Lung Transplantation for Pulmonary Fibrosis Associated With Hermansky-Pudlak Syndrome. A Single-center Experience

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Background. Hermansky-Pudlak syndrome (HPS) is an autosomal recessive disorder characterized by oculocutaneous albinism, platelet storage defect with resultant bleeding diathesis, and pulmonary fibrosis. The bleeding diathesis associated with HPS had long been considered a contraindication to lung transplantation; consequently, few reports of successful lung transplantation for HPS exist. Methods. In the largest case series on lung transplant for HPS, we describe the characteristics of 11 lung transplant candidates with HPS-related pulmonary fibrosis, and the management and outcomes of 7 patients who underwent lung transplantation. Results. Of the 7 patients transplanted, 30-d survival was 85.7% (6/7). Six patients had at least 2 y of follow-up available with a 1-y survival of 83.3% and a 2-y survival of 83.3% (5/6). The median age at referral was 48 y (range 29–62 y). Eight patients (72.7%) were of Puerto Rican ancestry with confirmed type 1 HPS mutation. Six out of 7 patients received prophylaxis for bleeding diathesis, with a majority receiving desmopressin; 1 patient was administered aminocaproic acid infusion, and another received 2 units of platelets before surgery. Estimated blood loss and the amount of intraoperative blood product administered was highly variable with or without prophylaxis. Median blood loss was 400 mL (range 125–750) and estimated blood products administered was 700 mL (range 490–4043). Conclusions. HPS should not be considered a contraindication for lung transplantation. Although patients with HPS seem to have an increased risk of massive hemorrhage, the risk is unpredictable. Transplant teams should prepare a preoperative plan in consultation with hematology and consider the use of prophylactic platelet transfusion and desmopressin.

INTRODUCTION

Hermansky-Pudlak syndrome (HPS) is a phenotypically diverse, autosomal recessive disorder defined by oculocutaneous albinism and platelet storage defect with resultant bleeding diathesis. Other clinical features vary based on subtype and include congenital nystagmus, neutropenia with recurrent infection, granulomatous colitis, and pulmonary fibrosis. There are 10 genetic loci associated with various subtypes of HPS.1 Pulmonary fibrosis typically occurs in HPS subtypes 1, 2, and 4.2 Symptoms manifest during the fourth and fifth decades of life with HPS subtypes 1 and 4 notable for accelerated rate of fibrosis.3 Radiographically, high-resolution computed tomography of the lung illustrates diverse fibrotic findings, including reticulonodular interstitial pattern, perihilar fibrosis, septal thickening, mosaic, ground glass opacities, and cystic changes.4 Antifibrotic therapy with pirfenidone has been largely unsuccessful with minimal, if any, benefit in slowing the rate of pulmonary function decline.5,6

The bleeding diathesis associated with HPS had long been considered a contraindication to lung transplantation until the first successful bilateral lung transplantation was reported from our center in 2005.7 Subsequently, a report of 6 lung transplant candidates, 3 of whom underwent lung transplantation, from 2 transplant centers was published more than a decade later.8 We aim to add to the existing literature by detailing the characteristics of 11 lung transplant candidates with...
HPS-related pulmonary fibrosis, and the management and outcomes of 7 patients who underwent lung transplantation at our center, which represents the world’s largest case series of lung transplantation for HPS-related pulmonary fibrosis to date. Some of our findings were presented in abstract form at the 2021 ISHLT Annual Meeting, and largely focused on the characteristics of evaluated and transplanted patients. We expand on this presentation by detailing the management and outcomes of our posttransplant cohort in this article.9

MATERIALS AND METHODS

This study was approved by the Institutional Review Board (AAAT2877). Medical records of all lung transplant candidates with a diagnosis of HPS in the Columbia University Lung Transplant Program at New York-Presbyterian Hospital were reviewed. Clinical characteristics and outcomes of these patients were obtained from the electronic health system. We divided the patients with HPS into evaluated, listed, and transplanted patients and summarized baseline characteristics using median and range. We further described the perioperative and postoperative outcomes of HPS transplant recipients using summary statistics.

RESULTS

Between 2003 and 2021, 11 patients with Hermansky-Pudlak–related pulmonary fibrosis underwent lung transplant evaluation. Of the 7 patients transplanted, 6 patients had at least 2 y of follow-up available with a 1-y survival of 83.3% and a 2-y survival of 83.3%. The baseline characteristics of patients are detailed in Table 1. The median age at referral was 48 y (range 29–62), and nearly half of the candidates were women. Eight patients (72.7%) were of Puerto Rican ancestry with confirmed type 1 HPS mutation. Four (27.2%) were former cigarette smokers. Comorbidities included obesity, obstructive sleep apnea, pulmonary hypertension, and cardiac dysfunction—including peripartum cardiomyopathy, history of congenital heart disease repaired in adolescence, and prolonged QTc interval. In the patients who eventually underwent transplantation, type II diabetes, hypertension, and history of childhood asthma were also noted; 1 patient had a history of hepatitis C successfully treated with ribavirin and interferon. Two transplanted patients also had nonobstructive coronary artery disease.

Six patients described a prior history of bleeding (Table 2). Types of bleeding history included sporadic epistaxis, menorrhagia, blood loss from lacerations, and upper gastrointestinal bleeding. Blood products were administered to 5 of these patients. In contrast, the remainder of patients without a history of bleeding tolerated earlier surgical interventions including lung biopsy and oophorectomy and did not experience prolonged bleeding. Platelet aggregometry was performed during lung transplant evaluation on 6 candidates, all of whom were eventually listed, confirmed storage pool or release defect.

Radiographic findings and pulmonary function varied among patients (Table 1). The majority of patients had chest computed tomography findings consistent with a nonspecific interstitial pneumonia pattern. Two patients did not require supplemental oxygen at the time of evaluation; the median supplemental oxygen requirement at the time of referral was

### TABLE 1

| Characteristics of lung transplant candidates | All evaluated, N=11 | Listed for transplant, N=8 | Declined listing, N=3 |
|---------------------------------------------|--------------------|---------------------------|-----------------------|
| Age, median (min–max)                      | 48 (29–62)         | 50 (29–56)                | 48 (48–64)            |
| Female sex, n (%)                          | 5 (45.4)           | 4 (50)                    | 1                     |
| HPS subtype-1, n (%)                       | 8 (72.7)           | 6 (75)                    | 2                     |
| Puerto Rican ancestry, n (%)               | 8 (72.7)           | 5 (62.5)                  | 3                     |
| Former smoker, n (%)                       | 3 (27.2)           | 2 (25)                    | 2                     |
| History of lung biopsy, n (%)              | 6 (54.5)           | 5 (62.5)                  | 1                     |
| Comorbidities, n (%)                       |                    |                           |                       |
| Noncritical CAD                            | 3 (27.2)           | 2 (25)                    | 1                     |
| Chronic kidney disease                     | 2 (18.1)           | 1 (12.5)                  | 1                     |
| Diabetes                                   | 3 (27)             | 2 (25)                    | 1                     |
| History of skin cancer                     | 1 (9.1)            | 1 (12.5)                  | 0                     |
| Obesity (BMI ≥ 30)                         | 6 (54.5)           | 5 (62.5)                  | 1                     |
| Obstructive sleep apnea                    | 4 (36.3)           | 3 (37.5)                  | 1                     |
| Prolonged QTc                              | 3 (27.2)           | 3 (37.5)                  | 0                     |
| Pulmonary hypertension                     | 9 (81.8)           | 6 (75)                    | 3                     |
| Forced vital capacity, L, median (min–max) | 1.81 (1.9–3.0)     | 1.84 (1.0–3.2)            | 1.45 (1.3–3.1)        |
| 6-min walk test distance ft, median (min–max) | 1193 (260–1513)   | 1352 (260–1513)           | 560 (420–1082)        |
| Oxygen requirement at referral, L/min, median (min–max) | 3 (0–55)         | 7.8 (0–65)                | 4 (3–4)               |
| Work capacity (Watts) by CPET, median (min–max) | 67.5 (35–100)     | 71.2 (35–100)             | 62.5 (60–65)          |
| Mean pulmonary artery pressure, median (min–max) | 27 (12–44)       | 21.5 (12–36)              | 37 (28–44)            |
| Pulmonary artery systolic pressure, median (min–max) | 44 (25–65)       | 37 (24–56)                | 60 (44–65)            |
| Mean right atrial pressure, median (min–max) | 6 (2–10)          | 5.5 (3–10)                | 6 (2–9)               |
| Cardiac index, median (min–max)            | 3.01 (1.57–4)      | 2.38 (1.57–3.4)           | 3.49 (3.01–4)         |
| Listing LAS, median (min–max)              | 37.35 (35.4–82.2)  | 37.35 (35.4–82.2)         | 37.35 (35.4–82.2)     |

*Patient on high flow nasal cannula at 55 L at time of referral.

*One patient that was denied listing and 2 patients who were listed and transplanted did not receive a CPET.

BMI, body mass index; CAD, coronary artery disease; CPET, cardiopulmonary exercise test; ft, feet; HPS, Hermansky-Pudlak syndrome; LAS, lung allocation score; n, number.
3 L/min (range 0–55 L/min). At the time of referral, the median forced vital capacity was 1.81 L (45%, range 0.94–3.31 L) and median 6-min walk test distance was 1193 feet (260–1513 feet, oxygen requirement 2–55 L/min). The mean pulmonary artery pressures ranged from 12 to 44 mm Hg, with a median of 27 mm Hg. Three patients did not complete cardiopulmonary exercise test—1 patient was hospitalized at the time of evaluation/referral, 1 patient could not complete the study because of severe deconditioning, and 1 patient was not referred for testing because cardiopulmonary exercise testing was no longer a component of our routine pretransplant evaluation.

The patients who were denied active listing for transplantation had similar oxygen requirements, 6-min walk test distances, and pulmonary function tests at the time of referral compared with those patients who were actively listed for lung transplant (Table 1). Mean pulmonary artery pressures were generally lower in listed patients; however, 2 listed patients with HPS had moderate secondary pulmonary hypertension with a mean pulmonary artery pressure of 36 and successfully underwent double lung transplant, with only one of these patients requiring postoperative extracorporeal membrane oxygenation (ECMO) support (Table 3). All 3 patients who were denied active listing had a history of clinically apparent bleeding diathesis, with 2 requiring prior blood product transfusions. Two had a history of allosensitization. One patient was deemed to be an unsuitable candidate because of multiple comorbidities, including chronic kidney disease and severe pulmonary hypertension placing him at high risk for perioperative complications. The other 2 candidates were given conditional terms for possible future listing.

### Table 2.

| Prior history of prolonged bleeding, n (%) | All evaluated, N=11 | Listed for transplant, N=8 | Declined listing, N=3 |
|------------------------------------------|---------------------|---------------------------|-----------------------|
| Prior blood product transfusion, n (%)   | 6 (54.5)            | 3 (37.5)                  | 3 (100)               |
| Allosensitization, n (%)                 | 5 (45.5)            | 3 (37.5)                  | 2 (66.7)              |
| Prior surgical intervention with bleeding, n (%) | 5 (45.5)            | 3 (37.5)                  | 2 (66.7)              |
| Prior surgical intervention—no complications, n (%) | 4 (36.4)            | 2 (25)                    | 2 (66.7)              |
| Platelet aggregometry performed, n (%)  | 6 (54.5)            | 6 (75)                    | 0                     |

### Table 3.

| Characteristics of posttransplant Hermansky-Pudlak patients |
|-------------------------------------------------------------|
| Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Prior history of bleeding | No | Yes | No | Yes | No | No |
| Prior blood transfusion | No | No | Yes | Yes | No | No |
| Anti-HLA antibodies | 36 | 15 | 21 | 22 | 36 | 27 |
| Mean PAP | 1.45 | 1.39 | 1.73 | 0.86 | 1.53 | 1.97 |
| Pretransplant FVC, L | 45.4365 | 37.6137 | 35.8093 | 35.7196 | 35.4349 | 38.0875 |
| LAS at listing | 46.922 | 37.054 | 41.7155 | 90.6216 | 90.1626 | 77.2265 |
| Type of transplant | Double | Single | Single | Single | Double | Double |
| Ischemic time, min | 330 | 216 | 245 | 247 | 390 | 240 |
| PGD grade at 48 h |
| PGD grade at 72 h | 0 | 0 | 1 | 3 | 3 | Expired |
| Estimated blood loss, mL | 200 | 125 | 400 | 500 | 200 | 500 |
| Blood products administered, mL | 595 | 490 | 1050 | 595 | 2160 | 700 |
| Types of blood products, mL | 350 pRBC, 245 pts | 490 pRBC, 1050 pRBC | 350 pRBC, 245 pts | 1400 pRBC, 490 pts, 270 FFP | 700 pRBC, 2100 pRBC, 1000 plt, 600 FFP, 113 cryo, 230 cell saver |
| Vasopressor d | 1 | 1 | 2 | 5 | 4 | 3 |
| Mechanical ventilation d | 2 | 1 | 2 | 5 | 4 | 3 |
| Posttransplant ECMO d | 0 | 0 | 0 | 2 | 3 | 3 |
| ICU d | 4 | 2 | 5 | 6 | 7 | 3 |
| Peak FVC, L | 3.56 | 2.07 | 3.08 | 1.44 | 2.49 | NA |
| Peak FEV1, L | 2.08 | 1.73 | 2.83 | 1.14 | 1.19 | NA |
| Bronchoscopies | 11 | 9 | 16 | 7 | 6 | NA |
| Transbronchial biopsies | 8 | 7 | 15 | 3 | 2 | NA |
| CLAD stage | Probable | 2 | 3 | Probable | 0 | NA |
| Vital status | Unknown | Alive | Deceased | Alive | Alive | Deceased |
| Survival time, mo | 1322 | 25 | 82 | 30 | 25 | 72 h |

*aPGD defined by ISHLT 2017 guidelines.*

*bVentilator days defined as time to extubation or free from mechanical ventilator support for 48 h.*

*Patient censored at 132 mo as patient was lost to follow-up.*

CLAD, chronic lung allocation dysfunction; cryo, cryoprecipitate; ECMO, extracorporeal membrane oxygenation; FEV1, forced expiratory volume in 1 s; FFP, fresh frozen plasma; FVC, forced vital capacity; ICU, intensive care unit; LAS, lung allocation score; NA, not available; PAP, pulmonary artery pressure; PGD, primary graft dysfunction; plt, platelet; pRBC, packed red blood cells.
lose weight and undergo additional pretransplant education. Another illustrated severe deconditioning (in a bed-bound state) and low body weight and was asked to participate in pulmonary rehabilitation and gain weight before listing. Both patients died before completing these goals.

Eight patients were listed for lung transplantation. Of the 8 actively listed patients, one was later delisted because of worsening multiorgan dysfunction with deconditioning and died shortly after. Three patients required ECMO as a bridge to transplant. Two patients had evidence of anti-HLA antibodies that were not donor specific; both were multiparous women, and one had also received blood products before transplant. Three bilateral and 4 single lung transplantations were performed with a median ischemic time of 247 min (range 216–390; Table 3). Six out of 7 patients received pretreatment for their bleeding diathesis, with a majority receiving desmopres- sin; one was administered aminocaproic acid infusion, and another received 2 units of platelets before surgery. Estimated blood loss and the amount of intraoperative blood product administered was highly variable with or without prophylaxis. The effect and benefit of prophylaxis were difficult to ascertain, as only one patient did not receive prophylaxis.

Primary graft dysfunction (PGD) at 72 h occurred in 3 out of 7 patients (42.8%) and 2 of the 3 patients had grade 3 but required veno-arterial ECMO for subsequent mixed car-

generation and ventilation. One patient had ungradeable PGD copy with transbronchial biopsies, the patient experienced lactic desmopressin. On a subsequent surveillance bronchos-

copy, the patient suffered major hemorrhage following biopsy. Three of the remaining patients have survived >24 mo posttransplant without significant disability or CLAD. Recurrent pulmonary fibrosis did not occur in any allograft, including one followed for longer than 10 y.

Of the 2 patients with pretransplant allosensitization, one had evidence of Class I anti-HLA antibodies that were not donor specific. Posttransplant, this patient developed addi-
tional nondonor-specific class I and II anti-HLA antibodies. The patient progressed to stage II CLAD, with transbronchial biopsies negative for acute cellular rejection, and was treated with azithromycin, corticosteroids, and antithymocyte globulin 21 mo posttransplant. The other patient illustrated nondonor-specific class II anti-HLA antibodies with nega-
tive crossmatch testing at time of transplant. Follow-up HLA antibody testing in this patient revealed fluctuating class I and II anti-HLA antibodies; none were donor specific. At the time of this article, lung function was consistent with prob-
able CLAD, and the patient was initiated on azithromycin 2 y posttransplant.

DISCUSSION

This case series describes the clinical characteristics of 11 lung transplant candidates with HPS-related pulmonary fibro-
sis and clinical outcomes in 7 patients who underwent lung transplantation. Our cohort was comprised predominantly type 1 patients with HPS of Puerto Rican descent. In com-
parison to other patients with pulmonary fibrosis evaluated at our center, patients with HPS were referred at a younger age, yet had similar reductions in pulmonary function and func-
tional capacity. Patients with HPS were not excluded from transplant solely based on potential bleeding diathesis, but on factors similar to those in other patients with pulmonary fibrosis undergoing transplant evaluation, such as the pres-
ence of multiple medical comorbidities and extreme func-
tional debility.

The bleeding diathesis associated with HPS did not sig-
ificantly complicate the transplant surgery in the majority of our case series. Nearly all patients received prophylactic desmopressin or other therapies to prevent bleeding. Three patients tolerated ECMO pretransplant and 2 patients post-
transplant without adverse events. One transplanted patient suffered major hemorrhage following transplantation while on ECMO, which was mainly related to a major mechanical complication of his cardiopulmonary support (dislodgement
of his aortic ECMO cannula); however, a clinically significant contribution of platelet dysfunction to his bleeding is distinctly possible. A second patient had seemingly unprovoked massive hemorrhage intraoperatively with a total of 4043 mL of blood products transfused intraoperatively. This patient received preoperative desmopressin and did not have a history of prolonged bleeding, and had tolerated a surgical lung biopsy before transplant without any bleeding complications. After transfer to the ICU, the bleeding continued for several days, resulting in hypovolemic shock, acute kidney injury with prolonged vasopressor support, prolonged mechanical ventilator and veno-venous ECMO support, and a prolonged ICU stay. The patient also required chest washout due to pleural hematomas and developed diaphragm paresis that hindered the patient’s recovery. Based on our experience, the bleeding complications are unpredictable after lung transplantation with patients with HPS and the benefit of prophylaxis is unclear.

Four out of 5 patients who underwent transbronchial biopsies with desmopressin pretreatment tolerated the procedures without incident. One patient experienced significant bleeding as a result of surveillance transbronchial biopsies requiring intubation. The patient had established normal platelet aggregometry and did not receive prophylactic desmopressin before the bronchoscopy, which led to bleeding. Before this event, the patient had previously tolerated transbronchial biopsies without prophylaxis again suggesting that risk of procedure-related major bleeding event is difficult to predict in patients with HPS.

The inherited functional platelet disorder of HPS has been historically treated with desmopressin, platelet transfusion, and activated factor VII. Although it is classically considered to place patients at low to moderate risk for surgical bleeding, a review noted that excessive bleeding was reported in 27.3% of patients with HPS who underwent surgery. Furthermore, excessive surgical bleeding occurred more frequently in those who did not receive prophylaxis. Although hematoologic evaluation with detailed bleeding history in HPS may be helpful in risk stratification for perioperative and bronchoscopic bleeding, we have successfully transplanted several HPS patients without excessive bleeding events. Consistent with other recommendations, we use platelet aggregometry to assist in confirmation of diagnosis and rely primarily on a detailed bleeding history for risk stratification, particularly a history of bleeding during or after any prior surgeries. Based on our growing experience with lung transplantation in HPS, the minimal risk associated with antihemorrhagic prophylaxis and the potential for major bleeding complications, we recommend the routine use of desmopressin/DDAVP before bronchoscopy.

As our transplant center has gained experience performing transplantation for HPS patients with pulmonary fibrosis, our practice has evolved. We recommend preoperative consultation with a hematologist to develop a comprehensive preoperative and perioperative plan in the event of major bleeding and the need for massive transfusion. Transplant centers should consider early activation of a massive transfusion protocol and a tailored transfusion plan in consultation with a hematologist. We recommend the routine use of desmopressin/DDAVP at 0.3 µg/kg intravenously and platelet transfusion immediately before the surgery given the low side effect profile.

Patients with HPS undergoing lung transplantation are at increased risk of major perioperative and postoperative bleeding that increases the risk of early operative mortality, prolonged hospital stay, and associated complications. Single lung transplantation remains a viable option for patients with HPS lung fibrosis undergoing lung transplantation and the reduced dissection and operative time may reduce the bleeding and transfusion burden. Transplant centers should remain cognizant of the increased risk of PGD and the potential need for postoperative support with ECMO.

Our case series demonstrates that lung transplantation should not be considered contraindicated in patients with HPS-related pulmonary fibrosis. Careful attention to past history of bleeding and hematoologic assessment may be helpful for risk stratification and appropriate prophylaxis. Despite the associated bleeding diathesis in HPS, our case series illustrates that these patients can tolerate ECMO as bridge to transplantation and safely undergo transplant surgery with the use of antihemorrhagic prophylaxis. Further experience with lung transplantation in HPS may help us determine how to better risk stratify and determine the optimal antihemorrhagic prophylaxis before surgery and bronchoscopic lung biopsy.

**ACKNOWLEDGMENTS**

We thank all members of the Lung Transplant Program for their selfless dedication to the care of patients with advanced lung disease.
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