Case 6

Clinical history
A 39 year old male patient received a deceased donor kidney in 2005 because of renal failure due to hypertensive nephrosclerosis. There were 5 HLA-mismatches and no donor-specific antibodies. Due to malcompliance with his immunosuppressive drugs, he experienced two biopsy proven episodes of interstitial cellular rejections 6 and 35 months after transplantation. 

40 months after transplantation a diagnostic biopsy was taken because of a rise in serum creatinine and a newly diagnosed proteinuria (140 mg protein/mmol creatinine; baseline 13).

Electron microscopic diagnosis
Transplant glomerulitis

Additionally (by light microscopy) there was a severe diffuse interstitial cellular rejection, a moderate arteriolosclerosis, and a focal interstitial fibrosis with tubular atrophy (10-20%). C4d was negative. Transplant glomerulitis was only found in the glomerulus investigated by EM.

Follow up
7 months later the patient had developed chronic renal failure and was dialysis-dependent again. A biopsy taken at that time showed a severe mixed T cell- and antibody-mediated rejection with vascular rejection, interstitial cellular rejection, C4d-positive capillaritis, and beginning transplant glomerulopathy. The patient remains on dialysis since.

Discussion
Transplant glomerulitis is infrequently found in renal transplant biopsies. In Basel we diagnose it in only 4.4% of our transplant biopsies, in around 30% of these transplant glomerulitis is associated with various degrees of transplant glomerulopathy. It is even more rarely seen in EM samples for two reasons: (1.) it is most often found early after transplantation when EM is rarely performed and (2.) it is a focal lesion often affecting only one or two glomeruli which are not sampled. In the Basel material the median time to diagnosis in cases without additional transplant glomerulopathy is 57 days, the interquartile range is 19 and 195 days. Few cases evolve late after transplantation.

The term “glomerulitis” was initially used synonymously for glomerulonephritis, especially the proliferative forms. In the transplant setting, the characteristic lesions of transplant glomerulitis were already described in the 1970ies in the context of rejection-related early graft failure [1] and is termed “pseudo-gglomerulitis” in the classic textbook of Zollinger and Mihatsch [2] evolving to “transplant glomerulitis” during the next years [3]. A prominent N Engl J Med paper connected the lesion to CMV infection [4] which proved to be a wrong track. It was integrated into the Banff grading scheme [5, 6], but was not used as a rejection criterion in this classification until antibody-mediated rejection was incorporated [7].

Unfortunately, the definition of transplant glomerulitis varies among renal transplant pathologists. The initial morphological descriptions emphasize four features:

- **An increased number of endocapillary leukocytes.** The majority of these cells are monocytes (CD68+) [8]. In cases early after transplantation there may be a substantial number of neutrophils [9]. In most cases, this hypercellularity is present in a focal and segmental manner.

- **Endothelial swelling.** This is readily appreciated if the lesion is investigated by EM, especially in adjacent capillary loops. It is much more difficult to recognize by light microscopy. Interestingly, a recent study using morphometry also showed glomerular endothelial cell enlargement of C4d+ cases without transplant glomerulitis indicating antibody- and complement-mediated endothelial damage [10].

- **Dilatation of capillary loops.** This is usually present in a focal and segmental manner only. The reason for capillary dilatation is unclear. It is unlikely that it is just the cell accumulation because this feature is not seen in immune complex-mediated glomerulonephritis. It may be thought of as mini- (or incomplete) mesangiolysis.

- **Occlusion or near occlusion of capillary lumina with cells.** Both leukocytes and endothelial cells contribute to the occlusion.
This definition was used in the first version of the Banff scoring system [5], but the dilatation and occlusion of capillary loops was lost in the later versions [6]. Thus, the current Banff definition of the g-score is based on endocapillary hypercellularity and endothelial swelling taking into account the number of affected glomeruli. A study from Pittsburgh explored the possibility of other definitions. As they had difficulties separating endothelial and mononuclear cells without immunohistochemistry, they mainly relied on a count of “unequivocal” endocapillary leukocytes using a cut-off of ≥5 leukocytes per glomerular cross section [11]. The “≥5 leukocytes” stems from the WHO-definition of glomerular “leukocytic infiltration” in native kidney diseases [12]. To my knowledge, this cut-off is based on (a probably much debated) expert opinion and not on studies designed to define a cut-off. In their hands, counting cells was superior to the endocapillary occlusive lesion, but their study design has several important limitations [13]. Regardless of the definition, transplant glomerulitis has a poor interobserver agreement. It appears that the more pathologists are involved the less agreement will be reached [14, 15] (Banu Sis, personal communication, August 2013). Currently, a Banff working group on glomerular lesions tries to redefine the definition of transplant glomerulitis using a data-driven approach.

The diagnosis of transplant glomerulitis in the context of established transplant glomerulopathy is only ill defined. Dilatation of capillary loops in the remodelled capillary loops is not possible. A mild increase in the number of endocapillary leukocytes is present in most cases of transplant glomerulopathy and quite often the endothelial cells will appear swollen. Therefore, we render the double diagnosis only in cases with “marked” endocapillary leukocytosis and occlusion or near-occlusion of the capillaries.

Transplant glomerulitis has been linked to antibody-mediated rejection right from the beginning. There is a strong association with donor specific antibodies and C4d deposition in the peritubular capillaries [11, 16, 17]. There may be an impact on transplant survival, which is obvious in cases that additionally have or progress to transplant glomerulopathy [18]. An increased number of CD68+ monocytes in the glomeruli has been found as an independent predictor of graft failure in two studies [19, 16].

Endothelial damage due to antibody binding and complement activation is thought to be the initial step in the pathogenesis of transplant glomerulitis. A recent review by Drachenberg and Papdimitriou provides a very good discussion of this concept [20]. The pathology that evolves depends whether the immunological attack proved to be lytic or sublytic to the endothelial cells. The reaction of the endothelial cells to sublytic injury can be divided into a proliferative/reparative, proinflammatory, and/or procoagulant pattern. Proinflammatory stimuli (upregulation of chemokines and adhesion molecules) are at least partly responsible for the attraction of monocytes in transplant glomerulitis. Importantly, often an overlap between the different patterns will be seen.

Summary

The glomerulus sampled by EM shows the classical diagnostic features of transplant glomerulitis. This finding was surprising because all other features of the biopsy pointed towards T cell-mediated rejection. Taking into account the follow-up information, we, by chance, caught a very early stage of the emerging antibody-mediated part of the mixed rejection that was clearly visible in the follow-up biopsy 7 months later.

Helmut Hopfer
Institute of Pathology
University Hospital Basel
Schönbeinstrasse 40
CH-4031 Basel
Switzerland
Phone: +41-61-2652890
Email: hhopfer@uhbs.ch
**Literature**