DISSEMINATED ASPERGILLOSIS IN AN IMMUNOCOMPETENT HOST WITH PREDISPOSING RISK FACTORS

(A Case Report)

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KEYWORDS :

Introduction

Aspergillus species number over 350 and are ubiquitous in nature, fortunately only a few are pathogenic. These fungi interact with humans to produce a spectrum of manifestations ranging from colonization to allergy to invasion and dissemination [1]. The usual risk factors for the development of dissemination are neutropenia and depressed cell mediated immunity. Thus such manifestations are common in patients with haematological malignancy, those on immunosuppressants and in the acquired immune deficiency syndrome [2]. A few cases with different predisposing risk factors for invasive and disseminated aspergillosis have been described in the world literature. These risk factors include viral, chlamydial, mycoplasma infection [3], thoracic surgery, glucocorticoid use, antibiotic therapy, previously damaged lungs and obstructive airway disease [4]. We report an immunocompetent patient with many of the latter risk factors, who developed disseminated aspergillosis.

Case Report

A 50-year-old veterinary surgeon was admitted in November 96 with complaints of fever, cough, weight loss, anorexia and dysuria of 2 months duration. The fever occurred daily with an evening peak of 100°F, with no chills, rigors or night sweats. The cough was productive of 15 to 20 ml of mucoid sputum per day. There was loss of appetite and 7 kg weight loss over the past 2 months. He had difficulty in initiating urine and found micturition painful. In February 1996 he had undergone an excision biopsy for a right side subclavicular skin nodule. This was diagnosed as a fungal infection, however, he had taken no treatment. In 1982 the patient had been treated for pulmonary tuberculosis with short term chemotherapy. In 1983 he had undergone resection of the right upper lobe. He was in good health thereafter except for episodes of cough and wheezing for which he self administered anti-

biotics and bronchodilators several times a year. As part of his occupation he had been exposed to birds and mammals. There was no history of hemoptysis or haematuria. He denied use of glucocorticoids. He had never smoked or consumed alcohol.

Physical examination at this time revealed a tall cachectic male with normal vital parameters but mildly elevated body temperature. Clubbing was present. Engorged pulseless neck veins were noted along with prominent veins on the thorax with drainage from above downwards. The skin, mucous membranes and upper respiratory tract examination was normal. The trachea was deviated to the right. The right infraclavicular area was retracted with an impaired percussion note and diminished breath sounds. In other areas a prolonged expiration and wheeze was present. The prostate was noted to be nodular. The rest of the examination was normal.

The haematological profile, bone marrow aspiration, serum immunoglobulins, CD-4 and CD-8 counts were normal. Sputum and urine studies for AFB and fungus were negative repeatedly. Metabolic parameters were in the normal range and serology for HIV antibodies was negative (Table 1). The chest X-ray showed a smaller right hemithorax with non-homogeneous opacities in the right upper zone bounded by a fissure and widening of the right upper mediastinal contour. A contrast enhanced CT of the chest revealed airspace shadows in the right middle lobe with a crescent sign and non-homogeneous nonenhancing cystic masses in the right anterior mediastinum (Fig 1). The right lower lobe showed multiple thin walled air cysts. A CT of the abdomen showed a cystic mass in the upper pole of the left kidney and multiple nodules in the prostate (Fig 2). Pulmonary function test revealed an obstructive defect with 10 per cent reversibility, a FVC which was 78 per cent of expected and a FEV-1/FVC ratio of 60 per cent. On tuberculin testing the response was 8 mm with 5 TU. Skin responses to tetanus and candida antigens were positive. On bronchoscopy the right upper lobe stump was unhealthy, no endobronchial abnormality was seen, lavage and biopsy were non contributory. Fine needle aspiration from the renal mass under ultrasound guidance as well as review of the excision biopsy slides revealed typical morphology of aspergillus hyphae in a back ground of granulomatous tissue reaction. *Aspergillus fumigatus* was grown in culture. A diagnosis of disseminated aspergillosis involving lung, mediastinum, kidney, prostate, skin with superior vena cava obstruction was made.

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TABLE I
Relevant haematological, immunological and metabolic tests

Haemoglobin	12.0 g%
Total leucocyte count	8600 cells/cu mm
Polymorphs	70%
Lymphocytes	26%
Eosinophils	04%
Peripheral smear Normocytic normochromic RBC series, No abnormal cells or haemoparasites seen	
CD-4 count	1028 cells/cu mm (by flow cytometry)*
CD-8 count	620 cells/cu mm (by flow cytometry)**
Serum immunoglobulins	
IgG	1480 mg/dl (N 650-1500 mg/dl)
IgM	160 mg/dl (N 55-300 mg/dl)
IgA	220 mg/dl (N 80 - 310 mg/dl)
Tuberculin test (5 TU)	8 mm
Candida antigen (Alcit labs)	6 mm (positive > 5 mm)
Tetanus toxoid (1:5 dilution)	7 mm (positive > 5 mm)
HIV-1 and 2	Negative by ELISA
HbsAg	Negative
Blood sugar : Fasting	80 mg% Postprandial 100 mg%
Blood urea	18 mg% S creatinine 1.0 mg/dl
S. Bilirubin	0.8 mg/dl S Albumin 3.5 g/dl S. globulins 2.5 g/dl
SGOT	28 IU/L SGPT 18 IU/L
Bone marrow aspiration . Adequate marrow particles. All the three series show normal maturation. The M:E ratio is maintained. No abnormal cells or intracellular organisms seen.	
Bone marrow culture for MTB by BACTEC - No growth	

*Normal range 420-1310 cells/cu mm, **Normal range 650-1130 cells/cu mm

Fig. 1. (A): CT scan chest: Lung window showing consolidation right middle lobe. Note crescent sign (arrow).
(B): Mediastinal window showing cystic lesions in the anterior mediastinum.

After an initial test dose, Amphotericin B was started and gradually increased to 1 mg/kg/day. Two weeks later the patient developed a lung abscess of the right lower lobe. The abscess wall showed irregular masses on the inner wall. There was also an increase in the size of the air cysts. *Pseudomonas aeruginosa* was grown in sputum culture. Cefizidime and Amikacin were added to the regimen and continued for 6 weeks along with postural drainage and an additional 5 mg/day Amphotericin B by nebulization. After one month, when the patient had received 1.2 gms of Amphotericin B, he was found to have fresh axillary lymphadenopathy, aspiration from which again yielded aspergillus. In view of the inadequate response, liposomal Amphotericin B 3 mg/kg/day was introduced along with Itraconazole 400 mg/day and Rifampicin 600 mg/day. There was apparent stabilization for one month, after which the patient developed haemoptysis from the site of lung abscess. Despite bronchial artery embolization and CT guided instillation of Amphotericin in the abscess, the haemoptysis proved fatal. The patient received 5.85 gms of liposomal Amphotericin and hence a total dose of 7.05 gms of Amphotericin B.

Autopsy confirmed diffuse aspergillosis of right middle lobe and cavity wall of right lower lobe, mediastinal nodes and prostate. Additional involvement of the liver was also seen, with multiple small granulomas containing hyphae. A necrotizing granulomatous reaction was seen in all the involved tissues (Fig 3-5). *Aspergillus fumigatus* remained culturable from the tissues.

Discussion

Virchow described 4 cases of pulmonary mycosis that were probably invasive aspergillosis in retrospect. Zimmerman attributed the dissemination of aspergillosis to a general lowering of body resistance, a local portal of entry and the use of antibiotics and steroids [5]. The radiological picture of pulmonary invasion is

Fig. 2: (A): CT scan abdomen showing cystic lesion upper pole right kidney.
(B): CT scan pelvis showing multiple prostatic lesions.

Fig. 3 : Liver Grocott stain showing necrotizing granulomatous lesions with hyphae of aspergillosis.

Fig. 4 : Lung Grocott stain X 200 showing hyphae of aspergillosis with typical branching pattern.

characterised by the crescent sign in an area of pneumonia resembling an aspergilloma but actually representing angioinvasion and infarction [1]. The prognosis in disseminated aspergillosis has been uniformly dismal. Most cases described, have shown a recurrence after an initial response. The drug of choice is Amphotericin B which has been combined variously with Flucystosine, Itraconazole or Rifampicin. Recently the liposomal form of Amphotericin has become available. Higher doses with minimal side effects are possible with this preparation. Amphotericin has also been used by nebulization and by local instillation into cavities [6].

Our patient was immunocompetent in view of normal WBC, CD-4, CD-8 counts and positive skin tests for tetanus and candida. The response to tuberculin suggests an old tubercular infection. Further the tissue response of necrotizing granulomatous inflammation also supports immune competence. On the other hand, the patient had occupational exposure, previously damaged lung, lung surgery, obstructive airways disease and frequent antibiotic use as multiple risk factors

Fig. 5 : Prostate Grocott stain X 400 showing aspergillosis hyphae in the prostatic stroma surrounding corpora amylacea.

for developing disseminated aspergillosis. The portal of entry appears to have been necrotizing pneumonia of the right middle lobe with angioinvasion and spread to other organs over a period of time. The commonly involved organs in dissemination have been lungs, brain, kidney, heart and thyroid, whereas involvement of mediastinum and skin is rare [7]. Superior vena cava obstruction and prostate involvement being reported for the first time by us.

The lack of response to therapy as well as the ability to culture the organism postmortem from involved tissue suggests drug resistance, or inadequate tissue levels of the drugs used. Unfortunately facilities for drug resistance studies and monitoring blood levels of the drugs used are not available in our institution. Unresponsiveness may have also been due to an overwhelming tissue fungal load and delay in exhibition of treatment.

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