FOR DEBATE

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Is "Ischemic" Colitis Ischemic?

ABSTRACT: Ischemic colitis appears to be a collection of diseases rather than a single entity. On the one hand, there is the colitis that truly appears to be caused by a lack of blood flow and, on the other hand, there is the disease that is called "ischemic" for lack of a better diagnosis—the colitis that is more "idiopathic" than "ischemic." Four widely held tenets of "ischemic" colitis are wrong: 1) the colon is not particularly sensitive to ischemia; 2) ischemic colitis is rarely preceded by a period of global hypoperfusion; 3) the "watershed areas" are not disproportionately affected; and 4) colonoscopy with biopsy is not specific for the disease. The cause of "ischemic" colitis is unknown. Therefore it is, until proven otherwise, "acute idiopathic colitis."

John Smith is a 72-year-old man with a 40–pack-year smoking history. On the morning after his abdominal aortic aneurysm repair, he complains of severe abdominal pain and starts passing bloody stools. He is brought urgently to the operating room where the left colon is found to be dark gray and no mesenteric pulse is detectable. The colon is resected. Final pathology: ischemic colitis.

Jane Smith is a 55-year-old woman who was in excellent health until she developed acute-onset, left-sided abdominal pain and bloody diarrhea. She is evaluated in the emergency room, where a CT scan shows a thickened left colon wall. Colonoscopy the next morning shows submucosal hemorrhage and patchy mucosal ulceration. Biopsies are obtained. Jane is treated with bowel rest and antibiotics and is discharged home feeling well on her third hospital day. Final pathology: ischemic colitis.

Jane's subsequent evaluation includes normal results on a cardiac echocardiogram and a mesenteric angiogram. Jane lives another 30 years and never has another similar episode.

Did Jane and John really have the same disease?

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Ischemic colitis was first recognized in 1963 by Boley and colleagues.[1] Today, most clinicians can recite the 4 most widely held tenets of the disease: 1) the colon is particularly sensitive to ischemia; 2) ischemic colitis is often preceded by a period of global hypoperfusion; 3) the most vulnerable portions of the colon are the "watershed areas," including the splenic flexure and the rectosigmoid; and 4) colonoscopy with biopsy confirms the diagnosis. Unfortunately, all of these statements are false.

Ischemic colitis is a spectrum of illnesses. On one end is the colitis that is clearly caused by ischemia. Ischemia can be caused by occlusion, ligation, or exclusion of the named vessels (ie, after an abdominal aortic aneurysm repair) or a combination of low flow and vasoconstriction (the ischemic colitis a patient with sepsis develops on high-dose pressors in the intensive care unit). However, the rest of the spectrum now known as "ischemic" colitis may have different causes entirely. In fact, there is very little evidence to suggest that the proximate cause of most "ischemic" colitis is ischemia.

MYTH ONE: THE COLON IS UNIQUELY SENSITIVE TO ISCHEMIA

Animal studies suggest that colonic ischemia is difficult to produce experimentally. Matthews and Parks[2] failed to produce ischemic damage to the canine colon after ligating the common colic artery, which gives rise to the ileocolic, right colic, and middle colic arteries. They were similarly unable to produce ischemic damage with ligation of the common colic artery followed by gradual occlusion of the inferior mesenteric artery (IMA). Immediate occlusion of both vessels was required to produce ischemic damage. In another set of experiments, these investigators showed that no ischemic colitis occurred when they used hypovolemia to effect a 75% reduction in mesenteric blood flow. Ligation of the common colic artery had to be added to produce ischemia.[3]

Elevated intraluminal pressure is often cited as a factor in ischemic colitis. To examine its contribution to ischemic colitis, Brookstein[4] used a combination of systemic hypoperfusion and increased intraluminal colonic pressures in

a dog model. He was unable to demonstrate ischemic damage using increased intraluminal pressures alone until he exceeded 60 mmHg, a level well beyond those encountered clinically, even in cases of complete large-bowel obstruction. Brookstein was unable to create full-thickness injuries with his model. He was able to demonstrate mucosal ischemia using a combination of elevated intraluminal pressures and systemic hypotension, but only when the differences between mean systemic and intraluminal pressures dropped below 30 mmHg. However, even at these extremely low perfusion pressures, the muscularis propria was spared.

The small intestinal mucosal appears to be far more vulnerable to ischemia than does the colonic mucosa. For example, Robinson and colleagues[5] demonstrated that dog enterocytes lost all ability to concentrate amino acids and sugars against a concentration gradient after 30 minutes of ischemia, whereas dog colonocytes showed only slight reduction in this ability after 60 minutes.

In humans, the relative resilience of the colon to ischemia is seen every day following aortic reconstructions. The aorta is cross clamped above the IMA, occasionally above the superior mesenteric artery, severely limiting the perfusion of the colon for more than 30 minutes. Despite this profound hypoperfusion of the hindgut, more than 95% of patients undergoing these procedures never experience ischemic colitis.[5–8] It is also worth noting that these are not otherwise healthy patients. People undergoing aortic repairs tend to share a common set of comorbidities: age greater than 60, peripheral vascular disease, diabetes, hypertension, hyperlipidemia, and a history of tobacco use. Considering 95% of patients with these comorbidities can tolerate a clamp across their aorta for more than 30 minutes, it becomes harder and harder to blame ischemia for the colitis that develops spontaneously in the otherwise asymptomatic, outpatient population.

MYTH TWO: "ISCHEMIC" COLITIS IS OFTEN PRECEDED BY A PERIOD OF GLOBAL ISCHEMIA

This assertion has persisted despite a lack of evidence to corroborate it. In fact, most "ischemic" colitis occurs spontaneously and no specific cause can be identified.[6,7,9–13] Williams and Wittenberg[10] were unable to identify a cause in 46 of 55 patients with "ischemic" colitis. Four cases occurred early after IMA ligation: one patient had colonic obstruction and 4 patients had "ischemic" colitis occurring late after abdominoperineal resection. Preventza and colleagues[11] examined 39 patients under the age of 50 years and found that in only 4 patients (10% of cases) was "ischemic" colitis preceded by hypovolemia or other low-flow states.

When the Kaiser Permenante group reviewed their last 424 cases of ischemic colitis (IC), they found that 400 (94%) cases occurred in outpatients. Only 6% occurred in people who were previously ill enough to be hospitalized. An increasingly reported form of IC, so-called "runner's colitis," occurs in endurance athletes. This fact underlines the point that IC is generally not caused by global ischemia. These individuals are generating cardiac outputs upwards of 25 L/min[15] when they incur their colitis. Splanchnic vasoconstriction, hypovolemia, hyponatremia, and polycythemia, but not global ischemia, are thought to cause "runner's colitis."[8,9]

MYTH THREE: MOST CASES OF ISCHEMIC COLITIS OCCUR AT THE TENUOUS "WATERSHED" AREAS

Watershed zones are said to exist where the colon is supplied by the terminal branches of 2 named vessels. It is widely assumed that colonic blood flow is most tenuous at these locations, thereby placing them at greatest risk of ischemic events. There are 2 watershed areas in the colon. The splenic flexure (Griffith's point) gets flow from both the superior mesenteric artery and the IMA via the marginal artery of Drummond, which is present in 95% of people. The rectosigmoid junction (Sudek's point) has a shared blood supply from both the IMA and the middle rectal arteries. For all the attention these so-called watershed zones receive, most IC does not occur at these 2 areas.

The Mayo Clinic examined their 15-year experience with IC between 1976 and 1991 and found that only 10 of 328 (3%) cases were isolated to Sudek's point.[16] Other authors have found that the rectosigmoid colon is only involved in 3% to 5% of cases.[6,9]

Between 1970 and 1982, 87% of all deaths in Malmö, Sweden were studied at autopsy. Of the 23,446 autopsies performed, IC was determined to be the cause-specific mortality for 1.7 of every 1,000 deaths. The most common areas affected by the disease were not the watershed areas; they were the sigmoid colon—involved in 83% of cases—and the descending colon (77%).[17]

The most famous watershed zone, the splenic flexure, is only involved in approximately 25% of "ischemic" colitis cases.[6,9,18] It is even less common (14%) for the splenic flexure to be the sole area involved.[19]

"Runner's colitis," a form of IC that affects endurance athletes, overwhelmingly affects the cecum and proximal colon,[20–23] 2 areas fed entirely by the superior mesenteric artery.

These data suggest that the watershed zones of the colon are not particularly vulnerable to ischemia. Perhaps it is more accurate to consider them ischemia-resistant, based on their dual circulation.

MYTH FOUR: COLONOSCOPY AND BIOPSY ARE SPECIFIC FOR ISCHEMIC COLITIS

Colonoscopic findings in IC include erythematous and edematous mucosa, ulcerations, and submucosal

hemorrhages, petechial bleeding, and sharply defined segments of involvement.[19,24] Pseudomembranes not related to *Clostridium difficile* infection may also be present.[25] Unfortunately, these findings are nonspecific and can be seen in inflammatory and infectious disease as well. Patients with chemical colitis can reveal similar endoscopic findings including ulcerations and friable, hemorrhagic, and necrotic mucosa.[26]

Likewise, histologic features of IC are also nonspecific. Lamina propria hemorrhage, hemosiderin-laden macrophages, capillary thrombosis, gland atrophy, granulation tissue with crypt abscesses, and pseudopolyps are seen in IC. However, combinations of these findings are also seen in Crohn's disease and infectious colitis.[9,19,24,25]

It is unfortunate that colonoscopy and biopsy are considered to be the standards for the diagnosis of "ischemic" colitis.[7] In actual practice, neither test measures up.

ADDITIONAL OBSERVATIONS

Ischemic colitis appears to be a collection of diseases rather than a single entity. On the one hand, there is the colitis that truly appears to be caused by a lack of blood flow (John Smith) and, on the other hand, there is the disease that is called "ischemic" for lack of a better diagnosis—the colitis that is more "idiopathic" than "ischemic" (Jane Smith).

Even among cases of true IC the large- and medium-sized arteries are rarely involved.[5,6,7,9] An important exception is the IC that develops after the IMA has been ligated or excluded during the open or endovascular repair of an abdominal aortic aneurysm. But the patient with sepsis who has pneumonia and develops IC after being placed on 4 pressors almost always has patent mesenteric vessels and arcades. Therefore, the disease likely occurs at the level of the arteriole. Established and emerging science strongly suggests that the renin-angiotensin axis causes splanchnic vasoconstriction, and not vasopressin or the α-adrenergic autonomic system.[11,27–30] The colons of pigs in shock are spared ischemic damage when the pigs are treated with captopril, and when their kidneys are removed, but not when they are given α or vasopressin blockade.[11]

Ninety-four percent of people with IC remain free of recurrences at 4 years.[14] Consider the following thought experiment. Assume that most IC is caused by a hyperresponsiveness of the colonic arteries to angiontensin II. Why then are these patients not getting more recurrences? Where are large studies of recurrent IC, and trials of angiotensin-converting enzyme inhibitor prophylaxis? Where are there precedents of noninfectious diseases happening once to an individual and never again? People with severe coronary artery disease experience angina again and again, not just once. Individuals with atherosclerotic peripheral vascular disease do not just have one episode of claudication in their lives; it plagues them until they are treated. Patients experiencing transient ischemic attacks frequently have cerebrovascular accidents if the causative carotid stenosis is not repaired. If there is a macroscopic vascular lesion causing "ischemic colitis," why do affected individuals not more commonly have repeat attacks? And if the disease is caused by hypersensitivity to angiotensin II, why do such hyperresponsive individuals have clinical problems just once in their life and never again? When viewed through this lens, IC more closely resembles infectious colitis. And just as "ischemic" colitis tends to be a localized process, so too do various colonic pathogens have predilections for one area of the colon or another. For example, *Escherichia coli* 0157:H7, CMV, and intestinal tuberculosis are known to preferentially affect the cecum/ascending colon, whereas *C difficile* most often affects the left colon.

CONCLUSIONS

The entity known as IC is truly a spectrum of illnesses, but it can be divided into 2 groups: one that is actually ischemic and another that almost certainly is not. In this second group, "ischemic" colitis has become a convenient catchall term for colitis whose actual cause is unknown.

No test is specific for IC, but there is very little evidence to suggest that ischemia is actually the cause of most cases of "ischemic" colitis. We do not know the cause of "ischemic" colitis, and indeed the lack of pathologic specificity leaves open the possibility that there can be more than one. Given the typical pattern of disease (acute onset, self-limited course, lack of recurrence), we are tempted to believe that the cause is infectious, and as *Helicobacter pylori* and *Tropheryma whipplei* attest, gastrointestinal pathogens can take many years to discover. But, be that as it may, for now, let us stop accepting the false certainty of the pathogenesis that the name "ischemic colitis" implies. It is, until proven otherwise, "acute idiopathic colitis."

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