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Original Article

The relationship of nodular endocardial infiltrates (Quilty lesions) to survival, patient age, anti-HLA antibodies, and coronary artery disease following heart transplantation

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Abstract

Background: Quilty lesions are mononuclear cell infiltrates identified in human heart transplant biopsies. The biologic significance of Quilty lesions remains undetermined. **Methods:** We monitored acute rejection by biopsy and lymphocyte growth assay (LGA) as well as transplant-related coronary artery disease (TRCAD) by yearly angiogram in 285 recipients of primary heart allografts. Patients showing Quilty lesions on biopsies during the first year posttransplant were compared with patients without such lesions. Recipients' sera were obtained at the time of biopsy and tested for anti-HLA Class I and II antibodies. **Results:** The actuarial survival of patients who developed Quilty lesions was significantly better than those who did not (P=.0074). Patients with Quilty lesions were younger and more likely to have a biopsy diagnosis of acute rejection (P=.002) and positive LGA (P<.0001) during the first posttransplant year. Among patients who do not form anti-HLA Class II antibodies, those with Quilty lesions were more likely than patients without Quilty lesions to develop TRCAD 5 years posttransplantation (P=.04). There was no correlation of Quilty status with the number of HLA donor–recipient mismatches or posttransplant development of anti-HLA antibodies. **Conclusions:** Quilty formers showed improved survival and are more likely to be diagnosed with acute rejection on biopsy and have positive LGAs. Allograft recipients who do not form anti-HLA Class II antibodies but do form Quilty lesions are more likely to develop TRCAD by 5 years posttransplantation than those who do not form Quilty lesions.

Keywords: Quilty lesions; HLA antibodies; Heart transplantation

1. Introduction

Described by Billingham in 1981 [1] and named after the first patient in whom they were observed, nodular endocardial infiltrates (Quilty lesions) are commonly identified in human heart transplant biopsies. These lesions, originally proposed to be a side effect of cyclosporine therapy because they had not been recognized prior to the use of the drug, remain pathologic enigmas. The infiltrates are composed of aggregates of lymphocytes, histiocytes, dendritic cells, and occasional plasma cells [1–3]. T-lymphocytes predominate, although exact percentages of the inflammatory cells are not well defined. Over the more than 20 years from their recognition, Quilty lesions have been associated with a wide range of events and potential etiologies, including early allograft rejection [4–6], subsequent acute rejection [7], chronic rejection [8,9], early stages of lymphoma [8,10], low interleukin (IL)-10 production genotype [11], and as localized inflammatory reactions to Epstein-Barr viral infection [2,8,10] or low cyclosporine concentrations in the endocardium [12]. They have also been described in association with rapamycin treatment in a heterotopic allograft animal model [13].

These lesions, however, are not just histologic curiosities. Quilty lesions are diagnostic dilemmas and may often be difficult to distinguish from Grade 2 or 3A/B rejection

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[14,15]. They are major contributors to interobserver variability in histologic diagnoses of rejection as well as to the overdiagnosis of rejection in posttransplant endomyocardial biopsies.

To better understand the pathogenesis and associations of these lesions to immunologic events posttransplantation, we have studied the relationships of Quilty lesions with HLA matching, anti-HLA antibodies, transplant-related coronary artery disease (TRCAD), patient demographics (age, sex, pretransplant diagnosis, and race), and survival.

2. Methods

2.1. Patient study population

The study population consisted of 285 adult recipients (224 men, 61 women) of primary orthotopic cardiac allografts between January 1997 and December 2001. The recipients' mean age was 52±13 years, and the population included 221 (77.5%) Caucasian, 34 (11.9%) African American, 24 (8.4%) Hispanic, and 6 (2.2%) Asian patients. All patients were typed for HLA Class I (A,B,C) and II (DR) antigens, screened for anti-HLA antibodies, and monitored for acute and chronic rejection through endomyocardial biopsy, lymphocyte growth assay (LGA), and coronary angiography. All patients received standard immunosuppressive therapy consisting of cyclosporine A, prednisone, and either azathioprine or mycophenolate mofetil.

2.2. Endomyocardial biopsies

Performed with the Stanford Caves technique, endomyocardial biopsies were obtained weekly for the first month, every 10 days during the second month, every 3 weeks for the subsequent 2 months, and at progressively longer intervals until a baseline schedule of every 6 months was attained. Four biopsy fragments were processed each time for histologic analysis. Histologic grades were then assigned using the International Society for Heart and Lung Transplantation (ISHLT) criteria [16]. Acute allograft rejection was defined as Grade 3A or higher. The mean number of biopsies assessed per patient was 19±7.

2.3. HLA typing

Recipients and donors were typed for HLA-A, -B, and -C by conventional serology. HLA-DR typing was performed by molecular techniques using sequence-specific primers and polymerase chain reaction (SSP-PCR).

2.4. Evaluation of anti-HLA antibodies

Obtained concomitantly with each endocardial biopsy, recipients' sera were tested for antibodies against HLA-A, -B, -C, and -DR antigens using the standard complement-dependent microlymphocytotoxicity method. All sera were screened on a multiracial HLA reference panel of 70 cells representing all known HLA Class I and II antigens. The mean number of sera tested per patient was 22±9. The assignment of antibody specificities was based on correlation coefficients ≥.70 between serum reactivity and the expression of the HLA antigen(s) on target panel cells. Sera reacting with T-, but not B-, lymphocytes were excluded from the analysis because the antibodies they contain cannot be anti-HLA. Sera were considered positive for anti-HLA antibodies when they reacted with more than 10% of the HLA reference panel.

2.5. Coronary angiography

Annual coronary angiography was performed on each patient, with at least two orthogonal views obtained of each coronary segment using standard angiographic techniques. After an initial review, the films with abnormalities were examined by a second angiographer. Angiographic coronary disease was defined by criteria described by Gao et al. [17]. Abnormalities included discrete and multiple stenoses of

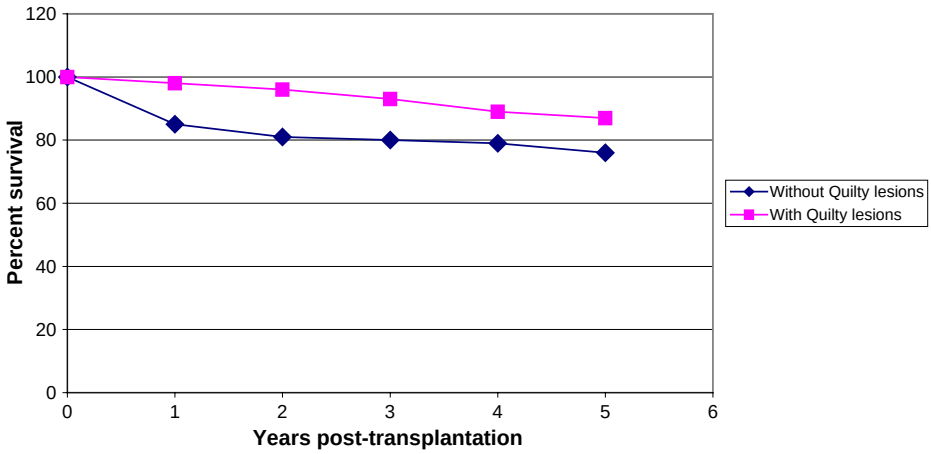

Fig. 1. Actuarial survival of heart allograft recipients with and without Quilty lesions.