

Bronchiectasis in children after renal or liver transplantation: A report of five cases

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Abstract: More effective immunosuppressive treatment in children following organ transplantation has significantly improved the survival of the grafts. Therefore, quality of life, long-term prognosis and adverse drug reactions have become more important. One of the main complications of immunosuppressive drugs is infections of the respiratory tract, but irreversible damage to the airways has not been described after renal or liver transplantation. Five children following transplantation of kidney or liver were referred to the Paediatric Pulmonology department because of chronic respiratory complaints. Pulmonary function tests and HRCT scan were performed as routine patient care. Four children with a renal transplant and one with a liver transplant showed chronic bronchitis and moderate to severe airways obstruction. HRCT showed bronchiectasis in all of them. We speculate that the immunosuppressive treatment (in) directly contributes to irreversible airway damage. We recommend including follow-up of lung function in the post-transplantation protocol and considering bronchiectasis in case of respiratory symptoms, to try preventing further damage to the lung.

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Survival of transplanted organs and prognosis in general has improved considerably in children who receive an organ transplant (1). The improved long-term survival is associated with more extensive and more potent immunosuppressive treatment. Therefore, the side effects of this treatment need more attention. The most relevant side effect of immunosuppressive agents is the increased susceptibility for (opportunistic) infections, the lung being one of the vulnerable sites.

Although not uncommon in developing countries, bronchiectasis is a rare disorder in children in the western world; no recent data are available on the incidence (2). Common causes of bronchiectasis are infections, and in developed countries, cystic fibrosis, immunodeficiencies and ciliary dyskinesia (3). Obstructive lung disease

and bronchiectasis have been reported after bone marrow transplantation, related to GVHD (4, 5). In pediatric heart transplantation, recurrent sinopulmonary infections and even bronchiectasis were described in children who had their transplant before the age of 4 yr. It was speculated that impaired maturation of antipolysaccharide responses caused by immunosuppression may be responsible for recurrent and damaging infections (6). Bronchiectasis as a radiographical feature of bronchiolitis obliterans may be seen after lung transplantation as part of chronic lung allograft rejection (7). However, no reports on bronchiectasis as a complication after liver or kidney transplantation are found in the literature. We describe four pediatric patients with a kidney transplant and one with a liver transplant, who developed chronic and progressive pulmonary symptoms, caused by bronchiectasis.

Patients

Characteristics of all five patients are summarized in Table 1.

Patient 1, a boy from a family with high socioeconomic status, received a cadaveric renal transplant at the age of

Abbreviations: BAL, broncho alveolar lavage; BALF, broncho alveolar lavage fluid; CsA, cyclosporin A; GVHD, graft-vs.-host disease; HRCT, high resolution computed tomography; MMF, mycophenolate mofetil; PEP, positive expiratory pressure; PFT, pulmonary function tests.

Table 1. Characteristics of five children who had kidney or liver transplantation and subsequently developed bronchiectasis

	Male, 17 yr	Male, 12 yr	Male, 11 yr	Male, 7 yr	Female, 11 yr
Age at TX (yr)	12	10 (second TX)	7	3	0.8
Age at respiratory symptoms (yr)	15	11	8	5	7
Primary diagnosis	Renal dysplasia	Asphyxia	Mesangioproliferative glomerulonephritis	Congenital nephrotic syndrome	Biliary atresia
Transplanted organ	Kidney	Kidney	Kidney	Kidney	Liver
Creatinine ($\mu\text{mol/L}$)	250	85	65	60	
Immunosuppression	P, CsA, MMF	P, CsA, MMF	P, CsA*, MMF	P, CsA*, MMF	P, CsA, MMF
Sputum cultures	<i>Pseudomonas aeruginosa</i> <i>Streptococcus pneumoniae</i>	<i>Haemophilus influenzae</i>	<i>Haemophilus influenzae</i> <i>Haemophilus parainfluenzae</i> <i>Stenotrophomonas maltophilia</i> <i>Flavobacterium</i> species <i>Pseudomonas aeruginosa</i>	<i>Haemophilus influenzae</i>	<i>Haemophilus parainfluenzae</i>
FVC (% pred) **	69/91	67/100	61/92	66/101	94/88
FEV1 (% pred)**	59/80	56/103	51/71	72/101	88/81
FEV1/FVC (%)**	71/73	69/86	70/64	93/84	80/79
MEF 25 (% pred)**	11/28	17/68	13/23	28/43	45/36
Location bronchiectasis	Both lower lobes, right upper lobe	Left lower lobe	Generalized	Right middle lobe, lingula	Both lower lobes, lingula

TX, transplant; P, prednisone; CsA, cyclosporin A; MMF, mycophenolate mofetil; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; MEF 25, maximal expiratory flow at 25% of vital capacity.

*prescribed during the first half year after transplantation, **at referral to the Department of Pediatric Respiratory Medicine/maximal value after treatment.

12.5 yr because of congenital renal dysplasia with vesico-ureteral reflux. Chest X-ray at transplantation was normal. Immunosuppressive prophylaxis consisted of corticosteroids, CsA and MMF; no induction treatment was used. Three months after transplantation, the CsA levels were between 75 and 125 mg/L, the MMF levels between 1.3 and 7 mg/L. Prednisone dose was 7.5 mg, once daily (0.16 mg/kg). Acute rejection episodes did not occur. Three months after transplantation, he had chickenpox, for which he was treated with intravenous acyclovir. One year after transplantation, he was treated for a *Bordetella pertussis* infection (confirmed serologically), after which he recovered completely. Eighteen months later, he was referred to the pediatric pulmonologist because of persistent productive coughing. He did not have any prior primary pulmonary complaints. PFT revealed severe airway obstruction (Table 1). Sputum cultures grew *Pseudomonas aeruginosa* and HRCT scan showed bronchiectasis in both lower lobes (Fig. 1). He was treated with ciprofloxacin, nebulized tobramycin and DNase, and PEP by mask. Despite this treatment, he had a severe exacerbation of symptoms at the age of 16.5 years, when BALF showed *Streptococcus pneumoniae* and rhinovirus. No other pathogens were found. He was treated with intravenous cefuroxime and recovered only slowly and incompletely. Cystic fibrosis and primary ciliary dyskinesia were ruled out by appropriate tests. It was hypothesized that the bronchiectasis could be explained by the proven *B. pertussis* infection.

However, within 18 months of this referral, four other patients on immunosuppressive treatment following kidney (3) or liver (1) transplantation were referred because of similar symptoms. They all presented with chronic productive cough without fever, dyspnea and with diminished exercise tolerance. The initial immunosuppressive therapy was the same for all four kidney transplant patients and consisted of corticosteroids, CsA and MMF. No induction therapy was administered. From 6 months post-transplant,

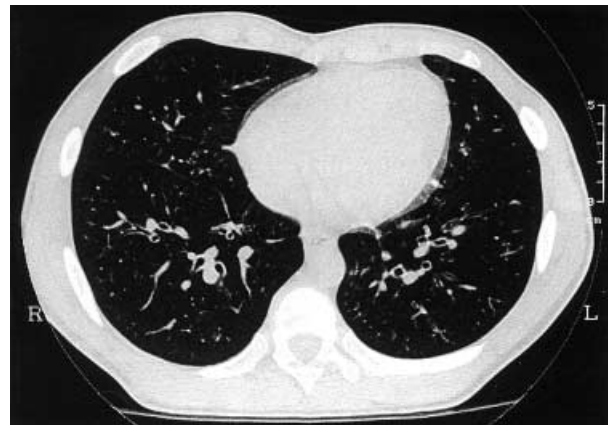


Fig. 1. Slide of HRCT scan, showing bronchiectasis in patient 1.

the dosage of prednisolone was 5 mg/m²/day, and MMF 600 mg/m² b.i.d.; CsA dosage was titrated to a serum concentration of 100 mg/L. In two cases (patients 3 and 4), cyclosporin was discontinued at 6 months post-transplantation in the framework of a study protocol. In patient 5, CsA was discontinued and replaced by MMF because of minimal impairment of renal function. Chest X-rays on the day of transplantation were normal in all patients. Kidney transplant patients 1, 2 and 4 received antibiotics continuously for urinary tract infection prophylaxis. The diagnostic workup, similar to patient 1, did not reveal any indication for the common causes of bronchiectasis. Patients 2 and 3 are from families with low income; the families of patients 4 and 5 are prosperous.

Patient 2 had a renal transplant at the age of 2 yr because of renal failure after perinatal asphyxia. Chronic pyelone-

phritis led to failure of this graft at the age of 8 yr, after which he was treated with peritoneal dialysis. A second transplant with a kidney from his mother was performed at the age of 9 yr. As a toddler, the boy had recurrent ear, nose and throat infections, treated with adenotonsillectomy and bilateral ventilation tubes. Chest X-ray before transplantation was unremarkable. One year after his second transplant he presented with chronic productive cough and recurrent pansinusitis. Sputum culture revealed *Haemophilus influenzae* and the chest X-ray showed increased markings. On HRCT, bronchiectasis in the left lower lobe was detected. The boy was treated with amoxicillin, DNase and PEP mask and only recovered slowly, partly because of low adherence to treatment.

A 11-yr-old boy was the third referral to our pediatric pulmonology department. He received a kidney transplant from his father at the age of 7 yr and presented with respiratory symptoms 1 yr later. His primary diagnosis was mesangioproliferative glomerulonephritis. At first presentation, severe airway obstruction was present. Sputum cultures revealed *H. influenzae*. He was treated with antibiotics based on sensitivity tests. However, his lung function did not recover and HRCT scan showed bronchiectasis. DNase was added and he was treated with a PEP mask. When he presented with an exacerbation of his complaints, a bronchoscopy was performed and BALF grew *H. influenzae*, and no opportunistic microorganisms. At 3 yr after referral, sputum was colonized with *Pseudomonas aeruginosa*, and the patient was treated with ciprofloxacin and tobramycin inhalations. *Stenotrophomonas* infection was treated with cotrimoxazole. At the last follow-up visit, he had a productive cough and crackles bilaterally on chest auscultation. His pulmonary function tests improved significantly, but did not recover fully.

The fourth patient was a 3-yr-old, who received a cadaveric kidney transplant for congenital nephrotic syndrome. Two years later, he presented with chronic productive cough; sputum culture grew *H. influenzae* and he was treated with amoxicillin/clavulanic acid. As symptoms persisted, antibiotics were switched to clarithromycin and nebulizations with DNase and PEP therapy were started. Only after an intravenous course of cefuroxime, did his pulmonary function normalize and symptoms disappeared. No other pathogens besides *H. influenzae* were cultured. Bronchoscopy and BAL were not performed.

A 11-yr-old girl was the fifth patient who developed bronchiectasis after a solid organ transplantation. She received a cadaveric donor liver because of biliary atresia when she was 10 months old. Initial immunosuppression consisted of prednisone, azathioprine and CsA. CsA was discontinued after 1 yr, but restarted at the age of 6 yr because of signs of rejection on a liver biopsy. Five years after transplantation, azathioprine was replaced with MMF. CsA was withdrawn after introduction of MMF. At the age of 9 yr, she presented with chronic cough and diminished exercise tolerance for 1.5 yr. Immunosuppression at that time consisted of MMF 500 mg b.i.d. and prednisone 12 mg on alternate days. MMF levels varied between 3.5 and 9.6 mg/L (4.0 mg/L at presentation). Immunoglobulins were within normal limits. Her pulmonary history was previously unremarkable, however, she had had recurrent ear, nose, and throat infections. Except for one antibiotic course, the patient did not receive any antibiotic treatment. In her sputum, *Haemophilus parainfluenzae* was cultured. The girl was treated with cotrimoxazole, DNase and PEP therapy. However, pulmonary function tests have not improved.

Discussion

This is the first report of bronchiectasis in children who underwent a kidney or liver transplantation. Airway infection with bronchial obstruction and retention of mucus are major factors in the pathogenesis of bronchiectasis (3). Well-known causes of bronchiectasis in children in the western world are cystic fibrosis, mucociliary clearance defects, recurrent aspiration and immunodeficiencies, but in up to 50% of patients with bronchiectasis, no cause is identified (8). In our current pediatric renal transplant population, we diagnosed bronchiectasis in four of 38 patients. Bronchiectasis has been reported after pediatric bone marrow, heart, heart-lung and lung transplantation (4–7). In bone marrow transplantation, bronchiectasis is associated with chronic GVHD (4). In adult bone marrow recipients, it was shown that ciliary beat frequency was severely reduced in those patients who developed bronchiolitis obliterans and chronic GVHD (9). Impaired maturation of anti-polysaccharide responses caused by immunosuppression may be responsible for recurrent infections leading to bronchiectasis, especially in children transplanted before the age of 4 yr, as was shown for pediatric heart transplant recipients (6).

Several mechanisms may account for the development of bronchiectasis in our patients. First, all patients have secondary immunodeficiency caused by immunosuppressive medication, which may have facilitated pulmonary infections. Besides, pulmonary infections may have been masked by the prophylactic antibiotic treatment these patients received to prevent urinary tract infections. We cannot exclude that the patients had opportunistic infections, but could not identify such microorganisms despite bronchoscopy with lavage in two patients. Patient 1 had had a serologically proven *B. pertussis* infection, a well-known but rare cause of bronchiectasis, 18 months before he presented with bronchiectasis.

As we did not feel lung biopsy would provide us with useful information or would change our treatment, lung biopsies were not performed in our patients.

An alternative hypothesis is that the immunosuppressive drugs were a causative factor. All patients used one shared immunosuppressive drug, MMF, a relatively new drug in our immunosuppressive regime, for a prolonged period of time. Pulmonary side effects of MMF have been described: coughing, bronchitis and shortness of breath. Two case reports document

acute respiratory failure with pulmonary fibrosis and pneumonitis most likely caused by MMF, but bronchiectasis is not known as an adverse effect of MMF (10, 11). *In vivo*, MMF severely depresses humoral immunity making patients more susceptible to infection (12). Before the introduction of MMF in our standard immunosuppression regime in 1997, we had not seen any patient with bronchiectasis after transplantation. We speculate that MMF may play a role in the development of bronchiectasis in our patients by facilitating or masking pulmonary infections more than other immunosuppressive drugs or by exerting a direct effect on the airway wall. Obviously, the exact mechanism remains to be elucidated and requires further research.

Therapeutic levels of CsA are not associated with serious pulmonary toxicity.

In our patients, no data on pre-transplant PFT were available nor did we have any pre-transplant CT scans. Diminished lung volumes have been described in chronic renal failure, but most transplanted patients showed normal spirometry (13, 14). We cannot exclude pre-transplant abnormalities in PFT in our patients, but there were no respiratory symptoms prior to transplantation.

As prognosis and survival of children after organ transplantation increased dramatically in the past decade, complications of the post-transplant therapy have become more and more important and may co-determine long-term prognosis (1). Once structural abnormalities of the bronchi are present, even control of infection and inflammation may not be sufficient to arrest the progression to disable irreversible airway obstruction.

In the presence of respiratory symptoms, bronchiectasis should be considered and, as spirometry is not sensitive enough in detecting early structural lung damage, HRCT should be performed (2, 15). However, we recommend including follow-up of lung function in the post-transplantation protocol as well, as peripheral airway obstruction may be a sign of bronchiectasis. By aggressively treating children with bronchiectasis who are receiving immunosup-

pressive drugs, further damage to the lung may be prevented and quality of life and long-term prognosis improved.

References

1. ELSHIHABI I, CHAVERS B, DONALDSON L, EMMETT L, TEJANI A. Continuing improvement in cadaver donor graft survival in North American children: The 1998 annual report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). *Pediatr Transplant* 2000; 4: 235–246.
2. CHANG AB, MASEL JP, BOYCE NC, WHEATON G, TORZILLO PJ. Non-CF bronchiectasis: clinical and HRCT evaluation. *Ped Pulmonol* 2003; 35: 477–483.
3. BROWN MA, LEMEN RJ. Bronchiectasis. In: CHERNICK V, BOAT TF, eds. *Kendig's Disorders of the Respiratory Tract in Children*. Philadelphia: W.B. Saunders Company, 1998: pp. 538–552.
4. MOREHEAD RS. Bronchiectasis in bone marrow transplantation. *Thorax* 1997; 52: 392–393.
5. SARGENT MA, CAIRNS RA, MURDOCH MJ, NADEL HR, WENSLEY D, SCHULTZ KR. Obstructive lung disease in children after allogeneic bone marrow transplantation: evaluation with high-resolution CT. *Am J Roentgenol* 1995; 164: 693–696.
6. GENNERY AR, CANT AJ, SPICKETT GP, et al. Effect of immunosuppression after cardiac transplantation in early childhood on antibody response to polysaccharide antigen. *Lancet* 1998; 351: 1778–1781.
7. LOUBEYRE P, REVEL D, DELIGNETTE A, et al. Bronchiectasis detected with thin-section CT as a predictor of chronic lung allograft rejection. *Radiology* 1995; 194: 213–216.
8. PASTEUR MC, HELLIWELL SM, HOUGHTON SJ, et al. An investigation into causative factors in patients with bronchiectasis. *Am J Respir Crit Care Med* 2000; 162: 1277–1284.
9. AU WY, HO JC, LIE AK, et al. Post-transplant complications: Respiratory ciliary function in bone marrow recipients. *Bone Marrow Transplant* 2001; 27: 1147–1151.
10. GROSS DC, SASAKI TM, BUICK MK, LIGHT JA. Acute respiratory failure and pulmonary fibrosis secondary to administration of mycophenolate mofetil. *Transplantation* 1997; 64: 1607–1609.
11. MORRISSEY P, GOHH R, MADRAS P, MONACO AP. Pulmonary fibrosis secondary to administration of mycophenolate mofetil. *Transplantation* 1998; 65: 1414.
12. RENTENAAR RJ, VAN DIEPEN FN, MEIJER RT, et al. Immune responsiveness in renal transplant recipients: mycophenolic acid severely depresses humoral immunity *in vivo*. *Kidney Internat* 2002; 62: 319–328.
13. PAUL K, MAVRIDIS G, BONZEL KE, SCHÄRER K. Pulmonary function in children with chronic renal failure. *Eur J Pediatr* 1991; 150: 808–812.
14. KALENDER B, ERK M, PEKPAK MA, et al. The effect of renal transplantation on pulmonary function. *Nephron* 2002; 90: 72–77.
15. TIDDENS HA. Detecting early structural lung damage in cystic fibrosis. *Pediatr Pulmonol* 2002; 34: 228–231.