Cultured Epithelial Autografts in the Treatment of Extensive Recalcitrant Keloids

Ann F. Haas, MD, Department of Dermatology; Debra A. Reilly, MD, Division of Plastic Surgery; University of California, Davis, Sacramento

The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

A 42-year-old black man presented with an extensive keloid on the anterior section of his chest wall. He had acne as a child and developed a number of significant keloids, the most symptomatic being the keloid on his chest wall. This keloid had been treated with excision approximately 10 years previously in another city, followed by placement of a number of mesh split-thickness skin grafts (STSGs) obtained from his thighs. According to the patient, the superior edge of the keloid had also been irradiated some time after surgery. The entire keloid located on his chest wall had regrown significantly, causing the patient problems with bending at the waist and with full range of motion in his shoulders. The recurrence had been treated with intralesional corticosteroids and cryotherapy (separately and combined), as well as silicone gel and flurandrenolide (Cordran tape, Lilly, Eli and Co, Indianapolis, Ind) without significant improvement. In addition, a smaller keloid had been excised on his back and the epidermis removed from the keloid and replaced over the wound, with significant regrowth of that keloid as well.

On physical examination the patient had an extensive keloid encompassing the surface area extending from the clavicle to the inframammary crease (Figure 1). The inferior portion of the keloid, which was the thickest portion, had curled under itself and had completely encased the patient’s areolae, which were not visible. In addition, the patient had a number of keloids located on his back and upper extremities. He had hypertrophic, but not keloidal, scars on his thighs at the donor sites from his previous STSGs.

THERAPEUTIC CHALLENGE

Provide treatment with minimal surgical trauma to uninvolved areas for an extensive recalcitrant keloid located in an area at high risk for keloid re-formation.

SOLUTION

Using local anesthesia, a 1-cm² piece of the patient’s epidermis was removed from the lateral section of his right thigh with a Weck blade. This skin specimen was cultured at the Epithelial Autograft Facility, University of California, Davis, in Sacramento. Sheets of keratinocytes were cultured and were ready for grafting approximately 2 weeks after receiving the skin biopsy sample. Extra cells were frozen for future grafting. With the patient under general anesthesia in the operating room, the entire keloid, measuring 300 cm², was removed with a carbon dioxide laser. The areolae were found to be embedded in the keloidal tissue and were dissected from the surrounding keloid with the laser. The keloid measured 4 cm at its thickest point. The autografts were then placed onto the defect (Figure 2), secured at the wound edge with a fine net, and his chest was wrapped with a bulky dressing. Dressing changes down to, but not including, the fine net were performed daily, and the grafts were irrigated using a cell culture medium. The complete dressing was removed at 1 week, after which the patient used hydrocolloid dressings to help speed reepithelialization and prevent friction.

Because of the size and location of the wound (anterior portion of the chest, which tends to be suscep-
tible to friction), the decision was made to perform more grafts approximately 2 months following the initial grafting session to correct for shearing of the neoepidermis. Stored frozen cells were thawed, grown into confluent sheets, and his chest area was regrafted.

The patient has been followed up for more than 2 years, with development of a hypertrophic, soft, and asymptomatic scar (Figure 3). He has not had a significant scar develop at the autograft biopsy donor site. Total reepithelialization of his chest took almost 1 year. However, the patient has had no other problems. He was so encouraged by the dramatic improvement and the lack of morbidity from the procedure that at his request, we went on to remove and place cultured epithelial autografts (CEAs) on an extensive keloid located on his elbow. He is now able to bend comfortably at the waist and has considerably more range of motion of his elbow following CEA grafting of both areas. This patient’s response has been similar to that in some patients with burns following excision and autografting of those keloids (Figure 4 and Figure 5).

**COMMENT**

Keloids are an overgrowth of fibrous tissue following healing of a skin injury. Surgery, vaccinations, skin infections, and burns are probably the most common causes of keloid formation in individuals who are predisposed to develop such formations. The fibrous tissue tends to extend beyond the borders of the original skin injury, recur after excision, and not regress spontaneously. Symptoms can include cosmetic disfigurement, pruritus, pain, tenderness, skin discoloration, and restricted movement.

One of the first descriptions of keloids has been found in a papyrus describing surgical techniques used in Egypt about 1700 BC. In addition to the nonsurgical modalities commonly used to treat smaller keloids, there have been a number of newer nonsurgical therapies proposed.
These have been recently thoroughly reviewed,\(^2\) and include such modalities as interferon, anti–transforming growth factor \(\beta\) (wounds treated with anti–transforming growth factor \(\beta\) healed with minimal scar formation and normal tensile strength),\(^3,4\) and others. Although proposed to treat keloids and hypertrophic scars, these newer agents may actually be more useful either for preventing recurrences or for treatment of smaller keloids.

The treatment of larger keloids is still primarily surgical, and since excisional surgery alone is associated with a high rate of recurrence,\(^5\) surgical treatment of keloids is generally followed by one of the more familiar treatments used adjunctively,\(^6,7\) such as pressure,\(^8\) radiation therapy,\(^9-12\) intralesional steroid injections,\(^13,14\) cysoturgy,\(^15,16\) zinc oxide tape,\(^17,18\) silicone gel sheeting,\(^19,20\) and others.

Following excisional surgery, excised areas have been allowed to heal by secondary intention,\(^21\) closed primarily or covered with either STSGs or full-thickness skin grafts. As for our patient, treating a traumatically induced problem with a procedure that can cause additional skin trauma is problematic. In addition, in individuals with large keloids, full-thickness skin grafts would not even be feasible. Grafting of the wound with the epidermis from the keloid has also been reported to be successful.\(^22\) This is somewhat impractical for extensive keloids and was not successful as an initial procedure in our patient.

Historically, CEAs have been used more extensively in patients with burns. However, CEAs also have been used to treat leg ulcers and other chronic wounds, such as those in epidermolysis bullosa, as donor site coverage for STSGs, to cover large postexcisional skin defects in giant congenital nevi, and for other nonburn indications.\(^23-30\)

The initial skin specimen for preparation of the autografts can be either a superficial shave biopsy sample or a 1-cm\(^2\) full-thickness biopsy sample (depending on the requirements of the laboratory growing the grafts). The method of preparing cultured skin in the laboratory was originally described by Green et al,\(^31\) in which human keratinocytes were grown in culture media. The cultured cells form colonies that ultimately coalesce to form the epithelial sheets used for grafting. The cultured cells are transferred to petrolatum gauze sheets and transported in sterile containers prior to grafting. The backing is necessary because the cultured skin is only a few cells thick and therefore friable. The grafts are draped over the wound, secured in place with fine net mesh, then dressed with bulky dressings, which are changed daily. The wound is irrigated with a cell culture medium with the requirements of the laboratory growing the grafts).

Healing CEAs undergo evolutionary changes over time.\(^24,32\) On application, CEAs are undifferentiated and have no granular or cornified cell layer. After 1 week, all the normal epidermal layers are present, but there are no rete ridges. After 1 month, a confluent basal lamina and mature hemidesmosomes are formed. Anchoring fibrils are immature until 6 to 12 months, when rete ridges and a neodermis with normal stroma and vascular organization can be seen. Elastin expression is seen in the CEA neodermis at 4 to 5 years. The skin that results from CEA application is comparable with mesh STSGs over time.

However, on long-term follow-up CEAs more closely resemble normal skin histopathologically.\(^24\) Not only have CEAs been shown to be able to regenerate a stable, normal epidermis and induce dermal regeneration from wound bed connective tissue, but the application of skin autografts may also provide a stimulus for healing.\(^24,33\)

The advantages of this technique are numerous for the treatment of extensive keloids. At any time, more epidermal sheets can be grown from the patient’s keratinocytes, which are in frozen storage. The initial small biopsy specimen permits an almost infinite quantity of the patient’s own epidermis to be placed on numerous or extensive postkeloid excision defects and reapplied at any time in the postoperative course. There is no harvesting of multiple skin grafts, no additional trauma from full-thickness skin grafts, and since these are autografts, complete take can be expected. In addition, placement of CEAs can easily be done in the clinic.

The disadvantages of this technique are related to the length of time necessary for CEAs to develop normal anchoring fiber attachments to the dermal layer. Consequently, late graft loss due to mechanical trauma has been reported in the burn literature,\(^25,34\) and these grafts are less likely to be successful if placed on dependent areas that are susceptible to shear forces. One solution would be to grow and apply additional grafts as needed. It also has been suggested that some form of dermal matrix replacement be placed before the surface application of the CEA as epidermis.\(^24,35,36\) In addition, development of a composite graft using a dermal substitute combined with the autograft is being explored. The other limitation of this procedure is that the ability to grow CEAs is generally limited to university settings, large burn centers, and commercial manufacturers. Consequently, shipping and manufacturing, depending on the facility, would tend to increase the cost of the grafts.

Although cost and other factors may not make application of CEAs the initial therapy of choice for smaller keloids for which a number of treatment alternatives already exist, we have found CEAs useful in the treatment of extensive recalcitrant keloids.

Presented at the 23rd annual meeting of the American Society of Dermatologic Surgery, Palm Desert, Calif, May 19, 1996.

We wish to acknowledge the clinical contributions of Seth Thaller, MD.

REFERENCES