

## Is lymphatic status related to regression of inflammation in Crohn's disease?

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### Abstract

**AIM:** To investigate the status of the lymphatic vessels in the small bowel affected by Crohn's disease (CD) at the moment of surgery.

**METHODS:** During the period January 2011-June 2011, 25 consecutive patients affected by CD were operated on in our Institution. During surgery, Patent Blue V was injected subserosally and the way it spread along the subserosa of the intestinal wall, through the mesenterial layers towards the main lymphatic collectors and eventually to the lymph nodes was observed and recorded. Since some patients had been undergone strictureplasty at previous surgery, we also examined the status of intestinal lymph vessels after previous strictureplasties. The same procedure was performed in a control group of 5 patients affected by colorectal cancer. Length of lesions, caliber, maximal thickness of the diseased intestinal wall, thickness of the wall at injection site and thickness of the mesentery were evaluated at surgery.

**RESULTS:** We observed three features after the injection of Patent Blue V in the intestinal loops: (1) Macroscopically healthy terminal ileum of patients with CD or colon cancer showed thin lymphatic vessels linearly

directed toward the mesentery; (2) In mild lesions in which the intestinal wall did not reach 8 mm of thickness, we observed short, wide and tortuous lymphatic vessels directed longitudinally along the intestinal axis toward disease-free areas and then transversally toward the mesentery; and (3) Injection in the severely affected lesions, that had a thickness of the intestinal wall over 10 mm, did not show any feature of lymphatic vessels at least on the subserosal surface. There was a correlation between the thickness of the parietal wall and the severity of the lymphatic alterations. Normal lymphatic vessels were observed at previous strictureplasties in the presence of complete regression of the inflammation.

**CONCLUSION:** Injection of Patent Blue V in the intestinal wall could help distinguish healthy tracts of the small bowel from those macroscopically borderline.

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**Key words:** Lymphatic vessels; Surgery; Patent blue V; Strictureplasty; Crohn's disease; Mesentery; Thickness; Intestinal wall; Inflammation

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### INTRODUCTION

Crohn's disease (CD) is a chronic inflammation occurring mainly in the terminal ileum, but potentially affecting any part of the intestinal tract. Although in recent

years several studies had clarified that CD occurs in genetically predisposed subjects and is associated with defective intestinal permeability and compromised immune response, a definitive etiology remains unknown. Pathologists who have studied surgical specimens of CD describe the microscopic appearance of the disease as a chronic lymphangitis<sup>[1]</sup>. These authors described focal collections of lymphocytes and histiocytes, dilation of the lymphatic channels, swelling and proliferation of the lymphatic endothelium with a consequent occlusion of the lymphatics<sup>[2-4]</sup>.

In experimental animals CD was induced by obstruction of the mesenteric lymphatics either by injecting formalin or acrylic resin into the regional lymph nodes or by ligation<sup>[5-8]</sup>. It was then observed that lymphatic vessels may play an important role in inducing or maintaining bowel inflammation. The primary aim of this paper is to observe the status of the lymphatic vessels in the small bowel of CD patients at the time of primary surgery or of recurrence of the disease by injecting Patent Blue V (a dark bluish synthetic dye used in lymphangiography and for sentinel node biopsy as a dye to color lymph vessels) in the subserosa of the affected intestinal loops. The opportunity to perform recurring surgery in some CD patients allowed us to observe the status of intestinal lymph vessels after previous stricturoplasties and to try to clarify whether a "restitutio ad integrum" of lymphatic channels is accompanied by regression of inflammatory lesions: it is the secondary aim of this paper.

## MATERIALS AND METHODS

During the period January 2011-June 2011, 25 consecutive patients (14 males and 11 females) affected by ileal CD were operated on in our Institution. The mean age was 38.7 years (range 17-58 years). Thirty-nine percent of the patients were at primary surgery while 61% were affected by recurrent CD. In this second group 5 patients had previously undergone a side-to-side isoperistaltic stricturoplasty, 5 were treated with stricturoplasty according to Finney technique and 6 with stricturoplasty according to Heineke-Mikulicz (H-M) technique. Former intestinal resections of the terminal ileum were performed followed by an ileocolic resection in 9 patients of this group. Seventeen CD patients underwent surgery for intestinal obstruction 6 for multiple intestinal fistulas.

No patient had been subjected to biological therapy for at least one month before the surgical operation.

During laparotomy, once the affected intestinal loops were freed from adhesions, 0.2 mL of Patent Blue V were injected using a 25-gauge needle introduced tangentially for a length of 3-4 mm and a depth of 1-2 mm under the surface of the intestinal serosa in macroscopically disease-free intestine some centimeters from the macroscopic lesions, in diseased intestine close to the resection limit and in CD lesions. If skip lesions or those previously treated with stricturoplasty were present, Patent Blue V injection was repeated at these sites.

Once the Patent Blue V was injected we observed if and how it spread along the subserosa of the intestinal wall and through the mesenterial layers towards the main lymphatic collectors and eventually the lymph nodes. The following parameters were evaluated at surgery or on the surgical specimen: length of lesions, caliber, maximal thickness of the diseased intestinal wall, thickness of the wall at injection site and thickness of the mesentery at that level. Furthermore, 5 patients (3 males and 2 females, mean age 64.4 years), operated on for colorectal cancer at our Institution during the same period, underwent the same procedure of Patent Blue V injection at the level of the terminal ileum, and they were evaluated as control sample.

Statistical analysis was performed on the data of patients affected by CD. These data collected in a database were checked and underwent a univariate statistical analysis using SPSS software version 15.0 (SPSS Inc. Chicago, IL). All data were studied through a log-rank test and a *P* value less than 0.05 was assumed as significant. Given the small number of patients, the *P* value was evaluated only for the parameters homogeneously distributed.

## RESULTS

We observed the following three features after the injection of Patent Blue V in the intestinal loops.

### Pattern I

Macroscopically healthy terminal ileum of patients with CD or colon cancer showed thin lymphatic vessels linearly directed toward the mesentery. The dye quickly reaches and colors the node in the mesentery a few centimeters distally (Figure 1).

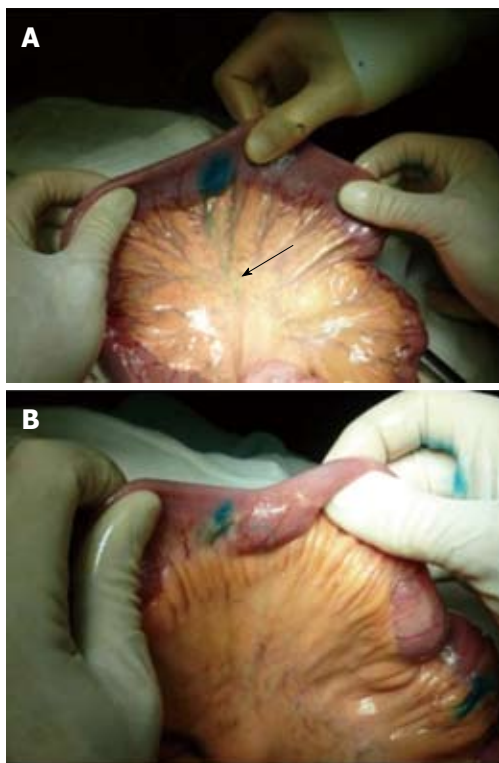
### Pattern II

In mild lesions in which the intestinal wall did not reach 8 mm of thickness, we observed short, wide and tortuous lymphatic vessels directed longitudinally along the intestinal axis either orally or aborally toward disease-free areas and then transversally toward the mesentery. In skip lesions the features were comparable to those we observed in mild lesions (Figure 2).

### Pattern III

Injection in the severely affected lesions, that had a thickness of the intestinal wall over 10 mm, did not show any feature of lymphatic vessels at least on the subserosal surface. The dye spread uniformly through the thick intestinal wall and reached the bowel lumen.

When we injected Patent Blue V in patients undergoing surgery at the site of previous stricturoplasty or anastomosis, the dye had two different patterns: (1) If the area was disease-free, the lymphatics appeared linear and thin, like those we found in healthy intestinal loops. This was evident either in some cases of short stenosis previously treated with H-M or Finney stricturoplasty,



**Figure 1 Healthy small bowel.** A: the Patent Blue injected into the subserosal layer outlines a lymphatic vessel which rectilinearly goes into the mesentery towards the lymph-node (arrow). Lymphatic vessels longitudinally directed are not observed; B: Small bowel affected by Crohn's disease: the Patent Blue injected at the level of a skip lesion outlines a lymphatic vessel longitudinally directed in the small bowel wall and only from this site can it spread into the mesentery.

**Table 1 Correlation between small bowel wall thickness and lymphatic vessels pattern (the pattern is reported as I, II and III as described in the text) n (%)**

Small bowel wall thickness	Lymphatic vessel pattern			P value
	I	II	III	
< 5 mm (n = 17)	14 (82)	3 (18)	0 (0)	< 0.05
5-8 mm (n = 22)	2 (9)	16 (73)	4 (18)	< 0.05
> 8 mm (n = 16)	0 (0)	3 (19)	13 (81)	< 0.05
P value	< 0.05	< 0.05	< 0.05	

but also in a case of a 36-cm long SISS. During surgery the intestinal tract treated with strictureplasty appeared soft with a thin intestinal wall and thin mesentery, and the injected dye had the features of the healthy intestine (Figures 3 and 4A). Once we opened the specimen the mucosa appeared completely normal without any macroscopic signs of inflammation (Figure 4B); and (2) If the area was affected by persistent or recurrent CD, the lymphatic vessels appeared like those we found in mild or severe lesions depending on the severity of CD. Also some intestinal tracts previously treated by strictureplasty, that did not appear severely affected macroscopically, showed an altered lymphatic pattern with a few short, wide and tortuous lymphatic vessels. In these cases, once we performed an enterotomy at the site of the previous



**Figure 2 Small bowel affected by Crohn's disease.** The Patent Blue injected into the subserosal layer soon leads to a high pressure spillage from the site of injection which highlights the absence of lymphatic drainage pathways (arrow).



**Figure 3 Intestinal tracts previously treated by Heineke-Mikulicz strictureplasty, that do not appear macroscopically affected by recurrence of Crohn's disease.** The injection of Patent Blue soon highlights a lymphatic vessel which rectilinearly goes into the mesentery towards the lymph node (arrows).

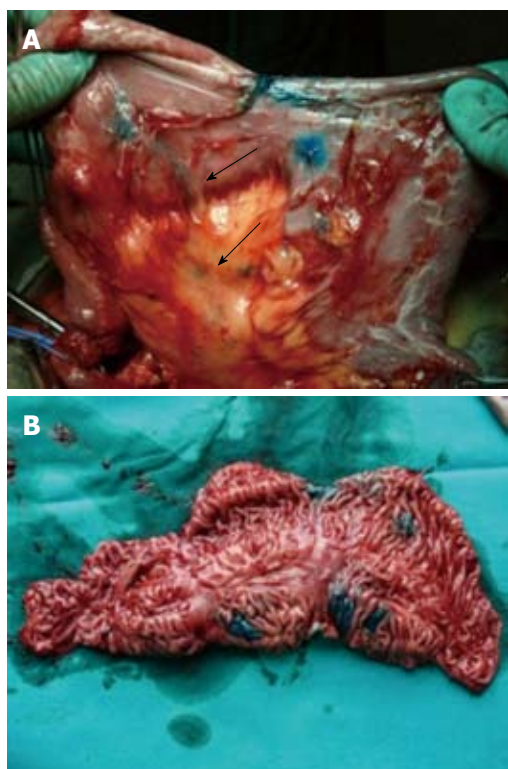
strictureplasty, we found signs of active disease such as ulcers at the mucosal site (Figure 5).

Length of lesions, caliber and maximal thickness of the diseased intestinal wall and thickness of the mesentery at that level have been evaluated. Statistical analysis showed a direct correlation between thickness of the diseased intestinal wall and thickness of its mesentery; furthermore, a significant ( $P < 0.05$ ) correlation between the different lymphatic patterns and wall thickness was found (Table 1).

## DISCUSSION

Although many reports have been clarified the peculiar features of immunologic and inflammatory features of CD, its pathogenesis and the reason why its main localization is the terminal ileum remain unexplained<sup>[9]</sup>. The inflammatory process of CD is characterized by mucosal ulcers, submucosal edema and transmural diffusion. This process results in parietal thickness and bowel stricture<sup>[10]</sup>. The peculiar distribution of the inflammation, the segmental intestinal involvement and the prevalent localization in the terminal ileum suggested a lymphatic disorder. Dilatation of the lymphatic vessels, occlusion



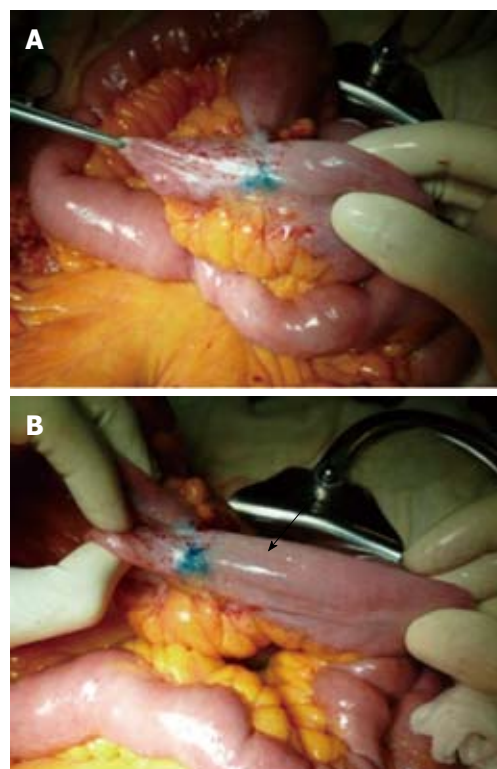


**Figure 4** Previously performed side-to-side isoperistaltic strictureplasty. A: The lymph vessels appear straight and thin and easily reach the mesentery and the lymphnodes (arrows); B: Once the side-to-side isoperistaltic strictureplasty was resected, Crohn's disease remission was visible at the internal site of dye injection, by the normal aspect of the mucosa.

of the lymphatics by endothelial proliferation and/or lymphocytic thrombi, and foci of lymphocytes are scattered throughout all layers of the bowel<sup>[11,12]</sup>. A specific lymphatic endothelial marker (D2-40), has allowed better characterization of the lymphatic channels in the context of the parietal inflammatory infiltrate<sup>[13]</sup>. A higher number of lymphatic vessels have been observed in the ileal and colonic wall in comparison to the healthy small and large bowel<sup>[14]</sup>. The diameter of the lymph vessels in the intestinal wall affected by CD was approximately ten times larger than normal controls and was significantly increased in comparison to other inflammatory bowel diseases, such as ulcerative colitis, ischemic ileitis or pseudomembranous colitis<sup>[15]</sup>. Interestingly, lymphangiogenesis and lymphangiectasia were present also in normal intestinal tract near the bowel affected by CD<sup>[15]</sup>. These last aspects suggest that alteration of the lymphatic system could be an inducer of CD<sup>[16]</sup>.

Our study clearly shows an alteration of the course and the features of the lymphatic vessels in the presence of CD bowel. In the tracts markedly affected by CD, the injection of the dye does not color the lymph vessels but is diffused in the subserosal layer. This could be due to the obstruction of the lymphatic vessels or to inflammation and thickening of the intestinal wall that could mask the lymphatic vessels at the subserosal layer.

In the tracts where the disease is less severe there is a distorted, tortuous, increase in size and longitudinally



**Figure 5** Intestinal tract previously treated by Heineke-Mikulicz strictureplasty, that appears macroscopically affected by recurrence of stenosis in Crohn's disease. A: the injection of Patent Blue quickly highlights a lymphatic vessel which rectilinearly goes towards the mesentery; B: However, the vessel is cut off before entering into the mesentery; in the meantime a lymphatic vessel that runs tangential to the wall of the ileum is drawn (arrow).

directed lymphatic network. This different aspect is also seen in the areas where CD recurs, either at the site of the ileocolic anastomosis or the strictureplasted bowel.

There is a direct correlation between the different lymphatic patterns and wall thickness (Table 1). We have previously demonstrated a correlation between wall thickness and perforating disease<sup>[17]</sup>. One of the theories of the formation of fistulas in CD is that it results from the spread of bacteria through altered and dilated obstructed lymphatic vessels<sup>[10]</sup>. We must assume that when the wall thickness reaches a critical point this happens more easily due to the alteration of the lymphatic network.

The dysfunction of the lymphatic vessels could have an essential role in inducing and maintaining chronic inflammation in CD, similarly to other pathological clinical or experimental situations<sup>[18]</sup>. On the other hand, the lymphatic vessels play a fundamental part in the resolution of inflammation by draining the activated inflammatory cells into the mesenteric lymph nodes and transporting extravasated fluids from interstitial tissue into circulating blood.

It has been clearly shown that CD strictures can be treated by strictureplasty instead of resection<sup>[19-26]</sup>. The regression of inflammatory activity of CD at the strictureplasty site has been well documented by radiological, ultrasonographic, endoscopic or histological investigations<sup>[27-31]</sup>. During a reoperation, the surgeon can ap-

preciate the softness and normal thickness of the healthy structured bowel and the normality of the mesenteric layers<sup>[17]</sup>. Yamamoto *et al.*<sup>[32,33]</sup> reviewed the experience with strictureplasty in the literature and, using meta-regressive analysis, showed that strictureplasty is accompanied by a 5-year recurrence rate of 28 percent: in 90 percent of these patients, recurrence occurred at non-strictureplasty sites, and the site-specific recurrence rate is only 3 percent. The mechanism of this inflammatory regression has not been clarified. One hypothesis is that by releasing bowel obstruction the pressure inside the intestine is markedly decreased and consequently the passage of the enteric allogenic or bacterial content through the fissures or ulcers dramatically disappears. This complex mechanism could be triggered by perturbation of the intracellular redox state (glutathione decreases and oxidized glutathione increases)<sup>[34]</sup>. The myofibroblasts of CD patients exhibit an increased oxidative state due to a decrease in the glutathione/oxidized glutathione ratio and that this alteration is strictly related to upregulated production of interleukin-6<sup>[35]</sup>. The reduction of endoluminal intestinal pressure where a strictureplasty has been performed, could determine better oxidative status, the progressive reduction of activated myofibroblasts and production of pro-inflammatory cytokines. The decrease in intestinal wall inflammation may induce a progressive disappearance of the obstruction of the lymph vessels. By restoring normal function of the lymphatic vessels, the tissutal edema of the mesentery and of the intestinal wall progressively disappear and finally return to normal.

Furthermore, the injection of Patent Blue V in the intestinal wall could clinically help distinguish healthy tracts of the small bowel from those who have macroscopical borderline inflammatory lesions, making it possible to perform a more appropriate surgical resection during the primary operation or at reoperation for CD.

In conclusion, the presence of lymphatic alterations in CD strictures and their disappearance after strictureplasty, both confirmed in our experience, demonstrates the pathogenetic role of the lymphatic damage in the progression and maintenance of CD and the possibility that strictureplasty restores a normal configuration of the lymphatic vessels and consequently a normal lymphatic function in the intestinal wall.

## COMMENTS

### Background

Crohn's disease (CD) is a chronic inflammation occurring mainly in the terminal ileum, but potentially affecting any part of the intestinal tract. Although in recent years several studies had clarified that CD occurs in genetically predisposed subjects and is associated with defective intestinal permeability and compromised immune response, a definitive etiology remains unknown. Pathologists who have studied surgical specimens of CD describe the microscopic appearance of the disease as a chronic lymphangitis

### Research frontiers

The primary aim of this paper is to observe the status of the lymphatic vessels in the small bowel of CD patients at the time of primary surgery or of recurrence of the disease by injecting Patent Blue V (a dark bluish synthetic dye used in lymphangiography and for sentinel node biopsy as a dye to color lymph vessels) in the subserosa of the affected intestinal loops. The opportunity to

perform recurring surgery in some CD patients allowed us to observe the status of intestinal lymph vessels after previous strictureplasties and to try to clarify whether a "restitutio ad integrum" of lymphatic channels is accompanied by regression of inflammatory lesions: it is the secondary aim of this paper.

### Innovations and breakthroughs

During the period January 2011-June 2011 25 consecutive patients affected by CD were operated on in the authors' Institution. During surgery, Patent Blue V was injected subserosally and the way it spread along the subserosa of the intestinal wall, through the mesenteric layers towards the main lymphatic collectors and eventually to the lymph nodes was observed and recorded. Since some patients had been undergone strictureplasty at previous surgery, the authors also examined the status of intestinal lymph vessels after previous strictureplasties. The same procedure was performed in a control group of 5 patients affected by colorectal cancer. Length of lesions, caliber, maximal thickness of the diseased intestinal wall, thickness of the wall at injection site and thickness of the mesentery were evaluated at surgery.

### Applications

The authors found that there was a correlation between the thickness of the parietal wall and the severity of the lymphatic alterations. Normal lymphatic vessels were observed at previous strictureplasties in the presence of complete regression of the inflammation. Injection of Patent Blue V in the intestinal wall could help distinguish healthy tracts of the small bowel from those macroscopically borderline.

### Peer review

The article revealed a correlation between small bowel wall thickness in CD and alteration of the lymphatic vessels, using Patent Blue V infection method. The authors discussed that such alteration in lymphatic drainage may contribute to the pathogenesis of chronic inflammation in CD.

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