

## Primary invasive aspergillosis with disseminated intravascular coagulation as a presenting feature of non-Hodgkin's lymphoma



Margaret Balsitis<sup>a</sup>, Maha Elgoweini<sup>a</sup>, Sarah J Martin<sup>b</sup>, Gillian S. Shankland<sup>c</sup>, Jane Paxton<sup>a</sup>, Abhijit M Bal<sup>d,\*</sup>

<sup>a</sup> Department of Pathology, University Hospital Crosshouse, Kilmarnock KA2 0BE, United Kingdom

<sup>b</sup> Infection Unit, University Hospital Crosshouse, Kilmarnock KA2 0BE, United Kingdom

<sup>c</sup> Clinical Mycology Reference Laboratory, Southern General Hospital, Glasgow G51 4TF, United Kingdom

<sup>d</sup> Department of Microbiology University Hospital Crosshouse, Kilmarnock KA2 0BE, United Kingdom

### ARTICLE INFO

#### Article history:

Received 11 June 2015

Accepted 22 June 2015

Available online 2 July 2015

#### Keywords:

Invasive Aspergillosis

Disseminated intravascular coagulation

Non-Hodgkin's lymphoma

### ABSTRACT

Invasive aspergillosis (IA) is a life-threatening infection. IA is usually seen in severely immunocompromised patients. However, IA as a presenting feature of non-Hodgkin's lymphoma is rare. The patient we describe had no signs or symptoms of lymphoma prior to hospital admission. *A. fumigatus* was isolated from respiratory tract specimens on the day of admission and fungal elements were detected on autopsy. Isolation of *Aspergillus* in patients with severe sepsis should trigger a search haematological malignancy.

© 2015 International Society for Human and Animal Mycology. International Society for Human and Animal Mycology Published by Elsevier B.V. All rights reserved.

### 1. Introduction

Invasive aspergillosis (IA) is very rarely a presenting feature of haematological malignancy. We report the case of a previously healthy woman who presented with signs and symptoms of sepsis and disseminated intravascular coagulation (DIC) secondary to IA. Post mortem findings confirmed non-Hodgkin's lymphoma as the cause of her immunosuppression.

### 2. Case

A 62 year old woman presented to the Accident & Emergency department (day 0) with acute abdominal pain, diarrhoea and confusion. Her past medical history was unremarkable except for chronic obstructive pulmonary disease. She had stopped smoking 2 years previously. On examination, she was found to be profoundly hypotensive (blood pressure 60/25 mm Hg), tachycardic (heart rate 135 per minute) and tachypnoeic (respiratory rate 33 per minute). Her abdomen was tender particularly in the right upper and lower quadrants. There was no organomegaly. Digital rectal examination revealed dark blood. She was resuscitated aggressively with intravenous fluids and inotropic support, started

on intravenous (IV) antibiotics (amoxicillin–clavulanic acid, gentamicin, and metronidazole) and transferred to the intensive care unit.

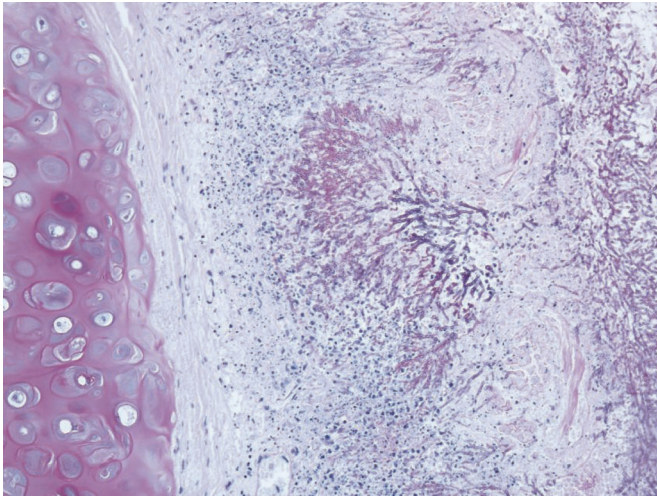
Initial blood results showed high bilirubin (30 µmol/L), low albumin (27 g/L) and modestly elevated C-reactive protein (35 mg/L). The white cell count was  $8.8 \times 10^9/L$  and the neutrophil count was  $5.2 \times 10^9/L$  with toxic granulations, reactive lymphocytes, and occasional blast forms on blood film. The clotting screen was grossly abnormal (platelets  $17 \times 10^9/L$ , prothrombin time 16 s, fibrinogen 67 mg/dl) consistent with DIC. She was administered four units of fresh frozen plasma, four cryoprecipitates and two pools of platelets. Abdominal computed tomography (CT) scan showed thickened right colon suggestive of pseudomembranous colitis, for which she was given oral vancomycin empirically. Stool was negative for *Clostridium difficile* toxin.

Chest X-ray showed extensive alveolar shadowing throughout the whole of the visualised right lung and the left upper zone in keeping with active infection. CT of the chest revealed right sided bronchopneumonia with parapneumonic effusion. *Aspergillus fumigatus* was isolated from her sputum and endotracheal aspirate on day 1 and although the significance of this finding was uncertain, she was commenced on IV voriconazole for a presumed active infection. Despite aggressive therapy, the patient died on day 2.

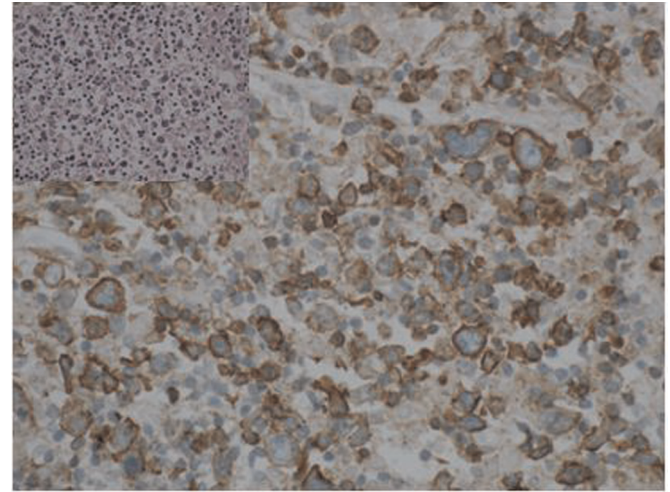
The most significant findings at post-mortem examination were pleural effusion, pulmonary oedema, and thrombosis of small pulmonary vein branches without infarction. There was no

\* Corresponding author. Fax: +44 1563 825000.

E-mail address: [abhijit.bal@nhs.net](mailto:abhijit.bal@nhs.net) (A. Bal).



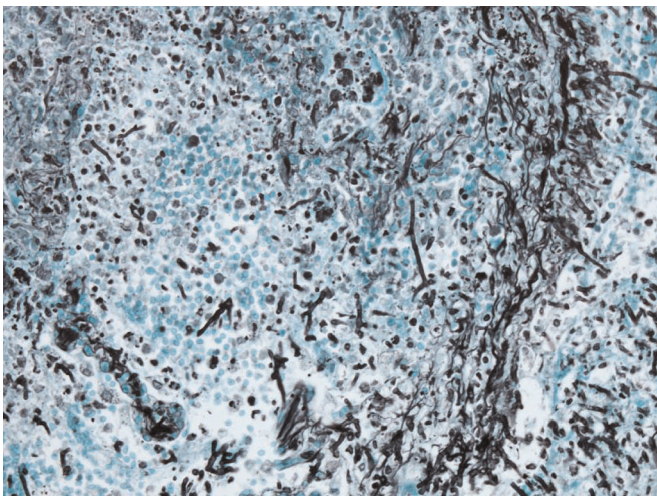
**Fig. 1.** Fungal hyphae in bronchial wall with adjacent necrosis and cellular debris. The mucus gland region has been destroyed but bronchial cartilage remains (left). Medium power. Periodic acid Schiff.



**Fig. 3.** Lymph node. Atypical lymphoid cells of T cell type with positive CD3 immunohistochemistry. High power. (Inset high power H&E).

definite evidence of pneumonia. The gastric mucosa was thickened and haemorrhagic with multiple ulcers, the largest being 20 mm in diameter with features of recent perforation. The liver was slightly enlarged (1821 g) and showed patchy pallor and congestion. The portal vein was focally thrombosed. The spleen was markedly enlarged (534 g) with focal infarction. There was minimal lymphadenopathy in the mediastinum. The small and large intestines were normal.

Histologically, small foci of intravascular thrombus were confirmed in lung and stomach, some of which were associated with septate fungal hyphae at both sites. Intra-bronchial fungal elements were also identified and were associated with underlying necrosis and destruction of the bronchial wall with invasion of hyphae into the adjacent lung parenchyma (Fig. 1). Fungi were also identified in the alveolar spaces and interstitium (Fig. 2). Portal vein thrombosis was confirmed. There was a neoplastic lymphoid infiltrate of medium and large sized cells with marked nuclear pleomorphism in the lymph nodes, the liver mainly in portal areas and widely in the stomach including the site of perforation. There was probable involvement of spleen but this showed marked post-mortem autolysis. On immunohistochemical staining, the neoplastic cells were positive for common leucocyte antigen, CD3, CD43, CD7, and focally for CD57, CD30 and granzyme (Fig. 3). The



**Fig. 2.** Fungi in alveolar spaces and interstitium. High power. Grocott-Gomori methenamine silver stain.

cells were negative for CD4, CD8, CD20, CD79a, ALK-1 and Epstein Barr virus. The immunoprofile was thus consistent with 'peripheral T cell non Hodgkin's lymphoma, not otherwise specified'. *A. fumigatus* DNA was detected in the tissue samples by polymerase chain reaction.

### 3. Discussion

IA is common in immunocompromised patients, particularly in those who suffer from prolonged neutropenia. *Aspergillus* is ubiquitous in the environment where it sporulates releasing conidia. Due to their small size (2.5–3  $\mu\text{m}$ ) the conidia remain airborne and when inhaled they reach the alveoli where they germinate and transform into hyphae. The hyphae invade local tissue and disrupt blood vessels causing pulmonary haemorrhage. Disseminated disease results from direct invasion of the intra-thoracic structures (heart and great vessels) or by haematological spread to distant organs. The most common site of metastatic disease is the central nervous system, but invasion of many solid organs has been reported including the thyroid, liver, kidneys and heart [1,2].

Leukaemia and lymphoma are the two most common haematological malignancies which predispose to IA [3]. However IA as a presenting feature of lymphoma is very rare with only two cases published in literature. Garcia-Gonzalez and colleagues [4] reported a case of diffuse small and large cell multi-centric lymphoma that was diagnosed at autopsy in a previously healthy man who presented with a sudden onset of a respiratory illness that progressed to respiratory failure leading to death. Histopathology sections of both lungs revealed septate hyphae with branching at 45° angles with vascular invasion consistent with IA. However, no extra-pulmonary foci of IA were detected. Nuss and colleagues reported a similar case in an infant [5].

Criteria for definitive diagnosis of invasive fungal disease have been published [6]. Definitive diagnosis of IA requires one of the following: microscopic documentation of infection namely presence of hyphae in histopathologic, cytopathologic or direct examination of a specimen obtained by needle aspirate or biopsy accompanied by evidence of tissue damage or a positive culture from a normally sterile material obtained by a sterile procedure from a clinically or radiologically abnormal site consistent with an infectious disease process (but excluding specimens such as bronchoalveolar lavage fluid, urine, and cranial sinus cavity specimens), or a positive blood culture consistent with infection. The diagnostic finding of *A. fumigatus* in sputum and tracheal aspirate

soon after admission is unusual in our experience and although it did not satisfy the criteria for definitive illness at the time of admission, it prompted us to start treatment with voriconazole. Voriconazole is recommended as the primary agent in for the treatment of IA [7]. Timely initiation of treatment for IA is a crucial determinant of survival and treatment should not be delayed while awaiting definitive diagnosis [8,9]. In scenarios where IA is suspected, the need for thorough investigation including high-resolution CT scan and serum galactomannan testing cannot be overemphasised [10]. The post-mortem evidence of hyphal invasion with necrosis in our patient established the diagnosis beyond doubt. It also established the diagnosis of non-Hodgkin's lymphoma. Isolation of *Aspergillus* from acutely ill patients presenting with community-acquired infection should trigger a search for an underlying cause including lymphoma.

#### Conflict of interest

None.

#### Ethical form

This patient died on day 2 following admission in the intensive care unit so it was not possible to obtain consent. However, no identifiable data are presented in this report.

#### Acknowledgements

None.

#### References

- [1] S. Schwartz, E. Thiel, Clinical presentation of invasive aspergillosis, *Mycoses* 40 (Suppl. 2) (1997) S21–S24.
- [2] T.J. Walsh, Invasive pulmonary aspergillosis in patients with neoplastic diseases, *Semin. Respir. Infect.* 5 (1990) 111–122.
- [3] S.J. Lin, J. Schranz, S.M. Teutsch, Aspergillosis case-fatality rate: systematic review of the literature, *Clin. Infect. Dis.* 32 (2001) 358–366.
- [4] M. Garcia-Gonzalez, A.L. Sanroman, R. Arribas, G. Torres, C. Cuesta, V. F. Moreira, Invasive pulmonary aspergillosis: a rare presentation of non-Hodgkin's lymphoma, *Postgrad. Med. J.* 70 (1994) 459–460.
- [5] R. Nuss, R.C. Ribeiro, N. Bunin, F. Behm, J. Jenkins, C. Berard, et al., Immunoblastic peripheral T-cell lymphoma confined to bone marrow in an infant presenting with aspergillosis, *Med. Pediatr. Oncol.* 16 (1988) 220–223.
- [6] B. De Pauw, T.J. Walsh, J.P. Donnelly, D.A. Stevens, J.E. Edwards, T. Calandra, et al., Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group, *Clin. Infect. Dis.* 46 (2008) 1813–1821.
- [7] T.J. Walsh, E.J. Anaissie, D.W. Denning, R. Herbrecht, D.P. Kontoyiannis, K. A. Marr, et al., Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America, *Clin. Infect. Dis.* 46 (2008) 327–360.
- [8] O.A. Cornely, J. Maertens, M. Bresnik, R. Ebrahimi, A.J. Ullmann, E. Bouza, et al., Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial), *Clin. Infect. Dis.* 44 (2007) 1289–1297.
- [9] R.E. Greene, H.T. Schlamm, J.W. Oestmann, P. Stark, C. Durand, O. Lortholary, et al., Imaging findings in acute invasive pulmonary aspergillosis: clinical significance of the halo sign, *Clin. Infect. Dis.* 44 (2007) 373–379.
- [10] S. Agrawal, W. Hope, J. Sinkó, C. Kibbler, Optimizing management of invasive mould diseases, *J. Antimicrob. Chemother.* 66 (Suppl. 1) (2011) i45–i53.