Venue: ISIS
23rd August 2007
1100-1215 hr

Symposium 5E: Transplant pathology

S5E-1. Liver transplant pathology: causes of late allograft dysfunction

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Most problematic liver allograft biopsies are obtained more than 1 year after transplantation, due largely to overlapping clinical, serological and histopathological features of native disease recurrence and other potential causes of late allograft dysfunction. More than one insult can be responsible. About 75% of biopsies from long-surviving recipients with abnormal liver function tests/symptoms show significant histopathological abnormalities. Native disease recurrence can be categorized as follows: (i) infections (viral hepatitis B, C, D), (ii) dysregulated immunity {autoimmune hepatitis, primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and sarcoidosis}, (iii) malignancies, (iv) toxic causes (e.g. alcohol, adverse drug reactions), (v) metabolic disorders, including nonalcoholic steatohepatitis, and (vi) others. The most common and problematic causes of late allograft dysfunction include late-onset acute and chronic rejection, recurrent and new-onset viral and autoimmune hepatitis, biliary strictures associated with preservation injury/prolonged ischaemia time, recurrent PBC and PSC, and idiopathic post-transplantation hepatitis. Differential diagnostic challenges include (i) rejection versus chronic hepatitis, (ii) chronic rejection, (iii) biliary strictures versus acute and chronic rejection, (iv) acute and chronic rejection versus PBC, (v) central perivenulitis, (vi) various causes of chronic hepatitis, and (vii) cholestatic or biliary disease versus chronic hepatitis. Practical problems and approach to allograft biopsy interpretation are discussed. Clinicopathological correlation with review of all previous allograft biopsies and close communication with the hepatology team are mandatory. One should be cognizant of the pre- and post-tranplantation significance of laboratory test results, and the possible alteration of histopathological features by immunosuppressive therapy. Occasionally, rendering a definitive diagnosis may not be possible. However, exclusion of a differential diagnosis may facilitate further therapeutic decisions.

S5E-2. Liver transplantation and new therapeutic approaches for familial amyloidotic polyneuropathy (FAP)

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Familial amyloidotic polyneuropathy (FAP) is a fatal hereditary amyloidosis in which amyloidogenic mutated transthyretin (ATTR), apolipoprotein A-I (AApoA-I), and gelsolin (Agel) have been identified as FAP-related amyloidogenic proteins. Of these proteins, ATTR is the most common throughout the world. Typical clinical features of the disorder include sensorimotor polyneuropathy, autonomic dysfunction, cardiomyopathy, vitreous opacity, carpal tunnel syndrome, renal dysfunction, and gastrointestinal tract disorders. Recently, liver transplantation has been considered as a promising therapy to halt the progression of clinical symptoms of progression in familial amyloidotic polyneuropathy (FAP) because most of transthyretin (TTR) is produced by the liver. In addition, domino liver transplantation using an FAP patient's liver has been performed because of shortage of donor livers in the worldwide. However,

the use of liver transplantation as therapy for FAP has given rise to several problems, an alternative treatment is needed. We have tried several other approaches: Recent studies suggested that certain metal ions affect amyloidogenesis. Among metal ions tested in an in vitro amyloid formation study, Cr^{3+} increased stability of both normal and mutant TTR tetramers and suppressed TTR amyloidogenesis induced by low pH. Our findings indicate that Cr^{3+} acts to suppress TTR amyloidogenesis. BSB, a Congo red derivative that binds to amyloid fibrils in FAP as well as to those in senile plaques in Alzheimer disease, effectively suppressed TTR amyloid formation in vitro. BSB may thus be useful for preventing amyloid formation. Free radical scavenger therapy was also tried with FAP patients but yielded no conclusive results. Immunization for transgenic mice having ATTR V30M gene using ATTR Y78P resulted in suppression of amyloid deposits. Finally, an RNA/DNA chimera and single-stranded oligonucleotides (SSOs) were tested in vitro and in vivo in an attempt to repair the amyloidogenic TTR gene in the liver and retina. On the basis of results achieved so far, SSO is a promising tool for gene therapy.

S5E-3. Neuropathology of bone marrow transplantation

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The aim of this presentation is to demonstrate the pathological abnormalities in the central nervous system detected in autopsies of bone marrow transplanted (BMT) patients, performed in the Division of Anatomic Pathology, Hospital de Clínicas – UFPR, Curitiba, Brazil. The central nervous system is affected in 90.56% of cases. The neuropathological findings detected were subarachnoid haemorrhage (31.67%), intraparenchymal haemorrhage (27.22%), fungal infections (8.33%), Wernicke's encephalopathy (5.55%), nodular encephalopathy (5.55%) and toxoplasmosis (4.44%). The nodular encephalopathy seems to be related to cytomegalovirus and *toxoplasma gondii* infections. Microglial activation was identified by the expression of class II molecules of the major histocompatibility complex, detected through electron microscopy and immunohistochemical study with anti-HLA-DR, CR3/43 monoclonal antibody. The epidemiological analysis of the population of this study showed that there was predominance of males, and of patients in the second decade of life. The main clinical diseases diagnosed prior to BMT were severe aplastic anaemia (31%), chronic myeloid leukaemia (29%), acute myeloid leukaemia (13%), Fanconi's anemia (9%) and acute lymphoblastic leukaemia (5%). The majority of patients died in the first three months after BMT (58.33%). Statistical analysis of clinical parameters and the main causes of death showed that in 17% of this population the brain seemed to contribute directly to death. In this group of patients there was predominance of intraparenchymal haemorrhage (70.97%), fungal cerebritis (25.81%) and toxoplasmosis (9.68%). The survival time of those patients who died due to severe cerebral pathology was half of the survival time of those who died due to extra-cerebral causes.

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