

CHAPTER 25

COMPOSITE TISSUE ALLOTRANSPLANTATION

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I. INTRODUCTION

- A. Also referred to as Vascularized Composite Allotransplantation (VCA) or Composite Tissue Allograft (CTA)
- B. Allograft (graft from cadaveric donor) composed of different tissue types (e.g. skin, muscle, bone, nerves, vessels)
- C. Introduced for major reconstruction of tissue defects from surgical excision of tumors, traumatic injury and congenital malformations
 - 1. Option for limb replacement and reconstruction of other non-reconstructible tissue defects including facial, abdominal wall and others
- D. Couples the principles of microsurgical reconstruction with those of human organ transplantation
- E. Goal: improve function, quality of life, integration with society

II. IMMUNOGENICITY

- A. CTA are histologically heterogeneous, composed of different tissue types including skin, fat, muscle, nerves, lymph nodes, blood vessels, bone, cartilage, ligaments, and bone marrow
- B. Each tissue has different antigenicity
 - 1. Skin most antigenic, likely owing to dendritic cell population and antigen variety
 - 2. CTA graft is not the sum of immunogenicity of its different components
 - 3. Whole limb allograft elicits a less intense immune response than does allografts of each of the individual components
- C. CTA elicit a stronger immune response as compared to solid organ transplants
- D. Split tolerance phenomenon: simultaneous tolerance to one tissue and rejection of another from the same donor

III. DEVELOPMENT

- A. Rapidly progressing field
- B. > 150 composite tissue allograft worldwide to date
- C. An estimated 7 million people per year in the United States could benefit from composite tissue allotransplantation
- D. Online international registry of hand and composite tissue transplantation:
<https://www.handregistry.com/>

IV. HISTORY

- A. 348 AD: 'The legend of the black leg' / Legend of Saints Cosmos and Damien
 - 1. Tale of twin brothers Cosmas and Damian who replaced the diseased leg of a man with that of a recently deceased person
- B. 1954: first successful human organ isograft, a kidney donated between identical twins; USA (Joseph E. Murray, John P. Merrill, and J. Hartwell Harrison)
- C. 1964: first case of hand CTA, failed due to rejection after 3 weeks; Ecuador (Robert Gilbert)
- D. 1990s: *progress in immunosuppression* → *composite tissue renaissance*
- E. 1998: first successful hand CTA; France (Jean-Michel Dubernard)
- F. 2000: first successful bilateral hand CTA; France (Jean-Michel Dubernard)
- G. 2005: first successful partial face transplantation; France (Devauchelle, Dubernard)

V. TYPES OF CTA PERFORMED TO DATE

- A. Hand / upper extremity
 - 1. Most common transplant
 - a. First 4 successful cases:
 - i. Right hand – transplanted in Lyon, France, on September 23, 1998
 - ii. Left hand – transplanted in Louisville, KY on January 23, 1999
 - iii. 2 right hands – transplanted to two individuals in Guangzhou, China, on September 21, 1999
 - 2. > 80 upper limbs reported in 2015
- B. Partial or total face
 - 1. first partial face transplant in 2005 in France
 - 2. > 25 cases reported in 2015
- C. Abdominal wall
 - 1. Typically, in the setting of abdominal multi-organ transplant
- D. Knee
- E. Larynx
- F. Flexor tendon apparatus
- G. Peripheral nerve
- H. Tongue
- I. Trachea
- J. Esophagus
- K. Scalp
 - 1. In the setting of active malignancy, and with simultaneous solid organ transplantation
- L. Penis
- M. Uterus
 - 1. with the first successful pregnancy following uterus transplant in 2015 in a Swedish woman

VI. ADVANTAGES

- A. Replace “like with like”
- B. An option when standard reconstructive options are exhausted or autologous tissues are not available
- C. Can achieve structural, functional, esthetic, and psychological result
- D. Avoidance of any donor site morbidity
- E. Good functional outcomes
 - 1. for example, for hand transplants:
 - a. Sensibility recovered 6-12 months
 - b. Motor function allows return to most daily activities (eating, driving, grasping objects, riding a bicycle or a motorbike, shaving, using the telephone, and writing)
- F. Majority of patients are satisfied and report improved quality of life

VII. DISADVANTAGES / LIMITING FACTORS

- A. Need to determine appropriate indications
- B. No consensus on which physical defects justify reconstruction with CTA

VIII. DONOR-RECIPIENT MATCHING CRITERIA

- A. ABO
- B. Graft size
- C. Skin pigmentation
- D. Age
- E. Gender

IX. DETERMINATION OF ORGAN ALLOCATION

- A. Patient level
 - 1. complex decision making
 - 2. important discussion with recipient regarding donor and recipient skin pigmentation, age mismatch, and gender
- B. Society level
 - 1. no current policy
 - 2. societal values variable on the benefits and risks of CTA
- C. Need for indefinite immunosuppressive
 - 1. Always at risk for rejection
 - 2. Predominant limiting factor: side effects of immunosuppression
- D. Opportunistic infections
- E. Drug toxicity

1. Metabolic disorders
 2. Nephrotoxicity
 3. End-organ damage
- F. Malignancies
1. Heightened antigenicity of composite tissues → difficult to develop an effective yet nontoxic immunosuppressive protocol
- G. Uncertain long term outcomes
1. Limited long term experience
 2. Unknown if CTA will undergo chronic rejection leading to diminished functional capacities

X. FUTURE DIRECTIONS

- A. Results of the first clinical cases are encouraging, but still controversial.
1. Significant progress in the last 2 decades
 2. Novel immunosuppression and medication regimens may improve motor and sensory function, and decrease episodes of rejection
 3. Novel donor-specific tolerance regimens (i.e., simultaneous bone marrow transplantation to induce bone marrow chimerism and central tolerance)
- B. Increasing application for a wider group of patients as surgery is streamlined, tolerance regimens are perfected, and outcomes are improved.

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