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Liver abnormalities in the immunosuppressed

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A B S T R A C T

The immunosuppressed state may arise due to medical illness or drug therapy, which can result in a diverse array of liver derangements. This article discusses the commonly-encountered immunosuppressed conditions and the associated specific liver diseases. Due to the frequency of blood-borne viral disease globally, viral hepatitis (hepatitis B and C) during chemotherapy, transplantation and the increasingly utilised biological therapies for autoimmune disorders is discussed. An overview of human immunodeficiency virus co-infection with hepatitis B and C is provided. This article aims to highlight the variety of liver diseases which can occur in clinically relevant, particularly iatrogenic, immunosuppressed conditions, and summarise learning and practice points for clinicians. Recognition and prevention of viral liver disease is crucial and early involvement of experts prior to administration of immunosuppressive therapy is advised.

Immunosuppression can occur in the form of congenital or acquired immunodeficient conditions or infections, or when induced therapeutically to treat cancer or other immunological disease, and to prevent rejection in transplantation. The state of reduced activation of the immune system puts a patient at risk of infections from opportunistic and conventional pathogens. Liver abnormalities may arise secondary to such infections, concurrent drug therapy, haemodynamic disruptions, amongst other causes.

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Table 1
Immunosuppressive conditions conferring increased risks in viral hepatitis.

Cancer chemotherapy – particularly in haematological cancers, use of high dose corticosteroids and rituximab
Immune modulation for autoimmune conditions – steroids, thiopurines, anti-TNFα
Bone marrow transplant
Solid organ transplant
Acquired immune deficiency – Human Immunodeficiency Virus (HIV) infection

Viral hepatitis in cancer therapy and other immunosuppressive therapies

The worldwide prevalence of chronic hepatitis B (HBV) is 350 million (5%) with two billion people previously exposed to HBV, and 180 million for HCV infection [1,2]. Administration of chemotherapy in patients with past or present chronic HBV and HCV poses a challenge. Even in low prevalence areas, the widespread use of chemotherapy in cancer and increasingly immunosuppressive therapy in rheumatology and autoimmune disease makes this an important clinical problem (Table 1).

Hepatitis B and cancer therapy

Active hepatitis B infection

Hepatitis B (HBV) infection is more frequent in patients with cancer [3,4]. Blood transfusions in haematological malignancies increase exposure to blood-borne viruses. There is also suggestion of aetiological association between HBV infection and non-Hodgkin lymphoma [5].

Immune suppression during chemotherapy enhances viral replication and viral protein expression. There is lower rate of spontaneous recovery following acute infection. In chronic infection there is accelerated progression of fibrosis and development of cirrhosis and hepatocellular carcinoma (HCC) [3].

In a rare condition unique to an immunocompromised host called fibrosing cholestatic hepatitis (FCH), massive viral replication and viral antigens directly cause hepatocyte damage. It is mostly seen with HBV in liver transplantation, but also in kidney and bone marrow transplant, as well as in hepatitis C and HIV infection. There is cholestatic jaundice and abdominal pain with rapid liver failure [6,7]. Anti-viral therapy such as lamivudine has demonstrated some success in treatment but FCH is frequently fatal [8].

Hepatitis B reactivation

HBV reactivation during chemotherapy has reported mortality ranging from 5 to 52% [2]. In addition there may be indirect morbidity from disruption to cancer therapies. It can be defined as re-emergence of HBV DNA in a previously negative patient, or a >1 $\log_{10}$ rise in HBV DNA levels, accompanied by $>$three-fold increase in alanine transferase (ALT) from baseline, in the absence of other causes of liver dysfunction [9]. Other infections (e.g. cytomegalovirus, herpes simplex, varicella-zoster, Epstein–Barr, adenovirus), drug reaction, cancer infiltration, ischaemia or sepsis must be excluded.

Reactivation is most common in patients with hepatitis B surface antigen seropositivity but can occur in several population groups (see Table 2).

The clinical course may range from asymptomatic hepatitis to fulminant liver failure (see Fig. 1). Intense immunosuppression leads to a sudden increase in HBV replication, accompanied by increased viral protein expression, with reappearance of hepatitis B e- and surface antigens, and decrease in anti-HBs (reverse seroconversion) [2]. 'Flares' of acute hepatitis follows, marked by elevation in ALT levels.

Table 2
Patient groups at risk of HBV reactivation during immunosuppression.

Patient group	Serological markers
Current infection (active or inactive)	Hepatitis B surface antigen (HBsAg) positive HBV DNA positive or negative
Previous infection (resolved)	Anti-hepatitis B core antigen (anti-HBc) positive Anti-hepatitis B surface antigen (anti-HBs) positive or negative
Occult infection	HBsAg negative HBV DNA positive