Case reports

Commentary: bronchiectasis and inflammatory bowel disease

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In 1861 Paul Broca and Louis Pierre Gratiolet spent more than six months arguing over the relevance of skull size to intelligence. Broca argued that “study of the brains of human races would lose most of its interest and utility if variation in size counted for nothing. Why had anthropologists spent so much time measuring heads if the results had no bearing upon the relative worth of different peoples?” Unfortunately time has proved that Broca and his followers contributed little by their studies. With this in mind, how are we to view the continuing appearance of case reports in medical journals? Surely if they are being written and published, they must be of some benefit, or do they in reality provide no more than an interesting anecdote that has no long term contribution to medicine?

The current issue of *Thorax* contains two cases of bowel disease and a relationship to bronchiectasis.1,2 Are these two reports yet further chance associations or do they provide some insight that may direct our thinking into the pathogenic processes involved in the lung condition?

Bronchiectasis, although often considered clinically, is based on a pathological definition. For many years the bronchogram had been the gold standard, although now high resolution CT scanning is being used with increasing frequency. There is some concern as to whether the use of such sensitive tests is, in a more widespread epidemiological way, detecting the same or a different disease condition from that which we have understood it to be in the past. For instance, one of the cardinal features of the disease on the CT scan is bronchial wall thickening and this may occur in other conditions where oedema of the airway wall is present. Clearly, classical bronchial dilatation or cystic change would be accepted by most as features of what was, in the past, recognised as bronchiectasis. However, tracking cylindrical changes through a scan is often difficult and the more subtle changes may indicate a different clinical condition from that recognised previously.

The pathogenesis of bronchiectasis has been extensively studied and many associations have been identified. Inflammation in the bronchial tree is thought to predate inflammatory damage leading to colonisation by bacteria and persistent inflammation and continuing tissue destruction (the much quoted vicious circle). With that as a background, inflammatory bowel disease has been well recognised as an association (although rare) with bronchiectasis. In particular, this is true of ulcerative colitis. This provides yet another tantalising epidemiological link between the bowel and the lung. For instance, the positive correlation of smoking with exacerbations of Crohn’s disease and the negative influence of smoking in ulcerative colitis are well documented but difficult to explain. Might the associations of bowel and lung disease be related to a common immunity between both systems, the fact that the epithelial lining of both organs is exposed to common antigens in the environment, or that epithelial antigens share similarities at both sites?

Discussions as to whether bronchial associated lymphoid tissue and gut associated lymphoid tissue are distinct or partly interrelated immune systems have yet to be resolved, but both IgA producing B cells and T cells are believed to migrate from the gut to the lung. Thus, if Crohn’s disease is related to an excessive immune response to a bacterial antigen, the immune cells may well be represented in the lung. Reactions against self antigens or the same bacterial antigen being inhaled may lead to inflammatory damage at both sites.

Of the current cases, Crohn’s disease has a less well recognised association with bronchiectasis than ulcerative colitis, although clearly from a clinical point of view (and even from a pathological point of view) there is some overlap with ulcerative colitis. With that as a background, one must question why removal of bowel would be associated with a precipitation of symptoms that led to the recognition of bronchiectasis. It could be the effect of surgery with intubation and postoperative atelectasis due to pain with or without infection (we are given no details).

However, the likelihood is that this in some way reflects the severity of the condition. Resection would only be undertaken in the presence of severe disease or of adhesions or fistulae and these, particularly the latter, could also be associated with pus. Such changes would lead to, or be due to, a heightened immune response as is often seen in idiopathic bronchiectasis. Whether these changes alone lead to a perversion of the immune system, such that activity against self antigens in the lung becomes a problem, remains an interesting but unproven concept. However, certainly neutrophil infiltration has often been implicated in the pathogenesis of the tissue destruction of both ulcerative colitis and Crohn’s disease and, of course, the same has been true in bronchiectasis. It remains possible therefore that primary defects in neutrophils may play a
part in some of the pathogenic changes that take place at both epithelial surfaces.
Of more interest, perhaps, might be the association with coeliac disease. The concepts of coeliac disease have changed in recent years as the immune mechanism has started to be dissected. In the past the diagnosis was based upon clinical evidence of malabsorption, the presence of a flat biopsy section on histological examination, and the fact that both symptoms and the biopsy changes resolved with diet.

It now becomes clear that many cases of coeliac disease are subclinical. There is a clear genetic predisposition and biopsy changes can be found in first degree relatives in the absence of symptoms.7 In addition, the hallmark of the diagnosis now rests on the detection of antigliadin antibodies which can also be found in subjects who have a normal mucosal profile. However, histological examination has shown an increase in T cell infiltration, particularly of cells expressing the γδ T cell receptor.8 Studies have shown that a decrease in the gluten content of the diet results in a decrease in cells of this phenotype in the biopsy specimens. In addition, rectal challenge with gluten has shown an increase in the CD3 γδ positive T cells within four hours.9 This does suggest that, in some way, γδ T cells play an early and important role in coeliac disease. Mucosal derived T cells have been shown to respond to gluten in a DQ w2 restricted manner.

Our understanding of lymphocytic infiltration in bronchiectasis is relatively superficial although elegant studies by Lapa ES Silva et al did indicate a major lymphocytic infiltration in patients with bronchiectasis with the T cells being predominantly of the CD8 (suppressor) subtype. T cell receptor restriction, however, has yet to be analysed. It would therefore be of importance to determine whether a similar expansion in the γδ T cell population also occurs in bronchiectasis. These cells are found in the lung and have been associated with tuberculosis, sarcoidosis, and asthma. In particular, in patients with asthma these cells have been shown to respond to steroids. However, it must be pointed out that, although the T cell infiltrate is clearly present in coeliac disease, the same cannot be said of other inflammatory cell infiltration such as the neutrophil as seen in bronchiectasis.

It is to be hoped that these two case reports may prompt some further thinking and research in the field of the pathogenesis of bronchiectasis. However, one important lesson that does arise from both of these case reports is that there was a significant response to steroids. Again, although this may suggest an immunological basis, the response clearly indicates that reversible airflow obstruction or inflammation is often a feature of bronchiectasis. It should therefore be clearly looked for and treated appropriately in patients with less rare associations. Of interest, however, would be whether such a response changes the appearance of bronchiectasis seen on CT scanning.

4 Kutlu T, Brousse N, Rambaud C. Numbers of T cell receptor (TCR) alpha beta plus but not TCR gamma delta plus. Intraepithelial lymphocytes correlate with the grade of villous atrophy in coeliac patients on a long term normal diet. Gut 1999;44:208.

Keywords: bronchiectasis; coeliac disease; anti-neutrophil cytoplasmic antibody

case history

A 48 year old woman presented with a history of fatigue, regular sputum production, and wheeze. High resolution computed tomographic scanning of the thorax demonstrated widespread bronchiectasis. Coeliac disease was diagnosed on the basis of an iron deficiency anaemia, subtotal villous atrophy on small bowel biopsy, and raised anti-gliadin and anti-endomysial antibodies. The temporal relationship of her bronchiectasis and coeliac disease, and the subsequent stabilisation of her clinical symptoms and improvement in pulmonary physiology following treatment with inhaled corticosteroids, suggests a relationship between the two conditions which may be due to immunological mechanisms.

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function showed a mixed restrictive and obstructive defect; forced expiratory volume in one second (FEV₁) 1.68 l (predicted 2.7 l), forced vital capacity (FVC) 2.41 l (predicted 3.19 l), total lung capacity (TLC) 4.43 l (predicted 5.11 l), residual volume (RV) 1.31 l (predicted 1.77 l), peak expiratory flow rate (PEFR) 180 l/min. Gas transfer factor (KCO) was mildly reduced at 1.28 (predicted 1.64) and arterial oxygen saturation was 98%.

Sputum samples grew *Pseudomonas aeruginosa*. A chest radiograph showed features suggesting bronchial wall thickening in the lower lobes, and high resolution computed tomographic scans (fig 1i and ii) demonstrated widespread cylindrical bronchiectasis affecting the middle lobe, lingula, and both lower lobes. The bronchiectasis was most severe in the basal segments of the lower lobes where there was also marked bronchial wall thickening and mucus plugging. Adjacent to several of the bronchi were areas of low attenuation suggestive of air trapping secondary to an associated oblitative bronchiolitis. Laboratory investigations failed to reveal a cause for her bronchiectasis; she had an increased polyclonal total IgG at 14.4 g/l (normal range (NR) 6–13), raised IgG₃ at >1200 mg/l (NR 320–1160), and normal IgA and IgM. Antinuclear factor, rheumatoid latex, and avian and aspergillus precipitins were all negative. Alpha₁-antitrypsin phenotype was MS. Sweat sodium levels were normal at 30 mmol/l and screening for the eight most common cystic fibrosis mutations found in our region was negative. Titres of antineutrophil cytoplasmic antibody (c-ANCA) directed against a recently characterised antigen bactericidal/permeability increasing protein (BPI) were raised at 74% (NR <17%) but were negative for proteinase 3.

She was also found to have a mild iron deficiency anaemia (haemoglobin 9.9 g/dl, mean corpuscular volume 71.5 fl, and ferritin 3 µg/l), a blood film showed evidence of microcytosis and hypochromia, and there were no features to suggest splenic atrophy. A duodenal biopsy specimen showed features of subtotal villous atrophy consistent with a diagnosis of coeliac disease which was supported by the finding of positive IgA anti-endomysial and raised antigliadin antibodies (IgG 106 U/ml, IgA 89 U/ml; NR 0–16 and 0–43, respectively).

Over the past two years she has been on and off a gluten free diet owing to poor tolerance. Her clinical symptoms have stabilised on treatment with inhaled beclomethasone and salbutamol and her lung volumes have all improved: FEV₁ 1.98 l, FVC 2.96 l, TLC 4.92 l, and RV 1.75 l.

**Discussion**

Previous reports have suggested an association of coeliac disease with fibrosing alveolitis, bird fancier’s lung, farmer’s lung, sarcoidosis, idiopathic pulmonary haemosiderosis, lung abscess, and asthma,¹ but this is the first reported association with bronchiectasis. “Partial fibrous obliteration of small airways and dilatation of larger airways” has been described following a necropsy from a single patient with coeliac disease and dyspnoea, though this patient had a purely restrictive physiological defect and did not have clinical or radiological features of bronchiectasis as in our case.² Changes of chronic bronchitis have been reported in the open lung biopsy specimen from another patient with diffuse pulmonary disease and pleural thickening but it was not recorded whether or not the patient was a smoker.³

The wide range of pulmonary conditions reported in association with coeliac disease is analogous to ulcerative colitis, in which steroid sensitive bronchial inflammation and bronchiectasis are recognised complications.⁴ The cause of the association of pulmonary disorders with coeliac disease remains poorly defined. Absorption of an extrinsic allergen or immune complexes through an abnormal gastrointestinal mucosa may lead to the pulmonary disease.⁵ Alternatively, the association of coeliac disease with HLA status and various autoimmune diseases⁶ suggests that a common disturbance in immunity may underlie both coeliac disease and pulmonary disorders. Our patient did not have either splenic atrophy or selective IgA deficiency⁷ which are associated with coeliac disease and which could predispose to development of recurrent infections and bronchiectasis. Interestingly, she had a positive ANCA recognising bactericidal/permeability increasing protein. This is found in the azurophilic granules of neutrophils and functions as an important inhibitor of lipopolysaccharide and endotoxin. It has recently been reported in association with both chronic inflammatory bowel disease⁸ and cystic...

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**Figure 1 (i) and (ii) High resolution computed tomographic sections through the lower lobes showing bronchiectasis with mucus plugging (A), bronchial wall thickening (B), and areas of low attenuation (C) suggestive of obliterative bronchiolitis.**
fibrosis. Its significance in our patient is uncertain but may be related to her bronchial infection with Pseudomonas aeruginosa. Previous reports of pulmonary disease complicating coeliac disease, the close temporal relationship of the onset of symptoms from her bronchiectasis and coeliac disease, the stabilization of her symptoms and the improvement in her pulmonary function tests with inhaled corticosteroids, and the absence of alternative factors to account for her bronchial disease all make it likely that her bronchiectasis is related to her coeliac disease.


Bronchiectasis following colectomy for Crohn’s disease

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Abstract

Bronchiectasis developing following colectomy for ulcerative colitis has been reported in a few cases. This may be the first report of bronchiectasis developing after colectomy for Crohn’s disease. The close temporal relationship to colectomy, lack of bacterial pathogens in the sputum, and an impressive response to oral steroids suggest a difference in pathogenesis from idiopathic bronchiectasis.

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Keywords: bronchiectasis; Crohn’s disease; colectomy

There is a well recognised association between inflammatory bowel disease and bronchiectasis. The development of bronchiectasis after colectomy has been described in ulcerative colitis. We present what may be the first reported case of bronchiectasis developing shortly after colectomy in Crohn’s disease.

Case report

A 30 year old woman with a 16 year history of inflammatory bowel disease, initially judged to be ulcerative colitis, underwent total colectomy and ileostomy in June 1994 and anorectal excision in August 1995. Histological appearances were diagnostic of Crohn’s disease with deep fissure-like ulcers extending into the submucosa and muscularis propria, transmural inflammation, and granulomas in the submucosa and regional lymph nodes. A diagnosis of Crohn’s disease was further supported clinically by the subsequent development of a vaginal fistula. Three months after colectomy she developed a severe cough productive of a quarter cup of purulent sputum daily requiring hospital admission in November 1994. In June 1995 computed tomographic (CT) scanning demonstrated marked bronchial wall thickening with widespread extensive bilateral cylindrical bronchiectasis of mild to moderate severity (fig 1B). No bronchiectasis had been seen on sections through the lower lobes from a CT scan of the abdomen performed two months after colectomy (fig 1A).

She had no previous respiratory symptoms and normal chest radiographic appearances. There was no history of asthma, pneumonia, significant respiratory illness in early childhood, hay fever, excema, rhinosinusitis, or significant gastro-oesophageal reflux. She had never smoked. There were no other extraintestinal manifestations of Crohn’s disease and she denied symptoms suggestive of collagen vascular disease. Intermittent medications have included inhaled steroids, mesalazine, antibiotics, and oral corticosteroids. There were no abnormalities on general or respiratory examination. Liver function tests and autoantibodies were normal apart from a smooth muscle titre of 160. The immunoglobulin profile, including immunoglobulin G subclasses, was normal. Aspergillus serology and skin prick tests to Aspergillus fumigatus were negative. A sweat test was normal. Repeated sputum cultures grew no respiratory pathogens and were negative for acid fast bacilli. The cell type was neutrophils. Spirometric and plethysmographic volumes were normal, as was gas transfer factor, but the expiratory limb of the flow-volume curve showed a moderate reduction in airflow at low lung volumes. Bronchofibroscopy demonstrated severe generalised mucosal inflammation and purulent secretions.

Despite regular postural drainage, high doses of inhaled corticosteroids (budesonide via Turbohaler 1600 µg twice daily), and broad spectrum antibacterial therapy, she required readmission in February 1996.
continued to produce half a cup of green sputum daily with no respiratory pathogens on multiple sputum cultures. She did not respond to intensive physiotherapy and intravenous antibacterial therapy (including cefuroxime, metronidazole, ceftazidine and gentamicin), but with the introduction of oral corticosteroids a large reduction in sputum and an increase in percentage predicted FEV₁, from 60% to 113% was observed. Despite compliance with high dose inhaled corticosteroids, she has shown a consistent requirement for oral steroids (fig 2) but remains well with minimal sputum production and normal lung volumes on a small maintenance dose of oral corticosteroids. Repeat CT scanning with expiratory sections in October 1996 showed unequivocal—albeit partial—regression of bronchial wall thickness with no change in the diffuse extent of bronchiectasis.

Discussion

We believe this to be the first report of bronchiectasis developing within a year of colectomy in a patient with Crohn’s disease. There is a well recognised, albeit rare, association between bronchiectasis and inflammatory bowel disease. Kraft et al reviewed 1400 patients with inflammatory bowel disease for respiratory symptoms over a 40 year period and found only six cases of bronchopulmonary pathology, consisting of five patients with ulcerative colitis and a single patient with Crohn’s disease (who had chronic bronchitis but not bronchiectasis).¹ Neilly et al performed a detailed respiratory assessment of 29 patients with Crohn’s disease relative to a control group matched for age, sex, and smoking.⁴ No patient had chronic sputum production or overt bronchiectasis and lung function indices were essentially normal.

A recent review of the literature included 33 well detailed cases with inflammatory bowel disease and pulmonary manifestations.³ The five patients with Crohn’s disease had airways obstruction, chronic bronchitis or cryptogenic organising pneumonia, but not bronchiectasis. Bronchiectasis was seen in six of the 28 patients with ulcerative colitis, including three who developed severe bronchopulmonary suppuration a few days or weeks after colectomy. Butland et al had previously described unexplained chronic bronchial suppuration in seven patients with ulcerative colitis, including three with rapidly progressive bronchiectasis developing within a year of colectomy.²

The absence of a documented association between bronchiectasis and Crohn’s disease does imply rarity and raises the possibility of a chance association. However, strong circumstantial support for a real association include a clear temporal relationship to colectomy and, unlike idiopathic bronchiectasis, a repeated failure to identify bacterial pathogens and an impressive response to oral corticosteroids. The diffuse nature of the inflammatory process, seen both at bronchoscopy and on CT scans, is also compatible with a link to inflammatory bowel disease.

Chronic bronchial suppuration developed within months of colectomy and within a year bilateral bronchiectasis had developed de novo, as judged by serial CT appearances. Failure to isolate bacterial pathogens on repeated sputum culture and a need for oral corticosteroid therapy are both reported features of bronchiectasis associated with ulcerative colitis, in contrast to idiopathic bronchiectasis. This suggests that the pathogenesis of bronchiectasis in inflammatory bowel disease may be primarily autoimmune and that infection does not play as prominent a role as in the genesis of idiopathic bronchiectasis by the “vicious circle” mechanism.⁵ ⁶ It has been suggested that, following colectomy, the bronchial tree (which

Figure 1 (A) CT section through lower lobes two months after colectomy showing no evidence of bronchiectasis. (B) CT section through lower lobes one year after colectomy showing unequivocal bronchiectasis with prominent bronchial wall thickening.

Figure 2 Serial measurement of FEV₁ in relation to oral corticosteroid therapy. Airflow obstruction increased markedly on two occasions when therapy was withdrawn. Prompt improvement was noted with reinstitution of therapy.
has the same embryological origin as the bowel) becomes the new epitopic target for the immune system.\(^7\)

In conclusion, we believe that this case demonstrates what may be the first report of bronchiectasis developing after colectomy for Crohn’s disease. The close temporal relationship to colectomy, failure to identify bacterial pathogens, and an impressive response to oral steroids suggest a difference in pathogenesis to idiopathic bronchiectasis.


Bronchiectasis in association with coeliac disease

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