Case report

New-onset asthma in a bilateral lung transplant patient

Daniel Benjamin Fyenbo , Kristine Bruun Degn, Johannes Martin Schmid, Elisabeth Bendstrup

Department of Respiratory Diseases and Allergy, Aarhus University Hospital, Aarhus, Denmark

Correspondence to

Dr Daniel Benjamin Fyenbo; daniel.fyenbo@gmail.com

Accepted 25 September 2019

SUMMARY

We present a case of new-onset asthma in a 35-year-old man who had undergone bilateral lung transplantation 11 years before due to idiopathic bronchiectasis and pulmonary hypertension. He presented with recurrent episodes of breathlessness, wheezing and coughing. Spirometry demonstrated severe airway obstruction. After treatment with systemic and inhaled corticosteroids and long-acting bronchodilators as well as short-acting beta-agonists as needed, his symptoms resolved and his spirometry normalised. A bronchial mannitol challenge test showed significant airway hyperresponsiveness and is thus consistent for a diagnosis of asthma. To our best knowledge, this is the first case of late new-onset asthma in a lung transplant recipient.

BACKGROUND

New-onset asthma has never been described after bilateral lung transplantation. This case presents the unexpected development of new-onset asthma, 11 years post-transplant. Asthma is normally considered an airway disease that cannot develop after the denervation that takes place during lung transplant surgery.

Previously, it has been reported that asthmatic recipients of normal lungs do not suffer from asthma after transplant.¹ In contrast, it also has been reported that asthmatic donor lungs have transferred the disease to non-asthmatic recipients who after a very short period complained of asthmatic symptoms.¹ We here present a case of what has been considered as ‘the impossible’, that is, asthma developing in a lung transplant patient 11 years post-transplant.

CASE PRESENTATION

A 35-year-old male lung transplant patient was evaluated acutely at the out-patient transplant clinic in July 2018 and February 2019 due to similar symptoms including breathlessness, wheezing and coughing.

The patient had undergone bilateral lung transplantation for idiopathic bronchiectasis and pulmonary hypertension 11 years before. His immunosuppressive regimen included cyclosporine, everolimus and low-dose systemic corticosteroid.

He had no history of asthma, asthma-related symptoms or allergy in childhood or before lung transplantation. However, he had a family history of asthma and allergy (half-sister and maternal

aunt). Over the preceding 5 years, he had suffered from hay-fever symptoms with runny nose, itchy eyes and intermittent wheezing during late spring season. Despite low-dose corticosteroid treatment (prednisolone 5 mg once a day), his blood tests had since 2015 shown intermittent elevated eosinophils up to $0.83 \times 10^9/L$ (normal value is $<0.30 \times 10^9/L$). His spirometry readings, that is, forced expiratory volume in one second (FEV_1) and forced vital capacity, had been stable and only moderately reduced at the standard transplant follow-up visits (figure 1).

INVESTIGATIONS

At the time of presentation with acute respiratory symptoms in July 2018 and February 2019, his vital signs were normal. His physical examination was unremarkable with the exception of severe expiratory rhonchi and prolonged expiration on lung auscultation. Routine blood test showed slightly elevated C reactive protein at admission in July 2018, but normal in February 2019 (table 1). Chest radiographs were without infiltrates. Spirometry indicated severe airway obstruction (figure 1).

During the admission in July 2018, an IgE test for the most common inhalant allergens against birch, grass, mugwort, house dust mites, cat, dog and horse dander were under detection level but supplementary tests showed elevated specific IgE serum levels for *Penicillium chrysogenum*, *Cladosporium herbarum*, *Aspergillus fumigatus* and *Alternaria alternata*. High-resolution CT (HRCT) was without any infiltrates and indicated neither air trapping nor bronchiectasis. A bronchoscopy including transbronchial biopsies (TBB) and bronchoalveolar lavage was without signs of acute rejection, infection or other inflammatory conditions.

During the admission in February 2019, a CT of thorax was repeated without any new findings.

Two and a half months after the admission in February 2019 a bronchial challenge test with mannitol dry powder was performed to ‘rule in’ asthma. The result showed a significant decrease in FEV_1 ($>15\%$) after inhalation of a cumulated dose of mannitol (PD15) of 396 mg (figure 2).

DIFFERENTIAL DIAGNOSIS

This 35-year-old patient who had undergone bilateral lung transplantation 11 years ago clearly presented symptoms, signs and investigations suggestive of asthma.

© BMJ Publishing Group Limited 2019. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Fyenbo DB, Degn KB, Schmid JM, et al. *BMJ Case Rep* 2019;**12**:e231654. doi:10.1136/bcr-2019-231654

Figure 1 Graphical representation of forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) at post-transplant standard follow-up visits and during both hospital admissions. First admission was from 4 July 2018 to 10 July 2018 and second admission from 26 February 2019 to 8 March 2019. Blue and red arrows indicate the day of admission and discharging, respectively.

The most important differential diagnosis was acute rejection of the lungs. Acute rejection would not usually manifest with expiratory rhonchi and obstructive pulmonary function decline as observed in this patient and was ruled out by TBB histopathology without any signs of rejection and HRCT without any ground glass opacities. Furthermore, if rejection had been present, we would not have expected the patient to improve on asthma exacerbation treatment including only moderate doses of systemic corticosteroid.

Another important differential diagnosis is chronic lung allograft dysfunction with bronchiolitis obliterans syndrome (BOS), but it does not manifest with acute wheezing, as in this case. The key feature of BOS is the development of irreversible airway obstruction with declining FEV₁ that does not respond to bronchodilators.² Contrary to BOS, asthma is characterised by reversible, intermittent airway obstruction, like in our patient.

Another important differential diagnosis is mucous plugging and bronchial stenosis, which may present with wheezing and breathlessness. However, the bronchoscopy did not show signs of these conditions. Finally, the CT of the thorax ruled out pulmonary embolism as a possible differential diagnosis to increasing dyspnea and reduced pulmonary function.

The most likely diagnosis in our case is asthma based on reversible airway obstruction, a positive response to a bronchial mannitol challenge test, hay-fever, blood eosinophilia and IgE-mediated allergic rhinoconjunctivitis, and despite the fact that this has been considered impossible in lung transplant patients.

Table 1 Routine blood test at admission in July 2018 and February 2019

	July 2018	February 2019	Normal values
C reactive protein (mg/L)	17.3	5.1	<8.0
Leucocytes (x 10 ⁹ /L)	12.3	7.2	3.5–10.0
Eosinophiles (x 10 ⁹ /L)	0.68	0.12	<0.5

Figure 2 Graphical representation of the bronchial mannitol challenge test with significantly reduction in forced expiratory volume in one second (FEV₁) after cumulated dose of mannitol of 396 mg.

TREATMENT

Admission in July 2018:

1. Systemic corticosteroid for 10 days (prednisolone 37.5 mg once a day).
2. Inhaled short-acting bronchodilators (fenoterol 1.25 mg and ipratropium bromide 0.5 mg four times a day).
3. Combined inhaled high-dose corticosteroids and long-acting bronchodilators (beclomethasone 400 µg and formoterol 12 µg two times per day) initiated at admission.

Admission in February 2019:

1. Systemic corticosteroid for 10 days (prednisolone 37.5 mg once a day).
2. Inhaled high-dose corticosteroids (ciclesonide 640 µg two times per day).
3. Inhaled short-acting bronchodilators (fenoterol 1.25 mg and ipratropium bromide 0.5 mg four times a day) initially.
4. Inhaled long-acting bronchodilators (initially formoterol 24 µg two times per day, during admission switched to 5 µg olodaterol with 5 µg tiotropium once a day).

OUTCOME AND FOLLOW-UP

All symptoms resolved completely and lung auscultation normalised on treatment with systemic and inhaled corticosteroid and long-acting bronchodilators as well as short-acting bronchodilators as needed. The spirometry improved significantly during admission with an increase of FEV₁ by 240 mL from 1.64 L at admission (15%) (figure 1) and was normalised after another 8 weeks. Due to oral candidiasis, the patient discontinued the treatment on his own accord in January 2019. A few weeks later, he was readmitted with similar symptoms as in July 2018. At the second admission, FEV₁ was 1.25 L and once again asthma exacerbation therapy was started. At discharge 10 days later, symptoms had completely resolved and lung auscultation was normal. Spirometry had improved significantly to FEV₁ 2.34 L, an improvement of 1090 mL (87%) (figure 1).

A bronchial mannitol challenge test 2.5 months after admission showed significant airway hyperresponsiveness, thus consistent with a diagnosis of asthma.

DISCUSSION

New-onset asthma in a bilateral lung transplant patient is normally considered impossible. Our patient presented with a combination of classical asthma symptoms, supported by physical examination findings, laboratory abnormalities, spirometry readings and provocation test, all indicating asthma.³ To our best knowledge, no similar case has yet been published.

Bronchial challenge test with mannitol is a very useful test but is associated with a certain amount of morbidity. A study by Brannan *et al* found that about 50% of subjects tested with bronchial mannitol challenge test reported potential adverse effects, and described these as being severe in about 5%.⁴ However, to

our knowledge, the test is not related to mortality. According to guidelines, a bronchial challenge test to confirm the diagnosis is not needed.³ The specificity of bronchial mannitol challenge test is reported up to 98%, thus only very few false-positive cases.⁵ In this very challenging and atypical case, positive bronchial challenge tests rules in asthma and makes the diagnosis unquestionable, which we found necessary, despite potential adverse events. The test was performed with continuous observation and in case of adverse events instant treatment was possible. The patient's inhaled long-acting bronchodilator was paused during test day, while his inhaled high-dose corticosteroid was continued. If the latter were paused too, the positive test result would probably have been achieved with a less cumulated mannitol dose as a sign of stronger positive result.

The transferral of asthma by donation of asthmatic lungs to a non-asthmatic recipient has earlier been reported by Corris *et al*, but signs and symptoms of asthma occurred already a few weeks after the transplantation without any other cases developing asthma during a 3-year follow-up period.¹ Ghosh *et al* also described a case of a non-asthmatic patient who received lungs from an asthmatic donor and developed acute airway obstruction shortly after the transplantation.⁶ A study by Oto *et al* questioned the use of asthmatic donors for lung transplantation and did not report any 'transmission' of asthma with the donor lungs during 12 years of follow-up.⁷ They only reported immediate post-transplant respiratory symptoms possibly related to asthma in those who received lungs from a donor with fatal asthma.

Immunosuppressive therapy to prevent rejection after lung transplantation could possibly be the reason why we have not seen any new-onset asthma in post-transplanted patients. This supports the aetiology of asthma as an inflammatory disease.⁸

Patient's perspective

When I recently was diagnosed with asthma, I was very happy that it was not worse. I was wondering if my symptoms were a sign of rejection, so when I was told it was asthma, I only felt happiness. After I received anti-asthmatic treatment my symptoms completely disappeared and I do not feel sick anymore. I do not have any problem with coughing or dyspnea. The only disadvantage about the diagnosis and treatment is the need of inhaled corticosteroids, which predisposes to oral candidiasis, and I do not like that. I think my asthma is under good control now. I do not have any symptoms and my latest spirometry was back to what it has been earlier.

Learning points

- Asthma must be considered in all patients complaining of recurrent wheezing, coughing and breathlessness, despite a history of bilateral lung transplantation.
- Lung transplantation does not exclude development of new-onset of asthma.
- The exact mechanism of the development of asthma in lung transplant patients is unclear.

However, in our case, immunosuppression did not prevent the development of asthma and supports asthma as a multifactor disease.

The aetiology of asthma includes both genetic and environmental factors and asthma has been considered a 'local' disease, since its development never has been seen in non-asthmatic patients receiving non-asthmatic lungs. Our case questions this notion and supports the importance of environmental factors in the aetiology of the disease. The most common environmental cause in new-onset asthma in adulthood is occupational exposure to sensitising agents or irritants or specific drug treatment.⁹ Our patient had no history of commonly asthma-associated occupations and exposures and his drug list did not raise suspicion of drug-induced asthma.

The vagal denervation in patients undergoing lung transplantation may result in supranormal flow rates.¹⁰ There is, to our knowledge, no evidence to support that vagotomy produces lasting objective benefit in asthmatic patients as well as there is no reported effect on diurnal variability.¹ Although anticholinergic treatment may reduce the characteristic variation in peak flow in asthmatic patients,¹¹ the observation in our case showed that vagotomy did not prevented the development of asthma.

The present case challenges the notion of asthma considered as a local disease, and supports asthma as a multifactor disease.

Contributors All authors (DBF, KBD, JMS and EB) designed the work of the case report. KBD, JMS and EB collected data, while DBF contributed with analysis and interpretation of data (with supervision from KBD, JMS and EB). DBF drafted the case report and KBD, JMS and EB critically revised the draft. All authors are in agreement with the content of this final version of the case report.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Daniel Benjamin Fyenbo <http://orcid.org/0000-0001-5898-1743>

REFERENCES

- 1 Corris PA, Dark JH. Aetiology of asthma: lessons from lung transplantation. *Lancet* 1993;341:1369–71.
- 2 Hayes D. A review of bronchiolitis obliterans syndrome and therapeutic strategies. *J Cardiothorac Surg* 2011;6:92.
- 3 Global Initiative for Asthma. Global strategy for asthma management and prevention, 2018. Available: <https://ginasthma.org/wp-content/uploads/2018/04/wms-GINA-2018-report-V1.3-002.pdf>
- 4 Brannan JD, Anderson SD, Perry CP, *et al*. The safety and efficacy of inhaled dry powder mannitol as a bronchial provocation test for airway hyperresponsiveness: a phase 3 comparison study with hypertonic (4.5%) saline. *Respir Res* 2005;6:144.
- 5 Porsbjerg C, Sverrild A, Backer V. The usefulness of the mannitol challenge test for asthma. *Expert Rev Respir Med* 2013;7:655–63.
- 6 Ghosh S, Latimer R, Tew D. Airway obstruction in lungs obtained from an asthmatic donor complicating heart-lung transplantation. *Anesthesiology* 1990;73:1270–1.
- 7 Oto T, Griffiths A, Lewvey B, *et al*. Donor history of asthma is not a contraindication to lung transplantation: 12-year single-center experience. *J Heart Lung Transplant* 2004;23:309–16.
- 8 Kudo M, Ishigatsubo Y, Aoki I. Pathology of asthma. *Front Microbiol* 2013;4:263.
- 9 Subbarao P, Mandhane PJ, Sears MR. Asthma: epidemiology, etiology and risk factors. *CMAJ* 2009;181:E181–90.
- 10 Estenne M, Ketelbant P, Primo G, *et al*. Human heart-lung transplantation: physiologic aspects of the denervated lung and post-transplant obliterative bronchiolitis. *Am Rev Respir Dis* 1987;135:976–8.
- 11 Morrison JF, Pearson SB, Dean HG. Parasympathetic nervous system in nocturnal asthma. *Br Med J* 1988;296:1427–9.

Copyright 2019 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <https://www.bmj.com/company/products-services/rights-and-licensing/permissions/>
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

Customer Service

If you have any further queries about your subscription, please contact our customer services team on +44 (0) 207111 1105 or via email at support@bmj.com.

Visit casereports.bmj.com for more articles like this and to become a Fellow