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Never too old to regenerate? Wound induced hair follicle neogenesis after secondary intention healing in a geriatric patient?

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ABSTRACT

Wound healing is a natural process to restore the structure and function of injured or diseased tissues. Repair of a skin wound usually leads to a scar while regeneration implies fully recovery of function and structure of the damaged tissue. Adult skin wound usually heals with scar while fetal skin heals scarless. Hair regeneration in elderly scalp wound has never been observed. We reported an 80-year-old patient with a large wound on the scalp after excision of a basal cell carcinoma healed by secondary intention wound healing. The patient's wound healed very well aesthetically. Interestingly, on approximate post wound day 180, a hair was observed to be growing towards the surface and eventually erupted in the center of the wound. The hair remained black at 42-month follow-up. This case demonstrated that neogenesis of hair is possible even in geriatric patient. To the best of our knowledge, this is the first report of hair regrow in human skin after wound healing.

1. Introduction

Wound repair is a self-preservation mechanism for species. Regeneration is the mechanism where a tissue or organ regains complete structure and function after injury. Ectodermal organ regeneration has been reported in mice and rabbits with large full-thickness dorsal wounds after healing with secondary intention [1–3]. The regenerated hair follicles occurred only in the center of the wound with re-epithelization in the wound margin. Furthermore, this wound induced hair follicle neogenesis (WIHN) becomes restricted with age, young mice regenerate much better than mature or geriatric mice. Cotsarelis' team discovered that fibroblast growth factor 9, initially secreted by γδ T cells, modulates WIHN after full-thickness skin wounding of adult mice. The authors hypothesized that humans do not regenerate hair after wounding due to limited quantities and no resident dermal γδ T cells [3]. In humans, there are anecdotal reports of digit regeneration after amputation of finger tips in young children. Illingworth reported excellent cosmetic and functional results in guillotine amputations of finger tips in young children with secondary intention healing [4]. However, hair regeneration has not been reported after full-thickness wound healing in human. Here, we report hair growth near the center of a large occipital healing wound, potential WIHN, in an 80-year-old gentleman. This regeneration occurred during secondary intension healing of a large full-thickness scalp wound due to surgical excision of a basal cell carcinoma. To the best of our knowledge, this may be the first case of hair neogenesis after wound healing in human.

2. Case report

An 80-year-old Taiwanese gentleman presented to the National Cheng Kung University Department of Dermatology outpatient clinic with a 5-year history of a growing mass on his occipital scalp (Fig. 1A). The patient has hypertension and diabetes which were under medical control. On examination, a 2.5 cm × 2.3 cm pigmented tumor with a rolling border was noted on the occipital scalp. The clinical diagnosis was basal cell carcinoma and was confirmed with histopathology. The submental and neck lymph nodes were not palpable. A surgical excision and a skin graft were suggested. The patient refused the skin graft but agreed to remove the tumor without reconstruction.

The tumor was excised with a CO_2 laser and contained a free

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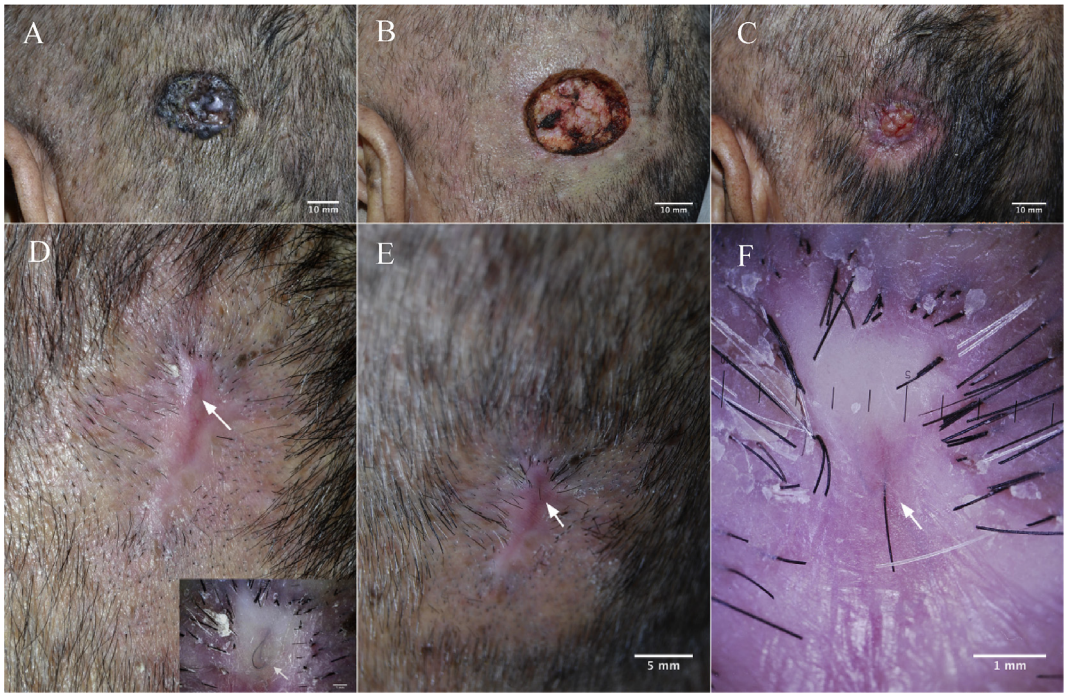

Fig. 1. Hair follicle regeneration in an elderly patient after secondary intention wound healing. **A**, A 2.5 cm × 2.3 cm pigmented basal cell carcinoma was noted on the occipital scalp in an eighty-year-old gentleman. **B**, The tumor was excised with CO_2 laser and the wound was left for secondary intention healing. **C**, The wound was healed in a month. **D**, Six month later, a black hair was noted in the upper portion of the center of the scar embedded in the dermis (arrow), insert: closer view. **E**, The new hair (arrow) erupted out of the epidermis a month later. **F**, The black hair (arrow) under dermatoscope.

margin of 0.5–1 cm. The wound size was 3.5 cm × 2.8 cm (Fig. 1B) and left for secondary intention healing. The wound was cared for by daily wound dressings with tetracycline ointment and covered by gauze. The re-epithelization was predominantly complete in one month and demonstrated no complications (Fig. 1C). On the 6-month follow-up after the operation, a new black hair was observed to be growing in the center of the scar and embedded under the epidermis (arrow, Fig. 1D). One month later, this new hair erupted out of the epidermis (Fig. 1E, and arrow, Fig. 1F). The hair remained black at 42-month follow-up after operation.

3. Discussion

This elderly man potentially demonstrated the first observation of follicular neogenesis in the center of a large healed scar in the geriatric population. Chuong proposed that wound repair and tissue regeneration are in competition [1]. If the wound is small, it heals with repair. If the wound is sufficiently large, it induces regeneration. The original description of WIHN by Breedis showed that delayed wound contraction was necessary for WIHN [5]. In fact, if normal contract occurred, then no WIHN was observed. The final healed wound size must be greater than 25 mm^2 in order for successful WIHN [2]. The patient's final healed wound area was much greater than 25 mm^2. African spiny mice demonstrate the ability to regenerate most of their dorsal skin after excisional injury [6]. However, no evidence for this in humans has been reported to date [7]. Taken together, the observation of this patient's regeneration and evidence from animal studies, we hypothesize the wound size in humans may be one of the critical factors that modulates wound healing for a repair or regenerative pathway.

A young child can regenerate accidentally amputated digit tips including the bone but this ability reduces during maturity from adolescence [4]. The regeneration exhibited by newts is unaffected by age or site of injury [8]. This lesson from newt regeneration is inspiring yet may not occur in mature humans [7]. The present observation of hair regeneration raises many interesting questions on wound healing and tissue regeneration. It is interesting to ask whether such large wounds in a younger patient would regenerate hair more successfully. In fetal skin, wounds heal and regenerate skin appendages without scar [9]. This patient exhibited terminal black hair in the wound center surrounded by scar. Early reports showed WIHN produced white hairs due to the lack of pigment producing melanocytes [5]. However, after further study, Ito et al. showed WIHN of white hairs was due to the time difference in synchronization of hair follicle cycling stage and wounding time [2]. Pigmented hairs form in significant higher numbers if the wound is created during the anagen stage of the hair cycle [10]. Interestingly, human hair follicles are predominantly in the anagen stage. The black color of the hair implies melanocytes may have regenerated as well. However, melanocyte migrating from the wound edge cannot be ruled out. Whether the skin adjacent to the hair follicle regenerated as well is unknown. Unfortunately, the patient refused all additional skin biopsies. A large full-thickness wound that performs WIHN has peri-lesional mesenchyme migration into the wound bed [11]. These mesenchymal cells are predominantly alpha-smooth muscle actin positive myofibroblasts. These cells have been identified as the source for regeneration of adipocytes during WIHN and showed reprogramming of mesenchymal fibroblasts by BMP induced adipogenesis. Interestingly, the new adipocytes only regenerate around new hair follicles during wound healing. We hypothesize that if our report is a case of geriatric WIHN, then a type of cellular reprogramming should have occurred. Other highly interesting questions are: Is the regeneration age related and site specific? Will other types of wound induced regeneration happen in glabrous regions of the human body, such as palms and soles? Do all skin appendages have equal potential to regenerate? How large should the wound be to stimulate skin appendage regeneration? When and why does age affect regeneration of hair in wound healing?

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4. Conclusion

The present case shows the possibility of hair regeneration in humans, even in old age. More cases are needed to confirm this observation and for further study to elucidate the mechanism. If we can understand more of the underlying principles, we may gain new knowledge to develop novel strategies to treat hair related diseases or severe full-thickness injuries.

Statement of ethics

The authors have no ethical conflicts to disclose.

Disclosure statement

The authors declare no conflicts of interest.

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Conflicts of interest

None.

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