Infection in the Immunocompromised Patient: Problem diagnoses.

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This discussion will concentrate primarily on three opportunistic infections of the liver: CMV, Herpes and Adenovirus.

CMV

A large percentage of the general population has been exposed to cytomegalovirus, and as with many other viruses in the herpes family, latent infection follows a generalized viral illness. Primary infection in the immune competent patient often results in a reactive lobular lymphocytic hepatitis without inclusions, similar to EBV. Viral inclusions are seen only in immunocompromised patients.

In transplant patients the greatest risk factor for development of CMV hepatitis is transplantation of an organ from a CMV serology positive donor to a serology negative recipient (D+/R-). Other risk factors for graft CMV infection include, fulminant hepatic failure as a cause for transplantation, cyclosporine (over tacrolimus), three drug regimen (over two drug) and prior treatment of rejection with OKT3. There is recent evidence that specific polymorphisms in the toll like receptor TLR2 are associated with an increased risk of graft injury secondary to CMV. 50% of serology negative patients develop positive titers without developing clinically evident liver disease. Only a small percentage will develop biochemical evidence of liver dysfunction.

Most transplant centers prophylactically treat high risk patients with oral valgancyclovir for three months. A few centers do not administer prophylaxis and instead closely follow PCR studies, treating only when they become positive for CMV DNA. In the past CMV infection has occurred most frequently 4-12 weeks following transplantation, however with extended prophylaxis of at risk patients, infection occurs later. In patients with HIV the primary risk factor for hepatitis and other organ injury is low cd4 counts.

The histologic findings of CMV infection are variable. In immune competent patients, systemic CMV infection generally results in a nonspecific lobular hepatitis. In immunocompromised
patients, viral inclusions may be seen in hepatocytes, endothelial cells, and cholangiocytes. After inclusions, the most common finding in liver biopsies from transplant patients with CMV infection is neutrophilic microabscesses (MA). These consist of small clusters of neutrophils within the lobules. They are frequently associated with parenchymal or endothelial cells displaying a characteristic viral inclusion. Other findings in the CMV infected liver include mild lobular hepatitis as is seen in nonimmunocompromised patients, Kupffer cell aggregates or microgranulomas, and portal infiltrates similar to those seen in acute rejection. In Patients with HIV, sclerosing cholangitis can be seen and there has been a case report of vanishing bile duct syndrome in a patient with HIV and CMV (Hindupur).

Neutrophilic microabscesses, while characteristic of CMV are neither specific nor sensitive. Lamps et al. found MA in 17% of post all OLT biopsies done for clinical dysfunction. Forty four percent of patients had MA in a liver biopsy at some point in their course. Of the 17% who had MA, 19% had CMV. Other associations with MA included other bacterial, viral, or fungal infections (27%), graft ischemia (10%), and biliary obstruction/cholangitis (15%). No explanation for MA was found in 26% of biopsies. There was no correlation between the size of the MA and the presence of CMV.

We retrospectively reviewed 55 transplant biopsies in which a diagnosis of CMV had been made. MA were seen in only 50%. In 9% (5) of our cases of CMV hepatitis, inclusions were not present by H&E and the diagnosis was made by immunohistochemistry. In these cases histologic features of acute rejection were seen in 2 cases, biliary obstruction in 1, chronic rejection in 1, and non-specific hepatitis in 1. In 9% (5) only one inclusion was present on multiple levels examined. It is our opinion that one must have a low threshold for cytomegalovirus investigation either by performing IHC or suggesting serum PCR studies.

HHV6 and HHV7 are two members of the herpes virus family which are closely related to CMV. They are not thought to cause significant disease in immune competent patients. The significance of infection in the immunocompromised is beginning to be appreciated. PCR on peripheral blood monocytes and serologic studies for antigenemia can be used to monitor infection. A significant percentage (up to 80%) of patients may develop infection following transplantation. A small percentage of these patients may develop a viral syndrome, and severe encephalitis attributed to the virus has been reported. Infection of the liver seems to be manifested as a mild lobular lymphocytic infiltrate without significant impact on graft outcome. There is however evidence that HHV6 infection is associated with a higher risk of CMV and fungal infection. HHV 6 infection may therefore either potentiate other forms of opportunistic infection or may be a marker of more severe immunosuppression.

**Herpes Simplex**

Herpes simplex virus is a rare but well known cause of severe hepatitis in the immunocompromised patient. While generally considered an opportunistic organism, severe liver injury in immune competent patients can occur. The histologic features are well described and the diagnosis is generally straightforward. Infection is associated with focal or massive hepatocellular necrosis associated with a predominantly neutrophilic infiltrate. Viral inclusions are usually evident and immunohistochemistry is confirmatory. Infection can result in rapid liver
failure so diagnosis is paramount. Norvell et al. recently described 5 cases of herpes hepatitis and reviewed the clinical circumstances surrounding another 132 cases of herpes hepatitis from the literature. Ninety four percent of the patients presented with fever; 45% with herpetic rash; 96% with coagulopathy and 80% with encephalopathy. In only 23% of the patients was herpes infection suspected prior to biopsy. Higher levels of AST and ALT were associated with worse outcome; however rapid treatment with acyclovir decreased the likelihood of progression to death. The average time from transplantation to diagnosis of herpes infection was 205 days. As expected, immunocompromised patients with herpes hepatitis were more likely to progress to death than immunocompetent patients.

**Adenovirus**

Adenovirus is a common pathogen which usually infects the respiratory tract. It is a rare cause of hepatitis in immunocompromised patients. In liver transplant patients, adenovirus hepatitis is seen primarily in children and is extremely uncommon in adults. It has been noted to cause fulminant hepatic failure in children and adults with HIV and in patients who have undergone bone marrow transplantation. The histology of adenovirus hepatitis is variable. Infected hepatocytes usually have smudgy, less discrete nuclear inclusions than CMV but may demonstrate well formed inclusions similar to those in CMV. In some cases infection is associated with focal coagulative necrosis with little or inflammation. Marked mixed inflammation similar to acute rejection can also be seen. In a very interesting and intriguing report of 3 pediatric patients (two transplant, 1 HIV), Bründler et al. describe a cholangiohepatitis caused by adenovirus resulting in necrotizing cholangitis, duct loss and hepatitis. Ascending adenoviral infection was hypothesized based on the ducto-centric distribution of disease and the presence of gastrointestinal infection in all three cases.

**Selected References:**


Razonable RR, Paya CV. The impact of human herpesvirus-6 and -7 infection on the outcome of liver transplantation. Liver Transpl. 2002 Aug;8(8):651-8

