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Effects of airway infection by *Pseudomonas aeruginosa*: a computed tomographic study

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Abstract

***Background* – *Pseudomonas aeruginosa* commonly infects the airways of patients with bronchiectasis. A study was undertaken to examine the relationship between infection of the airways with this pathogen, the morphological pattern of bronchiectasis on thin section computed tomographic (CT) scanning, symptom duration, smoking habits of the patients, and the presence of airflow obstruction.**

***Methods* – Thin section CT scans of 22 adult patients with bronchiectasis and concurrent sputum infected by *P aeruginosa* (Pa + ve) and those of 45 randomly selected patients not infected by *P aeruginosa* (Pa − ve) were analysed independently by two thoracic radiologists. Patients with cystic fibrosis were excluded. Each scan was scored at a lobar level for extent of bronchiectasis, severity of bronchial wall thickening and dilatation, predominant pattern of bronchiectasis, presence of mucus plugging, and degree of decreased attenuation of the lung parenchyma.**

***Results* – The Pa +ve group had more extensive bronchiectasis and a greater degree of bronchial wall thickening and dilatation on the CT scan than the Pa −ve group; more extensive decreased attenuation was seen in the Pa +ve group. These findings were robust on multivariate analysis; decreased attenuation was also independently related to the duration of sputum production.**

***Conclusion* – Patients with bronchiectasis infected by *P aeruginosa* have more extensive and severe bronchiectasis on thin section CT scanning than those without *P aeruginosa* infection. The bronchi and small airways are both involved, reflecting the end result of complex interactions between host airways and the numerous virulence factors produced by *P aeruginosa*.**

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Keywords: *Pseudomonas aeruginosa*, bronchiectasis, thin section CT scanning.

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Infection of the airways by *Pseudomonas aeruginosa* occurs commonly in patients with cystic fibrosis[1] but also occurs in patients with other forms of bronchiectasis.[2] Although much of the morbidity and mortality of patients with bronchiectasis may be due to chronic infection with *P aeruginosa*, chronic infection of the airways with this pathogen in patients with cystic fibrosis can be prevented by early institution of anti-pseudomonas chemotherapy.[3] Experiments in vitro have suggested that *P aeruginosa* plays an important part in the progression of bronchiectasis,[4–6] and mucociliary clearance measurements[7] and results in an experimental model of bronchiectasis in vitro are consistent with this.[8] Computed tomographic (CT) scanning is an accurate and non-invasive method of imaging the bronchial tree and is the technique of choice for the diagnosis of bronchiectasis.[9–11]

Nagaki *et al* investigated a group of non-smoking patients with a clinical diagnosis of chronic bronchitis whose airways had been infected by *P aeruginosa* for at least one year. They found that such patients had significantly more severe bronchiectasis on CT scanning than non-infected matched patients and asymptomatic controls.[12] Similar results were obtained in a study performed at our institution in which patients infected with *P aeruginosa* appeared to have more extensive bronchiectasis on CT scanning and more severe airflow obstruction than non-infected patients, independent of their smoking history.[13] However, in both these studies the assessment of bronchiectasis on the CT scan was limited.

In this study we have examined in more detail the relationship between infection of the airways by *P aeruginosa* and the morphological pattern of bronchiectasis on thin section CT scans, and any relation between these and the severity and duration of symptoms, patients' smoking habits, and respiratory function.

Methods

Consecutive adult patients undergoing investigation for known or suspected bronchiectasis between January 1991 and March 1993 were studied, provided that bronchiectasis was present on thin section CT scanning and either mucoid or non-mucoid strains of *P aeruginosa* were cultured from sputum within three months of the scan. Exclusion criteria were (1) an abnormal sweat sodium concentration (tested in all patients), (2) a history of lobectomy or pneumonectomy (since this would affect the forced expiratory volume in one second (FEV_1) and alter the CT scores), and (3) age below 16 years. The control group consisted of randomly selected patients with chronic purulent sputum production and bronchiectasis on CT scanning who were not infected by *P aeruginosa*. Twenty two patients infected with *P aeruginosa* and 45 controls were studied. The following information was ex-

Table 1 Comparison of the demographic and clinical features obtained from the case records in patients with sputum infected with Pseudomonas aeruginosa (Pa +ve group) and those not infected (Pa −ve).

	Pa +ve group (n=22)	*Pa −ve group (n=45)*	*p value*
Age (years)	54.1 (14.5)	43.5 (14.3)	<0.01
Sex (M:F)	10:12	16:29	0.44
No. of smokers (ever vs never)	9	16	0.67
Median (range) history (pack years)	0 (0–40)	0 (0–90)	0.46
No. with history of asthma	12	18	0.26
Age at onset of sputum production (years)	27.0 (22.0)	21.2 (18.3)	0.26
Duration of sputum production (years)	27.1 (14.6)	22.3 (17.4)	0.27
FEV_1 (% pred)	58.2 (30.1)	75.4 (22.9)	<0.02

FEV_1 = forced expiratory volume in one second. Values are mean (SD) on median (range).

tracted from case records: (1) demographic details; (2) smoking history ("ever" versus "never", pack years); (3) clinical history of asthma; (4) age at onset of sputum production; (5) duration of sputum production; (6) a predisposing cause, if any, for bronchiectasis. The percentage predicted FEV_1 was also recorded.[14]

The CT scans were performed on an ultrafast electron beam scanner (Imatron C-100, San Francisco, USA) with a scan time of 200 ms. Patients were scanned in full suspended inspiration from lung apex to diaphragm and 3 mm sections were obtained at 10 mm intervals. A high spatial resolution reconstruction algorithm was used and images were photographed on appropriate lung window settings (level −700 HU, width 1500 HU). Two thoracic radiologists (DMH and MBR) independently analysed the CT scans in random order with no knowledge of which patients were infected with *P aeruginosa*.

All CT observations were made at a lobar level with the lingula considered a separate lobe. The presence or absence of bronchiectasis on the CT scans was determined according to the criteria described by Naidich.[15] The CT scoring system used was that described by Reiff *et al* which has good interobserver agreement.[16] The extent of bronchiectasis, severity of bronchial wall thickening, and severity of bronchial wall dilatation were recorded for each lobe using a four point scoring system (0–3): grade 0 = no bronchiectasis, normal bronchial wall thickness, or no bronchial wall dilatation; grade 1 = bronchiectasis present in none or one bronchopulmonary segment, bronchial wall thickening equivalent to half the diameter of the adjacent vessel, or bronchial wall dilatation equivalent to less than twice the diameter of the adjacent vessel; grade 2 = bronchiectasis present in more than one bronchopulmonary segment, bronchial wall thickening equivalent to 0.5–1 × diameter of the adjacent vessel or bronchial wall dilatation equivalent to 2–3 × diameter of the adjacent vessel; grade 3 = gross cystic bronchiectasis present, bronchial wall thickening equivalent to more than the diameter of the adjacent vessel, or bronchial wall dilation present equivalent to more than three times the diameter of the adjacent vessel. The total score for each of these parameters was obtained by adding together the scores for the six lobes.

The predominant pattern of bronchiectasis present in each lobe as classified by Reid (cylindrical, varicose or cystic) was recorded.[17] The presence of either small centrilobular plugs or large plugs (plugging of the segmental and subsegmental airways) was recorded as present or absent. To assess involvement of the bronchioles by the disease process[18] areas of decreased attenuation of the lung parenchyma

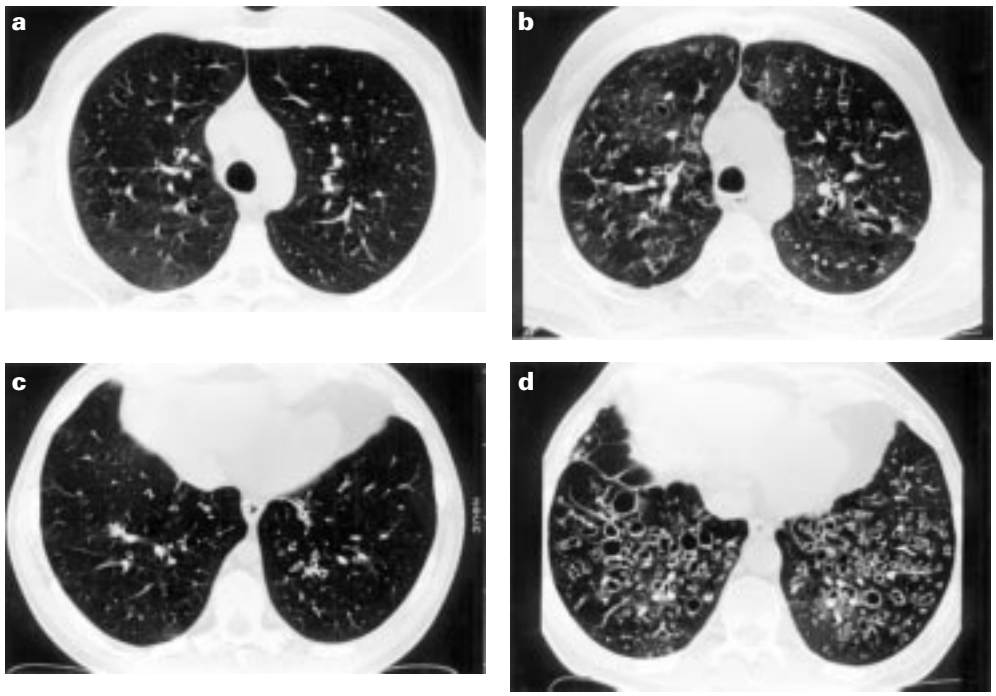

Figure 1 Thin section slices of a CT scan taken at two similar levels fom two patients with bronchiectasis, both with a 29 year duration of sputum production. Sections (a) and (b) are through the upper zones and (c) and (d) are through the lower zones. Sections (a) and (c) are from a patient not infected with P aeruginosa and (b) and (d) are from a patient infected with P aeruginosa.

Table 2 Median scores (with ranges) for morpholopical features on CT scans in patients with sputum infected with Pseudomonas aeruginosa (Pa +ve) and those not infected (Pa −ve).

	Pa +ve group (n=22)	*Pa −ve group (n=45)*	*p value*
Extent of bronchiectasis	9.5 (3.5–14.0)	5.0 (1.5–15.5)	<0.0001
Bronchial wall dilatation	9.5 (2.5–17.5)	4.0 (1.0–17.5)	<0.0005
Bronchial wall thickening	6.0 (2.5–12)	3.5 (0–17.5)	<0.0001
Global decreased attenuation	5.5 (0–12)	2.0 (0–11)	<0.0005
Large plug score	0.5 (0–2.5)	0 (0–2.5)	0.07
Centrilobular plug score	0.5 (0–5)	0 (0–5)	0.33

Statistical analysis performed by Wilcoxon's rank sum test.

were recorded as: grade 0 = normal, grade 1 = decreased attenuation involving <50% of the lobe, grade 2 = decreased attenuation involving >50% of the lobe; the total decreased attenuation score was the sum of the lobar scores. The mean scores of the two observers were used in the analysis.

Results are expressed as medians with ranges. A p value of <0.05 was regarded as statistically significant. Group comparisons were made using the Student's *t* test, χ^2 statistics, or Wilcoxon's rank sum test. Agreement between observers was expressed as the kappa coefficient; kappa values of >0.60 were taken to indicate good agreement between observers.[19] Correlations were examined by multiple linear regression or, when appropriate, by logistic regression (Stata Data Analysis, Computing Resonance Center, Santa Monica, California, USA).

Results

During the study period 327 patients with chronic purulent sputum and known or suspected bronchiectasis underwent CT scanning. Thirty five (10.7%) were infected with *P aeruginosa*, but 13 were excluded because of previous pneumonectomy or lobectomy (n = 9), *P aeruginosa* not cultured within three months of CT scan (n = 2), and incomplete data (n = 2). Of the remaining 22 patients, 14 (63.6%) were continuously infected by *P aeruginosa*. Patients positive for *P aeruginosa* and controls were well matched for sex, history of asthma, the age at onset of sputum production, and the duration of sputum production (table 1). Five of the 22 patients (22.7%) infected with *P aeruginosa* (Pa +ve) and 11 (24.4%) of the 45 control patients (Pa −ve) had an underlying cause of bronchiectasis (allergic bronchopulmonary aspergillosis, previous pulmonary tuberculosis, hypogammaglobulinaemia, primary ciliary dyskinesia, Kartagener's syndrome, or Young's syndrome).

P aeruginosa infection was associated with increasing age (p<0.01) and a lower FEV_1 (p<0.02; table 1). On logistic regression infection by *P aeruginosa* was independently associated with a longer duration of sputum production (odds ratio 1.06; 95% CI 1.01 to 1.12; p = 0.04) but not with increasing age at onset of sputum production (p = 0.08), pack years of smoking (p = 0.41), sex (p = 0.72), a history of asthma (p = 0.33), or the presence of an underlying cause of bronchiectasis (p = 0.97).

The extent and severity of bronchiectasis, the severity of bronchial wall thickening, and the extent of decreased attenuation were strikingly greater in the Pa +ve group than in the Pa −ve group (fig 1; table 2). Both observers agreed that cystic and/or varicose bronchiectasis was present in 15 of the 67 patients (22.5%); the kappa coefficient of agreement was 0.71. Cystic and/or varicose bronchiectasis was present more often in the Pa +ve group (10/22, 45%) than in the Pa −ve group (5/45, 11%; p <0.0002).

Multiple regression analysis was performed to evaluate associations between the presence of *P aeruginosa* and morphological features on the CT scan independently of other factors associated with *P aeruginosa* (age and duration of sputum production). As shown in table 3, the presence of *P aeruginosa* was associated with more extensive and severe bronchiectasis (both p<0.0005), greater bronchial wall thickening (p<0.0005), and more extensive decreased attenuation (p<0.005). A longer history of sputum production was associated with a more extensive decreased attenuation score (p<0.05) and a shorter history of sputum production was associated with more extensive centrilobular mucus plugging (p<0.04). There were no independent relationships between morphological features of the CT scan and patient age.

Logistic regression was performed to evaluate independent associations between individual CT morphological features and *P aeruginosa* infection. The presence of *P aeruginosa* was independently related to increasing bronchial wall thickness (odds ratio 1.74; 95% CI 1.00 to 1.73; p<0.05) but not to the severity of bronchial wall dilatation, the global extent of bronchiectasis, or the extent of regional air trapping.

Table 3 Multiple regression analysis of independent relationships between FEV_1 morphological features in the CT scan (examined as dependent variables), duration of sputum production and presence or absence of Pseudomonas aeruginosa. Age was also included as a covariate.

	Duration of sputum production	*Presence/absence of P aeruginosa*
Extent of bronchiectasis	0.02 (−0.03 to 0.06) p = 0.50	3.4 (1.7 to 5.0) p<0.0005
Bronchial wall dilation	0.04 (−0.03 to 0.10) p = 0.43	4.2 (2.0 to 6.5) p<0.0005
Bronchial wall thickness	0.02 (−0.01 to 0.05) p = 0.25	2.7 (1.5 to 3.8) p<0.0005
Global decreased attenuation	0.05 (0.00 to 0.09) p<0.05	2.5 (0.8 to 4.2) p<0.005
Large plug score	0.00 (−0.01 to 0.02) p = 0.38	0.26 (−0.14 to 0.65) p = 0.26
Centrolobular plug score	−0.02 (−0.04 to 0.00) p<0.05	0.34 (−0.29 to 0.97) p = 0.29
FEV_1	0.18 (−0.22 to 0.58) p = 0.38	−11.7 (−26.5 to 3.3) 0 = 0.12

Results are given as regression coefficients with 95% confidence intervals (in parentheses) and p values.

Discussion

We have shown that patients who persistently expectorate sputum infected with *P aeruginosa* have more extensive and severe bronchiectasis on thin section CT scanning than patients whose sputum is not infected with *P aeruginosa*. The global decreased attenuation score in these

patients was also significantly greater and related to the duration of sputum production.

P aeruginosa produces several virulence factors which are thought to result in the disorganisation of epithelial cells, loss of cilia, and mitochondrial damage that has been observed in vitro when intact respiratory mucosa is exposed to this pathogen.[4 5 20–23] *P aeruginosa* preferentially adheres to mucus and damaged epithelial cells rather than to cilia or unciliated cells.[5] In patients with bronchiectasis and cystic fibrosis in whom the mucus is poorly cleared *P aeruginosa* may persist for longer in the airway secretions and produce toxins which stimulate a vicious circle of chronic inflammatory damage to the mucosa, disrupting the normal host defence mechanisms and encouraging persistence of infection.[24] This hypothesis may explain why in our study patients infected with *P aeruginosa* had significantly more extensive and severe bronchiectasis, bronchial wall dilatation and thickening with a higher prevalence of cystic and varicose patterns present than non-infected patients, this relationship being preserved even after adjustment for the duration of sputum production.

Various hypotheses have been proposed for the mechanism of airway damage in bronchiectasis. Elastase detected in high levels in the sputum of patients with bronchiectasis[25] impairs ciliary function and damages bronchial epithelium;[4] its presence in sputum has been shown to be associated with gas trapping.[25] *P aeruginosa* produces its own elastase[4 26 27] and this may further exacerbate airway damage. Areas of decreased attenuation attributable to obliteration of the small airways are commonly observed in patients with a history of chronic purulent sputum production and bronchiectasis on HRCT scanning,[28] suggesting that disease of the small airways may play an important part in the pathogenesis of bronchiectasis.

Our study confirms that areas of decreased attenuation are a frequent finding in patients with bronchiectasis and patients infected with *P aeruginosa* achieved a higher global decreased attenuation score than the non-infected patients, indicating a greater degree of small airways disease. The decreased attenuation score in our study was significantly related to the duration of sputum production, suggesting that this feature may be associated with the process of mucus production as demonstrated by in vitro and in vivo experiments.[26 27 29] However, as there was also a significant negative relationship between the presence of centrilobular mucus plugging and the duration of sputum production, it is possible that centrilobular mucus plugging is indicative of inflammation early in the course of bronchiectasis which tends to regress as the bronchiectasis becomes more established when damage to the small airways by an obliterative bronchiolitis becomes the more dominant feature.

This study clearly shows that patients with bronchiectasis infected by *P aeruginosa* have a more extensive and severe spectrum of disease present on HRCT scanning than non-infected patients and the single feature on the CT scan that predicted the likelihood of sputum infection by *P aeruginosa* was increasing thickness of the bronchial wall. Undoubtedly, many complex mechanisms involving the numerous virulence factors produced by *P aeruginosa* are involved throughout the disease process resulting in damage to bronchi and bronchioles but, at present, these in vivo mechanisms are incompletely understood; whether *P aeruginosa* preferentially infects the airways of those patients with more severe bronchiectasis ab initio or whether the greater severity of bronchiectasis detected by HRCT scanning is the end result of infection by this organism has not been answered by this study. A reduction in sputum infection by *P aeruginosa* has been associated with an improvement in lung function in cystic fibrosis,[30] but it remains to be determined whether a significant improvement in morbidity can be achieved in patients with other forms of bronchiectasis who are chronically infected by this pathogen (although preliminary results appear encouraging[31]).

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