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Heterotopic ossification and hypertrophic scars

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Abstract

Burns and trauma lead to extensive superficial and deep soft tissue wounds which are unable to heal perfectly to the pre-injury state. Typically wound healing requires proliferation of cells capable of differentiating into the injured tissue type. As part of the structural requirements for tissue, these cells lay down extracellular matrix (ECM) often in the form of collagens. However, dysregulated cellular proliferation and collagen deposition often leads to wound pathology. Two conditions – heterotopic ossification (HO) and hypertrophic scarring – present a substantial challenge in the management of patients with large surface-area burns. HO is the pathologic formation of ectopic osseous lesions causing severe pain, non-healing wounds, and restricted range of motion. Current treatment strategies aimed at HO include prophylactic radiation therapy, non-steroidal anti-inflammatory drugs (NSAIDs), and bisphosphonates; ultimately patients who have developed HO may require surgical excision followed by prophylactic measures to reduce recurrence risk. Hypertrophic scars in contrast are non-osseous lesions caused by excessive collagen deposition. Similar to HO, hypertrophic scars are often painful, functionally limiting, and aesthetically displeasing. Treatment strategies include CO2 laser application, steroid injections, and excision with skin grafting. Here we review the biology, diagnosis, and treatment and outcomes associated with both forms of pathologic wound healing.

Keywords

Heterotopic ossification; Hypertrophic scar; Burn injury

INTRODUCTION

Heterotopic ossification

Heterotopic ossification (HO) is the formation of ectopic osseous lesions within soft tissue or joints. HO occurs in patients with genetic mutations in receptors responsible for bone

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morphogenetic protein (BMP) signaling and in patients with severe trauma without any known genetic predisposition. Patients with severe trauma including burns, musculoskeletal injury, and spinal cord injury (SCI)/traumatic brain injury (TBI) represent a much larger population of patients with HO. Patients with severe burns may develop HO in sites distant from the visible burn injury. These osseous lesions may cause nerve compression resulting in severe pain, open or non-healing wounds, and restricted range-of-motion due to physical obstruction within joints. In burn patients, HO is often documented in the upper extremities – most notably the elbow [1–3]. – despite burn injuries which are distant from this site. Ultimately, HO presents a substantial barrier to patient recovery after already devastating injuries; these patients have already required extensive medical, surgical, and rehabilitative care related to the original injury, only to require further surgery to remove the offending lesions.

Hypertrophic scarring

Hypertrophic scarring is a late complication of thermal cutaneous injury that can lead to substantial functional impairment as well as aesthetic disfigurement. Hypertrophic scars are characterized by excessive and disorganized deposition of extracellular matrix within the wound bed leading to raised scars. These can occur in any anatomic location but have especially detrimental consequences in areas involving joints and other mobile regions leading to scar contractures limiting free range of motion [4]. Reported studies estimate that hypertrophic scarring develops in up to 80% of all burn patients with greater than deep-partial thickness burns [5, 6].

EPIDEMIOLOGY

Heterotopic ossification

Patients with musculoskeletal injury/trauma, extensive burns, and spinal cord injury (SCI)/traumatic brain injury (TBI) are at risk for HO. In a study of 3,000 burn patients from six high-volume centers, 3.5% of patients formed HO[7]. Included patients were 18–64 years old with total body surface area (TBSA) greater than 20% in patients, 65+ years old with TBSA 10% or greater, or any patients with burn injury to face/neck, hands or feet[7]. Patients with the highest risk of developing HO had greater than 30% TBSA burns. Overall elbow HO has been reported to occur in 0.1–3.3% of burn patients[8–10]. A systematic review of reports describing excision of HO in the elbow found that 28% (174/626) of cases were in burn patients, 55% (343/626) of cases were in trauma patients, and 17% (109/626) were in TBI patients[11]. Studies of burn patients have found the elbow to be the most commonly involved joint, with formation approximately 3 months after the initial injury[1–3]. Schneider *et al* have reported on a risk scoring system based on data from the Burn Model System National Database including over 3,500 patients[12]. This 13-point system has led to an online calculator (available at <http://www.spauldingrehab.org/HOburncalculator>).

Patients with non-burn-related injury are also at risk for developing HO. Notably in these patients, HO develops directly within the site of injury thereby impeding wound healing. Patients who undergo orthopedic surgical operations (*e.g.* total hip arthroplasty (THA)) are

at risk, with studies reporting up to 58% of patients with THA developing ectopic bone[13–16]. Among trauma patients, injury severity score (ISS) is positively associated with odds of developing HO (ISS $\geq$ 16, O.R. 2.2, $p < 0.05$)[17, 18].

Hypertrophic scarring

Several risk factors for hypertrophic scar formation have been identified and include young age, infection, skin stretch and anatomic location (i.e. axilla, neck, small finger) [19]. In contrast to HO, hypertrophic scarring is a relatively common phenomenon among patients with burns, especially those with partial deep or deep thickness burns. While superficial burn wounds tend to heal without complications, deeper partial and full thickness burns have a significantly increased risk to result in hypertrophic scar formation [20]. Contracture is more common when burns are allowed to heal secondarily due to the prolonged inflammation [21]. Additionally, deeper burns are also at increased risk of hypertrophic scar even when grafted [22].

DIAGNOSIS

Heterotopic ossification

Examination—Signs of HO include limited range of motion, arthritis, pain, stiffness and swelling. Diagnosis among burn patients poses a challenge to physicians as HO lesions may develop outside of the area of the burn injury. When HO develops within the burn injury site it may go undiagnosed due to the more prominent appearance of burn scar contractures which present with similar signs including stiffness and pain. Plastic surgeons may diagnose HO in patients who have concomitant overlying hypertrophic scars which confound the diagnosis.

Current Imaging Techniques—Based on the initial examination, radiographic images may be obtained to make a conclusive diagnosis of HO. There are currently no published recommendations for obtaining radiographic images in patients who present signs concerning for HO. Spatial characterization may be performed using computed tomography (CT) imaging. Plastic surgeons can utilize this imaging information to assess the extent of resection that may be required in patients. Magnetic resonance imaging (MRI) may also delineate the proximity of nerves which may be compressed or encased by the offending lesion.

Experimental Imaging Techniques—Additional modalities for detecting HO lesions prior to ossification are now in preclinical and clinical investigation. Single-photon emission computed tomography (SPECT) is able to correlate metabolic activity using radioisotope uptake with the presence of osseous lesions. Areas of early HO may be non-ossified but have high metabolic activity, indicated by increased up take of the radioisotope [23, 24]. However because HO in burn patients may develop outside of the burn sites, it may be impractical to perform imaging prior to the formation of an ossified lesion with its presenting signs. Ultrasonography is also able identify HO even before the development of clinical signs[25]. The changes identified by ultrasound are likely due to extracellular matrix deposition occurring during cartilage [26]. Raman spectroscopy is another modality which is able to

identify tissue changes preceding ossification through identification of collagen and early mineral deposition [27].

Hypertrophic scarring—Diagnosis of hypertrophic scarring is made based on visual appearance. Hypertrophic scars clinically present as oftentimes raised, erythematous and pruritic lesions that have an abnormal texture and have lost the pliable and elastic attributes of healthy skin. Those involving extremities and especially joints can lead to contractures and decreased range of motion in the affected joint. When encountered in the head and neck region, hypertrophic scars may not only be disfiguring but can also lead to cicatricial ectropion, microstomia and reduced oral competence [28]. Plastic surgeons are therefore placed before a challenging task as reconstructive efforts need to address both functional and aesthetic concerns.

However, even prior to the formation of hypertrophic scars, at-risk patients should be identified. Burn depth is the primary predictor of hypertrophic scarring. In epidermal burns, the dermis remains entirely intact and re-epithelization occurs from preserved keratinocytes within the superficial dermis. Similarly, superficial partial thickness burns involve the epidermis and superficial dermis leading to blistering with complete regeneration occurring through migration of keratinocytes from preserved hair follicles and sweat glands. These superficial injuries may require careful monitoring alone. In contrast, in deep partial-thickness burns the density of skin adnexae is significantly decreased leading to prolonged time to re-epithelization and the exuberant collagen production characteristic of scars[29].

PREVENTION

Heterotopic ossification

The approach to patients at risk for HO involves both prevention and surgical excision. Due to the variable frequency and anatomic location of HO after burns, and the potential adverse effects associated with preventative therapy, routine prophylaxis is not standard practice for burn patients. However, options for prevention include non-steroidal anti-inflammatory drugs (NSAIDs) which reduce inflammation and have been used with patients after orthopedic procedures [30–36], radiation therapy which is directed to specific sites where HO may predictably form [10, 36–46], and bisphosphonates [47]. In burn patients, these preventative strategies may have more value for secondary prevention after initial excision – patients who have already undergone HO resection are at high risk for developing a second lesion or recurrence at the site of excision [48] and may be amenable to directed therapy.

Hypertrophic scarring

Comprehensive treatment in the acute phase of the burn injury including early excisional debridement and auto-grafting is a critical element in preventing progression to hypertrophic scarring and should be accomplished within the first 72 hours. While superficial burn injuries will often go on to heal normally, deep partial thickness and full thickness wounds, that require more than 2–3 weeks to re-epithelialize, will assuredly progress to pathologic scarring [29]. In the subacute phase the focus should be directed to establish an optimal wound healing environment in order to achieve physiologic healing. Silicone sheeting and

compression garments are frequently employed to reduce tissue edema and to off-load tension from the wound which is thought to be the culprit in formation of hypertrophic scarring [49]. Furthermore, if extremities are involved, elevation and early range of motion are critical to avoid contractures.

MANAGEMENT

Heterotopic ossification

Indications—Plastic surgeons may be involved in the care of burn patients with HO located in various anatomic sites. Around areas of burn injury, concomitant scarring and poor tissue quality can lead to increased risk of open wounds with surgical excision. Even after surgical excision, release of joint contractures and overlying burn scar contractures should be addressed through a combination of z-plasty and excision with skin grafting.

Operative Techniques—Surgical excision of HO in the elbow has been described in detail by various authors[50, 51],[52], [53]. Indications for operative intervention include arthritis with loss of motion more than 30-degrees and pain at the end of arc[52]. Contraindications to operative intervention include inadequate soft-tissue envelope, loss of motor function at the elbow which would preclude return of function, or inability to perform post-excision rehabilitation[52]. Care must be taken to avoid injury to the ulnar and radial nerves posteriorly and the median nerve anteriorly. HO may grow adjacent to the posterior structures and may even encase these nerves completely. Following excision, the capsule should be released as well and the soft tissue should be addressed to permit motion.

Hypertrophic scarring

Unlike heterotopic ossification, for which management is predicated on either observation or surgical management, hypertrophic scarring has a range of available treatment options.

Injectables—Several nonoperative techniques are available to improve hypertrophic scarring. Intralesional injections of anti-inflammatory and antimetabolic agents have been widely employed and demonstrate decrease in scar thickness as well as pruritic nature of the scar. Several treatments are oftentimes necessary to achieve the desired effect but can be accompanied by side effects including recurrence, hypo-pigmentation and ulcerations [54, 55]. Other agents that are commonly used include bleomycin and Mitomycin C which have been shown to reduce fibroblast proliferation and can lead to improvement in hypertrophic scarring [56]. Frequently, these agents are used in combination with operative and laser treatment modalities as these can synergistically improve outcomes.

Laser therapy—As laser technology has progressed over the recent years, photothermolysis has become an effective tool to address several aspects of hypertrophic scarring and to promote scar rehabilitation. Recent studies focusing on non-ablative as well as ablative lasers have demonstrated significant improvements in scar texture, coloration, pain and pruritus and have even been shown to treat contractures [57, 58]. Several lasers are commonly employed and are distinguished by a specific energy wavelength that targets a certain chromophore in the skin. The PDL has a wavelength of 585/595nm and has been

shown to selectively target microvessels within the hypertrophic scar leading to improved coloration while maintaining a low risk profile. Ablative lasers include the fractional CO₂ laser which has wavelength of 10,600nm and targets water molecules which is stored throughout all layers of the skin. The fractional CO₂ laser generates evenly spaced columns of microperforations that extend through dermis and allow for normalized wound healing characterized by rapid reepithelization and dermal reconstruction. This leads to breakdown of the abnormal scar associated with release of tension across the entire scar surface. Treatment with fractionated photothermolysis has been shown to results in reduced scar thickness as well as improved texture as commonly seen after meshed skin graft [59, 60]. Serial treatments are commonly required for all laser modalities to achieve a stable result and can be combined with other operative and nonoperative modalities.

Operative treatment—Hypertrophic scarring can occur in anatomically distinct locations with unique effects on functionality and appearance. While non-operative techniques offer excellent options for scar rehabilitation, operative approaches need to be considered when scar contractures develop that lead to decreased function. Scar contractures can oftentimes be addressed with Z-plasty techniques and local flaps which release the tension of the scar and bring in healthy tissue from the surrounding area. For example, linear palmar contractures that commonly occur after pediatric contact burns can be released with a series of z-plasties, while more complex webspace contractures are commonly addressed with 5-flap Z-plasty or V-Y advancement flaps [61]. Nail bed deformities frequently occur even after small burns to the hand and result in aberrant nail growth that can be very bothersome and aesthetically stigmatizing to the patient. The operative approach to correct this deformity includes raising a distally based bi-pedicled flap which is designed to release tension from the eponychial fold. The defect that remains after contracture release is then covered by a full-thickness skin graft allowing for restoration of normal nail growth [62]. Burns involving the chest wall can lead to detrimental aesthetic deformities especially in the female breast, as normal breast anatomy can be distorted or breast development entirely arrested due to a tight scar envelope. An effective method of reconstruction can be accomplished with expansion of adjacent healthy tissue and serial transfer to replace the hypertrophic scar. For this purpose, tissue expanders can be placed through the scar or using minimally invasive endoscopic techniques which have been demonstrated to minimize associated complications [63].

Scar contractures of the neck and axillary regions are oftentimes characterized by significant limitation in the range of motion leading to functional deficiency [64]. In these situations significant manipulation with local flaps may not be sufficient to achieve adequate results due to the extent and oftentimes surface area of the affected scar tissue. However, extensive scar release may lead to exposure of larger defects that need to be addressed with free tissue transfer. This can frequently be accomplished with a skin graft or even a free flap if large volume deficiency is present.

Hypertrophic scarring following facial burn injuries can result in disfiguring secondary deformities with detrimental consequences to the patient from both an aesthetic and functional perspective [22]. Reconstructive surgeons are challenged to restore normal facial appearance as even minor attenuation of the intricately dynamic facial anatomy can result in

very visible defects around the eyes, nose and mouth. One of the overarching principles in acute burn care is early debridement with skin grafting. In the face and neck region full thickness skin grafts are preferred over split thickness skin grafts due to reduced secondary contracture and superior overall appearance. Complete excision within boundaries of aesthetic subunits can oftentimes lead to better and more inconspicuous aesthetic outcomes. However, even with optimal initial management late complications including burn contractures cannot always be avoided and may lead to issues with oral function and globe protection. Burn scars of the cheek and malar region generate extrinsic downward forces on the lower eyelid resulting migration and eversion of the lower eyelid with globe exposure. Correction of eyelid ectropion is extremely challenging and requires a comprehensive approach in order to restore normal eyelid position at the lower limbus. Initial release of all extrinsic and intrinsic scarring should be accomplished. Furthermore, midface suspension techniques as well as cartilage grafts to the middle lamella have been employed to prevent further downward migration of the eyelid. Additional lateral and medial canthoplasties may be necessary to secure lid position. Finally, the skin defect after scar release must be reconstructed with a skin graft taking into consideration anticipated primary and secondary contractures. Perioral burn injuries can be similarly detrimental leading to microstomia, which may interfere with oral competence, speech articulation and oral hygiene [28]. Initial management should be directed at prevention after the acute burn and several splinting devices have been utilized to counteract contracting forces [65]. Operative techniques are directed at late complications with releasing and deepening of the oral commissures in order to increase oral circumference and incisal opening [66]. A commissuroplasty involves the release of the oral scar contracture and advancement of a healthy musculomucosal flap to the new apex of the commissure [28].

Other less invasive techniques for amelioration of hypertrophic scarring which can be utilized in conjunction with surgical scar release include fat grafting that may allow for correction of contour deformity and to fill in soft tissue deep to a scar. This technique has been utilized by Byrne et al for hand contractures with good outcomes [67]. However, fat grafting in previously burned area and tight scars can be challenging due to the lack of tissue pliability to allow for injection in multiple layers.

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KEY POINTS

- Two conditions – heterotopic ossification (HO) and hypertrophic scarring – present a substantial challenge in the management of patients with large surface-area burns.
- HO is the pathologic formation of ectopic osseous lesions causing severe pain, non-healing wounds, and restricted range of motion.
- Hypertrophic scars in contrast are non-osseous lesions caused by excessive collagen deposition.
- Current treatment strategies aimed at HO include prophylactic radiation therapy, non-steroidal anti-inflammatory drugs (NSAIDs), and bisphosphonates.