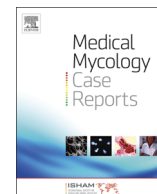




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Acute Aspergillus pneumonia associated with mouldy tree bark-chippings, complicated by anti-glomerular basement membrane disease causing permanent renal failure[☆]



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ABSTRACT

A non-immunocompromised man developed acute Aspergillus pneumonia after spreading mouldy tree bark mulch. Despite normal renal function at presentation, he developed rapidly progressive glomerulonephritis with acute kidney injury due to anti-glomerular basement membrane antibodies (anti-GBM) 4 weeks later. He remained dialysis dependent and died of sepsis 10 months later. We hypothesise that he contracted invasive pulmonary Aspergillosis from heavy exposure to fungal spores, leading to epitope exposure in the alveoli with subsequent development of GBM auto-antibodies.

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1. Introduction

Goodpasture's Syndrome has been widely described in the medical literature. It is characterised by a rapidly progressive glomerulonephritis due to circulating anti-glomerular basement membrane (anti-GBM) antibodies. The subject of this report developed acute pulmonary Aspergillosis following exposure to fungal spores in mouldy tree bark whilst gardening and this led to Goodpasture's Syndrome. We believe that this is the first presentation of Aspergillosis induced Goodpasture's Syndrome to be reported in the medical literature.

2. Case

A 69 year old retired man with no significant medical history was admitted to hospital with a 5 week history of increasing

dyspnoea and intermittent haemoptysis. He had worked in a metal foundry and cardboard works. Antibiotics in the community had not improved his symptoms. He was a lifelong smoker of 30 cigarettes per day.

On admission (day 0), his temperature was 37.2 °C, his pulse was 72, his respiratory rate 22 per minute and his blood pressure was 120/69 mmHg. His oxygen saturation on air was 90%, falling to 84% on walking. Bilateral crackles were present at the lung bases. Chest radiograph on day 0 revealed bilateral patchy infiltrates (Fig. 1a).

Initial blood tests revealed raised inflammatory markers (CRP 225 mg/L and leucocyte count $19.5 \times 10^9/L$ with a neutrophilia). Creatinine was 70 $\mu\text{mol/L}$. Initial urine dipstick was unremarkable. He was treated with amoxicillin and clarithromycin for community acquired pneumonia. Spirometry on day+5 was as follows: FEV1 1.69 L (55% predicted); forced vital capacity 2.59 L (65% predicted); FEV1/FVC ratio 65%.

On day+6, a high resolution CT of his thorax revealed widespread fine nodularity, maximal in the midzones and ill-defined peribronchial inflammatory shadowing. There was bronchiectasis (which had improved on a follow-up scan 2 months later) and patchy "tree-in-bud" change, but no radiological features of pulmonary haemorrhage. At bronchoscopy on day+7, endobronchial biopsies showed non-specific inflammatory changes, with no granulomata seen. Trans-bronchial biopsy was not possible as the patient's oxygen levels fell and so the procedure was abandoned. Serum ANA was weakly

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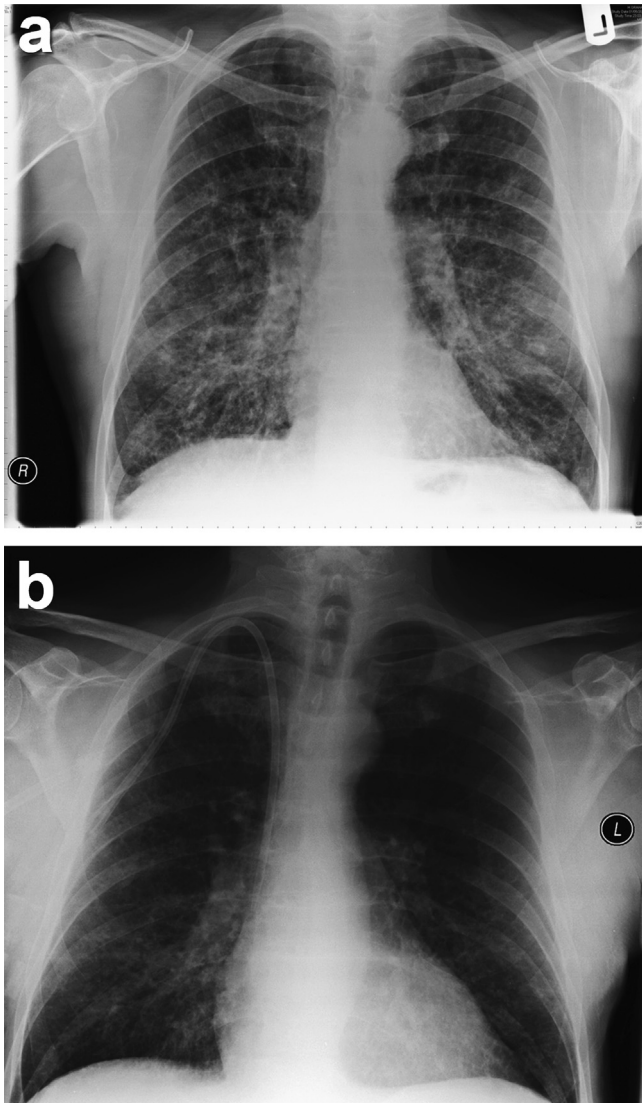


Fig. 1. Chest radiograph at presentation (a) and 2 months later (b).

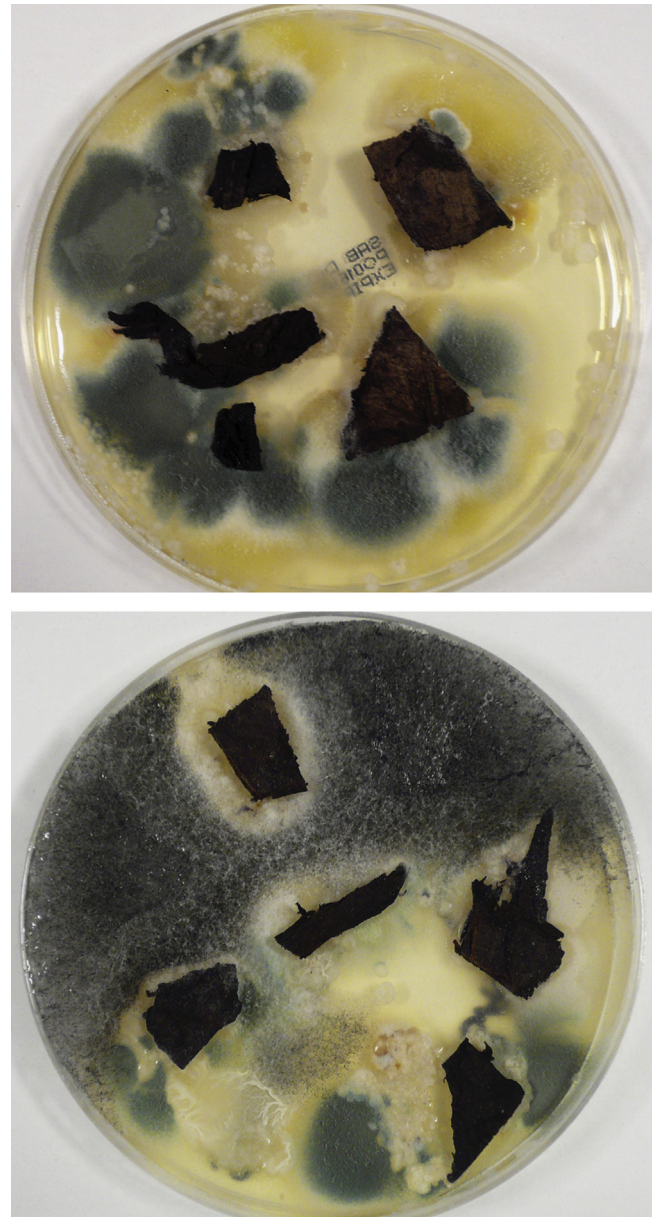


Fig. 2. Tree bark particles on fungal culture plates.

positive at 1/100 (speckled pattern) with negative ENA and ANCA. Blood levels of IgG and IgA were borderline elevated. Serum IgE was elevated at 1049 ku/L. He had elevated IgG to *Aspergillus fumigatus* of 47 mgA/L (reference range up to 40 mgA/L) but his *A. fumigatus* IgE level was normal. Galactomannan assay was not available at the time of this case report. A diagnosis of acute invasive pulmonary Aspergillosis (IPA) was made and he was discharged home on day+13, on oral Itraconazole, 200 mg twice daily. His discharge creatinine was 80 μ mol/L.

At clinic on day+27, his respiratory symptoms had improved substantially following treatment. His oxygen saturation was 95% at rest. He was able to climb 20 steps and the saturation did not fall below 90%. Spirometry was greatly improved at 2.4/3.9 (FEV1 78% predicted, vital capacity 90% predicted, FEV1/FVC ratio 61%). The chest radiograph showed substantial improvement (Fig. 1b). Direct questioning revealed that his symptoms had developed about 2 weeks after spreading eight, 40 L bags of foul smelling mouldy tree bark on the garden. This material was subsequently cultured in the National Aspergillosis Centre and it grew *A. fumigatus*, *Rhizopus* spp., *Sporobolomyces* spp. and bacteria (Fig. 2).

Blood results from clinic showed his renal function had dramatically deteriorated. His urea was 39.6 mmol/L and creatinine was 851 μ mol/L. He was readmitted urgently and itraconazole was stopped. Renal ultrasound revealed no urinary tract obstruction.

A renal immunology screen showed positive anti-glomerular basement membrane (anti-GBM) antibodies with a titre of 111 U/ml (ELISA assay) (reference range < 15 U/ml). Retrospective analysis of a blood sample from day 3 of his first hospital admission showed an anti-GBM titre of 67 U/ml at that time. Renal biopsy demonstrated necrotising crescentic glomerulonephritis with linear deposition of IgG along the basement membrane, consistent with anti-GBM disease.

On day+28, he was commenced on haemodialysis, pulsed methylprednisolone 500 mg once daily for 3 days, cyclophosphamide 750 mg (once monthly dose) and plasma exchange. Itraconazole was restarted due to the risk of reactivation of Aspergillosis. Despite these measures, he remained anuric. Subsequent anti-GBM antibody titres were significantly lower (20 U/ml 6 weeks post-presentation, 8 U/ml at 8 weeks and < 7 U/ml at 5 months post-presentation). *Aspergillus* IgG 6 weeks after his acute respiratory presentation had fallen to 7 mgA/L, and after 3 months total IgE was normal. Unfortunately the patient remained frail and

housebound despite haemodialysis and he died from severe sepsis and acute pneumonia 10 months after his first presentation.

3. Discussion

Invasive pulmonary Aspergillosis has specifically been reported in healthy individuals after spreading rotting tree bark whilst gardening [1–3]. In previous cases, massive inhalation of spores was thought to be the likely route of infection [3]. There is diagnostic difficulty in these cases and diagnosis is often made at post-mortem, because blood and sputum cultures have poor sensitivity [1,3]. Serological testing for *Aspergillus* IgG antibodies can be used in the diagnosis of IPA. In a study of patients developing IPA following bone marrow transplant, an IgG response to acute infection was noted [4]. *A. fumigatus* has been implicated in invasive disease.

Anti-GBM antibody disease is characterised by a rapidly progressive glomerulonephritis due to circulating anti-GBM antibodies. The target of these antibodies is the non-collagenous domain of the $\alpha 3$ chain of Type IV collagen [5]. There is a body of evidence to suggest that certain human leucocyte antigen (HLA) molecules, notably HLA-DR 15 and HLA-DR 4, are associated with the development of anti-GBM disease [6]. Subsequent analysis of our patient's HLA type revealed HLA-DR 17 and DR 4.

Hypothetically certain epitopes that are normally immunologically privileged can become exposed and perceived as foreign, leading to antibody development [7]. *A. fumigatus* conidia bind to type IV collagen (and fibrinogen), a process inhibited by free sialic acid and in particular N-acetylneuraminic acid [8]. Whether the binding of *A. fumigatus* to collagen IV in the lung altered the allergenicity of this major structural protein, allowing auto-antibodies to be formed, remains conjecture. It has been hypothesised that exposure to certain environmental factors may affect the molecular structure of $\alpha 3$ NC1 domain, making antibody binding more likely [5].

Development of Goodpasture's syndrome has been reported following exposure to inhaled chemicals, drugs and in association with infectious disease [9]. Hidden epitopes may become exposed during these episodes.

We hypothesise that our patient contracted invasive pulmonary Aspergillosis due to heavy exposure to fungal spores whilst gardening. This led to epitope exposure in the alveoli with subsequent development of GBM auto-antibodies and acute renal failure, in an individual with pre-existing genetic risk factors. We believe that this is the first such presentation in the medical literature.

Conflict of interest

We have no conflicts of interest in the publication of this article, including financial ones to declare.

Acknowledgements

All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication. The results presented in this paper have not been published previously in whole, or part, except in abstract form. The patient himself has since died and gave verbal consent for publication prior to his death. We have now obtained written consent from his wife for this case report to be published.

If our case report is accepted for publication we would wish the colour picture to appear in the printed journal (Fig. 2). We accept the charge for this.

The contributions of the individual authors are as follows. All of the authors were involved in the clinical care of the patient described in the case. Dr. T. Brockley performed the literature searches and drafted the discussion section. Dr. L. Butler drafted the case presentation. Both of the above authors were responsible for editing and revising the article prior to submission. Dr. O'Driscoll, Dr. Sinha, Professor Denning and Professor Richardson were involved in the editing process and also provided intellectual advice of critical importance regarding the proposed disease mechanism. Dr. Chisholm provided radiology advice regarding the patient. In addition, Dr. O'Driscoll initiated the writing of the article and edited each section. He also had final approval of the article prior to submission. Dr. Butler is the main contact correspondent. All authors have reviewed the article for final submission approval.

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