Salvage therapy with topical antifungal for *Aspergillus fumigatus* empyema complicating extrapleural pneumonectomy

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Abstract

We describe an unusual case of *Aspergillus fumigatus* empyema and bronchopleural fistulae after extrapleural pneumonectomy (EPP) and chemoradiotherapy (CRT), which was treated successfully under salvage conditions with debridement, an innovative topical antifungal application and supplemented systemic antifungal therapy and which went on for a definitive surgical procedure. Combinations of CRT and EPP have been recommended in a select group of patients with malignant mesothelioma. Irrespective of the combination, EPP is associated with mortality in the range of 4–15% and a complication rate as high as 62%.

Keywords: Mesothelioma • Extrapleural pneumonectomy • Empyema • *Aspergillus fumigatus* • Posaconazole • Amphotericin

CASE REPORT

A 63-year old male was admitted with a progressive cough and expectoration within 2 weeks of finishing adjuvant chemoradiotherapy (CRT) following a right extrapleural pneumonectomy (EPP) for stage 1b malignant epithelioid mesothelioma.

He was a fit ex-shipyard worker and a keen mountaineer, who presented with a brief history of shortness of breath and a right pleural effusion. Following investigations and diagnosis of mesothelioma, the patient was referred to the mesothelioma surgical trial centre. Surgical intervention included an EPP using an intercostal muscle flap to buttress the bronchial stump. This was followed with four cycles of chemotherapy and 30 fractions of radiotherapy without any major adverse effect.

Imaging revealed bronchopleural fistulae (BPF) and a collection in the right pleural cavity. Insertion of the intercostal chest drain drained a thick yellow fluid. The specimen remained negative on culture and empirical treatment with piperacillin-tazobactam 4.5 gm IV every 8 h was continued for a week. Investigations of note included haemoglobin 7.8 gm/dl, white cell count $12.1 \times 10^9/l$, C-reactive protein over 180 mg/l, creatinine clearance of 46 ml/min and alkaline phosphatase 146 units/l. The patient was observed to be malnourished and cachexic with a total protein of 50 gm/l (60–80 g/l) and albumin of 20 gm/l (30–52 gm/l).

Further surgical management included rib resection under general anaesthesia by which fifth and sixth ribs were partly resected to create a window for the free drainage of the empyema cavity. The patient received prophylactic cefuroxime 1.5 gm IV at induction and 750 mg IV every 8 h postoperatively for a few days, and was then switched to piperacillin-tazobactam 4.5 gm IV every 8 h and metronidazole 400 mg IV every 8 h for

a further 10 days. The postintervention period was associated with clinical deterioration including pyrexia, copious wound discharge and raised inflammatory markers. The antibiotic treatment was escalated to meropenem 1 gm IV every 8 h and teicoplanin 800 mg IV every 24 h after loading 800 mg every 12 h for two doses and continued for the next 2 weeks. *Aspergillus fumigatus* was revealed on a culture of swabs obtained from the pleural cavity during routine dressing. Antifungal treatment was initiated with voriconazole 4 mg/Kg IV every 12 h after loading doses of 6 mg/Kg IV during the first 24 h. Elevated liver enzymes prompted a change after 4 days to caspofungin 50 mg every IV 24 h after a loading dose of 70 mg IV on Day 1. Physical examination of chest wound and pleural cavity revealed an extensive lining of the cavity with a dirty grey layer with some thickened patches (Fig. 1). This included the area of the prosthetic mesh used to replace the right diaphragm and pericardium. Further culture of the samples obtained from the pleural cavity revealed a pure profuse growth of *A. fumigatus*.

A multidisciplinary team (MDT) discussed the management of this complex case with a rather unusual location of the fungal infection and the limitations of antifungal administration through various modes of delivery.

The MDT agreed on the use of a haemostat powder Spongostan® (Johnson & Johnson, Norderstedt, Germany), as a mode of local sustained delivery of amphotericin B. Spongostan is an inert substance made up of gelatine granules, has excellent adhesive property and is commonly used during cardiac surgery. Approximately 4-vials (200 mg) of reconstituted amphotericin B deoxycholate (Fungizone®) were mixed in 4 gm of Spongostan® to constitute the slurry. Following the patient consent for this salvage procedure, and under general anaesthesia, this slurry was applied to the whole of the right pleural cavity including the

Figure 1: Dirty grey layer of fungal growth on chest wall (A) and prosthetic sheath (B) as seen through the chest wall window created for the drainage of empyema.

prosthetic mesh replacing the pericardium and diaphragm, and the rib resection was refashioned.

Post-procedure, systemic posaconazole 400 mg orally every 12 h was supplemented for 6 weeks. The patient demonstrated a clinical response. His chest cavity cleared overtime, the amount of secretions decreased and inflammatory markers improved. Serial cultures remained negative for fungus but continued to be positive for pseudomonas and treated as per sensitivity. He went on to have an omental flap transposition and closure of chest wall defect and had a good recovery from this complication, but succumbed to mesothelioma 8 months latter.

DISCUSSION

Empyema and bronchopleural fistula formation are known complications of EPP with an incidence of up to 15.8 and 9.5%, respectively. Right-sided procedure, induction chemotherapy, prolonged procedure, blood transfusion and male sex have been identified as risk factors [1, 2]. This male patient had a right EPP with prosthetic reconstruction and did receive blood transfusion.

This fit and well patient tolerated his extensive surgery and CRT, but after developing empyema with BPF, became malnourished. His malnourished state, in combination with multiple broad spectrum antibiotics and prosthetic material in the chest made him prone to opportunistic infections.

An extensive literature review did not reveal any report of *A. fumigatus* empyema and BPF after EPP and CRT. Most cases of fungal empyema are caused by the *Candida* species in critically ill patients with high mortality. Fungal empyema by the *Aspergillus* species has been reported as associated with the

rupture of a pre-existing pulmonary aspergillus cavity or following surgery for a similar pathology [3].

The systemic antifungal treatment had limited response, possibly on account of a gross fungal infection in the chest cavity lined by fibrotic lining with limited vascularity and extensive prosthetic material.

Local (topical) antifungal application appeared to hold a potential benefit; however, the expanse of fungal infection over the topography of the pleural cavity with limited access posed a challenge for using any local delivery method, permitting an extended exposure to the antifungal agent.

There are reports of intra-pleural irrigation with amphotericin-B in *Aspergillus* empyema and fluconazole in *Candida* empyema [3, 4]. The time-tested well-established rib resection and creation of a window for the free drainage of the empyema cavity [5] for treating this dreaded complication excluded intra-pleural irrigation as an option.

There is no case report of the use of an antifungal agent mixed with a haemostat agent topically. Spongostan® is a sterile gelatine in a powder form and is commonly used as a topical haemostat in surgery. It is an inert substance that conforms to irregular surfaces and gets absorbed in 4–6 weeks.

Extensive radical surgery at this stage by removing all the prosthetic material and dealing with the BPF surgically was not possible because the mediastinal and abdominal organs were still very mobile and because of the severely malnourished and immunocompromised state of the patient.

Our case highlights that the topical application of an optimal antifungal in a vehicle permitting extensive local exposure in a topographically challenging cavity is effective in a complex case of fungal empyema.

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