

Relationship of erythema nodosum to other manifestations of Crohn's disease

Mark Jacobs, M.D.
Eugene I. Winkelman, M.D.
Richard G. Farmer, M.D.

Department of Gastroenterology

Erythema nodosum has been considered part of the clinical spectrum of inflammatory bowel disease (IBD) since Bargen¹ reviewed 693 cases of ulcerative colitis in 1929. He, as well as Kelley and Logan,² Samitz and Greenberg,³ Jacobs,⁴ and Brown et al⁵ noted that the skin lesions corresponded to intestinal and extra-intestinal manifestations of active ulcerative colitis. The same relationship for Crohn's disease and erythema nodosum can be inferred from their data. Many of these early reports included patients with segmental colitis or right-sided colon disease or both. Investigators who have specifically examined the relationship of active Crohn's disease and erythema nodosum have agreed that there is a positive correlation. Jacobs⁴ reported four cases and Sams and Winkelmann⁶ reported three cases of erythema nodosum and active Crohn's disease. Van Patter et al⁷ and Greenstein et al⁸ have reviewed various clinical manifestations of Crohn's disease and found that the typical patient had a parallel course of bowel disease and erythema nodosum.

The current thinking is that a positive correlation exists between other manifestations of Crohn's disease activity and the appearance of erythema nodosum. However, as reported

here, the relationship between erythema nodosum and the activity of the bowel disease is more variable than previous reports indicate.

Methods and definitions

Records of patients with Crohn's disease and erythema nodosum at the Cleveland Clinic in the period 1961 to 1976 were reviewed. In all patients, Crohn's disease was documented by accepted roentgenographic and pathologic criteria.^{7,9} Of the 12 patients who met the criteria for inclusion in the study, 9 had typical transmural inflammatory changes in resected portions of bowel. In the remaining three patients, one had transverse and left colon disease in a noncontinuous roentgenographic distribution; another had a rectal stricture, multiple skip areas of the colon, as well as ileal involvement; and the third had descending colon involvement with granuloma present on rectal biopsy.

Erythema nodosum was diagnosed by clinical observation and biopsy at the Cleveland Clinic. The clinical diagnosis was established by the presence of erythematous, tender nod-

ules over the extensor surfaces of the lower extremities. Skin biopsy performed in four patients was compatible with the clinical diagnosis.

Crohn's disease activity was defined as the onset of other extra-intestinal manifestations or increased bowel symptoms within 1 month of the onset of skin lesions. Increased bowel symptoms were defined as an increase in the number or a worsening in the consistency of bowel movements, increase in the frequency or intensity of abdominal pain, or the development of surgically treatable lesions such as obstruction or abscess. Three patients had the skin lesions during the course of this review. They were followed prospectively 1 to 5 months.

The age of onset for Crohn's disease was defined by the first occurrence of symptoms. Histories were taken, and physical examinations and chest films were done on all patients, as well as a review of medications. No other cause could be found for the erythema nodosum.

Results

The *Table* summarizes the clinical

Table. Clinical data on patients with Crohn's disease and erythema nodosum

Case	Age	Race	Sex	Age of onset Crohn's symptoms yr	Age of oc- currence of erythema nodosum yr	Change in Crohn's dis- ease activity	Extent of bowel disease
1	57	O	F	40	52	No	Terminal ileum, right colon
2*	27	W	F	23	27	No	Terminal ileum, cecum
3*	30	W	F	19	30	No	Terminal ileum, right colon
4	45	W	M	30	44	No	Terminal ileum, rectum
5	40	W	F	32	38	No	Terminal ileum, jejunum, colon
6	38	W	M	32	32	Yes	Left colon
7	32	W	M	27	28	Yes	Terminal ileum, colon
8	33	W	F	27	29	Yes	Left colon
9	48	W	M	42	42	Yes	Distal colon
10	24	W	F	13	22	Yes	Antrum, duodenum, colon
11	25	W	F	12	13	Yes	Terminal ileum, colon
12*	35	W	F	35	35	Yes	Left and transverse colon

*Prospective.

data. The patients were divided into two groups: seven patients with an increase in Crohn's disease activity, as previously defined, and five with no change. In the five patients who had no change in symptomatic Crohn's disease activity, the duration of bowel disease at the time of the development of erythema nodosum ranged from 4 to 14 years (mean 9.4 years). Two patients had histories of erythema nodosum-like lesions; one a year after the onset of Crohn's disease, and the other after an interval of 6 years. The documented erythema nodosum in these two patients occurred 11 and 14 years respectively, after the onset of Crohn's disease.

The other group of patients was also impressive in its uniformity. This group had recent onset of Crohn's disease (mean 1.8 years) coinciding with, or within a year of the appearance of the skin lesions. One patient did not fit into this temporal relationship since she had a 9-year history of bowel disease when the concurrent Crohn's disease flare and the erythema nodosum occurred. Aphthous stomatitis, as well as bowel manifestations of Crohn's disease developed in two patients. Erythema nodosum developed in one patient a month prior to the onset of Crohn's disease.

Discussion

Current evidence suggests that erythema nodosum develops in patients with IBD in the presence of active Crohn's disease.^{4, 6, 10-12} Despite this clinical impression, our patients did not reflect a direct relationship to other manifestations of Crohn's disease and erythema nodosum in all cases. Patients with recent onset (less than 2 years) of symptomatic Crohn's disease in whom erythema nodosum

develops, typically have a flare of other manifestations of disease activity associated with it. Those patients with long-standing Crohn's disease (longer than 4 years) usually had no change in their bowel habits, nor did any other extra-intestinal complications develop. Two of the three prospective patients had no change in other markers of Crohn's disease activity. This would seem to confirm the retrospective analysis. Evaluation failed to reveal another cause of the skin lesions. Thus, erythema nodosum does not necessarily correlate with other manifestations of Crohn's disease and may not represent the poor prognosis as suggested by other investigators.

Summary

The records of 12 patients with Crohn's disease and erythema nodosum were reviewed. Within 1 month of the onset of erythema nodosum other manifestations of Crohn's disease developed in seven patients. The mean duration of bowel disease in this group when erythema nodosum occurred was 1.8 years. In five patients, no other change in the status of clinical activity occurred during a 1-month period. The mean duration of Crohn's disease in this group prior to the erythema nodosum was 9.4 years. Erythema nodosum does not always indicate that other manifestations of Crohn's disease activity will worsen and may not be a poor prognostic sign.

References

1. Barga JA: Complications and sequelae of chronic ulcerative colitis. *Ann Intern Med* **3**: 335-352, 1929.
2. Kelley ML Jr, Logan VW: Erythema nodosum in association with chronic ulcerative colitis. *Gastroenterology* **31**: 285-295,

- 1956.
3. Samitz MH, Greenberg MS: Skin lesions in association with ulcerative colitis. *Gastroenterology* **19**: 476-479, 1951.
 4. Jacobs WH: Erythema nodosum in inflammatory diseases of the bowel. *Gastroenterology* **37**: 286-294, 1959.
 5. Brown ML, Kasich AN, Weingarten B: Complications of chronic ulcerative colitis. *Am J Dig Dis* **18**: 52-54, 1951.
 6. Sams WM Jr, Winkelmann RK: The association of erythema nodosum with ulcerative colitis. *South Med J* **61**: 676-679, 1968.
 7. Van Patter WN, Barga JA, Dockerty MB, et al: Regional enteritis. *Gastroenterology* **26**: 347-450, 1954.
 8. Greenstein AJ, Janowitz HD, Sachar DB: The extra-intestinal complications of Crohn's disease and ulcerative colitis; a study of 700 patients. *Medicine* **55**: 401-412, 1976.
 9. Hawk WA, Turnbull RB Jr, Farmer RG: Regional enteritis of the colon; distinctive features of the entity. *JAMA* **201**: 738-746, 1967.
 10. Edwards FC, Truelove SC: The course and prognosis of ulcerative colitis. *GUT* **5**: 1-22, 1964.
 11. McCallum DI, Kinmont PDC: Dermatological manifestations of Crohn's disease. *Br J Dermatol* **80**: 1-8, 1968.
 12. Kelley ML Jr: Skin lesions associated with chronic ulcerative colitis. *Am J Dig Dis* **7**: 255-272, 1962.