Case Presentation

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Case Presentation
Case Presentation

- Labs:

\[
\begin{align*}
7.11 & \quad 12.1 & \quad 209 \\
37.8 & \quad 142 & \quad 97 & \quad 48 & \quad 196 \\
& \quad 3.3 & \quad 27 & \quad 8.5
\end{align*}
\]

- HBSAb (-)
- HBSAg (-)
- HB Core Ab (-)
- CMV (+)
- RPR (-)
- HIV (-)
- HTLV I & II NR
Case Presentation

- Blood and tissue typing:

<table>
<thead>
<tr>
<th></th>
<th>ABO</th>
<th>HLA</th>
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<tbody>
<tr>
<td></td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Donor</td>
<td>26</td>
<td>32</td>
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<tr>
<td></td>
<td>B</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>DR</td>
<td>1</td>
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<tr>
<td></td>
<td>DR</td>
<td>13</td>
</tr>
<tr>
<td>Recipient</td>
<td>29</td>
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- T-cell crossmatch (-)

- Flow cytometry
  - T cell (-)
  - B cell (+)
Case Presentation

- Pre- and intraoperative induction immunosuppression given
  - Oral tacrolimus
  - Intravenous methylprednisolone
  - Intravenous thymoglobulin
Case Presentation

- Right laparoscopic donor nephrectomy performed
- Kidney iced and delivered to recipient’s OR
- Venous and arterial anastomoses performed
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Case Presentation

- Anastomoses inspected
  - No technical error identified
- Intraoperative biopsy sent for frozen section
  - Thrombosis and acute inflammation of glomeruli, consistent with antibody mediated rejection
Case Presentation

- Postoperatively
  - Patient given full therapy against cell- and antibody-mediated immunity
    - Tacrolimus
    - Mycophenolate mofetil
    - Methylprednisolone
    - Thymoglobulin
    - Rituximab
    - Plasmapheresis
  - Patient remained anuric
    - POD #2: Returned to OR for transplant nephrectomy
  - Discharged home three days after nephrectomy
Definition

- A process by which the immune system of the recipient of a transplant attacks the transplanted organ or tissue
- This is the normal response of the healthy human immune system, which can distinguish foreign tissues and attempts to destroy them
Definition

Hyperacute rejection: Mediated by preformed antibodies that bind to endothelium and subsequently activate complement

- Rapid thrombotic occlusion of the vasculature of the transplanted allograft
- Occurs within minutes to hours after host blood vessels are anastomosed to donor vessels
- Mediated predominantly by IgG antibodies directed toward foreign protein molecules, such as MHC molecules
- Result from prior exposure to alloantigens from blood transfusions, pregnancy, or previous transplantation
Definition

- **Acute rejection** developing after the first 5-7 post-transplant days is generally a manifestation of cell-mediated immune injury
  - Necrosis of parenchymal cells caused by infiltration of T cells and macrophages
**Definition**

- **Chronic rejection:** Fibrosis and scarring in transplanted organ
  - Multifactorial etiology, not strictly immunologic
  - Inflammation, ischemia, and other processes play a role
  - Episodes of acute rejection are significant risk factors
History

- Ancient Greeks: Imagination fuelled by concept of xenotransplantation
- Old Testament: "A new heart also I will give you, and a new spirit will be put within you; and I will take away the stony heart out of your flesh, and I will give you a heart of flesh."

1 Ezekiel 36:26
History

- Autotransplantation well-established
  - 2nd century BC: Sushruta pioneered skin grafting for rhinoplasty
- Virtually all allografts failed
  - Attempts at transplantation from slave to master ("sympathetic nose")
1596: Gaspare Tagliacozzi identified essence of difficulty:

"The singular character of the individual entirely dissuades us from attempting this work on another person. For such is the force and power of individuality, that if any one should believe that he could achieve even the least part of the operation, we consider him plainly superstitious and badly grounded in physical science".
1912: In his book “Heteroplastische und Homoplastische Transplantation” Georg Schöne formulated rules on “Transplantationsimmunität” based on contemporary research:

- Heteroplastic (xenogeneic) transplants invariably fail
- Homoplastic (allogeneic) transplants usually fail
- Autografts are almost always successful
- There is an initial take of a first allograft which is then followed by rejection
- Second grafts undergo accelerated rejection if recipient has previously rejected a graft from the same donor or, if recipient has been preimmunized with material from tumor donor
- Graft success is more likely when donor and recipient have a closer "blood relationship"
History

- Sir Peter Medawar at Glasgow Infirmary published “The Fate of Skin Homografts in Man”
  - The destruction of foreign epidermis is brought about by a mechanism of active immunization
  - “The accelerated regression of second-set homografts argues for the existence of a systemic immune state”
  - “The inflammation has in all likelihood the character of a local anaphylaxis… yet, the reaction is atypical; for the lymphocyte takes the place of the polymorph in the ‘classical picture’”
History

- 1933: Yu Yu Voronoy of the Soviet Union performed the first human-to-human kidney transplant
- 1954: Joseph E. Murray performed the first successful kidney transplant
  - Donor and recipient identical twins
History

- Early attempts at immunosuppression
  - Whole-body X-irradiation
  - Nitrogen mustard
  - 6-mercaptopurine
- 1957: George Hitchings and Gertrude Elion modify 6-MP to produce azathioprine
- 1963: Thomas Starzl observed that large doses of corticosteroids can reverse rejection episodes and stabilize allograft function
Pathophysiology
Pathophysiology – Immune cascade

- T lymphocytes are incapable of recognizing soluble antigen
  - Professional antigen presenting cell must phagocytose foreign cell
  - Presents antigen on surface in conjunction with class II major histocompatibility complex
  - Activated APC produces IL-1, augmenting T cell response
Pathophysiology – Immune cascade

- Foreign cell carrying antigen
- APC (macrophage)
- MHC class II molecule
- T cell receptor
- Antigen fragment
- CD4+ T cell
- Interleukin-1
Antigen binding induces a conformational change in the TCR complex.

TCR complex is phosphorylated and coupled via a G-binding protein to phospholipase C.

The activation of phospholipase C results in production of inositol 1,4,5-triphosphate (IP3).

Intracellular [Ca²⁺] increases.

Nuclear factor of activated T cells (NFAT) is activated by dephosphorylation.

Production of mRNA for IL-2.
Pathophysiology – Immune cascade
Immunosuppressants

- Steroids
- Purine analogs
  - Azathioprine
- Calcineurin inhibitors
  - Cyclosporine
  - Tacrolimus
- Other T lymphocyte inhibitors
  - Mycophenolate mofetil
  - Sirolimus
- Antibodies
  - Polyclonal
  - Monoclonal
Immunosuppressants: Glucocorticoids

- Pivotal role in treatment of acute rejection episodes and maintenance since early days of transplantation
  - Suppress interleukin-2 production and
  - Inhibit lymphocyte activation and both monocyte and neutrophil migration
  - Also modulate humoral immunity by regulating T-cell activation of B cells
  - At high doses directly inhibit B-cell activation and proliferation

- Worsen cardiovascular risk profiles
  - Post-transplant diabetes
  - Hypertension
  - Hyperlipidemia
  - Weight gain

- Bone loss, cataracts, growth retardation

- Steroid-sparing and steroid-minimizing regimens described

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Immunosuppressants: Purine analogs

- **Azathioprine**
  - Made organ transplantation across non-identical individuals a clinical reality
  - When ribosylated, competitively inhibits nucleotide synthesis
  - Side effects relate to antimetabolite activity
    - Bone marrow suppression
    - Liver toxicity
Immunosuppressants: Calcineurin inhibitors

- **Cyclosporine**
  - Extracted from *Tolypocladium inflatum*
  - Introduction in 1983 was a landmark development, ending the “azathioprine era”
  - Selective T cell inhibition
  - No myelosuppression
  - Nephrotoxic
  - Unpredictable bioavailability

- **Tacrolimus**
  - Extracted from *Streptomyces tsukubaensis*
  - Mechanism of action and side effect profile resemble cyclosporine’s
  - Increased incidence of PTDM
  - Levels must be monitored
Immunosuppressants: Other lymphocyte inhibitors

- **Mycophenolate mofetil**
  - Blocks lymphocyte proliferation by inhibiting inosine monophosphate dehydrogenate
  - As part of multidrug regimen significantly reduced incidence of biopsy-proven rejection during the first 12 months after transplant, leading to a 50% decrease in loss of renal allografts
  - Leukopenia
  - Gastrointestinal upset (diarrhea)

- **Sirolimus**
  - Close structural analogue of tacrolimus, binds to FKBP
  - Inhibits transduction of signals from the IL-2R to the nucleus
  - Acts synergistically with cyclosporine
  - Not significantly nephrotoxic

Induction of immunosuppression

- Prior to 1992: Vast majority (92%) of transplant recipients received no induction with antilymphocyte preparations
- By 2001 59% of recipients received induction
- Muromonab-CD3 (OKT3) predominant immunosuppressive agent used for induction through 1995
- In 2001, 26% of the 13,109 transplants for which information is available used basiliximab (Simulect) and 15% used daclizumab (Zenapax)
- Rabbit antithymocyte globulin (Thymoglobulin) was used in 18% of transplants in 2001
- OKT3 use has dropped to <1% of transplants

Antilymphocyte induction agents:
- OKT3
- Basiliximab
- Daclizumab
- Thymoglobulin

Mechanism of action of immunosuppressants
Allograft survival, patient survival, and rates of acute rejection in the first 12 months after transplantation are excellent and continue to improve.

For recipients of a first cadaveric kidney in the United States, current 1-year patient and graft survival probabilities are about 95% and 88%, respectively.

For recipients of a first living donor kidney, current 1-year patient and graft survival probabilities are 98% and 94%, respectively.

Statistics

- Acute rejection episode decreases 1-year graft survival by 20% and shortens half-life by four years.

- Rates of acute rejection in the first 6 months have decreased to less than 20% due to improvements in:
  - Crossmatching tests (pretransplantation in vitro assays to detect donor antibodies to recipient HLA antigens)
  - Immunosuppressive regimens
  - Antimicrobial prophylaxis
  - Overall surgical and medical care

Pretransplant evaluation

- Physical exam
- Chest x-ray
- Complete medical and surgical history
- Electrocardiogram
- Ultrasound with Doppler examination
- Blood tests
- Pulmonary function test
- Viral testing - hepatitis, CMV, EBV, HIV
Pretransplant evaluation

- Histocompatibility Laboratory Tests
  - Blood Typing
  - Tissue Typing
  - Crossmatch Testing
  - Panel Reactive Antibody (PRA)
Diagnosis of rejection

- Clinical signs:
  - Malaise
  - Fever
  - Oliguria
  - Hypertension
  - Graft tenderness

- Diagnosis hinges on serial creatinine measurements
  - Elevation of 20% over baseline triggers further evaluation
  - Rule out non-immunologic causes
  - Ultrasonography
  - Renal scanning
  - Percutaneous biopsy

Diagnosis of rejection

- **Banff criteria**
  - Interpretation of renal biopsy specimens for diagnosing rejection have been greatly facilitated and standardized
  - Based on scores for glomerular, vascular, interstitial, and tubular lesions
  - Has been shown to have clinical relevance when predicting rejection reversal and may prove useful for choosing first-line therapy of rejection episodes

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Diagnosis of rejection

- Banff criteria

Grade 1: Moderate interstitial mononuclear inflammation affecting 25-50% of the sampled parenchyma
Diagnosis of rejection

- Banff criteria

Grade 2: Moderate interstitial mononuclear infiltrate involving 26-50% of the renal parenchyma
Diagnosis of rejection

- Banff criteria

Grade 3: severe transmural arteritis and/or transmural fibrinoid change and necrosis of smooth muscle cells
Diagnosis of rejection

- **Biochemical markers**
  - Various markers reported to correlate with rejection
    - β2-microglobulin\(^1\)
    - Neopterin\(^2\)
  - Not widely adopted
- **PCR amplification of messenger RNA in urinary sediment\(^3\)**
  - Perforin mRNA
  - Granzyme B mRNA
  - Strong predictive value for acute rejection

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Reversal of rejection

- **Glucocorticoids**
  - Observation that steroids could reverse acute rejection was seminal\(^1\)
  - High dose steroid administration successfully treats rejection in 75\(%\)\(^2\)
  - First line treatment for acute rejection in most centers is pulse methylprednisolone, 500 to 1000 mg, given intravenously daily for 3 to 5 days

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\(^1\) Starzl TE, Marchioro TL, Waddell WR. The reversal of rejection in human renal homografts with subsequent development of homograft tolerance. Surg Gynecol Obstet. 1963 Oct;117:385-95
Reversal of rejection

- **OKT3**
  - A murine monoclonal antibody reactive with antigen-recognition complex on T cells
  - Reverses 94% of acute rejection episodes
  - Immunogenic
  - Toxic cytokine release syndrome

Reversal of rejection

- Thymoglobulin
  - Polyclonal antithymocyte antibody derived from rabbits
  - Efficacy appears similar to that of OKT3
  - More favorable side effect profile
  - More resistant to antibody deactivation
  - First line treatment for histologically severe and steroid-resistant rejection in many centers
Reversal of rejection

- Tacrolimus
  - 75% success rate in salvaging renal transplants undergoing steroid-refractory rejection\(^1\)

- Mycophenolate mofetil\(^2\) and sirolimus\(^3\)
  - Similar salvage rates

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\(^3\) Hong JC, Kahan BD. Sirolimus rescue therapy for refractory rejection in renal transplantation. Transplantation 2001;71:1579
Acute humoral rejection

- Antibody-mediated rejection frequently undiagnosed
  - Lack of typical morphologic characteristics
- C4d immunohistochemistry
  - C4 is an element of the complement cascade
  - Its degradation product (C4d) adheres to endothelial cells
  - Can be detected by pathologist
Acute humoral rejection

- Classification of rejection as either “cellular” or “humoral” is flawed
  - Significant overlap exists
- Treatment of humoral rejection
  - Plasmapheresis\textsuperscript{1}
  - Rituximab\textsuperscript{2}
    - Monoclonal anti-CD20 antibody (found on B cells)
    - May improve outcomes in antibody-mediated acute rejection episodes

\textsuperscript{1} Montgomery R, Zachary AA, Racusen LC et al. Plasmapheresis and intravenous immune globulin provides effective rescue therapy for refractory humoral rejection and allows kidneys to be successfully transplanted into cross-matchpositive recipients. Transplantation 2000;70:887–894
Investigational therapies

- **Leflunomide**
  - An orally administered antimetabolite
  - Action against NF-B and JAK3, key mediators in cytokine generation
  - Inhibits CMV

- **FTY720**
  - Reduces peripheral lymphocyte levels by causing sequestration in lymph nodes and Peyer patches

- **Efalizumab**
  - Monoclonal anti-CD11a antibody
  - Blocks T cell adhesion

- **Alemtuzumab (Campath 1H)**
  - Monoclonal antibody targeting CD52 (found on all lymphocytes)
  - Causes profound, prolonged lymphocyte depletion

- **Tolerance induction with full immunosuppression and bone marrow transplant**
Conclusions

- Organ transplantation induces a fundamentally abnormal physiologic state
- Steady improvement has been made in both prevention and treatment of organ rejection
- The potential for further improvement – both incremental and revolutionary – is great