Pathological Diagnosis of Antibody-Mediated Rejection*

Yong-Jin Kim, M.D.

Department of Pathology, Yeungnam University College of Medicine, Korea

항체매개성 거부반응의 병리학적 진단

영남대학교 의과대학 병리학교실

김 용 진

〈요 약〉

최근 미국 신장이식 센터들의 보고에 의하면 급성 거부반응에서 항체매개성 즉 체액성 거부반응이 20-30%에 이른다. 임상적으로는 세포 매개성 거부반응 보다 예후가 나쁘며 일반적인 면역억제 치료에 잘 반응하지 않는다. 조직학적 소견들은 세뇨관주변 모세혈관에 호중구의 침착, 동맥의 섬유성 괴사 및 세뇨관 손상 등이 있으나 다른 거부반응과 감별이 어려웠다. 최근 C4d가 세뇨관주변 모세혈관에 침착되는 특징이 발견되어 조직 면역화학 혹은 형광현미경 법으로 쉽게 진단을 할 수 있게 되었다. 이러한 임상 및 병리학적 소견을 바탕으로 2003년 Banff 모임에서는 급성 액성 거부반응을 포함하였으며 97년 분류의 급성세포성 거부반응의 제 3형 (혈관염 및 혈관괴사 형)을 여기에 포함시켰다. 만성 거부반응의 경우의 2/3에서 C4d 양성이 관찰되었으며 사구체 모세혈관이 두층으로 변하거나 동맥 내막의 섬유화 및 단핵 침윤 등 만성 혈관성 거부반응으로 분류했던 예들의 대부분에서 C4d가 양성이었으며 이들을 만성 액성 거부반응으로 인정한다. 우리나라에서는 뇌사자 이식이나 반복 이식이 적어서인지 아직까지 액성 거부반응이 흔하지는 않다.

Although a central role for T lymphocytes in organ allograft rejection has been established, several recent observations have led to a renewal of interest in antibody-mediated allograft rejection : numerous cases characterized by acute allograft injury resistant to potent anti-T cell therapy, the detection of circulating donor-specific antibodies (DSAs), and the deposition of C4d (a breakdown product of the complement component C4) in the graft[1]. Antibody-mediated rejection has been demonstrated in kidney and heart allografts, in both acute and chronic rejection, and is not restricted to pre-sensitized patients.

*Most content of this manuscript is summarized from reference 1).

Historical background

Trpkov et al.[2] found that anti-donor HLA class I antibodies were associated with a higher frequency of neutrophils in peritubular capillaries (PTCs) and glomeruli and fibrinoid necrosis of arteries, but these changes were present in a minority of cases. Furthermore, immunoglobulins and C3 were not often detected in these biopsies, raising some skepticism about the diagnosis of humoral rejection.

Independently, Feucht and colleagues[3, 4] reported that C4d staining of PTCs in allograft biopsies from pre-sensitized recipients with severe cellular rejection correlated with increased graft

loss, and suggested a humoral component to these 'mixed' rejections. C4d is an inactive fragment of complement component C4 released during the activation of the classical complement pathway. C4d contains a reactive thiol group that is exposed on C4 activation and binds covalently, and therefore durably, to adjacent structures.

Collins and colleagues[5] clarified these observations in 1999 by demonstrating that C4d deposition in PTCs was always present in biopsies from patients with circulating de-novo DSAs and neutrophils in PTCs or arterial fibrinoid necrosis. These patients were not generally pre-sensitized. The rarity of immunoglobulin and C3 in the PTCs was confirmed. Many cases also had features of acute cellular rejection (ACR). The study strongly suggested that C4d is a useful in-situ marker of antibody-mediated rejection, and led to prospective studies noted below and subsequent widespread acceptance of the validity of 'acute humoral rejection' (AHR).

Acute Humoral Rejection

1. Biopsy features

The histological features that distinguish C4d-positive acute rejection cases are neutrophils in PTCsand glomerular capillaries, neutrophilic tubulitis and fibrinoid necrosis of the arteries and glomeruli[2, 6, 7, 8]. However, these finding are variable and are not uniformly present. Some find neutrophils only infrequently[7]. Practically, the glomerulitis associated with AHR often shows neutrophils, whereas glomerulitis with only mononuclear cells is more commonly C4d-negative[6].

Endarteritis, defined as mononuclear cells infiltrating under the arterial/arteriolarendothelium, is not generally associated with C4d or other features of AHR[2, 6-8]. In contrast, fibrinoid necrosis of the arteries is usually mediated by humoral antibodies to the endothelium, as evidenced by circulating DSAs and C4d deposition in capillaries[6, 7, 9].

Table 1. Pathological Criteria for Acute Humoral Rejection[6]

C4d deposition in peritubular capillaries
At least one of the following :
Neutrophils in peratubular capillaries
Arterial fibrinoid necrosis
Acute tubular injury
Circulating donor-specific antibodies

2. Diagnostic criteria and classification

The histological and immunopathological criteria for AHR are given in Table 1[6]. Because of the confusing data in the literature that C4d deposition (at least focally) can occur in ischemic injury[9], we recommend for now that the definitive diagnosis of AHR requires demonstrating circulating DSAs. These criteria have been incorporated into the new Banff criteria[10].

Mauiyydi and Colvin[1] proposed classification (Table 2) retains the morphological criteria used by the revised Banff/CCTT for ACR types 1 and 2, and moves the former type 3 acute rejection to the more appropriate and specific AHR group. Two forms of AHR can thus be recognized his-

Table 2. Classification, Frequency and Outcome of Acute Renal Allograft Rejection[1]

	N	Frequency (%)	Graft loss at 1 year
Acute cellular rejetion			
Type 1 (tubulointerstitial)	32	48	3%
Type 2 (endateritis)	15	22	7%
Acute humoral rejection			
Type 1 (capillary)	15	22	27%
Type 2 (arterial fibrinoid necrosis)	5	7	40%

tologically : Type 1 AHR with capillary inflammation, i.e. neutrophils in PTCs and glomerular capillaries, and type 2 AHR with arterial fibrinoid necrosis. The proposed classification adds immunophenotypical criteria to the above, with pure ACR being C4d-negative and AHR being C4d-positive.

The cases with ATN alone have been a transient histological precursor to typical AHR, and they include these in type 1 AHR. The subset of the C4d-positive acute rejection biopsies that show morphological features of ACR alone or both ACR and AHR behave as AHR.

Chronic Humoral Rejection

The role of antibodies in chronic rejection is controversial. 'chronic rejection' has been used interchangeably with chronic allograft nephropathy and chronic allograft dysfunction, but we believe it should be reserved for those cases in which active immunological injury has been identified (either T cell or antibody) in conjunction with related structural changes of the graft. The cardinal features include arterial intimal fibrosis with intimal mononuclear cells (chronic allograft arteriopathy), and in the kidney the duplication of the glomerular basement membranes (chronic allograft glomerulopathy).

In a recent study[11], 61% of those cases that had arterial or glomerular lesions of chronic rejection as defined above (comprising 20% of the biopsies taken for chronic allograft dysfunction), had C4d in PTCs, versus 2% in those with other changes, including cyclosporine toxicity and non-specific interstitial fibrosis. The minimal frequency of C4d positivity among all those with chronic graft dysfunction was estimated to be 12% (20%×61%). All of the patients with DSAs at the time of biopsy had C4d deposition; 90% of those with

C4d had anti-donor antibodies. The implication is that C4d provides direct, in-situ evidence for an active, ongoing, humoral immune reaction, which has the potential to separate chronic renal allograft rejection from chronic injury of other etiologies (e.g. cyclosporine toxicity), and proposed the term 'chronic humoral rejection', analogous to AHR. The C4d-positive chronic rejection cases or chronic humoral rejection cases were similar histologically to C4d-negative chronic rejection cases, and curiously had no histological evidence of acute inflammation, suggesting resistance at the level of the endothelium to the effects of complement-mediated injury.

Peritubular capillary laminations

Lamination of the PTC basement membrane occurs in chronic rejection, as shown originally by Monga et al.[12] and most recently by Ivanyi et al.[13]. This lesion is not specific for graft rejection, but may serve as a marker of past or recent endothelial injury and repair. Marked lamination of the PTCs by electron microscopy correlates with the presence of C4d in the PTCs [11], suggesting that capillary changes are associated with ongoing alloimmune injury.

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