Infectious disorders of the upper gastrointestinal tract (excluding *Helicobacter pylori*)

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Abstract

The upper gastrointestinal (GI) tract, including the oesophagus, stomach and small intestine, is subject to a vast array of pathogens. While some may be a reflection of disseminated infection, others produce disease specific to the upper GI tract. This review focuses on the most common infectious disorders of the upper GI tract that may be encountered by the general surgical pathologist, including viral, bacterial, fungal and parasitic organisms. Clinical and diagnostic histological features are discussed, as well as useful ancillary diagnostic techniques.

Keywords bacteria; culture; fungus; infection; parasite; polymerase chain reaction, PCR; virus, molecular microbiology

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Viral infections of the upper gastrointestinal tract

The type of viral infection and the manifestations of disease vary with the site of infection and the immune status of the patient.

Cytomegalovirus

Cytomegalovirus (CMV) may be seen throughout the upper GI tract. CMV most commonly presents as an opportunistic pathogen in patients with a suppressed immune system. These include persons with acquired immune deficiency syndrome (AIDS) or those with history of solid organ or bone marrow transplantation. Primary infections in healthy persons are generally self-limited. Symptoms vary with the immune status of the patient and the site of infection. The most common clinical symptoms are diarrhea, abdominal pain, fever and weight loss.[1] A rare but important entity associated with CMV infection is hypertrophic gastropathy and protein-losing enteropathy resembling Menetrier disease.[2,3] Although initially described in children, this entity has also been reported in adults.

Patients with CMV infection have endoscopic abnormalities that include ulcers (most common),[1] erythema, hemorrhage, and inflammatory masses that may be segmental and patchy. The ulcers may be single or multiple, superficial or deep.

Histologic findings range from minimal inflammation to ulcers with extensive granulation tissue and fibrinopurulent debris (Figure 1a). The inflammatory infiltrate is typically mixed with numerous neutrophils. The characteristic inclusions may be seen on routine H&E preparations (Figure 1b and c), and can be either intracytoplasmic or intranuclear. Nuclear inclusions are consist of a basophilic inclusion surrounded by a clear halo, imparting the classic "owl's eye" appearance. Cytoplasmic inclusions are typically more eosinophilic and granular, and lack the "owl's eye" morphology. The inclusions are most commonly found in endothelial and stromal cells in granulation tissue, rather than epithelial cells, but occasionally they are found within epithelial cells, particularly within the stomach. Numerous apoptotic enterocytes may be seen as well.[1,4] In immunocompromised patients, characteristic inclusions may be identified with virtually no associated inflammatory reaction. CMV infection may also cause a vasculitis with resultant ischemia that has been well described in the upper GI tract.[5]

The diagnosis of CMV infection may be easily missed in biopsy specimens when only rare inclusions are present. Histologic examination of multiple levels and the use of immunohistochemistry may be invaluable in establishing a diagnosis. Distinction between CMV infection and graft-versus-host disease in bone marrow transplant patients may also be challenging, as there are overlapping clinical and histological features, and the two may coexist in the same patient. Immunohistochemistry may be especially helpful to exclude CMV infection in this setting. Other diagnostic aids include viral culture, polymerase chain reaction (PCR) assays, and serological studies/antigen tests. Importantly, isolation of CMV in culture does not necessarily imply active infection, as the virus may be excreted for months to years after a primary infection.[1] In addition, it is important to note that evidence of CMV in tissue does not always correlate with a positive PCR serum assay, and vice versa.[6,7]

Herpesvirus

Like CMV, Herpes simplex virus (HSV) infection may be seen throughout the GI tract and occur in both immunocompromised and immunocompetent patients. Within the upper GI tract, the most common site of infection is the oesophagus. Patients with herpetic oesophagitis may present with dysphagia, odynophagia, chest pain, nausea, vomiting, fever and bleeding. Particularly in immunocompromised persons, herpetic oesophagitis may be accompanied by life-threatening disseminated infection at the time of diagnosis.[8] In immunocompetent patients, herpetic infection is often self-limited.

Ulcers are the most common endoscopic finding, usually associated with exudate. Many patients, however, have a nonspecific erosive oesophagitis. In addition to ulcer, histological findings typically include a neutrophilic infiltrate and a fibrinopurulent exudate containing sloughed epithelial cells. Characteristic viral inclusions and multinucleate giant cells are variably present.[8] However, unlike CMV, the best place to find them is

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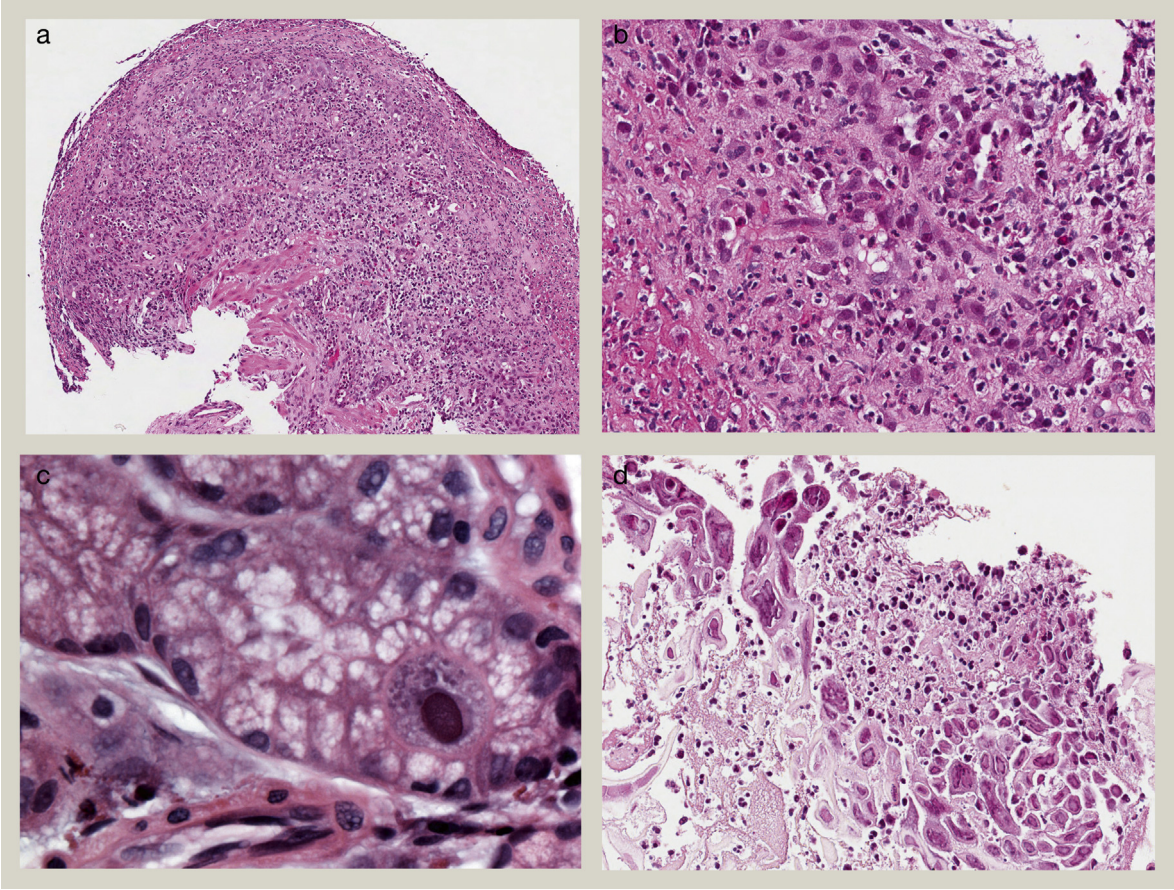

Figure 1 Viral infections of the gastrointestinal tract commonly cause ulcers that may appear nonspecific at low magnification, as in this case of CMV infection (**a**). At higher magnification, the characteristic inclusions of CMV are most commonly found within stromal cells within the ulcer base (**b**). Here is a rare example of a CMV inclusion within an epithelial cell in the stomach (**c**). In herpes oesophagitis, the characteristic viral inclusions and multinucleate giant cells are typically within the squamous mucosa at the edge of the ulcer.

within the squamous mucosa at the edge of an ulcer and in sloughed cells within the exudate (Figure 1d). Immunohistochemistry, viral culture and molecular studies may be useful diagnostic aids.

Human immunodeficiency virus

Chronic idiopathic oesophageal ulcers have been described in association with human immunodeficiency virus (HIV). The HIV p24 core protein has been detected in ulcerated mucosa, suggesting that HIV is capable of producing ulcers in the absence of other pathogens, although the causative ability of the virus remains controversial. The diagnosis of idiopathic HIV-associated oesophageal ulcer should only be made when other pathogens have been excluded.[9–11] More recently, these similar lesions have also been described in patients who have undergone bone marrow and solid organ transplants as well.[12,13]

Histological abnormalities of the bowel mucosa have been noted in HIV-positive patients both with and without diarrhoea. The histologic features may mimic celiac disease, including villous blunting, crypt hypertrophy, increased intraepithelial lymphocytes and lamina propria expansion by mononuclear cells. Increased mitotic figures in glandular epithelium and increased apoptotic enterocytes may also be seen, resembling mild graft-versus-host disease and medication-induced mucosal injuries.[14] Some authorities support the use of the term 'AIDS enteropathy' to describe these morphological findings, provided that the gut has been adequately sampled and all other pathogenic entities have been excluded.[14] However, others believe that this is a poorly understood term that does not clearly represent a specific disease entity and thus should not be used.

Bacterial infections of the upper gastrointestinal tract

Food and water-borne infections

Salmonella species, which are motile gram-negative bacilli, are transmitted through food and water and are prevalent where sanitation is poor. Clinically, *Salmonella typhi* and *paratyphi* are notable for causing enteric fever (typhoid fever), which typically presents with abdominal pain, headache evolving fever. Abdominal rash, leukopenia and diarrhoea often follow, beginning in the second or third week of infection. The diarrhoea may be watery initially, but progress to severe GI bleeding.[15] Non-typhoidal Salmonella are an important cause of both food-borne illness and traveller's diarrhoea.

In the upper GI tract, Salmonella infection is most prominent in the small bowel, particularly ileum, and is associated with Peyer patches. Grossly, the bowel wall may be thickened with raised nodules, corresponding to hyperplastic Peyer patches, and

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