Complement C3 Trend Before and After Transplant in C3 Glomerulopathy

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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[1]. 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.

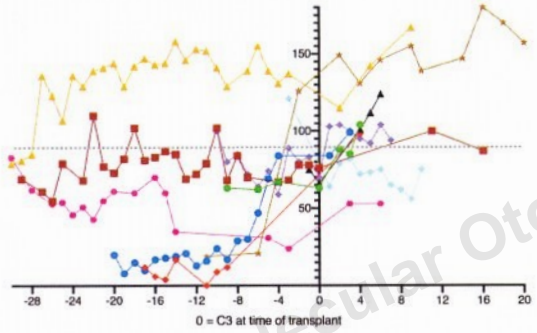
Methods

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).

Figure 1



Results

Table 1. Demographic and biomarkers data on transplant cohort

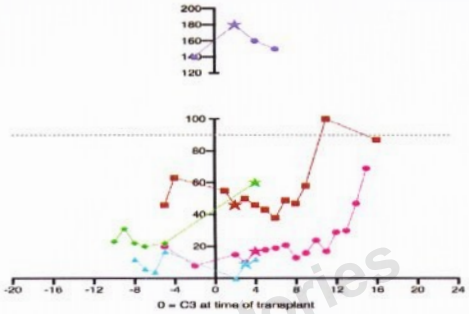
Age at Dx (years)	Dx	Transplant	Nephritic Factors: Presentation C3Nef	Nephritic Factors: Presentation C5Nef	Nephritic Factors: At Transplant C3Nef	Nephritic Factors: At Transplant C5Nef	Complement Gene Variant: Gene	Complement Gene Variant: Protein Change	Complement Gene Variant: Pathogenicity	CADD	MAF	Time to Transplant Recurrence	C3 Level [mg/dL] Prior to Recurrence
8	DDD	10/2016	3+	3+	2+	1+							
8	C3GN	10/2016	1+	1+	Neg	Neg						Histologic recurrence only	
15	C3GN	01/2019	2+	1+	3+	2+							
6	DDD	6/2000; 7/2019	1+	1+	1+	1+						from the 1st Tx - 3 mths	20
12	C3GN	11/2018	2+	2+	1+	Neg							
65	C3GN	06/2017	Neg	Neg	Neg	Neg	C3	p.Gly924Ser	VUS	31		10 mths	46
60	DDD	01/2013	Neg	Neg	Neg	Neg						Histologic recurrence only	
19	C3GN	01/2015	Neg	Neg	Neg	Neg	C3	p.Lys155Gln	VUS	5.731	0.27%		
16	C3GN	04/2016	Neg	Neg	Neg	Neg	CFH	p.Ser884Tyr	VUS	10.94	0.03%		
9	DDD	01/2007			1+	1+						12 mths	17
		07/2010			3+	3+	CFI	p.Gly379Arg	Likely Benign	0.002	0.36%	5 mths	17
		11/2016			Neg	1+						1 mth	13
14	C3GN	02/2008	2+		1+	1+	C3	p. Lys633Arg	Likely Benign	0.043	0.046%	1 mth	22
		12/2015					CFH	p. Ile1169Thr	VUS	23.8	0.002%		
19	DDD	02/2008	1+		1+							4 yrs	140
		10/2015	1+		1+	1+							
15	C3GN	09/2015	Neg	Neg									

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
   a. The nephritic factor remained positive at the time transplant recurrence in all 7 patients.
3. 6/13 (46%) had a gene variant
   a. 4 gene variants were considered variants of unknown significance, 2 as likely benign.
4. 5/13 (38%) had clinical recurrence in their allograft (Figure 2)
   a. 1 patient had recurrence in 2 allografts
   b. 2 Patients had histologic recurrence (biopsy only) recurrence
      1) Both patients with histologic recurrence are more than 5 years from transplant with no clinical markers of disease.
   c. 4/5 (80%) of those that recurred did so within the first year of transplant
   d. The average time to recurrence was 11 months (range: 1-48 months)
   e. No patients with recurrence had been exposed to anticomplement therapy
5. The C3 was known at the time of transplant in 7 patients. [The trend in C3 before and after transplant is depicted in Figure 1.]
   a. 6/7 (86%) of patients with a known C3 on the day of transplant had a low C3.
      1) Low C3's were less than 50% of normal.
      2) One patient with recurrent C3G retained a normal C3 both with native kidney disease and with renal transplant recurrence.
6. In patients without recurrence:
   a. 1/8 12.5% has retained a normal C3 throughout both native disease course and post transplant.
   b. 6 patients who had a low C3 with native kidney disease, have retained a normal C3 in the post transplant period.
   c. 2/8 (25%) patients who have not recurred, retain a low C3

Results

Figure 2



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 and a parall chronic C3 glomerulopathy in native kidney disease cohort. The stu team is designed to develop prediction models based on comprehensive array of clinical, histologic and complement biomarker with a goal toward identifying biomarkers for disease progression a surrogate markers for renal outcomes.

References

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Research is funded in part by the NIH (CMN and RJHS) and an unrestricted grant from Novartis.

ASN 2019