

MONITORING POSTTRANSPLANT COMPLICATIONS RELATED TO IMMUNOSUPPRESSIVE TREATMENT AND NON-REJECTED INJURIES

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Heart transplantation has become a viable therapeutic option and is today the treatment of choice for patients diagnosed with end-stage heart failure. Without this intervention the medical management of these patients has a very poor prognosis. Thus, in patients diagnosed with dilated cardiomyopathy and end-stage coronary heart disease, heart transplantation has proven to have an excellent long-term survival rate. The researches within the Doctoral Thesis were carried out within the Emergency Institute for Cardiovascular Diseases and Transplantation from Târgu Mureș, on a number of 53 patients, subjected to heart transplant intervention, in the period 2000-2017.

The research included cross-sectional studies, descriptive studies, but also statistical analyzes of the cumulated data, and the variables collected were multiple, being represented by: the age at which the transplant occurred, gender and area of origin of the patients, the diagnosis at hospitalization, comorbidities, virology and postoperative, pre- and postoperative laboratory tests, pre- and postoperative echocardiography aspects, post-transplant infections, complications and treatment. An important chapter of our research was dedicated to lesion quantifications on biopsy, according to the ISHLT classification, analyzes performed within the Department of Cell Biology at UMFST Târgu Mures. In the thesis we highlighted the immunosuppressants used in standard protocols, currently used in the country and in major transplant centers in the world, with indications, mechanism of action (pharmacokinetics and pharmacodynamics), with adverse effects. Our research also included immediate posttransplant immunosuppressive treatments, as well as those from the middle and late period, but also those used at the time of acute rejection.

Our research followed three distinct directions, which aimed to achieve the proposed objectives:

1. Analysis of the occurrence and frequency of post-heart transplant complications related to immunosuppressive treatment

2. A pre- and post-operative assessment, a comparative analysis of laboratory and pre- and postoperative echocardiographic results in patients who have undergone a heart transplant

3. Highlighting the most important aspects of histological diagnosis and differential diagnosis of postoperative myocardial lesions, associated or unrelated to rejection in heart transplantation, which is a significant step in monitoring heart transplant patients and has a major influence on the adjustment of immunosuppressive treatment .

The first study aimed at the frequency of post-transplant cardiac complications, unrelated to rejection, in direct relation to immunosuppressive medication and was a statistical and descriptive study. The results of the study showed that, although the primary pathology of a patient with heart failure is initially improved by transplantation, a number of potential pathologies can occur after heart transplantation, which are directly related to the effects of chronic immunosuppression, namely: infectious complications (bacterial and viral), diabetes, renal dysfunction, hyperlipidemia, malignancies, thyroid pathology.

The second study aimed at pre- and postoperative evaluation of patients with end-stage heart failure undergoing a heart transplant and was a descriptive study. The results of this study highlighted the following aspects: viral and bacterial serology was positive only for anti-Toxoplasma Gondii antibodies and anti-

cytomegalovirus IgG antibodies, both in pre- and postoperative evaluation, creatinine and liver enzyme levels decreased significantly after heart transplantation, due to improvement in cardiac function and liver congestion, as well as better renal perfusion after surgery due to improved left ventricular systolic function; echocardiographic examination revealed a significantly better left ventricular ejection fraction in the transplanted heart as well as significant diameters lower left and right heart chambers and lower systolic pulmonary arterial pressure; as anti-rejection drugs, mycophenolate mofetil and tacrolimus were administered in most cases, as recommended in current guidelines, post-transplant infections were reported in 13.21%, and 5 out of 16 deaths occurred intraoperatively.

The latest study highlighted key notions regarding the diagnosis of similar or unrelated postoperative myocardial lesions in heart transplant patients.

Patients were observed regularly according to a pre-established protocol, monitored by quantification of endomyocardial biopsy (EMB) lesions. Endomyocardial biopsy was performed in accordance with international guidelines for medical practice in the field of transplants. The diagnosis of lesions was established based on the evaluation of the material obtained from EMB, performed according to the clinic protocol in the early post-transplant period, as well as in the middle and late period. All cases with Quilty effect were analyzed both histologically and immunohistochemically, at the endocardial and subendocardial level at the myocyte level. All adipocyte biopsies, with or without mesothelium, were analyzed, identifying ventricular perforation when it was evident. During the histological analysis, the cases of perimycytic fibrosis, fibrotic scars, myocardial hypertrophy and the presence of cytomegalovirus (CMV) granulomas were also highlighted.

The results of this study showed the following: there were no fragments of tendon cords or tricuspid valve in any of the cases. Myocytes with coagulation necrosis were found mainly on restricted subendocardial areas - these lesions were reduced at the initial biopsy and more numerous at the biopsy material obtained in the middle and late periods after transplantation. In three cases, post-transplant micro-infarcts with small areas of neovascularization and loose connective tissue were reported around the affected area; ischemia and reperfusion lesions were diagnosed at all biopsies performed in the first 6 weeks post-transplant. In the case of a clear diagnosis of lesions caused by ischemia and reperfusion, subendocardial coagulation necrosis of several myocytes was observed, as well as a small number of monocytes and even rare neutrophils; biopsies obtained between 6 and 8 weeks post-transplant showed areas of necrosis with the appearance of micro infarcts in the process of organization, with the disappearance of necrotic myocytes and proliferation of connective tissue; In the examined paraffin sections, 9 cases of Quilty effect were identified, presenting the specific appearance of a dense endocardial lymphocyte infiltrate which, in most cases, extended to the basal myocardium. The degree of expansion varied from case to case and in two cases the lymphocyte conglomerate affected only the endocardium. Three of the cases presented capillaries with dilated lumen; in 26 of the cases subjected to the biopsy we observed the presence of fat cells in small numbers or even in the form of fragments of adipose tissue; a significant number of transplant patients had cytomegalovirus, which was difficult to diagnose on endomyocardial biopsies. For anti-CMV IgM antibodies, preoperatively there were negative results in all 45 patients examined, while postoperatively there were 43 patients (95.56%) with negative results and 2 patients (4.44%) with results positive for the same antibody. Only in four cases was CMV granuloma observed, with areas of myocyte necrosis, polymorphic inflammatory infiltrate and large cells, with characteristic inclusions of Cowdry.

In conclusion, the research conducted in the PhD thesis was completed with the following achievements, which are also elements of the originality of the thesis: the study makes notable contributions in the field of heart transplantation, in terms of immunosuppressive treatment, patient comorbidities or other risks during surgery or postoperatively, and immunohistological research, performed for the first time at IUBCVT in Târgu Mureş, bring important contributions regarding the evaluation of cardiac transplant patients.

