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Commentary

ERYTHEMA NODOSUM AND PERNICIOUS ANEMIA

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Abstract

Erythema nodosum (EN) often presents as a sudden onset of tender, erythematous, subcutaneous nodules on the legs and ankles. Although rare, pernicious anemia may be related to vitamin B12 deficiency. Discussion of this association in the context of a particular patient is presented.

Erythema nodosum

The clinical picture of EN is distinctive: patients experience the acute onset of indurated, tender, erythematous nodules on the legs, typically in the anterior tibial area. Lesions persist for a few weeks, then fade leaving a characteristic bruise-like appearance [1,2]. Although EN can occur in anyone, the typical patient is a young woman. The classic histologic picture is that of a septal panniculitis without associated vasculitis. In fact, however, the histologic findings of EN can be quite variable including both lobular and septal panniculitis (as was the case in this patient), neutrophilic infiltration, and focal areas of suppuration [3]. This variability relates to the age of the lesions and possibly to different pathogenetic mechanisms associated with the wide variety of inciting causes [1]. During the early, eruptive stage, edema, hemorrhage, thickening of fat septa, and neutrophilic infiltration are the predominant findings. As lesions mature, chronic inflammatory changes ensue. These changes consist of fibrosis and infiltration with lymphocytes, histiocytes, and giant cells. True vasculitis is not a feature of EN [1,4]. The exact pathogenesis of EN has not been completely elucidated. However, in early stages, immune complex deposition and complement activation around blood vessels of fat septa appear to play a role [5,8]. That neutrophils are the earliest infiltrating cells is consistent with a role for immune complexes and complement. As lesions age, cell-mediated immune responses predominate. In studies of erythema nodosum leprosum, B cells are hypothesized to play a role as antigen presenting cells [9].

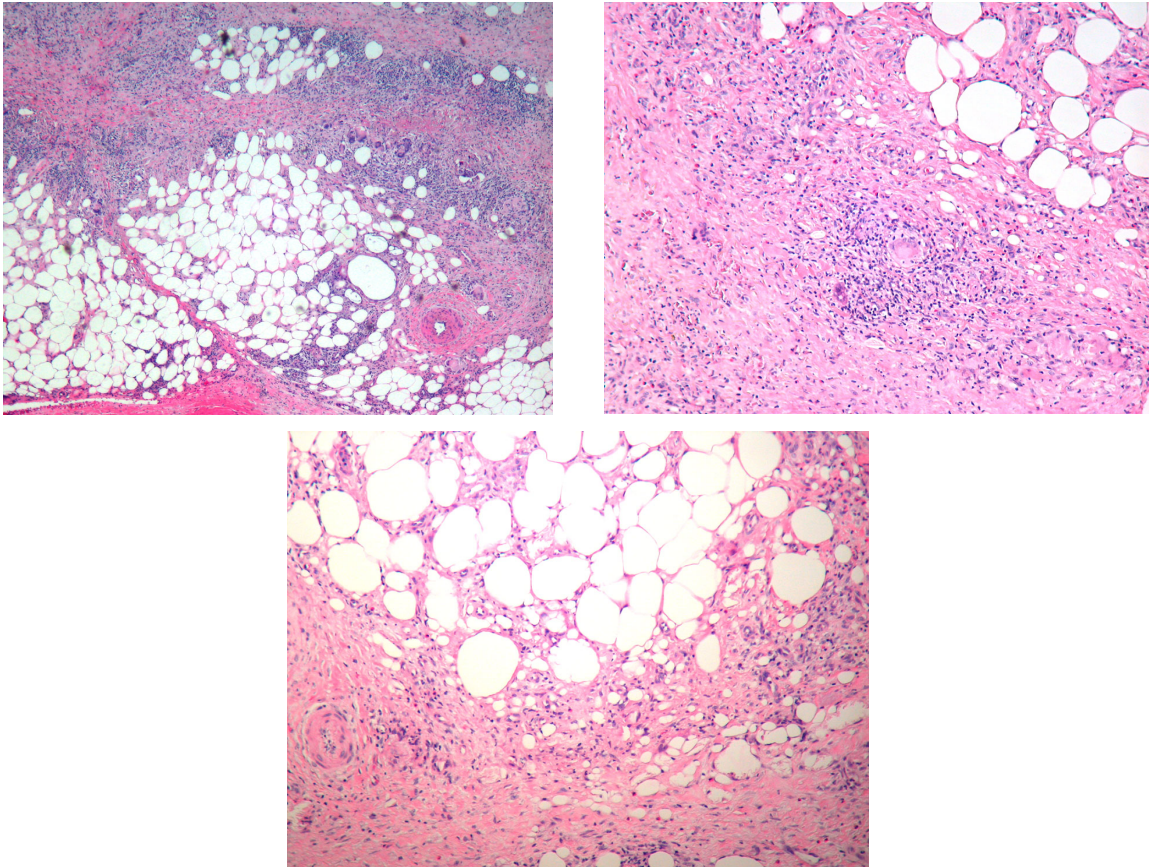
The condition is reactive in nature and represents a hypersensitivity response to a wide variety of antigenic stimuli [1]. Erythema nodosum has been associated with medications, infections, malignancies, autoimmune diseases, and autoinflammatory diseases [10]. A number of gastrointestinal disorders are associated with EN, particularly ulcerative colitis, Crohn disease, celiac disease, bowel bypass syndrome, and blind loop syndrome [11-19]. The common denominator in all these conditions is a compromised intestinal mucosa and/or abnormal bacterial overgrowth with release of bacterial antigen into the systemic circulation.

Autoimmune gastritis results from immunologic destruction of gastric parietal cells. It is characterized by atrophic gastric mucosa, achlorhydria, and loss of intrinsic factor. Intrinsic factor is a protein necessary for absorption of vitamin B12. Absence of intrinsic factor secondary to autoimmune gastritis is the most common cause of vitamin B12 deficiency. Megaloblastic anemia is the most obvious clinical manifestation of vitamin B12 deficiency, but other features include demyelination, glossitis, infertility, malabsorption, thrombosis, and reversible hyperpigmentation [20]. Autoimmune gastritis may also be associated with impaired absorption of iron. The resulting iron deficiency is usually clinically apparent before the vitamin B12 deficiency [20].

In the normal stomach, low numbers of bacteria are present because of the acidic environment. In the setting of achlorhydria or hypochlorhydria, either related to suppression of acid secretion by medication, advanced age, or autoimmune destruction of gastric parietal cells, bacterial overgrowth often occurs [21,22]. The predominant organisms found in the stomachs of very elderly persons or in persons taking acid-inhibitory drugs are gram-positive bacteria resembling the flora of the mouth and oropharynx. In patients with PA, gram-negative, coliform species are typically identified. The differences may relate to the more profound degree of achlorhydria resulting from autoimmune mechanisms [21]. In addition to abnormal bacterial overgrowth in the stomach, abnormal bacterial proliferation in the small bowel can also occur. A higher than normal risk of enteric infection has been observed in patients with achlorhydria [21,23].

Erythema nodosum is triggered by a very wide range of antigens, but bacteria play a prominent role. Given the presence of mucosal damage coupled with abnormal bacterial proliferation in PA, escape of bacterial antigen into the systemic circulation is likely. This antigen could then incite the development of EN in a predisposed individual. Why did this patient experience dramatic improvement following parenteral vitamin B12 (cyanocobalamin) therapy? Exogenous vitamin B12 does not heal damaged gastric mucosa nor does it eliminate the basic autoimmune derangement. Patients with PA must be given vitamin B12 for life.

Vitamin B12 has been shown to have immunomodulatory properties [24,25]. Exogenous administration of cyanocobalamin to patients with PA results in increased numbers of CD8 cells, thus normalizing the CD4/CD8 ratio, which is abnormal in PA [26,27]. In addition, B12 enhances natural killer cell activity, which is depressed in patients with PA [27]. It is thought that the rise in the number of CD8 cells results from inhibition of apoptosis [26]. CD8 lymphocytes are particularly sensitive to apoptosis in the setting of B12 deficiency. Alone or in concert, the immunologic changes induced by exogenous vitamin B12 may attenuate or eliminate the propensity of EN to occur in patients with PA.



Demonstrative case

A 34-year-old woman experienced the sudden onset of tender, erythematous, subcutaneous nodules on the legs and ankles. The clinical picture was that of erythema nodosum (EN). She was treated empirically with corticosteroids, NSAIDs, warm compresses, elevation of the legs, and compression. She responded poorly to treatment, and over the course of ten weeks, new lesions continued to erupt with no sign of abatement. A biopsy showed septal and lobular panniculitis with no associated vasculitis. An extensive search for a cause was undertaken, but none could be found. She took no medications prior to the onset of lesions, including oral contraceptives and NSAIDs. A skin test for tuberculosis was negative. Celiac antibodies, throat culture, anti-streptolysin O titers, anti-thyroid antibodies, angiotensin converting enzyme level, chest x-ray, and imaging studies of the abdomen and pelvis were all negative or within normal limits.

She had a documented past history of iron deficiency anemia, which was attributed to heavy menstrual flow. As part of her work up, however, she was also found to have a new-onset normochromic, normocytic anemia. Her vitamin B12 level was low, 147 pg/ml (normal 200-1100), but folate was normal. Anti-Intrinsic factor and anti-parietal cell antibodies were present. Serum gastrin was markedly elevated at 935 pg/ml (normal <100). Upper endoscopy revealed atrophic mucosa in the fundus and corpus of the stomach, and mucosal biopsies were consistent with autoimmune gastritis. Gastric pH was 6.86 (normal: 1.5-3.5), and *H. pylori* was not detected. Colonoscopy and video capsule endoscopy failed to reveal any abnormalities. A hematologist confirmed the diagnoses of pernicious anemia and iron deficiency anemia and the patient was treated with parenteral vitamin B12 (cyanocobalamin) and supplemental oral iron. Within a few weeks, her hematologic values returned to normal, and the EN lesions rapidly disappeared. After six months of follow up, there has been no recurrence of the EN. Our patient is the first reported case of documented PA and EN, whose EN lesions responded to treatment with vitamin B12.

Conclusion

In at least 50% of cases of EN, no cause can be identified. Although EN has been linked to many conditions, there has been only one report of its association with vitamin B12 deficiency [28]. The case was that of a 38-year-old woman who presented with EN, numbness of the soles of the feet, and a low serum vitamin B12 level. Her skin lesions completely resolved following treatment with vitamin B12. We report the first case of a pernicious anemia patient with persistent, treatment-resistant EN that showed no sign of abatement over a period of two months. An extensive evaluation revealed no specific etiology. Once the diagnosis of PA was made and treatment instituted, there was rapid resolution of the EN lesions. Thus, evaluation of hematologic parameters and screening for autoimmune gastritis and pernicious anemia should be considered as part of the routine work-up for patients with EN.

References

1. Requena L, Yus ES. Erythema nodosum. *Dermatol Clin*. [Review]. 2008 Oct;26(4):425-38, v. [PMID: 18793974]
2. Gilchrist H, Patterson JW. Erythema nodosum and erythema induratum (nodular vasculitis): diagnosis and management. *Dermatol Ther*. [Review]. 2010 Jul-Aug;23(4):320-7. [PMID:20666819]
3. Thurber S, Kohler S. Histopathologic spectrum of erythema nodosum. *J Cutan Pathol*. [Case Reports]. 2006 Jan;33(1):18-26. [PMID:16441407]
4. Gheith O, Al-Otaibi T, Tawab KA, Said T, Balaha MA, Halim MA, Nair MP, Nampoory MR. Erythema nodosum in renal transplant recipients: multiple cases and review of literature. *Transpl Infect Dis*. [Case Reports Review]. 2010 Apr;12(2):164- [PMID:20002354]
5. Akdis AC, Kiliclioglu K, Helvacı S, Mistik R, Oral B. Immunological evaluation of erythema nodosum in tularaemia. *Br J Dermatol*1993 Sep;129(3):275-9. [PMID:8286224]
6. Scollard DM, Bhoopat L, Kestens L, Vanham G, Douglas JT, Moad J. Immune complexes and antibody levels in blisters over human leprosy skin lesions with or without erythema nodosum leprosum. *Clin Immunol Immunopathol*. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S.]. 1992 Jun;63(3):230-6. [PMID:1623643]
7. Abdallah MA, Ragab N, Khalil R, Kamel N. Circulating immune complexes in various forms of Behcet's disease. *Int J Dermatol*1995 Dec;34(12):841-5. [PMID: 8647661]
8. Kellett JK, Beck MH, Chalmers RJ. Erythema nodosum and circulating immune complexes in acne fulminans after treatment with isotretinoin. *Br Med J (Clin Res Ed)*. [Case Reports]. 1985 Mar 16;290(6471):820. [PMID: 3156656]
9. Kahawita IP, Lockwood DN. Towards understanding the pathology of erythema nodosum leprosum. *Trans R Soc Trop Med Hyg*. [Research Support, Non-U.S. Gov't Review]. 2008 Apr;102(4):329-37. [PMID: 18313706]
10. Papagrigoraki A, Gisondi P, Rosina P, Cannone M, Girolomoni G. Erythema nodosum: etiological factors and relapses in a retrospective cohort study. *Eur J Dermatol*2010 Nov-Dec;20(6):773-7. [PMID: 21030339]
11. Caux F, Halimi C, Kevorkian JP, Pinquier L, Dubertret L, Segrestaa JM. Blind loop syndrome: an unusual cause of panniculitis. *J Am Acad Dermatol*. [Case Reports Review]. 1997 Nov;37(5 Pt 2):824-7.[PMID:9366844]
12. Joffe SN. Surgical management of morbid obesity. *Gut*. [Review]. 1981 Mar;22(3):242-54.[PMID:7014393]
13. Katugampola RP, Patel GK, Farrell AM. Intestinal bypass syndrome presenting as erythema nodosum. *Clin Exp Dermatol*. [Case Reports]. 2004 May;29(3):261-4.[PMID: 15115506]
14. Guerre-Schmidt AR, Pelletier F, Carbonnel F, Humbert P, Aubin F. [Dermatosis-arthritis syndrome associated with Crohn's disease in a teenager]. *Rev Med Interne*. [Case Reports]. 2006 Nov;27(11):874-7.[PMID:16997433]
15. Kennedy C. The spectrum of inflammatory skin disease following jejunio-ileal bypass for morbid obesity. *Br J Dermatol*1981 Oct;105(4):425-35.[PMID:7295554]
16. Geary RJ, Long LL, Mutasim DF. Bowel bypass syndrome without bowel bypass. *Cutis*. [Case Reports]. 1999 Jan;63(1):17- [PMID:9951588]

17. Fretzayas A, Moustaki M, Liapi O, Nicolaidou P. Erythema nodosum in a child with celiac disease. *Case Rep Pediatr* 2011;2011:935153.[PMID:22606523]
18. Bartyik K, Varkonyi A, Kirschner A, Endreffy E, Turi S, Karg E. Erythema nodosum in association with celiac disease. *Pediatr Dermatol. [Case Reports]*. 2004 May-Jun;21(3):227-30.[PMID:15165200]
19. Abenavoli L, Proietti I, Leggio L, Ferrulli A, Vonghia L, Capizzi R, Rotoli M, Amerio PL, Gasbarrini G, Addolorato G. Cutaneous manifestations in celiac disease. *World J Gastroenterol. [Research Support, Non-U.S. Gov't Review]*. 2006 Feb 14;12(6):843-52.[PMID:16521210]
20. Stabler SP. Clinical practice. Vitamin B12 deficiency. *N Engl J Med. [Review]*. 2013 Jan 10;368(2):149-60.[PMID:23301732]
21. Williams C, McColl KE. Review article: proton pump inhibitors and bacterial overgrowth. *Aliment Pharmacol Ther. [Review]*. 2006 Jan 1;23(1):3-10.[PMID:16393275]
22. Husebye E, Skar V, Hoverstad T, Melby K. Fasting hypochlorhydria with gram positive gastric flora is highly prevalent in healthy old people. *Gut. [Research Support, Non-U.S. Gov't]*. 1992 Oct;33(10):1331-7.[PMID:1446855]
23. Bures J, Cyrany J, Kohoutova D, Forstl M, Rejchrt S, Kvetina J, Vorisek V, Kopacova M. Small intestinal bacterial overgrowth syndrome. *World J Gastroenterol. [Research Support, Non-U.S. Gov't Review]*. 2010 Jun 28;16(24):2978-90.[PMID:20572300]
24. Tamura J, Kubota K, Murakami H, Sawamura M, Matsushima T, Tamura T, Saitoh T, Kurabayshi H, Naruse T. Immunomodulation by vitamin B12: augmentation of CD8+ T lymphocytes and natural killer (NK) cell activity in vitamin B12-deficient patients by methyl-B12 treatment. *Clin Exp Immunol. [Research Support, Non-U.S. Gov't]*. 1999 Apr;116(1):28-32.[PMID:10209501]
25. Sakane T, Takada S, Kotani H, Tsunematsu T. Effects of methyl-B12 on the in vitro immune functions of human T lymphocytes. *J Clin Immunol* 1982 Apr;2(2):101-9.[PMID:6461666]
26. Kubota K, Arai T, Tamura J, Shirakura T, Morita T. Restoration of decreased suppressor cells by vitamin B12 therapy in a patient with pernicious anemia. *Am J Hematol. [Case Reports]*. 1987 Feb;24(2):221-3.[PMID:2949604]
27. Erkurt MA, Aydogdu I, Dikilitas M, Kuku I, Kaya E, Bayraktar N, Ozhan O, Ozkan I, Sonmez A. Effects of cyanocobalamin on immunity in patients with pernicious anemia. *Med Princ Pract. [Clinical Trial]*. 2008;17(2):131-5.[PMID:18287797]
28. Volkov I, Rudoy I, Press Y. Successful treatment of chronic erythema nodosum with vitamin B12. *J Am Board Fam Pract. [Case Reports]*. 2005 Nov-Dec;18(6):567-9.[PMID:16322421]