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CASE REPORT

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Surgical treatment of Fournier's gangrene: use of cultured allogeneic keratinocytes

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Abstract We discuss the value of the use of skin culturing as an addition to the classic treatment of Fournier's gangrene. A 32-year-old morbidly obese man was admitted with signs of a severe septic shock syndrome due to Fournier's gangrene. He recovered completely after an aggressive surgical débridement, combined with the use of broad spectrum antibiotics and invasive ventilator support for respiratory failure. The surgical reconstruction of the extensive skin defects following removal of the infected skin and soft tissues was successfully achieved with a combined application of meshed autologous skin grafts and the use of cultured allogeneic keratinocytes. Early cover of large skin defects is a major therapeutic goal, regardless of the nature of the primary etiology. The combined use of meshed autologous skin grafts and cultured keratinocytes represents one of the newer techniques. The contribution of this technique on the quality of healing and coverage of extensive skin loss zones is being investigated, since it seems to be a valuable option in reconstructing some of the sequelae of Fournier's gangrene.

Key words Fournier's gangrene · Keratinocytes · Necrotizing fasciitis · Skin transplantation

Introduction

Fournier's gangrene is a relatively rare clinical entity, with extremely high mortality rates: as high as 22–60% [1]. This necrotizing fasciitis of the genital and perineal tissues was first described in 1883 by Jean Alfred Fournier, a French venereologist. Usually it is caused by a combination of aerobic and anaerobic micro-organisms, causing a rapidly spreading infection of the skin, subcutaneous soft tissues, and superficial fascia. It occurs predominantly on the male perineum and external genitalia. Most often the necrotizing fasciitis will spread into the anterior or posterior abdominal wall.

The known factors which predispose to the development of Fournier's gangrene are: elderly and mostly male patients; and diabetes or any concomitant pathology able to compromise the immunity system [1, 2].

The diagnosis and treatment should be established as early as possible; the latter should primarily consist of an aggressive surgical removal of all involved tissues, in order to try to reduce the very high mortality. Radiological imaging techniques, such as ultrasound and computed tomography facilitate early diagnosis and guide surgical treatment by identifying subcutaneous collections. The internationally accepted guidelines for treating this severe illness are: daily repeated and aggressive surgical débridements, with full excision and removal of all necrotic zones, drainage of identified collections and irrigation of cavities, combined with antibiotic treatment covering the bacterial flora which is usually mixed [3–5]. Multiple daily sessions of hyperbaric oxygen therapy are added whenever clinical suspicion or bacteriologic evidence reveals the presence of an anaerobic agent, mainly *Clostridium perfringens* or certain strains of gas-producing anaerobic *Streptococci* [6–8].

With successful removal of all debris and reversal of all infectious, septicemic or multiple organ failure features, early cover of larger skin defects is mandatory. This is achieved by meshed split-thickness skin grafts or myocutaneous flaps for reconstruction of damaged external genitalia, if they are required [4].

In the case presented, the skin defect was covered early and successfully by combining the use of meshed autologous skin grafts with allogeneic keratinocyte cultures. This technique is routinely used in our clinic to cover skin deficits in major burns; such cases form the majority of our patient population.

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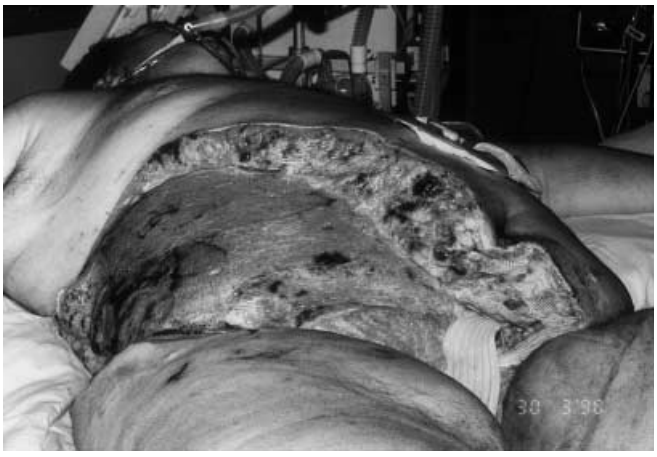

Fig. 1 First coverage of the huge full-thickness skin deficit with cryopreserved allograft skin, 16 days after admission

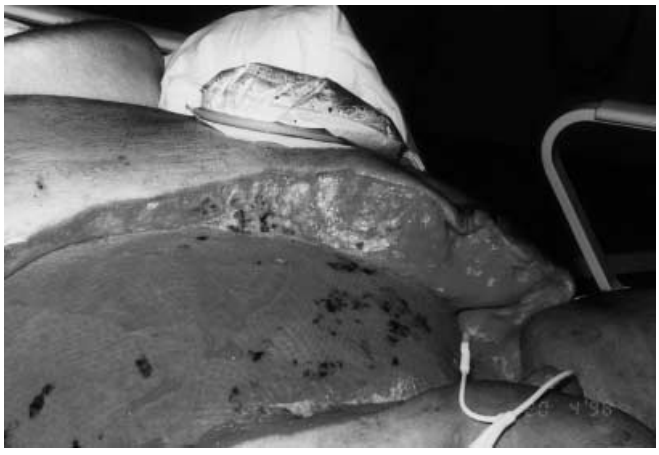

Fig. 2 Only small remaining deficits after allogeneic keratinocyte cultures were reapplied

Case report

A 32-year-old man, with several risk factors known to predispose to possible development of Fournier's gangrene – morbid obesity (185 kg, body surface of 2.8 m^2), untreated type II diabetes, untreated essential arterial hypertension, and severe peripheral venous insufficiency – was admitted into the intensive care unit (ICU) of a nearby university hospital. A superficial cutaneous inguinal infection progressed rapidly over a 24-h period and spread through the subcutaneous tissues of the perineum and external genitalia, towards the anterior abdominal wall. This was associated with high fever and the patient was critically ill.

The primary treatment consisted of surgical débridement of the infected area; the testicles were placed temporarily into clean subcutaneous wound pockets, and a urinary diversion was created through a percutaneous cystocath. A broad combination of antibiotics was started, to cover a wide polymicrobial spectrum. Onset of respiratory failure, due to adult respiratory distress syndrome (ARDS), necessitated endotracheal intubation, sedation, and artificial ventilation with a FIO_2 of 0.8; this was delivered through intermittent positive pressure ventilation (IPPV), by means of a volume controlled ventilatory mode [9].

After 24 h, the patient was transferred to the Burns Centre ICU for further management. The respiratory insufficiency was treated by invasive ventilation; this was achieved by applying volumetric diffusive respiration (VDR), which is also described as high-frequency percussive ventilation (HFPV) or intrapulmonary percussive ventilation (IPV). This technique is often used in ARDS patients as an alternative to inverse-ratio pressure-controlled ventilation (IR-PCV) [1]. It allowed for a quick reduction of the high FIO_2 and improved clearance of intrapulmonary secretions.

Computed tomographic investigations of the infected region guided surgical exploration, which was repeated daily until all of the infected tissues were removed and an initial improvement in the patient's general status was achieved. Cover of the huge full-thickness skin deficit using cryopreserved allograft skin was performed 16 days after admission (Fig. 1).

Four days later, the abdominal skin defect of 2.550 cm^2 (11% of BSA) was covered with autologous split-thickness meshed (1/3) skin grafts and cultured autologous keratinocytes. Closure of the relatively smaller perineal skin deficit was attempted 3 days later, using the same technique.

Definitive survival of the skin-keratinocyte graft combination was assessed after 2 weeks and revealed successful coverage of 85% of the grafted surface area. In order to stimulate closure of the remaining deficit, allogenic keratinocyte cultures were again applied. This resulted in further cover (Fig. 2), leaving only small areas, which were finally covered by application of meshed (1/1.5) autologous skin grafts. Complete coverage of the entire skin deficit was obtained 5 weeks after the initial attempt at reconstruction (Fig. 3).

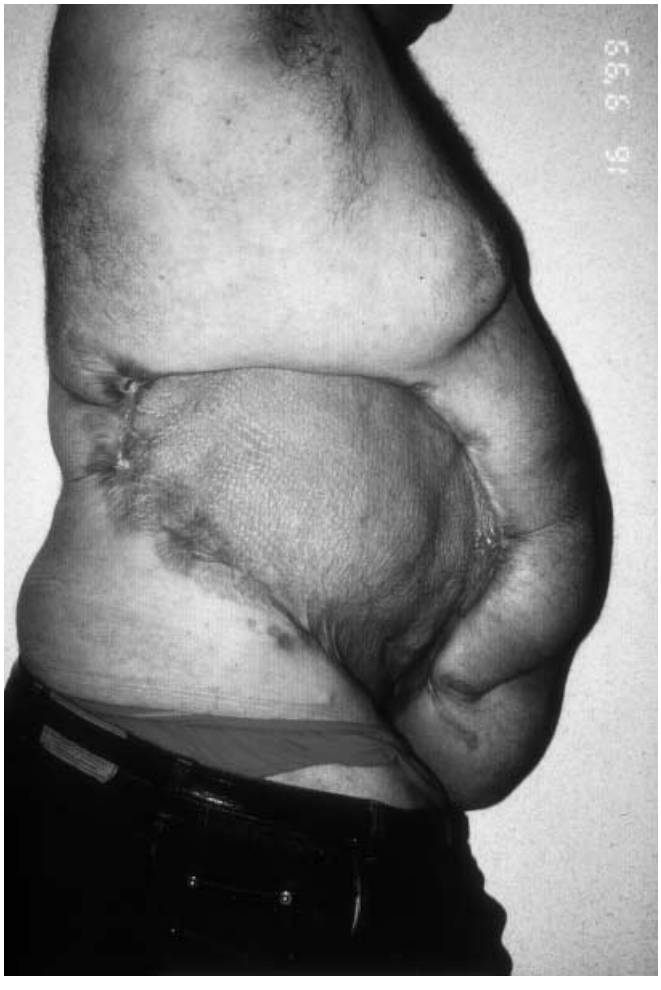

Fig. 3 Complete coverage of the entire skin deficit, 5 weeks after the initial attempt at reconstruction

At this point, the patient was no longer critically ill; he recovered from ARDS and acute renal failure and was weaned from ventilator support, allowing him to be discharged from the ICU.

Discussion

Fournier's gangrene is a rarely encountered clinical entity; although case reports and reviews are published quite frequently, these focus primarily on early aggressive surgical and antibiotic therapy. Due to very high mortality rates, the largest survival rate is observed in those patients who are referred early to a highly specialized centre.

The Burns Centre of our institution has been in existence for 15 years, and has considerable expertise in the management of skin loss occurring for a variety of reasons: extensive burns, a pathology resulting in primary skin loss (e.g. Lyell's syndrome) or secondarily, as a result of aggressive surgical treatment.

Annually, eight to ten patients suffering from Fournier's gangrene are admitted. Although the majority are moribund on admission, the survival rates are high, being approximately 80%. All treatment efforts are directed towards survival and initial healing. The final secondary reconstructive surgery of the soft tissue defects, which may be large and complex, is performed by the plastic surgeons. The main goals are to combat and overcome all of the possible ICU complications while our surgical teams focus on an initial quick, aggressive approach, followed by the use of any possible technique which will achieve early and rapid skin cover.

To achieve this goal, a standard treatment scheme includes an aggressive multidisciplinary approach, based on daily surgical excisions, guided by CT scans of the infected area; thus, all infected tissues are removed. A wide spectrum of antibiotics is started early; this covers all possible causative organisms. Antibiotic therapy is guided and its efficacy is constantly assessed by the bacteriological laboratory.

In the patient presented, hyperbaric oxygen therapy was not used, since the causative bacterial organisms were aerobic, non-gas producing strains of *Staphylococcus aureus* and *Enterococci* spp.

After about 16 days of difficult ICU management, the patient's condition gradually improved and permitted the beginning of surgical reconstruction. Covering of a surface as large as 2550 cm^2 presented a considerable challenge but it had to be attempted as soon as possible, because any major skin loss is associated with significant functional morbidity and mortality.

The larger the deficient surface area, the more urgent becomes the need for a skin replacement: full cover prevents the invasion of micro-organisms and normalizes fluid flux and hypermetabolism.

Techniques for temporary cover include the application of allogeneic skin grafts and keratinocyte cultures, to provide the necessary time to combat infection and to allow the cultivation of confluent sheets of autologous keratinocytes.

Banking of allogeneic skin grafts and allogeneic keratinocyte cultures must be performed and organized with the most rigorous attention, to prevent transmission of infectious diseases. Furthermore, it is a challenge to try to stimulate the population and medical institutes to give permission for harvesting cadaver skin, even with state laws facilitating these procedures.

As in full excision of third degree burns, the surgical excision destroys the dermal basement membrane, which contains the structural and circulating factors which are necessary to obtain skin re-epithelialization.

Cultured keratinocyte allografts do not survive transplantation, but supply a release of unepithelialized stem cells, growth factors, and matrix components that promote the proliferation of the host's epidermis in the absence of the basement membrane, thus facilitating and stimulating the success of autologous skin replacement techniques [10].

Definitive skin replacement has to be undertaken as soon as the patient's infectious and general status is such that the first attempt will have a reasonable chance of success. Concomitant illness factors such as septicemia, ARDS, renal failure, or other possible frequently occurring ICU conditions should not be an absolute indication to postpone reconstructive surgery. Since full closure of the skin deficit is very often the only way out of a seemingly hopeless situation, both the ICU and operating room must cooperate effectively and should be equipped with skilled staff and with the most advanced medical equipment, in order to provide the surgical team with the best possible operating conditions.

The classical coverage technique is to apply widely meshed split-thickness skin autografts. In the absence of complications such as infection of the wound, healing can be obtained in 10–14 days. Whenever larger damaged cutaneous zones have to be covered, one usually has to cope with the relative scarcity of donor sites. When they are used, there is a risk of infection.

In our Burns Centre, since 1987, a combined technique of placing keratinocyte cultures on top of split-thickness meshed skin autografts has been used to attempt to cover the cutaneous deficit area of our major burn patients. Previous studies have shown that this technique leads to a faster rate of healing and the minimum of donor sites [11,12].

Previous controlled studies in patients with third degree burns showed a 1.8-fold increase in stimulation of early epithelialization from day 0 to 5, when the sites were covered with meshed skin transplants in combination with fresh autologous keratinocyte cultures [11].

However, it is not possible to extrapolate the beneficiary results obtained in different studies [10–12]. and to decide that the results obtained are valid for a patient not belonging to the study population. In this patient, however, we had to cope with a significant lack of donor site area. Moreover, the total destruction of the dermal basement membrane is quite similar in burn patients to that caused by the destructive Fournier syndrome. Until more valid controlled studies are available, these arguments may perhaps warrant the presumption that at least some of the proven beneficiary effects as observed in burn patients could be obtained in the Fournier patient with total skin deficit.

We were able to observe the same positive impact of the applied skin transplant-keratinocyte combination technique, since they provided for definitive cover of 85% of the damaged area after 2 weeks, while full cover was obtained 5 weeks after admission.

Conclusion

Since the mid-1980s wound cover involving the combined application of autologous meshed split-thickness skin grafts and cultured allogeneic keratinocytes has become an effective standard practice in treating extensive skin deficits following major burns.

Thus, it was attempted to reproduce the beneficial effects of this treatment, namely, faster and better wound healing and limitation of the necessary donor area, in a morbidly obese young man with a very poor general health, suffering from widespread Fournier's gangrene.

To our knowledge, the use of meshed autologous skin grafts and cultured allogeneic keratinocytes to treat the sequelae of invasive surgery of Fournier's gangrene has not previously been reported. This could be a promising novel adjuvant option in the reconstructive surgery of some of the sequelae of Fournier's gangrene. However, it is necessary to perform controlled studies before this technique can be used as a standard treatment for the victims of Fournier's gangrene.

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