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ABSTRACT SUBMISSION TITLE: *C1 - Circulating Donor-Derived Cell-Free DNA:*

A Novel Non-Invasive Biomarker for Rejection in Vascularized Composite Allotransplantation

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Abstract Text:

PURPOSE:

Current diagnosis of rejection in vascularized composite allotransplantation (VCA) relies on clinical examination and skin histopathology. However, these remain subjective, semi-quantitative, and frequent biopsies carry the risk of infection, scarring, and/or inciting rejection through immune activation. Cell-free DNA (cfDNA) refers to circulating fragments of DNA in the blood originating from cells undergoing cell injury and death. Currently, cfDNA is an established biomarker in prenatal testing and oncologic screening/prognostics. Based on promising results in solid-organ transplantation, we evaluated whether circulating donor-derived cfDNA (dd-cfDNA) could be used as a noninvasive biomarker to detect rejection in VCA recipients.

METHODS:

One combined face/upper extremity transplant recipient was followed longitudinally, and plasma samples were collected prospectively in combination with clinical

photography and allograft biopsies at all routine appointments as well as for any suspected rejection episodes. Peripheral blood samples were collected and plasma levels of dd-cfDNA measured via targeted amplification and sequencing of a validated panel of single-nucleotide polymorphisms (SNPs). The percentage of dd-cfDNA to total-cfDNA (dd-cfDNA%) was calculated for each sample and correlated with rejection status, which was independently determined for each timepoint based on a combination of clinical exam and histopathology ('Non-rejecting' vs. 'Active Rejection'); Samples obtained within 2 weeks following steroid treatment for rejection were classified as 'Post-steroid treatment.' Data were compared between groups using the Mann Whitney test.

RESULTS:

The recipient demonstrated undetectable levels of dd-cfDNA pre-transplantation followed by a peak of 1.1% on postoperative day (POD) 26 with a subsequent decline to low levels (<1%), all in the absence of rejection. Beginning on POD-280, he experienced a 6-month period of multiple episodes of ongoing clinical rejection confirmed by histopathology and with corresponding elevations in dd-cfDNA levels (1.1-4.9%), which partially responded to pulse steroids but ultimately required lymphocyte depleting therapy. Following treatment, rejection resolved both clinically and histologically with corresponding return to baseline low levels of dd-cfDNA (0.17-0.88%). A total of 22 'Non-rejecting' samples (median 0.39%), 20 'Active Rejection' samples (median 2.15%), and 6 'Post-steroid Treatment' samples (median 0.84%) were collected, with significant differences observed between all groups ($p<0.02$ for all).

CONCLUSIONS:

Elevated levels of dd-cfDNA, representing allograft injury, appear to correlate with acute rejection and have the potential to help detect rejection through non-invasive means and monitor resolution following treatment. This safe, simple, and noninvasive test may prove useful for rejection surveillance, enabling more frequent and quantitative assessment while complementing traditional clinical and histopathological data for decision-making.