarrassing discharge, and incontinence. Usual management comprises medical treatments associated to surgery. The surgical management of most cases is successful whereas complex fistulas remain challenging. In Crohn's disease, the benefit in terms of sustained fistula closure has proven to be limited, with a relapse rate of 16, 31%, and 40% at 1, 3, and 5 years, respectively [2, 3]. Recurrence may be induced by limited surgery whereas fecal incontinence may result from an aggressive management [4]. Additionally, the need to use biological agents, even in association with conventional immunosuppressants, carries an increased risk of opportunistic infections and other complications [5]. Recently, the use of

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mesenchymal stem cell (MSC) injections in the fistula tract has yielded promising results [6]. MSCs' extraordinary properties (lack of substantial immunogenicity, homing towards sites of active inflammation and regenerative capacities, immunomodulating action on all cells involved in immune response and dampening inflammation while restoring tolerance, etc.) [7–10] render these cells particularly suitable for the treatment of conditions characterized by both chronic inflammation and tissue damage, such as perianal fistulas of cryptoglandular origin or in the context of Crohn's disease.

We report herein a case of successful management of a complex recurrent cryptoglandular fistula-in-ano by surgery combined with autologous bone marrow–derived mesenchymal stroma cells (MSCs) and platelet-rich plasma (PRP) injection.

Case report

A 37-year-old man presented with a recurrent perianal fistula. Inflammatory bowel disease was excluded by clinical history, endoscopy, and blood tests, thus confirming the cryptoglandular origin. From April 2014 to October 2016, three previous surgeries followed by recurrence took place: a fistulotomy with fistula recurrence at 5 months and two-staged fistulotomies using seton drainage with recurrence.

In June 2017, a new recurrence occurred and the patient was referred to our department. Physical examination and magnetic resonance imaging (MRI) evaluation showed an anterior external orifice on the midline, 5 cm from the anal verge, with an internal orifice on the same line (Figs. 1 and 2). Surgery was performed under general anesthesia in the lithotomy position, thus giving access to both perianal region and anterior tibial tuberosity. The internal fistula orifice was visualized, the fistula tract was de-epithelized by curettage and cleaned with saline solution, and the internal opening closed by a figure of eight full thickness bite of PDS II 4/0 suture (as previously described) [11] (Figs. 2 and 3). Bone marrow MSCs were obtained by centrifugation of tibial puncture specimen (Figs. 4 and 5). A peripheral whole blood sample was then retrieved from the patient and centrifuged to obtain platelet-rich plasma (PRP) (as previously described) [12]. The two solutions were then mixed, and the resulting 10 mL of MSC-PRP solution was split into two: 2.5 mL was injected in four quadrants (equal volume) in the submucosae around the internal orifice using a first syringe, and a second syringe of 7.5 mL was injected in the wall of the fistula tract from the internal to the external orifice via transcutaneous puncture, with a maximum depth of 2 mm in the fistula wall (Fig. 6) [11]. The external orifice was then closed (Fig. 7).

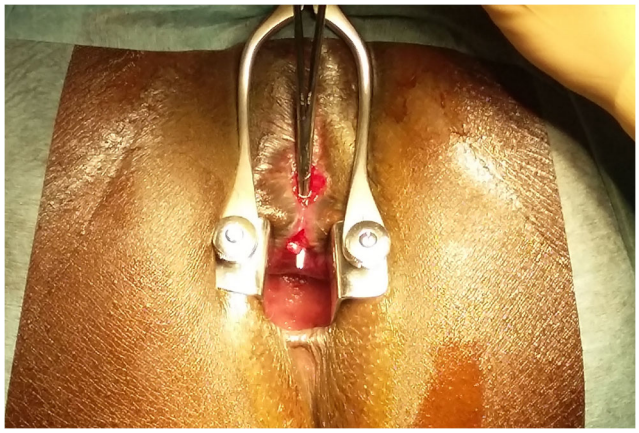

Fig. 2 Physical examination under anesthesia

There were no adverse events in the post-operative course or during the follow-up period. An assessment was conducted at 4 months after surgery. Clinical examination found no internal or external remaining orifice or fistula, a finding confirmed on MRI (Fig. 1). To this date, more than 2 years after surgery, there has been no recurrence.

Discussion

Although relatively rare, complex fistula-in-ano and its therapeutic management remain challenging. The high relapse rate despite a large therapeutic armamentarium and the risk of fecal

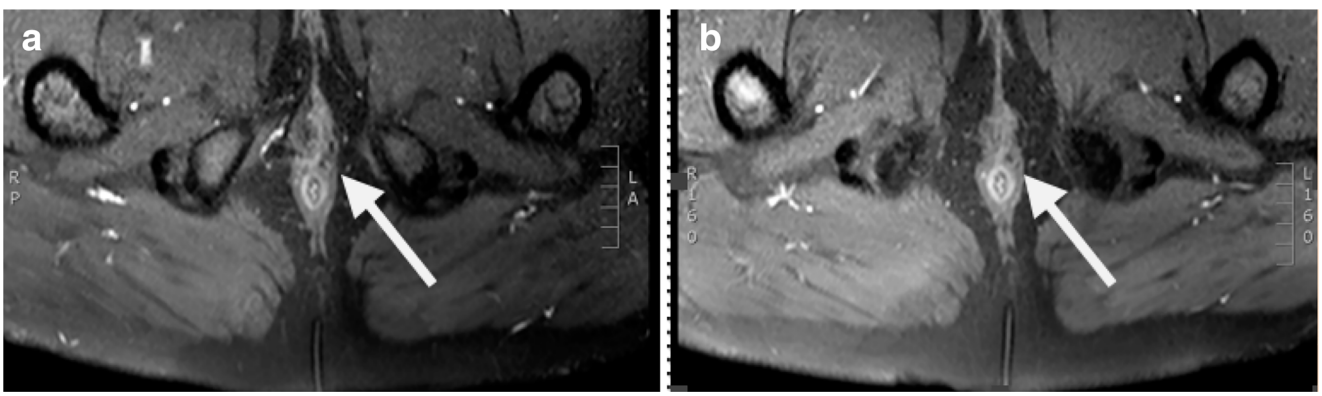

Fig. 1 MRI before (**a**) and 4 months after (**b**) treatment. White arrow: fistula-in-ano site

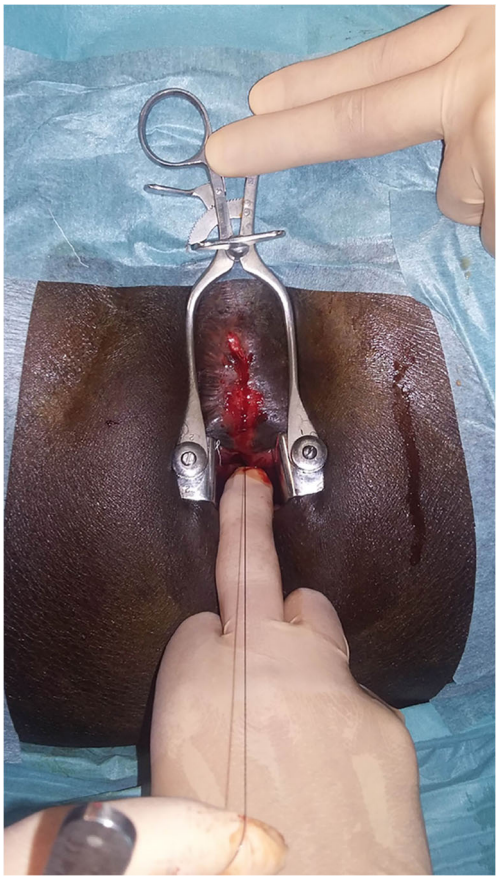

Fig. 3 Closure of internal orifice

incontinence question the iterative surgical management of recurrent fistulas. To this date, surgery, ranging from fistulotomy, use of seton drainage and staged fistulotomy, and fibrin glue injection to endorectal advancement flap closure, remains the recommended treatment of cryptoglandular fistulas, even if the level of evidence remains low [4].

In the meantime, MSCs have emerged as a promising therapeutic modality for tissue regeneration and repair during the last two decades. The current literature on the immunosuppressive properties of MSCs holds great promise for treating immune-mediated disorders. Even though relatively little is known about their in vivo biology, MSCs have already been introduced in clinical practice. At present, MSCs are extensively characterized in a culture-expanded state and relatively little is known of their biological properties in a non-manipulated state [13]. Nevertheless, multiple phase I and II trials have been conducted to assess the safety of MSCs used in the treatment of refractory perianal Crohn's fistulas. No significant adverse events were found [14] for both allogenic or autologous, and adipose tissue or bone marrow–derived MSCs [15, 16]. A single lymphoproliferative disease of the rectum has been reported 4 years after allogenic transplantation of bone marrow–derived MSCs for perianal Crohn's fistula [17].

Efficiency of MSCs in Crohn-related fistulas is starting to be demonstrated with encouraging phase II trials [14] and a positive phase III clinical trial [18], including allogenic adipose tissue–derived MSCs. This treatment modality tends to become a new therapeutic option in the armamentarium of perianal Crohn's disease [19]. However, to this date, such efficiency has not been demonstrated for cryptoglandular perianal fistulas as the only phase III randomized clinical trial was unable to obtain the superiority of autologous expanded adipose-derived MSCs [20]. In the meantime, PRP tends to develop as new harmless local therapy for chronic cavity wounds with low blood supply [12].

We herein report a novel, simple, and reproducible technique of autologous bone marrow–derived MSCs and PRP injection for the treatment of fistulas-in-ano. The autologous character of the transplant seems to be easier to manage in terms of patient safety, and allows procurement, conditioning, and injection of MSCs within the same general anesthesia, as

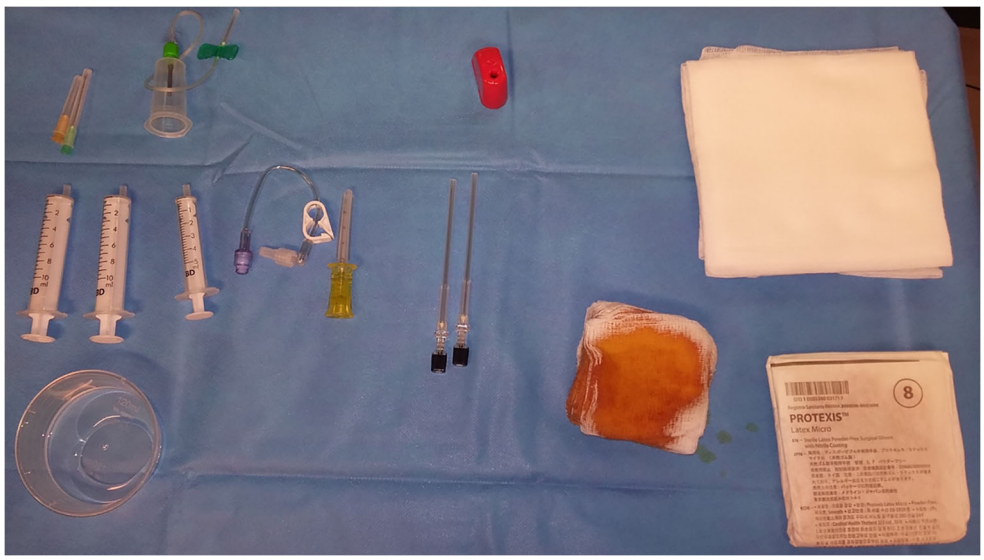

Fig. 4 Material useful for mesenchymal stroma cell extraction and resuspension

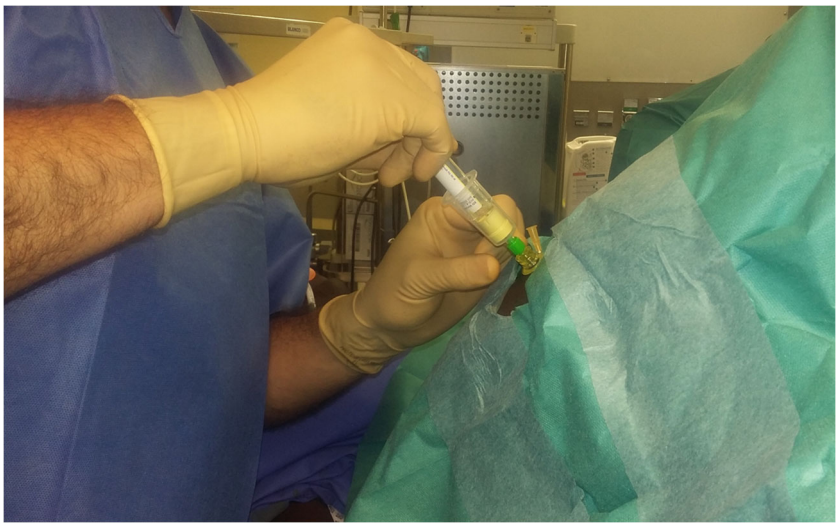

Fig. 5 Bone marrow puncture

the bone marrow puncture is realized in the tibia. It also renders the procedure more reproducible. Moreover, the actual trend is to use adipose tissue–derived and laboratory expanded MSCs; the use of bone marrow–derived MSCs with immediate expansion could maximize the immunomodulation properties of MSCs [21] and thus correct the lack of efficiency observed in the treatment of fistula-in-ano versus Crohn's fistula. Finally, our mixed MSCs and PRP procedure for the treatment of cryptoglandular fistulas is promising, safe and

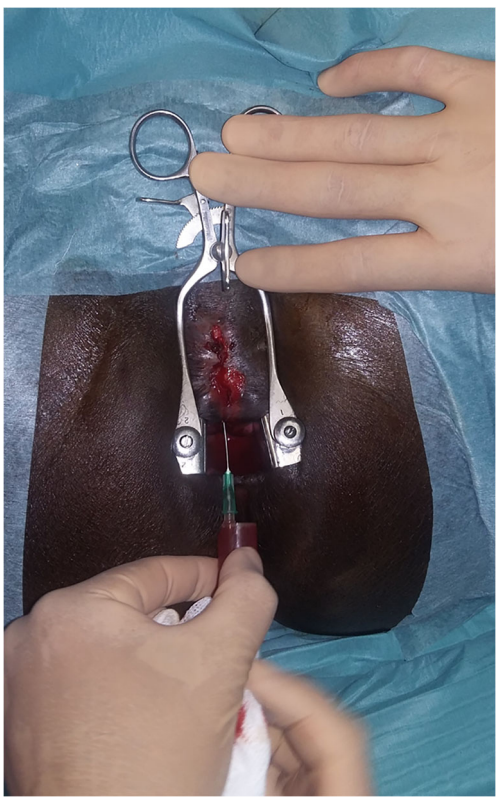

Fig. 6 MSC-PRP injection

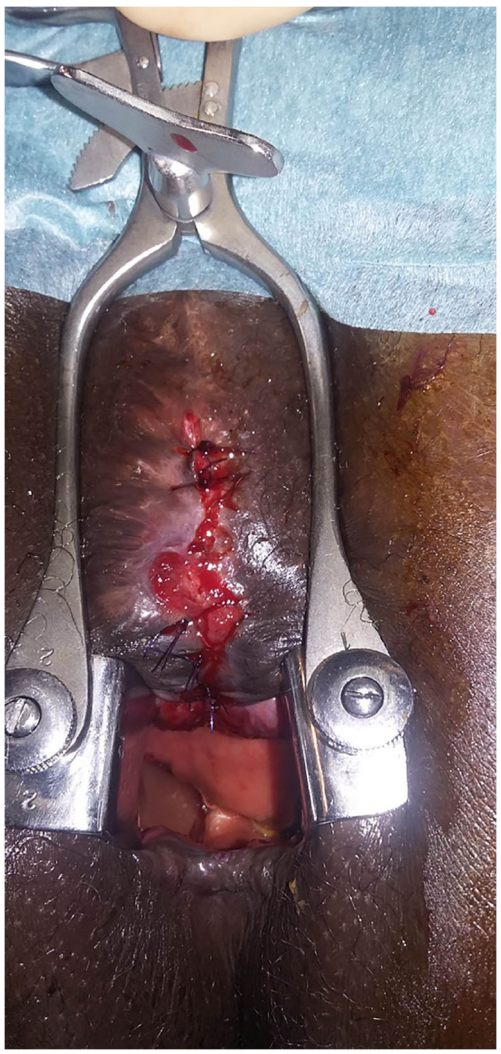

Fig. 7 Immediate post-operative result

efficient but needs further evaluation in phase I, II, and III trials before authorizing generalization of the procedure.

Conclusion

Therapeutic management of complex fistula-in-ano remains challenging. Surgery remains the recommended treatment of cryptoglandular fistulas but does not always offer prompt healing in cases of complex perianal fistulas. New techniques are emerging, such as MSC injection for refractory perianal Crohn's fistulas. However, to this date, such efficiency has not been demonstrated for cryptoglandular perianal fistulas. We reported here a rare case of treatment of complex recurrent fistula-in-ano by surgery combined to autologous bone marrow–derived MSCs and PRP injection with long-term healing. This procedure seems promising for the treatment of cryptoglandular fistulas in selected patients, but further evaluation by clinical trials is warranted.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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