The upper gastrointestinal tract in the immunosuppressed patient

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Abstract

There is a broad range of pathologies seen in the immunocompromised patient which relate primarily to their susceptibility to infection and complications arising from such infection, in particular tumorigenesis. A full spectrum of microorganisms may cause such infections ranging from viruses through bacteria to fungi, protozoa and even helminths. This review focuses on the infection-associated pathology including lymphoproliferative disorders seen in the upper GI tract of the immunocompromised patient. The clinical presentation, endoscopic features and histopathological findings of these pathologies are discussed.

Keywords immunocompromised host; Kaposi; leiomyoma; lymphoma; opportunistic infections; sarcoma; upper gastrointestinal tract

Introduction

Aside from those uncommon patients who have congenital immunodeficiency syndromes there are four main groups of immunocompromised patient who suffer varying degrees of immunosuppression. The largest group is the elderly and those with chronic debilitating diseases (e.g. diabetes mellitus) who may typically be mildly immunocompromised. The second group comprises patients who are more severely immunocompromised due to the iatrogenic use of immunosuppressive drugs in the treatment of chronic inflammatory conditions (e.g. psoriasis, IBD) and autoimmune diseases (e.g. SLE), and in the prevention of graft rejection in those undergoing solid organ and bone marrow transplantation. The third group is composed of patients who are being treated for malignancy with chemotherapeutics and radiation who may become profoundly immunocompromised secondary to both their therapy and disease. Lastly there is a large global population who are immunocompromised due to HIV infection. The diseases associated with immunosuppression vary both with the degree and aetiology of immunosuppression and the geographical location of the patient.

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Upper GI tract infections in the immunocompromised

The pattern of infections in the immunocompromised patient is constantly changing partly due to an increasingly aged population but also due to novel therapies used in the treatment of human disease which can either cause or ameliorate immunosuppression. Perhaps the best example of this is HAART therapy for HIV infection which since its introduction in 1996 has drastically reduced the incidence of AIDs in many parts of the world.[1] Patients with AIDs are profoundly immunosuppressed and can present with a wide range of different infections often with simultaneous infection with several microorganisms (e.g. CMV, HHV-8 and MAI). The frequency of particular infections also varies greatly depending upon geographical location such that profoundly immunocompromised patients in the Mediterranean basin may well acquire visceral leishmaniasis but it is extremely uncommon in the USA.[2] It should be noted that since the advent of HAART there has been a dramatic decline (>50% reduction) in the incidence and a change in the spectrum of gastrointestinal opportunistic infections seen in HIV-positive patients. *Helicobacter* gastritis is now the most prevalent gastric infection in HIV-positive patients in most Western countries.[1] However, in Western routine clinical practice there are patients with undiagnosed HIV infection, migrants who present with AIDs and also known HIV-positive patients who have failed HAART. Thus, when examining biopsies from HIV-infected patients it is very useful to have an idea of the patient's current CD4 count and travel history as this information may provide clues to the likely spectrum of opportunistic infections.

As already discussed the infections immunocompromised patients are susceptible to varies markedly depending on the degree of their immunosuppression such that most immunocompromised patients are susceptible to candidiasis or herpetic infection but only the profoundly immunosuppressed are at high risk of disseminated infection with microorganisms such as mycobacterium avium intracellulare complex. It should also be noted that although many infections present in the upper GI tract they are often already systemic in nature.

Viral infections

Herpes simplex infection: aside from the oral cavity, the oesophagus is the most common site of herpetic infection in the upper GI tract but herpes may less commonly affect both the stomach and small intestine. Herpetic oesophagitis is primarily a disease of the immunocompromised although it can be seen rarely in the normocompetent patient. The full spectrum of immunocompromised patients may develop herpetic oesophagitis with a disseminated infection in up to 35% of cases.[3] Herpetic oesophagitis is usually caused by HSV1 but can rarely be due to HSV2 infection. Typical symptoms include chest pain, odynophagia, dysphagia and nausea/vomiting although disease may be symptomless in some cases. At endoscopy the classical appearances are those of small discrete punched out ulcers in the distal to middle thirds of the oesophagus but they may vary from normal endoscopic appearances (in histologically proven

disease), through small discrete punched out ulcers to confluent ulceration and even a pseudomembranous appearance.[3]

The histological appearances are those of non-specific ulceration typically in squamous mucosa. Beyond the clinical and endoscopic findings the clue to the diagnosis lies in finding herpetic changes in squamous cells at the edges of ulcers including balloon degeneration, ground glass nuclei with margination of chromatin and eosinophilic nuclear inclusions.[4] Of these the Cowden type A (eosinophilic) nuclear inclusions are rarely present and can also be seen in zoster and cytomegalovirus infection, thus the ground glass nuclei and multinucleate giant cells are perhaps more dependable markers of herpes simplex infection.[4] A diagnosis of herpes simplex infection can be reached on basic histology alone in approximately 60–70% of cases.[5] Reliable immunocytochemistry for HSV1/2 is available and can be useful in confirming the nature of nuclear inclusions and highlighting infected cells in paucicellular biopsies. Serological testing, culture of biopsy specimens and PCR based assays may also be useful in diagnosis.[5] It is thought that herpes zoster may also rarely involve the oesophagus producing a similar histological picture to herpes simplex. Such herpes zoster infections are also associated with immunocompromisation.

CMV infection: CMV is a member of the herpes virus family. Primary infection usually occurs in childhood or early adulthood such that the vast majority (80–90%) of adults have been previously exposed to CMV. Primary infection is usually asymptomatic although it may produce an infectious mononucleosis-like illness. As with other herpes virus infections the virus becomes latent and can re-activate later typically on a background of immunosuppression. CMV reactivation is typically seen with the severe immunosuppression associated with patients with AIDs, organ transplantation and malignancy but it can also been seen complicating autoimmune disease (particularly IBD) and in the elderly. CMV can affect any part of the upper GI tract but in AIDs patients the oesophagus and small intestine are said to be the commonest sites of infection whilst the stomach is said to be the commonest site in organ transplantation and with malignancy.[6] Clinical presentation depends on the primary site of infection but most patients suffer from fever and malaise with abdominal pain and bleeding being other common manifestation. Histology is the gold standard for diagnosis with demonstration of classical "owl's eye" (Cowdry type A) nuclear inclusions. Immunohistochemistry for CMV is a specific and sensitive test which both highlights inclusions and confirms their nature.

Adenovirus infection: adenovirus infection in the immunocompromised is well described in association with both HIV infection[1,2] and following bone marrow transplantation.[7] Infection typically presents with a colitis but in the upper GI tract adenoviral infection may involve the small intestine and stomach. The histopathological features are those of non-specific active chronic inflammation sometimes with ulceration. The diagnosis depends on the identification of adenoviral nuclear inclusions which are amphophilic and glassy, typically fill most of the nucleus and primarily affect superficial epithelial cells unlike CMV inclusions (primarily endothelial and stromal cells). A specific immunostain for adenoviral inclusions is available and is very useful in confirming the nature of the inclusions.

HIV associated oesophageal ulceration: at least a third[8] and up to 56% of oesophageal ulcers in HIV are idiopathic with no organisms other than HIV detected within the ulcer. This has lead to suggestions that the ulcers are due to HIV infection of squamous epithelium. Such ulcers are often large (up to 3 cm diameter), deep and undermined. They are usually found in the mid to distal oesophagus, may be single or multiple and typically involve up to a third of the oesophageal circumference. Endoscopically these resemble CMV ulcers but are more often single and deeper in nature. Histological examination typically shows a deep ulcer extending into the muscularis propria lined by granulation tissue with eosinophils. HIV has been shown to be present both by immunostaining and RNA *in situ* studies for p24. Other causes of infection need to be excluded by histochemical and immunohistochemical staining. The aetiology of these ulcers remains controversial with some suggesting that as the rate of HIV detection is similar in idiopathic and other ulcers HIV infection of squamous mucosa is not causative. Clinical response to steroid therapy, thalidomide and HIV anti-viral therapy have been described.

Bacterial infections

Atypical mycobacteria: atypical mycobacterial infections are most commonly seen in patients with AIDs but are also occasionally seen in patients with haematological malignancy.[9] The vast majority of such infections are due to mycobacterium avium intracellulare complex (MAI) and most commonly involve the small intestine with only rare reports of gastric and oesophageal disease. Symptoms include fever, abdominal pain, weight loss and diarrhoea. The endoscopic appearances may mimic Whipple's disease with white nodules/plaques in the duodenum but there may also be erythema and ulceration. Histologically sheets of foamy macrophages are seen expanding the lamina propria with little evidence of an inflammatory response. Well formed epithelioid granulomas are not usually seen. Histochemical staining with Ziehl–Neelsen or PAS stains reveals the macrophages are packed with mycobacteria.[10]

Tuberculosis: *Mycobacterium tuberculosis* may involve the upper GI tract but this is unusual and most commonly presents as part of disseminated disease in patients with primary lung infection. The histological features are similar to those seen elsewhere with tuberculous infection but in the severely immunocompromised patients well-formed granulomas are rarely seen.

Fungal infections

Candidiasis is by far the most frequent fungal infection of the upper GI tract but a variety of other fungal species may cause infections. The spectrum of fungal infections associated with immunosuppression varies depending on its underlying cause such that profoundly neutropaenic patients (e.g. patients being treated for haematological malignancy) are at particular risk of aspergillosis and mucormycosis infections[11] whereas AIDs patients are particularly susceptible to histoplasmosis and cryptococcosis. Signs and symptoms tend to be similar regardless of the infecting species. Oesophageal infections are commonly associated with dysphagia and odynophagia. Other symptoms associated with upper GI tract fungal infection include vomiting, diarrhoea, abdominal pain, fever and GI bleeding.