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Histoplasma capsulatum as a cause for prolonged pulmonary illness in an immunocompetent returning traveller from Bangladesh

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ABSTRACT

Fungal infections can be challenging to diagnose in returning travellers due to their non-specific clinical manifestations and changing epidemiology. We present a case of progressive disseminated histoplasmosis in a returning traveller from Bangladesh. The patient had a progressive and prolonged respiratory illness necessitating mechanical ventilatory support. The clue to potential fungal aetiology was provided by serum fungal markers - 1-3-β-D-glucan and *Aspergillus* galactomannan. Diagnosis was eventually made using panfungal PCR on bronchioalveolar lavage fluid.

1. Introduction

Fungal infections are a rare cause of febrile illness in a returning traveller [1]. *Histoplasma capsulatum*, a dimorphic fungus (mould in the environment, yeast in human body), is endemic mainly in the Americas but also in parts of Africa, Asia and Australia [2,3]. In Europe, it is predominately seen as an imported disease [4]. *Histoplasma* can cause a range of clinical syndromes and the presentation is often non-specific. In immunocompetent individuals, histoplasmosis is typically self-limiting and minimally symptomatic, with predominant symptoms being pulmonary, whilst severe, disseminated disease is more commonly seen in the immunocompromised [5–8]. The infection is typically acquired by inhalation during activities resulting in exposure to high numbers of microconidia such as demolition or construction work, cleaning of bird or bat droppings, or caving [2–5,9]. Construction work, in particular, has been associated with outbreaks of pulmonary histoplasmosis [7,9]. There are precautions such as water sprays and dust suppression which can be used to minimise aerosolization as well as respiratory mask precautions [7]. Histoplasmosis may be under-diagnosed and under-reported in endemic areas due to a reduced diagnostic and reporting capacity [4]. The occurrence of histoplasmosis in non-endemic areas is rare and its nonspecific features and specific investigations make this a challenging diagnosis [10].

2. Case presentation

A 57-year-old male presented the day (day 0) after returning from a 2-month trip to Bangladesh with a 6-week history of dry cough, fever, shortness of breath and night sweats. He had no past medical history other than type 2 diabetes mellitus which was well controlled on metformin and sitagliptin. He reported progressive respiratory symptoms whilst abroad despite multiple courses of antibiotics, including a short course of anti-tuberculosis therapy which he did not tolerate. He reported no contact with any unwell individuals. He had no history of exposure to contacts with tuberculosis. Whilst in Bangladesh he was involved in supervising construction works and landscaping. He lived in a rural area with farm animals – cattle and goats – in vicinity.

On examination at the emergency department, he was profoundly hypoxic and had bilateral crackles on lung auscultation. Chest X-ray showed diffuse bilateral airspace shadowing (Fig. 1). He was critically ill and admitted to intensive care requiring high flow oxygen (day 1). His blood tests revealed elevated *C*-reactive protein, deranged liver

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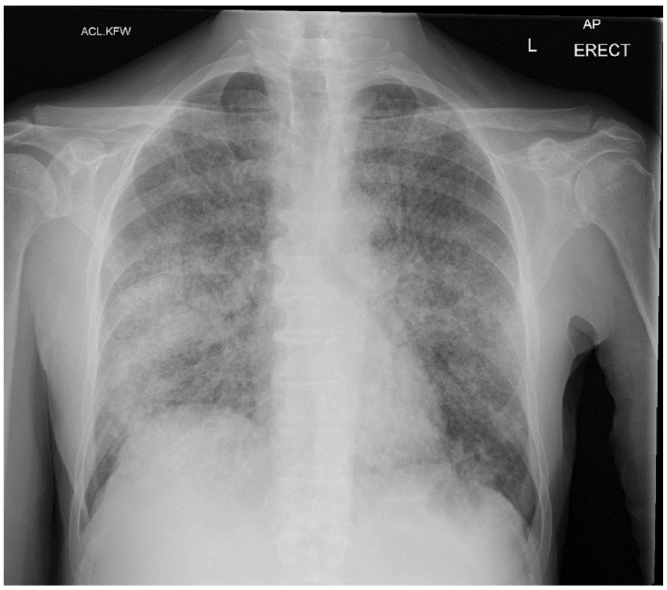

Fig. 1. CXR showing diffuse bilateral airspace shadowing.

function, hyponatraemia and metabolic acidosis (Table 1). Bacterial cultures of blood, urine and sputum were negative as was sputum staining for acid fast bacilli, and urinary antigens for *Legionella pneumophila* and *Streptococcus pneumoniae*. He was HIV negative. A respiratory viral PCR panel done on a throat swab detected *Rhinovirus* and *Parainfluenza virus* 2 RNA. One respiratory sample grew acid fast bacilli later identified as *Mycobacterium avium* in the reference laboratory.

CT scan of thorax (day 1) showed extensive ground glass opacification and consolidation in both lungs leading to air-bronchogram and grey hepatisation predominantly along the bases with wide differential diagnosis (Fig. 2). Serum 1-3-β-D-glucan was strongly positive (>500 pg/mL) and serum *Aspergillus* galactomannan positive (index of 0.995). He developed thrombocytopenia with a platelet nadir of 45 $\times$ 10^9/L one week into admission.

He progressively deteriorated and was intubated by the end of second week of admission. Following his intubation, a bronchioalveolar lavage (BAL) was performed and BAL fluid was sent for diagnostic testing. BAL fluid galactomannan was negative however it tested positive for *Aspergillus* PCR. As the patient neither had classical risk factors for nor imaging features suggestive of invasive aspergillosis, a panfungal PCR on BAL fluid was requested which showed presence of *Histoplasma capsulatum* DNA (day 44). Serological testing for *Histoplasma* antibodies using immunodiffusion assay was also positive.

Table 1
Patient's initial blood test results.

Haemoglobin (g/L)	138
White Blood Cells (x 10^9/L)	12.4
Neutrophils (x 10^9/L)	10.7
Lymphocytes (x 10^9/L)	1.2
Eosinophils (x 10^9/L)	0.1
Platelets (x 10^9/L)	552
Sodium (mmol/L)	125
Potassium (mmol/L)	4.8
Creatinine (umol/L)	100
Urea (mmol/L)	9.5
Albumin (g/L)	20
Bilirubin (umol/L)	19
Alkaline Phosphatase (u/L)	992
ALT (u/L)	164
CRP	261.1
pH	7.220
pCO2 (kPa)	3.9
Arterial pO2 (kPa)	7.4
Bicarbonate (mmol/L)	11.1
Lactate (mmol/L)	14.6

3. Differential diagnoses

The chronicity of symptoms, initial work up and lack of response to antibiotics given in Bangladesh prompted consideration of diagnosis beyond the common causes of fever in returning traveller and community-acquired pneumonia. Atypical pneumonia caused by intracellular bacterial pathogens, such as *Mycoplasma pneumoniae* and *Legionella pneumophila*, and *Mycobacterium tuberculosis* were the main differential diagnoses at admission. *Nipah virus* was not considered likely on the grounds of the chronicity of the symptoms and absence of exposure to bats, pigs, or date palm sap. The deranged liver function tests and transient thrombocytopenia along with his imaging, were considered non-specific.

Though *Rhinovirus* and *Parainfluenza virus 2* were detected in the respiratory tract it was not thought the clinical picture could be attributed solely to these pathogens. The patient's continued deterioration and lack of defervescence on conventional antibiotics or anti-tuberculosis therapy led to a broader consideration of potential causes. Non-infection differentials considered in this patient were autoimmune pathology such as vasculitis with lung involvement and malignancy, but imaging and immunologic screen did not support this.

A fungal cause seemed plausible especially in the context of a highly positive 1-3-β-D-glucan levels, considered less likely to be false positive. The differentials of fungal infection were invasive pulmonary aspergillosis, talaromycosis and histoplasmosis. Though a positive serum *Aspergillus* galactomannan and *Aspergillus* PCR on BAL were detected, aspergillosis was not considered a definitive diagnosis as the clinical picture and risk factors were not aligned. During the first three weeks of admission multiple consults were undertaken with centres external to our own to explore further possible diagnoses.

The finding by panfungal PCR of *Histoplasma capsulatum* DNA and a subsequent positive antibody for *Histoplasma*, along with presence of systemic features such as thrombocytopenia and markedly deranged liver function tests, confirmed a diagnosis of progressive disseminated histoplasmosis.

4. Treatment and outcome

Initially, the patient deteriorated quickly on admission and required management in intensive care unit. Broad-spectrum antibiotics were administered, as was anti-tuberculosis therapy on his second day of admission. Despite these treatments he remained febrile with no clinical improvement during his first week of admission.

Given his continued deterioration and raised fungal markers, empiric antifungal treatment with liposomal amphotericin B was commenced at the dose of 3 mg/kg once daily (day 12). Autoimmune disease was also considered when there was a failure to recover and covered with high dose IV methylprednisolone for 3 days and he defervesced following this. Despite this, in week two of his admission he continued to deteriorate clinically and was requiring ventilatory and inotropic support, as well as renal replacement therapy. His anti-tuberculosis treatment was withheld when his liver function worsened and discontinued when the diagnosis of histoplasmosis was established. Liposomal amphotericin B was continued until clinical improvement, where upon he was started on oral itraconazole at the dose of 200 mg twice daily, discontinuing liposomal amphotericin B when therapeutic levels for itraconazole were achieved. He has since been discharged from hospital (day 80) on a planned 12 months of antifungal therapy.

5. Discussion

The lack of travel history to classical endemic areas makes this case of histoplasmosis unusual and highlights the ongoing evolution of fungal

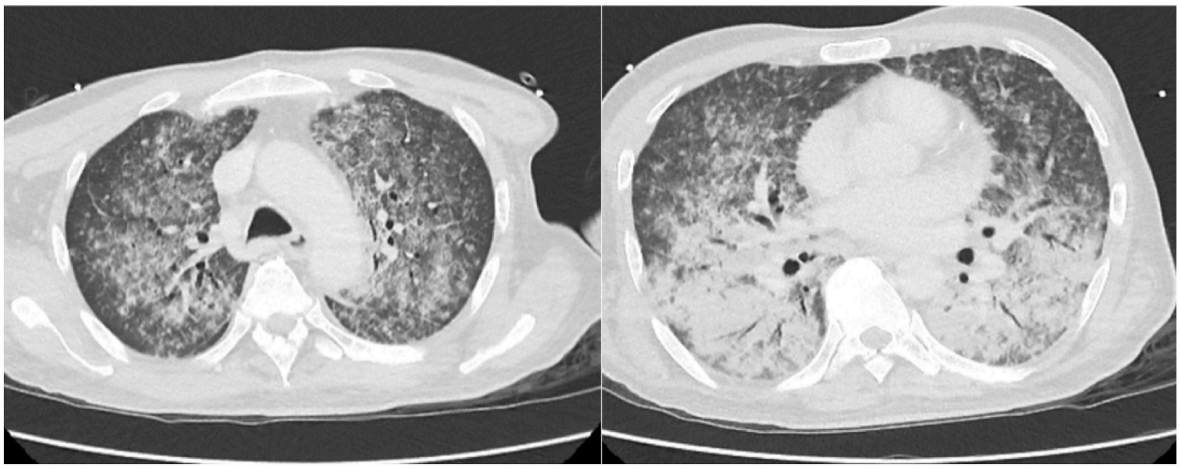

Fig. 2. CT scan of chest showing bilateral ground glass changes and consolidation.

epidemiology. Most cases seen in Europe are imported from the endemic regions such as South America and Africa [6]. *Histoplasma* is not a widely recognised cause of disease in Bangladesh, with only 26 cases reported in a 50-year period and the majority of cases were in the immunocompromised [8]. It is likely, that the true number of cases is much higher due to limited access to mycological diagnostics. Also, even when diagnostic tests are available, they are not always used as the clinical presentation of pulmonary histoplasmosis in immunocompetent individuals is very similar to that of pulmonary tuberculosis. As tuberculosis is very common, patients get treated empirically [8,11]. A study in a non-endemic area of US showed a mean of 41-day delay to diagnosis of histoplasmosis [3] which is consistent with our case.

The severity of pulmonary disease seen in this instance was likely to be at least partially due to a high initial inoculum of inhaled conidia he was exposed to whilst being involved in building work [9]. Working in occupations that involve exposure to soil containing bird or bat droppings is a risk factor for developing histoplasmosis and there have been outbreaks affecting bridge workers, construction or demolition workers, farmers, landscapers and tree removal workers [7]. Those living in endemic regions have often been exposed to *Histoplasma* and developed an immune response [5]. Our patient may have been more predisposed as he was a non-resident and non-immune. He was also type 2 diabetic which could have increased his risk for severe disease [8,11].

A broad range of investigations were performed, and it was vital they were interpreted in view of the clinical findings and history, with consensus on the significance of the various positive findings. The high level of 1-3-β-D-glucan (>500 pg/mL) directed the need for further investigations and a broad-spectrum antifungal agent. Whilst his serum *Aspergillus* galactomannan was positive this is known to cross react with the galactomannan present on *Histoplasma* [12]. Panfungal PCR was able to unequivocally establish the diagnosis, demonstrating its utility. This was despite concerns it would detect fungal respiratory commensals. However, panfungal PCR and the *Histoplasma* antigen test are only performed in reference laboratories and the total turnaround time is typically over 7 days. Therefore, initiating empirical treatment is critical for good patient outcomes like in our case. When suspected, histoplasmosis is commonly diagnosed through antigen or antibody testing and biopsy [5,8,13].

We feel a successful outcome in this case was through the combination of the use of newer technologies such as panfungal PCR combined with more classical medical skills of history taking and persistent open clinical discussion and appraisal of the patient's situation and results.

Declaration of competing interest

There are none.

Ethical form

Attached.

CRediT authorship contribution statement

Muhammad Rizwan Zafar: Writing – review & editing, Writing – original draft. **Thomas Whitfield:** Writing – review & editing, Writing – original draft, Supervision. **Sabeen Khurshid Zaidi:** Writing – review & editing. **Sanjeewani Weerakoon:** Writing – review & editing. **Joel Paul:** Writing – review & editing, Supervision. **Riina Rautemaa-Richardson:** Writing – review & editing, Supervision.

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