



Evolution of Surgery Offered to Aspergilloma over 2 Decades, Institutional Report

Hysam Abdelmohty^{1,*}, Salah Eldin Khalaf¹, Walid Hassan¹, Ahmed Mostafa¹, Mohamed-Adel Elanwar²

¹Cardiothoracic Surgery Department, Mansoura University, Mansoura, Egypt

²Cardiothoracic Surgery Department, Cairo University, Cairo, Egypt

Email address:

hysam.mohty@gmail.com (H. Abdelmohty)

*Corresponding author

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Abstract: *Background:* Aspergilloma is the localized form of pulmonary colonization by *Aspergillus* species, which often hosted within a pre-existing cavitory lesion. The Aspergilloma (commonly known as mycetoma or fungus ball) consists of fungal hyphae, aggregates of inflammatory cells, fibrin threads, and destructed tissues debris. *Aspergillus Fumigatu* is the commonest species responsible for such lesions. In this study, over 20 years, data were collected for examination, on the outcomes of surgery for pulmonary Aspergilloma. *Methods:* Retrospective study of 54 patients, dating from January 1996 and December, 2015. Each patient's preoperative, diagnostic, operative, postoperative and follow up data was collected for analysis. *Results:* Findings of 54 patients who underwent surgery for Aspergilloma, 47 had clinical diagnosis. While remaining 7 were confirmed post-resection. The median age was 46.3±7.8 (aged 17-64 years). Risk assessment identified that greater probability for the Left Lung to be infected and increase if gender was male (2.6:1). The main presentation was hemoptysis, seen in 70.4% of cases, while symptoms of cough and expectoration occurred in 83.3% of them. The most prevalent predisposing factor was tuberculosis (TB), present in 57.4% of cases. The indication for surgery was recurrent hemoptysis, asymptomatic simple Aspergilloma and complex Aspergilloma. All the patients underwent pulmonary resection, with 82.5% of cases having lobectomy. The main postoperative complication was prolonged air leak 29.6% (16/54). The in-hospital mortality rate was 7.5% (6/54) patients. Conclusion: Surgery offered to Aspergilloma patients (fungus ball) brought beneficial results with an acceptable morbidity. The mortality observed within these cases, was predominantly due to high risk patients, with complex Aspergillosis. Recommendations for a multidisciplinary approach, in future cases, are paramount for better selection criteria.

Keywords: Fungus Ball, Hyphae, Aspergilloma, Cavity, Hemoptysis, Lobectomy

1. Introduction

Aspergillus encompasses over 350 known species. Pulmonary forms of *Aspergillus* affection include 'Aspergilloma'; the localized form. *Aspergillus Fumigatu* is the commonest species responsible for such lesions. Another form; allergic bronchopulmonary Aspergillosis which represents immunologic response to non-invasive species, while the 'disseminated Aspergillosis' is well recognized as a life-threatening infection in immunocompromised patients, both acquired and inherited or under chronic

immunosuppression therapy mostly with steroids. In such cases, the pathology is multicentric and the surgical option is limited. Aspergillosis is the third cause of hospitalization due to fungal infection. In our study, we analyzed the outcome of surgical intervention in patients with Aspergilloma. [1-3]

2. Patients and Methods

2.1. Study Population

In this retrospective report encompassing a homogenous

cohort of 54 cases, over 20 years' period, data on the surgery offered and its outcomes for pulmonary Aspergilloma, at cardiothoracic surgery department, from the respected Cardiothoracic surgery department at Mansoura University Hospitals.

2.2. Data Collection

Through two decades interval from January 1996 and December 2015, an extensive review of the available data and records within our department was undertaken. Demographic data like age, sex and clinical data like symptoms, lobe involved and type of surgery and the results of surgical therapy, both morbidity and mortality, were analyzed. Radiologic examination data together with pathological findings were our keys for recruitment. Chest x-ray, computed tomography (CT) chest, fiber-optic bronchoscopy and bronchial lavage culture were routinely done.

2.3. CT Radiologic Signs

Our major radiological signs were:

Nodule: rounded opacity less than 3cm in diameter.

Mass: round opacity greater than 3cm in diameter.

Patch: opacity with irregular edges but cannot exceed a segment.

Massive consolidation: opacity in segments or lobes distribution, with air bronchogram inside. [4, 12]

Wedge shaped consolidation: broad base opacity and apex toward the lung hilum.

Cavity: radiolucency within a nodular area or mass consolidation.

Halo sign: mass surrounded by a zone of lower attenuation.

Atelectasis: lobar or segmental opacity with shrinking of the tissue volume.

Pleural effusion: a high density opacity obliterating the costophrenic angle with rising level towards the Axilla. [4, 12]

2.4. Histochemical Diagnosis

Patients were assigned with a proven diagnosis of pulmonary Aspergilloma if histological tissue examination revealed septated, branching fungi upon retrieval of any Aspergillus species from pulmonary tissues or positivity in immunohistochemical detection of anti-Aspergillus monoclonal antibody. Also, mycological evidence by culture or cytological analysis of bronchoalveolar lavage fluid.

2.5. Protocol for Surgery

Intravenous Amphotricin B was given for at least one week to sterilize the field except in true emergencies. Follow-up of the liver and kidney functions and Potassium level was mandatory with anti-fungal therapy. If the patient was on chemotherapy, 4 weeks interval of was mandatory and strictly followed except in cases of massive hemoptysis. Conventional lung resection was done for all patients using single lung ventilation. Postoperative pain control using both Pethidine and non-steroidal anti-inflammatory drugs as

needed. Postoperative complications were reported and managed accordingly. Follow-up in both thoracic surgery and chest medicine clinics was done monthly for most of the survivors. Clinical examination, chest x-ray and complete blood picture were routinely done in our follow-up.

3. Statistical Analysis

The data extracted was tabulated out using Microsoft Excel (Microsoft, 2016). Statistical analysis and processing was conducted using SPSS 20.0 (SPSS, Chicago, IL). Significance was defined as $P < 0.05$. Results were expressed as the mean \pm standard deviation (SD) for continuous normally distributed variables.

4. Results

Findings of this retrospective study on 54 cases of pulmonary aspergilloma surgically treated during the past 20 years are as follows: the mean age in this study was 46.3 ± 7.8 , range (17 to 64 years). There were 39 males, resulting with a ratio of 2.6:1 to the female sex. The most common predisposing factor was tuberculosis. TB present in 57.4% of cases. The main presentation was recurrent hemoptysis in 70.4% of patients. Three patients with severe or massive hemoptysis were encountered during the whole period and were operated urgently. The radiological findings showed 34/54 patients 62.9% showed positive meniscus sign while 16.6% showed a pulmonary nodule. There were 37 patients simple aspergilloma 68.5%, while 17 patients showed a complex form (31.5%). The left side was affected in 53.7% with predominant left upper lobe affection. The relevant laboratory tests revealed seropositive results in 64.8% and positive culture from protected bronchial lavage patients (35.1%). In this series majority of patients underwent lobectomy, except 7 patients had wedge resection, the mean operative time was 140 ± 15.6 min (75-220), two patients went to the ICU with packs to control apical adhesions bleeding and were re-explored 48 hours later. All patients were transferred to the ICU; the mean ICU stay was 48 hours, with next morning transfer to ward. Hospital stay ranged from 7-35 days with a mean of 9.5 ± 6.4 days. All patients after removal of the drains and free of complications were transferred to the medical ward to start their antifungal regimen according to the hospital policy and were followed up. Data analysis showed a follow up range of 1-5 years post-procedure.

Table 1. Preoperative patient data.

Age:	Mean 46.3 ± 7.8 (range: 17-64)
Sex:	Male no.: 39 Female no.: 15 (2.6:1)
Predisposing factor:	
TB	31/54 (57.4%)
Bullous lung disease	9/54 (16.6%)
Bronchial asthma	3/54 (5.5%)
immunosuppression	11/54 (20.4%)

Presentation	
Hemoptysis	38/54 (70.4%)
Shortness of breath	40/54 (74%)
Cough and expectoration	45/54 (83.3%)
Radiological findings	
Simple Aspergilloma	37/54 (68.5%)
Complex Aspergilloma	17/54 (31.5%)
Site of lesion	
Right side	25/54 (46.3%)
Upper lobe	18/54 (33.3%)
Middle lobe	2/54 (3.7%)
Lower lobe	5/54 (9.3%)
Left side	29/54 (53.7%)
Upper lobe	21/54 (38.9%)
Lower lobe	8/54 (14.8%)
Consolidation	6/54 (11.1%)
Nodule	9/54 (16.6%)
Cavity with Halo sign	34/54 (62.9%)
Destroyed lung with fibrosis	5/54 (9.3%)
Laboratory findings	
Positive Serological tests	35/54 (64.8%)
Positive Bronchial lavage	19/54 (35.1%)

During the follow up, we recorded prolonged air leak in 16 patients (29.6%) that ranged from 9-28 days with a mean of 13.5 ± 5.4 days. Wound infection was present in 8 patients 14.8% of which one patient needed vacuum assisted device. Re-exploration was needed in 6 patients (11.1%), two were packed and re-explored to remove packing. Cardiac arrhythmia was encountered in 4 patients (7.4%). In this series we encountered 6 mortality (12.3%) cases. Two patients suffered respiratory failure following severe chest infection and one patients developed deep venous thrombosis (DVT) and massive pulmonary embolism and 3 cases suffered circulatory failure.

Table 2. Postoperative complications

Prolonged air leak 16 (29.6%)
Residual pocket of pneumothorax 6 (12%)
Respiratory failure 2 (3.7%)
Massive pulmonary embolism 1 (1.8%)
Atelectasis (basal collapse) 9 (16.6%)
Repeated bronchoscopic aspiration 9 (16.6%)
Secondary Bleeding needed exploration 6 (12.3%)
Dysrhythmia 4 (7.4%)
Low cardiac output 3 (5.5%)
Surgical Wound infection 8 (14.8%)
Bronchopleural fistula 3 (5.5%)
Renal impairment 2 (3.7%)
Hematemesis 4 (7.4%)
Mortality 6 (12.3%)

Table3. Two decades time; trends and outcomes.

Presentation Period	1996–2005	2006–2015	P value
Mean age	44.6 \pm 6.5	48.7 \pm 8.9	0.439
Asymptomatic patients	6/33 (18.1%)	9/21 (42.8%)	0.043
Hemoptysis	12/33 (36.3%)	5/21 (23.8%)	0.021
Prevalence of TB	15/33 (45.4%)	6/21 (28.5%)	0.017
Need for thoracoplasty	2/33 (6.06%)	0/21	0.001
Pleural space problems	9/33 (27.3%)	7/21 (33.3%)	0.482
Prolonged hospital stay	12/33 (36.3%)	5/21 (23.8%)	0.716
Secondary bleeding	12/33 (36.3%)	3/21 (14.2%)	0.024
Mortality	4/33 (12.1%)	2/21 (9.5%)	0.024

5. Discussion

The aspergilloma (commonly known as fungus ball or mycetoma) is composed of fungal hyphae, aggregates of inflammatory cells, fibrin threads, and destructed tissues debris, which usually hosted within a pre-existing lung cavitory lesion like tuberculosis, sarcoidosis, histoplasmosis or bullous emphysema and fibrotic lung disease. See figure 1.

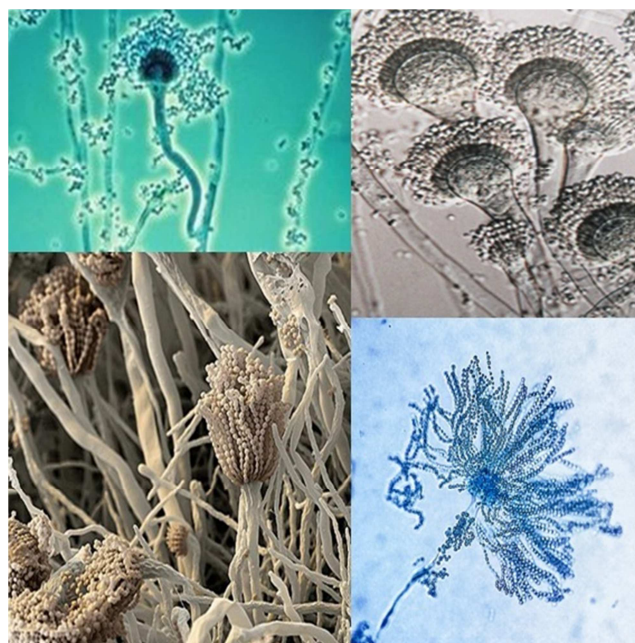


Figure 1. (top left & right) represents electron microscopic images of *Asperigillus fumigatus* colony. (bottom left) 3 D electron microscopic image of cultured colony. [2].

Mycetoma is avascular and chronic inflammation means endarteritis obliterans. These factors hinder the delivery of systemically administered antifungal agents into the cavity or the fungus ball; therefore, the logic is to resect. But still the surgery for mycetoma faces some technical difficulties and carries a high risk of complications if the patients were emaciated or under immunosuppression. [1, 2]

A dangerous symptom of mycetoma is recurrent hemoptysis. Minor degrees of hemoptysis can progress suddenly to massive hemoptysis in 30% of cases with an expected 25% mortality. [2] Air crescent sign is the cardinal radiological feature of the fungus ball of Aspergillosis. That is formed of condensed hyphae. The ball can be large or small, solitary or multiple. It may move when the patient's position changes or remain fixed, projecting into the cavity's lumen like a polyp. [2] Although it is often indolent with few or no symptoms in the beginning, the process frequently presents with massive hemoptysis, which can sometimes be fatal. Its differential diagnosis includes pulmonary Hydatid cyst, other fungi, blood clot or Rasmussen aneurysm in a tuberculous cavity, lung abscess with inspissated pus, Staphylococcal pneumonia, Nocardial infection, carcinoma of the lung, and lung gangrene or hematoma. [3]

The main presenting symptom in this series was hemoptysis, previous reports has recognized hemoptysis as

high as 70%. The radiological diagnosis of aspergilloma is positive when positive meniscus sign and mobile ball with patient position is confirmed. Chest CT scan are useful for diagnosis of simple and complex Aspergillois as well as underlying lung parenchyma. Aspergilloma colonizes a pre-existed cavitory space thus its localized lesion which doesn't extend to pleura. [13, 14] In the complex form, the process is more aggressive with more parenchymal destruction which reaches adjacent pleura. Pre-existing disease, most commonly tuberculosis is involved. [15] See figure 2. These patients are frequently sicker and have impaired pulmonary function tests due to widespread parenchymal involvement. Within the study, nine patients had a solitary pulmonary nodule and upon pathological report Aspergilloma was confirmed.

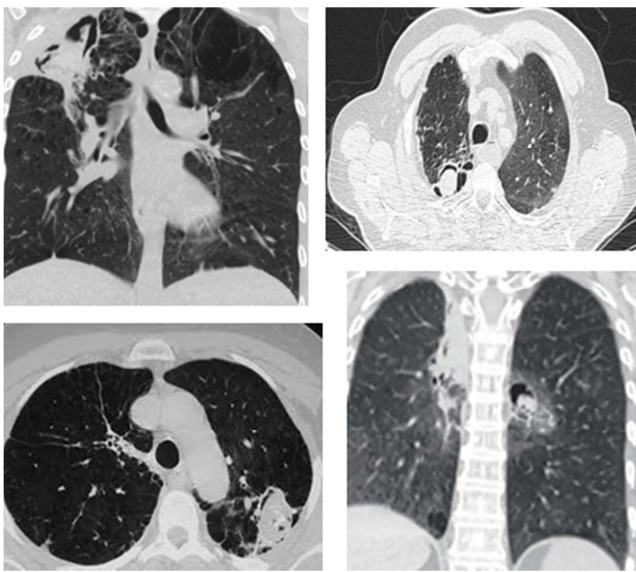


Figure 2. (2, a, b, top left & right) CT chest sagittal and coronal views showing right apical cavitory lesion containing fungus ball. (c, d bottom left & right) left upper lobe aspergilloma seated at posterior segment.

Since antifungal has a poor penetration to thick cavity wall; hence resection is accepted if they are suitable candidates for surgery. VATS resections started to get a role in the surgical treatment of pulmonary fungal ball. [5] The surgery aims to preventing hemoptysis and increase survival. The most common surgery offered to Aspergilloma was lobectomy. Limited resections such as wedge or segmental resections became fewer due to pleural dissemination produced later on. [6-8]

Within our study, surgery was indicated in asymptomatic simple Aspergilloma in 9 cases were to achieve a diagnosis, where postoperative pathology results showed Aspergilloma. The fundamental question remains whether to operate on asymptomatic patients or not. It is our preference to perform surgery in asymptomatic simple Aspergilloma as a prophylaxis against 20% chance of severe hemoptysis that can be encountered during the course of the disease. [3, 7]

Patients with recurrent hemoptysis either with or without previous bronchial embolization were enrolled in our indication. Failed medical treatment and complex forms were

indicated for resection as long as the residual lung showed good pulmonary function and patients have good functional performance. Complex form showed technical challenges with dense pleural adhesions, absence of interlobar fissure, fibrosis and inflammation at hilar vessels. These challenges reflected on postoperative complications as previously mentioned. See table 1. It is expected in this situation that patients suffer from prolonged air leaks, failure of lung expansion and postoperative bleeding. [1, 2] In our report, surgical procedures done were lobectomy in 43 cases, segmentaectomy in 7 cases, pneumonectomy in 2 cases and thoracoplasty in only 2 cases early in our series. Those patients were unlikely to survive conventional lobectomy, thus removal of fungus ball and collapsing lateral chest wall upon the residual cavity with acceptable postoperative outcome if compared to their debilitating status and the dangers of lobectomy. So, we still see thoracoplasty a viable solution but rarely used in modern practice. We done only 2 cases of pneumonectomy as we generally tend towards avoiding it whenever possible because of the fear of post-pneumonectomy empyema. Aspergilloma surgery doomed to be tedious technically coupled with complicated postoperative course. [5, 8]

We encountered 21/54 (39%) postoperative complications. Most of them were due to prolonged air leaks and failure of lung expansion. Uncontrolled apical oozing was encountered in two patients who were transferred to the ICU packed and were re-explored and packs were removed 48 hours later. Almost all previous experiences have faced the same complications and were proportion to the extensive pathology and residual lung condition, complications ranged from 25%-70%. [1, 9, 10] Our mortality of 12.3% was to the lower side of most series. Although mortality was variable in different reports experiences, ranging from 1% and up to 43%, this was due to the difference between each series in the percentage of high risk patients, complex Aspergillois and pneumonectomies per study. [16, 17] Our reasonable mortality could be explained in view that 68.5% were simple Aspergilloma with localized disease and less challenging. Our 6/54 mortality patients were in the complex group. Two developed respiratory infection and respiratory failure. The third developed DVT in spite of anti-coagulation and was lost when he developed massive pulmonary embolism. Last two cases suffered circulatory failure.

In our study, morbidity like secondary bleeding was 36.3% in the first decade and 14.2% in the second decade, pleural problems were 27.3% and 33.3% respectively and hospital stay was 36.3 and 23.8% respectively. In fact, during first decade group, 9 patients had cumbersome pulmonary re-expansion either by lung fibrosis or loss of elasticity but none required thoracoplasty. In our report, we recorded an important decrease in postoperative morbidity, due to the less morbid profile through two decades periods after successful nation-wide control of tuberculosis. See table 3.

It is our own insight and recommendation to manage these patients in multidisciplinary team (MDT) approach, the decision for management is usually taken with chest

physicians, intervention radiologist and the surgical team. Anti-fungal therapy at the perioperative period, as well as adjustment of preoperative co-morbidities as diabetes and nutrition status is paramount. The indication for anti-fungal therapy was directed to those with multiple cavities or those anticipated with the risk of pleural spillage during resection. Those with simple or contained Aspergilloma are in no need for antifungal therapy. In some patients with residual or other lung affection are given postoperative antifungal therapy to prevent recurrence. Other series adopted similar policy like ours. [1, 18]

6. Conclusion

Surgery for pulmonary aspergillosis (fungus ball) remains the mainstay of management which offered beneficial satisfactory outcomes with an acceptable morbidity. The surgical options are few but over 2 decades, surgery for Aspergillosis became less invasive and less challenging might be due to nationwide eradication of tuberculosis. Though, mortality observed was predominantly seen in high risk patients with complex Aspergillosis. Although we present a small group of patients within this study, we emphasized the valuable lessons learned and complications discovered within this complex group. Consequently, we recommend MDT approach for the management of these patients with close follow-up. Despite being high risk surgery, results are good with low rate of recurrence.

Ethical Approval and Responsibility

Approval of the study protocol was granted by our Ethical Committee for research and treatment. The need for informed consent was waived due to the retrospective nature of the study. This work complies to Helsinki declaration. All of the authors have confirmed the preservation of confidentiality and respect of patients' rights in discretion and privacy.

Availability of Data and Material

Available on request.

Disclosure

The authors have nothing to disclose.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

All authors: 1) have made substantial contributions to conception, design, acquisition, analysis and interpretation of data; 2) have been involved in drafting the manuscript and revising it critically for important intellectual content; and 3) have given final approval of this version to be published.

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