Renal Pathology - Transplantation

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Kidney has a **limited number of tissue reactions** by which the kidney tissue **responses to abundant types of injury**.

**Interpretation of a mixture of morphological changes** which are given by a complex anatomical structure of the kidney.

Only rarely one disease causes a kidney dysfunction.

The patient suffered from several diseases which influence the morphological features.

Kidney graft: in addition to all these things: the influence of humoral and/or cellular rejection episodes, recurrent and de novo diseases, and various types of treatment.
Kidney anatomy  Kidney has a complex anatomical structure with a special type of blood supply.

The arteries and arterioles are end vessels! if they are occluded, the tissue they supply downstream become ischemic, resulting in injury or necrosis.

Stenosing lesions: corresponding part of the tissue: ischemia and effect of lesser level of IS than in the circulation.

Almost all grafts had already varying degrees of preexisting chronic injury.
1. **Cellular theory (Peter Medawar):** the process of graft rejection is immunologically dependent. The cells (easy to see on histological slides) were recognized and identified as a cause of tissue damage. The antibodies are not seen in routine staining in histology. Surprisingly, we still share the same view as P. Medawar had, because we still accept that when we see lymphocytes which cause damage to the graft that the process is T-cell mediated.
Hyperacute rejection (HR)

- The antibodies are not seen in routine histological staining.
- HR can occur immediately after transplantation.
- HR was observed when the kidney was transplanted into a recipient with pre-existing DSA.
- HR can also be caused by antibodies directed at allogenic blood groups A and B.
- New generation of laboratory tests prevents HR.
2. Humoral theory (Paul Terasaki): evidence that also in later periods after transplantation antibodies must participate in graft damage.

They were unable to prove this theory: because no tissue marker was known which could confirm that antibodies can cause such damage.

H. Feucht: studied complement components and recognized the relationship of C4d deposition in PTCs in kidney grafts to graft dysfunction. Feucht’s observation represented a breakthrough and a great improvement in diagnosis of antibody-mediated rejection.
Positive C4d staining is a marker of antibody-mediated rejection and represents something like an imprint that the reaction occurred at the place of positive staining.
Classification of rejection changes

- various centers were developing their own protocols and their own definitions of the morphological features
- without standardization of the nomenclature the communication among various centers would remain unsatisfactory
- Banff classification since 1991
- The schema underwent considerable evolution, and was repeatedly revised and modified in follow-up meetings during a 2-year period
Banff schema

- **T cell mediated**: acute (i, t, v)
  chronic (ci, ct, cv)

- **Antibody mediated**: acute (g)
  chronic (cg)
Acute T-cell-mediated rejection


C: 4. Acute T-cell-mediated rejection \textit{(type/grade)}

- IA. + IB. Cases with significant \textit{interstitial infiltration (tubulitis)}
- IIA. + IIB. Cases with \textit{intimal arteritis (v1, v2)}
- III. Cases with "transmural" arteritis and/or fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (v3)

- \textbf{Significant lowering of the rate of episodes of ACR} to approximately 5-10% in the 1st year
- Grade I: 65-70%, grade II: 30%
- Huge progress was made in our understanding of immunological mechanisms of rejection
**Acute T-cell-mediated rejection, tubulitis-schema**

**CD8** recognize peptide antigens presented by class I MHC, produce IFNγ
Mediate direct cytotoxicity via granzymes and perforin

**CD4** recognize peptide antigens presented by class II, can be divided according to their cytokine production:
- **Th1**: IFNγ, IL2, TNFα, typically in infiltrate of acute rejecting grafts
- **TH2**: IL4, IL5, IL10, provide help for B cells and production IgE – promote eosinophils

Inflammatory cytokines produced by T cells activate **epithelial cells**, which in turn attract more T cells.
Acute T-cell-mediated rejection, type I
dg. problems and differential diagnosis

• How much inflammation is reactive in subcapsular space early posttransplant
• Resolving/partially treated rejection
• inflammation in areas of interstitial fibrosis with t1 in the interface areas

20-65% ATMR show C4d deposits along PTCs: mixed cellular- and antibody-mediated rejection

Differential diagnosis
• Drug-induced TIN
  Difficult or impossible to distinguish from ATMR
• Pyelonephritis
  neutrophilic casts
• Polyomavirus nephropathy
  plasma cells, IH detection
Acute T-cell-mediated rejection, type I
Dif. Dg.: polyoma virus nephropathy
Acute T-cell-mediated rejection, type II and III arteritis or endotheliitis
Acute T-cell-mediated rejection, **type II and III differential diagnosis**

If we strictly follow the Banff criteria, one lymphocyte is **enough** for the dg. type II ATMR rejection.

Pre-existing donor disease
Antibody-mediated rejection (AMR)

- AMR has occurred with all IS regiments, even profoundly depleting therapy.
- Today it is believed that the majority of cases of late graft dysfunction and loss are caused by the presence of DSA to HLA antigens.
- AMR: first the Abs occurs, which is followed by detection of C4d in biopsy samples, and then tissue damage started to be detected and finally graft dysfunction occurs.
- The target structures for immune attack are endothelial cells.

- **Acute/active** antibody mediated rejection
- **Chronic/active**
The pathology of AHR has a wide spectrum of findings. However, none of these features is specific.
Chronic/active antibody-mediated rejection

Dg. criteria of chronic active AMR:

**Triad** of tx glomerulopathy, C4d+, anti-DSA.

When the morphological features as multilayering of tubular BM and mainly Tx glomerulopathy once set-in, there is not any further known treatment options to reverse chronic rejection.
Antibody-mediated rejection

- C4d has been the cornerstone in the diagnosis of AMR for one decade, it has become more and more clear that some cases of AMR with DSAs which are otherwise similar, do not have detectable C4d in biopsy sample. These C4d negative cases showed peritubular capillaritis and/or increased endothelial activation.

- Gradually it became clear that both C4d staining and DSA titers are not stable and can increase and also vanish. Therefore at any given time, these factors may or may not be demonstrable, even if AMR is or has been present.
Acute T cell mediated rejection, type II (v1, v2) experiment first questioned this classification?

Some very interesting experiments break our simplified classification. 

**ACR type II**, prototype of T cell-mediated rejection  
Hirohashi et al. Am J Transplant 2010;10;510-517  
**Genetically T deficient mice develop similar morphology** (2 weeks after transfer of DSA) in morphology: macrophages, NK cells; 

**The question was:**  
It is possible that humoral rejection in human can have arterial component with endothelial inflammation???
Acute vascular rejection (v1, v2) and DSA

Analysis of 2079 recipients with 302 biopsy proven rejections. They tested all the patients for DSA in the stored sera.

71% of cases with vascular rejection (v1, v2) were associated with DSA.

More importantly, 45% v1 or v2 with DSA were C4d negative and classified as T-cell mediated rejection.

all patients with v1 or v2 lesion should be tested for DSAs

Modification of Banff classification, 2013

Inclusion:

1. antibody-associated arterial lesions (v1, v2)
2. C4d negative antibody mediated rejection.

2. **ABMR** active and chronic may now be diagnosed **in the absence of C4d deposition**. However, in the absence of C4d, additional evidence of current or recent antibody interaction with vascular endothelium must be present. Such evidence may be **morphologic or molecular**.

Recent evidence has demonstrated an important role of Th17 response against self-Aggs as a mechanism leading to CR.

- Perclan, collagen IV and VI, agrin
- The key point is inflammation
- Exposure of cryptic self Aggs or their determinants can lead to activation of both: cell- and Abs-mediated immune responses.
- Continuous detection of Abs
Summary

• C4d is still very useful marker for Ab mediated rejection.
• AMR may occur in the absence of peritubular capillary C4d staining and may be difficult to identify.
• The diagnosis of AMR in this setting is still challenging and searching for morphological features of AMR (g, cg, inflammation in peritubular capillaries) is required.
• Correlation with DSA is helpful.
• However, both C4d staining and DSA titers are not stable and can increase and vanish. Therefore at any given time, these factors may or may not be demonstrable, even if AMR is or has been present.
• Last Banff meeting in 2013 included into the classification schema 2 new categories:
  • First: All v1 and v2 lesions may be indicative for AMR and all patients with v lesion should be tested for DSA.
  • Second: AMR can be C4d negative. But, in the absence of C4d, additional evidence of current or recent antibody interaction with vascular endothelium must be present. Such evidence may be morphologic or molecular.
Other causes of graft dysfunction