Advances in the Medical Management of The Severe Cutaneous Radiation Syndrome

H. Carsin¹, J. Stephannazi¹ and P. Gourmelon²
¹Burn Treatment Centre, Percy Hospital, 101, rue H. Barbusse, 92141 Clamart (France)
²Institute for Protection and Nuclear Safety, BP n° 6, 92265 Fontenay aux Roses (France)

The cutaneous radiation syndrome is a dose dependant complex pathological syndrome which follows a brief localised exposure and characterised by erythema, swelling, moist desquamation, ulceration and necrosis (25-30 Gy). Highly penetrating gamma radiation induces severe dose dependent lesions involving skin, subcutaneous tissue, muscle, vessels, nerves and occasionally, bony structures.

The classical treatment of this syndrome includes the debridement of devitalised tissues, the application of bacteriostatic agents coated in non-adherent dressings, opiate-based drugs and in some cases the use of non-steroidal anti-inflammatory drugs. For ulceration necrosis treatment, the classical surgery is ulcerectomy, necrectomy and amputation for the distal extremity injuries. For the profound and large necrosis, the lesion should be excised ant the wound bed covered with a good quality, full-thickness skin graft.

Unfortunately the delayed or appearance of this syndrome results often in non specialised medical treatment. Furthermore, because of the chronic evolution (months or years) the management of the cutaneous radiation syndrome has not been considered as a priority for the medical management.

Recent accident like the Georgian accident demonstrated that new techniques such as artificial skin graft could change significantly patient prognosis. This technique is routinely used for thermal burn in specialised burn units.

We realised the first application of this methodology in the field of radiopathology. An important factor of this technique is that in the case of recurrence of radionecrosis, often observed, using this technique further grafting may be employed.

This technique was applied in the last accident in Georgia in two patients who suffered of a very severe cutaneous radiation syndrome of the lower limbs. The description of the main therapeutics used for the medical management of these patients is presented below.

Patient 1

The site of the principal lesion was on the antero-lateral surface of the middle third of the right thigh. Before admission to the hospital, several necrectomies have already been performed. Nevertheless, the wound was open. The lesion presented an extensive substance defect. Without sign of regeneration the wound was superinfected, with necrotic tissue on the surface and a fibrotic muscle deep down. The necrosis area was found to be 12 cm in diameter. The lesion was surrounded by a halo of inflammation but no lymphadenopathy of the inguinal region was found. There was severe muscular wasting and an antalgic flexure position of the hip.

On Day 6, surgery was carried out under cover with antibiotics (imipenem - cilastatin + ciprofloxacin) appropriate to the multiply-resistant pseudomonas aeruginosa P3 and to enterobacter cloacae. An initial exploration showed that the picture was less unfavourable than the Magneto-Resonance Imaging (MRI) had indicated. The conservative alternative of covering by graft after wide necrectomy was chosen. The excision was wide, into the healthy cutaneous zone. It was taken down to the healthy muscle by resecting the whole of the anterior rectus and a part of the external vastus. The loss of substance was 280g. The surgical scar of 750cm2 was covered by a porcine xenograft.

On Day 14, ablation of the xenograft showed a clean and high-quality surface. This surface was covered by layers of synthetic matrix (INTEGRA ®). This matrix is composed of a double layer with a sheet of collagen, treated to increase the colonization by cells from the underlying viable tissues. The upper surface is made of a silicone layer. This silicone layer is completely transparent and allows the survey of the underlying ground.
On Day 30, the silicon sheet was taken off, showing a complete integration of the artificial matrix. However, a lesion of recent appearance was noted on the antero-internal aspect of the femoris, at the junction of the upper and the middle third. This lesion, around 4cm in diameter, was poorly demarcated, brownish in colour, and was suspected to be necrotic. A skin graft of 0.2mm was taken from the left thigh, expanded twofold, then grafted on integrated dermal ground.

Initial progress was generally highly satisfactory. The graft provided good epidermization of the whole of the wound. However, beneath the graft, the area previously described was progressively developing into a typical eschar which was to be excised during dressing. Subsequently a secondary lesion developed on the middle third of the right thigh. It covered around 50 cm². Its contours were irregular, geographical in outline, and presented signs of bacterial superinfection.

On Day 90, after cleaning of the residual lesion, a new skin autograft was carried out. All through this time, neither the specific antibiotic cover with imipenem-cilastin + ciprofloxacin nor the local treatment with silver nitrate succeeded in eradicating the multiply-resistant pseudomonas aeruginosa constantly encountered in the lesion. However, no major infectious complication supervened. The patient was apyrexial, apart from a febrile peak of 39°C immediately after the surgery. The blood cultures and the catheter cultures remained sterile. The leucocyte count, which was around 11x10⁹/l on arrival, stabilized around 5-6x10⁹/l.

The pain on admission and during the surgery was generally well controlled with high doses of morphines (>100mg.day) but its severity during the second intervention necessitated the addition of Clonidine.

Mobilization and rehabilitation was not begun in until day 25 so as not to compromise the initial phases of the integration of the dermis. An MRI carried out on Day 42 showed the persistence of a strong signal at the level of the neurovascular bundle and the muscles of the antero-external compartment extending over the long head of the biceps and the semitendinosus in the posterior compartment of the thigh. This was associated with severe atrophy of the whole of the muscles of the posterior compartment.

The initial wound was fully healed 5 months after the surgical procedures. Functionally, the motility of the right leg was completely restored.

The time course of the clinical evolution is summarized in the table 1.
<table>
<thead>
<tr>
<th>D+1</th>
<th>D+6</th>
<th>D+14</th>
<th>D+26</th>
<th>D+30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burn of the right thigh</td>
<td>Skin and muscle excision (280 g) xenograft 750 cm²</td>
<td>Covering with artificial dermis (Integra®)</td>
<td>625 cm² amplified (x2) skin autograft from the left thigh</td>
<td></td>
</tr>
<tr>
<td>Satisfactory budding</td>
<td>Suspicion of limited necrosis (5 cm)</td>
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</tbody>
</table>

Local infection: enterobacter cloacae and pseudomonas aeruginosa P3

Antibiotics (Imipenem-Cilastatin + ciprofloxacin)

Morphin 120 mg/j, then progressive dose reduction; anxiolytics

MRI: zone of necrosis, muscular atrophy and signs of extended œdema into the antero-external compartment

Medullary biopsies and bone marrow cultures from both iliac crests: no abnormalities

<table>
<thead>
<tr>
<th>D+42</th>
<th>D+47</th>
<th>D+90</th>
<th>4th month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rehabilitation</td>
<td>Amplified (x2) skin autograft: 50 cm²</td>
<td>Progressive healing knee bending 50 °</td>
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<tr>
<td>Superficial necrosis confirmed, excised</td>
<td>MRI : signs of inflammation of the muscles of the antero-external compartment and muscular atrophy of the whole thigh</td>
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Table 1. Clinical evolution and therapeutic in patient 1
Patient 2

The patient presented a large radiation burn on the outer aspect of the right thigh, situated at the junction of the middle third and the lower third of the thigh. This lesion presented as a necrosis of 5 cm in diameter, sharply demarcated, "punched-out". The adjacent tissues and muscles of the whole thigh were oedematous and tense, indicating that major regional extension might occur, with a major inflammation reaction.

The time course of the clinical evolution is summarized in the table 1.

<table>
<thead>
<tr>
<th>PATIENT 2</th>
<th>D+1</th>
<th>D+5</th>
<th>D+6</th>
<th>D+14</th>
</tr>
</thead>
<tbody>
<tr>
<td>«punched-out» burn of the right thigh</td>
<td>Skin and muscle resection (380 g)</td>
<td>Xenograft 650 cm²</td>
<td>Covering with artificial dermis (Integra®)</td>
<td></td>
</tr>
<tr>
<td>Intense pain; good general condition</td>
<td>Local infection (pseudomonas aeruginosa P2; staphylococcus methi S)</td>
<td>Clinical improvement: decrease of inflammation and pain, vascularization, budding</td>
<td></td>
<td></td>
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<tr>
<td>Hyperleucocytosis: 7-12000</td>
<td>Normalization of leucocytes (6500)</td>
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<tr>
<td>Morphin 110 mg/j</td>
<td>Morphin 15 mg/j</td>
<td>Morphin arrest</td>
<td></td>
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<tr>
<td>Antibiotics (imipenem-cilastatin + ciprofloxacin)</td>
<td>MRI: zone of necrosis (6 cm) and signs of extended œdema into the antero-external compartment</td>
<td></td>
<td></td>
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<tr>
<td>Medullary biopsies and bone marrow cultures from both iliac crests: neither abnormalities nor asymmetry</td>
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</tbody>
</table>

Table 2. Clinical evolution and therapeutic in patient 2
On *Day 6*, a wide necrectomy was performed under cover with antibiotics (imipenem-cilastatin + ciprofloxacin) appropriate for the multiply-resistant pseudomonas aeruginosa P2 and *staphylococcus Méti-S* found on the lesion. The excision was made at some distance from the necrosis (>5 cm). It was extended downwards to the layer of healthy muscle by resecting an anterior part of the rectus femoris and a part of the external vastus. The loss of substance was 380g. The surgical wound of 650cm² was covered by a porcine xenograft.

On *Day 14*, ablation of the xenograft showed the surface to be granulating and clean. This surface was covered by an artificial dermis of the INTEGRA type.

On *Day 33*, removal of the siliconized layer of the INTEGRA showed a granulating and clean surface of very high quality. It was covered with a full thickness skin graft taken from the left thigh. The surgery and the dressings, carried out every other day under general anaesthesia and associated with an extended period of antibiotic prophylaxis, resulted in excellent local development. The pain abated and the consumption of morphine was reduced from 110mg/day (on arrival) to 15-40mg/day. There were no infectious complications. The patient remained apyrexial. The blood cultures were all negative and the samples from the wound were sterile. In parallel, the white cell count became normal from the second day after the first surgical intervention.

On *Day 44*, the patient began his rehabilitation and the wound was fully healed on the third month following surgery.

**Conclusion**

Artificial skin grafting was surprisingly efficient in the treatment of the wide necrotic lesions with extensive loss of substance in the cutaneous radiation syndrome. The long term effectiveness of this new therapeutic strategy versus the risk of radionecrosis recurrence or secondary fibrosis remains to be assessed. The fact that artificial dermis was sufficient to heal the wound shows that in the cutaneous radiological syndrome, dermal function is extremely important in the processes of healing.

However the success of this procedure depends on an effective control of the infection. These has sadly been illustrated in the last accident case in Peru where it was impossible to perform an artificial skin graft due to the persistence of a non-eradicated local infection.

Thus, our experience shows that in case of very severe cutaneous lesions involving deep tissues and large ulcerations caused by high penetrating radiation, it is essential that the patient be transferred rapidly to a specialised burn treatment unit for artificial skin engraftment.