Successful closure of persistent oro-cutaneous fistulas by injection of autologous adipose-derived stem cells: a case report

Erfolgreiche Behandlung persistierender oro-kutaner Fisteln durch Injektion mit autologen Fettstammzellen: ein Fallbericht

Abstract

Introduction: Oro-cutaneous fistulas are a possible complication of orofacial surgery. If recurrent they are difficult to treat and greatly affect the patient's functional and aesthetic integrity besides carrying the risk of infection. Usage of concentrated adipose-derived stem cells for chronic wounds is a new and experimental treatment strategy, so far only applied in a few selected studies. We report the case of two oro-cutaneous fistulas in one patient treated with adipose-derived stem cells leading to closure of the fistulas.

Case description: The patient was a 57-year old female immunosuppressed liver and kidney recipient who presented with a large mandibular and soft tissue defect after resection and irradiation of a squamous-cell carcinoma of the tongue base. After radical debridement, hardware removal and soft tissue reconstruction using a second free flap two oro-cutaneous fistulas reoccurred. Conventional surgical methods failed to consolidate the fistulas due to the severe radiation of the oral mucosa. Therefore autologous adipose-derived stem cells were extracted from lipoaspirate and applied in the surrounding fistula tissue in one session using the Cytori® Celution system. The fistulas closed spontaneously during the postoperative course within 4 weeks and remain closed after 6 months.

Conclusion: To our knowledge this is the first report of successful application of adipose-derived stem cells to two oro-cutaneous fistulas. Innovative stem cell therapy in combination with well established surgical methods can be a useful treatment strategy in certain cases.

Keywords: squamous-cell carcinoma, chronic wound, oro-cutaneous fistula, adipose-derived stem cells (ASC)

Zusammenfassung


Fallbeschreibung: Eine 57-jährige, immunsupprimierte Leber- und Nierentransplantatempfängerin stellte sich mit einem tiefen mandibulären Weichteildefekt vor. Dieser resultierte aus der radikalen Entfernung und Bestrahlung eines von der Zungenbasis ausgehenden Plattenepithelkarzinoms. Im postoperativen Verlauf der Defektrekonstruktion, die mit einem freien Lappen durchgeführt wurde, bildeten sich zwei oro-
kutane Fisteln. Da eine operative Revision zu keiner Heilung der Fisteln führte, wurde der Entschluss gefasst, autologe Stammzellen aus Fettgewebe um die Fisteln herum einzubringen. Die Stammzellen wurden mit Hilfe des Cytori® Celution Systems extrahiert und in der gleichen Sitzung appliziert. Im postoperativen Verlauf kam es nach 4 Wochen zum vollständigen Verschluss der beiden Fisteln und bis zum aktuellen Zeitpunkt (6 Monate postoperativ) trat kein Rezidiv auf.

**Fazit:** Nach unserem Wissen ist dies die erste erfolgreiche Applikation von konzentrierten Stammzellen aus Fettgewebe zur Behandlung von oro-kutanen Fisteln. Dieser Fall zeigt, wie innovative Stammzelltherapie in Kombination mit gut etablierten chirurgischen Methoden in besonderen Fällen eine sinnvolle Therapiestrategie darstellen kann.

**Schlüsselwörter:** Plattenepithelkarzinom, chronische Wunde, oro-kutane Fistel, Stammzellen aus Fettgewebe

**Introduction**

Oro-cutaneous fistulas are a possible complication of orofacial surgery, described mainly after facial reconstruction following tumor resection [1]. Literature on this topic is limited, a PubMed search containing “oro-cutaneous fistula” yielding no relevant results about incidence or treatment. This might be due to the fact that oro-cutaneous fistulas as complication of reconstructive facial surgery are not regarded a major complication and will normally close spontaneously over the long term. In case the fistula resists surgical intervention it can pose great discomfort for the patient by leakage of odorous fluids or even food besides being an aesthetic stigma. Furthermore the risk of infection can not be overestimated. In our opinion these kinds of recurrent, therapy resistant fistulas can be regarded as chronic (i.e. non-healing) wounds. Over the last years adipose-derived stem cells (ASC) have been successfully used to treat different kinds of chronic wounds, especially different kinds of fistulas [2], [3], [4], [5], [6]. This article reports the successful closure of two oro-cutaneous fistulas by injection of adipose derived stem cells and will discuss these results in reference to other clinical publications of this technique.

**Case description**

A 57-year old female suffered from a squamous-cell carcinoma of the tongue base and was referred to our outpatient department with a chronic soft tissue defect on her right medial mandible due to tissue breakdown after radiation (Figure 1).

In the patient’s history she had been diagnosed with a histologically proven squamous-cell carcinoma of the tongue base followed by tumor excision and right sided neck dissection. The resulting defect was bridged with plate osteosynthesis and insertion of methy-methacrylate copolymer (Palacos®), Heraeus Medical GmbH, Wehrheim, Germany). Subsequently she received fractionated radiation therapy with a cumulative dosage of 70 Gray and one cycle of chemotheraphy with the monoclonal IgG1-antibody against epidermal growth-factor receptor Cetuximab (Erbitux®, Merck KGaA, Darmstadt, Germany). Radiation led to atrophy of the skin and tissue break down in the mandible region accompanied by atrophy of the mucous membrane of the mouth and throat. In order to close the soft tissue defect a free radial fasciocutaneous forearm flap was transplanted. Partial flap necrosis led to referral of the patient to our department.

By first admission the patient presented with a tissue defect of the right, medial mandible 6.5 × 2 cm of size with partial exposure of the osteosynthesis plate over an area of 3 × 1.5 cm (Figure 1). On examination mouth opening was severely restricted because of advanced tissue fibrosis. Oral thrush was diagnosed and treated with Amphotericin B (Ampho-Moronal, Dermapharm AG, Germany) mouth wash. Furthermore the medical history of the patient revealed a polycystic liver and kidney disease that had required a combined liver – and kidney transplantation 5 years prior to the diagnosis of cancer. The patient’s chief complaints were facial disfigurement and intermitting leakage of fluids from the wound.
Surgical procedure

As part of an interdisciplinary approach the wound and fistula were radically debrided; the osteosynthesis plate was removed, leading to a tissue defect with an exposed oral cavity. In the same procedure a bilaminar transverse myocutaneous musculus gracilis free flap was performed using the dorsal portion of the flap as an intraoral lining. The flap was attached to the lingual artery and a side branch of the external jugular vein with interpositional saphenous vein grafts. The clinical course was complicated by an arterial thrombosis leading to successful revision of the microvascular arterial anastomosis. Two weeks later two oro-cutaneous fistulas were diagnosed prompting us to perform surgical revision of the enoral flap portion (Figure 2). Because fistula closure could not be achieved by re-suturing and controlled drainage due to the severe radiation damage and massive intraoral thrush we decided to apply concentrated ASC in a single session as a salvage procedure. The therapeutic protocol for ASC was presented to and approved by the Institutional Review Board of the Medical School Hannover. The patient was informed about the risks and potential complications of the procedure (i.e. tumour induction) and all parties gave written consent.

Isolation and application of ASC

Fat from both medial thighs was aspirated using the Cytori® Celution system (Cytori, Therapeutics, San Diego, CA, USA) as described previously [7]. The aspirate was treated and processed according to the protocol of the manufacturer. A total of 5 ml of ADC enriched cell suspension was injected enorally in the tissue surrounding the two fistulas using a 1.0 gauge needle (Cytori®) (Figure 3). Postoperative recovery was without complications and the patient could be discharged after 10 days. Fistula closure was documented weekly by close inspection and photography for the first postoperative month. During the following 4 weeks, the fistulas closed spontaneously without any further intervention and complete, long-lasting wound healing could be achieved (Figure 4). Follow up after 3 and 6 months showed no fistula recurrence. The patient was very content with the results and further mandible reconstruction is scheduled. However, persisting intraoral thrush is currently being treated again.

Figure 2: Lateral view of the patient. Depicted is the course of the two recurrent oro-cutaneous fistulas after successful second free flap transfer (transverse myocutaneous gracilis flap).

Figure 3: Intraoperative view. Application of adipose-derived stem cells (ASC) into the surrounding fistula tissue.

Figure 4: Lateral view of the patient. Spontaneous closure of fistulas within 4 weeks after injection of ASC without further intervention. Final results after 6 months.
Discussion

Impaired wound healing may result from a combination of co-morbidities such as diabetes, peripheral arterial disease, radiation, immunosuppression or infection. In our case, two chronic oro-cutaneous fistulas resulted from tumor excision on the right mandible, multiple reconstructive procedures, radiation and one cycle of chemotherapy closed after application of autologous, concentrated ASC into the surrounding fistula tissue.

Since ASC were described in 2001 they have gained particular attention among clinicians due to their extraordinary characteristics (i.a. promotion of neovascularization, secretion of growth factors, anti-inflammatory properties) besides being easily accessible and applicable.

Still, to our knowledge, there are only few studies and cases reporting the usage of autologous/allogeneic ASC for chronic wounds in humans. Garcia-Olmo et al. recently published the results of a phase III randomized multicenter clinical trial comparing ASC with fibrin glue application in complex cryptoglandular perianal fistulas. Surprisingly the overall findings showed no statistically significant advantage of ASC therapy in contrast to the excellent results of the pioneer center alone. Another recently published study presented encouraging findings using expanded allogeneic ASC for the treatment of complex perianal fistulas. In the light of these results we believe it was feasible to apply ASC in the patient described above, even though other treatment options would have been possible.

For careful consideration we decided to use ASC firstly to increase the healing potential of the irradiated and non-responsive tissue, secondly because of the urgency to achieve sustainable closure without the use of major surgery. In our opinion simple fat grafting would have failed because of the reduced perfusion in the fistula area and another free flap could have compromised the so far achieved closure. Obviously, it is subject of speculation if fistula closure could have been achieved spontaneously without any intervention. Even though this can’t be ruled out we believe that in regard to the case history it seems unlikely.

Using the commercially available Cytori® Celution system provides the clinician with the possibility to extract ASC from liposapirate in a safe and efficient way during the operation. Disadvantages are high costs and the so far unclear safety-profile of collagenase regarding tissue modifying, leading to FDA disapproval at the moment. Because of the lack of long-term in vivo results, associated risks as for example tumor induction can not be estimated. Therefore we only use ASC as a salvage procedure in especially selected cases, such as non-reactive irradiated tissues.

Conclusions

To our knowledge, this is the first case of successful treatment of oro-cutaneous fistulas resulting from radiation damage and surgery, using autologous, concentrated ASC. Even though a direct association between ASC application and fistula closure can not be proven we believe this procedure to be of great potential. We have shown how well-established methods (i.e. free-flap transfer) and innovative stem cell therapy can be combined to a novel approach regarding certain very complicated chronic wounds. Still, despite the encouraging results of ASC therapy in many medical fields, large controlled and randomized studies have to be conducted especially regarding efficacy and safety.

Notes

Competing interests

The authors declare that they have no competing interests.

References


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