Histopathology of infectious colitis

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ABSTRACT: Histopathology can play an important role in diagnosing infectious colitis for several reasons. First, colonic mucosal biopsy can often reliably differentiate acute self limited colitis (ASLC), or infectious type colitis, from idiopathic inflammatory bowel disease (IBD). In ASLC, crypt architecture is normal and the inflammatory infiltrate in the lamina propria is predominantly acute, ie, polymorphonuclear cells. In IBD, in contrast, crypt architecture is often abnormal and the inflammatory infiltrate in the lamina propria in both acute and chronic, ie, polymorphonuclear cells, plasma cells and lymphocytes are present in increased numbers. Second, biopsy may give a clue to the specific infection. Biopsy may reveal the presence of specific parasites such as *Entamoeba histolytica*, cryptosporidia or schistosomiasis. Viral inclusions are seen when cytomegalovirus or herpes simplex type II virus infect the colon. Granulomas usually indicate Crohn's disease but can be seen with infections due to *Chlamydia trachomatis*, *Treponema pallidum* and *Mycobacterium tuberculosis*. Both chlamydial and syphilitic proctitis are rare and usually seen in homosexually active men. Finally, pseudomembranes, when present, suggest pseudomembranous colitis due to an overgrowth of toxigenic *Clostridium difficile*. In summary, mucosal biopsy is helpful in differentiating ASLC from IBD in most cases. Sometimes, it provides a clue to the specific infection. *Can J Gastroenterol* 1989;3(4):165-169

Key Words: Acute self limited colitis, Colonic biopsy, Inflammatory bowel disease

Histopathologie de la colite infectieuse

RESUME: L'histologie pathologique peut jouer un rôle important dans le diagnostic de la colite infectieuse et cela, pour plusieurs raisons. Premièrement, une biopsie des muqueuses du côlon suffit souvent à distinguer avec certitude la colite aiguë spontanément résolutive (ASLC) ou la colite de type infectieux, des affections intestinales inflammatoires idiopathiques (IBD). Dans l'ASLC, l'architecture de la glande muqueuse est normale et l'infiltration inflammatoire dans le chorion de la membrane est surtout aiguë, c'est-à-dire qu'elle consiste de granulocytes. Dans l'IBD, au contraire, l'architecture de la glande muqueuse est

WHEN A PATIENT PRESENTS WITH colitis, a frequent question is whether this is an acute self limited colitis (ASLC), infectious type colitis or the first episode of inflammatory bowel disease (IBD), specifically ulcerative colitis or Crohn's disease. History and physical exam are rarely helpful in answering the question and sigmoidoscopy in infectious colitis is usually indistinguishable from acute ulcerative colitis. Stool cultures grow pathogens in 40 to 60% of cases of ASLC but can also be positive in patients with ulcerative colitis with superinfection. The clinical course may be helpful because patients with ASLC will often improve rapidly and no further diagnostic tests are necessary.

When the illness lingers, or there is no response to treatment, it becomes more important to distinguish ASLC from IBD. In these situations, mucosal biopsy is very helpful because it can often differentiate ASLC from IBD, especially ulcerative colitis. In addition, it may give a clue to the specific infection in ASLC.

DIFFERENTIATION OF ASLC FROM IBD

While a normal rectal biopsy demonstrates normal parallel crypts (Figure 1), one of the hallmarks of histologic diagnosis of ulcerative colitis is

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souvent anormale et l'infiltration inflammatoire dans le choriion de la membrane est à la fois aiguë et chronique; c'est-à-dire que les granulocytes, les plasmocytes et les lymphocytes sont présents en nombres accrus. Deuxièmement, la biopsie peut fournir un indice sur la spécificité de l'infection: elle peut révéler la présence de parasites tels *Entamoeba histolytica*, cryptosporidia ou la schistosomiase. Les inclusions virales sont repérées quand le cytomégalo virus ou le virus de l'herpès de type II infecte le côlon. Les granulomes indiquent habituellement la maladie de Crohn mais peuvent également accompagner les infections dues à *Chlamydia trachomatis*, à *Treponema pallidum* et le tuberculose miliaire. Les practites à chlamydia et syphilitiques sont rares et habituellement vues chez les homosexuels actifs. Finalement, les pseudomembranes, quand elles sont présentes, suggèrent une colite pseudomembraneuse due à une prolifération de bactéries toxigéniques *Clostridium difficile*. En résumé, la biopsie des muqueuses aide à distinguer l'ASLC des IBD dans la plupart des cas. Elle fournit parfois un indice sur la spécificité de l'infection.

crypt distortion (Figure 2). This is almost universal in ulcerative colitis, and is usually diffuse. In addition, there is diffuse mucosal inflammation, with increased numbers of both acute and chronic inflammatory cells, ie, polymorphonuclear cells as well as plasma cells and lymphocytes (Figure 2). Crohn's disease, in contrast, is segmental or focal and crypt architecture thus may be normal or abnormal. Similarly, the cellularity of the lamina propria may be normal or increased, depending on whether or not the colon is involved (Table 1).

In ASLC crypt architecture remains normal and the increased inflammatory cells in the lamina propria are predominantly acute, ie, polymorphonuclear cells (Figure 3). Because of these differences in crypt architecture and inflammation, mucosal biopsy can reliably differentiate these two diseases (1-3). In Crohn's disease, however, the distinction may not always be so clear-cut. Focal inflammation and preservation of normal architecture may occasionally be confused with resolving ASLC (2). Clinical correlation will usually resolve this. Granulomas are the diagnostic hallmark of Crohn's disease but can occasionally be seen with specific infections, such as tuberculosis or proctitis of homosexually active men (*Chlamydia trachomatis* and syphilis)(4).

The typical histologic picture of ASLC, then, is of acute inflammation with normal crypt architecture. This can be seen in colitis due to campylo-

bacter, salmonella, shigella, invasive *Escherichia coli* and other infections; biopsy alone cannot distinguish among

these infections (6,7). Others have suggested that rectal biopsy should be taken in the first four days of illness because histologic differentiation will be most accurate (2). This is impractical because in many cases, patients with ASLC recover quickly or positive stool cultures will become available, making biopsy unnecessary (5).

Occasionally, crypt architecture may be abnormal in infectious colitis including shigella and salmonella. Reports of colonic biopsies taken from patients during an epidemic of shigella dysentery in Calcutta revealed frequent distortion of crypt architecture and chronic inflammatory cells in the lamina propria (8). These changes, however, may represent differences in the patient population or a response to

TABLE 1

Histopathology of acute self limited colitis and inflammatory bowel disease

	ASLC	Ulcerative colitis	Crohn's disease
Crypt architecture	Normal	Diffusely abnormal	Focally abnormal (or diffuse)
Lamina propria inflammation	Acute inflammatory cells	Acute and chronic	Acute and chronic
Granulomas	Rare (specific infections*)	Never	Frequent

*Infections such as *Chlamydia trachomatis* or syphilitic proctitis as well as tuberculosis; ASLC Acute self limited colitis

Figure 1) Low power photomicrograph of a normal rectal biopsy. Note the normal surface epithelium, normal parallel crypts (C) and lack of inflammation in the lamina propria. M Muscularis mucosa; SM Submucosa. All biopsies stained with hematoxylin and eosin, alcian blue, saffron (X 28)

Figure 2) Rectal biopsy from a patient with chronic ulcerative colitis shows surface microulceration (arrow), distorted crypts and a diffuse increase in acute and chronic cells in the lamina propria (X 23.5)

Figure 3) Rectal biopsy from a patient with infectious colitis. Normal crypt architecture is preserved; there is a diffuse mild increase in polymorphonuclear cells in the lamina propria (X 20.5)

that specific pathogen which killed 2200 people in an epidemic affecting 78,000 people. Crypt architecture may also be abnormal in healed ischemic colitis. Clinical correlation may help to clarify this.

DIAGNOSIS OF SPECIFIC INFECTIONS

Mucosal biopsy can diagnose specific infections when the following histologic features are present: parasites, viral inclusions, granulomas or pseudomembranes and spirochetosis (Table 2)

Parasites: Most intestinal parasites infect the small intestine, but *Entamoeba histolytica* and schistosomiasis also cause colonic disease. In colonic amebiasis, superficial mucosal ulceration is seen.

When biopsied, the classic finding is erosions over lymphoid follicles. There is usually little associated inflammatory reaction in the colonic mucosa. Figure 4 shows amoeba trophozoites in the mucus adherent to the biopsy surface. Higher power is necessary to identify the organisms, often with phagocytosed red blood cells, indicating mucosal invasion.

Schistosomiasis is rare in Northern America and usually occurs in immigrants from areas where the disease is endemic. Mucosal biopsy reveals foreign body granulomas which form around the ova (Figure 5). It is not always possible to diagnose the specific infection unless characteristic morphology of the ovum is present.

Cryptosporidia usually infects the

small intestine (9), but with overwhelming infection in immunosuppressed patients the parasite can be seen in the colonic crypt lumen, adherent to surface epithelial cells. Stool examination is virtually diagnostic and rectal biopsy is rarely necessary.

Viruses: Two viruses of the herpes family can cause colonic disease: herpes simplex virus type II and cytomegalovirus. Both can cause disease in immunocompetent individuals but cause more severe colonic disease when immune function, especially cellular immunity, is impaired.

Herpes simplex proctitis follows receptive anal intercourse and is thus usually seen in homosexually active men (10). It causes a painful proctitis, usually limited to below 10 cm in the rectum. Associated symptoms of posterior thigh pain, voluntary constipation and difficulty in micturition

Figure 4) Rectal biopsy from a patient with amebiasis shows exudate adherent to the biopsy surface. The crypts are tangential due to sectioning artefact (X 21.5). Higher power view (right) reveals amoebae in the surface mucus (arrow) (X 86.5)

TABLE 2
Histologic findings in colonic biopsy which suggest specific infections

Histologic finding	Specific infection
Parasites	<i>Entamoeba histolytica</i>
	Schistosomiasis
	Cryptosporidiosis
Viral inclusions	Herpes simplex II
	Cytomegalovirus
Granulomas	Tuberculosis
	<i>Chlamydia trachomatis</i>
	<i>Treponema pallidum</i>
	Yersinia
	<i>Clostridium difficile</i>
Pseudo-membranes

Figure 5) Rectal biopsy from a Yemenite with schistosomiasis. Lower power view (left) shows normal mucosa with foreign body granulomas in the submucosa (arrows) (X47.5). A higher power view (right) of granuloma formation around the schistosome ova was taken from another area (X127).

suggest associated sacral nerve root involvement.

Histologically, acute and chronic inflammation is present in the lamina propria and submucosa. Viral inclusions are infrequent, as the virus has a propensity to infect squamous epithelial cells. The rectal mucosa has an intense inflammatory infiltrate in the lamina propria and/or submucosa. Multinuclear cells and intranuclear inclusions can be seen; inclusion cells are usually seen only if the base of an ulcer is biopsied.

Cytomegalovirus causes a self limited colitis in immunocompetent individuals (11) but this is not widely

recognized. It is an opportunistic pathogen in immunodeficient patients and is a frequent cause of disease in persons with the acquired immune deficiency syndrome (AIDS). Colonic involvement with cytomegalovirus ranges from aphthous ulcers to deep ulcers to diffuse colitis. The virus infects endothelial cells most commonly and is rarely seen in epithelial cells. A typical cytomegalovirus cell is large, with a large intranuclear inclusion surrounded by a clear halo; the cytoplasm is enlarged and may be granular, indicating the cytoplasmic component of the virus (Figure 6). When an ulcer is present, biopsies from the edge are most likely

to reveal cytomegalovirus inclusion cells.

Granulomas: Although classic epithelioid granulomas are the hallmark of Crohn's disease, they can occur with specific infections. Two organisms which cause proctitis in homosexually active men are *Chlamydia trachomatis* (Figure 7) and *Treponema pallidum*. *Yersinia enterocolitica* can also cause granulomas and may mimic Crohn's disease (12). In addition, tuberculosis is still frequent in some parts of the world as a cause of colonic disease.

Figure 6) A rectal biopsy (left) from a homosexual HIV negative man with a self limited cytomegalovirus proctitis showed intense lamina propria inflammation and typical cytomegalovirus inclusion (arrow) (X90). A higher power view (above) of the cytomegalovirus cell shows a large intranuclear inclusion with a clear surrounding halo and enlarged cytoplasm with granularity (X500).

Figure 7) Rectal biopsy from a homosexual man with *Chlamydia trachomatis* proctitis showed numerous granulomas. This higher power view shows a granuloma; it is a collection of epithelioid cells and a Langhans' type giant cell (arrow) (X 137.5)

Pseudomembranes: Classical pseudomembranous colitis is caused by an overgrowth of toxigenic *Clostridium difficile*, usually due to antibiotic therapy. The sigmoid appearance is classic, with yellow plaques adherent to the mucosa, with friable mucosa beneath. Histologically, there is normal architecture, superficial edema and little inflammation

in the lamina propria, but a dramatic pseudomembrane composed of fibrin and debris and inflammatory cells which 'erupt' from the surface.

Pseudomembranes can occasionally be seen in Crohn's disease, ischemic colitis and other diseases, including *Escherichia coli* O157:H7 (13).

Intestinal spirochetosis: Intestinal

spirochetosis, first described in 1967 (14), has been recognized with increasing frequency, especially in homosexual men (15,16). The organism, a non-*Treponema pallidum* spirochete, adheres to the luminal surface of the colonic mucosa and can be seen in asymptomatic patients, as well as patients with colonic symptoms. There continues to be controversy whether these organisms are pathogens.

SUMMARY

Colonic mucosal biopsy is useful in distinguishing ASLC from IBD. Sometimes it provides a clue to the infecting organism. All patients with suspected ASLC do not require biopsy. Biopsy may be helpful when the diagnosis is uncertain and symptoms persist, for instance, longer than a week. When a patient is severely ill or has a lingering course and therapy is contemplated, or when a patient fails to improve on specific therapy, biopsy may provide useful information. In these situations, colonic mucosal biopsy can help the clinician determine whether the patient has a self limited colitis or a first attack of ulcerative colitis. Sometimes histology does not give a definitive diagnosis. In these situations, only time will tell.

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