Preemptive Kidney Transplantation
~ Case study ~

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Department of Transplant Surgery

Makoto Tsujita
Statement of Disclosure

• The author does not have any financial conflict of interest regarding the material in this presentation.
Case 1

• Patient: 60 y.o. female
• Original kidney disease: chronic glomeruloritis
• Past History: at the age of 23 years, hyperthyroidism (already recovered)
• No family history of kidney disease
• No history of smoking and alcohol,
• No history of blood transfusion
• History of 3 times pregnancy, with one miscarriage
Present medical condition:
40y.o. urinary protein appeared
43y.o. given treatment by nephrologist
45y.o. initiated peritoneal dialysis (PD)
57y.o. additional hemodialysis once a week
60y.o. consulted to our hospital, and the husband (62y.o) decided to donate his kidney to her
Physical findings before KTx

Height: 147cm   Body weight: 41kg   BMI: 19.4
Blood pressure 115/75mmHg   HR 64/min
Lung: clear, no rale   Heart: regular, no murmur
Abdomen: soft and flat
Leg edema: none

Medication:
Warfarin K: 2.5mg/day, Lansoprazole: 15mg/day
Alfacalcidol: 0.25μg/day, Calcium carbonate: 3000mg/day
Bixalomer: 750mg/day, Cinacalcet 100mg/day
### Laboratory findings before KTx

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>WBC</td>
<td>6900/μL</td>
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<tr>
<td>RBC</td>
<td>414*10^4/μL</td>
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<tr>
<td>Hb</td>
<td>12.2 g/dL</td>
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<tr>
<td>Ht</td>
<td>38.3 %g/dL</td>
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<tr>
<td>Plt</td>
<td>21.0*10^4/μL</td>
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<tr>
<td>CRP</td>
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<tr>
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<td>6.71 g/dL</td>
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<tr>
<td>Alb</td>
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<tr>
<td>BUN</td>
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<td>K</td>
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<td>Cl</td>
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<tr>
<td>cCa</td>
<td>9.1 mg/dL</td>
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<tr>
<td>IP</td>
<td>3.9 mg/dL</td>
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<tr>
<td>T-Bil</td>
<td>0.25 mg/dL</td>
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<tr>
<td>AST</td>
<td>15 IU/L</td>
</tr>
<tr>
<td>ALT</td>
<td>7 IU/L</td>
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<tr>
<td>ALP</td>
<td>273 IU/L</td>
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<tr>
<td>LDH</td>
<td>238 IU/L</td>
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<tr>
<td>γGTP</td>
<td>15 IU/L</td>
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<tr>
<td>Che</td>
<td>222 IU/L</td>
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<tr>
<td>Ferritin</td>
<td>150 ng/mL</td>
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<tr>
<td>iPTH</td>
<td>173 pg/mL</td>
</tr>
<tr>
<td>BNP</td>
<td>1617 pg/mL</td>
</tr>
</tbody>
</table>
Low LV function due to uremia?

Image Studies before KTx

- Chest Xp: Cardiomegaly
- ECG: Sinus, negative T in V3-V6, LVH
- UCG: EF 0.23, Wall motion: diffuse hypokinesis
- Myocardial perfusion scintigraphy → Suspected ischemia in the apex of the heart

Coronary angiography: Normal

Low LV function due to uremia?
Image Studies before KTx

- Cervical ultrasound: Right upper parathyroid gland enlarged
  The size was 4.1*2.3*6.0mm
  → Suspected secondary hyperparathyroidism

No other abnormal findings were seen on image examinations before KTx
Immunological examination before KTx

Blood type compatible: A → A

HLA type
Donor: A(2402, -), B(5201, 1501), DRB1(1501, 1502)
Recipient: A(2402, 3101), B(5101, 5201), DRB1(1403, 1502)
→2 mismatch

X-match
LCT: T(1), B(1)
AHG LCT: T(1)
Direct FCM: T(−) 1.1%, B(−) 0.8%
Flow-PRA: class I (+) 45%, class II (−) 2%
DSA positive B1501 MFI: 964
Problem lists of this case before KTx

- History of long duration of dialysis
- Severe secondary hyperparathyroidism with normal calcemia under high dose of Cinacalcet
- Low LV function
- ABOc, weak DSA positive KTx
Q. She had severe hyperparathyroidism. Do you recommend Parathyroidectomy before KTx?

- Yes
- No
Q. She had low LV function (EF 0.23). Do you recommend KTx?

• Yes

• No
**Immunosuppression protocol for ABOc KTx**

**Transplant**

- **CNI**: CsA or TAC

**Protocol biopsy**: 1, 12 months PO

- **Prednisolone**
  - Starting dose: CsA 4mg/kg, TAC 0.1mg/kg BID.

- **Mycophenol mofetil**
  - 1500mg b.i.d with CsA
  - 1250mg b.i.d with TAC

- **Basiliximab**
  - 20mg D.I.V.

- **Target AUC0-4h**: CsA 3000-3500, TAC 80-100 ng・hr/ml

**CNI : CsA or TAC**

- 1000mg b.i.d with CsA
- 750mg b.i.d with TAC
Time course after successful KTx

- \(\text{sCre (mg/dL)}\):
  - 0w: 8 mg
  - 2w: 7 mg
  - 4w: 2500 mg
  - 6w: 1500 mg
  - 8w: 20 mg
  - 10w: 10 mg
  - 12w: 7 mg

- \(\text{sCa (mg/dL)}\):
  - 0w: 8 mg
  - 2w: 7 mg
  - 4w: 2500 mg
  - 6w: 1500 mg
  - 8w: 20 mg
  - 10w: 10 mg
  - 12w: 7 mg

- \(\text{TAC trough (ng/mL)}\):
  - 0w: 8 mg
  - 2w: 7 mg
  - 4w: 2500 mg
  - 6w: 1500 mg
  - 8w: 20 mg
  - 10w: 10 mg
  - 12w: 7 mg

- \(\text{Bone pain}\):
  - 6m after KTx:
    - cCa 11.6 mg/dL
    - IP 2.8 mg/dL
    - iPTH 320 pg/mL
    - Cre 1.3 mg/dL

- \(\text{6m after KTx:}\)
  - cCa: 11.6 mg/dL
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  - cCa: 11.6 mg/dL
  - IP: 2.8 mg/dL
  - iPTH: 320 pg/mL
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  - Cre: 1.3 mg/dL

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  - cCa: 11.6 mg/dL
  - IP: 2.8 mg/dL
  - iPTH: 320 pg/mL
  - Cre: 1.3 mg/dL
Symptomatic hypercalcemia had persisted

- Treatment of hyperparathyroidism after KTx
  ① Parathyroidectomy (PTx)
  ② Cinacalcet (not covered by insurance)
  ③ Bisphophonate
  ④ Active vitamin D analog
  ⑤ Teriparatide
  ⑥ Desunomab

→PTx has been chosen for the treatment

Hirukawa T, et al. CEN 2015
### Laboratory findings before PTx

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
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<tbody>
<tr>
<td>CRP</td>
<td>&lt;0.20 mg/dL</td>
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<tr>
<td>TP</td>
<td>6.59 g/dL</td>
</tr>
<tr>
<td>Alb</td>
<td>4.1 g/dL</td>
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<tr>
<td>BUN</td>
<td>22.0 mg/dL</td>
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<tr>
<td>Cre</td>
<td>1.28 mg/dL</td>
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<tr>
<td>Na</td>
<td>140 mEq/L</td>
</tr>
<tr>
<td>K</td>
<td>4.8 mEq/L</td>
</tr>
<tr>
<td>Cl</td>
<td>114 mEq/L</td>
</tr>
<tr>
<td>cCa</td>
<td>11.6 mg/dL</td>
</tr>
<tr>
<td>IP</td>
<td>2.3 mg/dL</td>
</tr>
<tr>
<td>T-Bil</td>
<td>0.29 mg/dL</td>
</tr>
<tr>
<td>AST</td>
<td>15 IU/L</td>
</tr>
<tr>
<td>ALT</td>
<td>7 IU/L</td>
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</table>

<table>
<thead>
<tr>
<th>Test</th>
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<tbody>
<tr>
<td>WBC</td>
<td>4800 /μL</td>
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<tr>
<td>RBC</td>
<td>505 10^4/μL</td>
</tr>
<tr>
<td>Hb</td>
<td>13.2 g/dL</td>
</tr>
<tr>
<td>Ht</td>
<td>41.2 %g/dL</td>
</tr>
<tr>
<td>Plt</td>
<td>26.4 10^4/μL</td>
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</tbody>
</table>

<table>
<thead>
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<tbody>
<tr>
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<td>671 IU/L</td>
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<td>LDH</td>
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<tr>
<td>γ GTP</td>
<td>15 IU/L</td>
</tr>
<tr>
<td>Che</td>
<td>222 IU/L</td>
</tr>
<tr>
<td>iPTH</td>
<td>332 pg/mL</td>
</tr>
<tr>
<td>BAP</td>
<td>73.6 μg/L</td>
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</table>
Image studies before PTx

99mTc-MIBI scintigraphy showed enlarged right upper parathyroid gland and smaller size of right lower and left upper gland as well.

US showed enlarged right upper parathyroid gland. The size was 7.2*6.6*7.1mm. Because of stopping cinacalcet, it became larger than before.

CT also showed the same result as followed.
**Time period after PTx**

**Calcium carbonate/day**
- 12g
- 6g

**Alfacalcidol/day**
- 3μg
- 2μg
- 1μg
- 0.25μg

Graph showing:
- sCa (mg/dL)
- TAC trough (ng/mL)
- sCre (mg/dL)
Development of parathyroid gland
~From CKD to transplantation~
What persist hyperparathyroidism causes?

- Hypercalcemia
- ★ Worse of graft function
- ★ Nephrocalcinosis
- ★ Vascular calcification

- Development of osteoporosis and fracture
Risk factors for persistent hyperparathyroidism before KTx

- Long duration of dialysis
- Maximum size of parathyroid gland before KTx
- Pretransplant PTH levels
- Ca levels before KTx

Change of graft function before and after PTx

The higher PTH levels before PTx, the more eGFR declines after PTx. A reduction of PTH level causes a decline of renal blood flow. Low graft function before PTx also might be involved.
Changes of the parameters before and after kidney transplantation

Tsujita M. Clin Exp Nephrol 2014

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**Graphs**

- **(a)**: cCa levels over time (pre, 1w, 3w, 24w) with a significant increase after transplantation marked by an asterisk (* p<0.05; ** p<0.001).
- **(b)**: Pi levels over time with a decrease after transplantation marked by an asterisk (* p<0.05; ** p<0.001).
- **(c)**: Ln FGF23 levels showing a significant decrease after transplantation marked by an asterisk (* p<0.05; ** p<0.001).
- **(d)**: iPTH levels showing a significant decrease after transplantation marked by an asterisk (* p<0.05; ** p<0.001).
## Improvement of LV function after KTx

### Examination of UCG

<table>
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<tr>
<th>Measure</th>
<th>Before KTx</th>
<th>6M after KTx</th>
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<tbody>
<tr>
<td>EF (%)</td>
<td>23</td>
<td>49</td>
</tr>
<tr>
<td>LVDd (mm)</td>
<td>53</td>
<td>45</td>
</tr>
<tr>
<td>LVDs (mm)</td>
<td>48</td>
<td>35</td>
</tr>
<tr>
<td>IVST (mm)</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>PWT (mm)</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>141.4</td>
<td>102.3</td>
</tr>
</tbody>
</table>
KTx improves LV dysfunction in patients with ESRD

Wali RK, et al. JACC 2005;45: 1051–60

A longer duration of dialysis before KTx was the only significant factor that had an impact on normalization of LVEF in post-transplant period.
Take home message ①

• Long duration of dialysis is likely to occur Calcium metabolism disorder and fail to improve low LV function after KTx.
Case 2

- Patient: 24 y.o. male
- Original kidney disease: IgA nephropathy
- Past History: no tonsillitis
- No family history of kidney disease
- No history of smoking and alcohol,
- No history of blood transfusion
• Present medical condition:

15y.o. urinary blood appeared.

23y.o. Catching a cold, elevating serum Cre level had been found, and was diagnosed IgA nephropathy by biopsy. He started to take steroid, but his kidney function still remained worsen.

25y.o. consulted to our hospital and had kidney transplantation from his mother, 52 y.o. without initiation of dialysis on Jan. 19th, 2015
Physical findings before KTx

Height: 167.8cm  Body weight: 55.2kg  BMI: 19.6
Blood pressure 125/80mmHg  HR 64/min, regular
Lung: clear, no rale  Heart: regular, no murmur
Abdomen: soft and flat
Leg edema: none

Medication:
Azilsartan: 40mg/day, Lansoprazole: 15mg/day
Alfacalcidol: 0.25 μg/day, Furosemide: 40mg/day
Atorvastatin: 10mg/day, Amlodipine 10mg/day,
Febuxostat 10mg/day
<table>
<thead>
<tr>
<th>Laboratory findings before KTx</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WBC</strong></td>
</tr>
<tr>
<td><strong>RBC</strong></td>
</tr>
<tr>
<td><strong>Hb</strong></td>
</tr>
<tr>
<td><strong>Ht</strong></td>
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<tr>
<td><strong>Plt</strong></td>
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<tr>
<td>CRP</td>
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<tr>
<td>TP</td>
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<td>Alb</td>
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<td>eGFR</td>
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<td>K</td>
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<td>Cl</td>
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<tr>
<td>cCa</td>
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<tr>
<td>IP</td>
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<td>T-Bil</td>
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<tr>
<td>Che</td>
</tr>
<tr>
<td>Ferritin</td>
</tr>
<tr>
<td>iPTH</td>
</tr>
</tbody>
</table>
Immunological examination before KTx

Blood type incompatible: A → 0,  
Anti A antibody: IgM 32 times, IgG 256 times

HLA type  
Donor: A(24, 26), B(54, -), DRB1(04, 09)  
Recipient: A(2, 26), B(48, 54), DRB1(04, 09)  
→ 1 mismatch

X-match  
LCT: T(1), B(1)  
AHG LCT: T(1)  
Direct FCM: T(-) 1.2%, B(-) 1.3%  
Flow-PRA: class I (-) 0%, class II (-) 2%
Problem lists of this case

- eGFR was 10.8 ml/min/m² at his first visit to our hospital
- ABO incompatible KTx with high anti A antibody without initiation of dialysis
- Original disease: IgA nephropathy
Was he referred promptly?

- The patient whose first contact with a nephrologist occurs later in the course of CKD (stage 5 or at initiation of dialysis) should be referred promptly for transplant evaluation. (CJASN 2008; 3(2): 471-480)

No
Q. This case was ABOi KTx without initiation of dialysis. Do you recommend KTx?

- Yes
- No
New Immunosuppression protocol for ABOi KTx

Transplant

- Rituximab 100mg/body
- DFPP
- PEX
- Prednisolone
- Mycophenol mofetil 750mg b.i.d
- Basiliximab 20mg D.I.V.
- CNI: CsA or TAC
- Target AUC$_{0-4h}$; CsA 3000-3500, TAC 80-100
- Sarpogrelate hydrochlorides (Unplaque 300mg/3x)

Starting dose; CsA 4mg/kg, TAC 0.1mg/kg BID.

Protocol biopsy: 1, 12 months PO

PEX
Blood → Blood cell

Plasma

- Cholesterol
- Protein
- Bilirubin
- Vitamin
- Glucose
- Urea, Cre
- Electrolyte
- H₂O

Immunoglobulin
- IgG
- IgM
- IgA

Albumin

Electrolyte

H₂O

PE = Plasma Exchange
DFPP = Double Filtration Plasmapheresis
PA = Plasma Absorption
Time course after successful KTx

No recurrence of IgA nephropathy was seen until now
Take home message

- ABO incompatible KTx could be done successfully in patients without initiation of dialysis.
Thank you very much for your attention