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Successful management of Aspergillus infection of an open window thoracostomy with topical liposomal amphotericin B

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ABSTRACT

We present the case of a previously healthy 54-year-old man who was hospitalized for an Aspergillus fumigatus infection of an open window thoracotomy. Patient was successfully treated for 8 consecutives weeks with daily topical pleural liposomal amphotericine B administered by soaked gauzes combined with systemic therapy.

1. Introduction

Empyema is a known complication of pulmonary resection. In less than 5%, fungus is found to be the source of pleural infection. [1] Exceptionally, *Aspergillus fumigatus* is identified as the pathogen. The diagnosis of pleural aspergillosis is made by demonstration of the organism in pleural effusion or in pleural biopsy. [2] This type of infection is generally lethal if not treated, but very few evidences exist in the literature to guide the clinician towards the best treatment of an *Aspergillus fumigatus* empyema [1–6]. Pleural aspergillosis is a rare manifestation of invasive aspergillosis and is not necessary associated with pulmonary manifestations. [2] Tuberculosis, bronchopleural fistula, pleural drainage and lung resection are known risk factor for pleural aspergillosis. [2].

Intrapleural therapy of amphotericin B administered by a thoracic drain has been successful in an 8 years old patient [3]. Furthermore, four adult patients were treated with an intrapleural infusion of amphotericin B [2], administered by a pleural drain as an instillation [4]. Finally, one patient who had a resistant *A. fumigatus* infection in an open thoracic window underwent a topical treatment using a haemostat Spongostan powder as a pleural delivery method [5].

2. Case presentation

The patient was a 54-year-old man with no known prior medical conditions. He was diagnosed with a right lower lobe pulmonary cancer and underwent a right lower lobectomy and a middle lobectomy in April 2020 (day 0). Final staging was a T1aN2M0 stage IIIA pleomorphic lung carcinoma. Adjuvant treatment was proposed but post-operative course was complicated by a prolonged air leak, followed by a bacterial empyema. Therefore, no chemotherapy could be given to the patient. A bronchopleural fistula was discovered on day 18 during a bronchoscopy. On the same day, the patient underwent an open window thoracostomy as a definitive treatment. *Streptococcus pneumoniae* was identified on the pleural culture done in the operative room. No fungus was identified at that moment neither on thoracic pus nor during bronchoscopy. He was discharged from the hospital with IV antibiotics for 6 weeks (Ceftriaxone 2g IV daily).

On day 49, a thoracic biopsy, specimen was collected from the thoracic window and grew *Aspergillus fumigatus*. Oral voriconazole 300 mg PO q12h for 2 doses, then 200 mg PO q12h was then started as an outpatient treatment on day 95. On day 102, the patient presented to the hospital with weight loss and asthenia, and looked malnourished (BMI 13.7). Upon admission, macroscopic fungal colonies were visualized in the thoracic window (Fig. 1.). White cell count, C-reactive protein and albumin were respectively 15.7×10^9/L, 163mg/L and 18g/L. Thoracic CT scan showed new posterior pleural thickening and hyper density in the thoracic window area (Fig. 2.). The presence of *Aspergillus fumigatus* was confirmed by culture once again. Voriconazole level was supratherapeutic at the admission with 200 mg PO q12h (Table 1).

For severe malnutrition, the patient received continuous enteral feeding via naso-enteric tube. To switch to intravenous voriconazole with a reduced weight adjusted dose based on previous dosage (Table 1) [7]. Systemic treatment of voriconazole was continued with a close

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follow up of blood concentration due to the low body weight of the patient (39kg). 23 days after the start of systemic antifungal therapy, the macroscopic aspect of the infection didn't change and because of complex medication management, the therapeutic level of voriconazole was never reached. No drug interactions were noted during voriconazole treatment and no explanations were found for the subtherapeutic level of voriconazole.

During a multidisciplinary meeting and after a literature review, it was decided to try liposomal amphotericine B applied topically with gauzes on concerned areas in the open window of the thoracostomy. Based on the case reported by Purohit and al. and on the weight of the patient, an initial dose of 50 mg Ambisome^{MD} (1.3 mg/kg daily) was selected and started on day 117 [6]. To the extent of our knowledge at that time, no similar case is listed in the literature and therefore, a conservative daily dose was picked to minimise systemic absorption.

The patient's bronchopleural fistula restrained our capacity of inserting a large quantity of liquid into the window. Consequently, the 50 mg vial was diluted in 100 ml of dextrose 5% and then divided equally into 2 syringes of 25 mg/50 ml that were used on gauzes locally each day. Macroscopic aspect of the pleura was assessed by pleuroscopy by weekly intra cavity pictures and videos. Improvement was noted weekly, so the liposomal amphotericine B dose remained the same throughout treatment. There was no sign of amphotericine B toxicity. Since serum galactomannan detection can be useful, this test was performed on pleural liquid obtained by wringing out gauzes used on fungus. Initial pleural galactomannan antigen was positive with an Optical Density Index (ODI) of 8.56. Throughout hospitalisation, therapeutic levels of systemic voriconazole were never reached (Table 1). The mean tourn around time for voriconazole serum levels was three days since it was done off site. It complicated the management of voriconazole dosing. Despite subtherapeutic IV anti-fungal concentration, we noted a progressive improvement of the macroscopic aspect of the fungus macroscopic colonies with topical amphotericine B. Systemic voriconazole was switched to oral posaconazole on day 138 because of non-therapeutic levels and the fact that oral posaconazole is better absorbed with food.

During the following weeks, subsequent control videos showed a regression of all fungus spots. A total of 8 weeks of topical treatment was used with no complications. Local amphotericine B and systemic posaconazole were stopped when complete disappearance of macroscopic aspect of the fungus was noted on day 173. The galactomannan antigen trend to diminish through the weeks with a last ODI index of 1.22. At one month follow up (day 213), there was no macroscopic sign of recurrence and the galactomannan on the pleural liquid (swab) was negative. The thoracic CT scan shows resolution of posterior pleural thickening (Fig. 3.). On day 402 there is still no sign of recurrence.

3. Discussion

Topical liposomal amphotericine B therapy can be safely used in the treatment of *Aspergillus fumigatus* empyema in an open window thoracotomy. Liposomal amphotericin B in thoracic instillation has been used successfully in previous case report with reported side effect of fever and increase protein C reactive after five days of administration. [1] Different methods of administration of topical amphotericin B have been used. Purohit et al. used successfully 200 mg of amphothericine B deoxycholate mixed in 4 gm of Spongostan ® to constitute a slurry that isn't available in Canada. [5] Bonatti et al. reported four cases of post-lung resection *Aspergillus fumigatus* empyema. [4] Two patients had pleural instillation and the two other had pleural rinsing (no information on doses and method). [4].

Ashizawa et al. also reported the used of local amphotericin-B up to 25 mg in 50 ml of NaCl 0,9% immersed-gauze dressing in a thoracic window. [8]In this case report, the lobectomy was done for a co-infection between *Mycobacterium avium* and *Aspergillus fumigatus* cavitary lesion, in this case the risk of fungal empyema was higher. Like in our patient, macroscopic fungus was visible in the thoracic window. They did pleural biopsy that confirm the diagnosis. After 2 months of daily amphotericin-B -immersed gauze dressing the pleural macroscopically improved and no fungi were detected [8].

Since our patient had sub therapeutic serum levels of antifungal medication for most of his treatment duration, we could question if topical therapy alone could be enough to cure Aspergillus open window thoracotomy infection. Systemic antifungal drugs have many

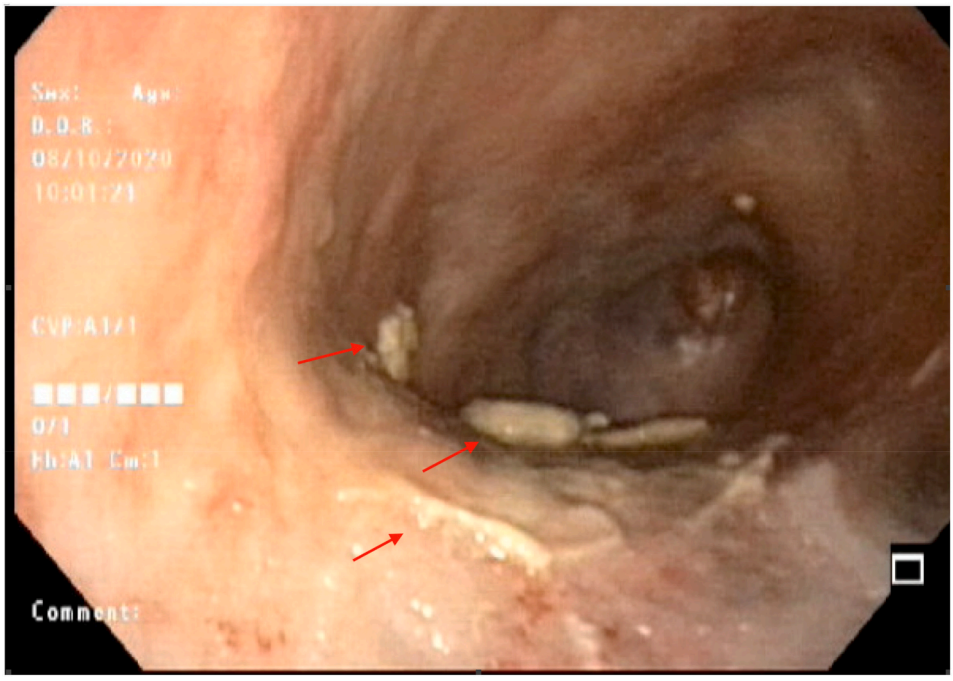

Fig. 1. Right pleuroscopy: Parietal pleura within the right chest cavity with macroscopic fungus disease (red arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

concerning side effects and drug-drug interactions that can be very difficult to manage. It could be of patient's interest to establish an efficient localized treatment bypassing those troubles. Unfortunately, the available data in medical literature published until now are insufficient to conclude if topical amphotericin alone would be enough to cure this infection. At this time, we do not recommend omitting systemic therapy.

Because of few case reports and with our difficulties with non-therapeutic level of IV anti-fungal, we cannot extrapolate on the optimal duration of topical therapy. Like in Ashizawa et al. case report, it took us 8 weeks of daily amphotericin-B immersed gauze dressing to see resolution of pleural fungi. [8] Galactomannan antigen is not validated for use in a thoracic cavity but can be used as a marker of infection control. It is interesting to observe that its level paralleled with resolution of the macroscopic colonies. Weekly pleuroscopy assessment of the pleura was key in this treatment. It allowed us to optimize our gauze packing where the macroscopic colonies were.

This case also demonstrates that when instillation by a pleural drain isn't available, it's possible to use, as an alternative, soaked gauzes applied directly in the thoracic cavity. There is no standardized approach to deliver amphotericin B to the pleura and no standardized duration. We think it is important to report successful treatment *Aspergillus fulmigatus* empyema so it can be used again.

Since *Aspergillus fumigatus* thrive in necrotic and aerobic environment, the thoracic window with the bronchopleural fistula may have promoted this infection [2]. We almost never used antifungal prophylaxis for bronchopleural fistula and we are not planning modification in our protocols but we should definitively consider treating earlier pleural fungal infection with topical antifungal.

In conclusion, topical anti-fungal therapy is a good therapeutic alternative in the treatment of Aspergillus fumigatus empyema in an open window thoracotomy. This case showed resolution of the infection with no side effect or toxicity.

Table 1
Therapeutic drug monitoring of antifungals regimen.

Date	Day 104	Day 109	Day 117	Day 123	Day 124	Day 132	Day 146
Voriconazole dosing regimen	PO: 200 mg q12h	IV: 100 mg q12h	IV: 150 mg q12h	IV: 150 mg q12h	IV: 150 mg q12h	IV: 150 mg AM + 200 mg PM	
Voriconazole levels (mcg/mL)	6.84	<0.3	0.55	0.38	<0.3	0.95	
Posaconazole dosing regimen							PO: 300 mg q24h
Posaconazole levels (mcg/mL)							1.61

IV: intravenous; PO: oral. Voriconazole target level = 1 à 5,5 mcg/ml. Posaconazole target level = > 1,8 mcg/ml.

Ethical Form

Please note that this journal requires full disclosure of all sources of funding and potential conflicts of interest. The journal also requires a declaration that the author(s) have obtained written and signed consent to publish the case report report/case series from the patient(s) or legal guardian(s).

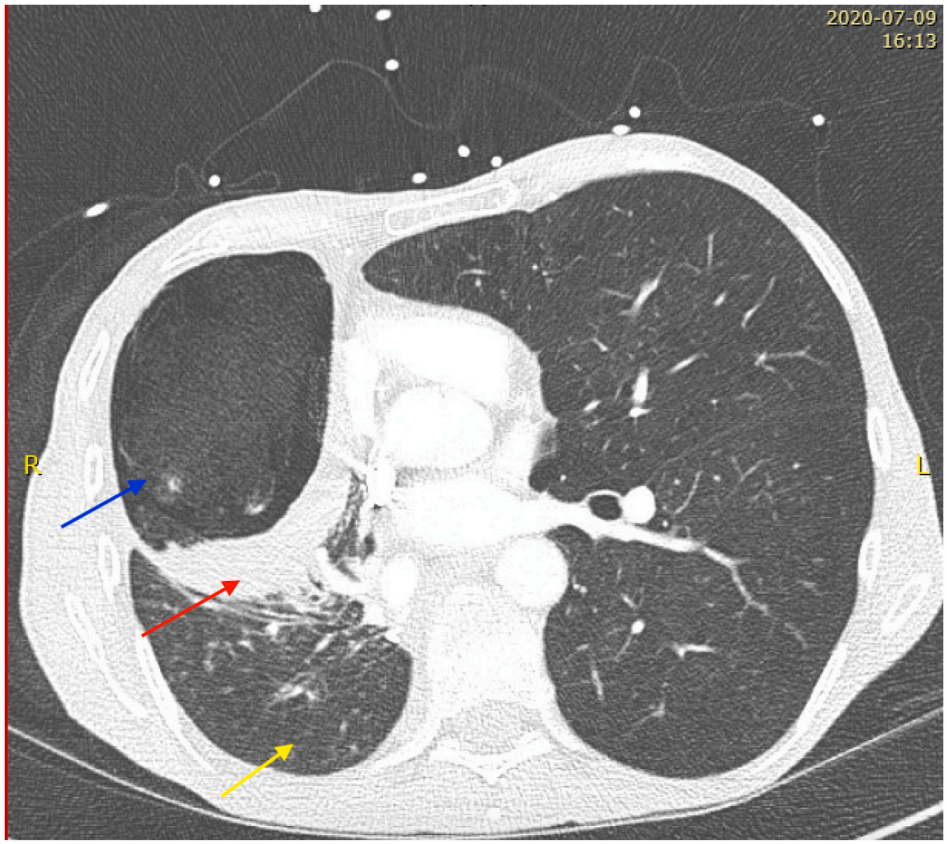

Fig. 2. Computed tomography (CT) scan of the chest before treatment: Right thoracic window (blue arrow), Pleural thickening (red arrow) caused by the fungus and inflammation, Right lung parenchyma (yellow arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

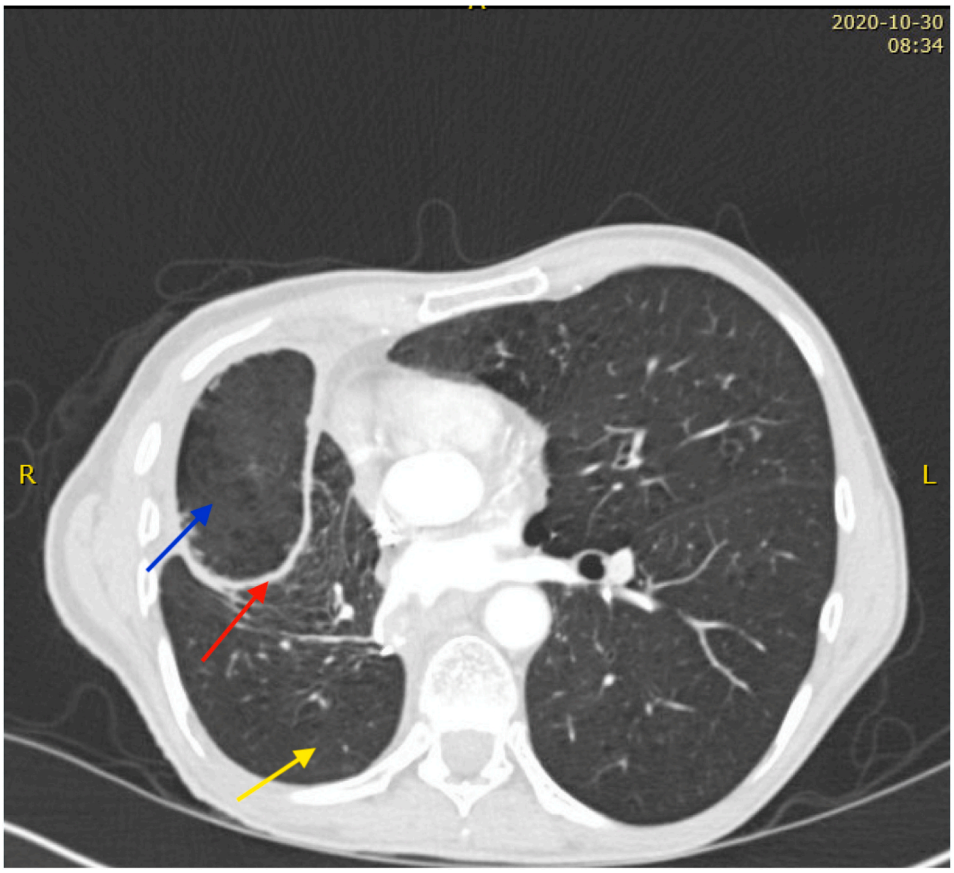

Fig. 3. Computed tomography (CT) scan of the chest after treatment: Right thoracic window (blue arrow), Reduced pleural thickening (red arrow), normal right lung parenchyma (yellow arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

The statements on funding, conflict of interest and consent need to be submitted via our Ethical Form that can be downloaded from the submission site www.ees.elsevier.com/mmcr. Please note that your manuscript will not be considered for publication until the signed Ethical Form has been received.

Declaration of competing interest

There are none.

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References

[1] I. Abraeu, M. Guedes, R. Duro, et al., Pleural aspergillosis in a patient with recurrent spontaneous pneumothorax: the challenge of an optimal therapeutic approach, Medical Mycology Case Reports 28 (2020) 4–7.

[2] H. Meredith, B. Cogan, B. McLauglin, Pleural aspergillosis Am.J Roentgeol. 130 (1978) 164–166.

[3] A. Almuhareb, Z. Habib, Management of Aspergillus pleural empyema with combined systemic and intrapleural antifungal therapy in a pediatric patient: case report, J Infect Public Health 11 (2) (2018 Mar-Apr) 280–282.

[4] H. Bonatti, C. Lass-Floerl, K. Angerer, N. Singh, M. Lechner, I. Stelzmueller, R. Singh, T. Schmid, C. Geltner, Successful management of postpneumonectomy Aspergillus pleural empyema by combined surgical and anti-fungal treatment with voriconazole and caspofungin, Mycoses 53 (5) (2010) 448–454.

[5] M. Purohit, A. Guleri, J. Zacharias, Salvage therapy with topical antifungal for Aspergillus fumigatus empyema complicating extrapleural pneumonectomy, Interact. Cardiovasc. Thorac. Surg. 15 (3) (2012) 518–519.

[6] B. de Vega Sanchez, I. Lopez Ramos, R. Ortiz de Larazu, et al., Empeima Fungico : una entitad con elevada mortalidad, Arch. Bronconeumol. 53 (2017) 641–642.

[7] R. White, V. Bradnam, Handbook of Drug Administration via Enteral Feeding Tubes, third ed., Pharmaceutical press is the publishing division of the Royal Pharmaceutical Society, 2015, pp. 693–694.

[8] N. Ashizawa, S. Nakamura, S. Ide, et al., Successful treatment of asperfillus empyema usinf open window thoracotomy salvage treatment and the local administration of an antifungal agent, Intern. Med. 55 (2016) 2093–2099.