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Brief communication

Soluble CD30 levels as a diagnostic marker for bronchiolitis obliterans syndrome following human lung transplantation

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Abstract

The long term survival of human lung allograft is hampered by the occurrence of chronic rejection, Bronchiolitis Obliterans Syndrome (BOS). This end-stage disease is normally diagnosed clinically by using the pulmonary function tests. This results in delay of BOS diagnosis and consequently prevents early intervention. It is generally accepted that alloimmunity plays an important role in chronic rejection of the allograft. In this study we analyzed serial serum samples from BOS+ and BOS− patients for sCD30 levels to determine the role of sCD30 to predict the onset of BOS. In contrast to BOS negative patients and normal subjects, 6 out of 9 BOS+ patients ($p<0.05$) studied had an increase in the sCD30 levels. Significantly, the rise was noted 7.57±2.63 months before the clinical diagnosis was evident. Therefore, we propose that the rise in serum sCD30 levels can be used as a marker for the detection of patients who are at risk of development of BOS.
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Keywords: Lung transplantation; sCD30; Chronic rejection; Bronchiolitis obliterans syndrome (BOS); FEV1

1. Introduction

Lung transplantation is a viable therapeutic intervention for many end-stage pulmonary diseases. The short-term survival post-transplantation has been improved with advanced surgical procedures and immunosuppressive therapy [1]. However, chronic rejection in the form of Bronchiolitis Obliterans syndrome (BOS) interrupts the long term survival of the allograft [2,3]. BOS is histologically characterized by cellular infiltration, fibrosis, collagen deposition and occlusion of small airways in the allograft [4]. The role of T cell immunity in the pathogenesis of chronic lung allograft rejection both in clinical lung transplantation and in animal models of obliterative airway diseases has been well established [5,6]. Therefore, it is reasonable to predict that sCD30 which is a marker for T cell activation may increase during rejection of the allograft. Previous studies from our laboratory have already shown that sCD30 levels are increased during chronic rejection post lung transplantation [1].

Since increased levels of sCD30 in the sera of lung transplant recipients represents T cell activation and previous data from our laboratory shows increased levels of sCD30 in the sera of BOS+ patients with the development of BOS, we hypothesized that the rise in sCD30 levels may precede the clinical evidence of BOS and therefore will assist in their clinical management. Our results strongly suggest that sCD30 levels increases several months prior to clinical evidence of BOS and therefore should assist in identifying lung transplant patients who are at high risk for developing BOS. This test therefore should help in devising strategies which will prevent or treat BOS earlier to clinical evidence of the disease.

2. Materials and methods

Eighteen Patients who received lung allografts at the Washington University Medical Center/Barnes-Jewish Hospital were studied retrospectively after

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obtaining informed consent in accordance with a protocol approved by the Institutional Review Board. The mean age of the patient at the time of transplant is 51.72±8.72 years.

Nine BOS+ and 9 BOS− patients were analyzed at an interval of 1–3 months, 1 year before the clinical diagnosis of BOS according to standard ISHLT guidelines [7]. Serum samples stored at −70 °C were analyzed in this study. 9 normal serum samples from healthy adult volunteer donors were obtained from Washington University Medical Center/Barnes-Jewish Hospital and included in this study.

2.1. sCD30 assay

The samples were analyzed for sCD30 by enzyme-linked immunoassay (ELISA) kit (Bender Med Systems, Vienna, Austria). Briefly, a 96 well plate coated with an anti-human sCD30 monoclonal antibody was used for the analysis. 25 μl of serum sample per well was incubated for 3 hours. All samples were run in duplicates. HRP-conjugated monoclonal anti-human sCD30antibody was used to bind to the sCD30 that was captured by the 1st antibody. Substrate solution reactive with HRP was then added and reading taken at 450 nm. The data was read in Units/ml (U/mL) using a sCD30 standard.

2.2. Statistical analysis:

Students *t*-test was used to determine the differences in sCD30 levels between normal and BOS+ as well as BOS− and BOS+ patients.

3. Results

The levels of sCD30 in the normal human sera were 19.81±3.44 U/mL. Serial samples from 9 patients each of BOS+ and BOS− were studied for soluble CD30 levels. The clinico-demographic distribution of these patients is shown in Table 1. There was no correlation between HLA mismatch, number of acute rejections, sex or race between the two groups. Further, there was no evidence for infection or rejection at the time of sample collection.

Table 1
Clinical and demographic characteristics of lung transplant recipients

	BOS+ $n=9$	BOS− $n=9$
Age	57.88±8.86 years	45.55±10.10 years
Sex		
Female	6	5
Male	3	4
Race		
Caucasian	9	9
African American	0	0
Original disease		
COPD	6	4
PPH	1	1
IPF	1	1
A1E	1	1
CF	0	2
HLA mismatch		
Class I	1	1
Class II	1	1
Both class I and II	0	4
Type of transplant		
Bilateral	6	8
Single	3	1
Patient survival	4	7

COPD = chronic obstructive pulmonary disease.
PPH = primary pulmonary hypertension.
IPF = interstitial pulmonary fibrosis.
A1E =alpha-1 antitrypsin deficiency emphysema.
CF = cystic fibrosis.

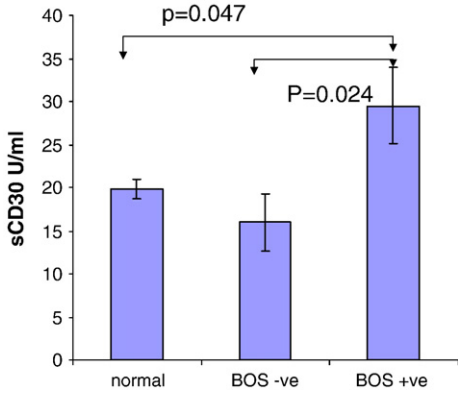

Fig. 1. sCD30 levels in serial plasma levels of normal, BOS− and BOS+ patients post transplantation. The plasma levels of sCD30 was analysed by ELISA in normal healthy individuals ($n=9$), BOS− patients ($n=9$) and BOS+ patients ($n=9$). The plasma sCD30 levels are significantly high ($p<0.05$) in 6 BOS+ Patients when compared with BOS− and normal.

sCD30 levels in BOS+ patients showed significant elevation in comparison to both normal values ($p<0.047$) and values of BOS- patients ($p<0.024$) (Fig. 1). These results are consistent with the

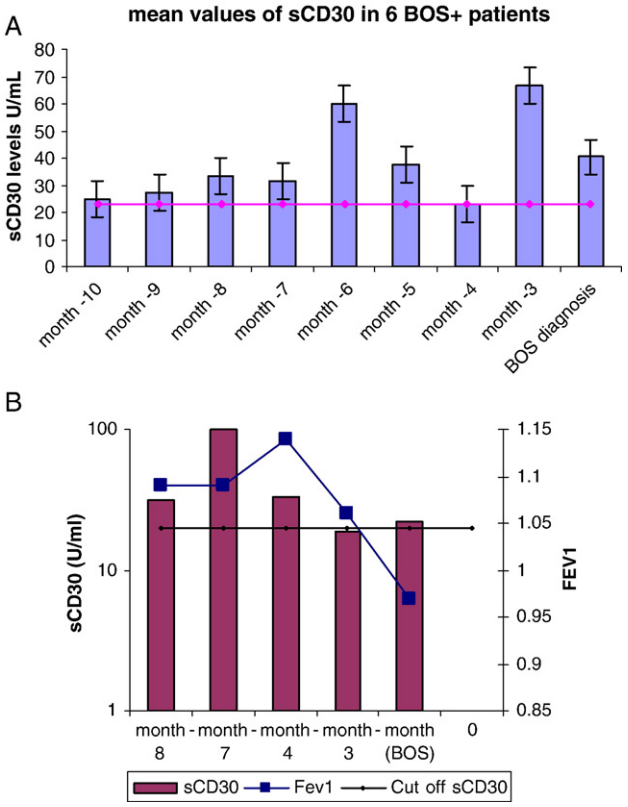

Fig. 2. Levels of soluble CD30 in serum increases prior to clinical diagnosis of BOS. Levels of soluble CD30 in serial serum samples from lung transplant recipients were measured by sCD30 ELISA before and at clinical diagnosis of BOS. A) The bars represent the mean±SD concentrations of soluble CD30 in serum at the given time point. The horizontal line represents the normal±SD concentrations observed in normal human subjects. The levels of the soluble CD30 were elevated above the mean values 5 to 8 months prior to clinical diagnosis of BOS. B) Serial CD30 measurements in serum from a single lung transplant recipient along with the FEV1 values are plotted. A significant increase in the soluble CD30 levels in the serum was observed 8 months prior to clinical diagnosis of BOS (FEV1 decline).

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