ELSEVIER
Journal of Cystic Fibrosis xx (2018) xxx – xxx
Journal of Cystic Fibrosis
www.elsevier.com/locate/jcf

Short Communication

Chronic infection sustained by a *Pseudomonas aeruginosa* High-Risk clone producing the VIM-1 metallo-β-lactamase in a cystic fibrosis patient after lung transplantation

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Received 19 November 2017; revised 16 January 2018; accepted 18 January 2018
Available online xxxx

Abstract

Background: The significance of chronic lung infection by multidrug-resistant (MDR) pathogens in Cystic Fibrosis (CF) transplanted patients remains controversial, and the available information is overall limited. Here we describe the case of a chronic infection, sustained by a metallo-β-lactamase (MBL)-producing *P. aeruginosa* strain, in a CF patient following lung transplantation.
Methods: Twelve *P. aeruginosa* isolates collected from a CF patient over a 15-years follow-up period after lung transplantation were analysed for their antibiotic susceptibility profile, MBL production and clonal relatedness. Available clinical and microbiological records were reviewed.
Results: The transplanted CF patient was chronically infected by an MBL-producing *P. aeruginosa* strain which harboured a bla_{VIM-1} determinant inserted into a novel class 1 integron. The strain exhibited an MDR phenotype and belonged to the globally widespread ST235 epidemic clonal lineage, which however is not a typical CF-associated epidemic clone. Despite the chronic infection, the long-term outcome of this patient during the post-transplant period was characterized by the absence of acute exacerbations and by a mostly stable pulmonary function.
Conclusions: This report provides one of the few descriptions of MBL-producing *P. aeruginosa* infections in CF patients, and the first description of such an infection after lung transplantation in these patients. Infection with the MBL-producing strain apparently did not significantly affect the patient pulmonary function.

Keywords: Chronic infection; Lung transplantation; *Pseudomonas aeruginosa*; ST235; Multidrug resistance; Carbapenemase

1. Introduction

In Cystic Fibrosis (CF) patients, when the end-stage lung disease is established, lung transplantation represents the only practice to prolong survival and improve the quality of life. Pre-transplant chronic infection by *P. aeruginosa* is very common, and is not generally considered a contraindication to transplantation

Abbreviations: MBL, metallo-β-lactamase; MDR, multidrug-resistant; HiRiC, High-Risk clone; MLST, Multi Locus Sequence Typing; PFGE, pulsed-field gel electrophoresis

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https://doi.org/10.1016/j.jcf.2018.01.007

Please cite this article as: Pollini S, et al, Chronic infection sustained by a *Pseudomonas aeruginosa* High-Risk clone producing the VIM-1 metallo-β-lactamase in a cystic fibrosis patient after lung transplantation, J Cyst Fibros (2018), https://doi.org/10.1016/j.jcf.2018.01.007

[1]. Allograft infection can occur soon after surgery as the consequence of de novo acquisition of this pathogen or, more frequently, of its spread from an already established upper airway reservoir [2]. This condition may be involved in the development of bronchiolitis obliterans syndrome (BOS), that represents the main cause of late mortality after transplantation [3,4]. Whether infection by multidrug-resistant (MDR) strains is detrimental for post-transplant survival remains controversial, with few studies addressing this topic [5,6].

Metallo-β-lactamases (MBL) are among the most challenging resistance determinants in *P. aeruginosa*, since they can confer resistance to nearly all β-lactams including carbapenems [7]. MBL-producing strains often belong to epidemic High-Risk clones (HiRiCs) that are widespread in the hospital settings worldwide, such as those of sequence type (ST) 235 and ST175 [8–10]. However, MBL-producing *P. aeruginosa* strains have rarely been described in the CF setting [11,12], and infection by such strains has never been reported in CF lung transplant recipients.

Here we describe a case of chronic infection sustained by an MBL-producing *P. aeruginosa* HiRiC in a CF patient, following lung transplantation and its impact on patient outcome.

2. Methods

Cultures for microbiological analysis were derived from the original stocks, stored at −70 °C. Antibiotic susceptibility was determined using the standard broth microdilution method [13] and interpreted according to the European Committee on Antimicrobial Susceptibility Testing breakpoints (v.8.0, January 2018; http://www.eucast.org/clinical_breakpoints). EDTA-inhibitable carbapenemase activity was detected by spectrophotometric assays [14]. bla_{VIM}- and bla_{IMP}-type genes were detected by PCR using primers designed on conserved regions [14]. MBL genes and their genetic context were characterized by a PCR mapping and sequencing approach [14]. Clonal relatedness was investigated by Multi Locus Sequence Typing (http://pubmlst.org/paeruginosa) and pulsed-field gel electrophoresis (PFGE) [14].

3. Results

A 35 years-old male patient with advanced CF lung disease (FEV_1 17% of predicted, BMI 23.3 kg/m^2, and chest X-ray with a Chrispin-Norman score of 15) underwent a bilateral lung transplantation in 1997.

The available clinical and microbiological records showed that, before transplantation, the patient was persistently infected by methicillin-resistant *Staphylococcus aureus* (MRSA), with a multi-susceptible *P. aeruginosa* being intermittently isolated until 1995 only. The patient had been subjected to repeated antimicrobial treatments with ceftazidime, carbapenems, tobramycin, vancomycin and teicoplanin. After transplantation, the patient

Table 1
Antimicrobial susceptibility and PFGE profiles of the *Pseudomonas aeruginosa* isolates, and patient clinical parameters during the observation period. MIC values in the susceptible range are highlighted in grey.

Isolate	Isolation date	Sample type	Pt[a]	PFGE variant	MIC μg/mL[b]										FEV_1[c]	BMI[d]
					CAZ	FEP	PZT	AZT	IMP	MEM	AK	TOB	CIP	COL		
Fi/00	2000 May 10	Sputum	M	A	>256	>64	128	16	>64	>64	64	>256	16	2	89	25.2
Fi/03	2003 Jul 11	Sputum	M	B	128	>64	16	1	64	32	8	64	8	1	101	22.6
Fi/05	2005 Mar 18	Throat swab	M	C	256	>64	64	4	8	8	64	128	8	1	113	23.9
Fi/08a	2008 Jan 17	Sputum	M	A1	64	64	32	8	64	64	16	256	8	1	100	23.3
Fi/08b	2008 Jun 23	Sputum	M	D	64	64	64	2	32	32	8	64	4	1	100	23.3
Fi/09	2009 Jul 08	Throat swab	R	A2	256	>64	64	2	16	16	64	256	8	2	105	23.7
Fi/10	2010 May 6	Throat swab	R	E	>256	>64	128	16	64	>64	64	>256	16	1	92	24.1
Fi/11a	2011 Apr 14	Nasal swab	M	A3	128	>64	128	2	64	>64	32	64	4	2	94	24.1
Fi/11b	2011 Jul 22	Throat swab	M	A3	64	>64	32	1	64	32	16	64	4	2	94	24.3
Fi/14a	2014 Aug 28	Nasal lavage	R	F	64	64	16	2	32	16	16	64	4	1	89	25.5
Fi/14b	2014 Aug 28	Sputum	R	F1	64	>64	32	2	32	32	32	128	4	2	89	25.5
Fi/15	2015 Jan 15	Throat swab	M	G	128	>64	32	1	64	32	32	64	4	2	90	23.8

[a]Phenotype; mucoid phenotype: M, rough phenotype: R.
[b]CAZ, ceftazidime; FEP, cefepime; TZP, piperacillin-tazobactam (tazobactam was used at a fixed concentration of 4 μg/mL); AZT, aztreonam; IMP, imipenem; MEM, meropenem; AK, amikacin; TOB, tobramycin; CIP, ciprofloxacin; COL, colistin.
[c]FEV_1% of the predicted value for the year of isolation of the strains.
[d]Body mass index.

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