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Original contribution

# Bowman capsulitis predicts poor kidney allograft outcome in T cell–mediated rejection☆

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**Summary** Acute T cell–mediated rejection (TCMR) is an important cause of renal allograft loss. The Banff classification for tubulointerstitial (type I) rejection is based on the extent of both interstitial inflammation and tubulitis. Lymphocytes may also be present between parietal epithelial cells and Bowman capsules in this setting, which we have termed "capsulitis." We conducted this study to determine the clinical significance of capsulitis. We identified 42 patients from the pathology archives at The University of Chicago with isolated Banff type I TCMR from 2010 to 2015. Patient demographic data, Banff classification, and graft outcome measurements were compared between capsulitis and noncapsulitis groups using Mann-Whitney *U* test. Capsulitis was present in 26 (62%) and was more frequently seen in Banff IB than in IA TCMR (88% versus 44%, $P = .01$). Patients with capsulitis had a higher serum creatinine at biopsy (4.6 versus 2.9 mg/dL, $P = .04$) and were more likely to progress to dialysis (42% versus 13%, $P = .06$), with fewer recovering their baseline serum creatinine (12% versus 38%, $P = .08$). Patients with both Banff IA TCMR and capsulitis have clinical outcomes similar to or possibly worse than Banff IB TCMR compared with those with Banff IA and an absence of capsulitis. Capsulitis is an important pathologic parameter in the evaluation of kidney transplant biopsies with potential diagnostic, prognostic, and therapeutic implications in the setting of TCMR.


## 1. Introduction

More than 18 000 kidney transplants are performed in the United States annually [1]. Although graft survival rates have increased since the 1980s with improved immunosuppressive regimens, the 10-year graft failure rate is still 53% for deceased donor transplants and 37% for living donor transplants. Although there are many causes of allograft dysfunction, T cell–mediated rejection (TCMR) affects 5% to 10% of allografts within the first year of transplantation and remains an important cause of renal allograft dysfunction and loss [2,3].

The Banff classification divides TCMR primarily into tubulointerstitial (type I) and vascular (type II and rarely type III) involvement [4]. TCMR with higher Banff grade correlates with worse allograft function and graft survival [5-7].

☆ Competing interests: Anthony Chang serves as a consultant for Alexion Pharmaceuticals and Regulus Therapeutics and is on the speaker bureau for Alexion Pharmaceuticals.

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Therefore, the Banff grade is a useful tool to stratify risk of graft failure in patients with cellular rejection, but tubulointerstitial rejection relies on 2 criteria, the extent of interstitial inflammation and tubulitis.

We observed that lymphocytes can be present between Bowman capsules and parietal epithelial cells, which we have termed "capsulitis." Because lymphocytic infiltration of parietal epithelial cells (capsulitis) is conceptually analogous to lymphocytic infiltration of the tubular epithelial cells (tubulitis) and because of the anatomic continuity between these 2 compartments, we believe that capsulitis extends the injury spectrum of tubulointerstitial TCMR. We conducted this study to determine the clinical significance of this novel pathologic finding in the setting of type I TCMR.

## 2. Materials and methods

We searched the pathology archives of The University of Chicago from 2010 to 2015 for kidney transplant biopsies with isolated type IA or IB TCMR as defined by the Banff classification for kidney allograft pathology. All biopsies were performed for clinical indication. Exclusion criteria included repeat biopsies from the same patient, presence of less than 7 glomeruli, and concomitant primary glomerular disease, polyomavirus nephropathy, or Banff type II/III rejection. A total of 42 cases were identified. These cases were assessed for capsulitis, defined as the presence of one or more lymphocytes between Bowman capsules and parietal epithelial cells in at least a single nonglobally sclerotic glomerulus (ischemic glomeruli were not excluded). The presence of free-floating lymphocytes in the urinary space, or lymphocytes adherent only to the surface of the parietal epithelial cells, was not considered adequate for a diagnosis of capsulitis. This identification was made on 6 to 8 levels of periodic acid–Schiff (PAS) and hematoxylin and eosin stains for each biopsy. In 6 cases, immunohistochemical studies for CD3 had previously been performed during the initial workup of the case and also were examined.

Clinical data on all cases was collected. Baseline characteristics including age, sex, ethnicity, living versus deceased donors, expanded criteria donors, graft age at biopsy, delayed graft function, and serum Cr at biopsy were compared between capsulitis and noncapsulitis groups. The presence of concomitant acute antibody-mediated rejection diagnosed on biopsy was also compared between the 2 groups. An interstitial fibrosis and tubular atrophy (IFTA) score from 1 to 3 was also assigned to each case, where a score of 1 indicated 1% to 25% IFTA; 2, 26% to 50%; and 3, greater than 50% IFTA. Donor and recipient HLA information, as well as induction, maintenance, and rejection treatment regimens, was collected.

Outcome measurements included recovery of baseline Cr and progression to dialysis within 1 year of biopsy. Recovery of baseline Cr was determined by comparing serum Cr up to 1 year after biopsy to baseline Cr preceding graft dysfunction. Patients who went onto dialysis were categorized as not recovering their baseline Cr.

Clinical and pathologic data were compared between capsulitis and noncapsulitis groups. Data analysis was performed using the Mann-Whitney *U* test. *P* values of less than .05 were considered statistically significant. This study was approved by the University of Chicago Medical Center institutional review board.

## 3. Results

### 3.1. Patient demographics and characteristics

Patient demographics and characteristics are shown in Table 1. There was no statistically significant difference in patient age (41 versus 42 years, $P = .4$), sex (54% versus 56% male, $P = .5$), ethnicity (73% versus 73% African American, $P = .4$), living versus deceased donors (23% versus 38% living donors, $P = .8$), expanded criteria donors (4% versus 0%, $P = .8$), graft age at biopsy (64 versus 53 months, $P = .3$), or delayed graft function (8% versus 13%, $P = .8$) between those with and without capsulitis. There was no obvious difference in HLA match between the capsulitis and noncapsulitis groups (Supplementary Table 1). Patients across both capsulitis and noncapsulitis groups underwent similar induction regimens of antithymocyte globulin or anti–interleukin 2 receptor antibodies. Both groups received similar maintenance therapy consisting primarily of tacrolimus, mycophenolate, and prednisone. Rejection treatment was also similar across both groups and consisted predominantly of steroids or antithymocyte globulin with or without intravenous immunoglobulin or rituximab. There was no significant difference in the incidence of concomitant acute antibody-mediated rejection (58% versus 69%, $P = .6$) between the capsulitis and noncapsulitis groups. In addition, there was no significant difference in the IFTA score between these groups (1.7 versus 1.6, $P = .3$), supporting that any differences between the groups were not due to differing degrees of chronic scarring.

**Table 1** Patient demographics and characteristics of capsulitis and noncapsulitis groups

| | Capsulitis | No capsulitis | *P* |
|---|---|---|---|
| n | 26 | 16 | – |
| Age (y) | 41 | 42 | .4 |
| Sex (% male) | 54 | 56 | .5 |
| Ethnicity (% African American) | 73 | 73 | .4 |
| % Living kidney transplant | 23 | 38 | .4 |
| % Expanded criteria donors | 4 | 0 | .8 |
| % Delayed graft function | 8 | 13 | .8 |
| Graft age at biopsy (mo) | 63.7 | 52.7 | .3 |
| Concomittant AMR (%) | 58 | 69 | .6 |
| IFTA score at biopsy | 1.7 | 1.6 | .3 |