Surgical treatment of pulmonary aspergilloma in pediatric patients: report of 3 cases

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ABSTRACT

Objective. To describe our experience in the surgical management of pulmonary aspergilloma (PA) and review surgery's role in PA treatment in pediatric patients.

Materials and methods. A descriptive study of patients diagnosed with PA undergoing surgical resection from 2017 to 2019 was carried out. A review of pediatric studies mentioning "aspergilloma", "surgical", and "treatment" was performed.

Results. During the study period, 3 patients with single PA aged 18 months old, 3 years old, and 13 years old underwent surgery. All of them had leukemia and little or no response to aspergilloma medical treatment. In all patients, the procedure was initiated using the thoracoscopic route, but conversion into thoracotomy was required in two cases. In all three cases, pulmonary segmentectomy was carried out with complete PA removal, without severe intraoperative or postoperative complications. No pulmonary recurrence was observed after 30-, 34-, and 16-month follow-up, respectively.

Conclusions. PA surgical resection is a feasible alternative in pediatric patients with a poor antifungal treatment response or related complications.

KEY WORDS: Aspergilloma; *Aspergillus*; Surgical treatment; Children; Antifungal resistance.

TRATAMIENTO QUIRÚRGICO DEL ASPERGILOMA PULMONAR EN PACIENTES PEDIÁTRICOS. A PROPÓSITO DE TRES CASOS

RESUMEN

Objetivos. El objetivo de este trabajo es describir la experiencia de nuestro centro en el manejo quirúrgico del aspergiloma pulmonar (AP) y la realización de una revisión sobre el papel de la cirugía en el tratamiento del AP en el niño.

Material y métodos. Estudio descriptivo de los pacientes diagnosticados e intervenidos mediante resección del AP desde el 2017 hasta el 2019. Se realizó una revisión con los términos "*aspergilloma*", "*surgical*", "*treatment*", descartando los estudios no referidos a pacientes pediátricos.

Resultados. Durante el periodo de estudio se intervinieron 3 pacientes con AP único, de 18 meses, 3 y 13 años de edad respectivamente, los 3 afectos de leucemia y con poca o nula respuesta al tratamiento médico habitual del aspergiloma. En todos los pacientes se inició la intervención por vía toracoscópica, siendo necesaria la conversión a toracotomía en 2 casos. En los tres casos se realizó segmentectomía pulmonar con exéresis completa del AP, sin complicaciones intraoperatorias ni postoperatorias graves. No se observaron recidivas pulmonares tras un seguimiento de 30, 34 y 16 meses respectivamente.

Conclusiones. La resección quirúrgica del AP, se presenta como una alternativa factible en pacientes pediátricos con pobre respuesta a tratamiento antifúngico o con complicaciones derivadas de este.

PALABRAS CLAVE: Aspergiloma; *Aspergillus*; Tratamiento quirúrgico; Niños; Resistencia antifúngicos.

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INTRODUCTION

Aspergillosis is a condition caused by *Aspergillus* fungi. Aspergilloma is a subtype of aspergillosis which leads to the formation of granulomas with fungal accumulations[1-3]. *Aspergillus* infections tend to occur in immunosuppressed patients, especially in those exposed to high-intensity chemotherapy or hematopoietic progenitor transplantation (HPT). They are rare in immunocompetent patients[2-4].

Thoracic CT-scan is recommended in all patients with PA suspicion. This allows the mass to be more accurately defined and provides information on which pulmonary lobe it is located at and which structures it is in contact with. This information proves particularly useful for surgical planning purposes.

Antifungal therapy is the baseline treatment for *Aspergillus* infections[1,5]. However, PA has a low response rate and tends to be resistant to antifungal treatment, with an 80-90% resistance according to the various series[1,3,5]. This is primarily due to the poor penetration of antifungal drugs into aspergillomas[3,4] thanks to their capsule. Recently,

Figure 1. Pulmonary aspergilloma. Axial (A) and coronal (B) pulmonary CT-scan cuts demonstrating a cavitated lesion in the left pulmonary lingula, with presence of a fungal mass inside.

certain mycetomas have been found to be colonized by multiple fungi, apart from *Aspergillus,* such as *Mucor* fungi. This multiple colonization is believed to favor medical treatment resistance[6].

Given medical treatment's high failure rate, early surgical removal is currently recommended as a therapeutic option in adult patients[5-11]. In pediatric patients, this has not been well defined, but various studies demonstrate that early surgical treatment improves patient survival[12,13].

This paper describes our experience with our first three cases of PA surgical treatment and reviews surgery's role in pediatric patients with PA refractory to medical treatment.

MATERIALS AND METHODS

A descriptive and retrospective study of PA patients undergoing surgery from 2017 to 2019 was carried out. Indication for surgery was agreed upon by the Pediatric Oncology Committee from our healthcare facility, and defined as lack of response at CT-scan following 4-6 weeks of specific treatment, or drug toxicity. Surgery was performed under general anesthesia and selective pulmonary embolization. In all cases, thoracoscopy was indicated, with three 5mm ports placed according to fungal mass location. In those cases where, out of technical reasons, thoracoscopy was not feasible, it was converted into thoracotomy. All patients were administered oral fluconazole antifungal treatment for at least 6 months postoperatively.

A review of pediatric studies mentioning "aspergilloma", "surgical", and "treatment" was carried out. Only studies on PA surgical treatment in pediatric patients –under 15 years of age– were selected and analyzed.

RESULTS

Clinical case 1

3-year-old patient diagnosed with M2 myeloblastic leukemia. The patient received two chemotherapy cycles. Subsequently, the patient had chronic cough and fever, so thoracic X-ray was performed, which demonstrated a cavitated lesion at the lingula of the left superior lobe, suggestive of PA. A thoracic CT-scan was carried out, which confirmed PA diagnosis (Fig. 1).

Antifungal therapy with caspofungin and liposomal amphotericin B was initiated. Three weeks following PA diagnosis, a hematopoietic progenitor transplantation (HPT) was carried out, as treatment timing was optimal. Given the persistence of the lesion and the development of antifungal hepatic and renal toxicity, surgery was decided upon.

The procedure was initiated through thoracoscopy, with adhesiolysis being performed until the left lung lingula was identified. The latter was explored, but the lesion could not be clearly found, so decision was made to convert into 5 cm thoracotomy. The lingula was removed through the incision, where an indurated nodule was palpated and removed using the automatic stapler. Voriconazole-impregnated hemostatic material was applied on the surgical bed.

The postoperative period was uneventful, except for a small, asymptomatic pleural effusion which spontaneously resolved. In the sample analysis, *Aspergillus* DNA was found, and in the pathological examination, no viable fungal structures were identified. After a 34-month follow-up period, the patient is now free of disease.

Clinical case 2

19-month-old patient with type B acute lymphoblastic leukemia. Two months after chemotherapy initiation, the patient had respiratory symptoms and back pain. The thoracic X-ray showed the presence of complicated right basal pneumonia. Medullary MRI revealed T6, T7, and T8 thoracic spondylodiscitis in continuity with a pleural-mediastinal collection (Fig. 2), so pleural fluid drainage was indicated.

Liquid analysis showed structures of fungal etiology and a positive *Aspergillus* PCR test, so amphotericin B treatment was initiated. Given the lack of significant clinical improvement and the progression of the infectious disease, intravenous voriconazole and anidulafungin were added as a triple therapy. The subsequent CT-scans showed the infectious process had aggravated, with persistence of PA consolidation.

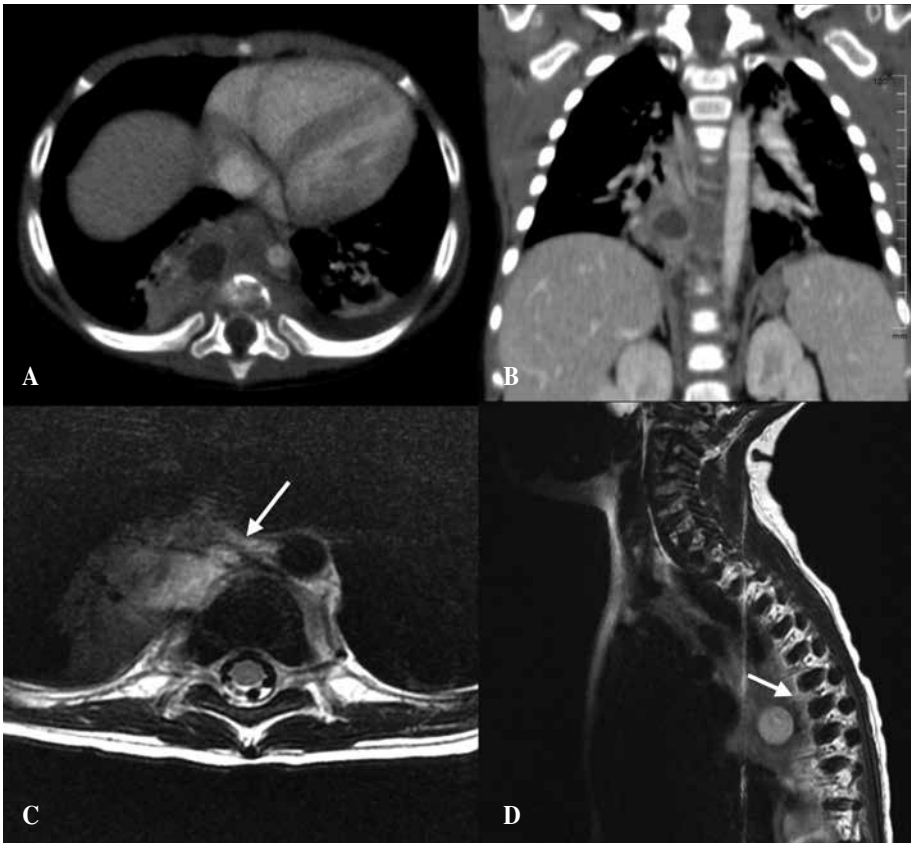

Figure 2. Pulmonary aspergilloma with spondylodiscitis. A) Pulmonary CT-scan axial cut: cavitated lesion in the right pulmonary base, with presence of fungal ball inside. Spondylodiscitis visible. B) Pulmonary CT-scan coronal cut. C) T1-weighted MRI axial cut demonstrating PA spondylodiscitis. D) T1-weighted MRI sagittal cut demonstrating T6-T8 PA spondylodiscitis.

Given the lack of response to antifungal treatment and the progression of the lesions, surgical removal was decided upon 6 weeks following diagnosis. The procedure was initiated through right thoracoscopy, but conversion into 5cm thoracotomy was required as there were multiple adhesions. Pulmonary untethering and resection using the automatic endostapler were carried out, and voriconazole-impregnated hemostatic material was applied in the area.

No complications were recorded. The patient was discharged with double antifungal therapy. After a 30-month follow-up period, the patient is now free of disease.

Clinical case 3

13-year-old patient with Down's syndrome and pre-B acute lymphoblastic leukemia. The patient received specific chemotherapy. 4 months following maintenance therapy initiation, the patient had cough, febricula, and hypoventilation in the right base. Thoracic X-ray demonstrated the presence of pulmonary effusion with an image suggestive of PA in the right pulmonary base. Given that fungal etiology was suspected, the study was completed with a pulmonary CT-scan, which confirmed PA diagnosis (Fig. 3).

Liposomal amphotericin B treatment was initiated, but it was converted into voriconazole treatment as a result of an allergic reaction. Caspofungin was subsequently associated. After 3 months of treatment and various CT-scan controls with no improvement, surgery was decided upon. A thoracoscopy was carried out, and the lesion was fully removed using an endostapler, while applying voriconazole-impregnated hemostatic material on the surgical bed (Fig. 3).

The only complication recorded was a right pleural effusion which spontaneously resolved. The pathological examination showed fungal structures. After a 16-month follow-up period, the patient is now asymptomatic and free of residual disease.

DISCUSSION

Owing to the advent of new immunosuppressive therapies and high-intensity chemotherapy for pediatric oncologic treatments, the number of immunosuppressed patients in this age group has increased over the last years[1,6]. These patients are prone to *Aspergillus* colonization and PA[4], so we should be prepared to fight these infections.

Due to PA's high resistance to antifungal treatment[1,3,5], early PA resection has been long considered as a healing treatment in resistant PAs in adult patients[5-11].

Table 1 features the various studies published on pediatric patients undergoing PA surgery[14-23]. Although this bibliographic review consists of 140 PA cases operated on,

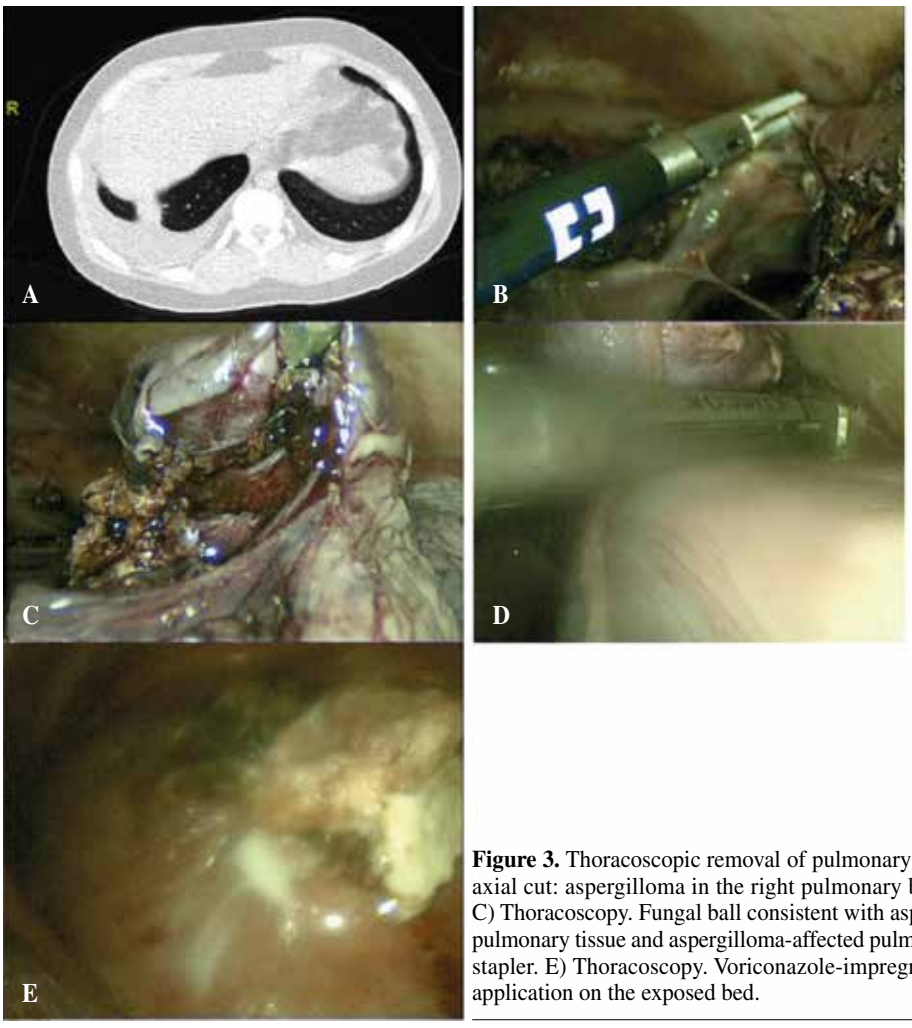

Figure 3. Thoracoscopic removal of pulmonary aspergilloma. A) Pulmonary CT-scan axial cut: aspergilloma in the right pulmonary base. B) Thoracoscopy. Adhesiolysis. C) Thoracoscopy. Fungal ball consistent with aspergilloma. D) Thoracoscopy. Healthy pulmonary tissue and aspergilloma-affected pulmonary tissue separation using an endostapler. E) Thoracoscopy. Voriconazole-impregnated hemostatic material (Tachosil®) application on the exposed bed.

the total number of pediatric cases published is difficult to calculate. Some of them are hidden in adult series[6,24,25], since these also include pediatric patients in their age range. These data suggest there are hundreds of pediatric cases of resected PA published, while there are thousands of adult cases. Therefore, given the lack of experience in children, it is often required to resort to the adult literature.

Based on the scientific evidence available in adult patients, a strict selection of patients eligible for surgery should be carried out. Patients should meet the following criteria[1,3-8]:

- Good general condition.
- Good pulmonary function and postsurgical functional reserve.
- Single nodule. To be assessed if there are various nodules, since they are associated with higher morbidity.
- Pathology located in a lobe or a lung.
- Patient eligible for thoracotomy/thoracoscopy.
- Antifungal intolerance and/or resistance.

Avoiding subpleural nodules is a relative contraindication in adult patients, since they are associated with higher morbidity (complications: 25%) and mortality (2-5%) postoperatively. In our opinion, this contraindication should not be considered as such in pediatric patients, since various studies have demonstrated a better survival when associated with early resection[12,13,22], even if nodules are subpleural. In the three cases described in our study, nodules were indeed subpleural, and a total resection was achieved.

In adult patients, even though the most adequate candidates are selected for surgery, these procedures are associated with many postoperative complications and a high mortality rate. Mortality is around 3-10%, and complications range from 5 to 15%[5-11].

Given that pediatric patients have less comorbidity, there should be fewer complications associated with the procedure. In the cases analyzed in this paper, no severe complications were recorded and there was no recurrence. Mortality in the series analyzed (Table 1) was 35%. Most deaths in pediatric patients are secondary to the progression of the baseline pathology –hematologic neoplasia in virtually all cases–, whereas, in adults, deaths are typically caused by surgery-related or PA-related complications.

Table 1. Bibliographic review of pulmonary aspergilloma surgical treatment in pediatric patients.

Study	*No. of cases*	*Age*	*Surgical procedure*	*Complications*	*Deaths*
AlShanafey S 2019[17]	25	9.4 years*	12 Seg. (48%) 8 Lob. (32%) 2 Neum. (8%) 3 Cavernoma debridements (12%)	2 Persisting aerial leaks (8%)	3 (12%) No response to baseline pathology
Aragón J 2013[14]	1	11 years	Seg. (100%)	–	None
García J. 2012[15]	1	11 years	Seg. (100%)	–	None
Isnard M 2018[16]	1	15 years	Lob. (100%)	–	None
Walicka-Serzysko K 2015[18]	3	–	2 Lob. (66%) 1 Neum. (33%)	–	None
Pabst S 2013[19]	2	13 and 14 years	1 Seg. (50%) 1 Lob. (50%)	1 Pleural effusion with pneumonia (50%)	1 (50%) No response to baseline pathology
Burgos A 2008[20]	61	9.9 years*	NA	NA	23 (32%)
Cesaro S 2007[21]	19	10.4 years*	5 Seg. (26%) 12 Lob. (63%) 2 Lob. + Seg. (11%)	1 Wound dehiscence (5%) 1 Pneumothorax (5%) 1 Pleural effusion (5%)	9 (47%) No response to baseline pathology
Gow KW 2003[22]	17	13.1 years*	10 Seg. (60%) 3 Neum. (17%) 4 Lob. (23%)	NA	14 (77%)
Wright JA 2003[23]	7	8.2 years*	NA	NA	1 (14%)
Crehuet D	3	1, 5, 3 and 15 years	3 Seg. (100%)	2 Pleural effusions (66%)	None
Total	**140**		**33 Seg. (45%)** **28 Lob. (38%)** **6 Neum. (8,3%)** **2 Lob. + Seg. (2,7%)** **3 Cavernoma debridements (4,2%)**		**50 (35%)**

**Mean. NA: not available; Seg.: segmentectomy; Lob.: lobectomy; Pneum.: pneumonectomy.*

However, overall survival of patients with hematologic neoplasia and PA has demonstrated to be higher in patients undergoing surgery and antifungal treatment than in patients undergoing antifungal treatment only[12,13,22,27]. Regarding treatment duration, various studies recommend both preoperative and postoperative antifungal therapy, which can be extended up to 6 months following surgery[1-3].

In case of fungal material dispersion throughout the pleura, amphotericin B or 2% taurolidine cleaning is recommended, but efficacy is still unknown[1]. In our study patients, voriconazole-impregnated hemostatic material (Tachosil®) was used, since we believe it reduces the risk of recurrence. However, this has not been proved by any study or literature series.

The non-use of chemotherapy or HPT in pediatric oncologic patients with active systemic fungal infection –on the basis that it could exacerbate it– is a controversial issue. Chemotherapy and HPT have been typically postponed until aspergillosis has resolved[6,24]. However, a recent study[27] has demonstrated that survival in patients with fungal infection undergoing HPT is higher than in patients with fungal infection not undergoing HPT. Therefore, PA is not considered a contraindication for HPT.

Regarding the type of surgery, various questions should be asked before it is carried out. Which technique is better – lobectomy or segmentectomy (sublobar resection)? Segmentectomy offers similar results as lobectomy and provides benefits over it as long as 1 cm of free margin can be

achieved[9]. Complications are similar, but segmentectomy is associated with less intraoperative bleeding and shorter operating times[9]. Therefore, according to the authors, segmentectomy is always recommended –if feasible–, since it allows more healthy pulmonary tissue to be preserved and has similar complications.

Is thoracoscopy an effective and safe technique in these patients? Thoracoscopy is a useful tool in simple and complex PA without panlobar involvement, hilar involvement, or calcified lymph nodes. It has fewer postoperative complications, as long as it is feasible[11]. In our opinion, each case should be considered individually. Thoracoscopic removal is recommended as long as it is viable and the surgeon has experience with it. However, if thoracoscopy does not allow the lesion to be fully delimited or removed, or if adhesiolysis is very complex, conversion to open surgery should be carried out, since it facilitates lesion palpation and provides a more accurate delimitation than thoracoscopy.

When should surgical treatment be indicated in PA cases? There are no references in pediatric literature regarding how long should PA resist to antifungal therapy to be considered drug-refractory and therefore resort to surgery. However, surgery is recommended in case of clear deterioration, lack of improvement, hemoptysis, or cavitation close to the pulmonary hilum, with early resection being the latest recommendation[12,15,20]. In our healthcare facility, the decision is made jointly by the pediatric oncology department and the pediatric surgery department. Periodic assessments with imaging tests are carried out, and if no changes are observed after 4-6 weeks, PA resection is indicated. In two of our cases, surgery was indicated after no antifungal response had been noted for 6 weeks, and in one patient, for 3 months, since the patient was asymptomatic. If the patient has antifungal toxicity or intolerance, or if the situation could get worse as a result of having to resort to high-intensity chemotherapy (for example, HPT), early PA removal is recommended[18,20].

In patients with risk of moderate or severe bleeding, patients with extensive disease, and patients where surgical treatment is not recommended, symptoms should be treated or the arteries irrigating the area where the aspergilloma is located should be embolized[1-3,8,20] as a prior step to surgical resection.

This study describes our experience with the first three cases undergoing surgery in our healthcare facility. However, our team has limited expertise considering the low prevalence of the disease. Finding pediatric cases in the literature is difficult as they tend to be hidden in adult series, which means there is less information available on PA surgical treatment in children than in adults. Given that pediatric patients have different comorbidities and baseline pathologies, wider scientific evidence is required to develop specific protocols for them.

CONCLUSION

Aspergilloma surgical removal is a useful and safe tool for PA treatment in pediatric patients. Given PA's low response rate to antifungals, early resection should be considered as a healing alternative. Patients with antifungal toxicity or lack of response, patients with risk of PA exacerbation, and patients in an unstable situation are eligible for mass removal.

Minimally invasive surgery is a safe and useful surgical tool as a baseline indication for PA treatment. However, this pathology is often associated with multiple adhesions secondary to the inflammatory process which increase the difficulty of the procedure, so conversion into open surgery is frequent.

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