Prognostic Significance of Severe Preoperative Lymphopenia in Patients with Crohn's Disease

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Nearly 30% of patients with Crohn's disease requiring operative treatment have severe peripheral lymphopenia. The surgical significance of this finding had not been previously determined. One hundred fifty-eight patients with Crohn's disease admitted for resection of the diseased bowel were studied. Forty-six had preoperative peripheral lymphocyte counts under 1000 cells per mm^3. Severely lymphopenic patients had a significantly higher incidence of skip areas and epithelioid granulomas than patients with higher lymphocyte counts. Also, lymphopenic patients were more likely to require separate resections of the diseased bowel and more than one anastomosis. Postoperative follow-up revealed that patients with preoperative lymphopenia had a markedly higher incidence of symptomatic recurrences within 3 years of operation (67 *vs.* 36%, $p < 0.01$). It appears that the preoperative peripheral lymphocyte count may be used as an indicator of disease severity and prognosis in patients with Crohn's disease.

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MANY PATIENTS with Crohn's disease requiring surgical treatment have marked immunological abnormalities.[1,2] These patients are frequently found to have very low peripheral lymphocyte and T- and B-cell counts, as well as lack of reactivity to skin tests with recall antigens.[3,4] Since Crohn's disease is a chronic inflammatory process, which is associated with significant nutritional abnormalities, and patients often require steroid medication, the source of this immunosuppression remains unclear.

The surgical significance of severe preoperative lymphopenia has not been well studied in patients with Crohn's disease.Previous studies have revealed that this lowering of the peripheral lymphocyte count is due to a decrease in both T- and B-cell counts.[1,2] Marked immunosuppression has been associated with an increased morbidity and mortality in other surgical conditions.[5-7] Whether this is also true of patients with Crohn's disease remains unclear. Surgical treatment offers an opportunity to study the changes in the immunologic status of the patient associated with removal of the diseased bowel, as well as the correlation of preoperative immunosuppression and the development of postoperative recurrence.

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Materials and Methods

One hundred fifty-eight patients with Crohn's disease admitted to the Mount Sinai Hospital for surgical treatment between April 1977 and April 1985 were studied prospectively. At the time of admission, a clinical history was obtained, and the weight of the patient was determined and compared to the ideal body weight as published in the Metropolitan Life Insurance Company Tables. The white blood cell count was measured by using an automated white blood cell counter. The percentage of lymphocytes was then determined from the differential count by manually counting 100 white blood cells under a microscope. The granulocyte count was calculated by subtracting the lymphocyte count from the white blood cell count. Serum albumin concentration was obtained from the automated chemical screening panel measured at the time of admission.

At operation, the location and extent of disease were determined, as well as the presence of skip areas. Patients with multiple areas of disease separated by a large segment of normal appearing intestine required separate resections with two anastomoses, and this finding was recorded. The presence or absence of epithelioid granulomas was determined at the time of histologic examination. There was no attempt to section serially the resected intestine to look for granulomas. Only the standard histologic slides consisting of the margins of resection plus representative

TABLE 1. *Preoperative Variables*

Lymphocyte Count	N	Mean Age	Mean Duration Symptoms	Patients with Previous Operations	Mean Per Cent Ideal Weight	Mean Serum Albumin	Patients on Steroids
<1000	46	23	10	20 (43)	86	3.67	27 (59)
>1000	112	24	12	57 (51)	86	3.76	56 (50)

( ) Percent.

samples of the diseased intestine and mesenteric nodes were examined.

Surgical outcome was measured by recording the number of days of hospitalization required after operation and the presence or absence of postoperative complications. Following discharge from the hospital, patients were contacted every 6 months to determine the development of recurrent disease. Symptomatic patients underwent either radiographic study with barium or endoscopy to evaluate the area of intestine adjacent to the site of resection. Patients developing symptomatic recurrent disease within 3 years of operation, confirmed by radiographic or endoscopic studies, were assigned to the early recurrence group.

The results obtained were tabulated and the data were analyzed using the computer services of the City University of New York. Patients with preoperative lymphocyte counts under 1000 cells per mm^3 were classified as having severe lymphopenia. This value was chosen because 95% of healthy controls had higher peripheral lymphocyte counts. The numerical data were compared using Student's t-test, and the chi square method was used for analysis of data classified into categories.

Results

The mean age of patients entered in the study was 35.5 years. They had been symptomatic for a mean of 11.5 years prior to the present operative procedure. Seventy-four patients (47%) were male and 84 (53%) were female. The disease was confined to the small intestine in 51 (32%) patient, involved the small and large bowel in 88 (56%), and was limited to the colon and rectum in 19 (12%). At the time of admission, 75 (47%) patients were not taking steroids, 23 (15%) required less than 10 mg of prednisone per day, and 60 (38%) were taking higher doses. Eighty-one (51%) patients were undergoing intestinal resection for the first time, while the remaining 77 (49%) patients had at least one previous resection for Crohn's disease. Obstruction was the major reason for operation in 67 (42%) patients, 75 (47%) had either a fistula or an abscess, only four (3%) had a free perforation, while the remaining 12 (8%) required operation for intractable symptoms.

The mean preoperative per cent of ideal body weight was 86 with a standard deviation of 15. The mean serum albumin on admission was 3.7 g per 100 ml (SD = 0.5). The mean preoperative white blood cell count was 9605 cells per mm^3 (SD = 4113). The mean lymphocyte count was 1478 cells per mm^3 (SD = 734). This was significantly lower than the lymphocyte count for 48 healthy volunteers, which was 2115 (SD = 814, $p < 0.01$). Forty-six (29%) patients in this study had peripheral lymphocyte counts under 1000 cells per mm^3, and only 35 (22%) patients had counts over 2000 lymphocytes, per mm^3. The mean granulocyte count was 8127 (SD = 4079). There was no significant difference in the granulocyte counts of patients with and without severe peripheral lymphopenia.

Patients with extreme preoperative peripheral lymphopenia (under 1000 cells per mm^3) were compared to those with higher lymphocyte counts (see Table 1). The mean lymphocyte count in the lymphopenic group was 695 cells per mm^3 (SD = 213), while it was 1799 cells per mm^3 in the remaining patients (SD = 621, $p < 0.0001$). There was not significant difference in age at operation, duration of disease, number of previous operations, or the indication for operation in the two groups of patients. Also, there was no difference in the preoperative per cent of ideal body weight, serum albumin, and steroid intake. Location of disease and length of diseased bowel were nearly the same in both groups.

Skip areas were significantly more common in the lymphopenic patients. Eighteen of 46 (39%) patients had skip areas in the group with decreased lymphocyte counts as opposed to 19 of 112 (17%) patients in the higher lymphocyte group (chi square = 8.93, $p < 0.01$). Also, lymphopenic patients were significantly more likely to require resections of two separate segments of bowel with two anastomoses. Separate resections were required in 10 (22%) patients in the lymphopenic group, as opposed to nine (8%) in the patients with higher lymphocyte counts (chi square = 5.79, $p < 0.05$). The identification of epithelioid granulomas in the resected intestine was also significantly more frequent in the patients with low peripheral lymphocyte counts. Twenty-five (55%) patients in the low lymphocyte group had granulomas. This incidence was nearly twice as high as in the remaining patients (38 patients, 33%, chi square = 5.67, $p < 0.05$, see Table 2).

There was no difference in the incidence of postoperative complications in either group of patients. Septic complications occurred in seven (16%) lymphopenic patients and in 21 (19%) patients with higher lymphocyte

TABLE 2. *Preoperative Lymphocyte Counts*

	N	Lymphocyte Count	SD
Double resection	19	1272	903
Single resection	139	1506	707
Skip areas	37	1242*	699
No skip areas	121	1550*	732
Granulomas	63	1298*	633
No granulomas	95	1597*	774

* $p < 0.05$.
SD = standard deviation.

counts. Nonseptic complications were present in five (11%) patients with severe lymphopenia and in 17 (15%) without low lymphocyte counts. The mean postoperative stay was 15 days for both groups, and there were no mortalities in this series.

Following operation, there was no change in the peripheral lymphocyte counts at 3 and 12 months when compared to initial values in the patients with higher preoperative lymphocyte counts (see Table 3). However, in the patients with severe preoperative lymphopenia, the postoperative peripheral lymphocyte count increased significantly from a mean of 695 cells per mm^3 to 1479 (SD = 738) cells at 3 months. There was no further improvement in this group and the lymphocyte count at one year remained essentially unchanged at 1426 (SD = 400) cells per mm^3. This value was still significantly below the mean lymphocyte count in the patients without severe preoperative lymphopenia, which at 1 year after surgery was 1846 (SD = 805, $p < 0.05$) cells per mm^3.

One hundred seven patients were followed for a period of at least 3 years after operation. Forty-seven (44%) of these have developed symptomatic recurrences adjacent to the site of resection of the diseased bowel within this period of time. The recurrence rate for patients with severe preoperative lymphopenia was nearly twice as high as that of patients with higher lymphocyte counts (67% *vs.* 36%, $p < 0.01$, see Table 4). This increase in recurrence rate is noticeable at 1 year after operation and reaches a peak after 3 years (see Fig. 1). There was no significant correlation between the presence of skip areas or granulomas and early symptomatic recurrence. None of the other

TABLE 3. *Postoperative Follow-up*

Preoperative Lymphocyte Count	Baseline	3 Months	12 Months
<1000	695 ± 213*	1479 ± 738‡	1426 ± 400†
>1000	1799 ± 621*	1859 ± 818‡	1846 ± 805†

* $p < 0.0001$.
† $p < 0.05$.
‡ $p < 0.1$.

TABLE 4. *Symptomatic Early Recurrence Rates*

Preoperative Lymphocyte Count	Number Followed for 3 Years	Patients with Symptomatic Recurrence	Per Cent with Symptomatic Recurrence
<1000	27	18	67
>1000	80	29	36
Total	107	47	44

Chi-square = 7.58.
$p < 0.01$.

variables recorded were helpful in the identification of patients prone to develop recurrent disease. The mean preoperative lymphocyte count for patients developing symptomatic recurrences was 1365 as opposed to 1652 cells per mm^3 in the patients doing well after 3 years ($p < 0.05$).

Discussion

Severe peripheral lymphopenia occurs in nearly 30% of patients with Crohn's disease admitted for operative treatment. Although it is difficult to determine the reason for this profound lymphopenia, it does not appear to be related to steroid intake or malnutrition since there was no significant difference in these findings in the two groups of patients.

It seems that there is some correlation between the disease process in the intestine and the peripheral lymphocyte count. Lymphopenic patients have a significantly higher incidence of skip areas and granulomas, and they often require multiple resections because of extensive involvement of the intestinal tract. Furthermore, removal of the diseased bowel is followed by significant improvement in the peripheral lymphocyte count in this group of patients.

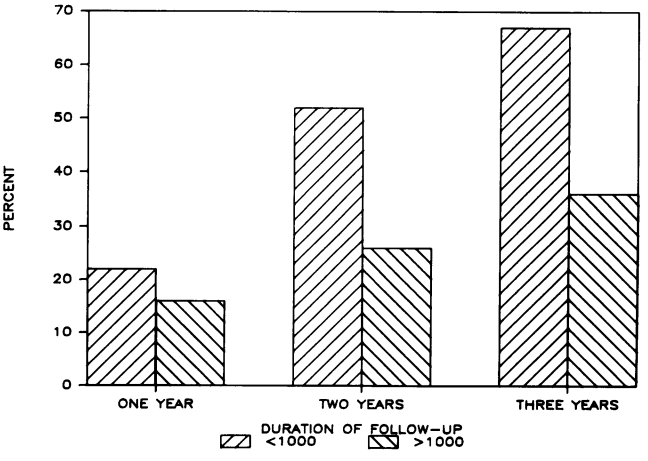

FIG. 1. The yearly recurrence rates for patients with preoperative peripheral lymphocyte counts above and below 1000 cells per mm^3 are shown. Patients with severe lymphopenia have nearly twice the recurrence rate at 3 years than those with higher lymphocyte counts.

However, patients with marked preoperative lymphopenia continue to have a significantly lower mean postoperative peripheral lymphocyte count when compared to those patients who had higher preoperative lymphocyte counts.

Severe preoperative lymphopenia does not appear to correlate with surgical complications. There was no mortality in this series and no difference in length of hospital stay or complication rate in lymphopenic patients when compared to those with higher lymphocyte counts. Skin test anergy and low serum albumin, however, have been found to correlate with surgical complications in patients with inflammatory bowel disease.[8,9]

The association of preoperative peripheral lymphocyte depression with subsequent development of symptomatic recurrences seems to indicate that preoperative lymphopenia may reflect a greater severity of disease or the patient's inability to respond to the inflammatory process. Since the percentage of circulating lymphocytes is routinely determined at the time of admission, the peripheral lymphocyte count can be easily calculated in every patient. Patients with extremely low preoperative lymphocyte counts are more likely to have extensive disease, require multiple resections, and develop early symptomatic recurrences. Although previous clinical trials using steroids or sulfasalazine in unselected patients with Crohn's disease have failed to demonstrate any significant improvement in recurrence rates,[10-12] further studies may be indicated to determine if patients in this high risk group are more likely to benefit from postoperative therapy.

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