Diverse manifestations associated with a single dermatosis

JENNIFER CLAY CATHER, MD, AND JOHN CHRISTIAN CATHER, MD

The patients in *Figures 1* through *3* have the same dermatologic disorder. What is the diagnosis, and what would be appropriate treatment?

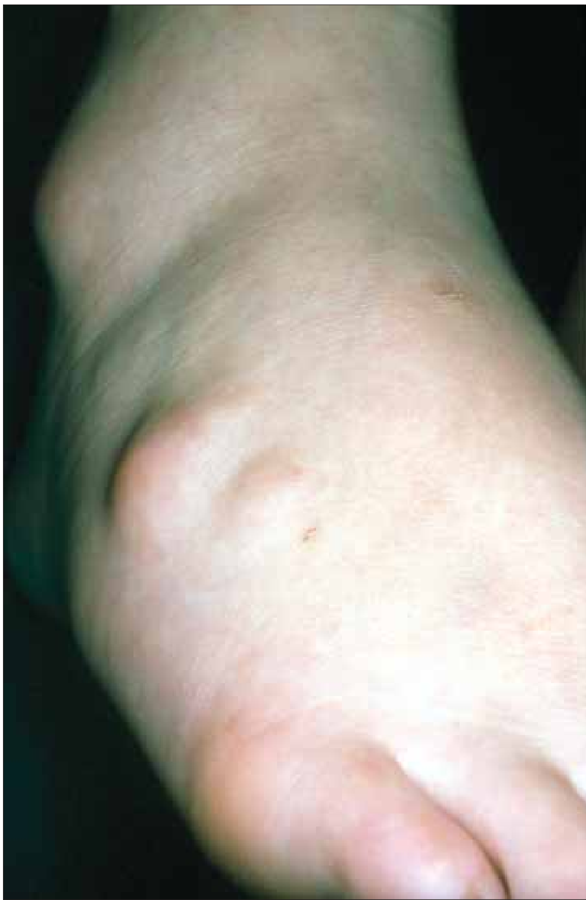

Figure 1. Multiple asymptomatic subcutaneous nodules on the dorsal foot of a 5-year-old girl.

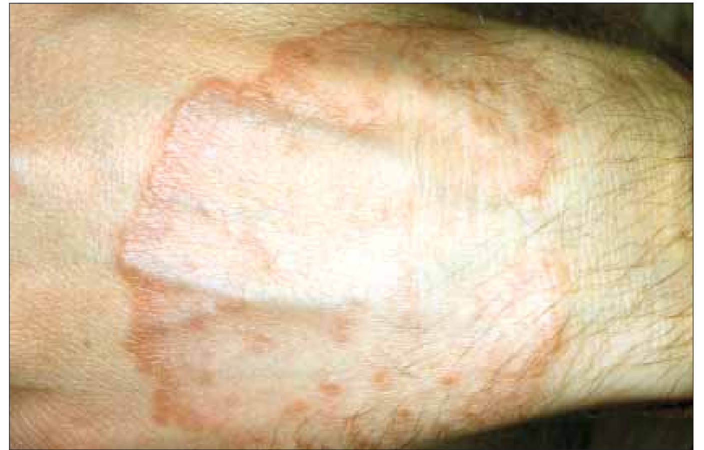

Figure 2. A solitary violaceous plaque with elevated margins on the dorsal hand of a 35-year-old man.

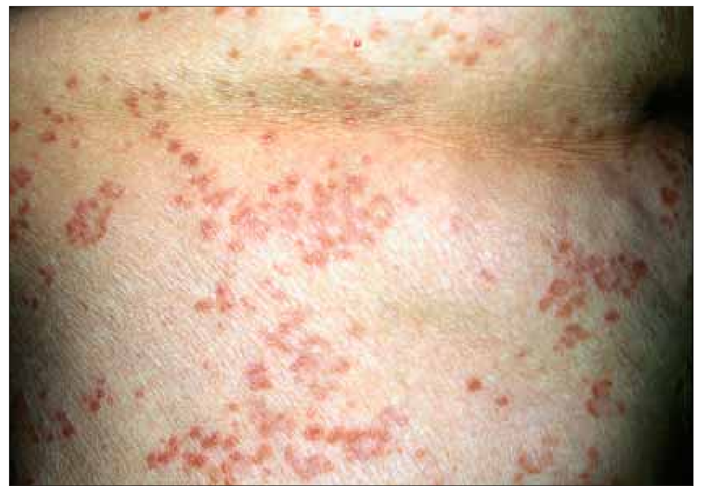

Figure 3. Widespread erythematous papules—some coalescing to form rings—on the back of an elderly diabetic woman.

From the Division of Dermatology, Department of Internal Medicine, Baylor University Medical Center (Jennifer Cather), and Texas Dermatology Associates (both authors), Dallas, Texas.

Corresponding author: Jennifer Clay Cather, MD, 5310 Harvest Hill Road, Suite 260, Dallas, Texas 75230.

DIAGNOSIS: Granuloma annulare.

DISCUSSION

Granuloma annulare is a benign, self-limited dermatosis of unknown etiology. Approximately two thirds of those affected are adults <30 years of age, and women are affected twice as often as men (1–3). Although the lesions usually arise for no known reason, most dermatologists believe that the disorder is immunologically mediated *(Table 1)*.

Clinically, the cutaneous lesions are categorized as localized, generalized, subcutaneous, or perforating *(Table 2)*. Localized lesions, the most common type, occur in children and young adults. Fifty percent of these patients have only one lesion. Generalized lesions, on the other hand, are seen only in 15% of reported cases and usually affect patients younger than 10 years or older than 40. Subcutaneous lesions may mimic rheumatoid nodules; however, arthritis is absent, and the test for rheumatoid factor is negative. Lastly, perforating lesions were reported in one series to be associated with diabetes in 30% of patients (24).

Patients with granuloma annulare are typically healthy. The exact relation between granuloma annulare and diabetes, necrobiotic granuloma, and rheumatoid nodules has been debated (24, 25). Granuloma annulare may coexist with rheumatoid arthritis and diabetes mellitus (26). Additionally, adult women with localized granuloma annulare may have an increased risk of autoimmune thyroiditis (27). Patients with painful lesions or lesions in atypical locations may have an underlying lymphoma (19–21, 28).

Routine laboratory tests usually yield normal results and are not recommended. A skin biopsy will confirm the diagnosis. Low-magnification examination of sections stained with hematoxylin and eosin reveals foci of granulomatous inflammation at the level of the subpapillary plexus of blood vessels (localized or generalized lesions) or deeper in the deep dermis or adipose (subcutaneous lesions). The foci have a central core of smudged basophilic degenerated connective tissue (necrobiosis) surrounded by a histiocytic infiltrate. Vascular damage is evident without an associated vasculitis. Serial sections of perforating lesions have a communication between the area of necrobiosis and the overlying ulcer. Immunohistochemical stains reveal the presence of $CD4^+$ lymphocytes and abundant interleukin 2 pro-

Table 1. Precipitating factors for granuloma annulare

Viruses	Varicella zoster virus (4, 5), adenovirus, Epstein-Barr, HIV (6, 7), hepatitis C (8)
Trauma	Bite (9), waxing (10), tattoo (11), tuberculin skin test
Vaccines	Bacille Calmette-Guérin (12), antitetanus (13), hepatitis B (14)
Drugs	Allopurinol (15), amlodipine (16)
Other	Erythema multiforme minor (17), malignancies (18–21)

Table 2. Types of granuloma annulare

Type	Characteristics
Localized	Usually in young adults or children. Mildly erythematous/violaceous annular plaques with no scaling on the dorsal hand or foot. Additionally, papules or nodules may occur on the fingers (1–3, 22).
Generalized	Numerous (may be hundreds) 1- to 2-mm slightly violaceous or waxlike papules (rarely patches) on the trunk, neck, forearms, legs, and extensor elbows, which may coalesce to form rings. Pruritic and recurrent lesions are more refractory to therapy (1–3).
Subcutaneous	Large solitary or multiple painless flesh-colored subcutaneous nodules on the hands, feet, legs, buttocks, or scalp (23). Most common in children. Lesions usually resolve without therapy. Recurrent lesions are common and do not mandate rebiopsy.
Perforating	Small papules with central ulceration localized on the hands or generalized.

Table 3. Differential diagnosis of granuloma annulare (30)

Type	Differential diagnosis
Localized/generalized	Amyloid
	Idiopathic: Annular lichen planus, erythema annulare centrifugum, erythema multiforme, sarcoid
	Infections: Cat-scratch disease, creeping eruption, erythema migrans of Lyme disease, syphilis, tinea corporis, mycobacterium (31)
	Insect bites
	Mycosis fungoides (32, 33)
	Subacute lupus erythematosus
	Xanthomas
Subcutaneous	Erythema elevatum diutinum, rheumatoid nodules, syphilis (34)
Perforating	Kyrle's disease

Table 4. Treatment of granuloma annulare

Topical	Corticosteroids (intralesional or topical with occlusion), vitamin E, imiquimod (36)
Destruction	Cryotherapy (37), laser therapy
Systemic	Psoralen and ultraviolet A (38) Isotretinoin (39) Cyclosporine (40) Nicotinamide (41) Niacinamide Dapsone (42) Interferon (43) Fumaric acid esters (44) 5-lipoxygenase inhibitor (zileuton) and systemic vitamin E (45) Tranilast (46) Pentoxyfylline, dipyridamole, salicylates Chlorpropamide Potassium iodide Thyroxine Antimalarials Chlorambucil

duction (29). Clinical correlation is important in the diagnosis of granuloma annulare because many entities can mimic the disorder both clinically and histologically *(Table 3)*.

In general, granuloma annulare is considered a self-limiting disease, with lesions expected to resolve within 2 years for >50% of patients (1–3). Lesions may recur intermittently, usually at the original site, and recurrent lesions resolve more quickly. Patients with generalized lesions usually have a more chronic course (1–3). Additionally, a chronic course is seen in patients with Blau syndrome, an autosomal-dominant syndrome that includes skin granulomas, granulomatous arthritis, and iritis (35).

Therapy is indicated only if patients are symptomatic or if the lesions are cosmetically unacceptable. While numerous therapies have been reported to hasten resolution, intralesional or topical glucocorticosteroids for localized lesions and phototherapy for widespread lesions are used most often *(Table 4)*.

1. Tan HH, Goh CL. Granuloma annulare: a review of 41 cases at the National Skin Centre. *Ann Acad Med Singapore* 2000;29:714–718.
2. Wells RS, Smith MA. The natural history of granuloma annulare. *Br J Dermatol* 1963;75:199–205.
3. Barron DF, Cootauco MH, Cohen BA. Granuloma annulare. A clinical review. *Lippincotts Prim Care Pract* 1997;1:33–39.
4. Gibney MD, Nahass GT, Leonardi CL. Cutaneous reactions following herpes zoster infections: report of three cases and a review of the literature. *Br J Dermatol* 1996;134:504–509.
5. Ohata C, Shirabe H, Takagi K, Kawatsu T. Granuloma annulare in herpes zoster scars. *J Dermatol* 2000;27:166–169.
6. O'Moore EJ, Nandawni R, Uthayakumar S, Nayagam AT, Darley CR. HIV-associated granuloma annulare (HAGA): a report of six cases. *Br J Dermatol* 2000;142:1054–1056.
7. Toro JR, Chu P, Yen TS, LeBoit PE. Granuloma annulare and human immunodeficiency virus infection. *Arch Dermatol* 1999;135:1341–1346.
8. Granel B, Serratrice J, Rey J, Bouvier C, Weiller-Merli C, Disdier P, Pellissier JF, Weiller PJ. Chronic hepatitis C virus infection associated with a generalized granuloma annulare. *J Am Acad Dermatol* 2000;43:918–919.
9. Trujillo-Santos AJ, Aguiar-Garcia F, Gonzalez-Hermoso C. Subcutaneous nodules after a cat bite. *Arch Intern Med* 2001;161:2043–2044.
10. Young HS, Coulson IH. Granuloma annulare following waxing induces pseudofolliculitis—resolution with isotretinoin. *Clin Exp Dermatol* 2000; 25:274–276.
11. Gradwell E, Evans S. Perforating granuloma annulare complicating tattoos. *Br J Dermatol* 1998;138:360–361.
12. Kakurai M, Kiyosawa T, Ohtsuki M, Nakagawa H. Multiple lesions of granuloma annulare following BCG vaccination: case report and review of the literature. *Int J Dermatol* 2001;40:579–581.
13. Baykal C, Ozkaya-Bayazit E, Kaymaz R. Granuloma annulare possibly triggered by antitetanus vaccination. *J Eur Acad Dermatol Venereol* 2002;16:516–518.
14. Wolf F, Grezard P, Berard F, Clavel G, Perrot H. Generalized granuloma annulare and hepatitis B vaccination. *Eur J Dermatol* 1998;8:435–436.
15. Brechtel B, Kolde G. [Granuloma annulare disseminatum as a rare side effect of allopurinol.] *Hautarzt* 1996;47:143.
16. Lim AC, Hart K, Murrell D. A granuloma annulare-like eruption associated with the use of amlodipine. *Australas J Dermatol* 2002;43:24–27.
17. Abraham Z, Feuerman EJ, Schafer I, Feinmesser M. Disseminated granuloma annulare following erythema multiforme minor. *Australas J Dermatol* 2000;41:238–241.
18. Cohen PR. Granuloma annulare associated with malignancy. *South Med J* 1997;90:1056–1059.
19. Li A, Hogan DJ, Sanusi ID, Smoller BR. Granuloma annulare and malignant neoplasms. *Am J Dermatol* 2003;25:113–116.
20. Setoyama M, Kerdel FA, Byrnes JJ, Kanzaki T. Granuloma annulare associated with Hodgkin's disease. *Int J Dermatol* 1997;36:445–448.
21. Barksdale SK, Perniciaro C, Halling KC, Strickler JG. Granuloma annulare in patients with malignant lymphoma: clinicopathologic study of thirteen new cases. *J Am Acad Dermatol* 1994;31:42–48.
22. Grant I, Mohammed P, Mahaffey PJ. Granuloma annulare in the hand. *J Hand Surg [Br]* 2002;27:556–558.
23. McDermott MB, Lind AC, Marley EF, Dehner LP. Deep granuloma annulare (pseudorheumatoid nodule) in children: clinicopathologic study of 35 cases. *Pediatr Dev Pathol* 1998;1:300–308.
24. Castro A, Hammond R, Potts J. Glucose, insulin HGH, and cortisol plasma levels in granuloma annulare patients during glucose tolerance and cortisone glucose tolerance test. *Clin Biochem* 1974;7:150–160.
25. Nebesio CL, Lewis C, Chuang TY. Lack of an association between granuloma annulare and type 2 diabetes mellitus. *Br J Dermatol* 2002;146:122–124.
26. Tam MM, Meehan CJ. Subcutaneous granuloma annulare in a patient with rheumatoid arthritis and diabetes mellitus. *Australas J Dermatol* 1996; 37:199–201.
27. Vazquez-Lopez F, Pereiro M Jr, Manjon Haces JA, Gonzalez Lopez MA, Soler Sanchez T, Fernandez Coto T, Perez Olivia N, Toribio J. Localized granuloma annulare and autoimmune thyroiditis in adult women: a case-control study. *J Am Acad Dermatol* 2003;48:517–520.
28. Bhushan M, Craven NM, Armstrong GR, Chalmers RJ. Lymphoepithelioid cell lymphoma (Lennert's lymphoma) presenting as atypical granuloma annulare. *Br J Dermatol* 2000;142:776–780.
29. Mempel M, Musette P, Flageul B, Schnopp C, Remling R, Gachelin G, Kourilsky P, Ring J, Abeck D. T-cell receptor repertoire and cytokine profile in granuloma annulare: defining a particular type of cutaneous granulomatous inflammation. *J Invest Dermatol* 2002;118:957–966.
30. Hsu S, Le EH, Khoshevis MR. Differential diagnosis of annular lesions. *Am Fam Physician* 2001;64:289–296.
31. Barr KL, Lowe L, Su LD. *Mycobacterium marinum* infection simulating interstitial granuloma annulare: a report of two cases. *Am J Dermatopathol* 2003;25:148–151.
32. Su LD, Kim YH, LeBoit PE, Swetter SM, Kohler S. Interstitial mycosis fungoides, a variant of mycosis fungoides resembling granuloma annulare and inflammatory morphea. *J Cutan Pathol* 2002;29:135–141.
33. Jouary T, Beylot-Barry M, Vergier B, Paroissien J, Doutre MS, Beylot C. Mycosis fungoides mimicking granuloma annulare. *Br J Dermatol* 2002;146: 1102–1104.
34. Wu SJ, Nguyen EQ, Nielsen TA, Pellegrini AE. Nodular tertiary syphilis mimicking granuloma annulare. *J Am Acad Dermatol* 2000;42(2 Pt 2):378–380.
35. Blau EB. Familial granulomatous arthritis, iritis, and rash. *J Pediatr* 1985;107: 689–693.
36. Kuwahara RT, Skinner RB Jr. Granuloma annulare resolved with topical application of imiquimod. *Pediatr Dermatol* 2002;19:368–371.
37. Rouilleault P. CO_2 laser and granuloma annulare. *J Dermatol Surg Oncol* 1988;14:120.
38. Setterfield J, Huilgol SC, Black MM. Generalised granuloma annulare successfully treated with PUVA. *Clin Exp Dermatol* 1999;24:458–460.
39. Adams DC, Hogan DJ. Improvement of chronic generalized granuloma annulare with isotretinoin. *Arch Dermatol* 2002;138:1518–1519.
40. Fiallo P. Cyclosporin for the treatment of granuloma annulare. *Br J Dermatol* 1998;138:369–370.
41. Ma A, Medenica M. Response of generalized granuloma annulare to high-dose nicatinamide. *Arch Dermatol* 1983;119:836–839.
42. Steiner A, Pehamberger H, Wolff K. Sulfone treatment of granuloma annulare. *J Am Acad Dermatol* 1985;13:1004–1008.
43. Weiss JM, Muchenberger S, Schopf E, Simon JC. Treatment of granuloma annulare by local injections with low-dose recombinant human interferon gamma. *J Am Acad Dermatol* 1998;39:117–119.
44. Kreuter A, Gambichler T, Altmeyer P, Brockmeyer NH. Treatment of disseminated granuloma annulare with fumaric acid esters. *BMC Dermatol* 2002;2:5.
45. Smith KJ, Norwood C, Skelton H. Treatment of disseminated granuloma annulare with a 5-lipoxygenase inhibitor and vitamin E. *Br J Dermatol* 2002;146:667–670.
46. Yamada H, Ide A, Sugiura M, Kurihara S, Tajima S. Treatment of granuloma annulare with tranilast. *J Dermatol* 1995;22:354–356.