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Session Title : Pathological Diagnosis of Allograft rejection: Recent Update

Heart

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Cardiac allograft rejection is classified by the type of immune response, target tissue, and time of onset. Acute cellular rejection (ACR) in heart is an immune response by cytotoxic T lymphocytes aimed primarily at the cardiac myocyte. The histologic hallmarks are myocardial inflammation and myocyte necrosis. Grading ACR in heart is based on the degree of these findings by the ISHLT grading system of ACR revised in 2005. One of the most difficult differential diagnoses in the diagnosis of ACR is tangential Quilty effect. Quilty effect is defined as nodular endocardial lymphocytic infiltrate and it can extend into the myocardium in endomyocardial biopsies. It is composed of a core of B lymphocytes, plasma cells, macrophages, and dendritic cells, surrounded by T lymphocytes. The pathophysiology of the Quilty effect remains uncertain but it discloses the characteristics of a tertiary lymphoid organ acting like ectopic lymph nodes. Antibody-mediated rejection (AMR) is manifest by injury of small vessels by donor-specific antibodies. Histopathologic and immunophenotypic criteria were proposed for cardiac AMR grading scheme by the 2013 ISHLT WF. The typical histologic feature is intravascular activated mononuclear cells including intravascular macrophages and swollen hyperplastic endothelial cells. The key immunopathologic findings are capillary C4d-postivity and/or intravascular CD68-postive macrophages by immunohistochemistry. Anti-HLA antibodies have been classically recognized as donor specific antibodies resulting in AMR. There has been increasing interest in non-HLA antibodies as mediators of AMR as well as chronic rejection. It is not clear yet whether these antibodies targeting intracellular antigens are direct pathogenic mediators or merely a marker of injury or bystanders of humoral activation. Non-HLA antibodies primarily target antigens on endothelial cells in the cardiac allograft and they subsequently activate antibody-mediated cellular cytotoxicity, complement reaction, and apoptosis. Some of them may even contribute to acute cellular rejection. The histological features of AMR in the presence of non-HLA antibodies may depend on which antigen they react to. A couple of recent reports on angiotensin II type 1 receptor AMR demonstrated neither intravascular monocytic cells nor C4d staining in capillary endothelial cells in cardiac myocardium, but they showed mild acute cellular rejection, focal reactive endothelium/endothelialitis, reactive endocardial cells/subendocardial lymphocytic infiltrate, thrombi within small vessels, interstitial edema, or hemorrhage by endomyocardial biopsy or autopsy. The possibility of

non-HLA antibody-related AMR may be raised when unexplainable graft dysfunction occurs in the absence of donor-specific HLA antibodies, even without the typical pathologic findings of AMR in endomyocardial biopsy. Further investigation is required for the clinical significance as well as for optimal testing strategy and treatment modalities of non-HLA antibody mediated AMR.