Percorsi Pediatrici della Val di Noto

Vittoria 25 Febbraio 2017

Caso Clinico

Giovanni Conti

Francesca Laganà

UO Nefrologia e Reumatologia Pediatrica con Dialisi
AOU Policlinico " G. Martino"
Direttore Prof. Carmelo Fede

Francesco - 12 anni

- **Macroematuria** da due giorni

- Anamnesi patologica remota
  Portatore di trait talassemico
- Anamnesi patologica prossima

Due settimane prima episodio di **faringotonsillite** trattata con amoxicillina + acido clavulanico.

Beneficio

Ricovero c/o la nostra Unità Operativa

Obiettivamente

- ✓ Pallore cutaneo
- ✓ Non edemi
- ✓ PA 133/73 mmHg

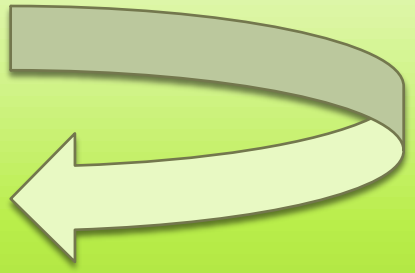
Esami bioumorali

- ✓ Anemia: Hb 9 g/dl
- ✓ Funzione renale nella norma
- ✓ Normoprotidemia e normoalbuminemia
- ✓ **C3: 9 mg/dl**
- ✓ C4: 16 mg/dl
- ✓ **TAS 843 U/L**

Dopo tre giorni

- ✓ Urine normocromiche.
- ✓ PA nella norma.
- ✓ Proteinuria delle 24 ore: oscillante tra **1 e 1.7 g/24h**
- ✓ Al sedimento urinario: **ematuria (30-40 emazie)**

Prima ipotesi diagnostica



GN post-streptococcica

✓Proseguiva monitoraggio PA ed esame urine

Dopo 4 settimane…

Francesco

- ✓ PA nella norma
- ✓ Microematuria importante
- ✓ Proteinuria 1.7 g/24h
- ✓ **C3 12 mg/dl**
- ✓ C4 20 mg/dl

Ipotesi Diagnostiche

GLOMERULONEFRITE
POST-INFETTIVA

- **Edemi, oliguria, ematuria**
- **Durata 2-3 settimane**
- **Attivazione del complemento, con C3 che si normalizza in genere entro 4-8 settimane**

NEFRITE LUPICA

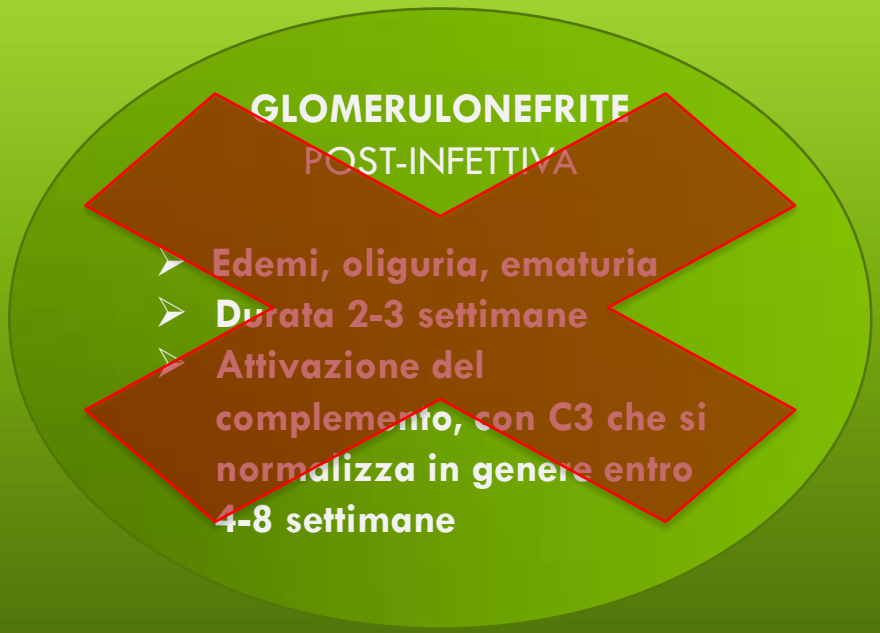
- **Proteinuria**
- **Ematuria**
- **+/- segni sistemici**
- **Ipocomplementemia (C↓ C↓)**
- **Positività ANA, nDNA, ENA**

GLOMERULONEFRITI MEMBRANOPROLIFERATIVE (GNMP)

- **Ematuria glomerulare**
- **Ipertensione**
- **Proteinuria o sindrome nefrosica**
- **Progressivo deterioramento della funzione renale**
- **C3↓ (C4 può essere normale)**

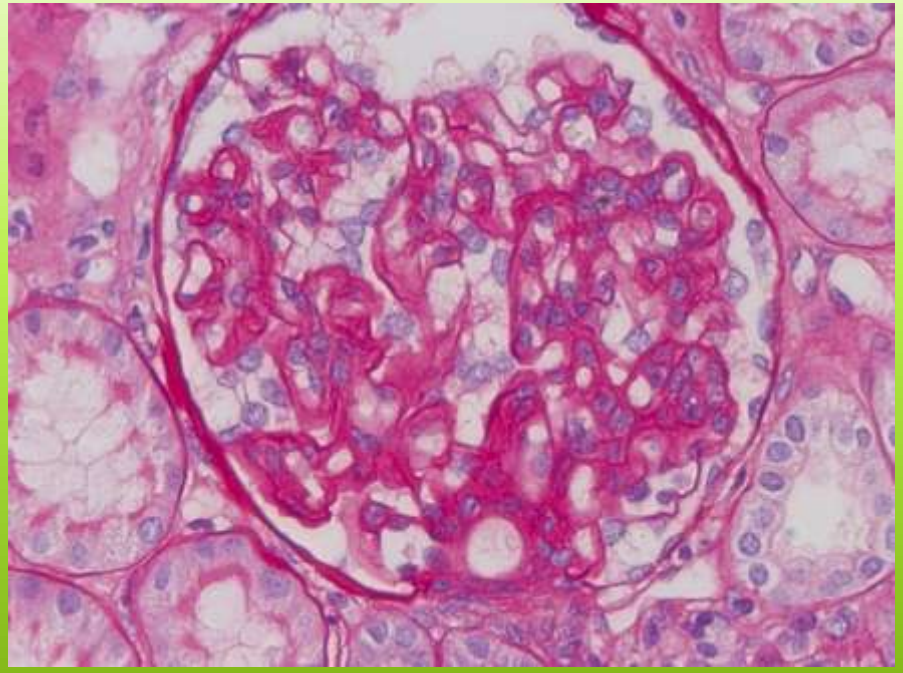
Dopo 8 settimane

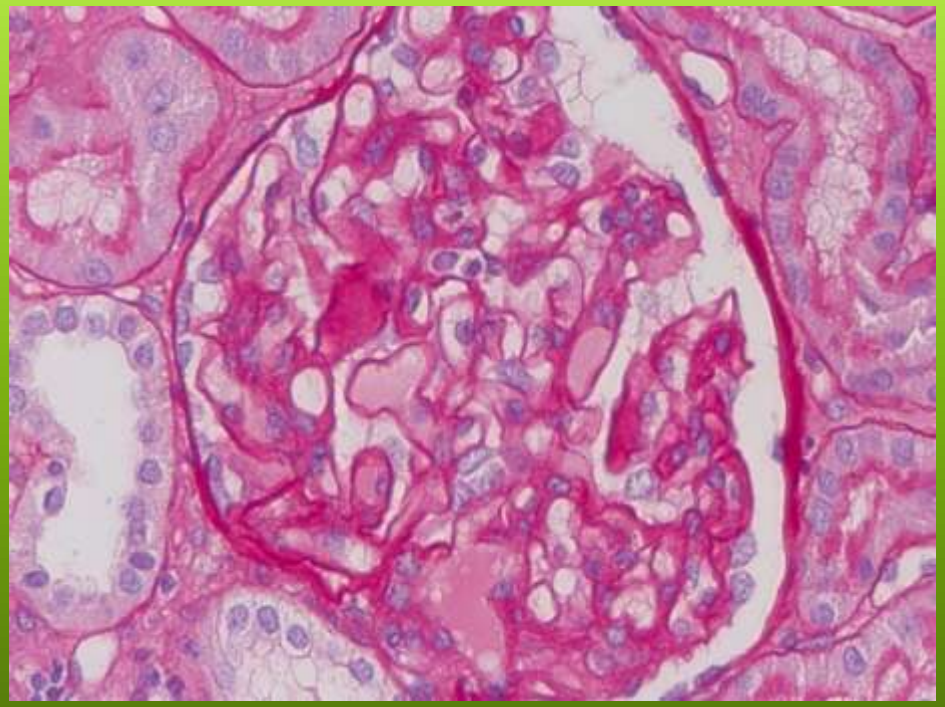
- Microematura (30-50 emazie pcm)
- Proteinuria: 1.5 g/24 h
- **C3 12 mg/dl**



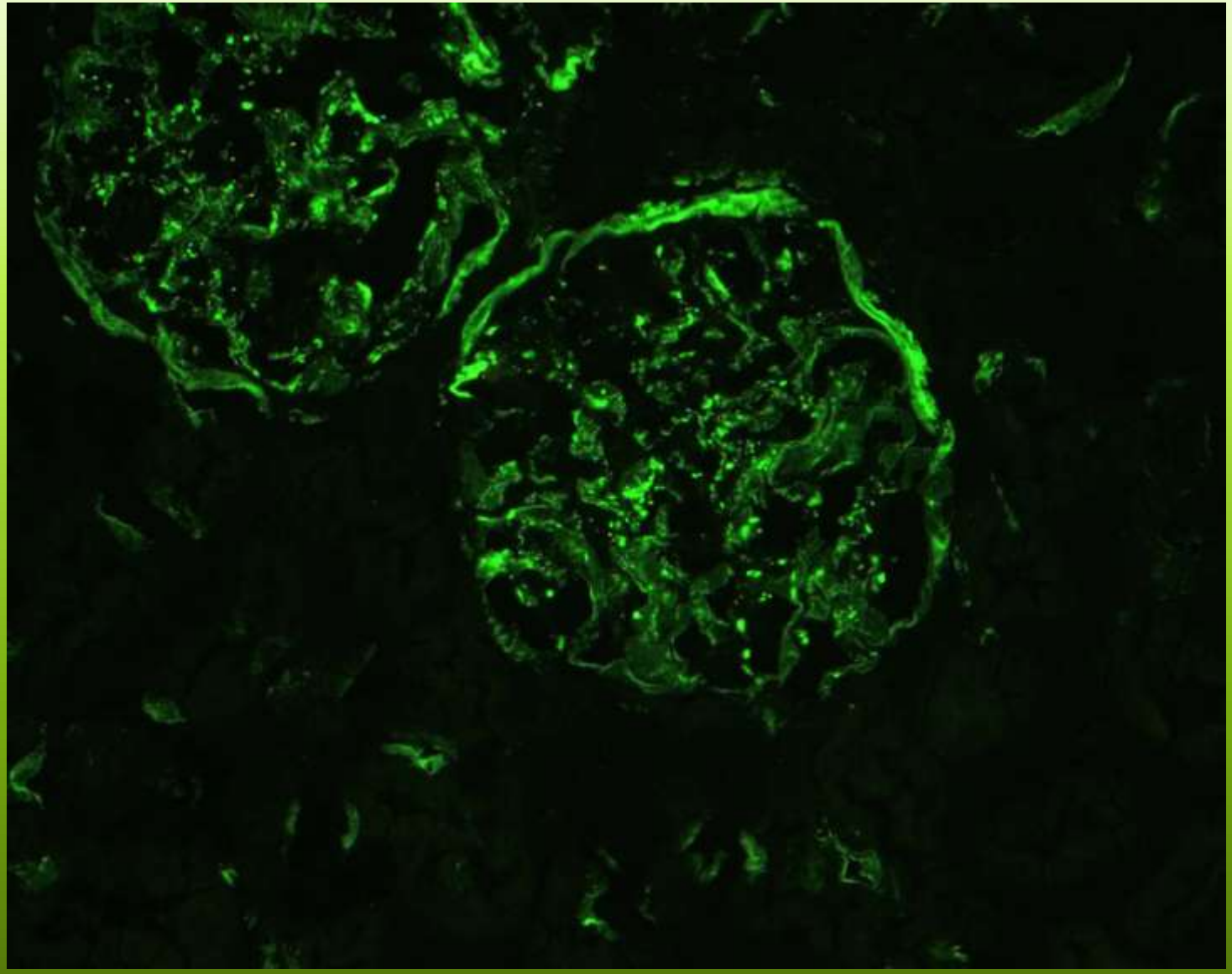
Biopsia Renale

Microscopia ottica

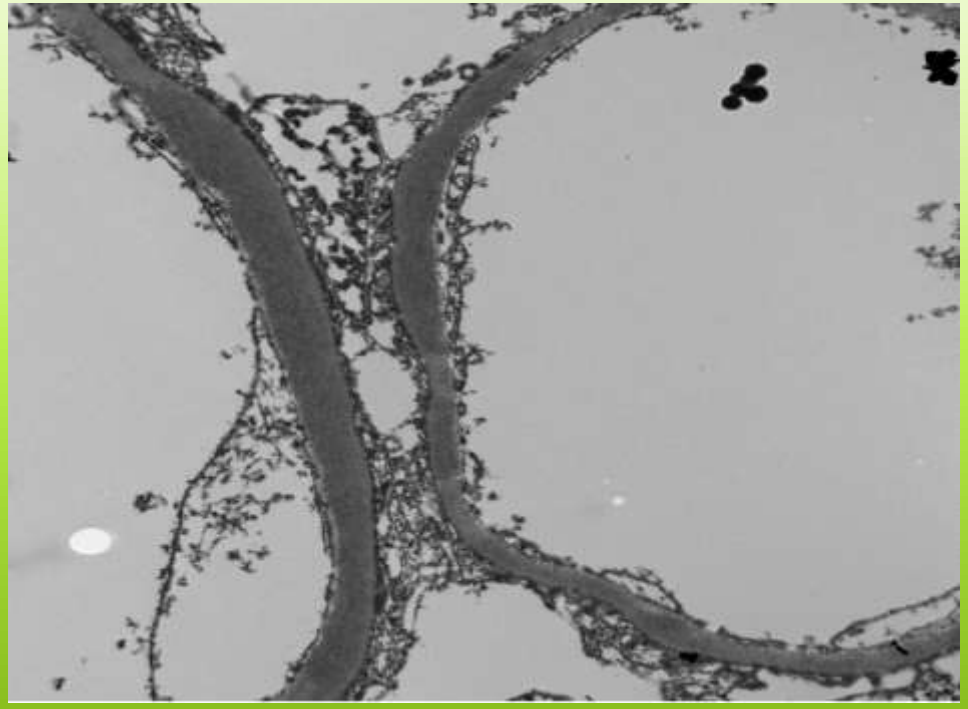


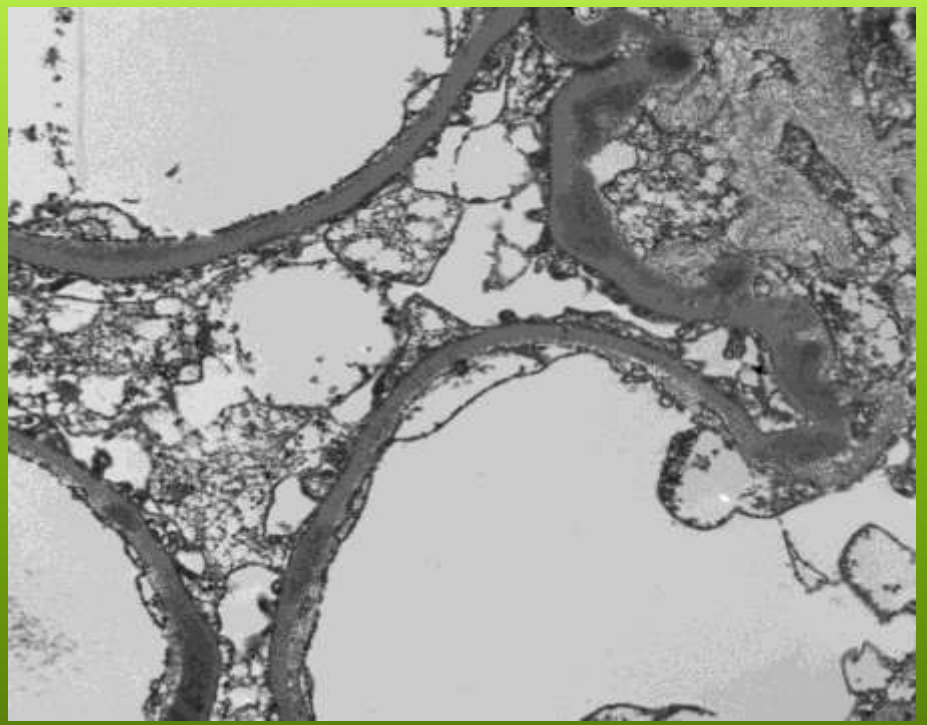


Immunofluorescenza



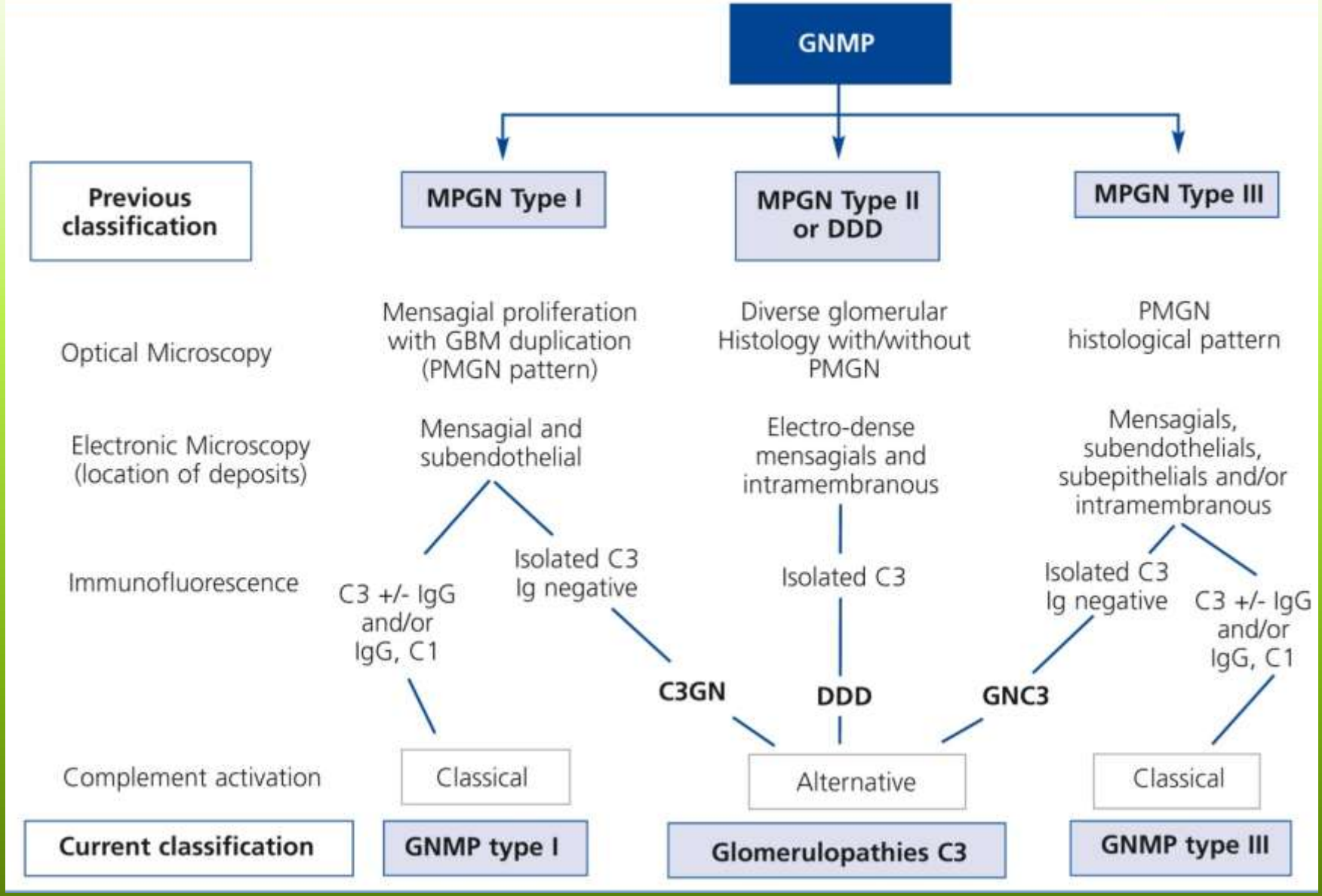
Microscopia elettronica





Confermata diagnosi di GNMP II o DDD

Classification of GNMP



D'Agati VD, Bomback AS. C3 glomerulopathy: what's in a name? Kidney international 2012; 83:379-81

Diagnosi differenziale
C3 Glomerulopatie

DDD

- Via alternativa
- ↓C3 sierico ma normale C4
- Attivazione via alternativa mediante C3 convertasi
- Depositi più addensati localizzati nella lamina media della membrana basale
- **Forma più aggressiva**

C3GN

- Via alternativa
- ↓ C3 sierico ma normale C4
- Attivazione via alternativa mediante C5 convertasi
- Depositi paramesangiali e subepiteliali
- **Forma meno aggressiva**

Glomerulonefrite a depositi densi (DDD)

- Glomerulopatia rara
- Incidenza 2-3% su 1milione di persone
- Esordio tra i 5 ed i 15 anni (descritti rari episodi in età adulta)
- Evoluzione verso l'insufficienza renale terminale
- **Presenza di C3 Nef** nell' 80 % dei casi

Analisi molecolare dei geni del complemento

- CFH → **DDD-GNC3-GNMP tipo1**
- CFI → **GNMP1-GNC3** (*Servais A. Kidney Int 2012*)
- MCP →
- C3 → **DDD** (*Martinez-Berricarte J Clin Invest 2010*)
- CFB → **Proteina del sistema del complemento potenzialmente associata a GNMP**

Trattamento sintomatico

- **ACE-inibitori**
- **Sartanici**

Ruggenenti 1999
Brenner 2001

- **Statine**

Nickolas 2003

CLINICAL RESEARCH

Pathology after and C3 GN

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Robert B. Colvin,‡ Gerald

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New York Presbyterian Hospital,
University Medical Center and th
Pathology, Massachusetts Gener

ABSTRACT

Eculizumab might benefit C3
pathway. Here, we report rer
dense deposit disease and t
ment membrane deposits th
there was reduction in active
consistent with effective C5 b
mild mesangial disease had n
activity and worsening chroni
C3 or C5b-9, and electron m
C5b-9 in extracellular matrix.
ment membranes, and vesse
physiologic levels of C5b-9 a
patients with dysregulation c
de novo monoclonal staining
deposition disease (MIDD). S
suggesting the binding of m
apparent drug-tissue interac

J Am Soc Nephrol 23: 1229–1237, 20

Eculizumab for the Treatment of Dense-Deposit Disease

TO THE EDITOR: Dense-deposit disease (also known normal, as were levels of factor H and factor B.

Eculizumab for Dense Deposit Disease and C3 Glomerulonephritis

Andrew S. Bomback, Richard J. Smith,† Gaetano R. Barile,‡ Yuzhou Zhang,† Eliot C. Heher,§ Leal Herlitz,‖ M. Barry Stokes,‖ Glen S. Markowitz,‖ Vivette D. D'Agati,‖ Pietro A. Canetta,* Jai Radhakrishnan,* and Gerald B. Appel**

Summary

Background and objectives The principle defect in dense deposit disease and C3 glomerulonephritis is hyperactivity of the alternative complement pathway. Eculizumab, a monoclonal antibody that binds to C5 to prevent formation of the membrane attack complex, may prove beneficial.

Design, setting, participants, & measurements In this open-label, proof of concept efficacy and safety study, six subjects with dense deposit disease or C3 glomerulonephritis were treated with eculizumab every other week for 1 year. All had proteinuria >1 g/d and/or AKI at enrollment. Subjects underwent biopsy before enrollment and repeat biopsy at the 1-year mark.

Results The subjects included three patients with dense deposit disease (including one patient with recurrent dense deposit disease in allograft) and three patients with C3 glomerulonephritis (including two patients with recurrent C3 glomerulonephritis in allograft). Genetic and complement function testing revealed a mutation in *CFH* and *MCP* in one subject each, C3 nephritic factor in three subjects, and elevated levels of serum membrane attack complex in three subjects. After 12 months, two subjects showed significantly reduced serum creatinine, one subject achieved marked reduction in proteinuria, and one subject had stable laboratory parameters but histopathologic improvements. Elevated serum membrane attack complex levels normalized on therapy and paralleled improvements in creatinine and proteinuria.

Conclusions Clinical and histopathologic data suggest a response to eculizumab in some but not all subjects with dense deposit disease and C3 glomerulonephritis. Elevation of serum membrane attack complex before treatment may predict response. Additional research is needed to define the subgroup of dense deposit disease/C3 glomerulonephritis patients in whom eculizumab therapy can be considered.

Clin J Am Soc Nephrol 7: 748–756, 2012. doi: 10.2215/CJN.12901211

Francesco ha praticato terapia con:

Deltacortene (1mg/kg/die) con successivo décalage + **ACE- Inibitori** per un periodo complessivo di 6 mesi

Attualmente è in terapia con:

- **ACE- Inibitori**
- **Sartanici**

FOLLOW-UP FRANCESCO

- PA 114/70 mmHg
- Funzione renale nella norma
- Proteinuria 135 mg/24h
- Microematuria (7-10 emazie)

Grazie per l'attenzione