CLINICAL MANAGEMENT extra

Major Histopathologic Diagnoses of Chronic Wounds

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PURPOSE:

To clarify the histopathology of acute osteomyelitis, chronic osteomyelitis, primary vasculitis, and secondary-type vasculitis.

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TARGET AUDIENCE:

This continuing education activity is intended for physicians and nurses with an interest in skin and wound care.

OBJECTIVES/OUTCOMES:

After participating in this educational activity, the participant should be better able to:

1. Describe the parameters and significance of this study.

2. Identify chronic wound diagnosis and treatment.

3. Differentiate the histopathology of osteomyelitis and vasculitis.

ABSTRACT

OBJECTIVE: The presence of a chronic wound can result in significant morbidity/mortality. Understanding the pathological alterations of wound tissue that are refractory to standard wound therapy is essential for effective wound management and healing. The authors describe 4 wound etiologies, specifically, acute osteomyelitis, chronic osteomyelitis, primary vasculitis, and secondary-type vasculitis.

SETTING: A tertiary care hospital.

DESIGN: A retrospective review of 1392 wound operations performed during a 24-month period at a tertiary care hospital was conducted. Tissue specimens reviewed included soft tissue infections of the lower extremity, sacrum, hip/pelvis, trunk, perineum, and buttocks.

MAIN RESULTS: Acute osteomyelitis is defined as bone tissue with a predominance of polymorphonuclear leukocytes, evidence of osteoclast bone resorption with scalloping of the cortical bone edges, and bone detritus. Chronic osteomyelitis is defined as bone tissue with a significant amount of fibrosis surrounding devitalized tissue and heavy infiltration of lymphocytes and plasma cells. Primary-type vasculitis is defined primarily as inflammation and necrosis of blood vessel walls. In cutaneous lesions of granulomatosis with polyangiitis, ulceration with numerous inflammatory granulomas is seen in the papillary dermis. Secondary vasculitis is defined by vessel wall infiltration by inflammatory cells and fibrinoid necrosis of the small vessel wall.

CONCLUSIONS: Pathologies of these 4 types of wounds can complicate standard algorithms designed for diagnosis and treatment, and accurate diagnosis through histopathologic analysis can help tailor targeted treatment.

KEYWORDS: granulomatosis with polyangiitis, histopathology, vasculitis, wound care

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INTRODUCTION

Chronic wounds are characterized clinically as wounds that have failed to proceed through a biologically predictable and timely healing process and either are unresponsive to initial therapy or persist following appropriate wound care.[1] They are often identified by the presence of a raised, hyperproliferative, yet nonadvancing wound margin.[2] Understanding the pathological alterations of wound tissue that are refractory to standard wound therapy is essential for effective wound management and healing. Wound healing is a complex physiological process including overlapping phases (hemostatic/inflammatory, proliferating, and remodeling phases).

Chronic wounds, such as pressure ulcers (PrUs), diabetic foot ulcers (DFUs), or venous stasis ulcers, are not defined by their duration, but rather by their physiological impairments to healing.[3] Morbidity and mortality associated with these wounds are significant, with mortality rates resulting from Stage IV PrUs as high as 68.9%[4] and a 6-fold increased risk of amputation in patients with DFUs.[5] Therefore, the correct identification and institution of effective treatment that stimulates healing are essential steps toward reversing the negative consequences of these wounds.

Sharp debridement is a preferred technique to remove impaired and devitalized tissue. It has been reviewed in multiple consensus guidelines, and the technique has been previously described in the literature.[6–9] Fundamental to successful debridement is knowledge of the histopathologic alterations present in chronic wound tissue. Previously, the authors described the pathology of DFUs, PrUs, and venous stasis ulcers at various histologic levels.[10] Results from that study revealed 15 histopathologic findings across 7 different tissue levels that were commonly identified in a variety of wound types.[10] Although a distinction between a healing and nonhealing wound edge on pathological evaluation may be important in guiding surgical debridement, it may be insufficient for chronic wounds refractory to standard debridement and treatment protocols. In this case, a more detailed analysis of wound edge histopathology may be required to suggest optimal therapeutic interventions and to guide debridement in preparation for a regenerative medicine-ready wound bed.

In this article, the authors describe 4 major histopathologic findings integral to guiding treatment in patients with refractory wounds.

Because every alteration in the mechanism of a given chronic wound has the potential to produce pathological conditions of different medical relevance, a precise treatment regimen is required for each wound based on histopathologic assessment.

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Proper analysis and diagnosis of a wound's histopathology are 2 of the most significant challenges a clinician faces when developing an effective treatment plan for a patient's wound. A lack of understanding of the mechanisms and pathogenesis of a chronic wound has the potential to lead to unnecessary suffering and even to amputation or death. This article seeks to uncover the pathological mechanisms underlying a majority of chronic wounds, so that improved treatments can be developed. If accurate and consistent diagnoses can be made across hospital settings, the potentially severe implications of misinterpreting histopathologic reports can be avoided and treatment greatly improved.

METHODS

With institutional review board approval, the authors conducted a retrospective review of 1392 surgical cases performed during a 24-month period at a tertiary care hospital in Mineola, New York. Debridements were based on standard indications such as nonhealing deep and superficial wounds, and soft tissue infection involving multiple sites, including lower extremity, sacrum, hip/pelvis, trunk, perineum, and buttocks. Minor cases not involving true acute or chronic wounds were excluded.

The tissue samples obtained from sharp debridement were submitted to the pathology laboratory for histopathologic evaluation. Tissue specimens were placed in 10% neutral phosphate-buffered formalin and were sampled with representative tissue submission. Hematoxylin-eosin slides were prepared from formalin-fixed, paraffin-embedded specimens.

RESULTS

The 4 major diagnoses include acute osteomyelitis; chronic osteomyelitis; primary-type vasculitides, specifically granulomatosis with polyangiitis (GPA); and secondary-type vasculitis. Acute osteomyelitis is defined histologically as bone tissue with a predominance of polymorphonuclear leukocytes, evidence of osteoclast bone resorption with scalloping of the cortical bone edges, and evidence of bone detritus. Chronic osteomyelitis is defined histologically as bone tissue that has a significant amount of fibrosis surrounding devitalized tissue, accompanied by heavy infiltration of lymphocytes and plasma cells with few polymorphonuclear neutrophilic leukocytes. A diagnosis of vasculitis should be considered in the context of other histologic findings and may be a secondary event in the setting of other pathological findings such as ulcer, infection, or trauma.

In primary-type vasculitis, injury to the vessel wall is an essential finding. It is defined histologically as inflammation and necrosis of blood vessel walls associated with various pathological findings depending on vessel size and stage of disease.

In cutaneous lesions of GPA, ulceration with numerous inflammatory granulomas is seen in the papillary dermis. Granulomas primarily comprise plasma cell and lymphocytic infiltrates, as well as multinucleated giant cells, such as histiocytes.

Secondary vasculitis of small and muscular vessels includes the following 2 histologic criteria: vessel wall infiltration by inflammatory cells and fibrinoid necrosis of the small vessel wall.

DISCUSSION

Acute Osteomyelitis

Osteomyelitis is defined histologically as acute or chronic inflammation in bone tissue, confirmation of which is important for clinical diagnosis.[11] Historically, osteomyelitis has been clinically categorized as acute or chronic in nature. The characterization of osteomyelitis is now predicated on pathological description and diagnosis as opposed to the clinical onset of disease. Tissue culture, specificity, and histologic findings in bone tissue of osteomyelitis specimens are crucial to treatment. Although clinical signs and symptoms may heighten clinical suspicion of osteomyelitis, the criterion standard for diagnosis is bone biopsy and microbiological analysis of bone culture. Clinical signs may include localized bone pain, erythema, and drainage around the affected area.

To date, only histology from bone biopsy and microbiologic analysis with bone culture are considered definitive for accurate diagnosis of osteomyelitis.[12–15] The diagnostic sensitivity of histologic examination for the presence of osteomyelitis has been reported as high as 95%, with a diagnostic specificity of 99%.[16] There were several key histologic features identified in all patients with acute osteomyelitis. Polymorphonuclear leukocytes were the predominant inflammatory cell type identified in these specimens. In many cases, there was evidence of osteoclast bone resorption with scalloping of the cortical bone edges (Figure 1). In addition, there was evidence of bone detritus as indicated by necrotic fragments of cortical bone in the bone marrow (Figure 2).

Chronic Osteomyelitis

Establishing a definitive diagnosis of chronic versus acute osteomyelitis in a wound, based on pathological evaluation, guides clinical decisions. Chronic osteomyelitis may be refractory to medical therapy when compared with acute osteomyelitis because of a more complex colonizing flora and may be treated with antibiotics and surgical debridement of wound soft tissue and bone.[17–21] Empiric antibiotics are not usually recommended. Although the literature is conflicted, many authors agree that without adequate debridement chronic osteomyelitis does not respond optimally to antibiotic regimens alone.[22–29] Even with thorough debridement, patients with osteomyelitis may be refractory to medical treatment and require adjunctive therapy.

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Figure 1.
ACUTE OSTEOMYELITIS

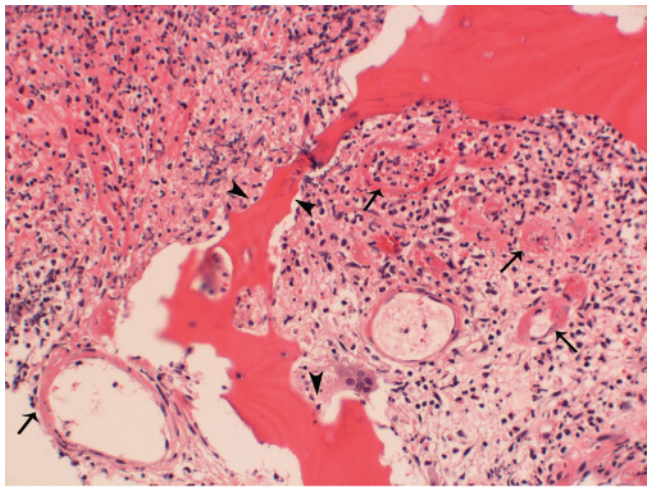

Image shows polymorphonuclear neutrophil infiltrate, eroded bone tissue (arrowheads), and fibrinoid necrosis of damaged blood vessels (small arrows) (original magnification x 200).

In chronic osteomyelitis, draining sinus tracts, limb deformity, joint instability, and local signs of impaired vascularity, range of motion, and neurologic status are commonly seen.[30]

Necrotic bone was identified histologically as bone tissue with loss of greater than 50% of osteocyte nuclei from osteocyte lacunae. In the specimens with chronic osteomyelitis, there was a significant amount of fibrosis surrounding devitalized tissue. Heavy infiltration of lymphocytes and plasma cells with few polymorphonuclear leukocytes was noted.

PRIMARY VASCULITIS

Granulomatosis with Polyangiitis

In contrast to secondary-type vasculitis, GPA (formerly known as Wegener granulomatosis) is a rare, autoimmune small vessel vasculitis that predominately affects the upper and lower respiratory tracts, kidney, eye, joints, skin, and neural tissues.[31–34] Symptomatology is predominately respiratory, such as cough, hemoptysis, and sinusitis; and may include renal symptoms (hallmark of generalized disease). A large percentage of patients, however, have cutaneous lesions as their initial presenting symptom. According to the Chapel Hill Consensus Conference, establishing the diagnosis of GPA requires (1) granulomatous inflammation involving the respiratory tract and (2) vasculitis of small to medium blood vessels.[35]

One patient was identified as having a lesion secondary to GPA located on the neck. Pathology from the patient's initial debridement revealed cutaneous ulceration with numerous inflammatory granulomas in the papillary dermis. The granulomas coalesced around a dermal vessel with the greatest confluence near the dermal vascular plexus. The granulomas were primarily composed of plasma cells and lymphocyte infiltrates, as well as multinucleated giant cells, such as histiocytes (Figure 3). There was extensive vasculitis, but no fibrinoid necrosis noted in the wall of the vessels (Figure 4).

Secondary-Type Vasculitis

The skin is the most common primary organ for vasculitis.[36–38] Etiologies of secondary-type vasculitides are vast, including infectious diseases, neoplastic causes, or drug-induced or inflammatory diseases of unknown etiology.[39] Histologically, only a few patterns of vascular inflammation are seen under the microscope. The clinical manifestations of secondary-type vasculitis depend on 3 core criteria: location, type, and size of the affected vessel.[39] Generally, the secondary-type vasculitides affect smaller-caliber vessels, such as capillaries and arterioles less than 0.1 mm, and intraorgan muscular small arteries and venules.[40] Clinical histopathologic criteria for small vessel vasculitis and muscular vessel vasculitis must include the following 2 criteria: perivascular infiltration of inflammatory cells and fibrinoid necrosis of the small vessel wall (Figures 5 to 7).[40,41]

CONCLUSIONS

In this article, the authors describe the pathological findings of 4 types of wounds that may complicate standard algorithms

Figure 2.
NECROTIC PERIOSTEUM

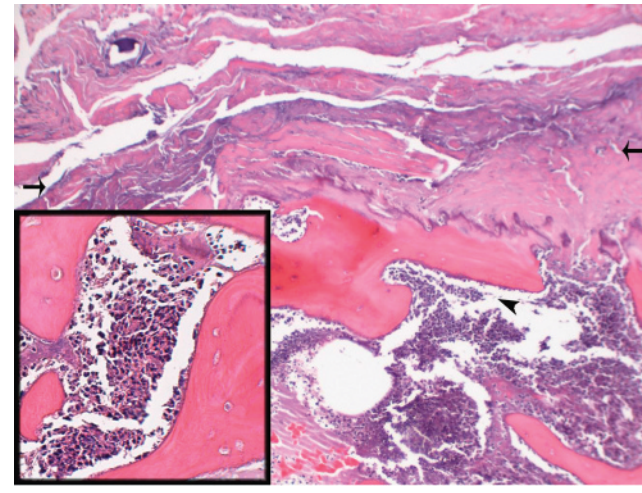

Image shows necrotic periosteum (between small arrows) and underlying acute osteomyelitis (arrowhead) (original magnification x100). Insert with acute osteomyelitis and necrotic bone (original magnification x 200).

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Figure 3.
CUTANEOUS GRANULOMATOSIS WITH POLYANGIITIS—PAPILLARY DERMIS GRANULOMA

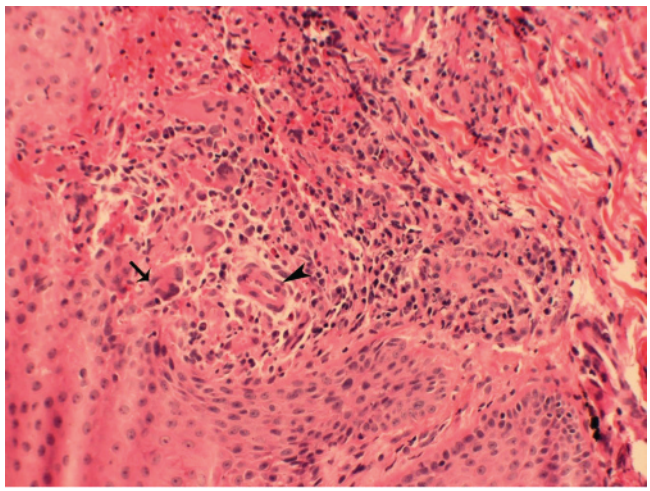

Image shows papillary dermis with granulomatous vasculitis and multiple histiocytes. Blood vessel (arrowhead) and histiocytes (small arrow) (original magnification x 20).

designed for diagnosis and treatment of complicated wounds, specifically acute osteomyelitis, chronic osteomyelitis, primary vasculitis (GPA), and secondary-type vasculitis. The afore-

Figure 4.
CUTANEOUS GRANULOMATOSIS WITH POLYANGIITIS—VASCULITIS

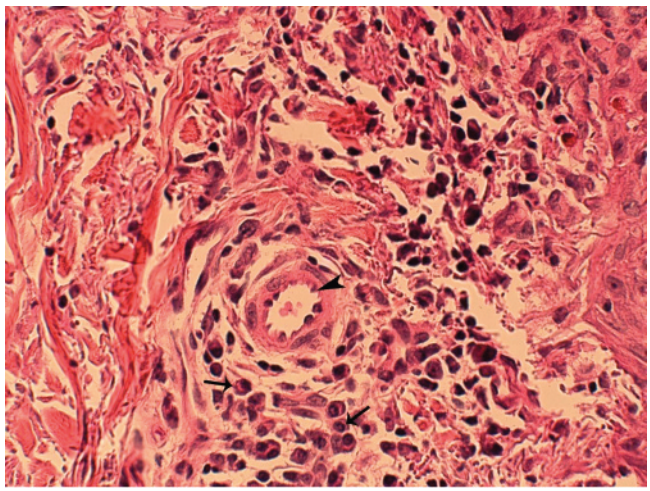

Image shows perivascular inflammation with plasma cell infiltration. Blood vessel (arrowhead) and plasma cells (small arrows) (original magnification x 400).

Figure 5.
ULCER BED: SECONDARY-TYPE VASCULITIS

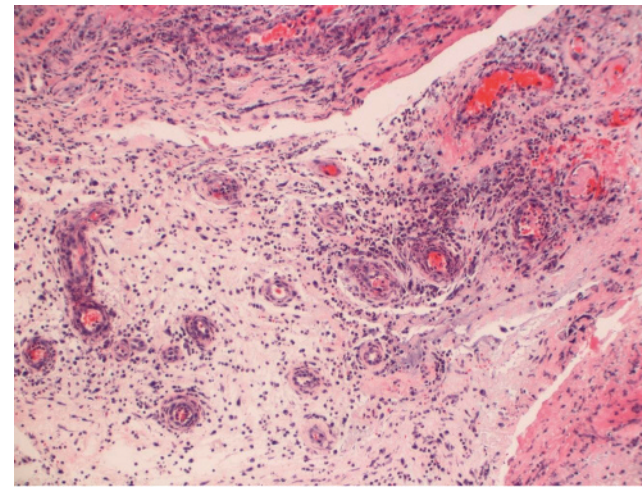

Image shows secondary-type vasculitis involving all small blood vessels (original magnification x 100).

mentioned diagnoses are less common and often difficult to diagnose. The authors believe that a thorough history and physical examination, multimodality specialty involvement, and treatments, along with accurate diagnosis through histopathologic analysis of wound biopsy specimens from routine debridements, can help tailor targeted treatment regimens.

Figure 6.
SUSPECTED PYODERMA GANGRENOSUM

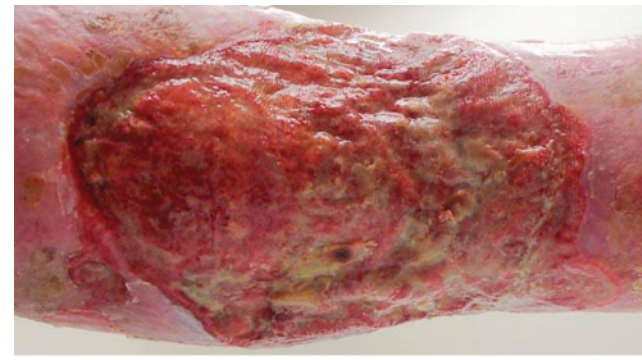

Image shows a 54-year-old woman suspected of having pyoderma gangrenosum, but on pathological evaluation was found not to have pyoderma gangrenosum, rather secondary-type vasculitis of the lower extremity (15 x 9 x 0.3 cm).

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Figure 7.
ULCER BED: SECONDARY-TYPE VASCULITIS

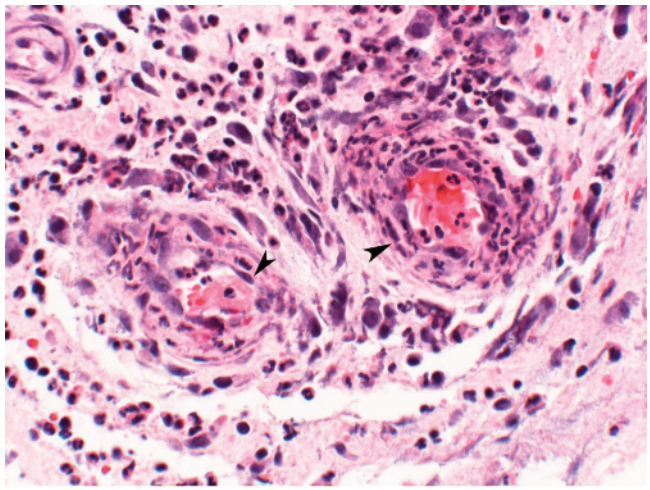

Image shows secondary-type vasculitis, neutrophilic infiltration of blood vessel walls (arrowheads) (original magnification x 400).

PRACTICE PEARLS

• Knowledge of histopathologic alterations present in wound tissue is fundamental to successful debridement and healing. Pathologic evaluation can help distinguish healing from a non-healing wound edge; however for chronic wounds refractory to standard debridement and treatment protocols, a detailed analysis of wound edge histopathology may be necessary to guide therapeutic interventions and debridement.

• Although clinical signs and symptoms may heighten clinical suspicion of osteomyelitis, tissue culture, specificity, and histologic findings in bone tissue are crucial to treatment.

• A thorough history and physicial examination, multimodality specialty involvement, and treatments, along with accurate diagnosis through histopathologic analysis of wound biopsies from routine debridements, can help tailor treatment regimens.

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