Erythema nodosum

Author: Daniela Kroshinsky, MD, MPH
Section Editor: Jeffrey Callen, MD, FACP, FAAD
Deputy Editors: Abena O Ofori, MD, Philip Seo, MD, MHS

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INTRODUCTION

Erythema nodosum (EN) is a delayed-type hypersensitivity reaction that most often presents as erythematous, tender nodules on the shins (picture 1A-D). Common triggers for EN include infection, drugs, pregnancy, malignancy, and inflammatory conditions, such as sarcoidosis or gastrointestinal diseases; however, many cases are idiopathic (table 1). The characteristic histologic finding in EN is a septal panniculitis without vasculitis.

EN usually resolves spontaneously within several weeks. When necessary, treatment can be given to reduce symptoms or hasten resolution.

The etiologies, diagnosis, and management of EN will be reviewed here. Other forms of panniculitis and erythema nodosum leprosum (a complication of leprosy that is also known as a type 2 reaction) are reviewed separately. (See "Panniculitis: Recognition and diagnosis" and "Leprosy: Epidemiology, microbiology, clinical manifestations, and diagnosis", section on 'Type 2 reaction (T2R, erythema nodosum leprosum, ENL)'.)

EPIDEMIOLOGY

EN occurs in all ages, sexes, and racial groups but is most common in women in their second to fourth decades [1]. Women are affected three to six times more often than men. The specific incidence of EN varies based upon the local prevalence of the associated triggering diseases [2]. (See 'Etiology' below.)

PATHOGENESIS

EN is considered a delayed-type hypersensitivity reaction resulting from exposure to various antigens; however, the pathogenesis is not fully understood. The pathogenic mechanism may involve immune complex deposition in the septal venules of the subcutaneous fat, neutrophil recruitment with resulting reactive oxygen species formation, tumor necrosis factor (TNF)-alpha production, and granuloma formation [3-5].

There may be a genetic predisposition to EN; however data are limited. There have been familial reports with a shared human leukocyte antigen (HLA)-type [6] as well as a study demonstrating a correlation of EN in sarcoidosis with the TNF alpha-II allele [7]. EN has also been associated with several established inflammatory bowel disease susceptibility loci [8].

ETIOLOGY

EN can occur secondary to a wide variety of conditions. However, in many patients, no cause of EN is found. A Spanish retrospective study of 106 patients with EN failed to find a precipitating factor in 37 percent of patients [9]. Moreover, in a Turkish series of 100 patients with EN, 53 percent had EN of unknown etiology [10].

Infection is the most commonly identified etiology, with streptococcal infection the most common cause. EN may also occur secondary to drugs (eg, oral contraceptives), inflammatory bowel disease, malignancy, sarcoidosis, pregnancy, and other conditions (table 1).

EN may offer some prognostic or predictive information regarding associated systemic diseases. EN tends to precede or accompany a flare of inflammatory bowel disease and is associated with a lower incidence of disseminated disease in coccidioidomycosis and a less aggressive form of sarcoidosis, termed Lofgren syndrome [4,11,12]. Lofgren syndrome comprises the triad of EN occurring in association with hilar adenopathy and acute arthritis or periarthritis (usually involving the ankles) and is often self-limiting. (See "Sarcoid arthropathy", section on 'Acute arthritis and Lofgren syndrome'.)

CLINICAL MANIFESTATIONS

Classically, EN manifests as erythematous, usually tender, nonulcerated, immobile nodules on the bilateral shins (picture 1A-D). The nodules are slightly raised and typically 2 to 5 cm in

diameter. Less frequently, lesions can coalesce into plaques or arise on other areas such as the ankles, thighs, arms, buttocks, calves, or face (picture 2) [13,14].

The nodules develop over several days and may follow a prodrome of fatigue, fever, malaise, arthralgias, or upper respiratory infection symptoms by one to three weeks [13]. Joint swelling, erythema, or pain may accompany the skin manifestations.

Nodules typically resolve spontaneously without scarring within eight weeks of presentation. Secondary bruising, also known as "erythema contusiformis," often occurs during resolution [4]. Residual hyperpigmentation may take weeks to months to resolve.

Chronic EN is a rare subtype of EN with no identifiable cause that flares intermittently over years [15]. Patients may develop solitary or multiple nodules on the lower legs. The degree of inflammation tends to be less pronounced than in classic EN [15]. Chronic EN is distinct from relapsing EN related to an underlying chronic condition (table 1).

PATHOLOGY

EN is a predominantly septal panniculitis without primary vasculitis (picture 3) [16]. Early lesions will demonstrate septal edema with mild lymphocytic infiltrates, though neutrophils may be prevalent [17]. A secondary vasculitis may be seen when there is a dense, mixed, or neutrophil-heavy inflammatory infiltrate [4]. Concomitant thrombophlebitis may be present, particularly in cases associated with Behçet syndrome [17,18], and an eosinophil-rich variant has been identified [19].

Miescher's radial granulomas are a characteristic feature of early EN consisting of groups of macrophages surrounding cleft-like spaces or neutrophils (picture 4) [13]. The macrophages may appear more epithelioid or as multinucleated giant cells in older lesions [4].

With time, septal thickening with a mixed and granulomatous infiltrate occurs with fibrosis and possible extension of the inflammation into the adjacent fat lobules. However, lobular inflammation should not be the predominant finding.

DIAGNOSIS

In most cases, a diagnosis of EN can be made based upon the patient history and physical examination. Findings that strongly suggest EN include the acute onset of tender nodules or plaques on the bilateral shins. Ulceration should be absent. Skin biopsy is helpful for confirming

the diagnosis in patients with an atypical presentation. Examples of features that would prompt a biopsy include a location other than the anterior lower legs as the primary site of involvement, purpura, ulceration, large nodules (eg, >5 cm), and underlying immunosuppression. (See 'Pathology' above.)

There are no laboratory abnormalities specific to EN; however, patients may have laboratory abnormalities related to the underlying disease (table 1). (See 'Evaluation for underlying disease' below.)

EVALUATION FOR UNDERLYING DISEASE

A diagnosis of EN should be followed by an assessment for an associated cause (table 1). Initial testing should focus on identifying the most common and important etiologies, particularly streptococcal infection, sarcoidosis, and tuberculosis, in addition to other conditions common to the patient's geographic area or suggested by findings on a review of systems. No cause is found in some patients. (See 'Etiology' above.)

- **Clinical assessment** – A medication history should be obtained to identify drug-associated EN. A travel history can be helpful to elucidate possible exposure to endemic infectious organisms. In addition, a review of systems with careful attention to respiratory, gastrointestinal, and constitutional symptoms is helpful for detecting patients at risk for underlying disease, such as sore throat, abdominal pain, diarrhea, bloody stools, unintentional weight loss, significant fatigue, other prior skin lesions, and joint pain. (See 'Etiology' above.)

  Given that streptococcal infection is the most common infectious cause of EN, examination of the throat and tonsils should be performed to assess for signs of streptococcal pharyngitis (eg, pharyngeal erythema, tonsillar hypertrophy, or purulent exudate). (See 'Etiology' above and "Evaluation of acute pharyngitis in adults".)

  Evaluation of the patient for additional physical findings or specialist referral may be indicated based upon the history (including the review of systems), the findings that are evident on examination, and laboratory and radiologic testing.

- **Laboratory and radiologic tests** – The following laboratory and radiologic tests are indicated at the time of diagnosis:

  - Complete blood count (to assess for infection and malignancy)

- Erythrocyte sedimentation rate and/or C-reactive protein (elevation is a sign of systemic disease and widespread inflammation)
- Diagnostic test for streptococcal pharyngitis (if patient has signs of acute pharyngitis) (see "Evaluation of acute pharyngitis in adults", section on 'Determining whom to test for GAS')
- Antistreptolysin O (ASO) titers (repeated two to four weeks later)
- Chest radiograph (to assess for sarcoidosis, tuberculosis, other pulmonary infections, and lymphoma)
- Tuberculin skin test or interferon-gamma release assay (see "Use of interferon-gamma release assays for diagnosis of latent tuberculosis infection (tuberculosis screening) in adults" and "Tuberculosis infection (latent tuberculosis) in adults: Approach to diagnosis (screening)")

Examples of chest radiograph findings that may suggest certain diseases include bilateral hilar lymphadenopathy (sarcoidosis), unilateral hilar lymphadenopathy (tuberculosis, coccidioidomycosis, brucellosis), and lower lobe infiltrates (psittacosis).

Additional investigation (eg, pregnancy test, referral to a gastroenterologist or hematologist) should be based upon the likelihood of other associated conditions based upon the patient history, physical examination, and the results of initial testing.

DIFFERENTIAL DIAGNOSIS

Alternate diagnoses should be considered, especially in cases with involvement of sites other than the legs, persistence of symptoms for more than eight weeks, or secondary ulceration. A biopsy is useful for distinguishing EN from other conditions.

- **Nodular vasculitis (erythema induratum, Bazin's disease)** – Nodular vasculitis is a lobular panniculitis that frequently occurs in association with tuberculosis and may also occur as an idiopathic condition or in association with other infections or drug exposure. Nodular vasculitis usually occurs on the posterior calves with ulcerated, draining nodules (picture 5). Patients with tuberculosis-associated disease are likely to have a positive tuberculin skin test or interferon-gamma release assay. In addition, mycobacterial DNA can be detected in lesions using polymerase chain reaction (PCR). (See "Erythema induratum (nodular vasculitis)".)

- **Subcutaneous bacterial, fungal, or mycobacterial infections** – Infections of subcutaneous tissue can arise from direct inoculation or hematogenous dissemination. Nodules or plaques most often present on legs and feet but also occur in other sites, such as the abdomen, axilla, arm, hand, or gluteal region. The lesions are fluctuant, ulcerate, and drain. There may be systemic signs of infection if the infection is widespread.

- **Cutaneous polyarteritis nodosa** – Cutaneous polyarteritis nodosa is characterized by painful subcutaneous nodules on the legs, usually accompanied by livedo racemosa, necrosis, and ulceration (picture 6A-B). Fever, arthralgias, myalgias, and peripheral neuropathy may also be present. Segmental necrotizing medium artery vasculitis is seen on biopsy. (See "Cutaneous polyarteritis nodosa" and "Clinical manifestations and diagnosis of polyarteritis nodosa in adults".)

- **Malignant subcutaneous infiltrates** – Malignant subcutaneous infiltrates are distinguished on histopathology by the presence of cells with atypical cytologic and organizational features and confirmed by staining with specific tumor markers.

- **Pancreatic panniculitis** – Patients with pancreatic panniculitis typically develop erythematous, subcutaneous nodules on legs (picture 7). The arms, chest, abdomen, and scalp are additional potential sites of involvement. The nodules may become fluctuant or ulcerative, draining oily fluid, and heal with scarring. Additional features may include fever, arthritis, and abdominal pain. Laboratory testing reveals elevated lipase, amylase, and/or trypsin levels. (See "Panniculitis: Recognition and diagnosis", section on 'Enzymatic destruction'.)

- **Alpha-1 antitrypsin deficiency** – Genetic deficiency in functional alpha-1 antitrypsin can result in erythematous, tender, subcutaneous nodules or plaques that frequently ulcerate and drain. Additional symptoms and signs include chronic liver disease/cirrhosis, pancreatitis, emphysema, membranoproliferative glomerulonephritis, rheumatoid arthritis, cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA) positive vasculitis, and angioedema. (See "Extrapulmonary manifestations of alpha-1 antitrypsin deficiency", section on 'Skin disease' and "Clinical manifestations, diagnosis, and natural history of alpha-1 antitrypsin deficiency".)

TREATMENT

EN is a self-limiting condition that typically resolves within several weeks. Treatment often is not necessary, particularly for mild cases. Reasons for treatment include significant discomfort,

inability to bear weight, extensive skin involvement, and/or chronic or recurrent disease.

No randomized trials have evaluated interventions for EN. Data on treatment efficacy are primarily limited to case reports and case series.

General measures — Measures that may help with associated discomfort include:

- Leg elevation.
- Rest.
- Compression (if tolerable), such as stockings providing low-grade compression (8 to 15 mmHg or 15 to 20 mmHg stockings). Elastic bandages may be of benefit in patients unable to tolerate or apply stockings.

Treatment of associated conditions — In patients with an identified associated disease, the underlying condition should be treated whenever feasible. Similarly, a causative drug should be withdrawn if feasible. Removal of a trigger for EN should result in resolution. Improvement can occur within several weeks.

First-line therapy — Initial medical interventions that can be helpful for patients who need relief from symptoms include nonsteroidal anti-inflammatory drugs (NSAIDs) and potassium iodide. NSAIDs are the most common first-line therapies for EN given the wide availability of NSAIDs and high clinician familiarity with these agents.

Potassium iodide can lead to rapid improvement in EN and is a favored choice when rapid resolution is desired. However, potassium iodide is difficult to obtain in some locations. In addition, caution is recommended for use of potassium iodide in patients with tuberculosis based upon limited historical data that suggest iodides may promote the appearance of tubercle bacilli in the sputum of patients with pulmonary tuberculosis [20,21]. Therefore, NSAIDs are our preferred first-line therapy for patients with EN and unknown tuberculosis status.

Patients with severe, debilitating EN may be best managed with a short course of systemic glucocorticoid therapy. (See 'Second-line therapy' below.)

Nonsteroidal anti-inflammatory drugs — NSAIDs may be particularly helpful for alleviating symptoms and accelerating resolution of nondebilitating, mild EN. Efficacy data are limited to small case series or reports, and a recommendation for use as first-line therapy is largely based upon widespread clinical use and limited adverse effects [12,22].

Sample regimens for oral NSAID therapy in adults include:

- Ibuprofen: 400 to 800 mg every four to six hours as needed (maximum 3200 mg per day)
- Naproxen: 250 to 500 mg twice daily as needed (maximum 1250 mg per day)

Indomethacin (25 to 50 mg every 8 to 12 hours as needed [maximum 200 mg per day]) is an alternative for patients who do not respond adequately to other NSAIDS but is used less often due to a greater frequency of adverse effects.

Adverse effects of NSAIDs are usually in the form of gastrointestinal intolerance (heartburn, pain, nausea) or skin rash. Side effects of NSAIDs are reviewed in greater detail separately. (See "Nonselective NSAIDs: Overview of adverse effects".)

Of note, caution is indicated in patients with EN associated with inflammatory bowel disease. NSAIDs may be associated with increased risk for exacerbations of inflammatory bowel disease [12]. (See "Definitions, epidemiology, and risk factors for inflammatory bowel disease", section on 'NSAIDs'.)

Potassium iodide — In small uncontrolled studies, potassium iodide therapy has been associated with improvement in pain within 24 hours and resolution of EN within a few days [23,24]. Clinical experience with the drug over several decades also supports its use. The mechanism of potassium iodide is unclear; the drug is thought to concentrate in granulomas and release heparin as well as inhibit neutrophil chemotaxis and reactive oxygen species formation [23,25-27].

Potassium iodide is commercially available in tablets, granules, and drops (supersaturated potassium iodide [SSKI]). A typical dose for adults with EN is 300 mg (six drops of SSKI 47 mg/drop or 0.3 mL of SSKI 1000 mg/mL) three times daily [25]. The bitter taste of SSKI can be lessened with dilution in juice or water.

The optimum duration of potassium iodide therapy for EN is unclear. If improvement does not occur within two to three weeks, we discontinue treatment. For patients who respond to potassium iodide, we typically continue treatment for two to three weeks after resolution.

Potassium iodide therapy generally is well tolerated. The most common adverse effects are mild and include nausea, vomiting, diarrhea, and stomach pain, all of which can be mitigated by slow increases in dose [25]. Caution is recommended for use of potassium iodide in patients with tuberculosis [20]. (See 'First-line therapy' above.)

Iodine or potassium toxicity is a potential adverse effect of potassium iodide but does not typically occur with the short courses used for erythema nodosum. Iodism symptoms include

mouth burning or increased salivation, metallic taste, tooth and gum soreness, and headache [25]. Symptoms of hyperkalemia include confusion, weakness, hand numbness, and arrhythmia; risk is increased in patients with impaired renal function or who are taking potassium-sparing diuretics or angiotensin-converting enzyme inhibitors [25]. Hypo- and hyperthyroidism can also result, and a thyroid-stimulating hormone level should be checked in patients receiving more than one month of potassium iodide [25]. Caution is warranted in patients taking potassium or iodine-containing medications. Other adverse effects include urticaria, angioedema, cutaneous small vessel vasculitis, acneiform eruptions, and enlargement of lacrimal and salivary glands [4]. (See "Iodine-induced thyroid dysfunction".)

Second-line therapy — Patients who fail to respond to NSAIDs and potassium iodide or who have severe, debilitating symptoms requiring rapid improvement can be treated with a short course of a systemic glucocorticoid. Intralesional corticosteroid injection is an alternative second-line treatment that is primarily used in patients with a limited number of EN nodules who cannot tolerate systemic glucocorticoids. Intralesional corticosteroid therapy is not practical for the treatment of numerous lesions.

Systemic glucocorticoids — Clinical experience suggests systemic glucocorticoid therapy can be rapidly effective with improvement in both pain and the appearance of EN. The optimal treatment regimen for EN is unclear. Our preferred regimen is prednisone 20 mg taken every morning for 7 to 10 days. Systemic glucocorticoids may be particularly useful for patients with underlying inflammatory bowel disease, as they improve both the cutaneous manifestations of EN and the bowel inflammation driving their formation [28,29].

Prior to systemic glucocorticoid therapy, infectious causes of EN should be ruled out and comorbidities that may increase the risk of adverse effects from systemic glucocorticoid therapy should be considered. Patients with tuberculosis should not be treated with systemic glucocorticoids. Dapsone, colchicine, and hydroxychloroquine are better next-line treatment options for patients with tuberculosis who do not respond sufficiently to NSAIDs (see 'Recalcitrant, chronic, or recurring disease' below). The risks of systemic glucocorticoid therapy are reviewed in detail separately. (See "Major side effects of systemic glucocorticoids".)

Recurrence of EN upon taper or discontinuation of systemic glucocorticoids is possible and may warrant a repeat course with a more gradual taper. Patients with repeated recurrences of EN may benefit from dapsone, colchicine, or hydroxychloroquine therapy. (See 'Recalcitrant, chronic, or recurring disease' below.)

Intralesional corticosteroid injections — Evidence for the efficacy of intralesional corticosteroid injections is experiential and longstanding despite, and perhaps resulting in, a

lack of published data. In general, a single dose of triamcinolone acetonide is injected into the center of an inflamed nodule. Concentrations from 10 to 20 mg/mL (depending on the degree of inflammation) should be sufficient. A response of reduced inflammation and pain should be seen within one week with ultimate resolution of lesions.

Atrophy and hypopigmentation can occur as side effects of intralesional corticosteroid injections. Use may be limited by pain associated with injection. Application of a topical analgesic or administration of an NSAID prior to injection may be helpful for pain control. (See "Intralesional corticosteroid injection", section on 'Side effects, complications, and pitfalls'.)

Recalcitrant, chronic, or recurring disease — Recalcitrant, chronic, or recurring EN may require chronic suppressive or repeated episodic treatment. Long-term treatment with systemic glucocorticoids is undesirable because of the potential for serious adverse effects.

Dapsone, colchicine, and hydroxychloroquine are more favorable choices for long-term treatment in patients with recalcitrant, chronic, or recurring EN, although these are uncommonly needed as nonacute and recalcitrant presentations are rare. The optimum duration of treatment and relative efficacy of these agents for EN is not known. Selection among these agents should be based upon the specific medical history of the patient. (See 'Clinical manifestations' above.)

Dapsone — Data on dapsone therapy are limited to case reports. Dapsone treatment may be initiated at a dose of 50 mg per day and increased up to 100 mg per day [4,30]. In a series of three patients with recalcitrant or recurrent EN treated with 50 or 75 mg of dapsone per day, improvement or resolution of EN occurred within three to four weeks [31].

Adverse events from dapsone are mainly hematologic, with an increase in reticulocyte count, hemolysis, methemoglobinemia, and a decrease in hemoglobin being most common. Dapsone therapy should be avoided in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency because of increased risk for hemolysis. Screening for G6PD deficiency should be performed prior to treatment to confirm sufficient enzyme levels for proper metabolism. Hematologic monitoring is indicated for patients receiving dapsone. Periodic assessment of liver function tests is also recommended. For additional information, refer to the Lexicomp drug information monograph included within UpToDate. (See "Diagnosis and management of glucose-6-phosphate dehydrogenase (G6PD) deficiency".)

Dapsone-induced peripheral neuropathy may also occur, particularly in patients receiving long-term therapy or high doses. Dapsone should be avoided in patients with a sulfone allergy or those with major cardiopulmonary disease [4].

Colchicine — Clinical experience suggests that colchicine can be useful for the treatment of EN [32]. Colchicine may be particularly helpful in cases associated with Behçet syndrome, given that colchicine is often used in the treatment of Behçet syndrome. (See "Clinical manifestations and diagnosis of Behçet syndrome" and "Treatment of Behçet syndrome".)

Regimens for colchicine therapy have varied. Suggested doses for adults include 2 mg once daily for three days, then 1 mg once daily for two to four weeks [33] or 0.5 or 0.6 mg two or three times per day [4]. Laboratory monitoring is not necessary for short-term use (eg, two to four weeks) but is indicated for patients receiving longer courses of treatment. For additional information, refer to the Lexicomp drug information monograph included within UpToDate.

Colchicine is associated with dose-related gastrointestinal symptoms such as nausea, vomiting, diarrhea, abdominal pain, and the less common side effects of peripheral neuropathy, myopathy, and bone-marrow suppression (in longer courses) [4]. Safety considerations for the use of colchicine are reviewed in detail separately. (See "Treatment of gout flares", section on 'Safety of colchicine'.)

Hydroxychloroquine — Data from case reports and case series suggest hydroxychloroquine can be useful for EN. The drug may be helpful particularly for chronic or recurrent EN associated with inflammatory bowel disease [4,28-30,34-36]. Adults can be treated with up to 200 mg twice daily, depending upon real body weight [30,34,35]. (See "Antimalarial drugs in the treatment of rheumatic disease", section on 'Administration, dosing, and monitoring'.)

The most concerning side effect of hydroxychloroquine is ocular damage, with possible irreversible retinopathy and vision changes. To minimize risk for ocular toxicity, the dose of hydroxychloroquine should not exceed 5 mg/kg of real body weight per day [37]. Baseline and periodic ophthalmologic examinations are necessary for long-term use. Pancytopenia, hemolysis, nausea, and vomiting may also be seen infrequently [4]. (See "Antimalarial drugs in the treatment of rheumatic disease", section on 'Ocular effects' and "Antimalarial drugs in the treatment of rheumatic disease", section on 'Administration, dosing, and monitoring'.)

Other therapies — There are case reports describing benefit of tumor necrosis factor (TNF)-alpha inhibitors for severe or refractory EN, particularly in patients with underlying inflammatory bowel disease. Benefit has been reported with etanercept [38], adalimumab [39,40], and infliximab [41-43]. These agents should only be utilized after infectious causes of EN, especially tuberculosis, have been excluded. (See "Tumor necrosis factor-alpha inhibitors: An overview of adverse effects".)

Treatment with cyclosporine, thalidomide, or methotrexate has also been suggested for cases triggered by Behçet syndrome or inflammatory bowel disease based upon clinical practice

[4,28,29]. However, primary literature to support the use of these agents is lacking.

In pregnancy — Treatment of EN in pregnant women is complicated by the fact that many of the medications used in EN have not been proven safe for use in pregnancy. Restricting management to nonpharmacologic interventions, such as bed rest, leg elevation, and compression is preferred [44]. If treatment is necessary, the pregnancy risk factors and pregnancy implications of these drugs should be considered carefully and treatment decisions should be made in consultation with the patient's obstetrician. Refer to the Lexicomp drug information monographs included within UpToDate. Treatment with potassium iodide should be avoided. (See "Safety of rheumatic disease medication use during pregnancy and lactation".)

PROGNOSIS

The prognosis for EN is good, with most cases resolving spontaneously or with supportive care over days to weeks. Relapses may occur in up to one-third of cases or in cases triggered by chronic, underlying disease [4]. Relapses usually can be rapidly controlled with treatments for EN and kept infrequent through aggressive management of the triggering condition.

INDICATIONS FOR REFERRAL

Patients with chronic, recurrent, or treatment-unresponsive EN may benefit from referral to a dermatologist for further evaluation and management. Similarly, patients suspected of an underlying disorder that may require additional evaluation and intervention should be referred to the appropriate specialist for such evaluation. (See 'Evaluation for underlying disease' above.)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Erythema nodosum (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Epidemiology** – Erythema nodosum (EN) is a form of panniculitis with features of a delayed-type hypersensitivity reaction. EN most often occurs in women in the second to fourth decade of life but may occur at any age and in males. (See 'Epidemiology' above.)

- **Etiology** – A wide variety of conditions may trigger the development of EN, such as infection, drug exposures, sarcoidosis, inflammatory bowel disease, pregnancy, and malignancy (table 1). Many cases are idiopathic. EN may follow a prodrome of fever, malaise, and symptoms of upper respiratory infection. (See 'Etiology' above.)

- **Clinical manifestations** – EN classically presents with erythematous, tender nodules on the shins (picture 1A-D). Less often, nodules occur on the thighs, arms, calves, buttocks, or face (picture 2). Patients may have concurrent fever and arthralgias. (See 'Clinical manifestations' above.)

- **Diagnosis** – A diagnosis of EN usually can be made based upon the clinical history and physical examination. A biopsy is useful for atypical cases. The characteristic histologic finding is a septal panniculitis without vasculitis. (See 'Diagnosis' above and 'Pathology' above.)

- **Treatment**:

  - **General measures** – EN usually resolves spontaneously within a few weeks. Leg elevation, rest, and compression aid in reducing symptoms. Associated underlying disease should be treated, and causative drugs should be discontinued if feasible. (See 'General measures' above.)

  - **Patients requiring additional symptom relief** – For patients who require additional symptom relief, we suggest a nonsteroidal anti-inflammatory drug (NSAID) or potassium iodide as first-line therapy (**Grade 2C**). We use NSAIDs as first-line treatment for most patients with EN and typically reserve potassium iodide for patients requiring rapid resolution of EN. (See 'First-line therapy' above.)

- **Patients who fail NSAIDs or potassium iodide and patients with severe symptoms** – For patients who fail to respond to NSAIDs and potassium iodide or who have severe, debilitating symptoms, we suggest a short course of systemic glucocorticoid therapy (**Grade 2C**). (See 'Treatment' above.)

- **Patients with recalcitrant, chronic, or recurring erythema nodosum** – Occasional patients have recalcitrant, chronic, or recurring EN. Preferred treatment options for this population include dapsone, colchicine, and hydroxychloroquine. (See 'Recalcitrant, chronic, or recurring disease' above.)

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REFERENCES

1. Requena L, Requena C. Erythema nodosum. Dermatol Online J 2002; 8:4.
2. Bondi EE, Margolis DJ, Lazarus GS. Panniculitis. In: Fitzpatrick's Dermatology in General Med icine, 5th ed, Freedberg IM, Eisen AZ, Wolff K, et al (Eds), McGraw-Hill, New York 1999. p.128 4.
3. Cox NH, Jorizzo JL, Bourke JF, Savage CO. Vasculitis, neutrophilic dermatoses and related dis orders. In: Rook's Textbook of Dermatology, 8th ed, Burns T, Breathnach S, Cox N, Griffiths C (Eds), Wiley-Blackwell, Hoboken 2010. Vol 3, p.50.1.
4. Patterson JW. Panniculitis. In: Dermatology, 3rd ed, Bolognia JL, Jorizzo JL, Schaffer JV (Eds), Elsevier Saunders, Philadelphia 2012. p.1641.
5. Kunz M, Beutel S, Bröcker E. Leucocyte activation in erythema nodosum. Clin Exp Dermatol 1999; 24:396.
6. Elkayam O, Caspi D, Segal R, et al. Familial erythema nodosum. Arthritis Rheum 1991; 34:1177.
7. Labunski S, Posern G, Ludwig S, et al. Tumour necrosis factor-alpha promoter polymorphism in erythema nodosum. Acta Derm Venereol 2001; 81:18.
8. Weizman A, Huang B, Berel D, et al. Clinical, serologic, and genetic factors associated with pyoderma gangrenosum and erythema nodosum in inflammatory bowel disease patients.

Inflamm Bowel Dis 2014; 20:525.

9. García-Porrúa C, González-Gay MA, Vázquez-Caruncho M, et al. Erythema nodosum: etiologic and predictive factors in a defined population. Arthritis Rheum 2000; 43:584.
10. Mert A, Kumbasar H, Ozaras R, et al. Erythema nodosum: an evaluation of 100 cases. Clin Exp Rheumatol 2007; 25:563.
11. Braverman IM. Protective effects of erythema nodosum in coccidioidomycosis. Lancet 1999; 353:168.
12. Hanauer SB. How do I treat erythema nodosum, aphthous ulcerations, and pyoderma gangrenosum? Inflamm Bowel Dis 1998; 4:70; discussion 73.
13. White WL, Hitchcock MG. Diagnosis: erythema nodosum or not? Semin Cutan Med Surg 1999; 18:47.
14. Cribier B, Caille A, Heid E, Grosshans E. Erythema nodosum and associated diseases. A study of 129 cases. Int J Dermatol 1998; 37:667.
15. Fine RM, Meltzer HD. Chronic erythema nodosum. Arch Dermatol 1969; 100:33.
16. Thurber S, Kohler S. Histopathologic spectrum of erythema nodosum. J Cutan Pathol 2006; 33:18.
17. Sentürk T, Aydintuğ O, Kuzu I, et al. Adhesion molecule expression in erythema nodosum-like lesions in Behçet's disease. A histopathological and immunohistochemical study. Rheumatol Int 1998; 18:51.
18. Honma T, Bang D, Lee S, Saito T. Ultrastructure of endothelial cell necrosis in classical erythema nodosum. Hum Pathol 1993; 24:384.
19. Winkelmann RK, Frigas E. Eosinophilic panniculitis: a clinicopathologic study. J Cutan Pathol 1986; 13:1.
20. www.upsher-smith.com/wp-content/uploads/SSKI_PI.pdf (Accessed on October 31, 2016).
21. Potassium iodide and streptomycin for tuberculosis. N Engl J Med 1949; 240:664.
22. Ubogy Z, Persellin RH. Suppression of erythema nodosum by indomethacin. Acta Derm Venereol 1982; 62:265.
23. Schulz EJ, Whiting DA. Treatment of erythema nodosum and nodular vasculitis with potassium iodide. Br J Dermatol 1976; 94:75.
24. Horio T, Imamura S, Danno K, Ofuji S. Potassium iodide in the treatment of erythema nodosum and nodular vasculitis. Arch Dermatol 1981; 117:29.
25. Sterling JB, Heymann WR. Potassium iodide in dermatology: a 19th century drug for the 21st century-uses, pharmacology, adverse effects, and contraindications. J Am Acad

Dermatol 2000; 43:691.

26. Honma K, Saga K, Onodera H, Takahashi M. Potassium iodide inhibits neutrophil chemotaxis. Acta Derm Venereol 1990; 70:247.
27. Miyachi Y, Niwa Y. Effects of potassium iodide, colchicine and dapsone on the generation of polymorphonuclear leukocyte-derived oxygen intermediates. Br J Dermatol 1982; 107:209.
28. Winter HS. Treatment of pyoderma gangrenosum, erythema nodosum, and aphthous ulcerations. Inflamm Bowel Dis 1998; 4:71.
29. Tremaine WJ. Treatment of erythema nodosum, aphthous stomatitis, and pyoderma gangrenosum in patients with IBD. Inflamm Bowel Dis 1998; 4:68.
30. Blake T, Manahan M, Rodins K. Erythema nodosum - a review of an uncommon panniculitis. Dermatol Online J 2014; 20:22376.
31. Song JS, Halim K, Vleugels RA, Merola JF. Dapsone for treatment of erythema nodosum. Dermatol Online J 2016; 22.
32. Wallace SI, Bernstein D, Diamond H. Diagnostic value of the colchicine therapeutic trial. JAMA 1967; 199:525.
33. De Coninck P, Baclet JL, Di Bernardo C, et al. [Treatment of erythema nodosum with colchicine]. Presse Med 1984; 13:680.
34. Wozniacka A, Carter A, McCauliffe DP. Antimalarials in cutaneous lupus erythematosus: mechanisms of therapeutic benefit. Lupus 2002; 11:71.
35. Alloway JA, Franks LK. Hydroxychloroquine in the treatment of chronic erythema nodosum. Br J Dermatol 1995; 132:661.
36. Jarrett P, Goodfield MJ. Hydroxychloroquine and chronic erythema nodosum. Br J Dermatol 1996; 134:373.
37. Marmor MF, Kellner U, Lai TY, et al. Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision). Ophthalmology 2016; 123:1386.
38. Boyd AS. Etanercept treatment of erythema nodosum. Skinmed 2007; 6:197.
39. Quin A, Kane S, Ulitsky O. A case of fistulizing Crohn's disease and erythema nodosum managed with adalimumab. Nat Clin Pract Gastroenterol Hepatol 2008; 5:278.
40. Ortego-Centeno N, Callejas-Rubio JL, Sanchez-Cano D, Caballero-Morales T. Refractory chronic erythema nodosum successfully treated with adalimumab. J Eur Acad Dermatol Venereol 2007; 21:408.
41. Kugathasan S, Miranda A, Nocton J, et al. Dermatologic manifestations of Crohn disease in children: response to infliximab. J Pediatr Gastroenterol Nutr 2003; 37:150.

42. Vanbiervliet G, Anty R, Schneider S, et al. [Sweet's syndrome and erythema nodosum associated with Crohn's disease treated by infliximab]. Gastroenterol Clin Biol 2002; 26:295.

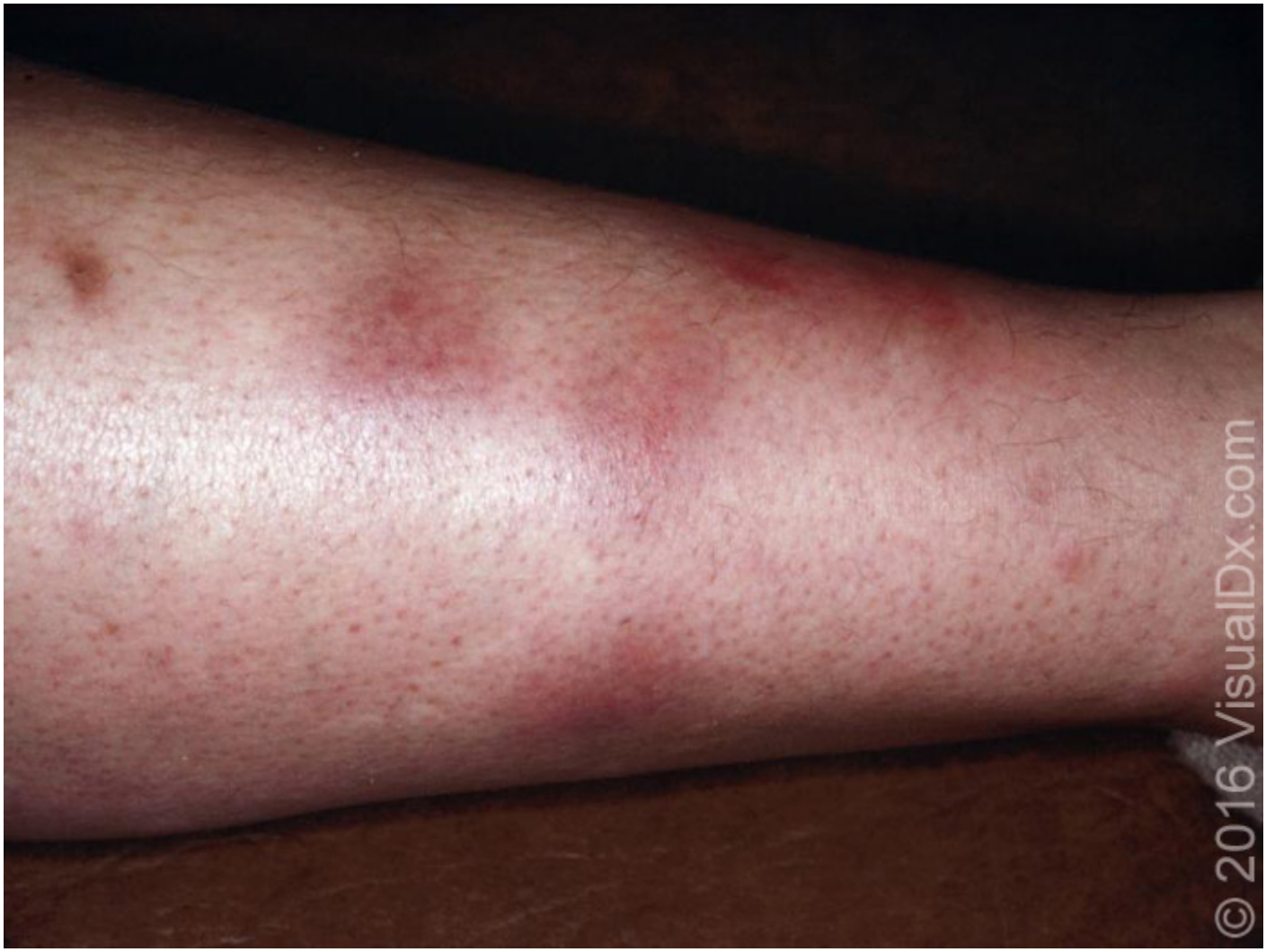
43. Clayton TH, Walker BP, Stables GI. Treatment of chronic erythema nodosum with infliximab. Clin Exp Dermatol 2006; 31:823.

44. Acosta KA, Haver MC, Kelly B. Etiology and therapeutic management of erythema nodosum during pregnancy: an update. Am J Clin Dermatol 2013; 14:215.

Topic 5612 Version 24.0

GRAPHICS

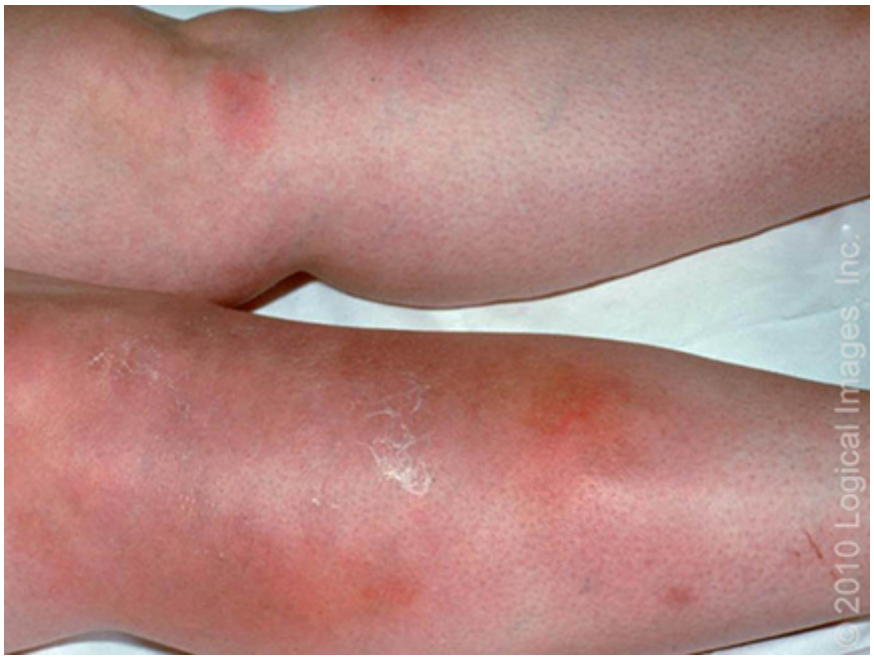
Erythema nodosum



Multiple erythematous nodules on the lower leg.

Graphic 108925 Version 3.0

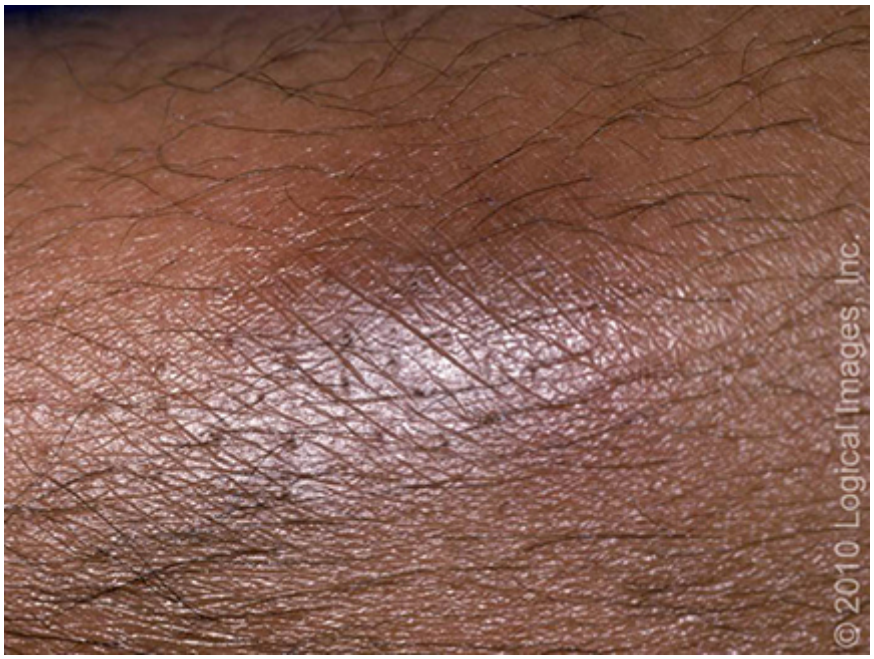
Erythema nodosum



Multiple erythematous nodules are present on the legs.

Graphic 76621 Version 4.0

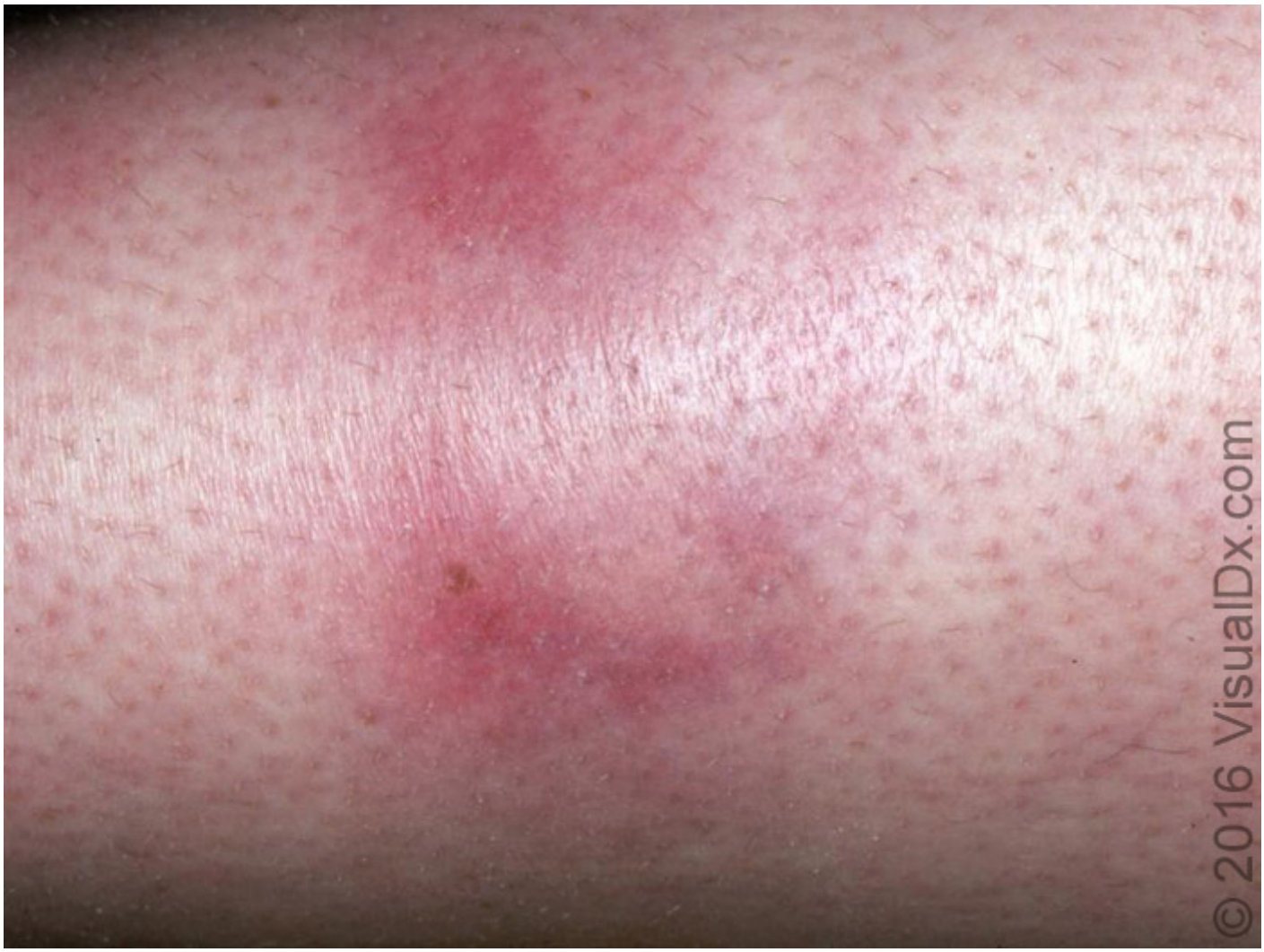
Erythema nodosum



An erythematous nodule is present on the lower leg.

Graphic 55744 Version 4.0

Erythema nodosum



Erythematous nodules on the lower leg.

Graphic 108926 Version 2.0

Conditions associated with erythema nodosum

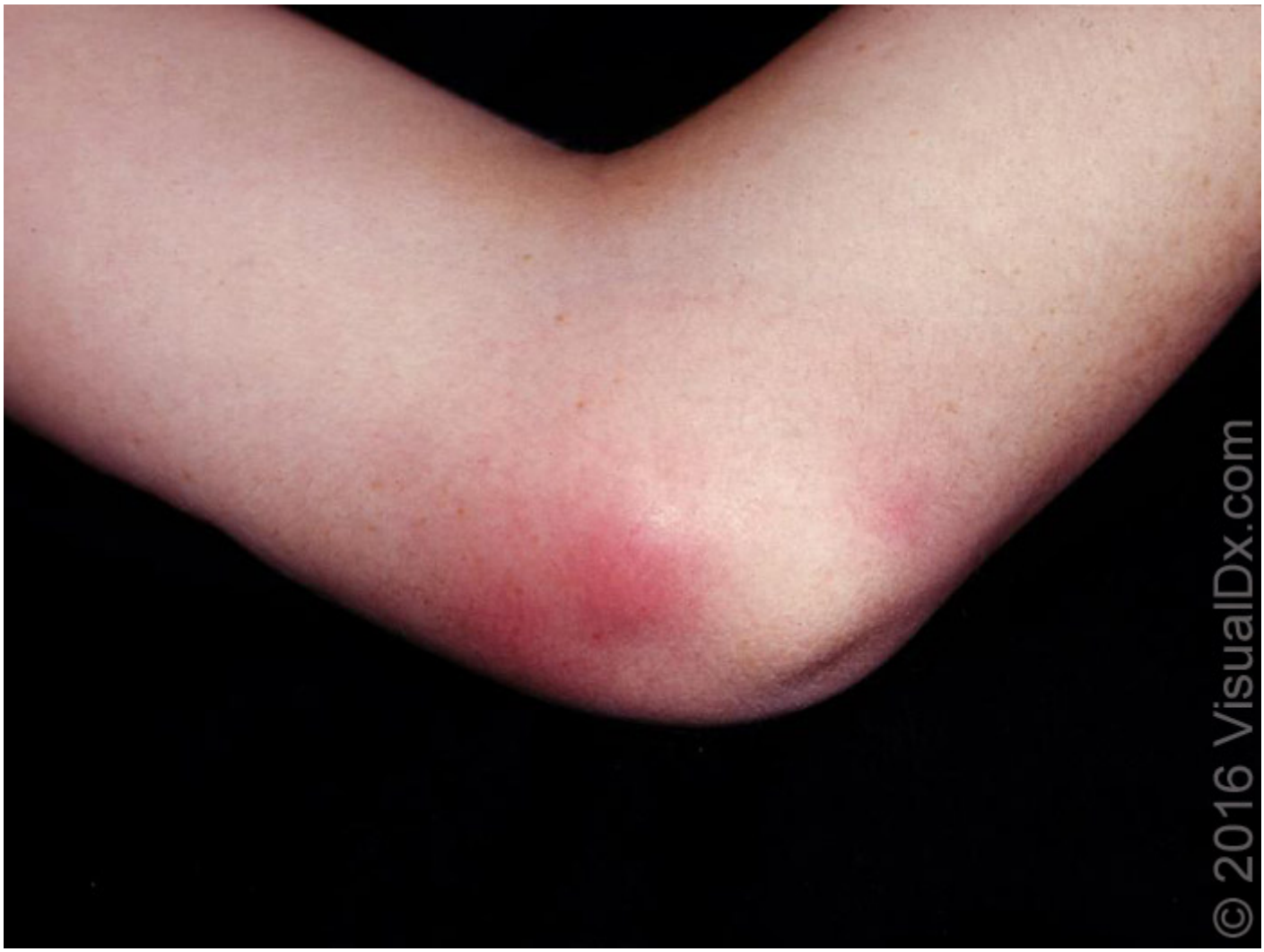
Infections
Bacterial
▪ Streptococcal infection (the most common infectious cause) ▪ Tuberculosis ▪ Leprosy ▪ *Yersinia*, *Salmonella*, *Campylobacter* gastroenteritis ▪ *Mycoplasma* pneumonia ▪ Tularemia ▪ Leptospirosis ▪ Brucellosis ▪ *Chlamydia trachomatis* ▪ Psittacosis ▪ Lymphogranuloma venereum ▪ Cat-scratch disease ▪ Q fever (*Coxiella burnetii* infection)
Fungal
▪ Coccidioidomycosis ▪ Histoplasmosis ▪ Blastomycosis
Viral
▪ Infectious mononucleosis ▪ Hepatitis B ▪ Paravaccinia
Drugs
Oral contraceptives
Penicillin
Sulfonamides
Bromides and iodides
TNF-alpha inhibitors (rare)
Inflammatory bowel disease
Crohn's disease (more often than ulcerative colitis)
Ulcerative colitis

Malignancy
Lymphoma (Hodgkin, most often)
Leukemia (acute myelogenous, most often)
Internal carcinomas
Miscellaneous
Sarcoidosis
Pregnancy
Whipple disease
Behçet disease
Sweet syndrome

TNF: tumor necrosis factor.

Graphic 109908 Version 3.0

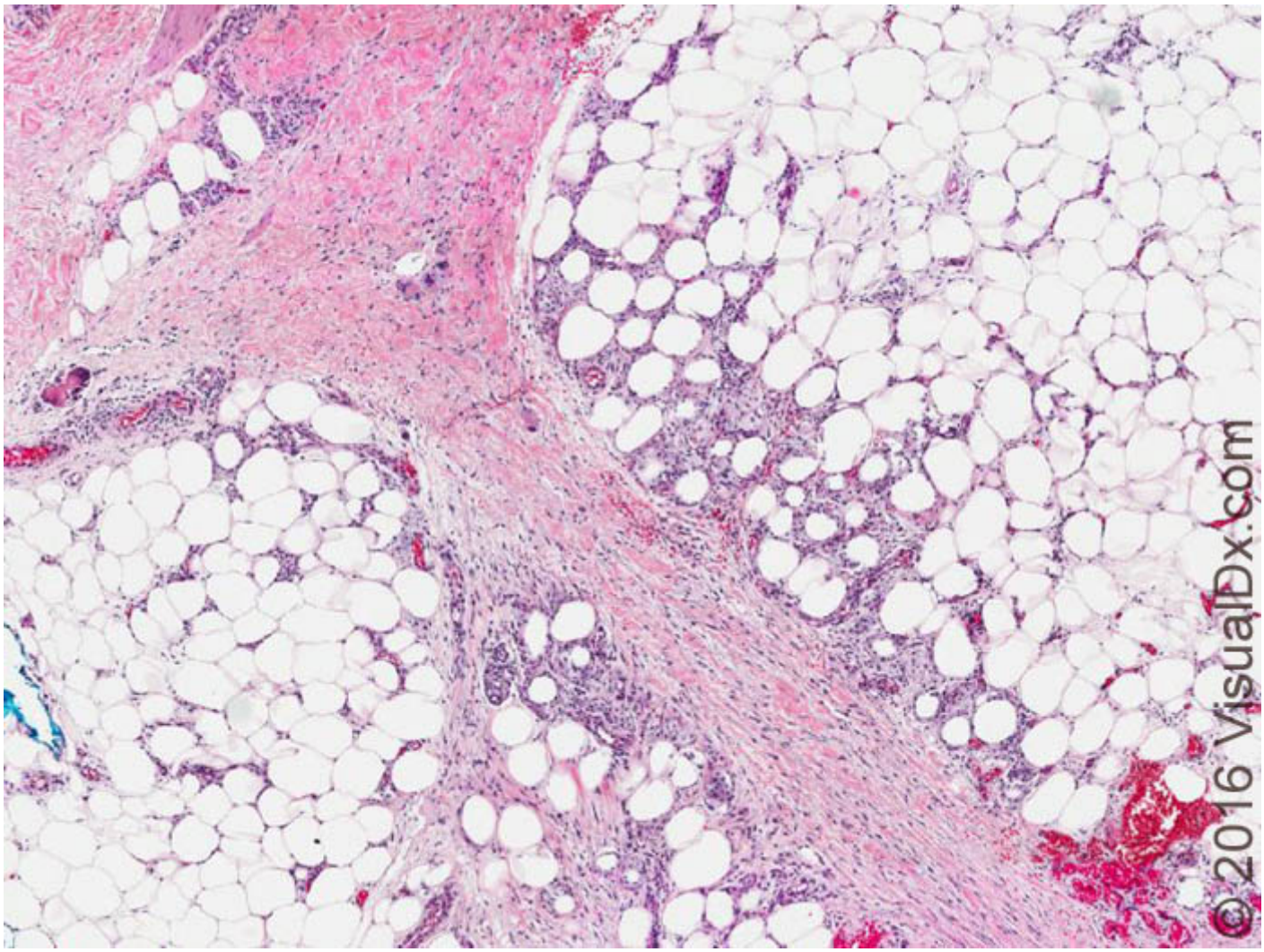
Erythema nodosum



Erythematous nodule on the arm.

Graphic 108927 Version 2.0

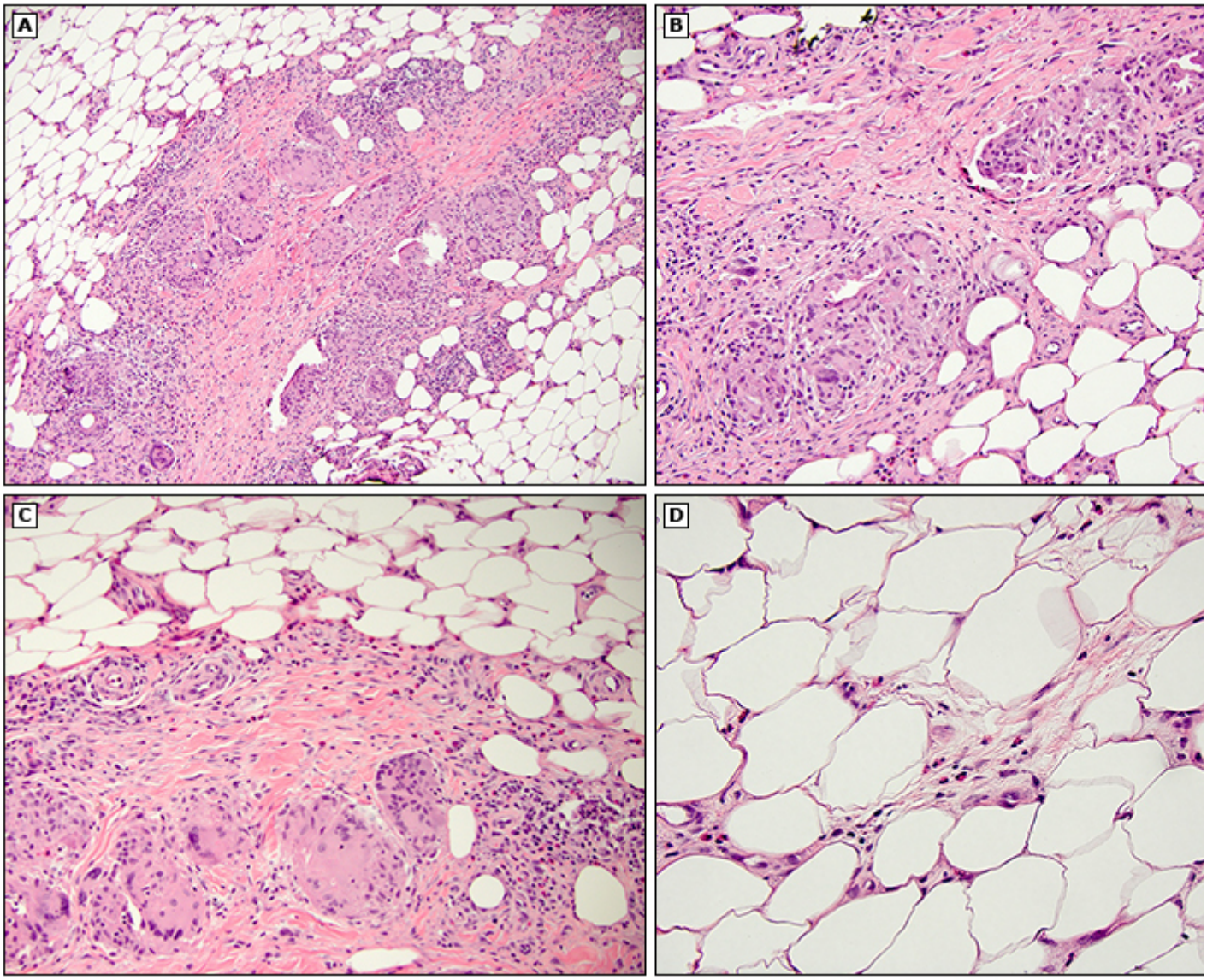
Erythema nodosum



Septal panniculitis with limited extension into the fat lobules.

Graphic 108928 Version 2.0

Erythema nodosum



(A) Septal panniculitis with mixed inflammatory infiltrate containing histiocytes, lymphocytes, neutrophils, a eosinophils.

(B) Meischer's radial granulomas (small, nodular aggregates of histiocytes surrounding "banana-shaped" extracellular clefts). Neutrophils surround the granulomas.

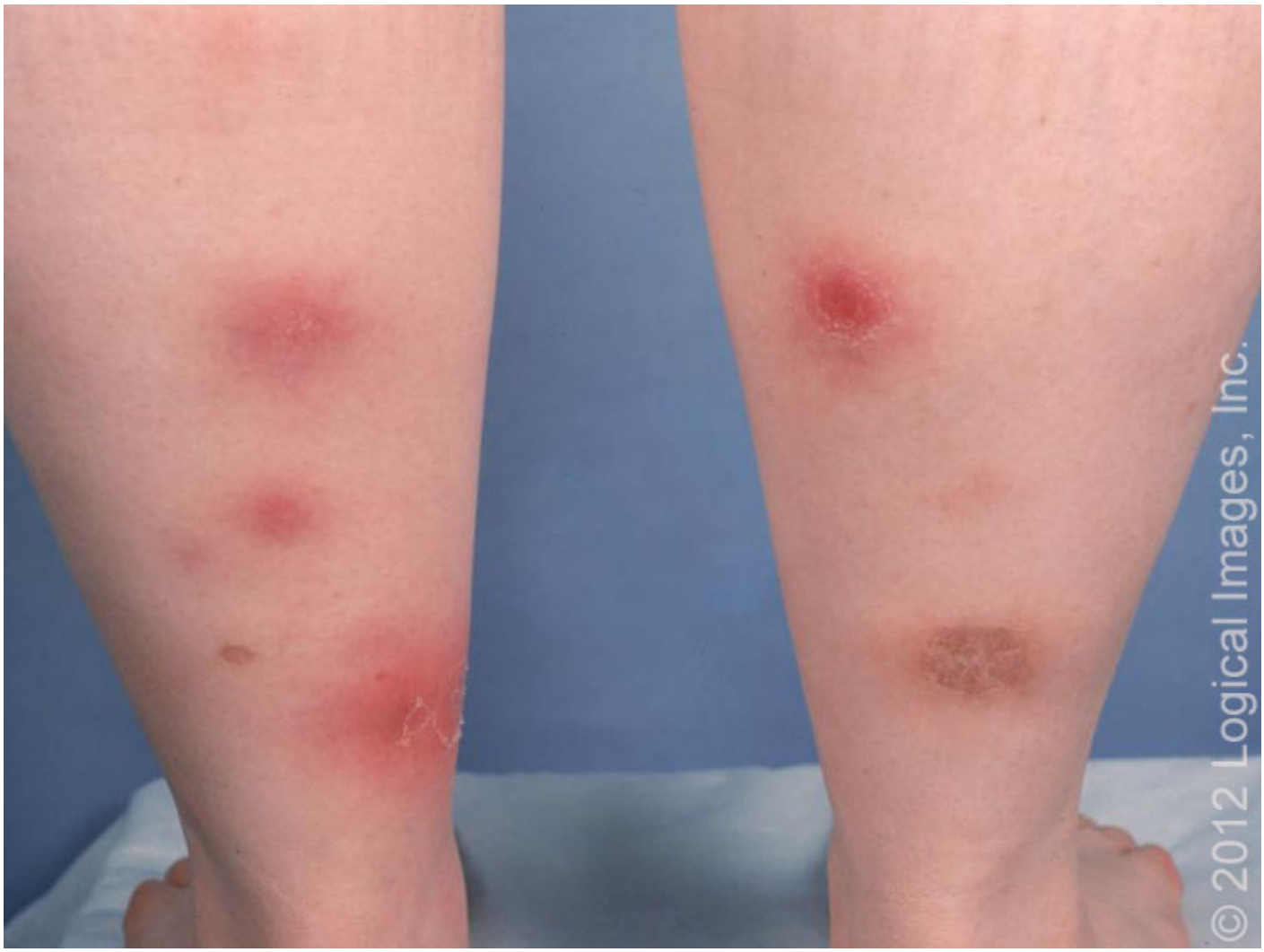
(C) Multinucleated giant cells (a feature of late-stage erythema nodosum).

(D) Septal inflammation with eosinophils, sparing the adipocytes.

Courtesy of Alireza Sepehr, MD.

Graphic 110243 Version 1.0

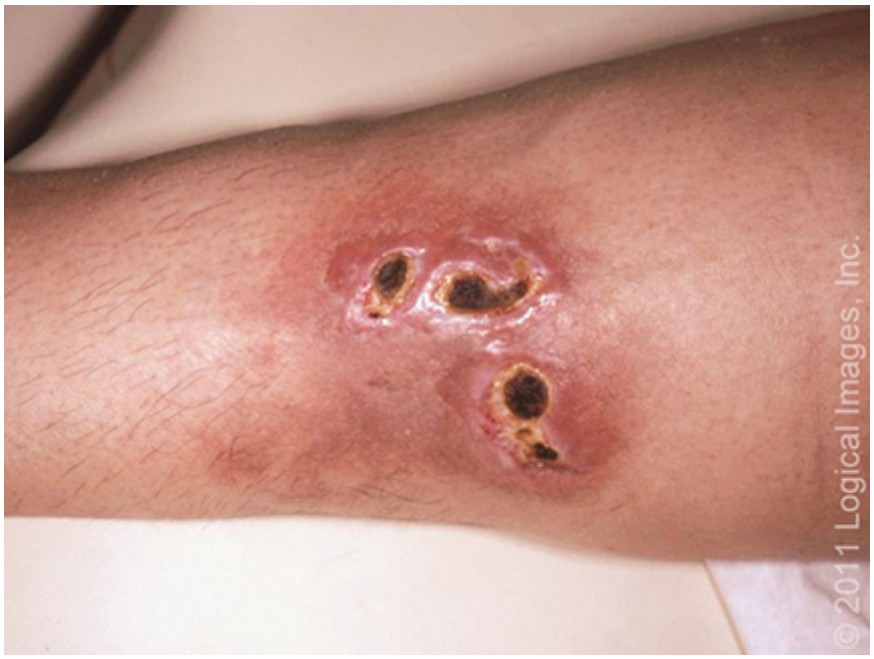
Erythema induratum (nodular vasculitis)



Multiple nodules are present on the posterior lower legs.

Graphic 53596 Version 5.0

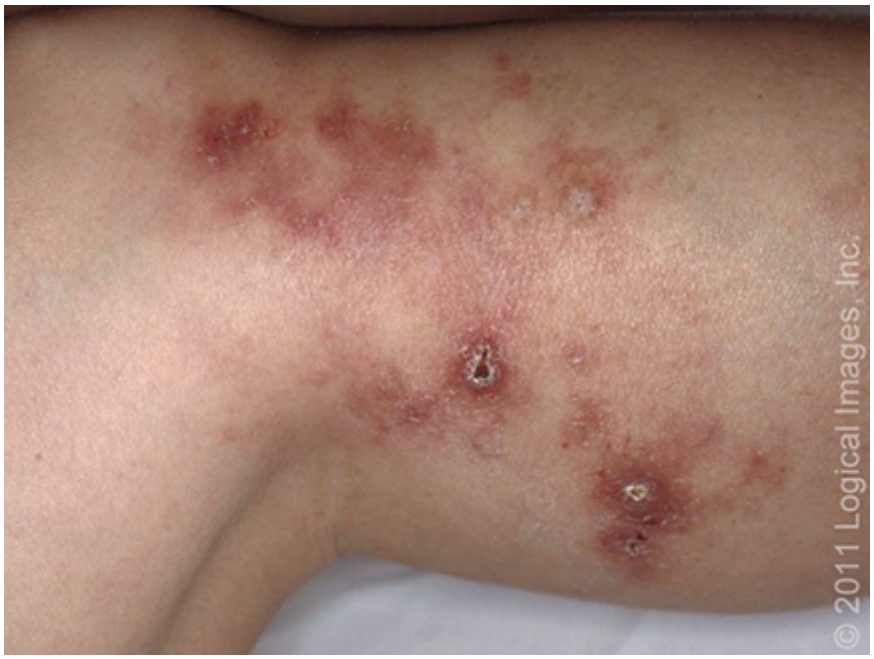
Cutaneous polyarteritis nodosa



Ulcerated, erythematous nodules in polyarteritis nodosa.

Graphic 75391 Version 5.0

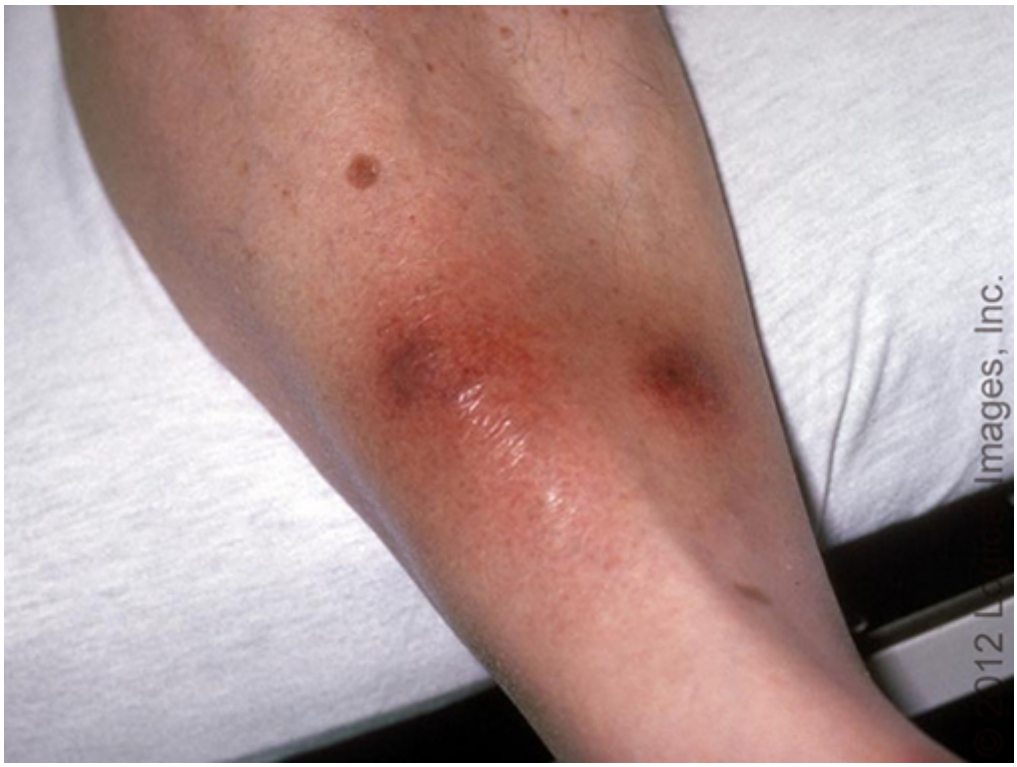
Livedo racemosa



An irregular, branched, vascular pattern (livedo racemosa) and a few healing ulcerations on the leg of a patient with polyarteritis nodosa.

Graphic 64023 Version 6.0

Pancreatic panniculitis



Inflammatory nodules on the distal leg.

Graphic 83789 Version 5.0

Contributor Disclosures

Daniela Kroshinsky, MD, MPH No relevant financial relationship(s) with ineligible companies to disclose. **Jeffrey Callen, MD, FACP, FAAD** Equity Ownership/Stock Options: AbbVie [Various dermatologic conditions]; Bristol Myers Squibb [Various dermatologic conditions]; CVS [Various dermatologic conditions]; Johnson and Johnson [Various dermatologic conditions]; Merck [Various dermatologic conditions]; Pfizer [Various dermatologic conditions]; Procter and Gamble [Various dermatologic conditions]; Walgreens [Various dermatologic conditions]. Consultant/Advisory Boards: Genentech [Pyoderma gangrenosum]. Other Financial Interest: Principia Biopharma [Safety monitoring board member]. All of the relevant financial relationships listed have been mitigated. **Abena O Ofori, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Philip Seo, MD, MHS** No relevant financial relationship(s) with ineligible companies to disclose.

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