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Chronic renal allograft dysfunction – current state of knowledge

Współczesne poglądy na przewlekłą dysfunkcję przeszczepu nerki

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Summary

Both early and long-term outcomes of kidney transplantation are improving steadily. However, still about 5% of patients restart hemodialysis every year because of graft function loss. The main reason is chronic allograft dysfunction (CAD), the pathogenesis of which is complex. It usually develops more than a year since surgery. Clinical manifestation of this process involves gradual decline of GFR accompanied by hypertension and proteinuria. Progressive vascular changes of endarteritis proliferativa type are accompanied by ongoing inflammation within interstitial space and tubules (tubulitis). As a result, interstitial fibrosis and tubular atrophy (IF/TA) develop. According to the results of several recent studies, chronic nephrotoxicity of calcineurin inhibitors seems to be not the main cause of CAD. In contrast, in most cases immune-dependent destruction of the graft can be observed. The process of chronic antibody-mediated rejection (ABMR) is recognized by the presence of diffuse C4d deposits in peritubular capillaries accompanied by the development of donor-specific antibodies in the recipient. It seems likely that in nearly half of cases, ABMR and subsequent graft loss are due to inadequate (poor) immunosuppression because of patient's nonadherence to the treatment.

Streszczenie

Wyniki zarówno wczesne, jak i odległe, przeszczepiania nerek ulegają systematycznej poprawie. Tym niemniej, nadal około 5% chorych rocznie wraca do programu leczenia hemodializami z powodu utraty funkcji przeszczepionej nerki. Główną przyczyną tego stanu jest występowanie u chorych przewlekłej dysfunkcji przeszczepu (pdp), której patogeneza ma charakter złożony. Proces ten rozwija się najczęściej po roku od zabiegu i charakteryzuje się klinicznie powolnym postępującym spadkiem filtracji kłębuszkowej w powiązaniu z nadciśnieniem tętniczym i białkomoczem. Zmianom naczyniowym typu endarteritis proliferativa towarzyszą wykładniki zapalenia toczącego się w tkance śródmiąższowej i w cewkach (tubulitis) oraz włóknienie śródmiąższowe i zanik cewek (ang. *interstitial fibrosis* – tubular atrophy, IF/TA). W świetle nowych badań, główną przyczyną pdp nie jest jak dotąd sądzono nefrotoksyczność inhibitorów kalcyneuryny, lecz toczący się w przeszczepie proces immunologiczny przewlekłego odrzucania humoralnego (ABMR). Typowa jest przy tym obecność rozlanych linijnych złogów C4d w kapilarach okołocewkowych kory i rdzenia nerki, a także stwierdzenie we krwi biorcy przeciwciał anty-HLA specyficznych dla dawcy (DSA). Główną przyczyną ABMR jest nieadekwatna immunosupresja wynikająca często ze złej współpracy chorego i nieprzestrzegania zaleceń regularnego przyjmowania leków immunosupresyjnych.

Both early and long-term outcomes of kidney transplantation are improving steadily, which should be attributed to a modern and effective immunosuppression, as well as an increasing experience of transplant surgeons and comprehensive care provided to the graft recipients. According to the data of United States Renal Data System (USRD) from 1999 (1), median cadaveric graft survival improved from 5.2 years in the mid-1980s to 10.2 years the mid-1990s, and the European data from the Collaborative Transplant Study (CTS) (2005) revealed that the expected graft half-life exceeded 15 years (2). Despite that, still about 5% of patients return every year to the hemodialysis treatment due to graft function loss. The main reason is chronic allograft dysfunction (CAD), the pathogenesis of which is complex, and the prevention of and treatment have not been very effective so far. The chronic allograft dysfunction may be sometimes diagnosed as soon as a few months after transplantation, but it usually develops

move than a year from the surgery. Clinical manifestation of this process involves gradual decline of the glomerular filtration rate (GFR), accompanied by hypertension and proteinuria. Morphological signs of CAD involve progressive vascular changes of endarteritis proliferativa type with myofibroblast hyperplasia and vascular wall fibrosis, resulting in arteriole stenosis and invariably leading to secondary ischemic changes within the graft. These changes are of concentric nature and involve interlobar, arcuate and interlobular arteries. Sometimes they also affect the afferent glomerular arterioles. The internal elastic membrane remains intact. These alterations are accompanied by the markers of ongoing inflammation within interstitial tissue and tubules (tubulitis), mediated by infiltration of immunologically competent cells in the course of cellular response to alloantigens (3).

As a result interstitial fibrosis and tubular atrophy (IF/TA) develop. IF/TA replaced the previously used term – chronic allograft nephropathy (CAN). However, the diagnosis of CAN or IF/TA does not explain the pathogenesis of the process resulting in progressive CAD. Reasons and risk factors of CAD, according to Ekberg and Johansson (4), are summarized in tables 1 and 2.

Since their introduction into the clinical practice, calcineurin inhibitors (cyclosporine A, tacrolimus) were associated with nephrotoxicity. What is more, they are believed to be among the main nonimmunological factors of the graft function loss (tab. 1). Indeed, Nankivell et al., (5) who evaluated 961 renal biopsy specimens from 120 recipients of kidney and pancreas grafts treated with calcineurin inhibitors (CNI), found progressive arteriolar hyalinosis, glomerular sclerosis, and interstitial tissue damage, typical for CNI-induced nephrotoxicity, in all patients 10 years after transplantation. However, the histological changes did not attenuate the very good 10-year survival, which was observed in 95.2% of renal graft cases and in 86.5% of pancreatic graft patients. It should be stressed that the changes in renal histology assigned to CNI nephrotoxicity are non-specific, and their pathogenesis may be different, and involve damage present in the donor prior to organ collection, ischemia-reperfusion injury, hypertension, chronic rejection, etc. Snanoudj et al. (6) investigated nephrotoxicity markers not only in 91% of patients treated with CNI, but also in 64% of patients never treated with CNI. El-Zoghby et al. (7) analysed the causes of 153 renal graft losses in 1317 recipients and confirmed CNI-induced nephrotoxicity only in 0.7% of cases. Glomerular diseases and interstitial tissue damage accounted for a total of 68% of the graft loss causes. Long-term Deterioration of Kidney Allograft Function (DeKAF) study published in 2010 (8), investigating 173 biopsy specimens taken on indications, revealed changes typical to CNI nephrotoxicity in 35% of cases, and in 49% of cases CAN without nephrotoxicity features was diagnosed. Interestingly, graft failure occurred less frequently in patients with nephrotoxicity markers and was significantly more common in patients with C4d deposits in biopsy specimens, accompanied by the presence of donor-specific antibodies (DSA) in blood. Regele et al. (9) detected C4d deposits in peritubular capillaries in 34% of renal grafts biopsies, performed due to CAD after over a year from transplantation. C4d product is a result of degradation of the complement C4 component after the system activation via the classical pathway. It forms a stable covalent complex with the endothelial surface. The presence of diffuse linear C4d deposits in peritubular capillaries of the renal cortex and medulla is specific for acute and chronic humoral rejection (antibody mediated rejection – ABMR). The deposits are usually accompanied by reduplication of the glomerular basement membrane and multilayering of peritubular capillary basement membrane. The above described morphological lesions constitute the criteria for diagnosis of chronic humoral rejection based on Banff'09 classification (10). Another primary criterion is the presence of anti-HLA donor specific antibodies (DSA) in the recipient's blood. It should be noted that the absence or presence of only focal C4d deposits (50-60% of cases) does not exclude the diagnosis of chronic humoral rejection. In these cases, however, activation of endothelial cells was observed, manifested by increased expression of mRNA for von Willebrand factor, PECAM1 adhesion molecule, selectin etc. (11). DSA seem to be very important in this process, mediating the adhesion and activation of leukocytes and platelets, accompanied by cytokine release, that in turn increase endothelial cell activation. As a result the endothelial cells are destroyed by NK cells and monocytes/macrophages (12). DSAs may be preformed (present before transplantation) or created *de novo*. They belong

Table 1. Causes of kidney graft failure.

Immunological factors	Non-immunological factors
Humoral rejection	Basic disease (recurrent or *de novo*)
T-cell mediated rejection	Urinary tract infection
Inadequate immunosuppression (noncompliant patient, drug withdrawal/nonadherence to treatment)	Polyoma BK induced nephropathy
Inadequate immunosuppression (including drug withdrawal/ nonadherence to treatment)	Calcineurin inhibitor nephrotoxicity
	Obstructive nephropathy
	Ischemia
	Venous thrombosis

Table 2. Risk factors for kidney graft failure.

Donor dependent	Recipient dependent	Immunological
Deceased donor Donor after cardiac death	Female gender	HLA mismatch
Age > 60	Body weight mismatch (kidneys)	Prior sensitization of a donor (PRA)
Female gender	Obesity	Inadequate immunosuppression
Comorbidities	Comorbidities	
Ischemia time	Proteinuria	
Delayed graft function	Smoking	
	Nonadherence	

to IgG class and are capable of binding the complement C1q component. They may be directed against HLA class i or II, or against HLA-unrelated antigens, such as endothelial antigens. The most important predictor of *de novo* DSA synthesis include mismatch of class II HLA (DRβ1), previous episodes of acute cellular rejection, and inadequate immunosuppression resulting from poor patient cooperation (nonadherence). It was particularly common in the younger patients (24 vs. 13%). Furthermore, nonadherence rate was much higher in DSA than non-DSA patients (49 vs. 8%) (13). The presence of DSA significantly affects graft survival time. Ten-year graft survival in 315 recipients of renal allograft was achieved in 57% of patients with de novo DSA and in 96% of non-DSA recipients. Preformed DSA also predispose to the episodes of acute humoral rejection, often of subclinical course (14). In these cases the so-called protocol biopsies may reveal the features of renal microcirculation inflammation in the form of peritubular capillaritis and glomerulitis which, when present as diffused lesions accompanied by C4d deposits, are the predictor of chronic humoral rejection in over 60% of patients (15).

A good summary of this chapter is the prospective study by Sellares et al. (16), investigating 60 cases of renal graft loss in 315 recipients. The most common causes of the graft failure included chronic humoral rejection – 64% (including mixed rejection 5%), *de novo* or recurrent glomerulopathy – 18%, and BK polyoma infection – 7%. In the case of transplant loss due to rejection, as much as 47% of recipients did not strictly follow treatment recommendations, which resulted in inadequate (poor) immunosuppression. Therefore, the patients should be made well aware that regular taking of the prescribed medications is of the utmost importance, or else even the best-matched immunosuppression will not prevent the graft rejection and consequently organ loss.

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