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Reviews

Malignant Transformation of a Chronic Venous Stasis Ulcer to Basal Cell Carcinoma in a Diabetic Patient: Case Study and Review of the Pathophysiology

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ABSTRACT

The degeneration of chronic wounds into basal cell carcinoma is rare. We present an atypical case of basal cell carcinoma diagnosed by soft tissue biopsy in a long-standing wound that had been treated for 3 years as a chronic venous stasis ulcer. In addition to the case report, we review the biomedical literature describing malignant transformation of long-standing wounds. Foot and ankle specialists should be on the lookout for changes that signal malignant transformation in long-standing ulcers.

Basal cell carcinoma (BCC) is the most common form of skin cancer, and it most commonly develops in the sun-exposed areas of light-skinned individuals (1). Furthermore, most BCCs present as a small, dome-shaped papule or nodule with a pearly appearance and rolled, well-rounded borders with adjacent crusting; these features are pathognomonic for BCC and are important markers for definitive diagnosis of these typically indolent lesions that are slow growing and rarely metastasize (1). Although unusual, cutaneous metastasis can occur (2). Primary BCCs respond well to surgical excision, cryosurgery, or electrosurgical ablation; however, metastatic BCC has a median survival of just 8 months (3).

Although most BCCs occur in the head and neck, approximately 8% occur in the lower extremities (4). The incidence of BCC arising from chronic wounds is very low, and as few as 2.4% of malignancies develop from chronic leg ulcers of vascular origin. The authors present a case of BCC diagnosed via soft tissue biopsy in a long-standing wound that had been treated for 3 years as a chronic venous stasis ulcer. Moreover, this report also entails a review of the literature related to malignant transformation in skin wounds localized to the lower extremities.

Historical Review of the Literature

To date, most of the biomedical literature describing the malignant transformation of chronic wounds is in the form of case reports (3, 5–8). In an effort to put such transformation into perspective, we provide, in addition to a case report, an overview of the literature on malignant transformation of wounds in the lower extremity. Wounds that undergo malignant transformation are referred to as Marjolin's ulcerations, after the French physician who originally documented the occurrence in 1827 (9). Kirsner et al (10) have estimated that 1.7% of chronic wounds develop malignant properties; however, this estimate could be low, considering the incidence of misdiagnosis and subsequent failure to report the occurrence. Malignancies that arise from inveterate wounds include BCC, Kaposi's sarcoma, melanoma, squamous cell carcinoma (SCC), and lymphoma (9). Hansson and Andersson (11) identified basal cell and squamous cell as the most frequently encountered cutaneous, ulcerative malignancies, at 60% and 15%, respectively.

Several theories exist regarding the mechanism of malignant transformation in chronic ulcers (12–14). The principal factors presumed to be responsible include (1) exposure to cytotoxic by-products of chronic inflammation (15), (2) an impaired mitotic cycle, and (3) epidermal implantation resulting in a dermal foreign body reaction (13). In regard to the mitotic cycle, Ch'ng et al (16) delineated the role of peri-wound mast cells as catalysts for malignant development. Mast cells are stimulated to degranulate in response to UV-B radiation, resulting in neuropeptide and protease release into the surrounding tissues. These agents interrupt the normal cutaneous cell cycle, and protease release also causes stromal disruption that allows endothelial migration of cancerous cells. In addition to harmful interruption of the normal cell mitosis, mast cell mediators such as fibroblast growth factor-2 and interleukin-8 also stimulate mitosis of dormant malignant cells. Furthermore, mast cells stimulate the necessary angiogenesis for tumor cells to flourish in healthy tissues.

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Despite a theoretical basis, the precise nature of the pathogenesis of malignant transformation of a chronic wound has not been established. Arons et al (13) proposed a progression from acanthosis, an increased thickness of the prickle cell layer of skin, to basal cell hyperplasia and atypia, then pseudoepitheliomatous hyperplasia, and eventually epidermoid carcinoma. Gan et al (14) proposed that infection stimulated dormant neoplastic cells to develop into cutaneous malignancy. Fleming et al (15) surmised that local deposition of toxins released from chronically inflamed tissue would induce malignant mutation of cells. Both Arons et al (13) and Fleming et al (15) proposed that repetitive mechanical deposition of epidermal cells into the dermal layer would cause a foreign body reaction and cellular alteration resulting in a granulomatous degeneration similar to the development of an inclusion cyst. Despite these proposals, however, there is little consensus regarding central versus peripheral malignant degeneration in the literature.

Tissue biopsy is the gold standard for diagnosis of cutaneous malignancy. And, although the ideal time to obtain a specimen has not been firmly established, the general consensus is that earlier is better, because an early diagnosis can, in many cases, decrease morbidity and mortality associated with a delay in treatment. Ackroyd and Young (17) recommended performing a biopsy if a chronic wound failed to satisfactorily respond after 3 months of reasonable treatment, whereas Hansson and Andersson (11) recommended waiting 4 months. Neither author provided a clear-cut rationale for the 3- and 4-month waiting periods, and these recommendations remain anecdotal. There is clear consensus that any wound that appears atypical, namely one that shows jagged and irregular surface contours and margins, or invasive and aberrant epithelium, and responds poorly to mechanical debridement, should undergo biopsy regardless of wound duration.

In regard to biopsy technique, it is important to keep several factors in mind. For instance, representative specimens should be prepared for inspection by both the microbiology and pathology laboratories, and, in most cases, more than one site should be biopsied to reveal the extent of the pathology. In general, a biopsy from the proximal or leading edge of the wound should be obtained in a manner that procures a tissue specimen that is composed of 50% wound and 50% adjacent normal-appearing soft tissue, so that the interface between the pathology and the surrounding tissues can be described. A second specimen should be obtained from the center of the wound, and include the full thickness of the abnormal tissue.

For small lesions (which is usually not the case in a chronic nonhealing dermal lesion) a single en block tissue specimen can be obtained and then hemisected, submitting a portion to both the microbiology and histopathology laboratories. Of course, transporting the pathology specimen in formalin and the microbiology specimen in a dry, sterile container are important considerations. Although wound swabs are the most commonly prepared specimens for study of the microbial environment of the wound bed, excised specimens are preferred. A tissue preparation is the best means to determine the number of microorganisms present per volume of tissue and can be used to discriminate between colonization and frank infection.

It is also best to label each specimen both on the requisition slip and with suture material in larger specimens, as it is important for the pathologist to understand which portion of the specimen is proximal, which side is deep, and which represents superficial tissue. When looking at geographic or circular wounds, the general approach is to label the specimens as if they were removed from the face of a clock (the 12 o'clock position or the 3 o'clock position) or the center of the wound. Although we realize that different surgeons will procure and label specimens in different manners, we offer these tips as basic guidelines, and encourage every surgeon to give careful consideration to the process and to the needs of the histopathology and microbiology technicians in the respective labs. Histopathological analysis is necessary to confirm the presence or absence of malignancy, and microbiological examination of the tissue is recommended in an effort to identify bacteria (colonized or pathogenic) that may be impeding wound healing. In cases that involve substantial amounts of wound fluid, tissue fluid specimens can be examined in lieu of procuring en bloc tissue specimens (18), although excisional biopsies remain the preferred method of analysis.

Case Report

An 83-year-old male presented to St. Vincent's Mercy Medical Center, Toledo, Ohio, with a chief complaint of abdominal pain and hematuria of 3 days' duration, at which time the Division of Podiatric Surgery was consulted for evaluation and treatment of a coincident right leg ulceration. The ulcer had been present for approximately 3 years and the patient could not recall any trauma to the area. The patient had understood the ulcer to be related to his venous stasis. Because he had been cared for at a veteran's clinic, he had been under the care of numerous physicians using multiple topical therapies over the course of the preceding 3 years. Most recently, in-home nursing care had entailed the application of dressings with a protective and supportive Unna-paste (zinc oxide) boot biweekly and a wound care specialist had assessed the wound approximately every 2 weeks. The Unna boot had been helpful in controlling leg swelling and the ulcer was reportedly as small as it had ever been at the time of the admission to our hospital.

The patient's past medical history included bladder cancer, a left above-knee amputation (AKA) as a complication of vascular disease, type 1 diabetes mellitus, myocardial infarction, hypertension, peripheral vascular disease, esophageal strictures, and an abdominal aortic aneurysm. His surgical history included an aorto-femoral bypass surgery and multiple aortic bi-femoral bypass surgeries. The patient admitted to social alcohol consumption and a 60-pack year tobacco smoking history, although he had quit smoking 12 years before the admission.

Physical examination revealed generalized peripheral neuropathy with loss of protective sensation beginning at the level of the knee, based on the 5.07-g monofilament assessment of the right lower extremity. There were sparse, superficial, bluish, tortuous varicosities throughout the right lower leg. Mild pitting edema was noted in the pretibial region and the dorsum of the right foot. The ulceration was in the central portion of the anterior medial aspect of the right leg, and it displayed a dry, pale pink granular base with smooth, regular borders and localized blanching erythema about the periphery (Figure 1). The ulcer measured 5.5 × 2.5 × 0.2 cm in its greatest dimensions. There was no undermining of the adjacent soft tissues and the ulcer did not probe to bone. There was no malodor or drainage appreciated and there were no other dermal defects localized to the extremity. The center of the wound was pale rather than exhibiting the typical beefy red appearance of granulation tissue. There were also skin islands with fresh epidermal tissue, indicating that some portions of the ulcer were attempting to heal. The borders of the wound were well rounded as opposed to the typical punched out margins usually seen with venous stasis ulceration. The wound bed was free of fibrinoid ingrowths or exudates, which also distinguished it, to our thinking, from a typical venous stasis ulcer (Figure 2). The patient's complete blood count and C-reactive protein levels were within normal limits.

Based on the long-standing nature of the wound and its location in the central third of the leg, as well as the pale center without granulations and the rounded margins, we recommended biopsy in an effort to ascertain the biological nature of the tissues. After discussing the suspicious nature of the ulcer and its reported recalcitrance to therapy, informed consent was obtained for biopsy of the lesion using

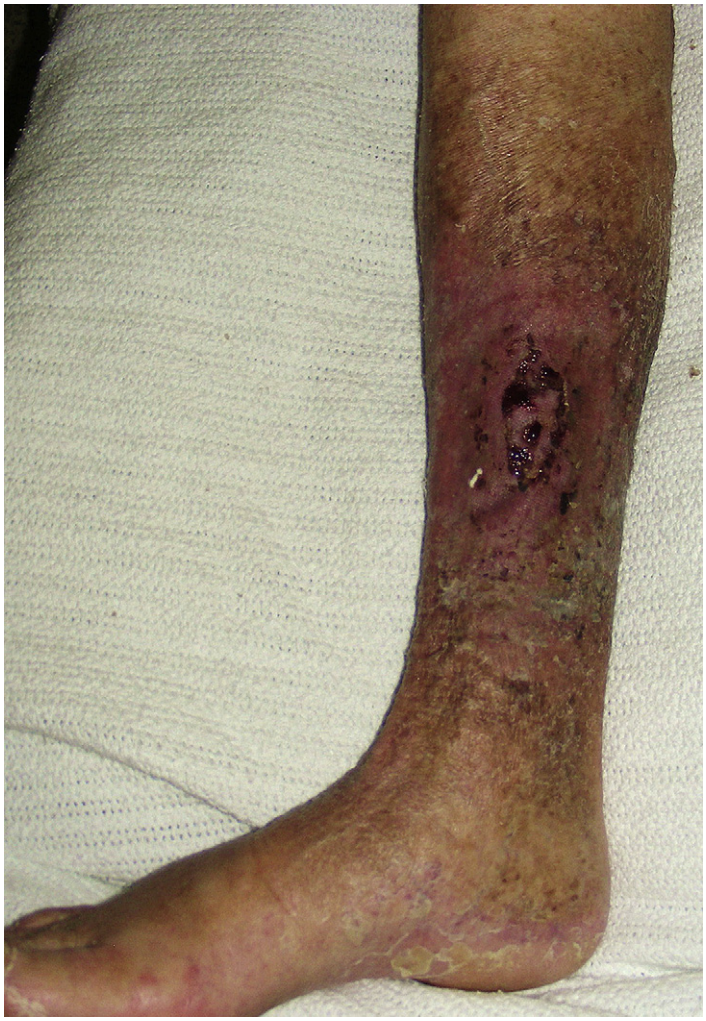

Fig. 1. The clinical photograph was taken after 24-hour use of a modified Unna paste compression dressing. Note only trace edema about the pretibial region and dorsal foot.

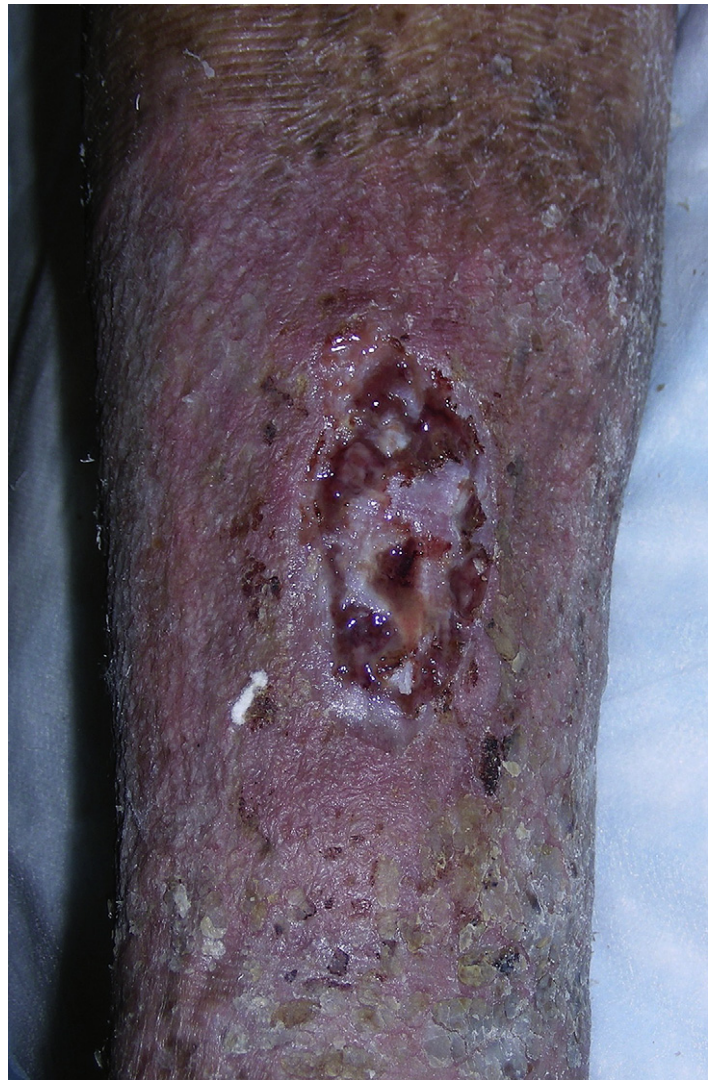

Fig. 2. Clinical photographic close-up of the medial leg lesion after 3 years of local wound care. Notice that the center of the wound is pale rather than the typical beefy red appearance of granulation tissue. Fresh skin islands with active epithelialization indicate patchy healing. Note the well-rounded borders and absence of fibrinoid ingrowths or exudates.

local anesthetic of 1% plain lidocaine, after which three 5-mm punch biopsy specimens were obtained. The first 2 punch specimens were taken from the 12 o'clock and 3 o'clock positions of the wound periphery, each including a portion of the normal-appearing adjacent soft tissue. A final 5-mm punch was taken from the central aspect of the wound bed (Figure 3). Superficial wound swabs for bacterial culture were also obtained.

The microscopic analysis revealed an ulcerated BCC arising from the epithelium, with surrounding fibrosis and numerous small, dilated dermal blood vessels (Figures 4 and 5). Nests of basaloid cells were seen budding from the undersurface of the epidermis. Scattered inflammatory cells were also noted, along with hemosiderin-laden macrophages. Immunoperoxide and iron staining revealed an infiltrating neoplasm with positive staining for pancytokeratin and negative for melanoma markers. The iron stain revealed brown pigment consistent with hemosiderin. There was no mention of mitotic bodies. This combination of microscopic findings was consistent with a chronic ulceration complicated by BCC, which may or may not have been associated with chronic venous insufficiency. The patient was referred to the plastic surgery department for consultation regarding excision and local tissue transfer, which the patient ultimately refused.

Discussion

Malignant degeneration of wounds is rare, although not unheard of. Since the earliest description of the cancerous potential of chronic ulcers (9), numerous case reports of fungating ulcers have been presented in the literature. However, a causal relationship has not been established because of the rarity of the condition, even though it has been described in the literature as far back as 1828 (19). In fact, as early as 1932, the risk of malignancy developing in a chronic leg ulcer of vascular origin was recognized (20). It wasn't until 1995, however, that a large-scale epidemiological study was conducted in an effort to correlate chronic venous ulceration with SCC (21). In that study, Baldursson et al (21) demonstrated that patients with long-standing chronic leg ulcerations of vascular origin were at a 5.8 times increased risk for developing SCC based on the criteria of Tenopyr and Silverman (20).

Most malignancies arising from chronic wounds take the form of SCC. In a recent retrospective study of 80 patients and 85 tumors arising from malignant degeneration, 98% were SCC whereas just 2%

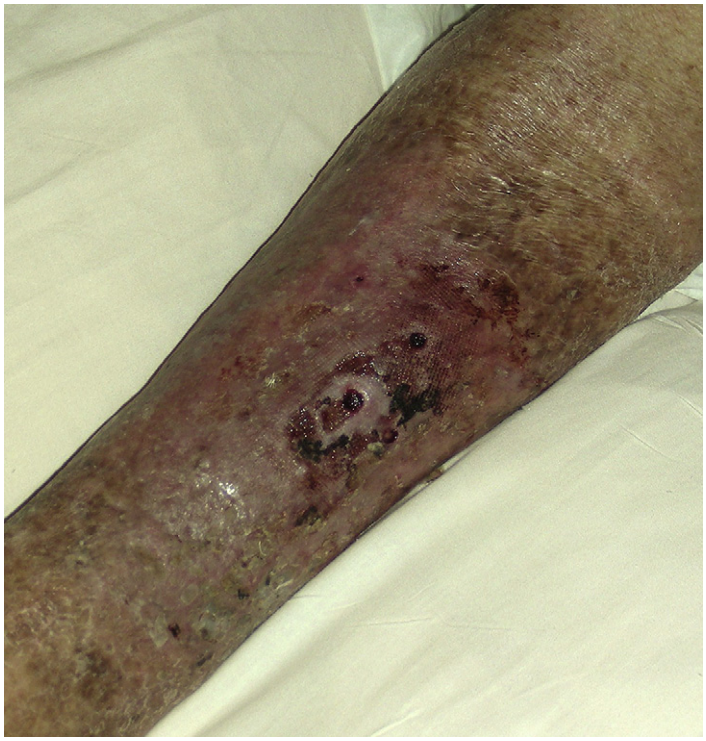

Fig. 3. Clinical photograph of punch biopsy sites taken from the central wound, 12 and 3 o'clock positions.

represented BCC (22). Regardless of the degree of histological differentiation present in these cases, 57% (29/51 patients) went on to amputation of the leg. In that same study, moreover, the 32% death rate associated with these lesions increased to 66% when lymph nodes were involved and to 83% when visceral metastases were identified.

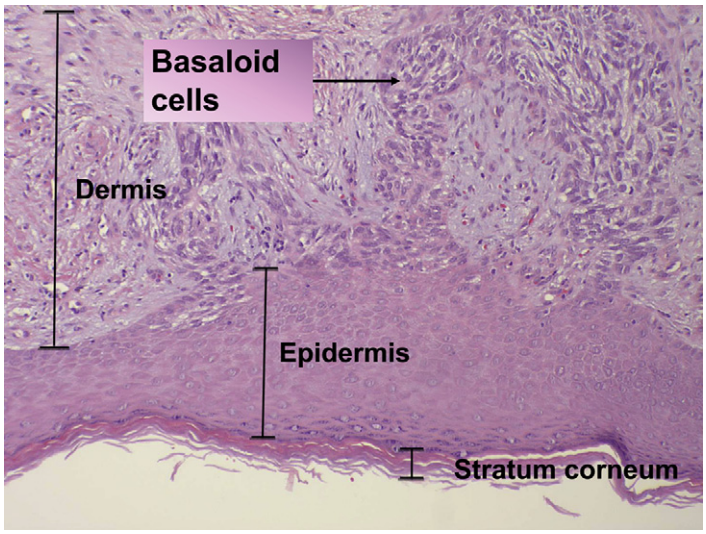

Fig. 4. Microscopic exam (magnification ×10) revealing an ulcerated basal cell carcinoma arising from the epithelium with surrounding fibrosis and numerous small dilated dermal blood vessels. Nests of basaloid cells are seen budding from the undersurface of the epidermis. These tongues of atypical basaloid cells (*arrow*) extending into the superficial dermis are accompanied by a desmoplastic fibrous reaction consistent with the pathology.

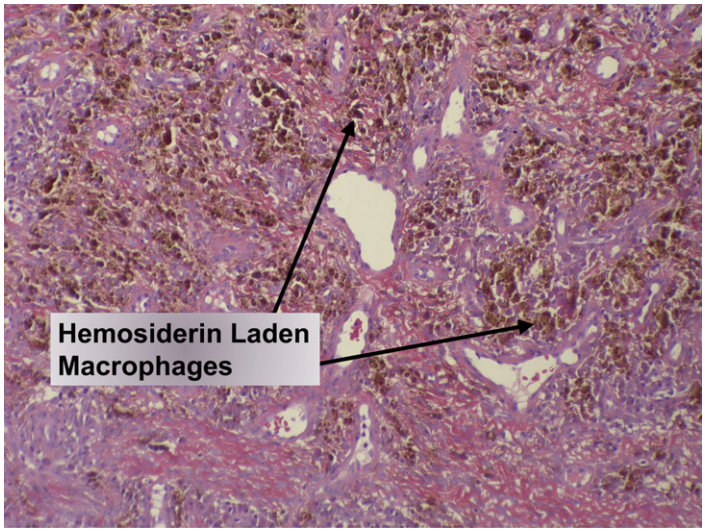

Fig. 5. In this micrograph (magnification ×40), there are scattered inflammatory cells along with hemosiderin-laden macrophages (*arrows*) commensurate with the pathology.

In the current literature, 2.2% of leg ulcers are considered to be skin cancer, more often BCC (75%) than SCC, and 2.4% of ulcers arising from chronic venous stasis will undergo malignant transformation (23). The incidence of BCC arising from chronic ulcerations, however, is quite low when one thinks of the vast number of these wounds encountered in everyday practice (24). Interestingly, a study of 125 cases found that 25% of patients with BCC had concomitant chronic venous stasis (25), suggesting a relationship between venous disease and BCC.

In the case that we have described, it is likely that morbidity, including infection and prolonged wound care, could have been reduced had the suspicion of malignancy been raised earlier. The location of the wound was not classical for a chronic venous stasis ulcer, as it was nested in the central one third of the leg on the medial pretibial border as opposed to the medial malleolar region, which is more typical for this type of lesion. Other hallmarks of a stasis ulcer were also absent, including the presence of local soft tissue changes such as chronic edema or hyperpigmentation complicated by micro- and macrovascular congestion (Figures 1 and 2). The most notable features of this wound were soft tissue atrophy and minimal edema. Although our patient was elderly, his medical condition was complicated by peripheral arterial disease rather than by simple venous stasis and congestion, as evidenced by the history of vascular surgeries ultimately resulting in a contralateral limb above-knee amputation secondary to occlusive arterial vascular disease.

Soft tissue biopsy is the gold standard for the diagnosis of cutaneous malignancy, although some physicians are hesitant to pursue it without a clear rationale. Because local invasion into bone and lymph nodes has been reported, it is important to identify primary malignancy of the skin as well as wounds at risk for malignant degeneration. Plain radiographs and magnetic resonance imaging (MRI) may reveal early osteolysis, and are valuable tools in delineating the nature and extent of the soft tissue invasion and bone involvement (26, 27). Lymph node involvement is reported to occur in only 20% of patients (28) and visceral spread of metastases has been reported to occur without concomitant lymph node involvement (29). Of course, the prognosis is poor with any metastatic development.

In cases where there is no distinct clinical evidence of malignancy, histological specimens can shed light on factors impeding wound healing. Certain histochemical reactions are necessary to effect wound healing and, similarly, there are some chemicals that interfere

with healing. For instance, matrix metalloproteinases IX and II (MMP-IX and MMP-II) interfere with wound healing. These can be identified in the wound bed by biopsy prepared with special immune histochemical staining techniques (18, 30). When high concentrations of MMP-II and MMP-IX are present, the wound is considered to be in a lag phase and is unlikely to heal (18) without a change in the treatment protocol.

Whether the biopsy serves to identify a malignancy, an occult or indolent infection, or simply a nonhealing wound with the potential to heal, such information will help to direct the plan of care. When malignancy is identified, the patient should be educated with regard to the nature and extent of the condition and the prognosis. The plan for excision of the lesion and appropriate consultations should be discussed at this point to expand the caregiving team as necessary. For most patients, excision of the lesion and skin grafting is a logical stepwise approach to a well-differentiated, localized lesion. Poorly differentiated lesions that are grossly disseminated are often best managed via amputation. Close follow-up care to ensure complete healing of primary wounds and autograft harvest sites (when applicable) are important. Routine monitoring to identify early evidence of recurrence is an important element of the long-term care plan.

Because the natural progression from ulceration to dysplasia is insidious, the primary harbinger of malignant transformation seems to be the long duration of the wound. Other clinical signs of malignant degeneration of a wound include abnormal granulation tissue and extension of the wound margins. The case presented in this report had been treated for 3 years, failed numerous regimens of local wound care, and exhibited pale-colored granulation tissue, all of which were unusual characteristics that called for biopsy. Furthermore, this case included clinical characteristics that were unusual for venous stasis ulceration. The borders of the wound were well rounded rather than punched out and the wound bed was free of the fibrinoid ingrowths or exudates typically seen in venous stasis ulcers.

It is the authors' contention that the foot and ankle surgical community should be aware of the tell-tale signs of malignant transformations in chronic wounds, in an effort to reduce morbidity and mortality from these unusual occurrences. One report supports this notion by presenting a very unusual presentation of a Merkle cell carcinoma diagnosed incidentally upon examining a chronic ulceration of the leg (31). Unusual location, the lack of a granular and beefy red base, rounded margins, and prolonged failure to heal despite reasonable therapy, are considered ominous signs of potential malignancy in a cutaneous wound.

In conclusion, the overall incidence of malignant transformation of wounds is rare. However, close wound inspection and monitoring for unusual changes should be performed diligently on chronic wounds, and the threshold for obtaining a wound biopsy should be low, to reduce both morbidity and mortality associated with complications of malignancy or infection.

Acknowledgments

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