Painful Subcutaneous Nodules of the Lower Extremities

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Painful subcutaneous nodules of the lower extremities are dermatologic manifestations that may be associated with multiple underlying etiologies. Various infectious diseases, autoimmune disorders, and physical and chemical agents may precipitate such a clinical presentation. Keeping the differential diagnosis in mind, appropriate medical workup is essential to accurately diagnose and treat underlying disorders.

Painful subcutaneous nodules of the lower extremities are cutaneous processes that tend to be attributed to a variety of underlying medical conditions. Infectious diseases, sarcoidosis, reactions to medications, autoimmune disorders, and malignancies are some examples of underlying disorders that may simulate such a clinical presentation. A clearly definable cause may be determined by generating a complete differential diagnosis, which is necessary for proper workup and effective management of potentially serious underlying conditions.

CASE REPORT

A 66-year-old white woman presented with pain in the left lower extremity of 1 years' duration. Prolonged standing exacerbated the pain and resulted in erythema. The patient reported sometimes having symptoms of pruritus along with a burning sensation. The patient had a medical history of hypothyroidism.

Physical examination revealed tender, indurated, erythematous to hyperpigmented nodules on the left lower extremity with evidence of edema and varicose veins (Figure 1). A 5-mm punch biopsy specimen revealed dermal sclerosis with compact eosinophilic collagen bundles and slight thickening of subcutaneous septae with sparing of the overlying epidermis (Figure 2A). The subcutaneous tissue exhibited microcyst, lipomembranous changes, and evidence of fat necrosis. Blood vessels were thickened with an area of calcification and mild superficial perivascular infiltration of lymphocytes also was present (Figure 2B). A diagnosis of lipodermatosclerosis was highly suggested.

LIPODERMATOSCLEROSIS

Lipodermatosclerosis is a condition that predominately affects patients in the setting of chronic venous insufficiency. A retrospective study of 97 participants demonstrated lipodermatosclerosis was more common in women (87%), with a mean participant age of 62 years (range, 25–88), a mean body mass index of 34.3 (range, 17.8–71.5), and bilateral involvement of lower extremities in 45% of participants.[1]

In this condition, failure of venous blood return and increased capillary pressure lead to stasis dermatitis and changes often occur in the deeper dermis and subcutis.

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Figure 1. Tender, indurated, erythematous to hyperpigmented nodules on the left lower extremity with evidence of erythema and varicose veins.

Early in this condition, superficial capillaries are damaged and vascular fragility leads to repeated hemorrhage in the dermis that causes an erythematous and hyperpigmented discoloration of the lower extremities due to hemosiderin deposition. Persistent edema, fibrosis, and ulceration eventually develop in some cases.[2] Venous liposclerosis and potential venous ulceration are caused by the deposition of an impermeable fibrin cuff surrounding dermal capillaries that results from venous hypertension and aggravated by a reduction of blood flow and tissue fibrinolytic activity.[3] Fibrin deposition also is responsible for blocking oxygen diffusion that leads to local hypoxia and ultimately results in ulceration.[4] In acute lipodermatosclerosis the leading clinical symptom is severe unremitting pain accompanied by extreme skin sensitivity. In the acute setting compression therapy is intolerable for the patient.[5] The lesions may occur for several months and develop into chronic lipodermatosclerosis, which is a more common form. Typically, the distal third of the lower extremity is affected by circumferential, erythematous, edematous telangiectatic plaques that demonstrate hyperpigmentation, induration, and depressed lesions with the characteristic "inverted bottle" or "piano leg" appearance resulting from atrophy of the subcutaneous tissue secondary to deep fibrosis.[6] Histopathologic examination of early lesions shows superficial perivascular infiltration of lymphocytes involving the fibrous trabeculae and peripheries of the fat lobules. With time lesions show progressive fibrosis and sclerosis of the septa with gradual obliteration of fat lobules. Late stages of these lesions exhibit sclerosis of the septa with diminished or absent inflammatory cells.[6]

PANNICULITIS

Panniculitis is a term used to describe a wide spectrum of disease manifestations defined by infiltration of the subcutaneous tissue by inflammatory or neoplastic cells. Classification of panniculitis relies on histologic differentiation of predominant inflammation in the septae or within the fat lobules.[2] Therefore, panniculitis is categorized into lobular or septal subgroups, but because a clear distinction often is not possible a mixed lobular/septal pattern commonly is designated. Various forms of panniculitis may present as painful subcutaneous nodules of the lower extremities, which are discussed later in this article.

ERYTHEMA NODOSUM

Erythema nodosum (EN) is the most common form of septal panniculitis.[7] A painful, nodular, erythematous eruption that represents a hypersensitivity reaction to a variety of antigenic stimuli, EN may be associated with several disease states or medications.[8] Most cases appear between the second and fourth decades of life but can occur at any age. Studies have demonstrated EN occurs 3 to 6 times more commonly in women than in men.[7] Typically, EN presents as a sudden onset of erythematous, indurated, painful, warm nodules ranging from 2 to 6 cm mostly on the anterior lower legs often in a bilateral distribution. The nodules turn livid red or purplish in hue during the following days until finally exhibiting a yellowish appearance. The eruption lasts for 3 to 6 weeks but may persist longer with potential frequent recurrences.[9] Histopathology of EN demonstrates
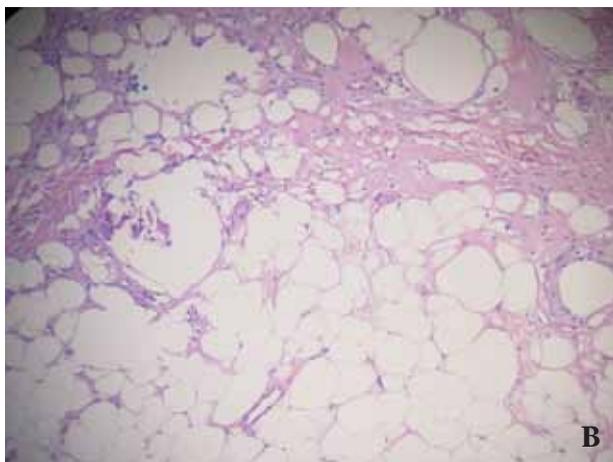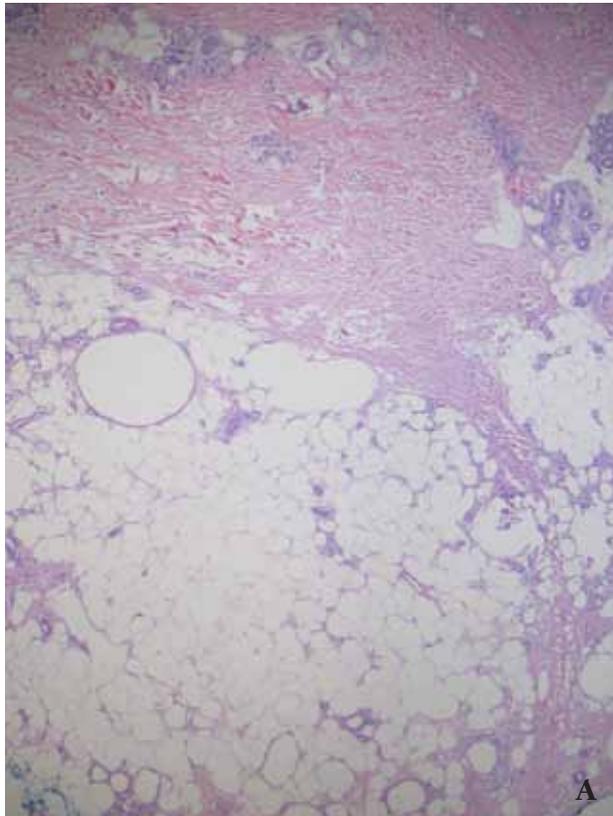
Figure 2. Dermal sclerosis with compact eosinophilic collagen bundles and slight thickening of subcutaneous septae (H&E original magnification ×10)(A). Subcutaneous tissue exhibits microcysts, lipomembranous changes, and evidence of fat necrosis (H&E, original magnification ×40)(B).

predominately septal panniculitis with inflammation in the panniculus and around blood vessels in the septum and adjacent fat.[10]

Although approximately 55% of cases of EN are idiopathic, there are possible identifiable causes. β-Hemolytic streptococcal infections are the most common identifiable cause of EN in children and also may be a causative agent in adults. Usually the cutaneous lesions appear 2 to 3 weeks after an episode of streptococcal pharyngitis.[11]

Clinical evaluation of patients with EN should include taking a thorough medical history, throat cultures for evaluation of group A streptococcus, and obtaining streptococcal antistreptolysin O titers.

Other infectious causes of EN have been linked to tuberculosis, *Yersinia* infection, lymphogranuloma venereum, *Mycoplasma* infection, coccidioidomycosis, histoplasmosis, and more rarely Epstein-Barr virus and hepatitis B and C viruses.[12]

Erythema nodosum is the most common cutaneous manifestation of sarcoidosis that occurs in up to 39% of cases.[13] Sarcoidosis with bilateral hilar adenopathy, polyarthritis, and EN is called *Lofgren syndrome,* which tends to be self-limiting and resolves in 6 to 8 weeks, whereas sarcoidosis can be chronic and progressive.[14] Therefore, radiologic testing should be performed in all patients with EN to rule out associated pulmonary disease.

Hypersensitivity reactions to medications such as oral contraceptives, bromides, antibiotics such as amoxicillin, and sulfonamides may cause EN. Erythema nodosum also has been associated with pregnancy and inflammatory bowel disease.

α_1-ANTITRYPSIN DEFICIENCY PANNICULITIS

α_1-Antitrypsin (AAT) deficiency panniculitis is categorized as a mixed, lobular, and septal form of panniculitis. α_1-Antitrypsin is a protease inhibitor produced by the liver that is active against trypsin and other serine proteases.[2] It is a serum protein produced by autosomal codominant alleles that determine its serum concentration. Individuals homozygous for the Z allele protease inhibitor phenotype ZZ (PiZZ) have only 10% to 15% of the normal protease inhibitor serum concentration that leads to an increased risk for development of chronic obstructive pulmonary disease and panniculitis.[15] Clinically, AAT deficiency panniculitis is characterized by recurrent, painful, erythematous, subcutaneous nodules commonly located on the lower extremities and occasionally in areas of physical trauma.[2,15] Nodules may break down and weep a clear, serous, or oily discharge.[16] Trauma initiates uninhibited complement activation, inflammation, endothelial cell damage, and tissue injury due to unopposed elastase activity. Histopathologic features exhibit 2 patterns of panniculitis, a lobular form with fat necrosis and a septal form with proteolysis of collagen and necrosis of the fibrous trabeculae.[17] Diffuse neutrophilic infiltration of the reticular dermis and

liquefactive necrosis of the dermis and fibrous septa with resultant separation of fat lobules is thought to be characteristic of AAT deficiency panniculitis.[18]

PANCREATIC PANNICULITIS

Pancreatic panniculitis also is a form of mixed panniculitis. It is a rare condition in which necrosis of fat occurs in subcutaneous tissue and elsewhere in the setting of pancreatic disease.[19] Several diseases have been associated with pancreatic panniculitis, such as acute or chronic pancreatitis, pancreatic pseudocyst, pancreatic carcinoma, and traumatic pancreatitis. Cutaneous lesions may precede other manifestations of underlying pancreatic disease by several weeks to months.[20] The release of pancreatic lipolytic enzymes, particularly lipase and amylase, into the systemic circulation from a diseased pancreas is thought to be the underlying pathogenesis leading to enzymatic destruction of fat.[21] Clinically, pancreatic panniculitis exhibits painful erythematous nodules, usually in the lower extremities, but may fluctuate and occur at other sites. They may be indistinguishable from EN. However, these lesions may be more widespread than typical EN and may break down and drain a creamy oily substance resulting from liquefactive necrosis.[6] Furthermore, patients commonly may exhibit systemic involvement including fever, arthralgia, and arthritis. Histopathologic examination demonstrates necrosis of adipocytes with formation of ghost cells, thickened eosinophilic cell walls, and absence of nuclei. There also is variable calcification resulting in a basophilic lamellation that constitutes saponification.[22]

ERYTHEMA INDURATUM

Erythema induratum, also known as nodular vasculitis, is a form of mixed panniculitis with mainly lobular infiltrate. It was first described by Bazin in 1861[23] as a skin eruption resulting from a hypersensitivity reaction to tuberculosis.[24] However, in 1945, Montgomery et al,[25] while acknowledging tuberculosis-associated erythema induratum, coined the term *nodular vasculitis* for chronic inflammatory nodules of the legs that showed similar histologic changes to EN. Therefore, Bazin disease is a term currently reserved for erythema induratum with concurrent *Mycobacterium tuberculosis* infection. In Hong Kong between 1993 and 2002, erythema induratum was the most common form of cutaneous tuberculosis found mainly on the lower extremities and more frequently in women.[26] The resurgence of tuberculosis, particularly with the human immunodeficiency virus pandemic, has led to an increased incidence of Bazin type erythema induratum, at times being the essential factor that leads to the correct diagnosis of tuberculosis infection.[27] Clinically,

this form of panniculitis presents with chronic, recurrent, often bilateral, tender, subcutaneous nodules, which may ulcerate and eventually resolve with atrophic scars. Initially, lesions are erythematous and found predominantly on the lower third of the legs, most commonly on the calves. Diagnosis of erythema induratum and differentiation from Bazin type is made by polymerase chain reaction testing.[28] Histopathologic features of these lesions are nonspecific. In early lesions, neutrophils are interspersed throughout the fat lobules where ischemic necrosis is found. The fat lobules also have extensive inflammatory infiltrates consisting of lymphocytes, multinucleated giant cells, and epithelioid histiocytes, which contribute to the granulomatous inflammation and caseation necrosis. Although not an absolute finding, vasculitis also may be identified with the theory that venous vessels primarily are involved and arteries are affected as they become trapped within the areas of caseation.[6]

FACTITIOUS PANNICULITIS

Factitious panniculitis is a form of subcutaneous tissue injury that is either self-induced or produced by external agents. Most commonly, factitious panniculitis is caused by self-injection of different foreign substances. Paraffinoma, also known as sclerosing lipogranuloma, is a form of factitious panniculitis caused by injection of liquid paraffin (mineral oil). Such substances reportedly have been injected for cosmetic purposes in the scrotum, lower extremities, breasts, and face.[29] Painful subcutaneous nodules may be present on physical examination and may be ulcerated. Histopathologic evaluation reveals a classic "Swiss cheese" pattern with vacuoles within the fibrous fatty tissue that consist of abundant macrophages and foreign body multinucleated giant cells.[30] Polarizing microscopy may be used to detect the presence of refractile foreign material within tissue sections. Traumatic forms of panniculitis may result from blunt trauma that leads to fat necrosis and soft tissue injuries particularly on the shins, thighs, breasts, arms, and buttocks with women being especially susceptible.[31] The initial injury causes bruising of the skin with hematoma and deeper indurated lesions in the subcutis appear later. Focal liquefaction may occur in the injured fat leading to discharge.[32]

OTHER

Polyarteritis nodosa (PAN) is a multisystem necrotizing vasculitis of small- and medium-sized arteries originally described by Kussmaul and Maier in 1866.[33] A cutaneous variant of PAN exists that is limited to the skin; however, the systemic form of PAN additionally may target the kidneys, gastrointestinal tract, and joints.[34] Cutaneous

PAN primarily involves the lower extremities.[35] Polyarteritis nodosa is diagnosed most commonly in middle-aged patients with peak incidence in the sixth decade of life.[36]

Although PAN may be idiopathic, there have been data suggesting certain associations. The cause of PAN has been attributed to an autoimmune etiology, which is supported by direct immunofluorescence studies that show immune complex deposits of IgM, C3, and fibrin.[37] Hepatitis B virus also has been attributed to the pathogenesis of PAN, and it has been suggested that circulating hepatitis B virus antigen and antibody immune complexes play a role in the pathogenesis of the vasculitic lesions.[38] Streptococcal infection also has been reported to be associated with this immune complex–mediated disease, with patients reported to have previous upper respiratory tract infection with pharyngitis, elevated antistreptolysin O titer, or positive streptococcus throat culture.[39] Crohn disease, ulcerative colitis, and hepatitis C virus infection also have been associated with PAN.[40,41]

An estimated 25% of classic PAN cases will have cutaneous involvement, most commonly deep painful nodules, but can also present as ulcers and livedo reticularis on the lower extremities.[42] The erythematous to bluish subcutaneous nodules, ranging from 0.5 cm to 3 cm in diameter, follow the course of involved arteries. A livedo reticularis pattern usually is seen after a flare and radiates out from new nodular lesions in a characteristic "starburst" appearance.[43] Multiple small nodules less than 1 cm in size, numbering as many as 100 in lesions also have been reported.[41] Arthralgia, myalgia, neuropathy, and constitutional symptoms also may be present.[44] Skin lesions in cutaneous PAN are indistinguishable from classic PAN.[42] A deep wedge biopsy is the preferred technique for obtaining a specimen.[45] Histologically, PAN is characterized by 4 stages. The initial acute stage exhibits endothelial loss and fibrin thrombi with infiltration of neutrophils. The second, subacute stage demonstrates fibrinoid necrosis with mixed cell infiltrates and fibrinoid leakage into the media from the internal elastic lamina. Intimal fibroblastic proliferation and perivascular infiltrates are seen in the third, reparative stage, and the final healed stage shows minimal cellular inflammation with occlusive intimal thickening.[46]

Neuroendocrine tumors arise from neuroendocrine cells of neural crest origin. Metastases to the skin may be a late manifestation of advanced disease and may present as extremely painful subcutaneous nodules.[47] Carcinoid tumors, particularly in elderly patients, may metastasize to the skin with cutaneous findings being the initial recognizable manifestation of tumors from sites such as the bronchi and small intestine.[48] One possible explanation of the pain caused by some skin metastases is that it may be due to the infiltration of nerve bundles by tumor deposits.[47] A second theory suggests that different peptide hormones and vasoactive agents caused by carcinoid tumors, such as kallikrein and serotonin, lead to local necrosis and fibrosis that result in severe pain.[49] Histopathologically, cutaneous metastases of carcinoid tumors demonstrate islands, nests, and cords of uniform cells with round nuclei and clear or eosinophilic cytoplasm with occasional eosinophilic granules.[50] Clinical presentation of painful subcutaneous nodules should include possible cutaneous metastasis in the differential diagnosis.[51]

SUMMARY

Painful subcutaneous nodules of the lower extremities are a challenging clinical presentation to appropriately diagnose and manage. Because of the potential severity of possible underlying etiologies, a proper workup and complete differential diagnosis are important. Appropriate diagnostic tests, sufficient biopsy, and careful histologic analysis should provide assistance to properly identify, diagnose, and treat these underlying conditions.

REFERENCES

1. Bruce AJ, Bennett DD, Lohse CM, et al. Lipodermatosclerosis: review of cases evaluated at Mayo Clinic. *J Am Acad Dermatol*. 2002;46:187-192.
2. Phelps RG, Shoji T. Update on panniculitis. *Mt Sinai J Med*. 2001;68:262-267.
3. Burnand K, Clemenson G, Morland M, et al. Venous lipodermatosclerosis: treatment by fibrinolytic enhancement and elastic compression. *Br Med J*. 1980;280:7-11.
4. Weingarten MS. State-of-the-art treatment of chronic venous disease. *Clin Infect Dis*. 2001;32:949-954.
5. Greenberg AS, Hasan A, Montalvo BM, et al. Acute lipodermatosclerosis is associated with venous insufficiency. *J Am Acad Dermatol*. 1996;35:566-568.
6. Requena L, Sánchez Yus E. Panniculitis. part II. Mostly lobular panniculitis. *J Am Acad Dermatol*. 2001;45:325-361.
7. Requena L, Yus ES. Panniculitis. part I. Mostly septal panniculitis. *J Am Acad Dermatol*. 2001;45:163-183.
8. Requena L, Requena C. Erythema nodosum. *Dermatol Online J*. 2002;8:4.
9. Wu YL, Tsai MH, Liu LL. Erythema nodosum and hepatitis B: a case report and literature review. *J Microbiol Immunol Infect*. 2008;41:437-439.
10. Fitzpatrick TB, Freedberg IM. *Fitzpatrick's Dermatology in General Medicine*. 6th ed. New York, NY: McGraw-Hill; 2003.
11. Kakourou T, Drosatou P, Psychou F, et al. Erythema nodosum in children: a prospective study. *J Am Acad Dermatol*. 2001;44: 17-21.
12. Schwartz RA, Nervi SJ. Erythema nodosum: a sign of systemic disease. *Am Fam Physician*. 2007;75:695-700.
13. Wilsher M. Seasonal clustering of sarcoidosis presenting with erythema nodosum. *Eur Respir J*. 1998;12:1197-1199.
14. Cribier B, Caille A, Heid E, et al. Erythema nodosum and associated diseases. a study of 129 cases. *Int J Dermatol*. 1998;37: 667-672.

15. Gross B, Grebe M, Wencker M, et al. New findings in PiZZ alpha1-antitrypsin deficiency-related panniculitis. demonstration of skin polymers and high dosing requirements of intravenous augmentation therapy. *Dermatology*. 2009;218: 370-375.

16. Stoller JK, Piliang M. Panniculitis in alpha-1 antitrypsin deficiency: a review. *Clin Pulmonary Med*. 2008;15:113-117.

17. Su WP, Smith KC, Pittelkow MR, et al. Alpha 1-antitrypsin deficiency panniculitis: a histopathologic and immunopathologic study of four cases. *Am J Dermatopathol*. 1987;9:483-490.

18. Loche F, Tremeau-Martinage C, Laplanche G, et al. Panniculitis revealing qualitative alpha 1 antitrypsine deficiency (MS variant). *Eur J Dermatol*. 1999;9:565-567.

19. Dahl PR, Su WP, Cullimore KC, et al. Pancreatic panniculitis. *J Am Acad Dermatol*. 1995;33:413-417.

20. Hughes SH, Apisarnthanarax P, Mullins F. Subcutaneous fat necrosis associated with pancreatic disease. *Arch Dermatol*. 1975;111: 506-510.

21. Förström TL, Winkelmann RK. Acute, generalized panniculitis with amylase and lipase in skin. *Arch Dermatol*. 1975;111: 497-502.

22. Lewis CT 3rd, Tschen JA, Klima M. Subcutaneous fat necrosis associated with pancreatic islet cell carcinoma. *Am J Dermatopathol*. 1991;13:52-56.

23. Bazin PAE. *Leçons théoriques et cliniques sur la scrofule, considérée en ellemême et dans ses rapports avec la syphilis, la dartre et l'arthritis*. Paris, France: Delahaye; 1861:145-501.

24. Cho KH, Lee DY, Kim CW. Erythema induratum of Bazin. *Int J Dermatol*. 1996;35:802-808.

25. Montgomery H, O'Leary PA, Barker NW. Nodular vascular diseases of the legs: erythema induratum and allied conditions. *JAMA*. 1945;128:335-341.

26. Ho CK, Ho MH, Chong LY. Cutaneous tuberculosis in Hong Kong: an update. *Hong Kong Med J*. 2006;12:272-277.

27. Feuer J, Phelps RG, Kerr LD. Erythema nodosum versus erythema induratum: a crucial distinction enabling recognition of occult tuberculosis. *J Clin Rheumatol*. 1995;1:357-363.

28. Schneider JW, Jordaan HF, Geiger DH, et al. Erythema induratum of Bazin. a clinicopathological study of 20 cases and detection of *Mycobacterium tuberculosis* DNA in skin lesions by polymerase chain reaction. *Am J Dermatopathol*. 1995;17:350-356.

29. Hazani R, Engineer N. Surreptitious injection of mineral oil: a case report of sclerosing lipogranulomatosis. *Ann Plast Surg*. 2008;61:555-558.

30. Krayenbühl B, Panizzon RG. Silicone granuloma. *Dermatology*. 2000;200:360-362.

31. Braun-Falco O, Plewig G, Bergdorf WHC, et al. *Dermatology*. 2nd ed. New York, NY: Springer-Verlag; 2000:867.

32. Weedon D. *Skin Pathology*. New York, NY: Churchill Livingstone; 1997:452.

33. Kussmaul A, Maier R. Ueber eine bisher nicht beschriebene eigenthumliche arteriener-krankung, die mit morbus brightii und rapid fortschreitender allgemeiner muskellahmung einhergeht. *Dtsch Arch Klin Med*. 1866;1:484-518.

34. Sheth AP, Olson JC, Esterly NB. Cutaneous polyarteritis nodosa of childhood. *J Am Acad Dermatol*. 1994;31:561-566.

35. Diaz JL, Winkelmann RK. Cutaneous periarteritis nodosa: a study of 33 cases. In: Wolff K, Winkelmann RK; eds. *Major Problems in Dermatology*. Philadelphia, PA: WB Saunders; 1980.

36. Mahr A, Guillevin L, Poissonnet M, et al. Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome in a French urban multiethnic population in 2000: a capture-recapture estimate. *Arthritis Rheum*. 2004;51:92-99.

37. Soufir N, Descamps V, Crickx B, et al. Hepatitis C virus infection in cutaneous polyarteritis nodosa: a retrospective study of 16 cases. *Arch Dermatol*. 1999;135:1001-1002.

38. Trepo CG, Zucherman AJ, Bird RC, et al. The role of circulating hepatitis B antigen/antibody immune complexes in the pathogenesis of vascular and hepatic manifestations in polyarteritis nodosa. *J Clin Pathol*. 1974;27:863-868.

39. Halle F, Brousse N, Prieur AM. Cutaneous polyarteritis nodosa: study of eight cases. *J Rheumatol*. 1992;19(suppl 33):119.

40. Goslen JB, Graham W, Lazarus GS. Cutaneous polyarteritis nodosa. report of a case associated with Crohn's disease. *Arch Dermatol*. 1983;119:326-329.

41. Gibson LE, Su WP. Cutaneous vasculitis. *Rheum Dis Clin North Am*. 1995;21:1097-1113.

42. Kim LH. Polyarteritis nodosa. *Dermatol Online J*. 2001;7(1):17.

43. Lindberg K. Ein beitrag zur kenntnis der periarteritis nodosa. *Acta Med Scand*. 1931;76:183-225.

44. Daoud MS, Hutton KP, Gibson LE. Cutaneous periarteritis nodosa: a clinicopathological study of 79 cases. *Br J Dermatol*. 1997;136:706-713.

45. Khoo BP, Ng SK. Cutaneous polyarteritis nodosa: a case report and literature review. *Ann Acad Med Singapore*. 1998;27: 868-872.

46. Ishibashi M, Chen KR. A morphological study of evolution of cutaneous polyarteritis nodosa. *Am J Dermatopathol*. 2008;30:319-326.

47. Rodriguez G, Villamizar R. Carcinoid tumor with skin metastasis. *Am J Dermatopathol*. 1992;14:263-269.

48. Keane J, Fretzin DF, Jao W, et al. Bronchial carcinoid metastatic to skin. Light and electron microscopic findings. *J Cutan Pathol*. 1980;7:43-49.

49. Zuetenhorst JM, van Velthuysen ML, Rutgers EJ, et al. Pathogenesis and treatment of pain caused by skin metastases in neuroendocrine tumours. *Neth J Med*. 2002;60:207-211.

50. Reingold IM, Escovitz WE. Metastatic cutaneous carcinoid. report of a case of functioning malignant bronchial carcinoid. *Arch Dermatol*. 1960;82:971-975.

51. Quaedvlieg PF, Visser O, Lamers CB, et al. Epidemiology and survival in patients with carcinoid disease in The Netherlands. an epidemiological study with 2391 patients. *Ann Oncol*. 2001;12:1295-1300. ■