Clinicopathological conference
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Disclosures

Janewit Wongboonsin – no relevant disclosures

Nelson Leung
  • Research grant from Omeros
  • Stocks with AbbVie, Checkpoint therapeutics

Astrid Weins
  • Consultancy: Pfizer Inc, Sail Bio Inc, Goldfinch Bio Inc, Judo Bio Inc
  • Research Funding: NephCure, NIDDK, DoD
  • Honoraria: Sysmex Inc
  • Patents: Assays to detect anti-nephrin antibodies in nephrotic syndrome
  • Royalties: Elsevier

Anil Chandraker – no relevant disclosures
46-year-old female presents to nephrology clinic with:

**Persistent proteinuria**
History of present illness

**2 month prior**
- Developed sudden onset severe headache
- CT showing subarachnoid hemorrhage
- Admitted to neuro ICU
- MRA/MRI negative for aneurysm

**1 month prior**
- PCP visit
- Complained of dysuria
- Trimethoprim-sulfamethoxazole x 10 days

**1 week prior**
- PCP visit
- Noted persistent frothy urine
- UA showed 3+ protein
- Started on lisinopril
- Urgent referral to nephrology
Nephrology clinic

**Interval events**
- Feeling well
- Noted continued foamy urine
- Reported no prior history of kidney disease
- Legs swell up on and off
- Review of system
  - No cough, rash, hemoptysis, chest pain, shortness of breath
  - Slight bleeding from the nose when she blows her nose in the morning
Other history

**Past Medical History**
- Anxiety
- Hypertension
- Dyslipidemia
- Recent subarachnoid hemorrhage

**Past Surgical history**
- None

**Allergies**
- Penicillin

**Medications**
- Lisinopril 20 mg
- Atorvastatin 10 mg

**Social history**
- Smoker 1 pack per day for 30+ years
- Rare alcohol use
- No intravenous drug use

**Family history**
- No family history of kidney disease
Physical exam

Vital signs: Afebrile, BP 113/56, P 60, RR 16, SpO₂ 100% on room air
General – adult female, comfortable at rest, not in acute distress
HEENT – unremarkable
Neck - supple, trachea midline
CV - RRR S1 and S2, No JVD
Chest - Clear to auscultation without wheezes/crackles bilaterally
Abdomen - soft, not tender, no distension
Skin - no rashes or lesions
Workup

- Serum albumin 3.2
- LFTs: normal
- Lipid panel
  - Cholesterol 244
  - LDL 135
  - Triglyceride 131
- Renal ultrasound: normal 12 cm kidneys
- Urine studies
  - UA: specific gravity 1.011, glucose negative, ketone negative
  - 10-20 RBC, non-dysmorphic
  - No casts
  - Urine protein to Cr ratio: 4.5 g/g
  - Urine albumin to Cr ratio: 3.6 g/g
Workup

Paraprotein studies
- SPEP: no M-spike
- Immunofixation: no M-spike
- UPEP: no M-spike
- Free light chain ratio: 0.78
  - Kappa 29.7
  - Lambda 38

Autoimmune serologies
- Complement
  - CH50 63 (42-95 U/ml)
  - C3 124 (90-180 mg/dl)
  - C4 29 (10-40 mg/dl)
- Negative
  - ANA, dsDNA
  - ANCA, Anti-GBM
  - Rheumatoid factor, cryoglobulins
  - PLA2R
Questions for discussant: Dr. Nelson Leung

1. Can this patient have a monoclonal gammopathy of renal significance without an M spike?
2. What is the differential diagnosis for this patient?
3. What are your next steps in evaluating this patient?
Course

- Kidney biopsy arranged
- Multiple cancellations due to work up needed for subarachnoid hemorrhage
- Renal biopsy performed 1 year after the initial nephrology evaluation
Pathology

Dr. Astrid Weins
Light Microscopy

PAS

H&E

JMS
Light Microscopy
Immunofluorescence Microscopy

IgA

IgM
Immunofluorescence Microscopy

IgG

C3

C1q
Immunofluorescence Microscopy

Kappa

Lambda
Immunofluorescence Microscopy

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Electron Microscopy
Electron Microscopy
Kidney Pathology

- Monoclonal immunoglobulin deposition disease, with IgG3/kappa specificity and a membranoproliferative and nodular pattern of glomerular injury and large intracapillary paraprotein aggregates and confluent subendothelial and many discrete subepithelial electron dense deposits
- Nodular glomerulosclerosis
- Moderate chronic changes of the parenchyma, including:
  - Focal global and segmental glomerulosclerosis and glomerular hypoperfusion (26% of glomeruli)
  - Focal tubular atrophy and interstitial fibrosis (20-30% of the cortex)
  - Severe arterial and hyaline arteriolar sclerosis
Hematology/Oncology work up

**Flow cytometry**
- Small population of CD38-positive/CD138-positive plasma cells that are negative for CD56 and exhibit polytypic cytoplasmic immunoglobulin light chain staining
- Negative for B-cell lymphoproliferative disorder and plasma cell neoplasm

**Bone marrow biopsy**
- Normocellular marrow (50% fat).
- Minimal marrow involvement by a plasma cell neoplasm.
  - 4% plasma cells
  - Unable to perform FISH due to limited quantity of plasma cell
  - Immunoperoxidase and in-situ hybridization studies performed on paraffin sections reveal monotypic cytoplasmic reactivity of the CD138-positive plasma cells for immunoglobulin kappa light chain.
  - Scattered plasma cells exhibit cytoplasmic reactivity for immunoglobulin lambda light chain.
Questions for discussant: Dr. Nelson Leung

Given this patient’s diagnosis, how would you manage him?
Clinical course

- 4 cycles of CyBorD (cyclophosphamide, Bortezomib, Dexamethasone)
- 2nd bone marrow: 5% plasma cell, polytypic
- Stem cell mobilization with filgrastim and plerixafor
- Unable to tolerate maintenance lenalidomide

- 1st Renal biopsy
- Chemo
- 2nd Renal biopsy
- 3rd BM biopsy: polytypic
- Rituximab x 4
- PD
- 1st  2nd  3rd  4th  5th years
Transplant evaluation

At 52-years-old: transplant evaluation clinic
- Potential living donor identified
- **Immunologic risk**
  - No prior transfusion/transplant/severe infection
  - G2P2
  - PRA/anti-HLA antibodies negative
- **Cardiac risk**
  - Hx of SAH
  - TTE: LVEF 40-45%, mild to moderate mitral regurgitation
  - Stress test negative
  - Peripheral arterial disease s/p left leg stent

**Medications**
- Aspirin 81 qd
- Atorvastatin 80 hs
- Calcitriol MF
- Clonidine patch 0.3 qweek
- Cholecalciferol
- Cyanocobalamin
- Isosorbide mononitrate ER 60 qd
- Lorazepam 0.5 mg as needed
- Metoprolol XL 25 qd
- Omeprazole 20 bid
- Sacubitril-valsartan 24-26 2 tabs qod
- Sevelamer 1600 tid
- Torsemide 40 qd
Questions for discussant: Dr. Anil Chandraker

What are some considerations when evaluating patients with MIDD for transplant?
Kaplan–Meier plot of patient survival after listing by transplant status and center quality on the basis of deceased donor transplantation at a transplant center with a given performance at the time of listing.
Why do we transplant ESRD patients?

Better quality of life
Decreased morbidity/mortality compared with dialysis treatment

However...

• Weigh the likelihood of success - will disease return?
• Additional risks to patient - risk of additional immunosuppression
9.13.2 Monoclonal immunoglobulin deposition disease (MIDD)

9.13.2.1: We suggest that candidates with light chain deposition disease (LCDD) be excluded from kidney transplantation unless they have received a potentially curative treatment regimen and are in stable remission (2D)

(Same as the recommendation for Multiple Myeloma!)

MIDD is not infrequently diagnosed as recurrence in a transplanted kidney.

Twenty-three patients (LCDD, n = 20; LHCDD, n = 2; HCDD, n = 1) received a kidney transplant from a cadaveric donor. In 9 patients, MIDD was diagnosed after recurrence on the allograft, after a median time of 32 months (23-42) after transplantation.¹

Of 19 patients with LCDD the diagnosis of LCDD was made in 3 patients after a post-transplant recurrence and confirmed by a review of the native kidney biopsy.²

Aim for ‘complete response’ prior to Transplantation

- Negative immunofixation on serum and urine studies
- Disappearance of any soft-tissue plasmacytomas
- ≤5% plasma cells in bone marrow
- (normal FLC ratio)
- (absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence)
Characteristics of patients with LCDD diagnosis who had no histological evidence of recurrence post transplantation

Characteristics of patients with LCDD diagnosis who had histological evidence of recurrence post transplantation.
Other Tx considerations

- Patients who do not have a complete response may be considered for transplantation
- Transplant patients have a significant risk of morbidity and mortality related to infection and cancer
- Increased immunosuppression for treatment of MIDD increases risks of infection and other malignancies
- Consider protocol biopsies after transplantation as early detection of recurrent diseases increases chances of better outcomes
- Even under the best circumstances expectations of transplant survival need to be realistic and transplantation may not be the best option for all patients
Clinical course

Early transplant course
• Living donor kidney transplant at 6.5 years after the presentation
• Induction with basiliximab
• No complication
• Maintained with MMF, Tacrolimus and prednisone
• Cr nadir at 0.9 mg/dL
• Pre-transplant on PD FLC ratio 1.44
  – Kappa 155
  – Lambda 108

Transplant clinic follow up
• Last follow up July 2022 (11 months after KT)
• Cr ~ 1.1 – 1.3 mg/dL
• Intermittent hyperkalemia
• Undetectable urine protein
• Post-transplant FLC ratio 1.3
  – Kappa 29.5
  – Lambda 22.1
Take home points

• Diagnosis: Negative blood/urine biomarkers for paraprotein disease **does not rule out** monoclonal related diseases in the kidney
• Therapy: Disease monitoring require **careful attention to both renal and oncologic biomarkers**. In this case, loss of monotypic plasma cell was demonstrated in the repeat bone marrow biopsy
• Kidney transplant: Kidney transplant should be considered for select patients with MGRS