RECURRENT C3 GLOMERULOPATHY FOLLOWING KIDNEY TRANSPLANTATION

ANJH 2025

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Hôpital Bicêtre / GHSIF Melun

- Case report: recurrences in transplantations
  - *First KTx : CS pulse / PEX / RTX / ECULIZUMAB*
  - *Third KTx : ECULIZUMAB / IPTACOPAN*

- Literature review

- Discussion

Competing interest

- I received remuneration from Novartis, for the present presentation

M. B, 44 years old

- Nephrotic syndrom at age 17
- Histology: MPGN C3Nef + / C3 consumption
- Treatment: CS / MMF
- Renal failure - Dialysis at age 25

- No genetic mutation of ACP
- HLA DR4

First transplantation 2008 -> 2012

- C3 consomption / C3Nef positive
- Living donor renal transplantation (MMF TAC CS)
- Infectious complications:
  - *Pneumocystis carinii pneumoniae / ARDS*
  - *Cryptosporidiosis*

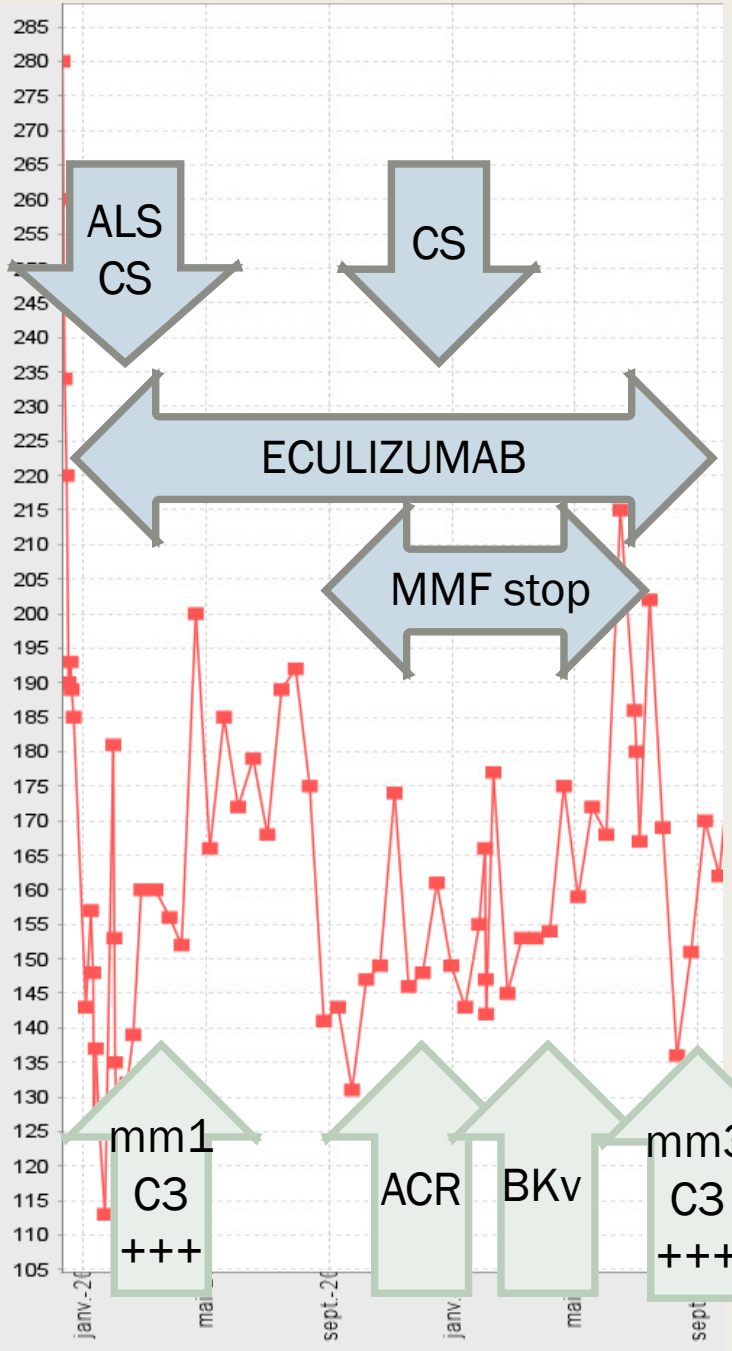
    => STOP MMF
- AKI / Nephrotic Sd:
  - *Mesangial hypercellularity*
  - *GBM thikening*
  - *Extra-capillar cell proliferation*
- CS pulse / IVIG / ECULIZUMAB : failure
- Explant : MPGN

Third transplantation: 2019

- C3 consomption / C3Nef neg
- Deceased donor (DSA free) ALS MMF TAC CS
- Preemptive ECULIZUMAB
- Protocolar biopsy:
  - *M3: mesangial stems thickening + C3 deposits (+++)*
  - *M12: histological ACR IA (Banff iIFTA3 t2 cpt1 mm2) : CS Pulse*
- M15: BK virus nephropathy: IS minimization (MMF reduction)

Third transplantation: 2019

- 2021: switch ECULIZUMAB – IPTACOPAN
- M20: iIFTA 1 mm3 sv40 neg (no immunofluorescence)
- Creatinine stability 150µmol/l
- No Proteinuria / hematuria
- A5: Onset of microalbuminuria
- Histology: mm3 reduced deposits C3(+)
- Infectious: 2 hospitalizations in 5 years for pneumoniae / diarrhea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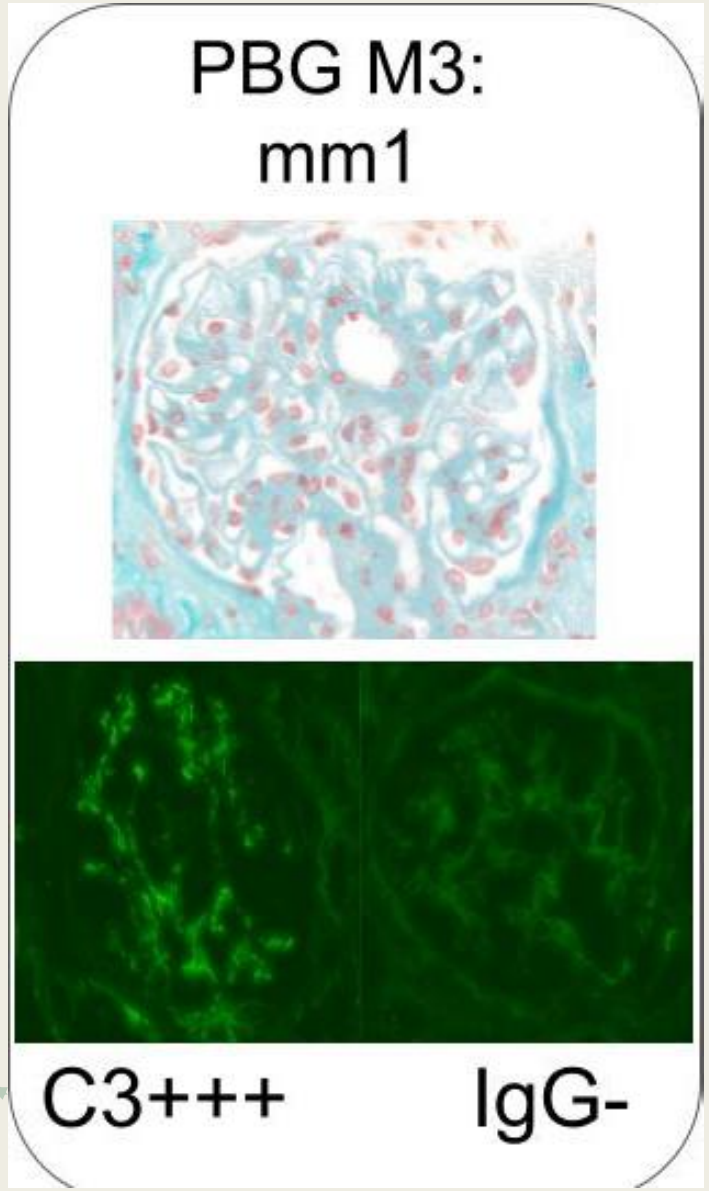
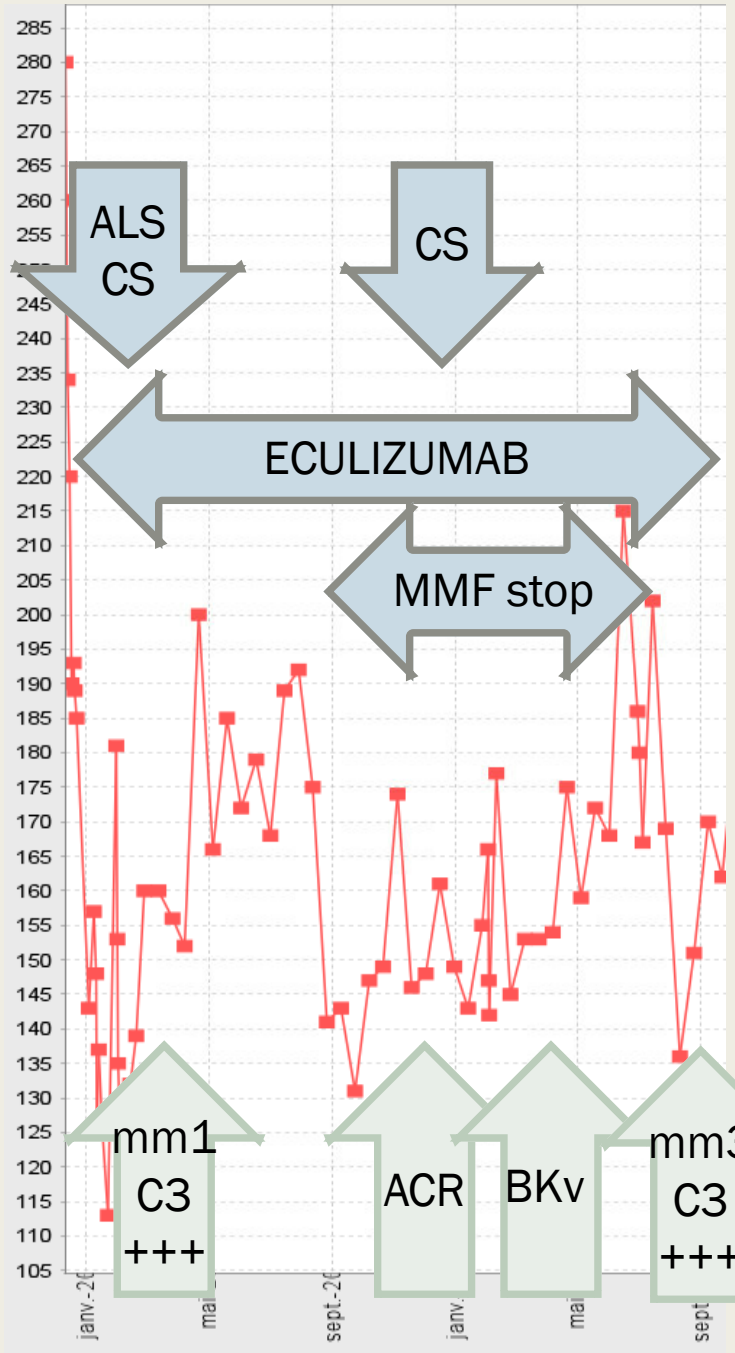
ALS
CS
CS
ECULIZUMAB
MMF stop
mm1
C3
+++
ACR
BKv
mm3
C3
+++


PBG M3:
mm1
C3+++
IgG-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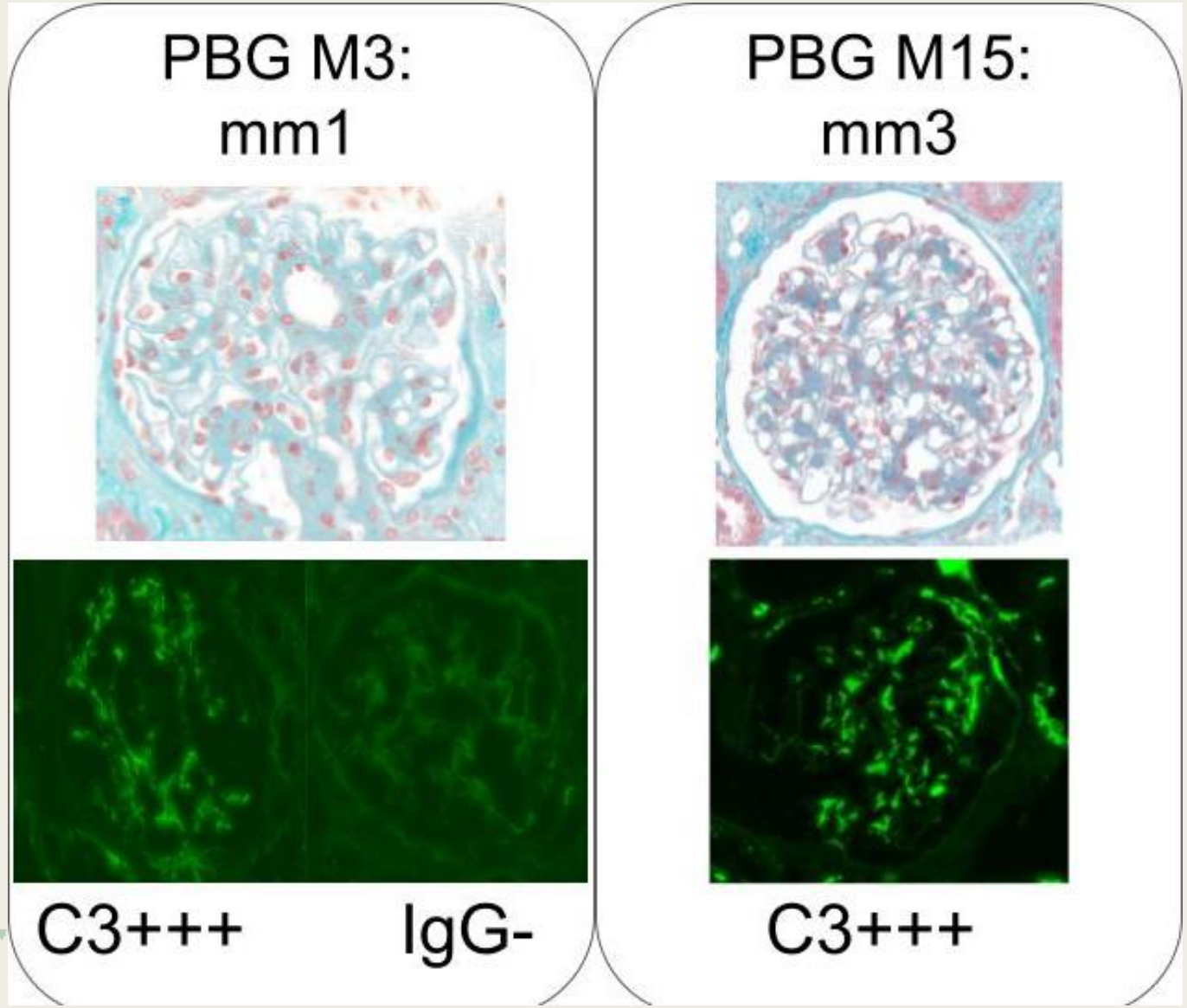
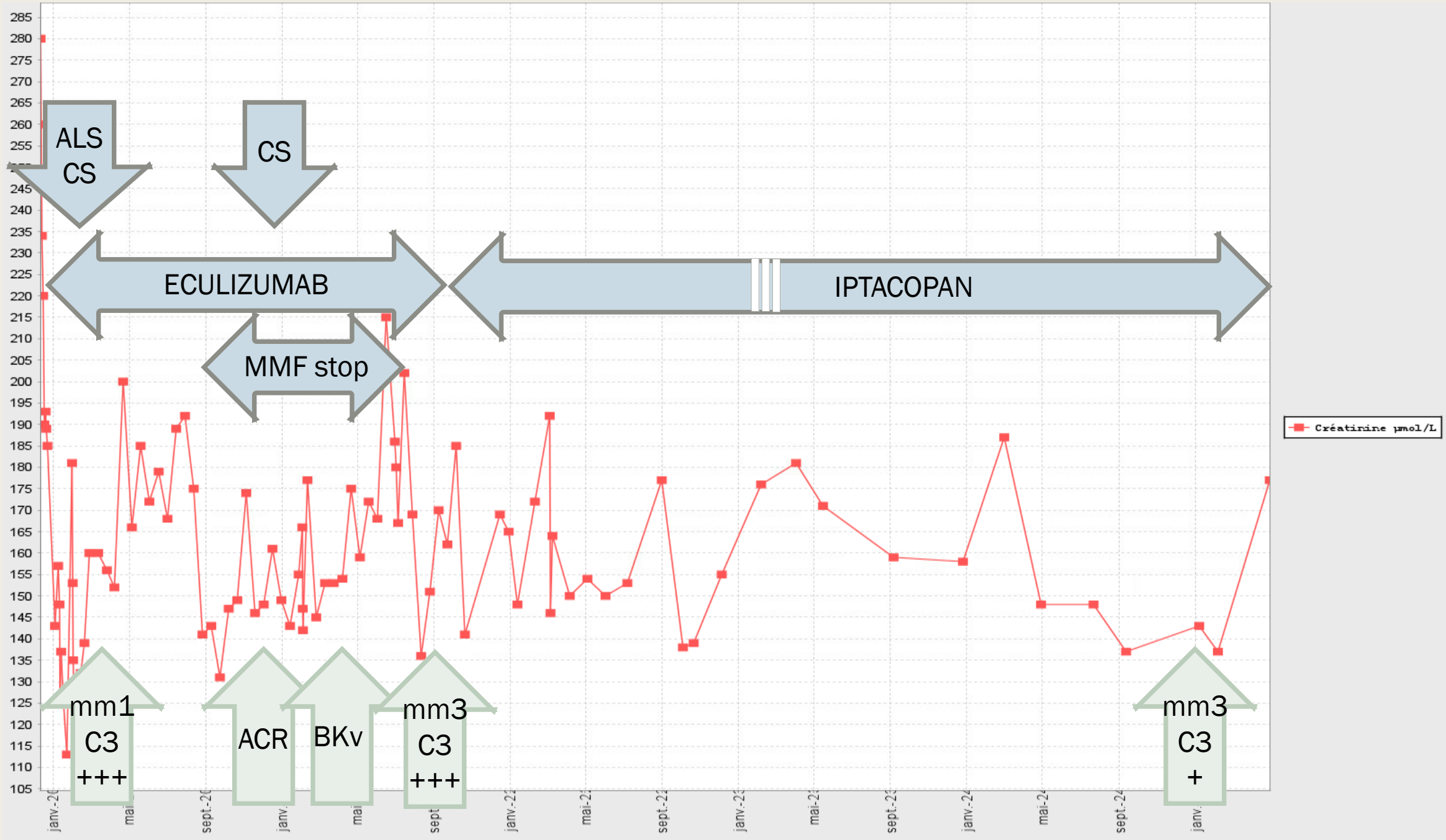

PBG M3:
mm1
C3+++
IgG-
PBG M15:
mm3
C3+++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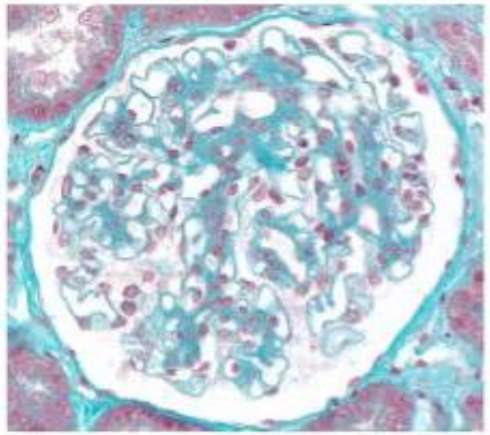
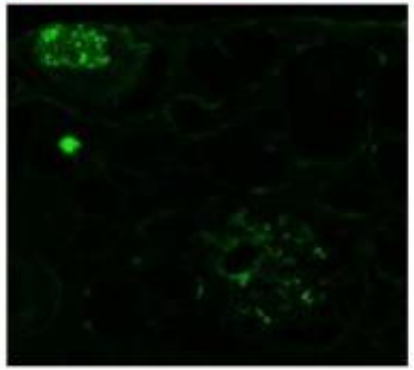
CS
ECULIZUMAB
IPTACOPAN
MMF stop
mm1
C3
+++
ACR
BKv
mm3
C3
+++
mm3
C3
+
Créatinine µmol/L

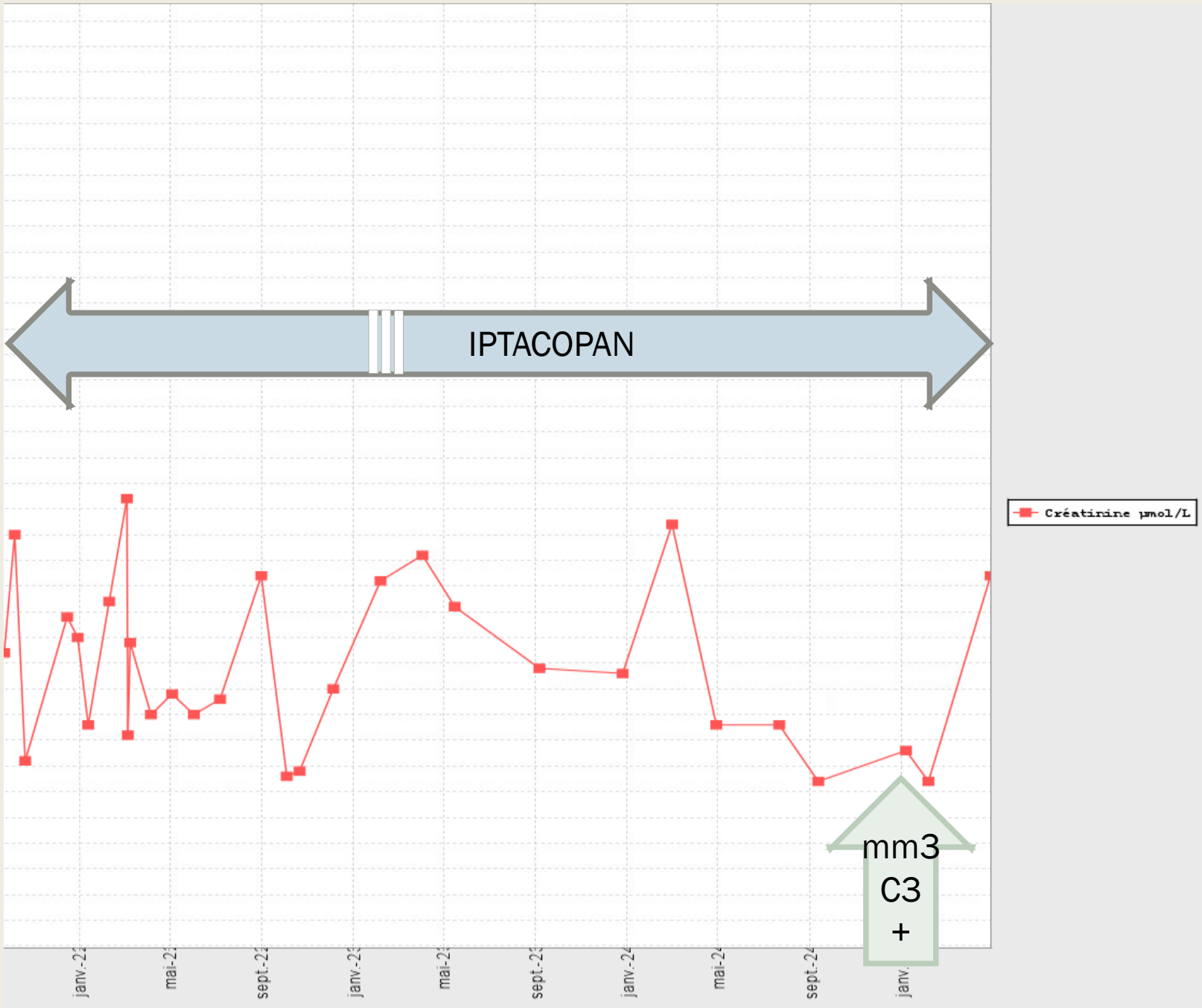
PBG A5:

mm3





C3+


IPTACOPAN
Créatinine µmol/L
mm3
C3
+
janv.-22
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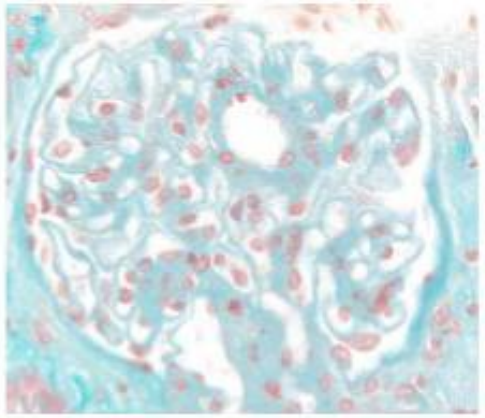
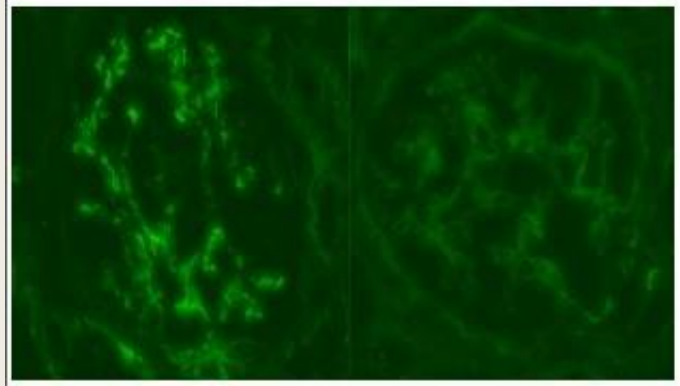
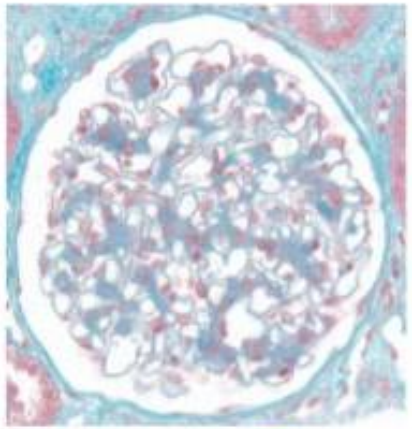
PBG M3:
mm1

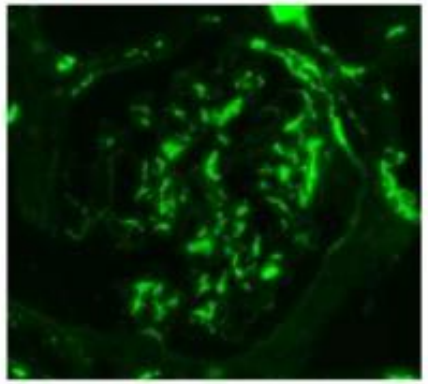




C3+++ IgG-

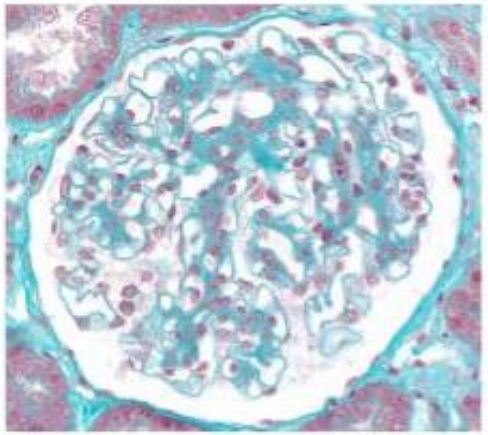
PBG M15:
mm3

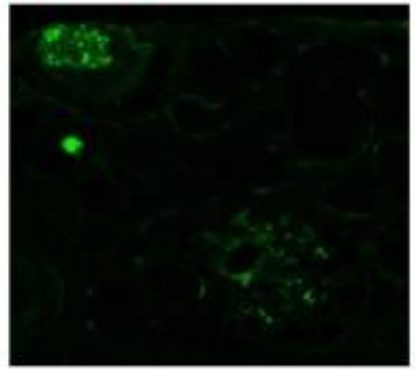




C3+++

PBG A5:
mm3





C3+

C3G recurrence

- Incidence 73 %
- Graft failure : 40 / 83 %
- Time to failure : 48 months
- Factors associated with recurrence
- Treatment

Table 4. Comparison With Published Data for C3G Posttransplantation

	French C3GN[5]	Mayo C3GN[9]	Columbia C3GN	French DDD[5]	Dutch DDD[10a,b]	Columbia DDD
Recurrent cases	6/10 (60%)	14/21 (67%)	10/12 (86%)	6/11 (55%)	11/13 (85%)	6/7 (86%)
Graft failure	NA	7/14 (50%)	3/10 (30%)	NA	5/6 (83%)	5/6 (83%)
Time to failure, mo[a]	NA	77	59	NA	14	41

Abbreviations: C3G, C3 glomerulopathy; C3GN, C3 glomerulonephritis; DDD, dense deposit disease; NA, not available.
[a]Median unless otherwise indicated.
[b]Mean

C3G Recurrence

- 1999 – 2016 Washington DC
- 19 transplanted patients
  - *12 C3G*
  - *7 DDD*
- Median time to recurrence 14 / 15 months

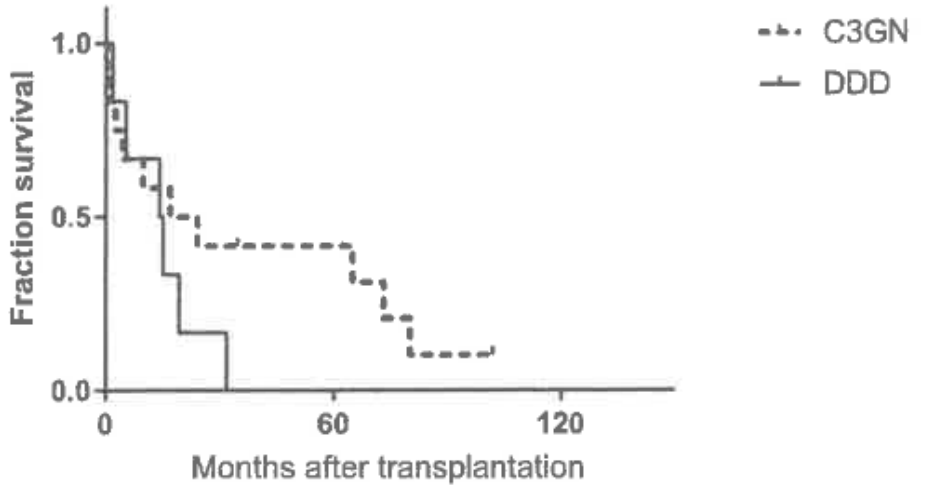


Figure 1. Recurrence-free survival in C3 glomerulonephritis (C3GN) and dense deposit disease (DDD; $P = 0.2$, Mantel-Cox log-rank test). Patient DDD5, who developed near-immediate failure after transplantation, was excluded from this analysis.

Original Investigation AJKD

Kidney Transplantation in C3 Glomerulopathy: A Case Series

Renu Regunathan-Shenk, Rupali S. Avasare, Wooin Ahn, Pietro A. Canetta, David J. Cohen, Gerald B. Appel, and Andrew S. Bomback

C3G Recurrence

- Graft failure at 42 months
  - *Attributed R C3G in 50% cases*
- Rare genetic variant or autoAb of ACP in 9/10 patients

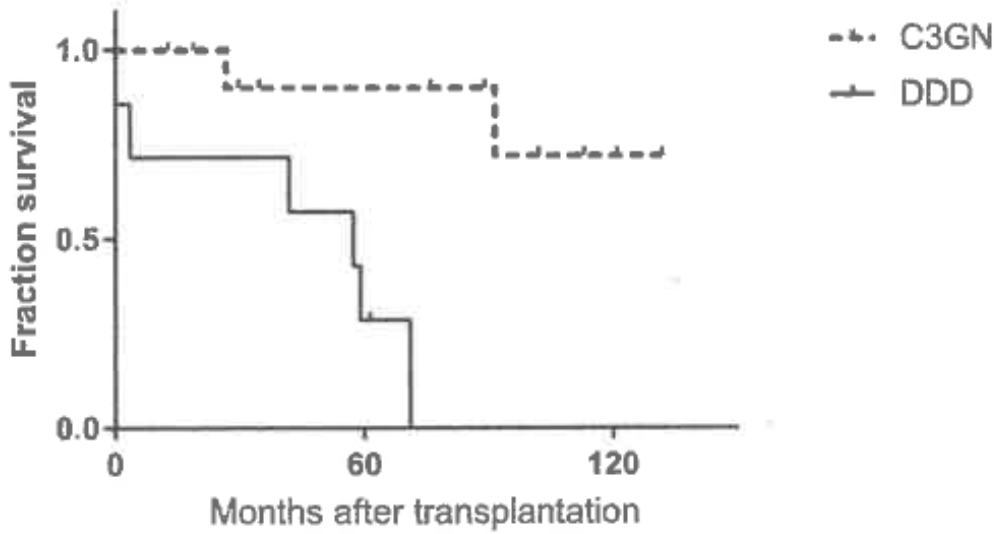


Figure 2. Allograft survival in C3 glomerulonephritis (C3GN) and dense deposit disease (DDD; $P = 0.002$, Mantel-Cox log-rank test).

Original Investigation AJKD

Kidney Transplantation in C3 Glomerulopathy: A Case Series

Renu Regunathan-Shenk, Rupali S. Avasare, Wooin Ahn, Pietro A. Canetta, David J. Cohen, Gerald B. Appel, and Andrew S. Bomback

Alasfar et al. BMC Nephrology (2016) 17:7
DOI 10.1186/s12882-015-0219-x

BMC Nephrology

RESEARCH ARTICLE Open Access

Membranoproliferative glomerulonephritis recurrence after kidney transplantation: using the new classification

Sami Alasfar[1], Naima Carter-Monroe[2], Avi Z. Rosenberg[3], Robert A. Montgomery[4] and Nada Alachkar[1*]

- 40 KTx for MPGN in 34 patients
- Post transplantation MPGN recurrence : 18/40 (45%)
- higher recurrence rate in:
  - *living related allografts (P = 0.045)*
  - *preemptive transplantations (P = 0.018)*
  - *low complement level (P = 0.006)*
  - *presence of monoclonal gammapathy (P = 0.010)*

Table 2 Reasons for renal allografts loss

Reason for graft loss	Frequency
MPGN recurrence	6
Antibody-Medicated Rejection	2
Cell-Medicated rejection	2
MPGN recurrence & rejection[a]	3
ATN	2
Bleeding	1
Thrombosis	1

[a]In the three cases recurrence preceded rejection and the rejection was antibody mediated

Recurrent Membranoproliferative Glomerulonephritis Type I After Kidney Transplantation: A 17-Year Single-Center Experience

Hefziba Green,[1,2] Ruth Rahamimov,[1,2,3] Benaya Rozen-Zvi,[1,2] Barak Pertzov,[4] Ana Tobar,[2,5] Shelly Lichtenberg,[1] Uzi Gafter,[1,2] and Eytan Mor[2,3]

- Recurrence impact graft survival
- HLA B49 DR4 : autoimmunity risk (Grave's / IgAN / RA) (OR: 16)

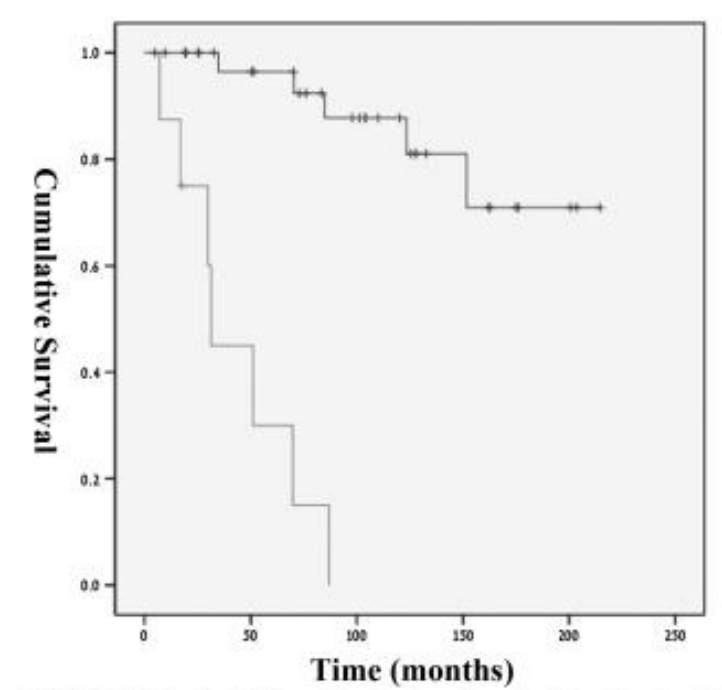


FIGURE 1. Kaplan-Meier estimate of graft survival in patients with (*gray*) and without (*black*) recurrence of MPGN type I. MPGN, membranoproliferative glomerulonephritis.

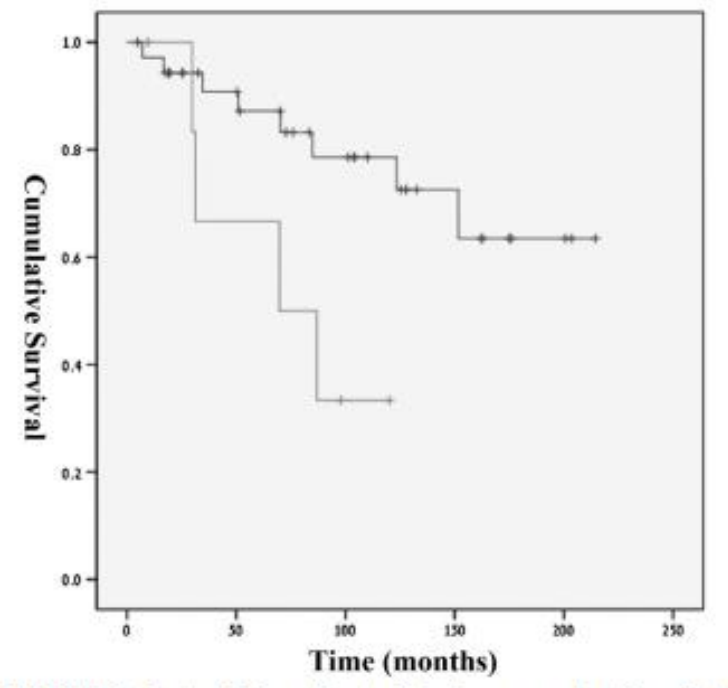


FIGURE 2. Kaplan-Meier estimate of death-censored graft survival in patients with (*gray*) and without (*black*) HLA B49 allele. HLA, human leukocyte antigen.

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DOI: 10.1097/TP.0000000000000459

Transplantation ■ June 2015 ■ Volume 99 ■ Number 6

Recurrent membranoproliferative glomerulonephritis after kidney transplantation

Elizabeth C. Lorenz[1], Sanjeev Sethi[2], Nelson Leung[1], Angela Dispenzieri[3], Fernando C. Fervenza[1] and Fernando G. Cosio[1,4]

[1]Division of Nephrology and Hypertension, Department of Internal Medicine, Mayo Clinic College of Medicine, Rochester, Minnesota, USA; [2]Department of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, Minnesota, USA; [3]Division of Hematology, Mayo Clinic College of Medicine, Rochester, Minnesota, USA and [4]William J. von Liebig Transplant Center, Mayo Clinic College of Medicine, Rochester, Minnesota, USA

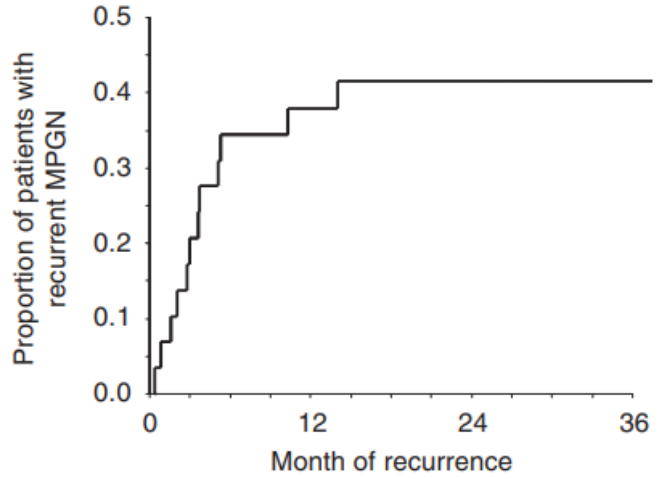


Figure 1 | Kaplan–Meier plot of the cumulative incidence of recurrent membranoproliferative glomerulonephritis (MPGN) after kidney transplantation.

Kidney International (2010) **77**, 721–728

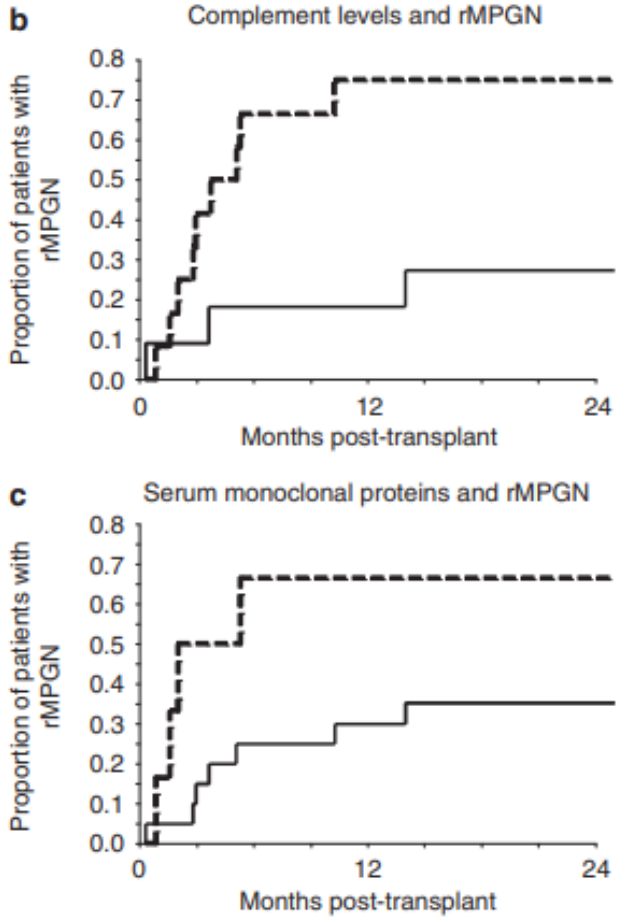
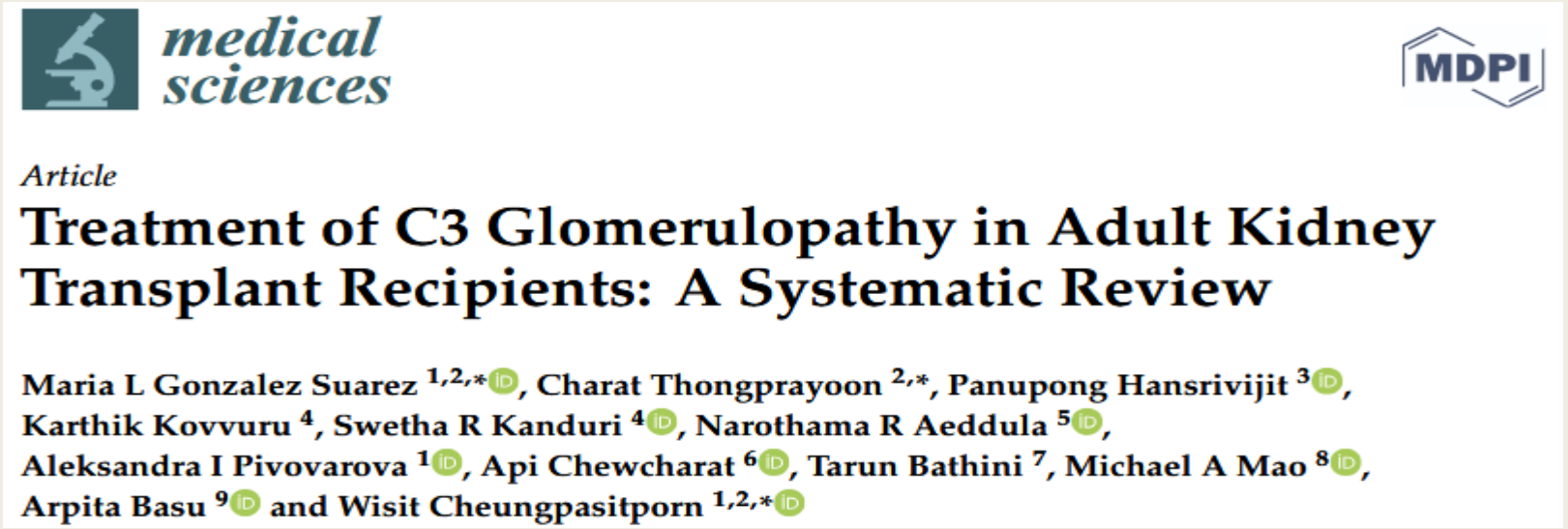


Figure 2 | Incidence of recurrent membranoproliferative glomerulonephritis (rMPGN). (**a**) Incidence of rMPGN in recipients of living donor kidneys (—) and in recipients of deceased donor kidneys (– – –) ($P = 0.063$ log rank). (**b**) Incidence of rMPGN in patients with low complement levels (– – –) and in patients with normal complement levels (—) ($P = 0.020$, log rank). (**c**) Incidence of rMPGN in patients with serum monoclonal proteins (– – –) and in patients without these proteins (—) ($P = 0.083$, log rank).

C3G R : Treatments

- The pooled estimated rates of allograft loss :
  - 33% for eculizumab
  - 42% for TPE
  - 81% for rituximab
  - *40% for no treatment*



IPTACOPAN: Spanish experience

- Case 1: 30s
  - *CFHR3/1 double heterozygoty*
  - *C3G: CS MMF RTX CYC*
  - *KTx (Maastricht III)*
  - *Primary recurrence*
  - *Clinical and histological control*
  - *Effect « ON – OFF »*

  in 5 days treatement discontinuation
  - *Partial Remission*

- Case 2: 40s
  - *CFH Ab, DGKe variant*
  - *C3G: ECULI RTX*
  - *Early recurrence*
  - *Complete Remission*

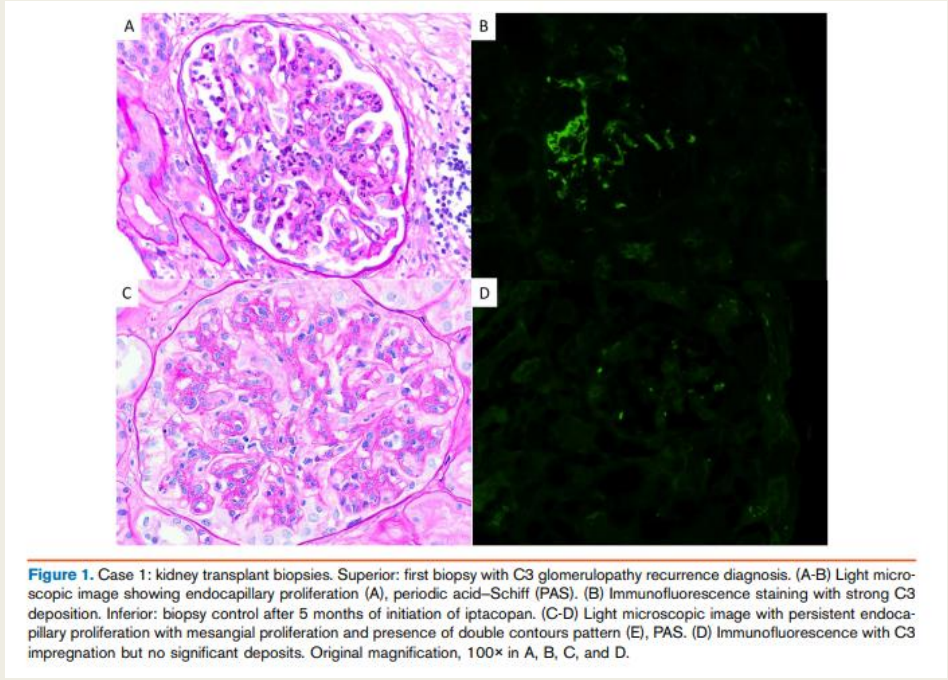


Figure 1. Case 1: kidney transplant biopsies. Superior: first biopsy with C3 glomerulopathy recurrence diagnosis. (A-B) Light microscopic image showing endocapillary proliferation (A), periodic acid–Schiff (PAS). (B) Immunofluorescence staining with strong C3 deposition. Inferior: biopsy control after 5 months of initiation of iptacopan. (C-D) Light microscopic image with persistent endocapillary proliferation with mesangial proliferation and presence of double contours pattern (E), PAS. (D) Immunofluorescence with C3 impregnation but no significant deposits. Original magnification, 100× in A, B, C, and D.

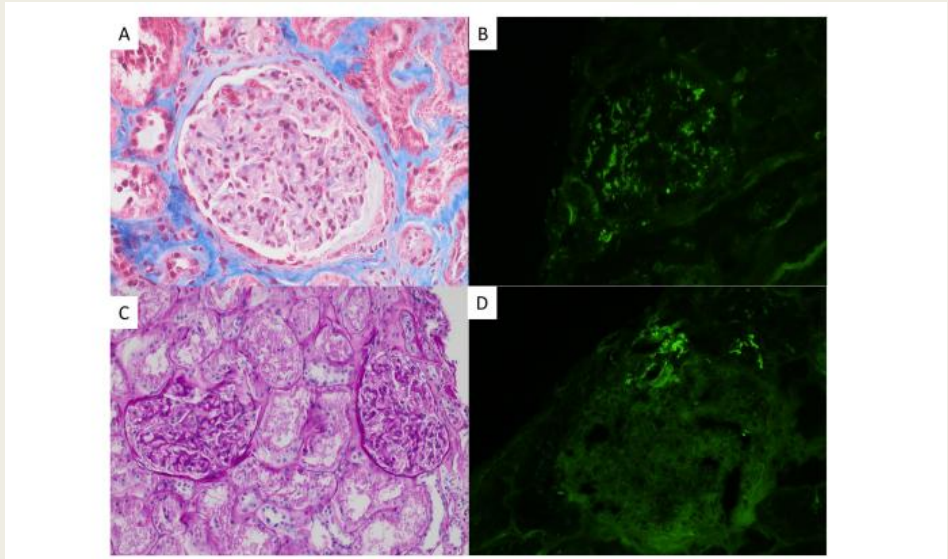


Figure 2. Case 2: kidney transplant biopsies. Superior: first biopsy with compatible initial signs of C3 glomerulopathy recurrence. (A) Light microscopic image showing mild expansion of mesangium with slight hypercellularity, Masson's trichrome. (B) Immunofluorescence with C3 deposition in the mesangium (++). Inferior: biopsy control after 8 months of the initiation of iptacopan. (C) Light microscopic image with normal glomeruli with no hypercellularity in any compartment, periodic acid–Schiff. (D) Immunofluorescence staining with no C3 deposition in the glomeruli (vascular pole deposit as internal control). Original amplification, 100× in A, B, C, and D.

Classic scenario

- Uptitration of MMF
- Infectious /neoplasic risk
- MMF discontinuation
- C3G recurrence

- Importance / timing of resumption after discontinuation

- Necessity of a specific agent targeting C3

PERSPECTIVES : IPTACOPAN in C3G R

- Efficacy must be proven in larger series in transplantation

- Preemptive treatment ?
- Histological / clinical recurrence ?

- Duration of treatment ?

thanks

- Nephrologie Bicêtre
  - *Pr Mohamad ZAïDAN*
  - *Pr Renaud SNANOUDJ*
- Anapath Bicêtre
  - *Dr Charlotte MUSSINI*
  - *Pr Sophie FERLICOT*
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