Gastrointestinal Infections: Pathologist's role

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The ability to endoscopically visualize the entire mucosal surface of the gastrointestinal tract and to biopsy or cytologically sample normal and abnormal appearing areas allows clinicians to diagnose and manage gastrointestinal diseases. In the best of circumstances, mucosal biopsies yield information concerning disease patterns, distribution, extent and/or severity, activity versus chronicity, clinical state of remission or relapse, and complications. More often, however, because of the limitation on the patterns of tissue response to a varied range of insults, the endoscopic biopsy does not provide a specific diagnosis but rather narrows down the differential diagnosis[1] which involves a variety of gastrointestinal inflammatory diseases.[2] Among these, despite the use of many sophisticated means of diagnosis, less than 50% of the cases will prove to have a microbiological cause.[3]

Infectious diseases of the gastrointestinal tract are one of the grey zones of pathological diagnosis since they are rarely biopsied mainly because they are usually self-limited clinically and those that are biopsied demonstrate nonspesific findings with a high rate of mimicry of other entities involving the gastrointestinal tract.[4]

This review will focus on infective disorders of the gastrointestinal tract with an emphasis on the role of the pathologist in the differential diagnosis. Organ/site specific problems will be discussed together with diagnostic histological features of various infectious diseases, including those that mimic other inflammatory conditions of the gastrointestinal tract.

Despite the fact that they are rarely biopsied, gastrointestinal infections are a major cause of morbidity and mor-

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tality worldwide. As numbers of transplant patients and those with other immunocompromising conditions increase, and as global urbanization and transcontinental travel become more frequent, the surgical pathologist must be familiar with infectious diseases that were previously encountered only infrequently.[5,6]

Infectious agents that affect gastrointestinal tract can be grouped as food-borne and water-borne bacteria, opportunistic infections (bacterial, fungal, viral), viral infections (extremely rarely biopsied), parasitic and helminthic infections.[5] The majority of these infections are, however, self-limited. Those patients that undergo endoscopic biopsy often have chronic or debilitating diarrhoea, systemic symptoms, or a history of immunocompromise or other significant clinical scenarios. A discussion with the gastroenterologist regarding exact symptomatology and colonoscopic findings, as well as facts including travel history, food intake (such as sushi or poorly cooked beef), sexual practices and immune status, can greatly aid in the evaluation of a biopsy for infectious diseases.[3,5,7] Moreover, the pathologist have useful techniques including histochemistry, immunohistochemistry, and molecular methods like in situ hybridization and PCR in order to increase diagnostic accuracy.

Gastrointestinal infectious diseases can cause mucosal inflammation which respresents various patterns of tissue response. Histologic patterns of gastrointestinal infections can be classified as follows[6]:

- Infections producing minimal or no histologic changes (eg, *Vibrio* species)

- Infections producing nonspecific inflammation (e.g. Campylobacter jejuni…)

- Infections with suggestive/diagnostic features (e.g. granulomas, pseudomembranes etc..)

- Infections where infectious agent can be visualized on tissue sections (giardiasis, cryptosporidiasis, amebiasis etc..)

Though the above patterns can be observed in any part of the gastrointestinal system, there are some organ/site specific findings of infectious diseases.

Oesophageal infections:

Most inflammatory processes of the oesophagus are due to reflux of gastric content. However, some cases are secondary to infection, or follow the ingestion of noxious material (drugs), result from radiation injury, or are part of a systemic inflammatory disease, affecting either the digestive tract (Crohn's disease, eosinophilic gastroenteritis), the skin, or other sites in systemic diseases.

The oesophagus is resistant to most infections in the immunocompetent. The only two relatively frequent infections of the oesophagus are oesophagitis due to Candida species and oesophagitis resulting from *Herpes simplex* virus infection.

Typical herpetic oesophagitis, as seen in the immunocompromised patient, presents with the acute onset of odynophagia, fever, and retrosternal pain. When severe, herpetic oesophagitis may cause haemorrhage. The disease also develops in rare cases in immunocompetent subjects. Reactivation of a latent herpes infection and herpetic oesophagitis should be considered when patients develop odynophagia following oesophageal instrumentation.

Candidial oesophagitis typically presents with erosions or ulcerations. The inflammatory exudate usually consists of rigid, non-branching candidial hyphae or spores. [8,9]

Gastric infections:

The most common microorganism found in gastric biopsies is the world famous pathogen Helicobacter pylori. However, it is not going to be discussed here. All other pathogens that affect the oesophagus, small intestine and colon can also cause infectious gastritis. Similar to other parts of the gastrointestinal tract opportunistic infections such as CMV, Candida, Aspergillus, Histoplasmosis, Mucormycosis can also involve the stomach. They may cause a nonspecific gastritis or severe ulceration of the mucosa. [1,10]

Enteric infections:

Although biopsy is more invasive, use of this procedure allows detection of other diseases, including Whipple's disease, other protozoan forms of diarrhea (e.g. cryptosporidiosis, isosporiasis, or cyclosporiasis), Crohn's disease, or lymphoma, that may also present as diarrhoea and malabsorption. Small intestinal mucosal changes range from normal mucosa to flat mucosa as seen in Coeliac disease. [11] Giardiasis is a typical example of enteric infection which typically presents with normal mucosa. Cryptosporidiosis may also be associated with normal duodenal histology in mild infections whereas severe inflammation and villous atrophy complicate serious infections. Cryptosporidia, microsporidia and Isospora belli are often missed, because of their small size, intracellular location, and poor staining with usual tissue stains thereby require special stains such as Gram, Warthin-Starry, modified trichrome, PAS or Giemsa. [1,11,12]

Biopsies from patients with enteric viral infections seldom if ever cross the stage of the surgical pathologist, as they are detected in stool samples rather than biopsy specimens. Some common enteric viruses known to cause diarrhoea include, adenovirus, rotavirus, coronavirus, echovirus, enterovirus, astrovirus and Norwalk virus. Rotavirus is the most common cause of severe childhood diarrhoea and diarrhoeal mortality worldwide, followed by adenoviruses. Biopsy changes are very non-specific and include increased inflammatory cells in the lamina propria, degenerative epithelial changes and widening of villous tips. The diagnosis of rotavirus is generally made by stool immunoassay and/or culture, and the disease is rarely biopsied. [1,13] Adenovirus infection is second only to rotavirus as a cause of childhood diarrhoea. However, it has also gained much attention in recent years as a cause of diarrhoea in immunocompromised patients, especially those with HIV and AIDS. Histological features of adenovirus infection include epithelial cellular changes such as loss of maturation, dysorganisation and degeneration. Characteristic inclusions may be seen, especially in immunocompromised patients, within the nuclei of surface epithelium (particularly goblet cells). Useful aids to diagnosis of adenovirus infection include immunohistochemistry, stool examination by electron microscopy and viral culture. [13]

Other, less common but well-recognized causes of food and water-related gastrointestinal disease include brucellosis, *Bacillus cereus* and *Listeria monocytogenes*. It is also important to remember that many serious food-borne gastrointestinal pathogens may produce little or no inflammatory infiltrate at all, particularly in immunocompromised patients, even in the face of grave clinical disease. These include *Vibrio cholerae* and non-cholera *Vibrio* infections, enteropathogenic and enteroadherent *E. coli* and infection with many enteric viruses. [10-12]

Infectious colitis:

Colitis can be caused by a host of bacteria, including camylobacter, salmonella, and, shigella species, S. aureus, N. gonorhoea, E. coli, T. pallidum, yersinia, and mycobacterium species. Histologic evaluation, although helpful in

suggesting an infective origin, can only rarely be suggestive for a specific agent while microbiology can be helpful in 40% of cases.[14,15] Colonic mucosal appearances in these infections can vary greatly from normal to lesions simulating inflammatory bowel disease, however, a large number of specimens demonstrate focal active pattern of injury strongly suggesting infective/acute self-limited type of colitis.[16-18]

Acute infectious-type colitis characteristically features intact crypt architecture with neutrophilic infiltrates in the crypt epithelium causing cryptitis. Lamina propria may be hypercellular, containing a mixture of lymphocytes, histiocytes and neutrophils; plasma cells are generally not prominent, and basal plasma cells should not be seen in acute infectious-type colitis as these are a marker of chronicity. Crypt abscesses and granulomas associated with damaged crypts may also be seen. Since patients often do not come to endoscopy until several weeks after onset of symptoms, pathologists frequently do not see the classic histological features of acute infectious-type colitis. This is important, as the resolving phase of infectious colitis is more challenging to diagnose, as one may find only occasional foci of neutrophilic cryptitis with a patchy increase in lamina propria inflammation, which may contain numerous plasma cells and increased intraepithelial lymphocytes. As these features can also be seen in smoldering Crohn's disease, ulcerative colitis, and lymphocytic colitis, it is important to know the patient's symptoms and, ideally, culture results as this differential diagnosis may be difficult to resolve on histological grounds alone.[15,18] In severe cases due to *Shigella, Amebiasis and clamidia infection* there may be crypt architectural distortion which may cause diagnostic difficulty due to its similarity to ulcerative colitis.[14,19]

Although granulomas are typical of Crohn's disease, they are only seen in a 25% of biopsies.

True granulomas can also be seen in tuberculosis, syphilis, chlamydia, yersinia infections while microgranulomas are described in salmonella, campylobacter and yersinia enterocolitica infections.[14,20]

CMV infection may be diagnosed in patients with immunosupression or inflammatory bowel disease even when the patients have not been treated with steroids. It is particularly important to consider this diagnosis in patients with steroid resistant disease as treating the CMV may prevent the need for other medical therapy or surgery.[4,21]

In summary, gastrointestinal infections are common, although they are underdiagnosed and under-reported. Many of these infections mimic other inflammatory gas-
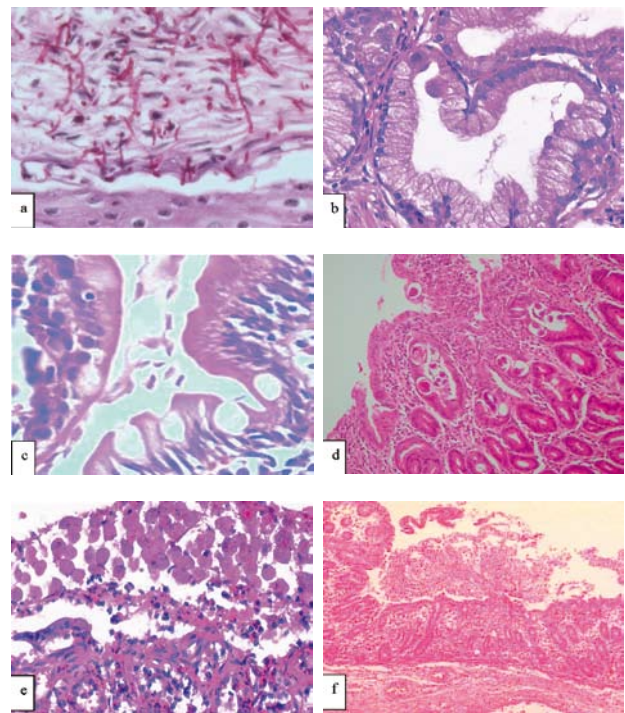
Fig. 1. Histopathology of various gastrointestinal infections. a) candida oesophagitis; b) CMV gastritis; c) giardiasis; d) strongyloidiasis; e) amebiasis; f) C. difficile colitis

trointestinal disease processes, such as ischemic colitis, and inflammatory bowel diseases. It is important for surgical pathologists to keep infectious agents in the differential diagnosis as they cause inflammatory lesions. The availability of immunohistochemical antibodies and PCR assays for infectious agents is increasing, and these techniques seem to be valuable in associating specific infectious micro-organisms with histologic patterns of disease, thus facilitating the diagnosis of infectious processes.

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