

## EASILY MISSED?

# Bronchiectasis

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This is a series of occasional articles highlighting conditions that may be commoner than many doctors realise or may be missed at first presentation. The series advisers are Anthony Harnden, university lecturer in general practice, Department of Primary Health Care, University of Oxford, and Richard Lehman, general practitioner, Banbury. If you would like to suggest a topic for this series please email us ([easilymissed.bmj@bmjgroup.com](mailto:easilymissed.bmj@bmjgroup.com)).

Bronchiectasis is mostly an acquired bronchopulmonary disorder with abnormal thickening of the bronchial wall and dilation of central and medium sized bronchi, due to a vicious circle of transmural infection and inflammation with mediator release. Though many underlying conditions may induce or contribute to the development of bronchiectasis (table), it is idiopathic in about 50% of adults<sup>1</sup> and 25% of children.<sup>2</sup>

### How common is it?

The prevalence of bronchiectasis varies with time period and geography, due to differences in antibiotic prescription, availability of vaccinations, and prevalence of associated disorders. Additionally, the doctor's alertness for bronchiectasis and the availability of sensitive diagnostic tools may affect reported prevalence. In the United States the prevalence of non-cystic fibrosis bronchiectasis among adults between 1999 and 2001 was estimated to be 51 per 100 000 population.<sup>3</sup> The prevalence was higher among women than men (71 v 32 per 100 000) and increased markedly with age (4 per 100 000 for people aged 18-34 years v 272 per 100 000 for those aged 75 or over). In Australia the prevalence among Aboriginal children aged under 15 years was reported to be as high as 1470 per 100 000.<sup>4</sup>

In the United Kingdom, a full time, single handed practice of 2500 patients will have one or two patients with

### Causes of and conditions associated with bronchiectasis<sup>1</sup>

Cause	No (%) (n=150)
Idiopathic	80 (53)
Infection	44 (29)
Immune defect	12 (8)
Congenital	1 (<1)
Condition	
Allergic bronchopulmonary aspergillosis	11 (7)
Aspiration	6 (4)
Young's syndrome	5 (3)
Cystic fibrosis	4 (3)
Rheumatoid arthritis	4 (3)
Ciliary dysfunction	3 (2)
Ulcerative colitis	2 (<1)
Panbronchiolitis	1 (<1)

In this case series no patients were found with  $\alpha_1$  antitrypsin deficiency, but in a case series of 74 patients deficient in  $\alpha_1$  antitrypsin, 70 were found to have bronchiectatic changes.<sup>17</sup>

bronchiectasis, compared with 75 with asthma and 50 with chronic obstructive pulmonary disease.

### Why is it missed?

Symptoms of bronchiectasis (such as chronic cough and sputum production) may be mild, particularly at the beginning. These symptoms may resemble asthma, chronic obstructive pulmonary disease, rhinosinus diseases, tracheobronchial infection, and gastroesophageal reflux, which are much more common than bronchiectasis in an average UK general practice. In an Australian cohort study, 40% of patients with bronchiectasis who developed chronic productive cough in adulthood also smoked.<sup>5</sup> This may mislead the doctor to a diagnosis of chronic bronchitis induced by smoking. Basal crackles may suggest heart failure. Spirometry may show coexisting airway obstruction, leading to a misdiagnosis of chronic obstructive pulmonary disease instead of bronchiectasis. Chest x rays sometimes do not show mild bronchiectasis.

### Why does it matter?

Patients with newly diagnosed bronchiectasis were found to have a poorer prognosis than those with asthma (matched for age and sex), but a better prognosis than those with chronic obstructive pulmonary disease.<sup>6</sup> Over a follow-up period of 8.8 years, 25% of 372 Finnish patients with bronchiectasis died (mean age at the start of the follow-up was 56 years). In a Turkish cohort study in 98 patients with bronchiectasis, vaccination, scheduled visits to the doctor, and high body mass index seemed to improve survival.<sup>7</sup>

### CASE SCENARIO

A 29 year old, non-smoking kindergarten teacher with mild asthma often visited her general practitioner with recurrent respiratory tract infections, which they both attributed to daily contact with her students. After seven courses of oral antibiotics in one year, the doctor requested sputum cultures. These showed *Pseudomonas aeruginosa*. Given this unusual result and her recurrent infections, he referred her to a lung physician, and high resolution computed tomography of her lung showed mild bronchiectasis, which was later found to be due to  $\alpha_1$  antitrypsin deficiency.

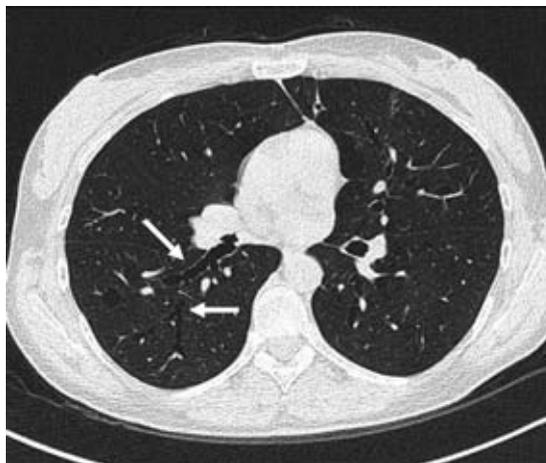
### KEY POINTS

Bronchiectasis may be easily missed because its clinical features may overlap with more common conditions, such as asthma, chronic obstructive pulmonary disease, rhinosinus disease, gastroesophageal reflux, and common upper and lower airway infections. General practitioners in the UK have one or two patients, on average, with bronchiectasis in their practice.

Diagnosis is based on daily production of mucopurulent phlegm and chest imaging that shows dilated and thickened airways; high resolution computed tomography of the lung is the optimum diagnostic procedure.

The diagnosis of bronchiectasis should lead to investigation and treatment of possible causes and associated conditions.

Treat acute exacerbations promptly with short courses (less than four weeks) of antibiotics.



High resolution computed tomography scan of chest of a young non-smoking woman with mild bronchiectasis. White arrows indicate airway dilation and lack of tapering

No controlled intervention studies have been done on the effect of an early diagnosis, a higher alertness of the general practitioner, or an active screening programme. Nevertheless, evidence based guidelines of the American College of Chest Physicians say that once bronchiectasis is discovered, looking for an underlying cause is important, as the results of diagnostic evaluation “may lead to treatment that may slow down or halt the progression of the disease.”<sup>8</sup> The diseases that are described as underlying causes are among others listed in table 1.

### How is it diagnosed?

#### Clinical features

Cough is present in 90% of the patients, and 76% produce sputum daily.<sup>9</sup> Haemoptysis occurs in 51% of patients and tends to be recurrent. The usual abnormalities on chest examination are crackles (70%) and wheezes (34%).

#### Investigations

Requesting sputum cultures in patients with frequent respiratory infections may help to identify unusual infections that increase the suspicion of bronchiectasis, as the case scenario shows. Chest x rays may show linear markings, crowding, cystic spaces, and honeycombing.<sup>10</sup> In a small study the sensitivity for chest x rays to detect bronchiectasis was found to be 88%, with a specificity of 74%,<sup>11</sup> but other studies indicate that these figures will be less positive in mild bronchiectasis.

A normal chest x ray does not exclude bronchiectasis definitively. So, if there is a high clinical suspicion for bronchiectasis, a high resolution computed tomography scan of the chest should be considered. This scan has replaced contrast bronchography as optimal for diagnosis of bronchiectasis. Major features are airway dilation, lack of tapering (figure), thickening of the bronchial wall, mucopurulent plugs or debris, and cysts.<sup>12</sup> The sensitivity of the scan is 82-97% and the specificity 99-100%.<sup>13</sup>

Specific tests to identify underlying causes or contributing conditions depend on the clinical setting and the patient's history and age. Tests might include a white blood cell count and differentiation, IgG, IgG subclasses, IgM, IgA, total IgE,  $\alpha_1$  antitrypsin levels, rheumatoid factor, and aspergillus serology.

### How is it managed?

The evidence base for management is contentious, but expert consensus advocates advising patients who smoke to quit. Treat acute exacerbations with short courses (<4 weeks) of antibiotics targeted to likely organisms such as *Pseudomonas aeruginosa*, *Haemophilus influenzae*, or *Mycobacterium avium-intracellulare*; or on basis of the results of sputum culture. Consider prolonged use of antibiotics (>4 weeks)<sup>14</sup>; although the criteria for doing so are not well established, we believe this might be beneficial in patients who often relapse (more than six times per year) or show progressive decline of lung function. The effectiveness of continuous mucolytics, anti-inflammatory agents, and bronchodilators is not clear but can be considered on individual basis.<sup>15</sup> Physical therapy techniques that improve bronchial clearance of mucus are widely used, yet there is little evidence to support or refute them.<sup>16</sup>

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## A PATIENT'S JOURNEY

## Living with lymphangioleiomyomatosis

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This is one of a series of occasional articles by patients about their experiences that offer lessons to doctors. The *BMJ* welcomes contributions to the series. Please contact Peter Lapsley (plapsley@bmj.com) for guidance.

Since being diagnosed with lymphangioleiomyomatosis, Havi Carel has learnt much about the adaptability of the body and quality of life issues for patients with chronic illnesses

I need to walk my dog. She is delighted to be heading out. She is a runner. I, on the other hand, have a cystic lung disease that has damaged my lungs. Running is out of the question. At best, I can walk at a measured, matronly pace. I can only dream about running.

It has been four years since my diagnosis with lymphangioleiomyomatosis (LAM), a rare lung disease that affects mostly women, during which I have experienced a dramatic decline in my lung function, followed by a transplant assessment. The transplant team said I was too well to go on the list but have kept an eye on me since. I then asked—begged—to be put on an experimental drug, sirolimus, which stabilised my condition. I went from being a healthy, fit, 35 year old woman with a wonderful husband and a great job as a philosophy lecturer, to being ill and scared. My diagnosis felt like everything was being taken away from me—suddenly, unfairly, and with no prospect of compensation.

For quite a while I had been feeling breathless. I could feel my lung capacity falling. Eventually, I went to my GP. She shrieked in horror when she saw my spirometry results. “I’ve never seen anything like this. I have no idea what this could be.” I was alarmed and asked my father, a director of a medical screening centre, to arrange a computed tomography (CT) scan for me. I had the scan in the morning, and returned to collect the results in the afternoon.

The radiologist clearly did not want to break the bad news to me in person. He said, “Sit down. I’ll let you read about what you’ve got,” and handed me a heavy diagnostic manual. It was open at a page headed “lymphangioleiomyomatosis.” I read the description of this strange disease, my illness, and got to the bottom of the page: “Prognosis: ten years from onset of respiratory symptoms.” I could not speak or move. My only thought was: 45—I will be dead by the time I am 45.

The first month was terrible. I tried to reach out to my friends, but many of them mumbled that they didn’t know what to say and disappeared. A new awkwardness entered my life. The awkwardness of nurses doing my breathing tests showing a sharp decline; the awkwardness of my parents, paralysed by their inability to help; the awkwardness of the healthy, to whom illness is a foreign and exotic land.

In the months that followed I learnt that illness is multifaceted and complex; that it is a process, not a static entity; and that it is possible to go on living well and experiencing wellbeing even within the context of a terrible and incurable illness. This surprised me, as I had always thought of health as the sine qua non of happiness. And yet, all of a sudden, I found myself changing, responding to constraints, learning to make sense of my life in the light of my illness. The work of realigning my life, its values, and the meaning I gave its different elements surprised me.

**Amazing adaptability**

At first, I still tried to move around briskly, run for the bus, cycle up a hill. After nearly fainting a few times, I realised that I had to slow down. But there was a more subtle change instigated by my body. Whenever I tried to do something that was no longer possible, like chew gum while walking, or lift and swing my nephew, my body quietly registered the failure and removed the action from its repertoire. This change happened slowly, subtly, but cumulatively. The result was quite amazing: I stopped sensing, and therefore no longer think much about, what I cannot do.

I started seeing that the lived experience of illness was very different from its textbook descriptions or third person view of it. I realised that the first person experience of illness was varied, changed continuously, and shifted

**BACKGROUND AND CLINICAL DATA**

Lymphangioleiomyomatosis is a rare disease that almost exclusively affects women and generally presents before the menopause. It occurs sporadically in only one in 400 000 adult women, but it is found on CT scan in up to 40% of those with tuberous sclerosis complex, an autosomal dominant disease.<sup>1</sup>

In lymphangioleiomyomatosis an abnormal clone of benign cells (called LAM cells) metastasises and proliferates diffusely in the lungs and axial lymphatics. The cells can also form angiomyolipomas,<sup>2</sup> benign tumours of mixed lineage that occur in the kidneys of almost half of all patients with the condition.<sup>3</sup> In the lungs, LAM cells form nodular proliferations that cause multiple lung cysts, probably through secretion of proteolytic enzymes. The cysts replace the lung parenchyma and can rupture, leading to pneumothorax.

Respiratory features generally predominate with most patients presenting with either dyspnoea or pneumothorax. Occasionally, bleeding from angiomyolipomas or enlarged abdominal lymphatic masses is the presenting problem.<sup>1</sup>

The clinical spectrum of the disease is highly variable; some patients develop progressive respiratory failure punctuated by recurrent pneumothorax, whereas others stay stable for many years. On average, 10 years after the first symptom, over half of patients are breathless walking on the flat, a quarter will be using supplemental oxygen, and about one in 10 will have died.<sup>4</sup> Diagnosis is made either by lung biopsy or from the combination of lung cysts visible on high resolution computed tomography and angiomyolipoma or tuberous sclerosis complex.<sup>5</sup>

Treatment has been mostly aimed at complications including pneumothorax and symptomatic control of dyspnoea, with lung transplantation being an option for patients with advanced disease. Impressive progress in the molecular pathology of lymphangioleiomyomatosis has demonstrated that LAM cells have constitutive activation of the mTOR pathway (a pivotal cellular kinase governing proliferation) resulting from bi-allelic loss of either *TSC-1* or (more commonly) *TSC-2*, the genes that are abnormal in tuberous sclerosis complex.<sup>6</sup> This finding has led to trials of mTOR inhibitors in lymphangioleiomyomatosis that have caused regression of angiomyolipomas and possible improvement in lung function.<sup>7,8</sup>

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Previous articles in this series

- ▶ Through and beyond anaesthesia awareness (*BMJ* 2010;341:c3669)
- ▶ Joint hypermobility syndrome (*BMJ* 2010;341:c3044)
- ▶ Endometriosis (*BMJ* 2010;340:c2661)
- ▶ External aortic support for Marfan's syndrome (*BMJ* 2010;340:c1692)
- ▶ Two hip replacements (*BMJ* 2010;340:c1502)

from being in the foreground, as during my diagnosis, to being in the background. When it is in the background I think I am no less happy, but a lot wiser than I was before I was ill.

This first person perspective became important to me. I felt that during my frequent dealings with medical and healthcare professionals it was neglected. No one asked me what had changed in my life or what had I had to give up because of my illness. Overlooking the lived experience of illness is a mistake because there is so much important knowledge to be gleaned from it—for example, knowing that the most effective intervention might be helping the patient to retain their everyday life despite their illness. The ultimate aim of medicine is to help those who are ill regain their life, habits, and activities. But it is impossible to do this without knowing about the patient's usual life and how it has been affected by illness.

**Helping researchers help me**

As it turned out, the 10 year prognosis is now out of date. My family and I did a lot of research into the illness and made contact with clinicians, researchers, and lymphangioliomyomatosis organisations to get the best advice. I joined three organisations, which were a source of support and information and gave me the opportunity to assist in the search for a treatment. Joining a mailing list and meeting other women with lymphangioliomyomatosis was a great help as, with rare diseases in particular, a lot of information is held by patients who have had the condition for many years. But raising funds for research and coordinating tissue retrievals are even more important to me. I am now the European tissue coordinator for the Lymphangioliomyomatosis Treatment Alliance, a research organisation that collaborates with another United States based organisation, the National Disease Research Interchange (NDRI).

The NDRI keeps a database of patients with a particular disease who have given consent for their tissue to be

**RESOURCES FOR PATIENTS AND CLINICIANS**

The LAM Treatment Alliance ([www.lamtreatmentalliance.org](http://www.lamtreatmentalliance.org))—Founded in 2005 in Boston, Massachusetts, the LAM Treatment Alliance funds collaborative, high-impact research and patient partnerships

The LAM Foundation ([www.thelamfoundation.org](http://www.thelamfoundation.org))—Founded in 1995, the LAM Foundation funds research and offers information, resources, and a worldwide network of support

LAM Action ([www.lamaction.org](http://www.lamaction.org))—A UK charity for women with LAM. It provides patient support, fundraising for research, and information for clinicians and researchers

LAM Australasia Research Alliance ([www.lara.org.au](http://www.lara.org.au))—Aims to improve diagnosis, educate medical practitioners, support patients, and fund research

used in research and of researchers working on that disease. When a patient has a procedure or dies, her tissue is retrieved and shipped to researchers around the world. Since the scarcity of tissue is a big obstacle for lymphangioliomyomatosis research, making sure that no tissue is wasted is crucial. I explain the importance of tissue donation to patients with the disease and coordinate individual shipments from patient to researcher.

I wanted to incorporate my illness into my work as a philosopher. I began to write and talk about illness, which linked to my work on embodiment. Philosophers spend much of their time thinking about consciousness and its relationship to the body. Through my ill health I realised that illness represents one such relationship, the importance of which has not been recognised by philosophers. I now head a research project funded by the Arts and Humanities Research Council on the concept of illness. I also published a book, *Illness*, which ties together the philosophical ideas around illness with my experience of it. I hope that by talking about the experience of illness with medical professionals I can make this experience and its dramatic affects on the patient's life better understood.

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**A DOCTOR'S PERSPECTIVE**

Havi was referred to my clinic at the age of 35 with exertional breathlessness. She had no wheeze and no trigger factors, and the problem was not episodic. She had never smoked and was fit and active. Her lung function showed airflow obstruction with reversibility after bronchodilators. Her chest radiograph images showed marked hyperinflation. She was given inhaled corticosteroids and  $\beta_2$  agonists. After some discussion about the appearance of the radiograph films a CT scan was arranged, which showed lymphangioliomyomatosis.

Caring for patients with rare conditions is a challenge. They may take longer to diagnose, and few good quality data may be available to inform management decisions. Sharing care with a national expert in the condition is helpful, allowing both patient and physician to benefit from specialist knowledge.

The psychological effect of diagnosing a life changing condition, particularly in a younger person, should be remembered.

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