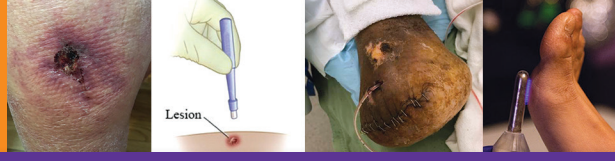

Atypical Wounds: Cracking the Code of the Uncommon

An estimated 20% of all chronic wounds are due to unusual causes.

BY WINDY COLE, DPM

Goals and Objectives

After completing this CME, the reader should be able to:

1) Recognize the importance of identifying atypical wounds

2) Examine the role of complete wound assessments

3) Explain the need for tissue biopsies in determining the etiology of an atypical wound

4) Describe the various clinical manifestation of atypical wounds

5) Understand evidence-based therapies available for treating atypical wounds

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*Following this article, an answer sheet and full set of instructions are provided (pg. 140).—**Editor***

Introduction

The prevalence of atypical wounds has not been studied extensively, but it has been estimated that 20% of all chronic wounds are due to unusual causes.[1,2] As our population ages, clinicians are caring for patients with increased numbers of comorbidities and pathological processes that can contribute to the development of hard-to-heal wounds. The negative impact of chronic wounds is well recognized in the literature. It is not uncommon for wound patients to suffer daily with pain, malodor, exudate management, and reduced physical mobility. Patients dealing with chronic wounds often relate feelings of isolation and depression. Therefore, the ability to identify and treat chronic wounds caused by uncommon etiologies is an important skill. Unfortunately, it can take years of clinical experience to master this. To this argument, it is imperative that all wound care clinicians are knowledgeable about uncommon wound etiologies. The goal of this CME article is to introduce the clinical features of several types of atypical wounds caused by inflammation, malignancy, and chronic illnesses. Wound care

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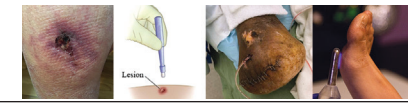

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providers are encouraged to be proactive when faced with hard-to-heal wounds of the lower extremity.

Clinical Features

One of the first indications that a chronic wound may be atypical is that it lacks a history of an acute trauma and it does not fit into a known clinical category. Common wound presentations include arterial wounds caused as a result of poor blood supply. Arterial ulcers often present as necrotic, well-defined wounds that are most often localized on the dorsum of the foot or distal toes.[3] In cases of arterial wounds, pain typically occurs with leg elevation. Venous leg ulcers (VLUs) are due to venous insufficiency. Most VLUs occur around the medial malleolus.[3] These wounds are highly exudative and display irregular borders and tend to be covered by a layer of fibrin. Prolonged pressure can lead to pressure injuries. Pressure ulcers often occur in areas of boney prominences due to increases in stress and shearing forces.[3] Diabetic foot ulcers (DFUs) occur in a patient with long-standing diabetes, neuropathy, and/or peripheral arterial disease.[3] If a wound does not seem to fit into any of these categories and fails to respond to standardized wound therapies, clinicians should dig deeper in order to ascertain the correct diagnosis and begin to provide the appropriate wound care.

There are several wound characteristics that can alert the clinician that a wound may have an atypical etiology (Figure 1).[4]

- *Unusual location:* A wound that appears to be venous in nature, but it does not appear on the typical location for a VLU.
- *Asymmetry:* Wounds with irregular edges should be closely monitored.
- *Excessive or friable granulation tissue:* When granulation tissue has disproportionate cell growth or bleeds very easily, this may be an indication of an underlying pathologic process.
- *Patient age:* It would be very unusual for a young patient to present with PAD and gangrene of a toe.
- *Radiation to the area:* Radiation can lead to cell death and tissue necrosis.

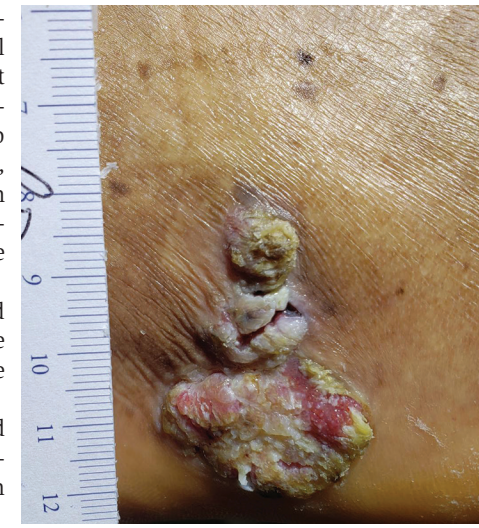

Figure 1: An example of an atypical wound displaying multiple abnormal wound characteristics.

- *Remote history of trauma:* Repetitive trauma can lead to pathological changes in the skin and surrounding tissues.
- *Pain:* When patients present with pain out of proportion to clinical appearance, an atypical wound should be ruled out.
- *Pigmented lesions:* This can indicate an inflammatory or malignant process is occurring.
- *Vegetative growth:* Fungating tissue growth can indicate an infective process or be a sign of malignancy.

It has been estimated that 20% of all chronic wounds are due to atypical causes.

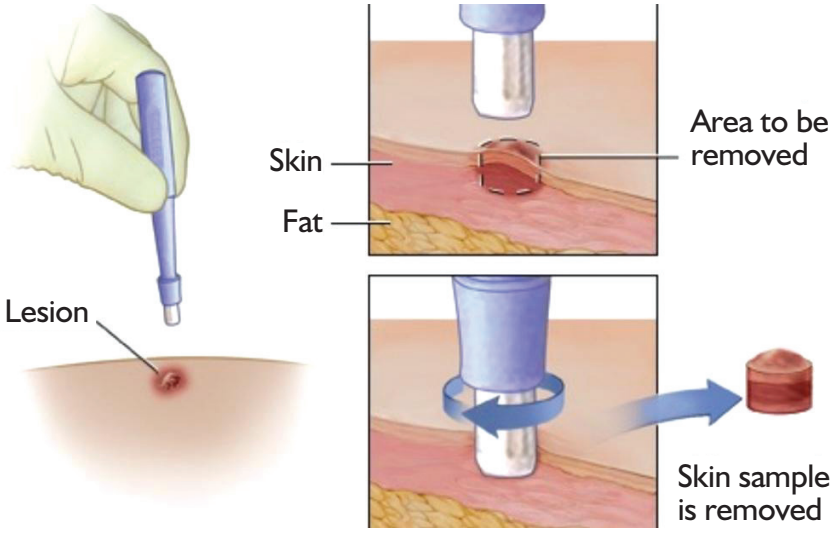

Figure 2: Proper punch biopsy technique.

Diagnosis

Identifying an atypical wound can be a difficult undertaking. A detailed history and physical exam are the two most critical factors in assuring an accurate diagnosis is made. Obtaining in-depth medical, travel, recreational, and occupational histories should be gathered from the patient. A complete physical exam and wound assessment including wound measurement, location, staging, tissue character and color, odor, exudate quality and amount, peri-wound tissue appearance, and pain are important details to notate. If a chronic wound persists despite appropriate wound care treatments and typical wound etiologies are ruled out based on these findings, additional diagnostic testing is appropriate.

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Tissue Biopsies

Atypical ulcers exhibit random clinical features, histology, and location. Resistance to standard therapies and difficulty in diagnosing often results in delayed treatment. Tissue biopsies should be considered in all wounds not responding to standard of care and/or presenting with an atypical appearance. In many cases, the histopathological features found in the tissues are pathognomonic for specific disease states. There are distinct differences seen between wounds caused by malignancies, vasculopathies, infections, metabolic disorders, and other inflammatory processes. Site selection is of paramount importance. Perilesional tissue biopsies are frequently the key to confirming a diagnosis.

Best practices include obtaining a punch or incisional biopsy of the ulcer border.[5] Multiple biopsy samples are helpful to aid in difficult diagnoses.[5] If possible, an additional sample should be collected from the center of the wound.[5] The biopsy specimen should contain the epidermis, dermis, and subcutaneous tissue (Figure 2). It is preferable to engage a dermato-pathologist for histological examination of specimens. Routine histology specimens can be placed in 10% formalin solution. If direct immunofluorescence or microbiology studies are indicated, specimens should be placed in saline solution with the sample reaching the lab in less than 24 hours. Correctly marking the tissue for orientation in cases of suspected malignancy can be achieved with permanent marker or suture material. The orientation should be clearly marked and the information conveyed to the pathologist. Specimen containers labeled with the name of the patient, date, time the specimen was collected, and tissue site are essential. Additionally, providing a brief history and clinical description of the lesion may be helpful in developing a diagnosis.

Examples of Atypical Wound Types

Calciphylaxis

Calciphylaxis is a rare but highly morbid pathological syndrome of vascular calcification and tissue necrosis predominantly seen in patients treated with dialysis for chronic renal failure. This condition is characterized by painful violaceous skin lesions. Clinically, patients present with areas of tissue necrosis and non-healing wounds. Vascular calcification of the dermis is a consistent finding in cases of calciphylaxis, but calcifications of the muscle, brain, lungs, intestine, and mesentery have also been reported.[6-10] The term calciphylaxis was coined from experimental animal studies conducted by Selye in 1962.[11] This condition is poorly understood and continues to be a treatment challenge to clinicians even today.

Making the diagnosis of an atypical wound is very difficult.

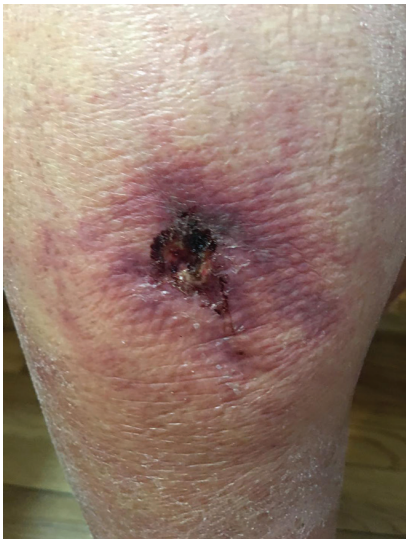

Figure 3: An atypical wound caused by calciphylaxis.

Typically, not only is calciphylaxis associated with chronic renal failure, but also hyperphosphatemia, hypercalcemia, hyperparathyroidism, and vascular calcifications.[12] Upwards of 4% of the population with ESRD on dialysis may show signs of calciphylaxis.[13] The overall prognosis is not good, with complications such as amputation, sepsis, or death occurring in 60-80% of patients affected.[14] Patients who suffer from calciphylaxis have a one-year mortality of 45-80%. The presence of ulcerated lesions lead to a greater mortality rate than non-ulcerated lesions with sepsis being the leading cause of death.[14,15]

Primary lesions appear as painful nonspecific stellate purpura, violaceous mottling, red papules, or necrotic plaques (Figure 3). Ninety percent of calciphylaxis lesions occur on the lower extremity.[16] Differential diagnosis includes atherosclerotic disease, coumadin necrosis, subacute bacterial endocarditis, disseminated intravascular necrosis, bullous systemic lupus erythematosus, pyoderma gangrenosum, venous ulcer, brown recluse spider bite, erythema nodosum, and necrotizing fasciitis. A thorough history may divulge additional risk factors for calciphylaxis such as obesity, diabetes, malnutrition, liver disease, connective tissue disorders, PVD, hypercoagulabitity, concomitant anticoagulation therapy, and vitamin K deficiency.[17-19]

Definitive diagnosis of calciphylaxis requires obtaining a tissue biopsy. A 4-5mm punch biopsy from the margin of the lesion or an incisional tissue biopsy are likely to produce the best specimen.[20] Histologic findings typically consist of calcification and within the media and intima of both the small and medium arterioles with considerable hyperplasia and fibrosis and inflammatory infiltrate.[21] Subcutaneous calcium deposits, fat necrosis, and vascular microthrombi are also commonplace.[21] It has been theorized that these vascular calcifications eventually lead to endothelial dysfunction and subsequent injury.[22]

Laboratory evaluation should be conducted to further evaluate potential risk factors: 1) Renal function evaluation—serum blood urea nitrogen, creatinine, and estimated glomerular filtration rate (urinalysis, urine protein: creatinine ratio, and 24-hour urine collection for creat-

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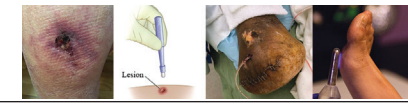

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inine clearance to be considered for non-dialysis patients), 2) Mineral bone parameters evaluation—serum calcium, phosphorous, alkaline phosphatase, intact parathyroid hormone, and 25-hydroxyvitamin D, 3) Liver evaluation-serum transaminases, alkaline phosphatase, and albumin, 4) Infection evaluation -complete blood count with differential (in all cases), and blood cultures (if leukocytosis or fever present), 5) Coagulation evaluation—prothrombin time, international normalized ratio, and partial thromboplastin time, 6) Inflammation evaluation—serum high sensitivity C-reactive protein and albumin, 7) Hypercoagulation evaluation- protein C, protein S, antithrombin III, and antiphospholipid antibody, and 8) Evaluation for autoimmune disease and malignancy as guided by the clinical suspicion.[23] Treatment for calciphylaxis is not well standardized. It involves different medications, wound care modalities, and possible hemodialysis session adjustments.

Malignant Neoplasms

Over the past 40 years, skin cancer incidence has been on the rise, growing on average 4-8% annually.[24] Non-melanoma cancers make up the majority (97%) of skin cancers, with basal cell carcinomas accounting for 80% of these lesions and squamous cell carcinomas rounding out the remaining 20%.[24] Due to the increasing commonality of skin cancers, wound care providers are likely to encounter these malignancies over the course of their clinical practice. Malignant wounds can manifest and present in several ways. Frequently, wounds can develop from primary skin cancers which have eroded the surrounding tissue.

The presentation of malignant wounds primarily depends on the rate of growth and the level of infiltration of the malignancy.[25] Initially, the development of a non-tender nodule can occur. As the nodule enlarges, it may begin to interfere with the function of skin and the underlying vascular and lymph vessels.[25] In time, this can lead to lack of skin perfusion, edema, skin breakdown, and necrosis.[25] Clinically, these ulcerative wounds can resemble a crater with raised or abnormal borders. Alternatively, proliferative wounds will appear fungating or raised like a cauliflower (Figure 4). Some malignant wounds can demonstrate both patterns of growth. If left unmanaged, these tumors may continue to grow and penetrate deep structures. It is not uncommon for malignant wounds to cause pain, exhibit excessive exudate, have malodor, and bleed profusely.[26] These wounds rarely heal and often deteriorate despite adequate wound care.

Best practices include obtaining a punch or incisional biopsy of the ulcer border. The biopsy specimen should contain the epidermis, dermis, and subcutaneous tissue.

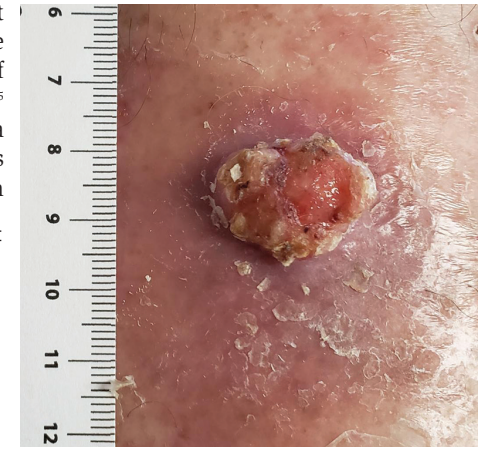

Figure 4: A wound caused by squamous cell carcinoma.

Squamous cell carcinoma (SCC) is most commonly detected in sun-exposed areas including the head, neck, chest, upper back, ears, arms, hands, legs, and feet.[27] Although SCC is a relatively slow-growing form of skin cancer, it has the ability to spread deeply into tissues, bones, and adjacent lymph nodes.[28] When detected early, SCC can easily be successfully treated as demonstrated in this case report. SCC initially may begin as a nodule or red, scaly patch of skin that is rough and crust-covered and bleeds easily.[25] Although anyone can develop SCC, there are certain traits such as: advanced age, chronic wounds, previous trauma, fair skin, excessive sun-exposure, burns, long-term chemical exposure, tanning bed use, immunocompromised states, and inherited conditions that predispose its development.[25]

Although uncommon, cutaneous malignancies presenting as chronic wounds have been well documented. In 1827, Marjolin was first to report this pathophysiological process when he noted a malignant change occur in the peri-wound tissue in a chronic ulceration.[29] The etiological factors leading to the development of what is commonly known as a Marjolin's ulcer, have been debated for over 100 years. One such theory is that chronic irritation in areas of previous injury and scar tissue formation may stimulate cell proliferation and increase cellular mutations causing the development of carcinomas.[30] Kirsner and colleagues estimate that 1.7% of chronic wounds undergo a malignant degeneration.[31] It was found that men 40-70 years of age with a history of osteomyelitis and chronic wounds are most commonly affected.[31] SCC has been reported second-

When a malignant wound develops in an area of chronic irritation or trauma it is referred to as a Marjolin's ulcer.

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ary to burns, trauma, diabetes and radionecrosis.[32]

In this case, the patient had previous knee surgery on the right limb paired with a more recent history of a fall with a skin tear. Taking these factors into consideration, it is hard to determine if the development of SCC was the primary cause of the ulcerative lesion or if this wound was, in fact, a Marjolin's ulcer. In either case, early diagnosis and aggressive treatment are key. Early-stage, well-differentiated lesions are less aggressive and have an overall better prognosis.[33] The 5-year survival rate for patients undergoing a wide-excision of a Marjolin's ulcer is 60%.[33]

Pyoderma Gangrenosum

The name pyoderma gangrenosum (PG) is a historical misnomer. This condition is not an infection (pyoderma) nor does it lead to gangrene. PG is rather an inflammatory process of uncertain etiology. PG is widely regarded as an autoinflammatory disease. It is believed that patients develop an excessive response to an internal antigen that leads to neutrophil and T-cell dysfunction. A pathway to protect the epidermis from the neutrophilic infiltrates is lacking; thus the end result is tissue necrosis. PG affects both men and women, but is more frequently seen in females.[34] The disorder is more common in people 50 years of age or greater.[34]

A genetic predisposition is often seen in patients with a history of PG. The general incidence of patients diagnosed with PG is 3-10 per million annually.[34] Patients typically will have a history of rapidly appearing small pustules or blisters that deteriorate into large painful ulcers. Wounds caused by PG most commonly present in the lower extremity and are full-thickness with purple or blue, undermined borders (Figure 5).[35] These wounds will commonly display signs of pathergy, therefore it is not unusual for PG wounds to increase in size and severity after debridement.[35] Multiple ulcers can develop at the same time. Older lesions, when healed, will display cribriform scar formation.[35]

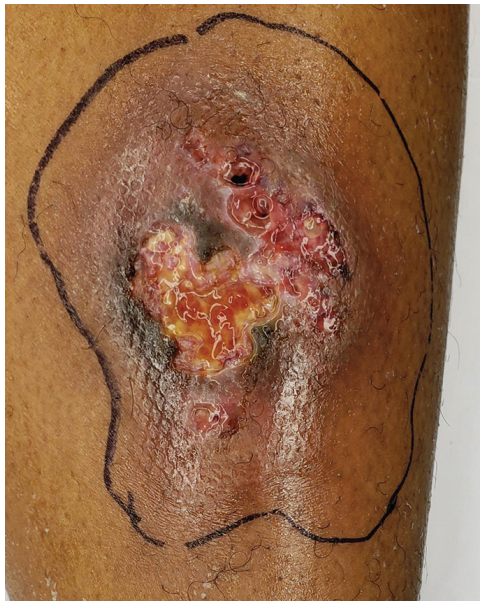

Figure 5: An atypical wound caused by pyoderma gangrenosum.

PG is idiopathic is 25-50% of patients, but underlying system autoimmune disorders or immunogenic abnormalities can exist.[34] PG has been reported in about 30% of patients with rheumatoid arthritis.[34] This condition is also fairly common in patients having been diagnosed with inflammatory bowel disease with 10% of occurring in patients with ulcerative colitis and 3% seen in those with Crohn's disease.[34] It is important for clinicians to take an extensive history and wound assessment as the diagnosis of PG is heavily dependent on clinical signs and symptoms. There is no gold-standard test for PG. Clinical suspicion of the disorders is often corroborated by histological findings of dense neutrophilic infiltrate in the affected tissue. There are no known consistently abnormal laboratory parameters; therefore, PG is often considered a diagnosis of exclusion. The Maverakis Criteria, published following the Delphi consensus exercise in 2018, has an 86% sensitivity and 90% specificity for PG (Figure 6).[36]

PG is a recurrent condition. Successful therapy depends on the appropriate selection of various immunosuppressant agents. Local disease can be controlled with high-potent topical corticosteroids.[37] In mild forms of the disease, topical or intralesional steroids can be effective. In cases of wide-spread disease, glu-

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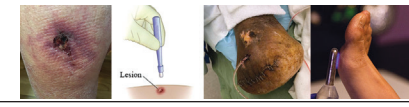
Maverakis Criteria

- **Major criterion must be positive**
- The addition of 4 or more of the 8 minor criteria yields a sensitivity of 86-90% for the diagnosis of PG

- **Major Criterion:**
  - Ulcer edge must show a neutrophilic infiltrate
- **Minor Criteria:**
  - Exclusion of infection
  - Pathergy
  - History of IBS or arthritis
  - History of papule or vesicle that ulcerates within 4 days
  - Peripheral erythema, undermining border, tenderness at ulcer site
  - Multiple ulcers, at least one on the lower leg
  - Cribriform or wrinkled paper scars at site of healed ulcer
  - Decreased size of ulcer within one month of initiating immunosuppressive Tx

Figure 6: Maverakis Criteria.

In Maverakis Criteria, when the major criteria and at least 4 minor criteria are met the diagnosis of PG can be made with roughly 90% sensitivity.



Atypical Wounds *(from page 137)*

cocorticoids are the only approved systemic therapy.[37] Other immunosuppressants or anti-inflammatory agents can be helpful in resolving symptoms. Systemic antibiotics are only indicated if signs and symptoms of bacterial infection are noted. Local wound care based on the principles of moist wound healing is of paramount importance.

Conclusions

Atypical wounds are rare and their pathophysiology is not well understood. The diagnosis and management of these ulcer types are a real challenge to physicians. Skin biopsy plays a pivotal role in making the diagnosis and should be performed in all cases of refractory wounds. Additional microbiological, immunohistochemical, and laboratory testing may be warranted to confirm the proper diagnosis. Wound progression is often unpredictable and wound care therapies are not standardized. Prospective multicenter clinical trials are needed in order to develop well-defined treatment algorithms. Early suspicion and an expert examination is of the utmost importance in the treatment of atypical wounds. A 'wait and see' attitude may be detrimental when dealing with complex atypical wounds. **PM**

Early suspicion and an expert examination is of the utmost importance in the treatment of atypical wounds.

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CME EXAMINATION

SEE ANSWER SHEET ON PAGE 141.

1) Which is a true statement in regard to the prevalence of atypical wounds?

A) Wounds caused by atypical etiologies are most commonly seen in young patients.
B) Atypical wounds heal easily within 30 days.
C) It has been estimated that 20% of all chronic wounds are due to atypical causes.
D) Atypical wounds are so rare, physicians do not need to concern themselves with learning about them.

2) Which of the following wound characteristics can serve as an alert that a wound may be atypical?

A) A history of repetitive trauma to the area.
B) Irregular or asymmetrical wound edges.
C) Oddly colored or pigmented wound tissue.
D) All of the above.

3) All statements about atypical wounds are true except:

A) Making the diagnosis of an atypical wound is very easy.
B) A detailed history and physical exam are the two most critical factors in assuring an accurate diagnosis is made.
C) A wound assessment including wound measurement, location, staging, tissue character and color, odor, exudate quality and amount, peri-wound tissue appearance, and pain are important details to notate.
D) If a wound persists despite appropriate wound care treatments, then atypical wound etiologies should be ruled out.

4) What are the key elements in obtaining appropriate tissue biopsies?

A) Best practices include obtaining a punch or incisional biopsy of the ulcer border.
B) Shave biopsies are preferred by dermatopathologists.
C) The biopsy specimen should contain the epidermis, dermis, and subcutaneous tissue.
D) Both a and c.

5) What tissue characteristics are commonly seen in biopsy specimens in patients with calciphylaxis?

A) Calcification and within the media and intima of both the small and medium arterioles.
B) A heavy neutrophilic infiltrate.
C) Large numbers of melanocytes.
D) Coagulase-negative bacterial contamination.

6) Laboratory evaluations that should be performed when calciphylaxis is suspected include all except:

A) Blood urea nitrogen, creatinine, and estimated glomerular filtration rate.
B) Mineral bone parameters evaluation including serum calcium, phosphorous and alkaline phosphatase.
C) Coagulation evaluation with prothrombin time, international normalized ratio, and partial thromboplastin time.
D) Glucose tolerance test.

Continued on page 140

Continuing Medical Education

CME EXAMINATION

7) When a malignant wound develops in an area of chronic irritation or trauma it is referred to as:

A) A venous stasis ulcer.
B) A Merakis ulcer.
C) A giant cell tumor.
D) A Marjolin's ulcer.

8) What is thought to be the primary pathophysiology in wounds caused by pyoderma gangrenosum?

A) PG is caused by an infective process.
B) Gangrene causes PG wounds
C) There is an excessive response to an internal antigen that leads to neutrophil and T-cell dysfunction.
D) Lack of patient hygiene is responsible for wound formation.

9) Which statement is correct regarding the Maverakis Criteria?

A) All major and minor criteria must be met to make the diagnosis of PG.
B) When the major criteria and at least 4 minor criteria are met the diagnosis of PG can be made with roughly 90% sensitivity.
C) This is the only known criteria for making the diagnosis of malignancy.
D) The Maverakis is an outdated metric and no longer used.

10) What statements regarding atypical wounds are true?

A) Atypical wounds are rare and their pathophysiology is not well understood.
B) Skin biopsy plays a pivotal role in making the diagnosis and should be performed in all cases of refractory wounds.
C) Wound progression is often unpredictable and wound care therapies are not standardized.
D) All of the above.

SEE ANSWER SHEET ON PAGE 141.

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EXAM #6/21
Atypical Wounds: Cracking the Code of the Uncommon
(Cole)

Circle:

1.	A	B	C	D	6.	A	B	C	D
2.	A	B	C	D	7.	A	B	C	D
3.	A	B	C	D	8.	A	B	C	D
4.	A	B	C	D	9.	A	B	C	D
5.	A	B	C	D	10.	A	B	C	D

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Strongly agree [5]	Agree [4]	Neutral [3]	Disagree [2]	Strongly disagree [1]

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2) The educational objectives were accomplished ____

3) I will apply the knowledge I learned from this lesson ____

4) I will makes changes in my practice behavior based on this lesson ____

5) This lesson presented quality information with adequate current references ____

6) What overall grade would you assign this lesson?

A B C D

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