Background

C3 Glomerulopathy (C3G) is characterized by dysregulation of the alternative pathway of complement. The majority of patients will approach ESRD within 10 years of diagnosis. Recurrence in renal transplants is as high as 84%\(^2\). Little is known about the natural history of disease, including the markers of progressive disease. Similarly, no data exist to define the predictors of poor renal outcome in transplant. The degree of C3 consumption (represented by a low C3) has been postulated as a predictor of disease activity in the setting of native kidney disease. Whether C3 abnormality plays a similar role in the transplant setting is unknown.

Methods

We studied a sub-cohort of the University of Iowa's C3G Natural History Study. All patients met the renal biopsy consensus definition of C3G. Included patients had at least 3 pre-transplant and 3 post-transplant C3 values. All patients in the cohort were tested for complement gene abnormalities. In addition, a biomarker panel including complement protein functional assays, protein levels (including breakdown product) and nephritic factor assays was performed on all patients. Complement biomarker results were correlated with recurrence of C3G in a renal allograft. In our cohort.

Results

Thirteen patients were included in the evaluation: 7 Male and 6 Female. The average age at diagnosis was 20.5 years. The average time to ESRD in the native kidney was 3 years. The median follow-up time post-transplant was 5 years. Drivers of disease included nephritic factors (NF, n=8), gene variants (n=6), and a monoclonal protein (n=1).

Table 1. Demographic and biomarkers data on transplant cohort

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<th>Sex</th>
<th>Date Transplant</th>
<th>Pre-nephritic</th>
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<th>CFI Results</th>
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Cohort Characteristics (Table 1):

1. C3 Glomerulopathy Subtype: 5 DDD, 8 C3GN
2. 7/13 (62%) had a positive nephritic factor at the time of native kidney diagnosis
3. 3/13 (46%) had a gene variant
4. 3/13 (46%) had low C3 at the time of transplant
5. 7/13 (54%) had a history of a nephritic factor
6. 5/13 (38%) had clinical recurrence in their allograft (Figure 2)
7. 2/13 (15%) had histologic recurrence

Conclusions

• A low C3 at the time of transplant appeared to be associated with a greater risk of recurrence of disease in a transplant.
• Recurrence can occur in the setting of a normal C3
• The C3 measurement alone is not a clear predictor of risk for recurrence of C3G in an allograft.
• Histologic recurrence without clinical recurrence can occur.
• The effect of this on renal outcome is unknown.

Limitations of the study:

• Low patient number and variable treatment approach
• Nephritic factor status not known on all patients
• The C3 was not known in all patients immediately at the time of transplant
• Patients were not subject to protocol biopsy. Therefore, whether more patients have histologic recurrence alone is not known.

Future Directions

Longitudinal follow-up is ongoing for this cohort and a parallel, chronic C3 glomerulopathy in native kidney disease cohort. The study team is designed to develop prediction models based on a comprehensive array of clinical, histologic and complement biomarkers, with a goal toward identifying biomarkers for disease progression and surrogate markers for renal outcomes.

References