

Erythema Nodosum

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Erythema nodosum is the most frequent clinicopathologic variant of panniculitis. The process is a cutaneous reaction that may be associated with a wide variety of disorders, including infections, sarcoidosis, rheumatologic diseases, inflammatory bowel diseases, medications, autoimmune disorders, pregnancy, and malignancies. Erythema nodosum typically manifest by the sudden onset of symmetrical, tender, erythematous, warm nodules and raised plaques usually located on the lower limbs. Often the lesions are bilaterally distributed. At first, the nodules show a bright red color, but within a few days they become livid red or purplish and, finally, they exhibit a yellow or greenish appearance, taking on the look of a deep bruise. Ulceration is never seen, and the nodules heal without atrophy or scarring. Histopathologically, erythema nodosum is the stereotypical example of a mostly septal panniculitis with no vasculitis. The septa of subcutaneous fat are always thickened and variously infiltrated by inflammatory cells that extend to the periseptal areas of the fat lobules. The composition of the inflammatory infiltrate in the septa varies with age of the lesion. In early lesions edema, hemorrhage, and neutrophils are responsible for the septal thickening, whereas fibrosis, periseptal granulation tissue, lymphocytes, and multinucleated giant cells are the main findings in late stage lesions of erythema nodosum. A histopathologic hallmark of erythema nodosum is the presence of the so-called Miescher's radial granulomas, which consist of small, well-defined nodular aggregations of small histiocytes arranged radially around a central cleft of variable shape. Treatment of erythema nodosum should be directed to the underlying associated condition, if identified. Usually, nodules of erythema nodosum regress spontaneously within a few weeks, and bed rest is often sufficient treatment. Aspirin, nonsteroidal antiinflammatory drugs, such as oxyphenbutazone, indomethacin or naproxen, and potassium iodide may be helpful drugs to enhance analgesia and resolution. Systemic corticosteroids are rarely indicated in erythema nodosum and before these drugs are administered an underlying infection should be ruled out.

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Erythema nodosum is the most frequent clinicopathologic variant of panniculitis. The disorder usually exhibits an acute onset and is clinically characterized by the sudden eruption of erythematous tender nodules and plaques located predominantly over the extensor aspects of the lower extremities. The lesions show spontaneous regression, without ulceration, scarring, or atrophy, and recurrent episodes are not uncommon. Erythema nodosum is a cutaneous reactive process that may be triggered by a wide variety of

possible stimuli, being infections, sarcoidosis, rheumatologic diseases, inflammatory bowel diseases, medications, autoimmune disorders, pregnancy, and malignancies the most common associated conditions.

Etiology

Erythema nodosum may be associated with a wide variety of disease processes, and its observation must always be followed by a search for underlying etiology. A review of the literature reveals that the list of etiologic factors that can lead to erythema nodosum is long and varied, including infections, drugs, malignant diseases, and a wide group of miscellaneous conditions (Table 1).¹⁻¹⁰⁴ Although there are considerable geographic variations related to endemic infections, in our country streptococcal infections are the most frequent

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Table 1 Etiologic Factors in Erythema Nodosum

Infections
Bacterial infections
Atypical mycobacterial infections ²
<i>Borrelia burgdorferi</i> infections ³
Boutonneuse fever ⁴
Brucellosis ⁵
<i>Campylobacter</i> infections ⁶
Cat-scratch disease ⁷
Chancroid ²
<i>Chlamydia psittaci</i> infections ⁸
<i>Corynebacterium diphtheriae</i> infections ²
<i>Escherichia coli</i> infections ¹⁰⁴
Gonorrhea ⁹
<i>Klebsiella pneumoniae</i> infections ¹⁰
Leptospirosis ¹¹
Lymphogranuloma venereum ¹²
Meningococemia ¹³
<i>Moraxella catarrhalis</i> infections ¹⁴
<i>Mycoplasma pneumoniae</i> infections ¹⁵
<i>Pasteurella pseudotuberculosis</i> infections ¹⁶
<i>Propionibacterium acnes</i> ¹⁷
<i>Pseudomona aeruginosa</i> infections ¹⁸
Q fever ¹⁹
<i>Salmonella</i> infections ²⁰
<i>Shigella</i> infections ²¹
Streptococcal infections ²²
Syphilis ²³
Tuberculosis ²⁴
Tularemia ²⁵
<i>Yersinia</i> infections ²⁶
Viral infections
Cytomegalovirus infections ²⁷
Hepatitis B ²⁸
Hepatitis C ²⁹
Herpes simplex ²
HIV infection ³⁰
Infectious mononucleosis ³¹
Measles ³²
Milker's nodules ³³
Parvovirus B19 infections ³⁴
Varicella ³⁵
Fungal infections
Aspergillosis ³⁶
Blastomycosis ³⁷
Coccidioidomycosis ³⁸
Dermatophytes ³⁹
Histoplasmosis ⁴⁰
Protozoal infections
Amebiasis ⁴¹
Ascariasis ⁴²
Giardiasis ⁴¹
Hydatidosis ⁴³
Hookworm infestation ²
<i>Sparganum</i> larva ⁴⁴
Toxoplasmosis ⁴⁵
Trichomoniasis ⁴⁶
Drugs
Acetaminophen ⁴⁷
Actinomycin-D ⁴⁸
All-trans retinoic acid ⁴⁸
Aminopyrine ²

Table 1 Continued

Amiodarone ⁴⁷
Amoxicillin ¹⁰⁴
Ampicillin ¹⁰⁴
Antimony ²
Arsphenamine ⁹
Azathioprine ⁴⁷
Bromides ⁴⁹
Busulfan ⁴⁷
Carbamazepine ⁴⁷
Carbenicillin ⁵⁰
Carbimazole ⁴⁷
Cefdinir ⁴⁷
Chlordiazepoxide ⁴⁷
Chlorotrianisene ⁴⁷
Chlorpropamide ⁴⁷
Ciprofloxacin ⁴⁷
Clomiphene ⁴⁷
Codeine ⁴⁷
Cotrimoxazole ⁴⁷
D-penicillamine ⁵¹
Dapsone ⁴⁷
Diclofenac ⁴⁷
Dicloxacillin ⁴⁷
Diethylstilbestrol ⁵²
Disopyramide ⁴⁷
Echinacea herbal therapy ⁵²
Enoxacin ⁴⁷
Erythromycin ¹⁰⁴
Estrogens ⁴⁷
Fluoxetine ⁴⁷
Furosemide ⁴⁷
Glucagon ⁴⁷
Gold salts ⁵³
Granulocyte colony-stimulating factor ⁴⁷
Hepatitis B vaccine ⁵⁴
Hydralazine ⁴⁷
Ibuprofen ⁴⁷
Indomethacin ⁴⁷
Interleukin-2 ⁵⁵
Iodides ⁴⁹
Isotretinoin ⁵⁶
Leukotriene modifying agents (zileuton and rafirlukast) ⁵⁷
Levofloxacin ⁴⁷
Meclofenamate ⁴⁷
Medroxyprogesterone ⁴⁷
Meprobamate ⁴⁷
Mesalamine ⁴⁷
Methicillin ⁴⁷
Methimazole ⁴⁷
Methyldopa ⁴⁷
Mezlozillin ⁴⁷
Minocycline ⁵⁸
Naproxen ⁴⁷
Nifedipine ⁴⁷
Nitrofurantoin ²
Ofloxacin ⁴⁷
Omeprazole ⁵⁹
Oral contraceptives ⁶⁰
Oxacillin ⁴⁷
Paroxetine ⁴⁷

Table 1 Continued

Penicillin ⁵⁴
Phenylbutazone ³⁶
Phenytoin ³³
Piperacillin ⁴⁷
Progestins ⁴⁷
Propylthiouracil ⁶¹
Pyritinol ⁹
Sparfloxacin ⁴⁷
Streptomycin ⁴⁷
Sulfamethoxazole ⁴⁷
Sulfixoxazole ⁴⁷
Sulfonamides ⁶²
Sulfosalazine ⁴⁷
Thalidomide ⁶³
Ticarcilin ⁴⁷
Trimethoprim ⁶⁴
Typhoid vaccination ⁶⁵
Verapamil ⁴⁷
Malignant diseases
Adenocarcinoma of the colon ⁶⁶
Carcinoid tumor ⁶⁷
Carcinoma of the uterine cervix ⁶⁸
Hepatocellular carcinoma ⁶⁹
Hodgkin's disease ⁷⁰
Leukemia ⁷¹
Lung cancer ⁷²
Non-Hodgkin's lymphoma ⁷³
Pancreatic carcinoma ⁷⁴
Post-radiotherapy for pelvic carcinoma ¹
Renal carcinoma ⁵⁵
Sarcoma ⁹
Stomach cancer ¹⁰⁴
Miscellaneous conditions
Acne fulminans ⁷⁵
Acupuncture therapy and flu-like infection ⁷⁶
Adult Still's disease ⁷⁷
Ankylosing spondylitis ⁷⁸
Antiphospholipid antibodies syndrome ⁷⁹
Behçet's syndrome ⁸⁰
Berger's disease ⁸¹
Breast abscesses ⁸²
Chronic active hepatitis ⁸³
Coeliac disease ⁸⁴
Colon diverticulosis ⁹
Crohn's disease ⁸⁵
Diverticulitis ⁸⁶
Granulomatous mastitis ⁸⁷
IgA nephropathy ⁸⁸
Jellyfish sting ⁸⁹
Lupus erythematosus ⁹⁰
Pregnancy ⁹¹
Radiotherapy ⁹²
Recurrent polycondritis ⁹³
Reiter's syndrome ⁹⁴
Rheumatoid arthritis ⁹⁵
Sarcoidosis ⁹⁶
Sjögren's syndrome ⁹⁷
Smoke inhalation in a house fire ⁹⁸
Sweet's syndrome ⁹⁹
Systemic lupus erythematosus-like syndrome due to C4 deficiency ¹⁰⁰

Table 1 Continued

Takayasu's arteritis ¹⁰¹
Ulcerative colitis ¹⁰²
Vogt-Koyanagi disease ⁹⁷
Wegener's granulomatosis ¹⁰³

etiologic factor for erythema nodosum in children, whereas other infectious processes, drugs, sarcoidosis, autoimmune disorders, and inflammatory diseases of the bowel are the most commonly associated disorders in adults.

The relationship between a previous episode of upper respiratory tract infection by group A beta-hemolytic streptococcus and erythema nodosum is well-known, especially in children and young adults. Usually, the cutaneous lesions appear 2 or 3 weeks after the throat infection, and they are accompanied by an elevation of the antistreptolysin O (ASO) titer. An intradermal positive test to streptococcal antigens is often found in patients with erythema nodosum secondary to streptococcal infections, although when the cutaneous nodules develop, the cultures of routine throat swabs usually do not detect microorganisms.^{22,104}

Tuberculosis is now an uncommon etiologic factor for erythema nodosum in our country¹⁰⁴ and other areas of southern Europe.^{105,106} These cases are seen mostly in children, and the cutaneous lesions usually indicate a primary pulmonary infection, being concomitant with the conversion of the tuberculin test.²⁴

Drugs frequently are implicated as the cause of erythema nodosum. Sulfonamides, bromides, and oral contraceptive pills have been long recognized as the most common medications responsible for acute bouts of erythema nodosum, but the list of possibilities is very large (Table 1). In recent years, the amount of hormones in contraceptive pills has been lowered markedly and, thus, erythema nodosum secondary to this medication is now rare. In those cases in which the patient develops erythema nodosum when is taken an antibiotic for an infectious disease is difficult to discern whether the cutaneous reaction is due to the antiobiotic or the infectious agent.

Sarcoidosis constitutes one of the most common etiologic factors in adult patients with secondary erythema nodosum in our country.¹⁰⁴ In some countries, specially in northern Europe, erythema nodosum and bilateral hilar adenopathy frequently are seen as early manifestations of sarcoidosis (Löfgren's syndrome).¹⁰⁷ However, erythema nodosum and bilateral hilar adenopathy are not exclusive of sarcoidosis, and they also have been associated with lymphoma, tuberculosis, streptococcal infections, coccidioidomycosis, histoplasmosis, and acute infections by *Chlamydia pneumoniae*.^{108,109}

In adults, erythema nodosum associated with enteropathies often correlates with a flare-up of the disease, although the cutaneous eruption may precede the clinical appearance of the inflammatory bowel disease. Ulcerative colitis¹⁰² is more frequently associated with erythema nodosum than Crohn's disease.⁸⁵

Many patients with Behçet disease develop lesions that clinically resemble those of erythema nodosum.⁸¹ Histopathologic studies, however, have demonstrated that a significant proportion of these patients with Behçet syndrome and erythema nodosum-like lesions showed a mostly lobular panniculitis with the frequent finding of leukocytoclastic or lymphocytic vasculitis^{110,111} and therefore some patients with Behçet disease show a panniculitis different from that of erythema nodosum.

The simultaneous occurrence of Sweet's syndrome and erythema nodosum have been considered a rare association.¹¹²⁻¹¹⁷ In these patients, the concomitant development of Sweet's syndrome and erythema nodosum is associated with sarcoidosis,¹¹³ upper respiratory tract infection,^{113,114} acute myelogenous leukemia,^{115,116} and Crohn's disease.¹¹⁶ However, recently Ginarte and Toribio¹¹⁷ commented that the association between Sweet's syndrome and erythema nodosum is not as rare as the review of the literature seems to indicate, because 15% to 30% of patients of several series of Sweet's syndrome showed biopsy-proved erythema nodosum.¹¹⁸⁻¹²² On the basis of these data, Ginarte and Toribio concluded that the simultaneous occurrence of these 2 reactive processes is a frequent feature that may be caused by a common underlying mechanism of pathogenesis (streptococcal upper respiratory tract infection or inflammatory bowel disease) and they respond to the same treatment (corticosteroids, potassium iodide), also supporting a close relationship between them.¹¹⁷ The same opinion has been recently supported by other authors.¹²³

Despite thorough clinical and laboratory investigations, the etiology of erythema nodosum remained uncertain in a significant percentage of the cases that ranged from 37% to 60% of the cases in all reported series.^{36,104,106,124-127}

Pathogenesis

Erythema nodosum is considered to be a hypersensitivity response to a wide variety of inciting factors. The variability of possible antigenic stimuli that can induce erythema nodosum indicates that this disorder is a cutaneous reactive process and that the skin has limited responses to different provoking agents. Erythema nodosum probably results from the formation of immune complexes and their deposition in and around venules of the connective tissue septa of the subcutaneous fat. Circulating immunocomplexes¹²⁸ and complement activation^{129,130} have been recorded in patients with erythema nodosum. Histopathologic features in fully developed lesions also suggest a delayed hypersensitivity mechanism¹³¹ and direct immunofluorescence studies have shown deposits of immunoglobulins in the blood vessels walls of the septa of subcutaneous fat.¹³² However, other authors failed to demonstrate circulating immunocomplexes in patients with erythema nodosum,¹³³ and a type IV delayed hypersensitivity reaction may also play an important role in the pathogenesis of the disorder.

Early lesions of erythema nodosum are histopathologically characterized by a neutrophilic inflammatory infiltrate involving the septa of the subcutaneous tissue. Recent investi-

gations have demonstrated that patients suffering from erythema nodosum had a fourfold higher percentage of reactive oxygen intermediates (ROIs) produced by activated neutrophils in their peripheral blood compared with healthy volunteers. Furthermore, the percentage of ROI-producing cells in patients with erythema nodosum correlated with the clinical severity. These data support the fact that ROI might play a role in the pathogenesis of erythema nodosum. ROI might exert their effects by oxidative tissue damage and by promoting tissue inflammation.¹³⁴

Patients with erythema nodosum associated with sarcoidosis produce an uncommon tumor necrosis factor (TNF)- α II. These patients showed a nucleotide exchange, (G-A) at position -308 in the human TNF- α gene promoter, whereas patients with erythema nodosum without underlying sarcoidosis displayed a similar allele frequency compared with controls. These results support the notion that erythema nodosum in association with sarcoidosis might be pathogenetically linked to altered TNF-alpha production due to a genetic promoter polymorphism.¹³⁵ In contrast, other authors have found that the proinflammatory cytokine pattern showed increased interleukin-6 serum concentrations both in infectious and non infectious disease-related erythema nodosum, whereas a minor involvement of TNF was found in these patients.¹⁰⁰

The reason why the anterior aspects of the legs are so susceptible for the development of lesions of erythema nodosum is unknown. Some authors have proposed that there is no other site in the skin surface where the combination of a relatively sparse arterial supply is associated with a venous system subject to gravitational effects and cooling and a lymphatic system which is hardly rich enough to meet the requirements of any increase in fluid load and which has no mechanical stimulus. The skin of the shins has no underlying muscle pump and receives little in the way of massage. All these local anatomic factors would favor the location of the lesions of erythema nodosum on the shins.¹

Clinical Features

Erythema nodosum can occur at any age, but most cases appear between the second and fourth decades of the life, with the peak of incidence being between 20 and 30 years of age, probably attributable to the high incidence of sarcoidosis at this age.¹³⁶ Several studies have demonstrated that erythema nodosum occurs 3 to 6 times more frequently in women than in men,¹³⁷ although the sex incidence before puberty is approximately equal.¹²⁴ Racial and geographic differences of incidence vary depending on the prevalence of diseases that are etiologic factors. Prevalence of erythema nodosum in a semirural area of England during a 2-year period gave a figure of 2.4 per 1000 population per year.¹³⁸ Prevalence varies also according to the type of the patients attended to in a clinic: the average hospital incidence was approximately 0.5% of new cases seen in Departments of Dermatology in England¹ and approximately 0.38% of all patients seen in a Department of Internal Medicine in Spain.¹³⁹ In a recent study, the average annual incidence rate

of biopsy-proven erythema nodosum in a hospital of the northwestern Spain for the population 14 years and older was 52 cases per million of persons,¹⁰⁴ although certainly this rate underestimated the authentic incidence of the disease because only included cases confirmed by biopsy. Most cases of erythema nodosum occur within the first half of the year,¹⁰⁴ probably because of the more frequent incidence of streptococcal infections in this period of the year, and there is no difference in distribution between urban and rural areas.¹ Familial cases are usually due to an infectious etiology.

The typical eruption is quite characteristic and consists of a sudden onset of symmetrical, tender, erythematous, warm nodules and raised plaques usually located on the shins, ankles and knees. The nodules, which range from 1 to 5 cm or more in diameter, are usually bilaterally distributed (Fig. 1). Nodules may become confluent resulting in erythematous plaques. In rare instances, more extensive lesions may appear, involving the thighs, extensor aspects of the arms, neck, and even the face. At first, the nodules show a bright red color and are raised slightly above the skin. Within a few days, they become flat, with a livid red or purplish color. Finally, they exhibit a yellow or greenish appearance often taking on the look of a deep bruise ("erythema contusiformis"). This contusiform color evolution is quite characteristic of erythema nodosum and allows a specific diagnosis in late stage lesions.



Figure 1 Characteristic eruption of erythema nodosum consists of bilateral erythematous nodules and plaques on the anterior aspect of the legs of an adult woman.

Ulceration is never seen in erythema nodosum and the nodules heal without atrophy or scarring. Usually acute bouts of erythema nodosum are associated with a fever of 38 to 39°C, fatigue, malaise, arthralgia, headache, abdominal pain, vomiting, cough, or diarrhea. Episcleral lesions and phlyctenular conjunctivitis may also accompany the cutaneous lesions. Less frequent clinical manifestations associated with erythema nodosum are lymphadenopathy, hepatomegaly, splenomegaly and pleuritis.¹²⁵ The eruption generally lasts from 3 to 6 weeks, but persistence beyond this time is not unusual. Recurrences are not uncommon. Erythema nodosum in children has a much shorter duration than in adults. Arthralgias are seen in a minority of the patients, and fever is an accompanying manifestation in fewer than half of the cases.¹⁴⁰⁻¹⁴²

Some clinical variants of erythema nodosum have been described under different names. These variants include erythema nodosum migrans,¹⁴³⁻¹⁴⁶ subacute nodular migratory panniculitis of Vilanova and Piñol,^{147,148} and chronic erythema nodosum.¹⁰⁵ In our opinion, the proposed clinical and histopathologic differences are not enough to separate these variants from classic erythema nodosum, and probably they are just expressions of the different stage of evolution of lesions of a single pathologic process rather than different entities. At present moment, most authors believe that erythema nodosum migrans, subacute nodular migratory panniculitis, and chronic erythema nodosum are clinical variants which may all be included within the spectrum of erythema nodosum.¹⁴⁹ We agree with them.

A rare variant of erythema nodosum in children and young adults is characterized by lesions only involving the palms and soles and, often, the process is unilateral.¹⁵⁰⁻¹⁵³ These children developed painful erythematous nodules usually after physical activity. Histopathologic features of these lesions of unilateral palmar or plantar erythema nodosum are similar to those of classical erythema nodosum.

Laboratory Anomalies

Because the list of possible etiologic factors in erythema nodosum is extensive, a rational, cost-effective diagnostic approach in patients with erythema nodosum is desirable. A complete clinical history should be elicited in all patients, with reference of previous diseases, medications, foreign travel, pets and hobbies, as well as familial cases.

Initial evaluation should include complete blood count, determination of the sedimentation rate, ASO titer, urinalysis, throat culture, intradermal tuberculin test and chest roentgenogram. The white blood count is normal or only slightly increased, but the erythrocyte sedimentation rate is often very high, returning to normal when the eruption fades. In children, the elevation of the erythrocyte sedimentation rate correlates significantly with the number of cutaneous lesions.¹⁴² The rheumatoid factor is usually negative, and there is a temporary increase in the α_2 -globulin. A high anti-streptolysin titer is seen in those cases of erythema nodosum associated with a sore throat streptococcal infection. Usually, a significant change, at least 30%, in ASO titer in two con-

secutive determinations performed in a 2 to 4 weeks interval indicates recent streptococcal infection.¹⁰⁴ When the etiology is doubtful, a sample of blood should be serologically investigated from those bacterial, virological, fungal or protozoal infections more prevalent in that area.

In those cases suspected of being tuberculous an intradermal tuberculin test should be performed, but the results must be valued in the context of the tuberculous prevalence in the studied area. In Spain a significant percentage of healthy adults show positive results for tuberculin test. In sarcoidosis, there is a decrease in the degree of reactivity of previously positive patients. The Kveim test is now less used because of fears of AIDS.

A chest radiograph should be performed in all patients with erythema nodosum to rule-out pulmonary diseases as the cause of the cutaneous reactive process. Radiologically demonstrable bilateral hilar lymphadenopathy with febrile illness and erythema nodosum with no evidence of tuberculosis characterize Löfgren's syndrome, which in most cases represents an acute variant of pulmonary sarcoidosis with benign course, more frequent in females, specially during pregnancy and puerperium.¹⁰⁷

Histopathology

Histopathologically, erythema nodosum is the stereotypical example of a mostly septal panniculitis with no vasculitis. The septa of subcutaneous fat are always thickened and infiltrated by inflammatory cells that extend to the periseptal areas of the fat lobules. Usually, a superficial and deep perivascular inflammatory infiltrate predominantly composed of lymphocytes is also seen in the overlying dermis. The composition of the inflammatory infiltrate in the septa varies with age of the lesion. In early lesions, edema, hemorrhage, and neutrophils (Fig. 2) are responsible for the septal thickening,¹²⁶ whereas fibrosis, periseptal granulation tissue, lymphocytes, histiocytes (Fig. 3) and multinucleated giant cells (Fig. 4) are the main findings in late stage lesions of erythema nodosum. In rare instances eosinophils are the predominant inflammatory cells in early lesions of erythema nodosum.¹⁵⁴ Sometimes, in these early lesions, the inflammatory cell infiltrate may be more apparent in the fat lobules than in the septa, because inflammatory cells extend into the periphery of the fat lobules between individual fat cells in a lace-like fashion, and the process appears as a predominantly lobular panniculitis. However, in contrast with authentic lobular panniculitis, necrosis of the adipocytes at the center of the fat lobule is not seen. A histopathologic hallmark of erythema nodosum is the presence of the so-called Miescher's radial granulomas,¹⁵⁵⁻¹⁵⁷ that consist of small, well-defined nodular aggregations of small histiocytes around a central stellate or banana shaped cleft (Fig. 3). The nature of the central cleft is unknown and, although some authors have considered them as lymphatic spaces,¹ our immunohistochemical and ultrastructural studies of cases of Miescher's radial granulomas have failed to demonstrate endothelial or other cellular lining of these clefts.

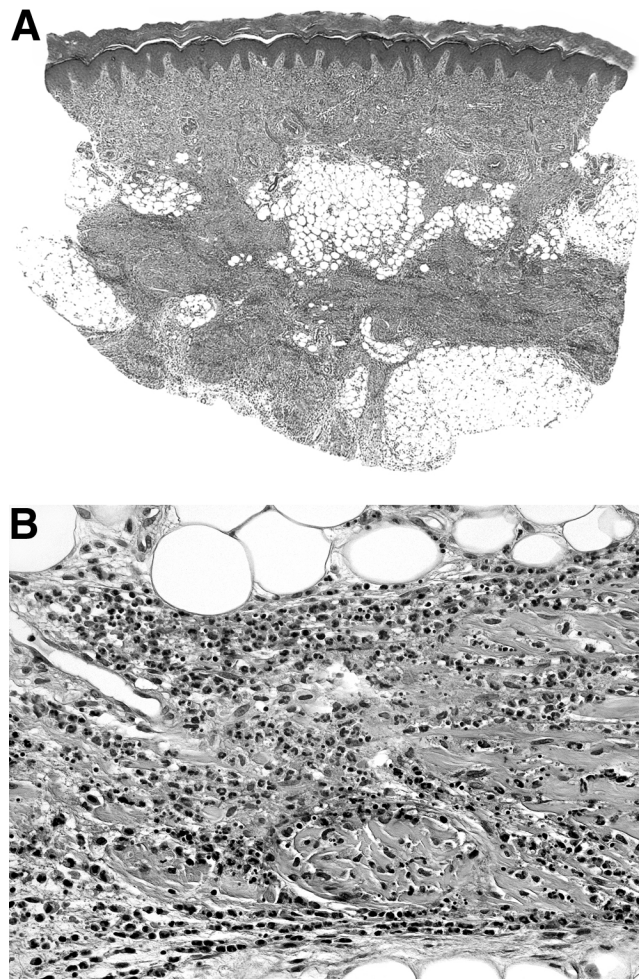


Figure 2 Histopathologic features of an early lesion of erythema nodosum. (A) Scanning power showing a mostly septal panniculitis with thickened connective tissue septa of the subcutis. (B) Higher magnification demonstrated numerous neutrophils interstitially arranged between collagen bundles of the septa.

In early lesions, Miescher's radial granulomas appear scattered in the septa and surrounded by neutrophils. In older nodules of erythema nodosum, histiocytes coalesce to form multinucleated giant cells, many of which still keep in their cytoplasm a stellate central cleft reminiscent of those centers of Miescher's radial granuloma. Sometimes Miescher's radial granulomas are conspicuous in the septa, but occasionally serial sections may be necessary to identify them. In our experience, these Miescher's radial granulomas are present in all stages of the evolution of erythema nodosum lesions and they should be searched for to make a specific diagnosis.¹⁵⁷ However, other authors consider that similar granulomas may be present in lesions of Sweet's syndrome, erythema induratum of Bazin, Behçet disease, and necrobiosis lipoidica.¹⁴⁹ Recent immunohistochemical studies have demonstrated that the central cleft of Miescher's radial granulomas express myeloperoxidase, which suggest that myeloid cells were present in some stage of the Miescher's radial granuloma formation.¹⁵⁸ Myeloperoxidase immunorexpression has been also described in the small, elongated, twisted ap-

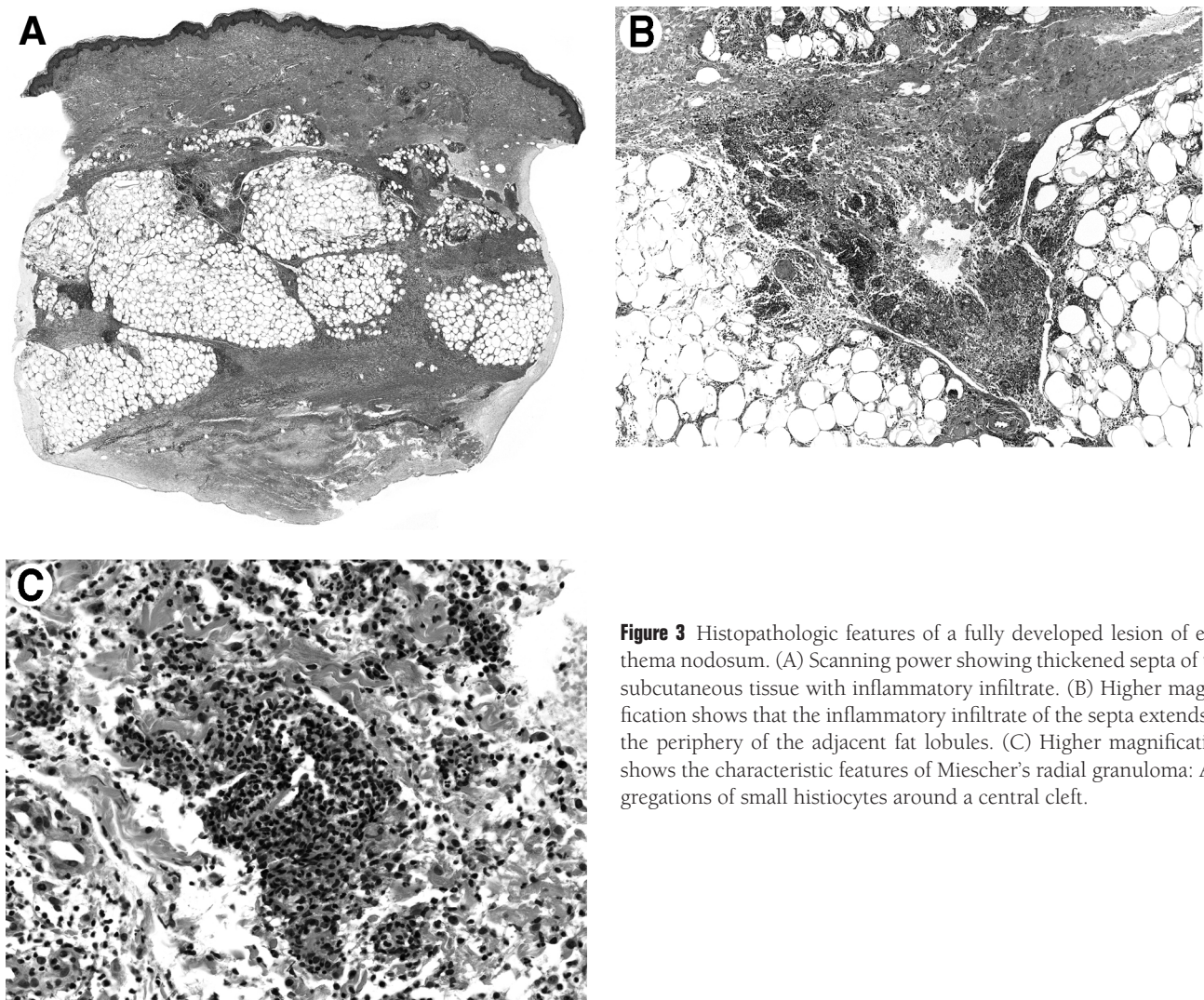


Figure 3 Histopathologic features of a fully developed lesion of erythema nodosum. (A) Scanning power showing thickened septa of the subcutaneous tissue with inflammatory infiltrate. (B) Higher magnification shows that the inflammatory infiltrate of the septa extends to the periphery of the adjacent fat lobules. (C) Higher magnification shows the characteristic features of Miescher's radial granuloma: Aggregations of small histiocytes around a central cleft.

pearing mononuclear cells of the so-called histiocytoid Sweet syndrome,¹⁵⁹ which are actually immature myeloid cells, providing a link between erythema nodosum and Sweet syndrome, two conditions in which neutrophils participate.

Another histopathologic characteristic of erythema nodosum is the absence of vasculitis although, in rare instances, a necrotizing small vessel vasculitis with fibrinoid necrosis of the vessel walls has been described in the septa.¹⁶⁰ Sanchez Yus et al, in a histopathologic study of a series of 79 cases of erythema nodosum,¹⁵⁷ demonstrated that authentic leukocytoclastic vasculitis is usually absent, and only 18 of 79 specimens disclosed slight nonspecific changes in some isolated veins and venules, whereas many other vessels were intact in the middle of the inflammatory nodule. In a recent histopathologic study of four cases of erythema nodosum the authors described unusual findings that consisted of lobular panniculitis with neutrophilic infiltrate and vasculitis of medium size arteries. In our opinion, however, these features cannot be interpreted as histopathologic findings of erythema nodosum and the inflamed vessels that they interpreted as medium sized arteries are in our opinion medium size veins and the illustrated histopathologic features

show findings of superficial thrombophlebitis rather than erythema nodosum.¹⁶¹ Ultrastructural studies in lesions of erythema nodosum have not demonstrated authentic vasculitis, although damage to endothelial cells of the small vessels of the septa of subcutaneous fat with some extension of inflammatory cells into the vessel walls have been described.¹⁶²⁻¹⁶⁴

In late stage lesions of erythema nodosum, the inflammatory infiltrate in the septa is sparse, and there are markedly widened septa with granulation tissue at the interface between connective tissue septa and fat lobules. As erythema nodosum evolves, the septa become fibrotic and replaced by granulomas, and the fat lobules become progressively replaced and effaced by widening septa, which can even completely obliterate the lobules. In these late lesions may be difficult to establish whether the lesion is a mostly septal or mostly lobular panniculitis, because the entire subcutaneous tissue is effaced by a fibrotic and granulomatous process. With time, despite the striking fibrosis, the lesions resolve without atrophy or scarring of the involved septa. Lipomembranous or membranocystic panniculitis, a histopathologic pattern that has been described in residual lesions of different

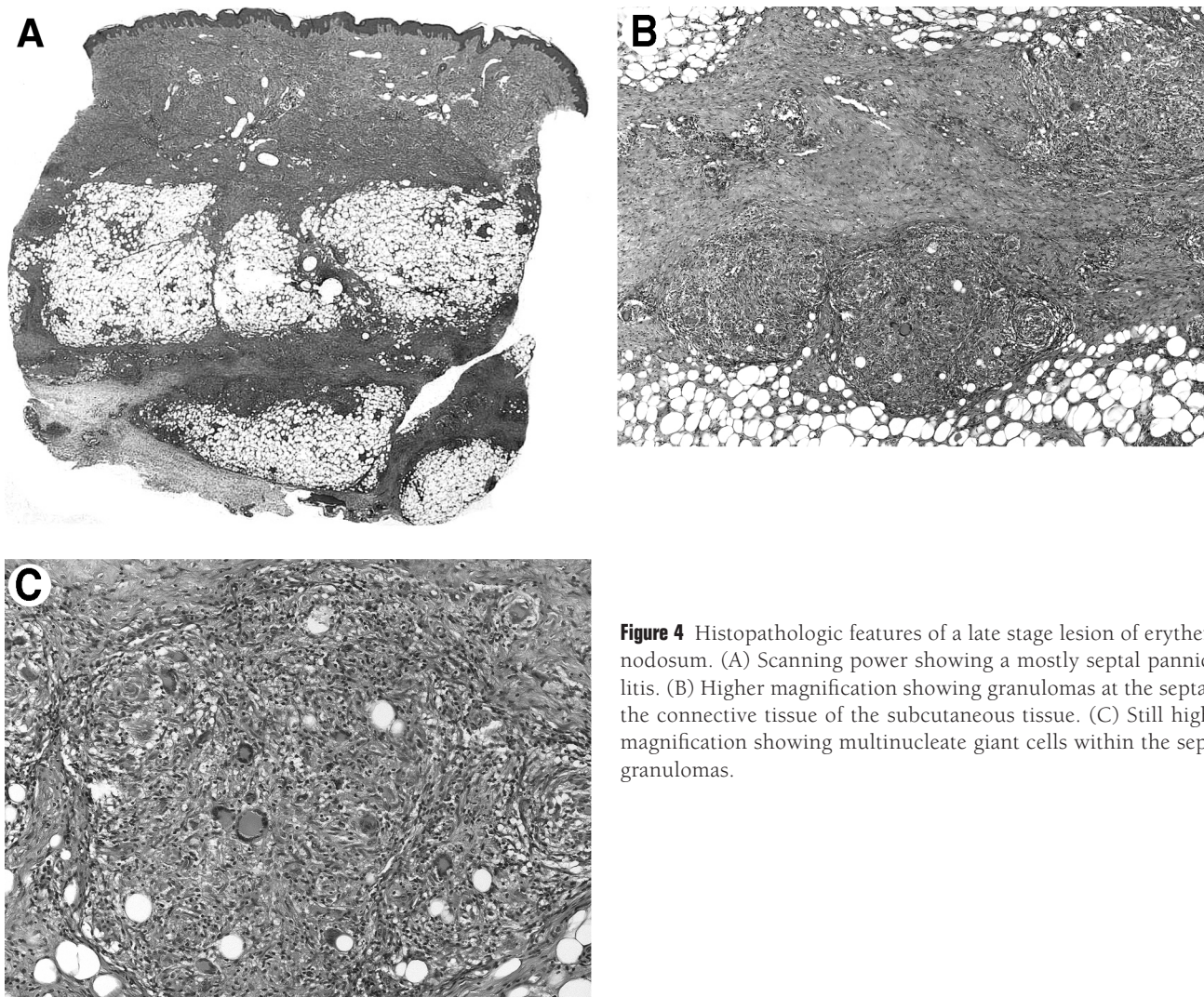


Figure 4 Histopathologic features of a late stage lesion of erythema nodosum. (A) Scanning power showing a mostly septal panniculitis. (B) Higher magnification showing granulomas at the septa of the connective tissue of the subcutaneous tissue. (C) Still higher magnification showing multinucleate giant cells within the septal granulomas.

types of panniculitis, has been also seen in late stage lesions of erythema nodosum.¹⁶⁵

Prognosis

Most cases of erythema nodosum regress spontaneously in 3 to 4 weeks. More severe cases need about 6 weeks. Relapses are not exceptional, and they are more common in patients with idiopathic erythema nodosum and erythema nodosum associated with nonstreptococcal or streptococcal upper respiratory tract infections. Complications are uncommon. A patient developed retrobulbar optic nerve neuritis during the acute episode of erythema nodosum,¹⁶⁶ and another patient with chronic hepatitis C had erythema nodosum with concomitant erythema multiforme and lichen planus that coincided with the reactivation of viral replication.¹⁶⁷

Treatment

Treatment of erythema nodosum should be directed to the underlying associated condition, if identified. Usually, nodules of erythema nodosum regress spontaneously within a

few weeks, and bed rest is often sufficient treatment. Aspirin and nonsteroidal antiinflammatory drugs such as oxyphenbutazone, in a dosage of 400 mg per day,¹⁶⁸ indomethacin, in a dosage of 100 to 150 mg per day,¹⁶⁹ or naproxen, in a dosage of 500 mg per day,¹⁷⁰ may be helpful to enhance analgesia and resolution. If the lesions persist longer, potassium iodide in a dosage of 400 to 900 mg daily or a saturated solution of potassium iodide, 2 to 10 drops in water or orange juice three times per day, has been reported to be useful.¹⁷¹⁻¹⁷³ The mechanism of action of potassium iodide in erythema nodosum is unknown, but it seems that it causes heparin release from mast cells and heparin acts to suppress delayed hypersensitivity reactions. The reported response in some patients with erythema nodosum lesions to heparinoid ointment under occlusion supports this proposed mechanism of action.¹⁷⁴ On the other hand, potassium iodide also inhibits neutrophil chemotaxis.¹⁷⁵ Potassium iodide is contraindicated during pregnancy, because it can produce a goiter in the fetus. Severe hypothyroidism secondary to exogenous intake of iodide has been also described in patients with erythema nodosum treated with potassium iodide.¹⁷⁶

Systemic corticosteroids are rarely indicated in erythema nodosum and before these drugs are administered an underlying infection should be ruled out. When administered, prednisone in a dosage of 40 mg per day has been followed by resolution of the nodules in few days. Intralesional injection of triamcinolone acetonide, in a dosage of 5 mg/mL, into the center of the nodules may cause them to resolve. Some patients may respond to a course of colchicine, 0.6 to 1.2 mg twice a day,^{177,178} and hydroxychloroquine 200 mg twice a day has been also reported to be useful in a recent report.¹⁷⁹

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