Precautions in Transplantation of Podocytopathy Patients

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Agenda

- Introduction
- Possible risk after kidney transplantation
- Precautions
  - Pre-transplantation
  - Post-transplantation
- Diagnosis of recurrence
- Treatment of recurrence

Podocytopathy

- Podocytopathies are a group of proteinuric glomerular disorders caused by primary podocyte injury

- Typical pathological picture in kidney biopsy

➢ Minimal changes (MC)

➢ **Focal segmental glomerulosclerosis (FSGS)**

➢ Diffuse mesangial sclerosis (DMS)

➢ Collapsing glomerulopathy (CG)

Possible Risk after Kidney Transplantation

- Risk of recurrence of primary kidney disease
- Risk of graft loss
- Most of the literature about disease recurrence in podocytopathies refers to **FSGS**

Risk of Recurrence

- The risk of FSGS recurrence is 10-56% (average 30%) in the first graft and 80% up to100% in the second

- With a risk of graft loss of 30%–50% of them due to recurrence of FSGS

Pathogenesis of Recurrence

Primary FSGS (idiopathic FSGS or circulating factor disease, non-genetic FSGS):

- Pathogenic mechanism is thought to be an immune system dysregulation and/or **circulating permeability factor** (CPF)

- Recurrent FSGS is postulated to be caused by CPF affecting podocyte structure and function

Pathogenesis

Genetic FSGS:

- These patients have defective components of the kidneys, rather than circulating factors
- Therefore their risk of recurrence is low
- The reported risk of 4%–8% likely depends on an expired attribute of pathogenicity to genetic variants (e.g. in NPHS2)

Risk Factors

- Recurrence in a previous graft
- Age at starting KRT >12 years
- White and Asian recipients
- Rapid course to ESKD (< 3 years)
- Initial steroid sensitivity
- High level of pre-transplant proteinuria

Risk Factors

- Living donor (but no difference in graft survival even better especially with zero mis-match)

Protective Factors

- Age at starting KRT < 6 years
- African–American recipients
- Genetic and syndromic NS

Precautions Pre-transplantation

Genetic testing before transplantation for NPHS1 & NPHS2 gene mutation to inform risk of recurrence:

- SRNS
- Clinical coarse consistent with genetic FSGS

Precautions Pre-transplantation

Native Nephrectomy

➢ Why?

- Proteinuria derived from the native kidneys after transplantation may confuse with recurrence
- No role in prevention of recurrence

Precautions Pre-transplantation

Native Nephrectomy

- When?

  Heavy range proteinuria (usually 24-h urine protein > 1 g)

- How?

  Surgical or medical

Precautions Pre-transplantation

Protocol of immunosuppressant medications:

- Induction: ATG/ basiliximab
- Maintenance: Triple therapy

(Steroids, CNI, MMF)

Precautions Pre-transplantation

<u>Prevention of recurrence</u>

- Plasma exchange
- Combined plasma exchange with rituximab

Role?

Routine before kidney transplantation?

Precautions Pre-transplantation

Prevention of recurrence

- **Plasma exchange:**

- The use of an extracorporeal clearance mechanism to remove CPF
- Not routine
- No reduction in risk of recurrence

Precautions Pre-transplantation

<u>Prevention of recurrence</u>

- **Rituximab**

- Monoclonal antibody against CD20 on B cells that leads to B cell depletion (anti-CD20 depleting Abs)

- It may directly affect podocyte structure and function

Precautions Pre-transplantation

Prevention of recurrence

- **Rituximab**

- An antibody depleting therapy: several potential CPF proposed as pathogenic in recurrent FSGS are Abs directed against glomerular Ags

- Not routine

- No reduction in risk of recurrence

Precautions Pre-transplantation

Prevention of recurrence

- **Combined plasma exchange with rituximab**

- Not routine

- No reduction in risk of recurrence

Precautions Post-transplantation

Close follow up of proteinuria

- Daily during 1st week
- Weekly during the rest of 1st month
- Monthly during 2nd & 3rd month
- Every 3 months from 4th & 12th month
- Annually

Diagnosis of recurrence

- Rise in the urinary protein / creatinine ratio (UPC) above 0.2 mg/mg needs close follow up

But,

- Rise in the UPC ratio above 1 gram

Or

- Nephrotic range proteinuria of no other cause (as transplant rejection, infection)

Diagnosis of recurrence

Graft biopsy

- **Electron microscope**

- An early biopsy does not show glomerular abnormalities

Treatment of Recurrence

Plasma exchange:

- Daily for 4 sessions

- Followed by every other day sessions as long as UPC > 0.5 mg/mg

- Tapering of frequency, with achievement of complete remission (UPC < 0.2 mg/mg)

Treatment of Recurrence

Plasma exchange:

- Partial but persistent remission, (UPC ratio 0.2 and 2), prompted a slower tapering of PE
- 1.5 plasma volume
- Replacement is by 5% albumin
- IVIG replacement (0.4 g/kg/dose) with intensive PE (more than twice weekly)

Treatment of Recurrence

Rituximab:

- 375 mg / m2 per dose for 4 doses
- Weekly
- First dose after 3 session of PE
- Wait at least 24 hours (ideally 48 hours)
- Premedicating with steroids, paracetamol and diphenhydramine (oral or IV)

Treatment of Recurrence

- Cyclophosphamide
- High-dose CNI
- RAAS blockade

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Pediatric focal segmental glomerulosclerosis: favorable transplantation outcome with plasma exchange

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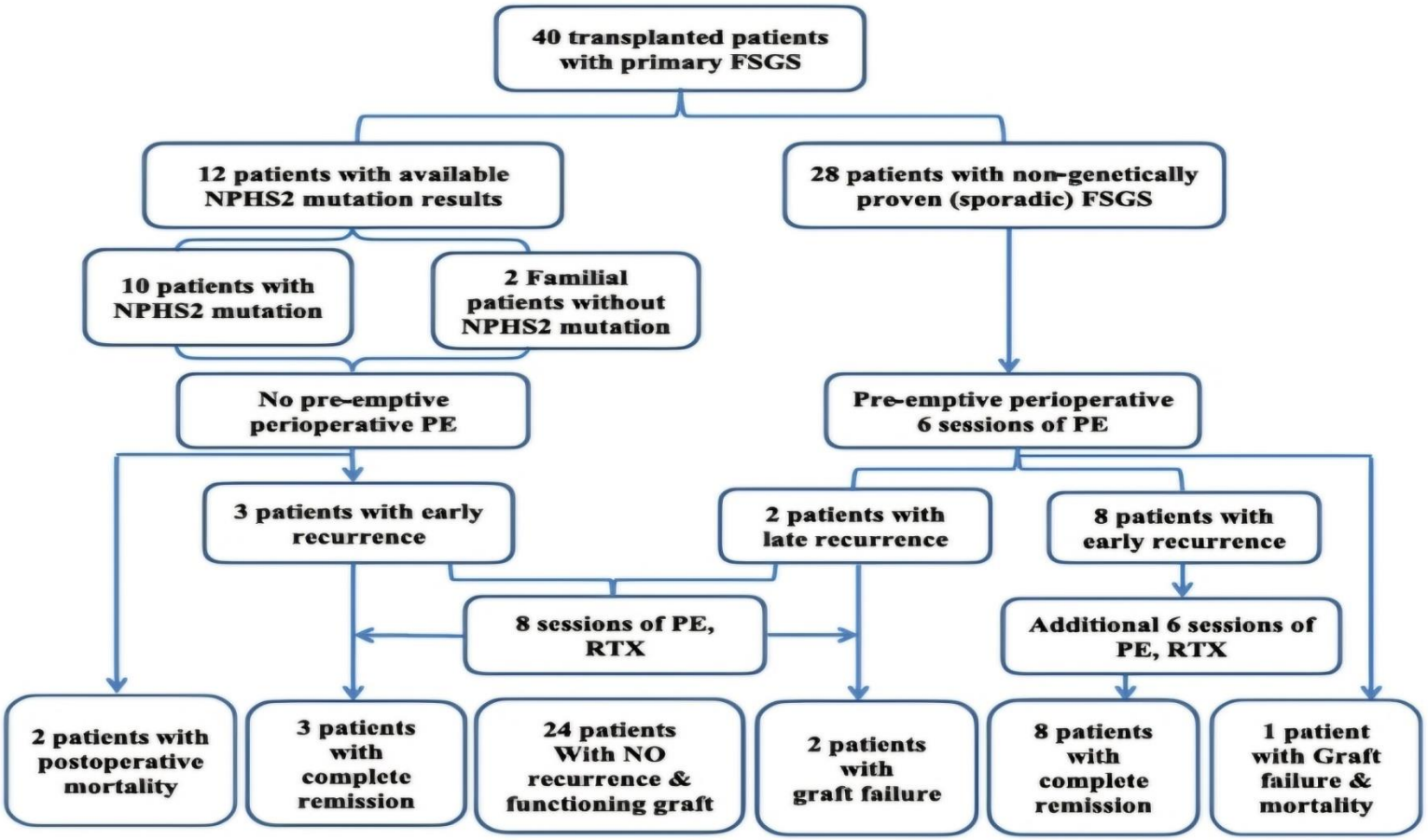

Flowchart describing FSGS type, patient management and their outcome

Case (1)

Female child, 8 years old, 18 kg, NS, genetic type, renal biopsy FSGS. ESKD on regular hemodialysis. Positive family history of FSGS. Her brother died at the age of 7 years with the same condition. Mismatch 2/6.

Genetic testing: showed positive results

Bilateral native nephrectomy (pre-Tx nephrotic range proteinuria 2 grams)

Outcome:

- No significant proteinuria
- Good graft function (creatinine 0.6 mg/ dl (1 year after Tx)

Case (2)

Female child, 11 years old, 35 kg, SRNS, renal biopsy FSGS. ESKD on regular hemodialysis. Mismatch 2/6.

Genetic testing: showed positive results

Bilateral native nephrectomy: (pre-Tx nephrotic range proteinuria 2 grams)

- On day 3 post Tx, acute graft dysfunction, nephrotic range proteinuria
- Graft biopsy: early: acute tubular injury. Second biopsy: recurrent FSGS

Case (2)

Management:

- PE: 5 sessions daily, then 5 sessions every other day……30 session
- Rituximab: 4 doses
- High-dose CNI
- RAAS blockade
- Cyclophosphamide

Outcome:

- Partial remission
- Creatinine 1.7 mg/ dl UPC ratio 0.48 (1 year after Tx)

Case (3)

Female child, 8 years old, 22 kg, SRNS, renal biopsy FSGS. ESKD on regular hemodialysis. Mismatch 2/6.

Genetic testing: showed negative results

Bilateral native nephrectomy

- On second week post Tx, acute graft dysfunction, nephrotic range proteinuria
- Graft biopsy: recurrent FSGS

Case (3)

Management:

- PE: 5 sessions
- Rituximab: 2 doses

Outcome:

- Complete remission
- Creatinine 0.6 mg/ dl (2.5 year after Tx)

Case (4)

Male child, 10 years old, 29 kg, SRNS, renal biopsy FSGS. ESKD on regular hemodialysis. Mismatch 0/6.

Genetic testing: showed negative results

No bilateral native nephrectomy (anuric)

- After 4 weeks, nephrotic range proteinuria (raising UPC 0.6…1.2…2.1), creatinine 0.9 mg/dl

Graft biopsy: recurrence of FSGS???

Are these patients considered as candidates for kidney transplantation?

Take home massage

- Podocytopathies represent a challenge for kidney transplantation.

- We do not recommend exclusion of them as candidates for kidney transplantation.

- Genetic testing before transplantation to inform the risk of recurrence.

Take home massage

- The risk of recurrence after transplantation should be considered and discussed with candidate.

- No definitive recommended preventive measures for recurrence of the disease post kidney transplantation.

- Post-transplantation follow up of proteinuria is mandatory.

Take home massage

- Plasma exchange & rituximab therapy are used in treatment of recurrence.

- Re-transplantation with history of graft loss due to recurrence of FSGS is major risk factor in determination of candidacy.


THANK
YOU