clinical investigations

Adhesion Molecules (E-Selectin and ICAM-1) in Pulmonary Allograft Rejection*

Revati Shreeniwas, MD; Larry L. Schulman, MD, FCCP; Mangala Narasimhan; Carlton C. McGregor, MD; and Charles C. Marboe, MD

Vascular endothelial cells act as antigen-presenting cells in the lung allograft and stimulate allo-reactive host lymphocytes. Activated lymphocytes and cytokines can induce expression of leukocyte-endothelial adhesion molecules that facilitate invasion of the allograft by circulating leukocytes. To define the role of endothelial HLA class II antigen and adhesion molecule expression in lung allograft rejection, we prospectively analyzed endothelial expression of HLA class II, E-selectin, and intercellular adhesion molecule-1 (ICAM-1) antigens in 52 transbronchial biopsy specimens from 24 lung allograft recipients as compared to normal control subjects. Thirty-one of 52 specimens showed histologic rejection and 8 of 24 patients developed histologic obliteratorive bronchiolitis (OB) by the end of the study period. Increased expression of HLA class II antigen was seen in 32 of 52 (62%) lung allograft specimens, but increased expression did not correlate with acute rejection or OB. In contrast, E-selectin expression was seen in 30 of 52 (58%) biopsy specimens and was associated with acute rejection (p<0.005) and with the development of OB (p<0.05). Increased expression of ICAM-1 was seen in only 18 of 52 (35%) biopsy specimens and did not correlate with acute rejection or OB. These data suggest that E-selectin expression may be a tissue marker of acute and chronic lung rejection possibly by promoting leukocyte adhesion to the allograft endothelium. The high levels of endothelial HLA class II expression may reflect long-term antigenic stimulation of the allograft even in the absence of rejection.

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Key words: E-selectin; ICAM-1; lung rejection; lung transplant; obliterative bronchiolitis

Abbreviations: CMV=cytomegalovirus; ICAM-1=intercellular adhesion molecule-1; OB=obliterrative bronchiolitis; PBS=phosphate-buffered saline solution; TBB=transbronchial biopsy

In lung transplantation as a therapeutic option for severe pulmonary disease, there is a high incidence of acute and chronic rejection that may be more frequent as compared with other organ allografts.1-3 Although acute allograft rejection episodes are common, the major cause of long-term morbidity is the development of obliterative bronchiolitis (OB), which is generally considered to represent chronic allograft rejection.4-6 Recurrent episodes of acute rejection and infection have been implicated in the pathogenesis of OB.7,8

Acute lung rejection is characterized by perivascular and mucosal inflammatory cell infiltrates.8-10 HLA class II antigens are known to be involved in the rejection response11-13 in part by vascular endothelial cells acting as antigen-presenting cells. Increased expression of class II antigens on the endothelial surface can stimulate alloreactive T lymphocytes, inducing a local inflammatory response. Activated lymphocytes and cytokines in conjunction with activated vascular endothelium in the allografted lung initiate the process of acute rejection.14 Though capillary endothelium from normal lung tissue can express low levels of HLA class II antigens,15 there are little data regarding upregulation of class II antigen expression and pulmonary allograft rejection.

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In the acute rejection process, activated alveolar macrophages and cytokine-primed T lymphocytes in conjunction with cytokines can stimulate endothelial cells, inducing expression of several adhesion molecules, such as E-selectin, and intercellular adhesion molecule-1 (ICAM-1). These adhesion molecules mediate leukocyte-endothelial interactions and may facilitate invasion of the allograft by circulating leukocytes, further amplifying the local inflammatory response.

E-selectin is a representative of a novel class of adhesion molecules called selectins. Both in vivo as well as in cell culture, this molecule is not expressed on resting endothelium. E-selectin is induced on endothelium by cytokines such as interleukin-1 and tumor necrosis factor-α and also by direct contact with primed CD4+ T cells. In endothelial cell monolayers in culture, it is rapidly induced, within 4 h following cytokine stimulation and is transiently expressed, returning to baseline after 8 h. E-selectin binds to sialated Lewis X glycoproteins on the surface of leukocytes and mediates the adhesion of polymorphonuclear leukocytes, monocytes, and some memory T cells to the surface of activated endothelium.

ICAM-1 (CD54) is a member of the immunoglobulin gene superfamily. Though constitutively expressed by endothelium, epithelium, and macrophages, its level of expression is increased by cytokine stimulation. In endothelial cell monolayers in culture, increased expression of ICAM-1 is seen beginning at 6 h after cytokine stimulation and levels stay elevated for periods up to 24 h. The ligands for ICAM-1 on the leukocyte are the integrins LFA-1 and Mac-1. Interaction between LFA-1 on T lymphocytes with ICAM-1 on antigen presenting cells has been shown to be costimulatory in activation of the T-cell receptor complex and could potentially amplify the population of activated T lymphocytes in the allograft.

In this preliminary study, we prospectively analyzed endothelial expression of HLA class II antigen expression in transbronchial biopsy specimens from lung transplant recipients to determine the level of antigenic stimulation in the allograft. We also analyzed expression of E-selectin and ICAM-1 in the same tissue in an attempt to identify tissue markers of rejection and possibly predict the subsequent development of obliterative bronchiolitis (OB).

**Materials and Methods**

**Study Group**

Twenty-four lung transplant recipients underwent 52 transbronchial biopsy (TBB) procedures from 1991 to 1993. Twenty-three of the 52 bronchoscopies were performed for clinical indications (suspicion of infection or rejection), and 29 were performed for routine surveillance which was done every 3 months in the absence of symptoms. Mean timing of biopsy with respect to date of transplant surgery was 401 (SD, 358; range, 10 to 1,815) days. Mean number of biopsy episodes subjected to immunohistochemistry was 3.2 (SD, 1.9; range, 1 to 6) biopsy episodes per patient. All patients received a standard immunosuppressive regimen of cyclosporine, azathioprine, and prednisone.

**Control Group**

Five patients who underwent TBBS for evaluation of solitary nodules or lung masses provided samples for control lung tissue. Biopsies were performed in a radiographically normal area adjacent to the lesion. All control patients were former smokers.

**Tissue Sampling**

The bronchoscopic procedure was performed under local anesthesia by the transnasal approach. TBBS were performed using alligator forceps (Olympus FB-13C; Olympus Corp; Lake Success, NY) under fluoroscopic guidance from multiple subsegments of a lower lobe in the study group, and as described in the control group. At least six and usually eight specimens were obtained. Biopsy specimens were fixed in formaldehyde solution and processed for routine histopathologic study. One or two biopsy specimens were embedded in OCT compound (10.24% w/v polyvinylchloride, 4.26% w/v polyethylene glycol, 85.5% nonreactive ingredients: Miles Inc, Elkhardt, Ind) and frozen for immunohistochemical evaluation. Rejection was graded according to the standard criteria set forth by the Lung Rejection Study Group.

**Monoclonal Antibodies**

Antibody to ICAM-1 is a mouse monoclonal antibody RR.1 and was used at a concentration of 5 μg/mL. Antibody to E-selectin is a mouse monoclonal antibody 3B7 and was used at a concentration of 5 μg/mL. Antibody to HLA class II antigen is a mouse monoclonal against the β chain of the DR complex and was used at a concentration of 5 μg/mL.

**Immunohistochemical Staining**

One or two biopsy specimens of adequate size were subjected to immunohistochemical staining at each time point. Ten-micrometer-thick frozen sections were washed with 0.3% hydrogen peroxide in methanol for 15 min to block endogenous tissue peroxidase, and blocked with 1% horse serum in phosphate-buffered saline solution (PBS) for 30 min. The sections were then incubated with the primary antibody overnight at 4°C, washed with PBS, and incubated with biotinylated horse antimouse IgG (PK 6102 Vectastain Elite Kit; Vector Labs; Burlingham, Calif). Color development was with 3,3’ diaminobenzidine 0.6 mg/mL in 0.1 mol/L Tris-saline solution buffer with 0.005% hydrogen peroxide for 10 min and counter staining was with hematoxylin. To determine background staining for every sample, tissue sections were incubated overnight with mouse IgG of the same subclass as the monoclonal antibodies in question diluted 1:10 in PBS instead of the primary antibody. In each instance, at least three to five sections from a biopsy piece were examined. One or two biopsy specimens were examined at each time point. To minimize day-to-day variability in immunohistochemical staining, positive and negative controls were run each time a batch of TBB specimens was stained.

**Scoring Systems**

Stained sections were examined in a blinded manner by one of us (C.C.M.). To quantify antigen expression, sections were scored on the basis of intensity of focal staining and the percentage of included vessels in a given field. At least five high-power fields were counted, and the mean score was taken. Based on this approach, the biopsy specimens were graded as follows: 0, absence of staining; 1, faint staining on 0 to 25% of vessels per high-power field; and
increased, intense staining on more than 25% of all vessels per high-power field.

Statistics

Positive staining was correlated to the presence of rejection by contingency analysis and significance tested by Fisher’s Exact Test. Multivariate analysis was performed using a stepwise logistic regression model. In no case did the logistic regression analysis give a different result from the univariate model.

Results

Fifty-two biopsy specimens from 24 lung transplant recipients were studied. Thirty-one of 52 (60%) allograft specimens showed evidence of histologic rejection. Eight of the 24 patients developed OB (proved by histologic study) by the end of the 15-month study period. In addition, three patients developed a clinical OB syndrome by the end of the study period. Three of the 11 patients had OB at the time of biopsy.

Expression of HLA Class II Antigen, E-Selectin, and ICAM-1 on Pulmonary Vascular Endothelium

Control Group: In lung tissue samples from the control group (n=5), there was no E-selectin seen (absent staining). In one of five cases there was low-level (basal) staining for HLA class II antigen on the capillary endothelium, increased in one of five cases, and absent in three of five. In four of five cases there was low-level (basal) of staining of ICAM-1 and absent in one of five (Table 1). This pattern of expression of HLA class II antigen, E-selectin, and ICAM-1 on uninfamed endothelium agrees with previous reports in the literature.21,22,25,30 We therefore considered increased expression of HLA class II antigen, E-selectin, and ICAM-1 in the study group to include those allograft samples that displayed greater than basal level of staining for ICAM-1 and HLA class II antigen and any level of staining for E-selectin.

Study Group: Increased expression of HLA class II antigen was seen in 32 of 52 (62%) biopsy specimens. There was no staining for HLA class II antigen in 4 of 52 (8%) allografts and basal staining in 16 of 52 (31%) (Table 1). Increased HLA class II antigen expression did not correlate with acute rejection in that increased staining was seen on vascular endothelium in 17 of 31 (55%) allografts with rejection and in 15 of 21 (71%) allografts without rejection. In addition, there was no correlation between increased HLA class II antigen expression and the development of OB. An example of increased staining for HLA class II antigen expression in an allograft with acute rejection is seen in Figure 1, top. Basal levels of staining are seen in an allograft without rejection (Fig 1, bottom).

E-selectin expression was observed in 30 of 52 (58%) lung allograft specimens (Table 1). E-selectin expression was seen in 23 of 31 rejections (74% sensitivity) and in 7 of 21 nonrejecting tissue samples (67% spec-

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<tr>
<th>Antigen</th>
<th>Grade</th>
<th>Control (%) (n=5)</th>
<th>Allograft (%) (n=52)</th>
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<tr>
<td>HLA class II</td>
<td>Absent</td>
<td>3/5 (60)</td>
<td>4/52 (8)</td>
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<tr>
<td></td>
<td>Basal</td>
<td>1/5 (20)</td>
<td>16/52 (31)</td>
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<td></td>
<td>Increased</td>
<td>1/5 (20)</td>
<td>32/52 (62)</td>
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<tr>
<td>E-selectin</td>
<td>Absent</td>
<td>5/5 (100)</td>
<td>22/52 (42)</td>
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<td></td>
<td>Increased</td>
<td>0/5 (0)</td>
<td>30/52 (58)</td>
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<td>ICAM-1</td>
<td>Absent</td>
<td>1/5 (20)</td>
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<td></td>
<td>Basal</td>
<td>4/5 (80)</td>
<td>23/52 (44)</td>
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<td></td>
<td>Increased</td>
<td>0/5 (0)</td>
<td>18/52 (35)</td>
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ificty; Table 2, panel A). The odds ratio for E-selectin expression in predicting acute rejection was 5.75 (p<0.005). There was no significant difference noted in the pattern of staining on bronchial or pulmonary vessels. There was, however, an increased number of E-selectin positive vessels near lymphoid aggregates. An example of increased expression of E-selectin on capillary endothelium in an allograft with acute rejection

![Figure 1. Immunohistochemical staining for HLA class II antigens in TBB specimens (hematoxylin counterstain, original magnification x250). Frozen sections stained with monoclonal antibody to HLA DR, color developed with horseradish peroxidase and diaminobenzidine, and intensity of staining graded as described in the text. Top: allograft lung with grade A2c rejection showing increased staining for HLA class II antigens on endothelium (arrowheads). Increased staining is also seen on alveolar epithelium and macrophages. Bottom: basal staining in an allograft with no (AO) rejection. Herein the staining is mainly on alveolar macrophages.](http://journal.publications.chestnet.org/pdffileaccess.aspx?url=/data/journals/1996/110/5/1145.png)
is shown in Figure 2, top. Absent staining for E-selectin in a nonrejecting allograft is shown in Figure 2, bottom.

In three patients, initial biopsy specimens showed E-selectin expression, but tissue taken at later time points did not show staining for E-selectin, at which time in all three instances there was no evidence of acute rejection on histologic study. In one patient, increased expression of E-selectin was seen in the face of acute rejection, but on an earlier and on a later biopsy specimen where there was no evidence of rejection, no E-selectin staining was seen. One patient with persistent rejection had increased expression of E-selectin seen at six time points; she had histologic rejection in four of six time points.

There was an association between E-selectin expression on vascular endothelium and the development of histologic OB (Table 2, panel B), with a sensitivity of 100% and a specificity of 50% (p<0.05). When clinical OB and histologic OB were considered together as a single entity (Table 2, panel C), this relationship with E-selectin was maintained (sensitivity, 91%; specificity, 61%; p<0.1). E-selectin expression was seen concomitantly with histologic OB in three of eight patients and preceded manifestations in the three patients who developed clinical OB.

Increased expression of ICAM-1 was noted in 18 of 52 (35%) biopsy specimens. Eleven of 52 (21%) allografts had no staining for ICAM-1 and basal expression was seen on 23 of 52 (44%) allografts (Table 2). When present, staining was seen in capillary endothelium, alveolar epithelium, alveolar macrophages, and lymphocytes. Tissue samples that showed staining in nonendothelial cells showed concomitant staining in endothelial cells. There was no difference in the staining of bronchial and pulmonary vessels. There was increased ICAM-1 staining adjacent to lymphocyte aggregates. Unlike E-selectin, increased endothelial expression of ICAM-1 did not correlate with acute rejection or with the development of OB. Increased endothelial staining for ICAM-1 was seen in 11 of 31 (36%) allografts with rejection, and in 7 of 21 (33%) allografts without rejection. An example of increased staining for ICAM-1 in an allograft with acute rejection is shown in Figure 3, top. An example of basal staining for ICAM-1 in allograft lung without rejection is shown in Figure 3, bottom.

### Table 2—Contingency Analyses*

<table>
<thead>
<tr>
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<th>Rejection</th>
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<tr>
<td>A. E-selectin vs rejection (p&lt;0.005)</td>
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<td>E-selectin</td>
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<td>14</td>
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<td>B. E-selectin vs histologic OB (p&lt;0.05)</td>
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<tr>
<td>E-selectin</td>
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<td>0</td>
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<td>C. E-selectin vs clinical and histologic OB (p&lt;0.1)</td>
<td>OB</td>
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<td>E-selectin</td>
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<td>D. HLA class II antigen vs ICAM-1 (p&lt;0.005)</td>
<td>ICAM-1</td>
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<td>HLA class II</td>
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*Contingency tables showing the number of biopsy specimens from lung allografts in each category. Tissue was processed and stained for HLA class II antigen, E-selectin, and ICAM-1. Positive staining and histologic rejection were determined as described in the text.
There was overlap in the pattern of expression of HLA class II antigen and ICAM-1 (Table 2, panel D), and biopsy specimens that had increased expression of ICAM-1 also had increased expression of HLA class II antigen (p<0.005; odds ratio, 9). There was no correlation between the expression of E-selectin and HLA class II antigen.

Respiratory Infection: Fifteen of the 52 bronchoscopies had cytomegalovirus (CMV) cultured from the BAL fluid (CMV infection), but none of the biopsy sections had inclusion bodies characteristic of CMV pneumonitis. There was no correlation between CMV infection and histologic rejection, nor was there any correlation between CMV infection and increased E-selectin or ICAM-1 expression or the development of OB.

There was a single instance of mild *Pneumocystis carinii* infection. Foamy alveolar exudates and organisms were seen in the section stained for adhesion molecule expression. In this instance, E-selectin expression was absent.

**Discussion**

In lung allografts, the vascular endothelium is the main interface between immunologically active recipient leukocytes and the donor lung. Donor HLA class II antigens expressed on the allograft endothelium are recognized by the T-cell receptor complex on circulating lymphocytes prior to initiation of specific immune reactions. Inducible adhesion molecules such as E-selectin and ICAM-1 may play an important role in the initiation of the acute rejection process and ultimately in the development of OB.

In our study, we analyzed transbronchial biopsy specimens from lung allografts and found that there was upregulation of class II antigen expression on vascular endothelium that was present even in the absence of rejection. However, we found that there was an association between E-selectin expression and acute rejection as well as the subsequent development of OB. We did not find an association between increased ICAM-1 expression and rejection, although there was overlap between the pattern of expression of ICAM-1 and HLA class II antigen expression.

Ligand binding to major histocompatibility complex class II molecules has been shown to activate leukocyte function-associated antigen-1 function, thereby providing a reciprocal mechanism for the stimulation of T cells by antigen presenting cells, possibly via ICAM-1. The increased HLA class II antigen expression in the allograft specimens examined suggests ongoing antigenic stimulation in the allograft even in the absence of rejection. However, although enhanced ICAM-1 expression was associated with increased expression of HLA class II antigen, this pattern of ICAM-1 expression on the allograft endothelium did not correlate with either acute rejection or OB. One reason for this may be that ICAM-1 is constitutively expressed on the surface of vascular endothelium, and immunohistochemical techniques may be too insensitive to detect subtle increases in expression of ICAM-1. Another consideration may be that ICAM-1 is shed from the surface of activated endothelium. Other adhesion molecules such as vascular cell adhesion molecule-1 (CD106) have been shown to be associated with allograft rejection in other organ systems and are also costimulatory in T-cell activation, and will be studied in pulmonary allografts to see if vascular cell adhesion molecule-1 expression rather than ICAM-1 expression is related to acute lung rejection.

E-selectin plays a central role in the cascade of leukocyte adhesion to endothelium. It is hypothesized that the initial “rolling” leukocyte adhesion with a selectin is a prerequisite for stable adhesion to vascular endothelium under conditions of flow. Our data...
show that E-selectin is expressed during acute rejection episodes. Such expression may promote leukocyte adherence to endothelium and facilitate invasion of the allograft by circulating leukocytes. Alternatively, E-selectin expression may be a result of endothelial stimulation by cytokines such as interleukin-3 released by activated T lymphocytes during acute rejection.\(^3\) In either case, expression of E-selectin in a TBB specimen is associated with acute rejection.

OB represents a significant source of morbidity and mortality in lung transplant recipients.\(^7\) Endothelial inflammation in the allograft could lead to disruption of the vascular barrier leading to infiltration of tissue by activated T lymphocytes, which can secrete mitogenic substances, including tumor necrosis factor and platelet-derived growth factor. These mediators have been implicated in the fibroproliferative and inflammatory response seen in OB.\(^3\) but a tissue marker predicting the subsequent development of OB has not been defined (to our knowledge). We correlated E-selectin expression in tissue with histologic OB to examine tissue expression in this setting. Our data show that E-selectin staining in the vascular endothelium is closely associated with the subsequent development of OB, and positive staining for E-selectin may have a potential predictive value in this context. In addition, E-selectin expression in tissue also correlated with clinical OB in three instances. However, our data show that while the sensitivity of tissue staining for E-selectin was high, the specificity and negative predictive value of E-selectin was low. This would preclude its use as a diagnostic assay for pulmonary allograft rejection or OB.

Several studies have shown that endothelial adhesion molecules are involved in kidney,\(^3\) liver,\(^3\) and cardiac\(^40,\) rejection. In concordance with these studies, our data suggest that E-selectin staining may have a predictive value in identifying an episode of acute rejection as well as separating a subset of patients at risk for developing OB. However, there are other environmental influences in the lung that could influence E-selectin expression, such as regional hypoxia\(^41\) and bacterial products such as lipopolysaccharide.\(^13\) In addition, E-selectin may be locally expressed in response to infection.\(^42\) In a small survey of nontransplant lung biopsy specimens, there was focal endothelial staining for E-selectin in the region of infection and CMV pneumonitis. In our study, there was only a single instance of mild \(P\) carinii and no cases of CMV pneumonitis.

The histologic picture of rejection and the detection of antigens in the allografted lung tissue are influenced by sampling error in TBB specimens. It should also be noted that our control group consisted of persons who had been exposed to tobacco smoke, which may have an effect on cytokine release in the lung and HLA class II antigen expression. These clinical and technical problems, which are inherent in dealing with small samples of TBB tissue, preclude broad generalizations of our data and dictate the need for further investigation in a larger study. Despite these limitations, our data suggest that E-selectin expression on endothelium in the lung allograft may be associated with the pathophysiologic condition of acute and chronic rejection.

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