The nonspecific nature of fibrin thrombi in ischemic bowel disease

ALI H. QIZILBASH, FRCP[C]

Twenty cases of ischemic bowel disease were analysed to determine the frequency and significance of fibrin thrombi in this condition. Fibrin thrombi were present in all 10 patients with occlusive ischemic bowel disease and in 7 of the 10 patients with nonocclusive ischemic bowel disease. In addition, fibrin thrombi were noted in a wide variety of specific and nonspecific inflammatory bowel diseases and in acute appendicitis. We conclude that fibrin thrombi are a nonspecific feature of tissue necrosis and that their mere presence in the bowel should not be regarded as an expression of disseminated intravascular coagulation.

Vingt cas de maladie ischémique de l'intestin ont été analysé dans le but de déterminer la fréquence et la signification des thrombi de fibrine retrouvés dans cette maladie. Des thrombi de fibrine étaient présents chez les 10 patients souffrant de maladie ischémique occlusive de l'intestin et chez 7 des 10 patients présentant une maladie ischémique nonocclusive de l'intestin. De plus, des thrombi de fibrine ont été observés dans une grande variété de maladies inflammatoires spécifiques et nonspécifiques de l'intestin et dans l'appendicite aiguë. Nous concluons que les thrombi de fibrine représentent une caractéristique nonspécifique de nécrose tissulaire et que leur seule présence dans l'intestin ne devrait pas être considérée comme l'expression d'une coagulation intravasculaire disséminée.

The spectrum of clinical features and of roentgenographic and pathologic changes observed following episodes of intestinal ischemia has been extensively described over recent years.[1-4] Ischemic bowel disease may have as its basis either occlusive or nonocclusive vascular disease. Renton[5] has estimated that in 32% of the reported cases there was no evidence of vascular obstruction. However, in a recent review we found that definite vascular occlusion accounted for only 41% of the cases of ischemic bowel disease.[4]

Intestinal infarction secondary to nonocclusive mesenteric ischemia is being recognized with increasing frequency. Most investigators believe that the majority of these cases are caused by a low flow state affecting the bowel circulation. The basic causes of such low flow states are cardiac failure, hypovolemia and splanchnic vasoconstriction.[6] Margaretten and McKay[7] and Whitehead[8] postulated that ischemic enterocolitis, in the absence of demonstrable vascular occlusion, is an expression of intravascular coagulation. Whitehead[8] believed that conditions such as staphylococcal enterocolitis, necrotizing enterocolitis and pseudomembranous enterocolitis probably represent examples of ischemic bowel disease of which the common denominator is fibrin thrombi in capillaries and venules. Bogomoletz[9] described fibrin thrombi in five cases of clindamycin-associated colitis and suggested that these thrombi were probably the primary cause of the colitis, with clindamycin playing a secondary role. In a recent study Brandt and colleagues[10] analysed the significance and frequency of fibrin thrombi in occlusive and nonocclusive bowel ischemia. Their results suggested that the presence of fibrin thrombi was a nonspecific feature of necrosis since they could be identified not only in occlusive and nonocclusive bowel ischemia but also in other examples of inflammatory bowel disease.

The study reported in this paper was undertaken to determine the frequency and significance, if any, of fibrin thrombi in various types of ischemic and inflammatory bowel disease.

Methods

Sections of small and large intestine from 10 patients with occlusive bowel disease were studied. The group comprised six patients with venous thrombosis, two with arterial thrombosis and two with mechanical vascular obstruction. In addition, histopathologic examination was made of specimens of intestine taken from patients suffering from other forms of bowel disease — 10 patients with ulcerative colitis, 10 with Crohn's disease, 2 with clindamycin colitis, 1 with staphylococcal enteritis, 1 with amebic colitis and 10 with acute appendicitis. All tissue sections studied, except that from the case of staphylococcal enteritis, were obtained at operation.

All material was fixed in 10% formalin and embedded in paraffin. Sections were stained with hematoxylin–eosin. Lendrum's MSB method[11] was used to stain fibrin. Multiple sections were examined in each case, from both the infarcted and the nonnecrotic bowel. Sections were carefully scrutinized for the presence of fibrin thrombi. When found, their number was not quantitated, as in the study of Brandt and associates,[10] but merely recorded as few, moderate or numerous.

Results

Occlusive ischemic bowel disease

Necrosis was present throughout the thickness of the bowel in all 10 cases. Fibrin thrombi were identified in sections from 9 of the 10 patients in this group. They were a prominent feature in six, while in the other three only a few were noted. No fibrin thrombi were found in one patient with an incarcerated hernia. Thrombi were present in all layers of the intestine in seven cases. However, they were most numerous in the mucosa and submucosa and were seen mainly in the capillaries and venules (Fig. 1).

Nonocclusive ischemic bowel disease

Fibrin thrombi were identified in 7 of the 10 specimens studied but were not as numerous as in the former group. They were generally noticeable in the mucosa, while the submucosa showed marked hemorrhagic conges-

From the departments of laboratory medicine, McMaster University and Henderson General Hospital, Hamilton

Reprint requests to: Dr. Ali H. Qizilbash, Department of laboratory medicine, Henderson General Hospital, 711 Concession St., Hamilton, Ont. L8V 1C3

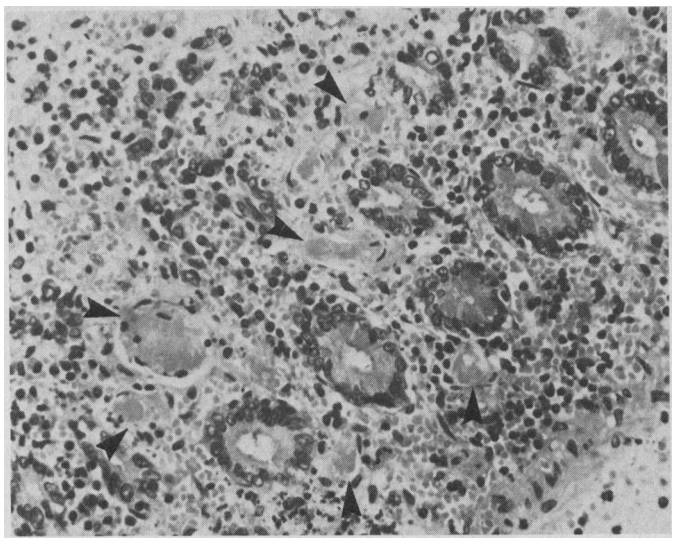

FIG. 1—Fibrin thrombi (arrows) in capillaries and venules of mucosa of patient with mesenteric venous thrombosis (hematoxylin–eosin [H–E]; ×312, reduced 25%).

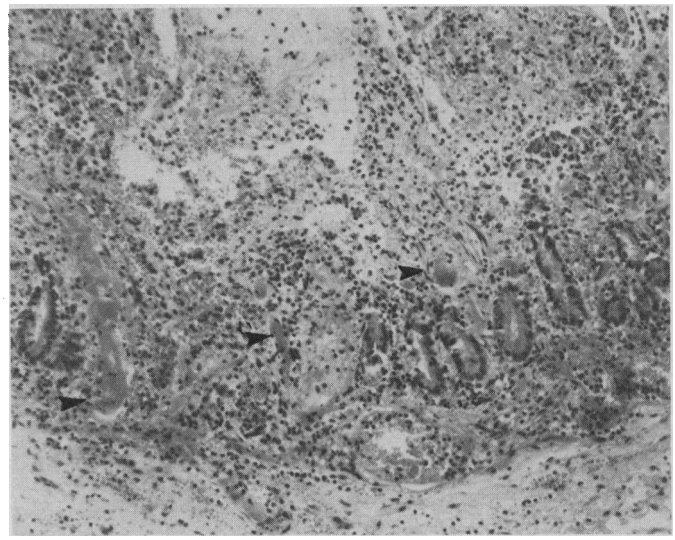

FIG. 2—Fibrin thrombi (arrows) in small vessels of mucosa of patient with nonocclusive intestinal ischemia (H–E; ×125, reduced 25%).

tion and edema (Fig. 2). In the three cases in which no thrombi could be found the sections of intestine showed scanty surviving mucosa, with transformation of the superficial portion of the bowel wall into granulation tissue.

Miscellaneous diseases

Among the 20 cases of ulcerative colitis or Crohn's disease, fibrin thrombi were noted adjacent to the ulcerated areas or in severely inflamed areas in only 5 cases. They were few in number and found only after careful search. Seven of the cases of Crohn's disease involved the small bowel and in three the colon was affected. No relation could be established between the presence of thrombi and the extent or location of the disease.

The intestinal wall of each of the two patients with clindamycin colitis contained numerous fibrin thrombi and areas of mucosal necrosis. The thrombi were present in small capillaries and venules. In one case thrombi extended into the underlying submucosa, which was very hemorrhagic and edematous.

In the patient with staphylococcal enteritis moderate numbers of fibrin thrombi were noted in the intestinal mucosa. The mucosa showed inflammation and necrosis and was covered by a layer of fibrinous exudate containing large colonies of staphylococci.

One patient underwent emergency colectomy because of toxic dilatation of the colon. Histologic examination of the specimen showed amebic colitis with numerous flask-shaped ulcers, in the walls of which were numerous trophozoites of *Entamoeba histolytica*. In the small capillaries and venules of necrotic zones fibrin thrombi were identified.

Ten surgical specimens from cases of acute appendicitis were also studied. Eight of the appendices contained moderate numbers of fibrin thrombi. The thrombi were present in all layers of the appendix in three cases. All the appendices showed transmural necrosis, hemorrhage and polymorphonuclear infiltration.

Discussion

It has been suggested that intravascular fibrin thrombi play an important role in the pathogenesis of ischemic necrosis of the bowel in patients in whom no occlusion of the larger vessels is demonstrable.[7,8] We found that fibrin thrombi could be demonstrated with relative ease in both occlusive and nonocclusive bowel ischemia. The thrombi were of recent origin and showed no evidence of organization. They were present in 9 of the 10 cases of occlusive ischemic bowel disease and in only 7 of the 10 with nonocclusive bowel ischemia. The fibrin thrombi were more numerous in the former group. They were prominent in areas of fresh mucosal necrosis and were no longer detected once the mucosa was shed and replaced by granulation tissue. In the three cases of nonocclusive bowel ischemia in which no fibrin thrombi were demonstrated the colon showed large areas of mucosal ulceration with formation of granulation tissue. Fibrin thrombi may have been present initially but they were not by the time the specimen was surgically removed. Colonic ischemia is generally the result of episodes of hypoperfusion not attended by vascular occlusion and is generally associated with good recovery. In a review of ischemic bowel disease that I and my colleagues reported earlier,[4] conservative management resulted in complete recovery in 5 of 11 patients with ischemic colitis.

In the present study fibrin thrombi were found not only in both occlusive and nonocclusive ischemic bowel disease, but also consistently in a wide spectrum of specific and nonspecific inflammatory bowel disease. Fibrin thrombi were identified in the mucosal capillaries and venules of the appendix in 8 of the 10 patients with acute appendicitis. They were also noted in two cases of clindamycin-induced pseudomembranous colitis and in one case each of amebic colitis and staphylococcal enteritis.

It appears that, in a wide variety of conditions, fibrin thrombi represent a nonspecific feature of necrosis. Their formation in ischemic tissues is probably a terminal event rather than the primary cause of ischemia, as suggested by some earlier workers.[7,8] Why thrombi are found in some cases and not in others may be explained by the loss of large areas of mucosa as a result of necrosis and shedding. My findings confirm the observation

of Brandt and colleagues,[10] who also have recently emphasized the nonspecific nature of fibrin thrombi in ischemic bowel disease.

References

1. MARSTON A, PHEILS MT, THOMAS ML, et al: Ischemic colitis. *Gut* 7: 1, 1966
2. MCGOVERN VJ, GOULSTON SJM: Ischemic enterocolitis. *Gut* 6: 213, 1965
3. MARSHAK RH, LINDNER AE: *Radiology of the Small Intestine,* Philadelphia, Saunders, 1970, pp 111-34
4. CASTELLI MF, QIZILBASH AH, SALEM S, et al: Ischemic bowel disease. *Can Med Assoc J* 111: 935, 1974
5. RENTON CJC: Non-occlusive intestinal infarction. *Clin Gastroenterol* 1: 655, 1972
6. MARCUSON RW: Ischemia of the colon. *Br J Hosp Med* 11: 203, 1974
7. MARGARETTEN W, MCKAY DG: Thrombotic ulceration of the gastrointestinal tract. *Arch Intern Med* 127: 250, 1971
8. WHITEHEAD R: Ischemic enterocolitis: an expression of the intravascular coagulation syndrome. *Gut* 12: 912, 1971
9. BOGOMOLETZ WV: Fibrin thrombi, a cause of clindamycin-associated colitis? *Gut* 17: 483, 1976
10. BRANDT LJ, GOMERY P, MITSUDO SM, et al: Disseminated intravascular coagulation in nonocclusive mesenteric ischemia: the lack of specificity of fibrin thrombi in intestinal infarction. *Gastroenterology* 71: 954, 1976
11. LENDRUM AC, FRASER DS, SLIDDERS W, et al: Studies on the character and staining of fibrin. *J Clin Pathol* 15: 401, 1962

Carotid body tumours

Two thirds of carotid body tumours occur in males. These tumours are familial and may be associated with other chemoreceptor tumours. Since they grow and spread locally all carotid body tumours may be considered functionally malignant; few metastasize to local lymph nodes, and even fewer to distant locations.

In a recent issue of Surgery *(80: 365, 1976) Dent, Thompson and Fry review their experience with carotid body tumours; they restrict the term to chromaffin paragangliomas arising from the carotid body at the bifurcation of the common carotid artery. Over a 30-year period there were only 15 patients, 1 of whom had bilateral tumours. All were followed up for at least 7 years.*

At the time of initial assessment all patients had a palpable neck mass at the angle of the jaw. In growing, the tumour pushes the internal and external carotid arteries apart and extends up either or both for a variable distance; the tumour may metastasize to local lymph nodes and may erode through the skull as it follows the internal carotid artery. For initial evaluation the authors recommend arteriography, which they claim is diagnostic. Biopsy is contraindicated because microscopic findings do not influence treatment decisions; it is not possible to differentiate benign from malignant tumours histologically.

For subadventitial excision Dent and colleagues recommend a transverse skin incision and sacrifice of the external carotid artery; a groin and upper thigh were prepared in case saphenous vein replacement of the carotid artery should become necessary. The hypoglossal nerve must be handled with great care to avoid its damage. If the tumour surrounds the artery it must be incised vertically to be completely removed. When the tumour is most adherent at the angle of the carotid bifurcation carotid artery repair, by direct suture or by the use of a vein or prosthetic patch, may become necessary. When a subadventitial plane cannot be developed the tumour is considered invasive and excision of the carotid artery may be required, as in 25% of cases in this series. The risk is substantially greater for the patient, but when the choice lies between subtotal excision of the tumour and replacement of the carotid artery the authors favour the latter.

After total excision there were no serious complications in this series. The operation results in considerable blood loss; the average volume replaced in this series was 2 L. To help reduce blood loss some surgeons have used an internal shunt.

Preoperative radiation leads to fibrosis and makes definition of tissue planes more difficult. The authors recommend radiation therapy only if the patient carries a prohibitive surgical risk. ■