The most common presentation of sulfasalazine pulmonary toxicity is simple eosinophilic pneumonia diagnosed by peripheral pulmonary infiltrates and blood eosinophilia, with 19 cases described in this manner. Several patterns of sulfasalazine-related lung damage have been described on tissue biopsy specimens, including interstitial pneumonitis, eosinophilic pneumonia, and BOOP, suggesting a variety of different mechanisms for lung damage.

Although our patient recovered rapidly after sulfasalazine therapy discontinuation, other patients have a less favorable outcome. Three fatalities have been reported, one after long-term sulfasalazine therapy and two several weeks after starting treatment with the medication.11

We conclude that sulfasalazine pulmonary toxicity can mimic limited WG clinically and radiologically. We also believe that although c-ANCA has been reported as highly sensitive and specific marker for WG, false-positives can occur in UC.

REFERENCES

Hyperacute Rejection Following Lung Transplantation*

Adaani E. Frost, MD; Cory T. Jammal; and Philip T. Cagle, MD

Although hyperacute rejection has been clinically and pathologically fully described in recipients of other solid organ transplants, to our knowledge, there have been no previous fully documented cases in recipients of lung transplants. This case of clinical hyperacute rejection is corroborated by a positive, donor-antigen-specific IgG-mediated lymphocytotoxic crossmatch (LXM), and demonstrated histopathologic, immunofluorescent, and electron microscopic features consistent with hyperacute rejection as described in other organs. Features of diffuse alveolar damage, neutrophil infiltrates, and endothelial and epithelial damage with IgG-fluorescent staining within alveolar spaces and septae were demonstrated. The management of hyperacute rejection and its outcome are reviewed. Historically a pretransplant crossmatch is not considered a routine part of lung transplantation. The outcome of this patient suggests that LXM should be performed routinely prior to lung transplant in all patients with high panel-reactive antibodies, and should be performed whenever circumstances permit.

(CHEST 1996; 110:559-62)

Key words: hyperacute rejection; lung transplant; lymphocytotoxic crossmatch

Abbreviations: LXM=lymphocytotoxic crossmatch; PRA=panel-reactive antibody

Hyperacute rejection is a well-recognized cause of immediate graft failure in recipients of transplanted hearts and kidneys. Although histological descriptions of hyperacute rejection have been described in animal lung xenografts, hyperacute rejection has not, to our knowledge, been documented and fully described histologically in recipients of lung transplants. The limitations of current preservation techniques preclude prolonged ischemic times, making pretransplant crossmatches a luxury relative to some other frequently transplanted organs, and thus the possibility of hyperacute rejection is theoretically greater. We report the first fully documented case of hyperacute rejection following lung transplantation.

CASE REPORT

A 48-year-old white woman, blood type O, had smoking-associated emphysema. Radiologic features of her emphysema were suggestive of α1-antitrypsin deficiency, but α1-antitrypsin levels were normal, and her Pi type was MS. The patient was gravida 2 para 2. Her last pregnancy was 24 years prior to transplantation. There was no history of blood transfusion. Routine pretransplant

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Reprint requests: Dr. Frost, The Methodist Hospital, SM 1237, 6550 Fannin, Houston, TX 77030
hypercapnia (PCO$_2$ was highly for the day)

Massive reperfusion and time in immunosuppressives. "Quick" and "long" included chest and initial donor almost almost.

Donor recipient was pink, frothy blood started to pour from the orifice of the double-lumen endobronchial tube serving the transplanted lung. The lumen ventilating the native lung remained patent with no change in airway pressures. Oxygenation decreased dramatically, and initially blood pressure fell. A chest radiograph revealed homogeneous dense infiltrates throughout the transplanted lung. Diuretics and a second bolus of steroids were administered without a beneficial effect on gas exchange, chest radiograph, or airway pressures.

Three hours after implantation of the donor lung, the crossmatch results were reported as positive. A donor-specific IgG HLA antibody to B8 was subsequently identified (Table 1). Plasmapheresis was initiated, and 1 g of cyclophosphamide was administered in an attempt to salvage the lung. The massive edema flooding the endobronchial tube decreased. Over the following 2 days, the patient developed thrombocytopenia and evidence of a marked consumptive coagulopathy. A bedside perfusion lung scan demonstrated only 15% blood flow to the transplanted lung—a probable explanation for the decrease in pulmonary edema. A transesophageal echocardiogram demonstrated that the venous vascular anastomoses were widely patent with minimal flow. In the face of massive requirements for coagulation factors and platelets, the patient underwent a transplant pneumonectomy on her third postoperative day and was relisted for urgent transplant.

The empty hemithorax was allowed to drain. The remaining highly compliant, emphysematous lung gradually hyperinflated despite small tidal volumes, no positive end-expiratory pressure, high peak flows, prolonged expiratory times, and permissive hypercapnia (PCO$_2$ ultimately ranged between 70 and 100 mm Hg).

**Table 1—HLA Status**

<table>
<thead>
<tr>
<th>Patient Type</th>
<th>Donor Antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>A2</td>
<td>A1</td>
</tr>
<tr>
<td>A11</td>
<td>Abblank</td>
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<tr>
<td>B35</td>
<td>B8*</td>
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<tr>
<td>DR11</td>
<td>DR15</td>
</tr>
<tr>
<td>DR13</td>
<td>DR17</td>
</tr>
</tbody>
</table>

*Donor antigen to which patient reacted.*

**Figure 1. Intra-alveolar hemorrhage (hematoxylin-eosin, original ×300).**

Oxygenation became increasingly difficult.

No donor became available, and the patient died 10 days after pneumonectomy due primarily to complications of sepsis and renal failure.

**Pathology**

At the time of transplant pneumonectomy, the explanted organ weighed 850 g and appeared markedly congested. The bronchus and vascular anastomoses were grossly unremarkable and widely patent. The parenchyma was mottled and reddish-purple.

Multiple sections of the lung revealed marked pulmonary edema and congestion with focal areas of interstitial and intra-alveolar hemorrhage and extravasation of fibrin (Fig 1). The alveolar spaces were focally filled with proteinaceous material with hyaline membranes (Fig 2) and focal mild alveolar lining cell hyperplasia. Some of the smaller muscular arteries showed separation of the endothelial cell layer from the underlying intima. Perivascular lymphocytic infiltrates characteristic of conventional acute rejection were not present. No vasculitis or fibrin deposition was identified in the vessels by routine microscopy. The alveolar septae were congested and edematous. Focal aggregates of neutrophils were identified within alveolar spaces and the interstitium (Fig 3). Neither necrosis nor infarct was identified.

Immunofluorescent studies performed on paraffin block re-

**Figure 2. Intra-alveolar fibrin and hyaline membranes (hematoxylin-eosin, original ×300).**

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Figure 3. Intra-alveolar neutrophils (hematoxylin-eosin, original x300).

vealed intense fluorescence for fibrinogen within the alveolar spaces and along the alveolar septae. Fluorescence for IgG was noted in a similar distribution. No staining was seen for IgA, IgM, C3, or albumin within the alveolar septae, although albumin was present in the alveolar space. No staining was noted in larger vessels. Although larger- vessel vasculitis is seen in cardiac transplant recipients, the deposition in the alveolar septa is consistent with the predominantly vascular localization of deposits of immunoglobulin and complement in cardiac humoral rejection.12

Electron microscopy (Fig 4) revealed fibrin deposition and evidence of acute cell injury. The endothelial cells showed a swollen cytoplasm with accumulation of lipid droplets, swollen mitochondria (some with flocculent, electron-dense material), and dilated endoplasmic reticulum. In other areas, endothelial cells were lifted off the basement membrane and the space created contained fibrin fragments. Fibrin was also present in the vessel lumens, interstitial spaces, and airspaces. Erythrocytes were present in the interstitial spaces and airspaces. Neutrophils were found attached to endothelial cells in the interstitium and airspaces, and showed a range of changes from normal to loss of granules with cytoplasmic swelling. These findings were believed to reflect severe acute lung injury affecting mainly endothelial cells with fibrin deposition and neutrophilic infiltration, and were consistent with the diagnosis of hyperacute lung rejection.

DISCUSSION

Hyperacute rejection has not been fully described previously in the lung transplant population. This probably reflects the relatively small population sample and the relatively low incidence of sensitization. Unlike cardiac, renal, and liver transplant recipients, prior operation- or illness-dicted blood transfusions are a relatively uncommon feature in this patient population. This patient had an unusually high PRA 1 year before transplant, but had no clear historic reason for her reactivity. Her last pregnancy was 24 years prior to transplantation and was followed by a tubal ligation.

We considered other potential causes for this patient’s pulmonary edema. ARDS due to unrecognized recipient factors (sepsis, volume overload) should have compromised native and transplanted lung.

We investigated the possibility that the pulmonary injury in our recipient was due to unrecognized donor abnormality or inadequate preservation. There was no evidence of abnormality at the time of donor evaluation by chest radiograph, history, or Gram’s stain of secretions. The right and left lungs were harvested and preserved en bloc by the same surgeon. The right lung was used in a remote recipient at another center. The right lung ischemic time (both cold and warm) was slightly longer than in our recipient. The recipient of the right lung from the same donor had an uneventful postoperative course and was extubated 24 h postoperatively. We concluded that donor abnormality or poor preservation would be highly unlikely to account for our patient’s outcome.

Therefore, we believe that this represents a clear example of hyperacute rejection and raises many issues. That the patient was able to survive the massive rejection at least in the short term was due to the presence of the native lung. This represents a good argument for single rather than double lung transplant in this disease, even if both lungs are fortuitously available for implantation.

Routine pretransplant crossmatching is not often possible, and therefore, few centers have historically used it. In addition, hyperacute rejection and organ failure can occur despite a negative donor-specific lymphocytotoxic crossmatch (LXM).5 Similarly, in a review of cardiac transplant recipients dying of hyperacute rejection, lymphocytic donor-specific crossmatches were infrequently positive and PRA results were only occasionally highly reactive4 calling into question the predictive value of such evaluations, at least for hyperacute rejection. In those articles, however, the positive crossmatches reviewed were not always IgG and rarely against donor-specific HLA antigens. There is a clear negative correlation between high PRAs associated with positive LXM and long-term cardiac graft survival.

This case makes a small but dramatic argument for pretransplant LXM for all patients when circumstances permit, and mandatory LXM in all patients with high PRAs, with the intention of refusing organs when circumstances preclude crossmatching or in the event of a positive crossmatch. This might have the effect of wasting some organs; however, it is unquestionably wiser to waste an organ rather than a patient. The effect of such a decision on organ availability and usage, as well as on results of lung transplantation, warrants multicenter review.

Our findings show that a histopathologic finding of acute diffuse alveolar damage is consistent with hyperacute rejection.

The final issue relates to the optimal management of hyperacute rejection. Data exist in renal and cardiac transplant on the utility of plasmapheresis combined with aggressive immunosuppression (usually cyclophosphamide) for the management of accelerated acute rejection. In the previously referenced review by Lavee et al4 all 15 patients with hyperacute cardiac rejection died. It is unlikely that the highly immunogenic lung, with its delicate interface for gas exchange, would achieve sufficient benefit from such aggressive immunotherapy to permit extubation and normal lung compliance and gas exchange—the object of lung transplantation. With the risks of cyclophosphamide-induced neutropenia and concomitant sepsis, urgent retransplantation with transplant pneumonectomy, as needed, would seem the wiser course. For those centers unwilling or unprepared to retransplant, plasmapheresis with concomitant suppression
of both B and T cells would be the only option.

**CONCLUSION**

We report the first clearly documented case of hyperacute rejection in a recipient of a lung transplant (to our knowledge). Clinical features of this hyperacute rejection included sudden onset pulmonary edema within the first hours post-reperfusion of the graft, with patent pulmonary vascular anastomoses, marked diminution of blood flow to the transplanted organ, and an IgG donor-specific HLA antibody positive crossmatch.

The histopathologic picture of hyperacute rejection is one of alveolar damage with immunofluorescent studies demonstrating IgG deposition in alveolar septae, and electron microscopy revealing endothelial damage and fibrin deposition.

Management options are limited and include urgent retransplantation and/or plasmapheresis with aggressive immunosuppression.

To avoid this disastrous consequence of transplant, donor-recipient crossmatching should be undertaken in all patients with evidence of high immunoreactivity (by PRA), and whenever time permits in those patients at less risk.

**REFERENCES**


**Diagnosis of Cardiac Sarcoidosis Aided by MRI**

Mukul Chandra, MD; Mark E. Silverman, MD; John Oshinski, PhD; and Roderic Pettigrew, MD, PhD

We describe herein a case of dilated cardiomyopathy. The diagnosis of myocardial sarcoid was suggested by abnormal findings on an MRI of the chest. This was subsequently confirmed by a histology of a subcutaneous nodule. MRI is well suited in imaging myocardial scarring associated with sarcoidosis. Its use should be considered where sarcoidosis is suspected.

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