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CLINICAL CASE

# Pulmonary nodule in pediatrics: beyond the infection

## Nódulo pulmonar en pediatría: más allá de la infección

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**What do we know about the subject matter of this study?**

A pulmonary nodule in the pediatric patient is a diagnostic challenge. Although its main causes are infectious, primary pulmonary neoplasia should be considered within the diagnostic options

**What does this study contribute to what is already known?**

We present a case of a primary pulmonary mucoepidermoid carcinoma in an adolescent girl, highlighting the importance of considering primary neoplasms within the etiological options of a pulmonary nodule in pediatrics.

## Abstract

The study of a pulmonary nodule in pediatrics is a diagnostic challenge where multiple pathologies must be taken into account, especially infections. In developing countries, where tuberculosis infection is endemic, it is one of the most likely diagnoses; however, the diagnostic possibility of malignancy should never be overlooked. **Objective:** To describe a case report of a patient with a pulmonary nodule, that after ruling out the most frequent causes, a primary malignant tumor was diagnosed. **Clinical Case:** 17-year-old female patient with a one-month history of cough, dyspnea, and hemoptysis, without other symptoms. Since she did not respond to conventional antibiotic management, a chest CT scan with contrast was performed which showed a pulmonary nodule with irregular contours, and with the bronchoalveolar lavage pulmonary infections were ruled out (pulmonary tuberculosis, fungal infection, and others bacteria). Biopsy of the lesion was performed to complete the study which histopathology was compatible with a mucoepidermoid carcinoma (MEC). The patient

**Keywords:**
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underwent right low lobectomy and lymph node resection with good clinical response during three years of follow-up. **Conclusion:** Pulmonary nodule in pediatrics is a finding usually associated with infection, nevertheless, neoplastic conditions have to be considered, not only metastasis but also primary pulmonary malignant lesions due to prognosis implications.

## Introduction

The pulmonary nodule in pediatrics is a rare condition, defined as the image of a rounded lesion in the pulmonary parenchyma of up to 3 cm in diameter as in adults[1]. It may be incidentally found or present in association with respiratory symptoms, observing that incidental nodules in children do not show evident growth over time with low risk of malignancy, as described by Assega et al. following 36 patients[2]. Most nodules and masses in children are non-malignant and have granulomatous origin; infections and congenital lesions outnumber neoplastic lesions in frequency, where primary lung tumors are rare in children[3].

In the diagnostic approach, the following should be considered: Is the child healthy, with normal growth and development? o Does the child have a significant weight loss, hemoptysis, respiratory distress, lymphadenopathy, or paraneoplastic syndrome? Does the child have positive findings on physical examination to guide the diagnosis? Is the child at risk for granulomatous lung disease? Does the child have a history of recent travel, exposure, or inhalation? As well as history of malignancy and immunodeficiency[4].

Nodules due to pulmonary metastatic disease are frequent in children with Wilms tumor and sarcomas[3]. In patients immunocompromised, it is possible to find nodules due to infection by bacteria, aspergillosis, nocardiosis, and mucormycosis[5]. The prevalence and characteristics of nodules in children without history of malignancy are less clear[2].

Once the most frequent etiologies have been ruled out, one must consider primary malignancy as the cause of the pulmonary nodule. The epidemiology of primary malignant neoplasms of the lung is not well known, there are only reports and case series, and it is estimated that they represent less than 7% of all tumors in pediatrics[6]. The frequency varies according to age and the most commonly described types are carcinoid tumors, inflammatory myofibroblastic tumors, pleuropulmonary blastoma, and less frequently described are small cell lung cancer, adenocarcinoma, infantile pulmonary hemangioma, and mucoepidermoid carcinoma (MEC)[7].

Thus, in pediatrics, the finding of a single pulmonary nodule is infrequent and diagnostic possibilities are considered different from adults, who most often present lung cancer[8]. However, there are not many data in pediatrics nor reports of patients with malignancy and, although in children without oncologic disease or immunodeficiency the most common finding is an infection due to subacute germs such as tuberculosis and fungi, lung neoplasia is an option in the diagnosis and it is not clear in which pediatric patients it should be suspected[4].

The objective is to describe the clinical case of a patient with a pulmonary nodule who, after ruling out the most common causes, was diagnosed with a primary pulmonary malignancy, highlighting the importance of this diagnostic possibility in pediatrics.

## Clinical Case

A 17-year-old female patient with history of asthma without crises or symptoms in the last ten years, with no other significant pathological or exposure history, consulted due to a one-week history of cough, dyspnea, chest pain, and hemoptysis, without fever or other associated symptoms, presenting with right lower lobe opacity on chest X-ray (Figure 1).

Bacterial infection was suspected starting antibiotic treatment, however, since there was no satisfactory clinical response after four days of treatment, complementary tests were performed with a high-resolution CT scan of the chest which showed a ground-glass opacity in the right lower and middle lobes and a decrease in their volume, bronchus obliteration in the right lower lobe, with hypodense material that could correspond to bronchiectasis with mucoid impaction.

A fibrobronchoscopy was performed which showed concentric reduction of the bronchial lumen in the posterior segment of the right lower lobe with a platelet plug in it. After a week of clinical stability and improvement of dyspnea, it was decided to continue with expectant management, after performing a transbronchial lung biopsy which was negative for malignancy.

After three weeks, she consulted again due to recurrence of hemoptysis and dyspnea and, based on the clinical evolution with prolonged symptoms, we considered a subacute infection such as tuberculosis, fungal infection, a systemic disorder such as vasculitis

or allergic bronchopulmonary aspergillosis (ABPA), given the presence of asthma. A chest CT scan with contrast was performed, which showed a 2.0 x 2.7 cm nodule, with soft tissue density of irregular contours and without calcifications in the posterior segment of the right lower lobe, no ground-glass opacity or signs of previous bronchial obliteration, and no findings suggestive of arteriovenous malformation, therefore studies were continued (Figure 2).

Fibrobronchoscopy with bronchoalveolar lavage was performed again with no positive anatomical findings and negative studies for tuberculosis, fungi, and other bacteria (microbiological staining, fungal and mycobacterial cultures, galactomannan antigen, and polymerase chain reaction (PCR) for *Mycobacterium tuberculosis*); tuberculin test and serial sputum smears were negative. Total immunoglobulin E was increased compatible with previous asthma, however, the specific IgE for *Aspergillus fumigatus* was negative, ruling out ABPA, and vasculitis was also ruled out through the laboratory tests (Table 1).

Since there was no evidence of infection, pulmonary metastasis was ruled out, so thyroid, breast, and abdominal ultrasonography was performed without finding the presence of primary neoplasia. In order to make a diagnosis of primary neoplasia or congenital malformation, the study was complemented with a biopsy of the lesion by thoracotomy.

The biopsy revealed a 4.2 x 2.8 x 2.5 cm mass in the right lower lobe. Histopathology showed a well-defined lesion consisting of acinar mucus-secreting cells, as well as smaller cell nests, a mainly glandular pattern with cyst-like areas, so it was not possible to be sure of the histogenesis, suggesting a mucoepidermoid tumor as the main diagnostic possibility (Figure 3).

Immunohistochemistry studies showed diffusely positive cells expressing CK7 and some positive foci for CK5/6, in addition to focal positivity for CD117, CA125, and HER2 with overexpression of p53 and a proliferation index around 10%. It was negative for S100, HMB45, PAX8, napsin, thyroid transcription factor 1 (TTF1), estrogens, CDX2, CK20, and chromogranin (Figure 3), therefore we considered, both by histology and immunohistochemistry, compatible with an intermediate-grade MEC.

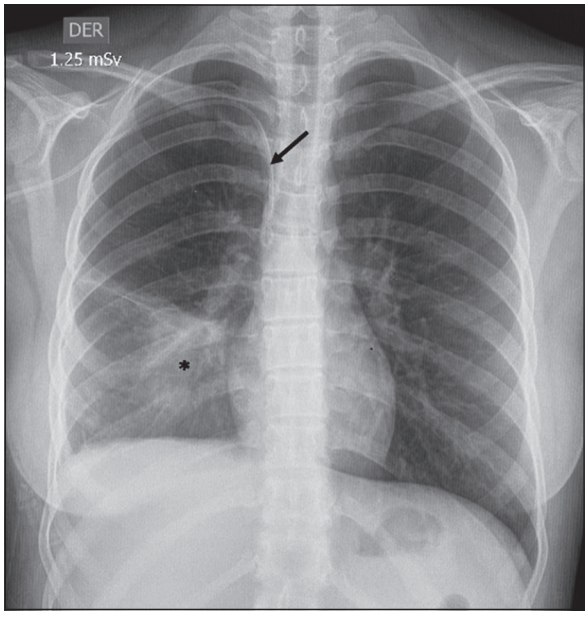


**Figure 1.** Chest radiograph. Evidence a triangle opacity (asterisk) in right lower lobe posterior segment. Central venous catheter is observed (arrow).

Right lower lobectomy with lymph node removal was performed since the biopsy showed involvement of the resection borders. The myRisk® hereditary cancer panel was performed, which included complete sequencing and analysis of deletions and duplications of 28 genes, without finding mutations of clinical significance and ruling out syndromes such as Li-Fraumeni.

The patient presented an adequate clinical evolution without complications or recurrence at three years of follow-up.

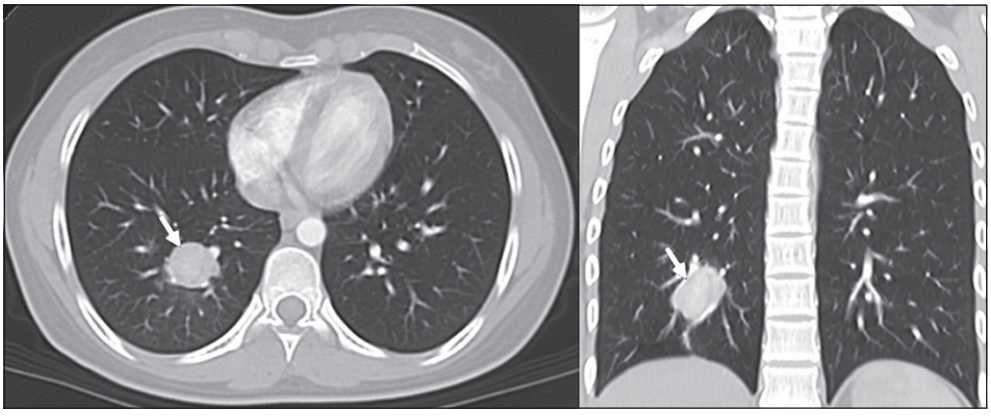

**Figure 2.** High-resolution chest computed tomography. Presence of nodule with soft tissue density in the posterior segment of the right lower lobe of 2.0 x 2.7 cm (arrow).

**Table 1. Laboratory tests on admission and the hospitalization**

| Variables | Result | Reference values |
|---|---|---|
| Serial sputum smear #3 | Negative | |
| Tuberculin skin test (Purified Protein Derivative) | 0 mm | Less than 4 mm in tuberculosis suspect according to clinical and radiological finds |
| Immunoglobulin E (IU/mL) | 1499 | 1.53-114 |
| Aspergillus fumigatus specific IgE (kUA/L) | Less than 0.1 | Less than 0.35** |
| Alfa-fetoprotein (ng/mL) | 1.7 | 0.6-4.2 |
| Human chorionic gonadotropin Beta-subunit (mIU/mL) | Less than 0.3 | |
| Anti-neutrophil cytoplasm antibodies p-ANCAS and c-ANCAS | Negative | Negative |
| Anti-nuclear antibodies | Negative | Negative |
| Galactomannan antigen *Apergillus* spp from BAL* | 0.1 | |
| KOH test, Gram stain and Ziehl-Neelsen stain from BAL* | Negative for fungi, bacteria or acid-fast bacilli | |
| Culture from LBA* | Negative for bacteria, fungi or mycobacteria | |
| *Polymerase chain reaction for Mycobacterium tuberculosis* | Negative | |
| Histologic stains from BAL* | Positive for hemosiderophages around 60%, Periodic acid–Schiff stain and Grocott stain negative, macrophages 90%, scant polymorphonuclear and lymphocytes cells | |
| Cytomegalovirus (CMV) from BAL* | Undetectable | |
| Thyroid, breast and abdominal ultrasonography | Without alterations | |

*BAL: Bronchoalveolar lavage. **Laboratory reference value. Reference values from: Hughes H, Kahl L. The Harriet Lane handbook. Philadelphia, PA: Elsevier; 2018.

## Discussion

Unlike considerations in adults, in pediatrics, the first diagnostic option when presenting a single pulmonary nodule is not primary pulmonary malignancy[8]. The diagnostic approach of a pediatric patient with hemoptysis and a pulmonary nodule should lead to evaluate infectious processes (bacterial or fungal), and in countries such as Colombia, pulmonary tuberculosis, since it is a country endemic of this disease[9]. It should be noted that pulmonary tuberculosis in pediatrics is still a public health challenge, especially in Latin America, where it is considered that there is a great gap between its detection and management[10].

Its incidence is much higher than primary pulmonary neoplasms and this, together with the varied clinical manifestations or radiological findings, makes its initial study essential in patients with high suspicion, representing an important differential diagnosis[9,10]. However, the presence of neoplasms or vascular malformations cannot be dismissed[4]. We present a case of a previously healthy patient who presented a pulmonary nodule of neoplastic etiology.

MEC of the lung is a low-frequency tumor, which is around 0.2% of all malignant lung tumors at any age[11]. It accounts for approximately 9 to 10% of malignant lung tumors in pediatrics[12]. Cases have been reported in patients as young as two years of age[13] and about half of the patients at the time of diagnosis are younger than 30 years of age[14]. This type of tumor mainly affects the salivary glands, and it was only in 1952 that Smetana et al. described the first tracheobronchial tumor with these characteristics[14]. The MEC consists of mucus-secreting cells high in mucins and with mitotic figures, along with non-keratinized squamous cells which grow in a sheet-like pattern and, finally, intermediate or transitional cells[15].

Since MEC is rare, it presents symptoms that are

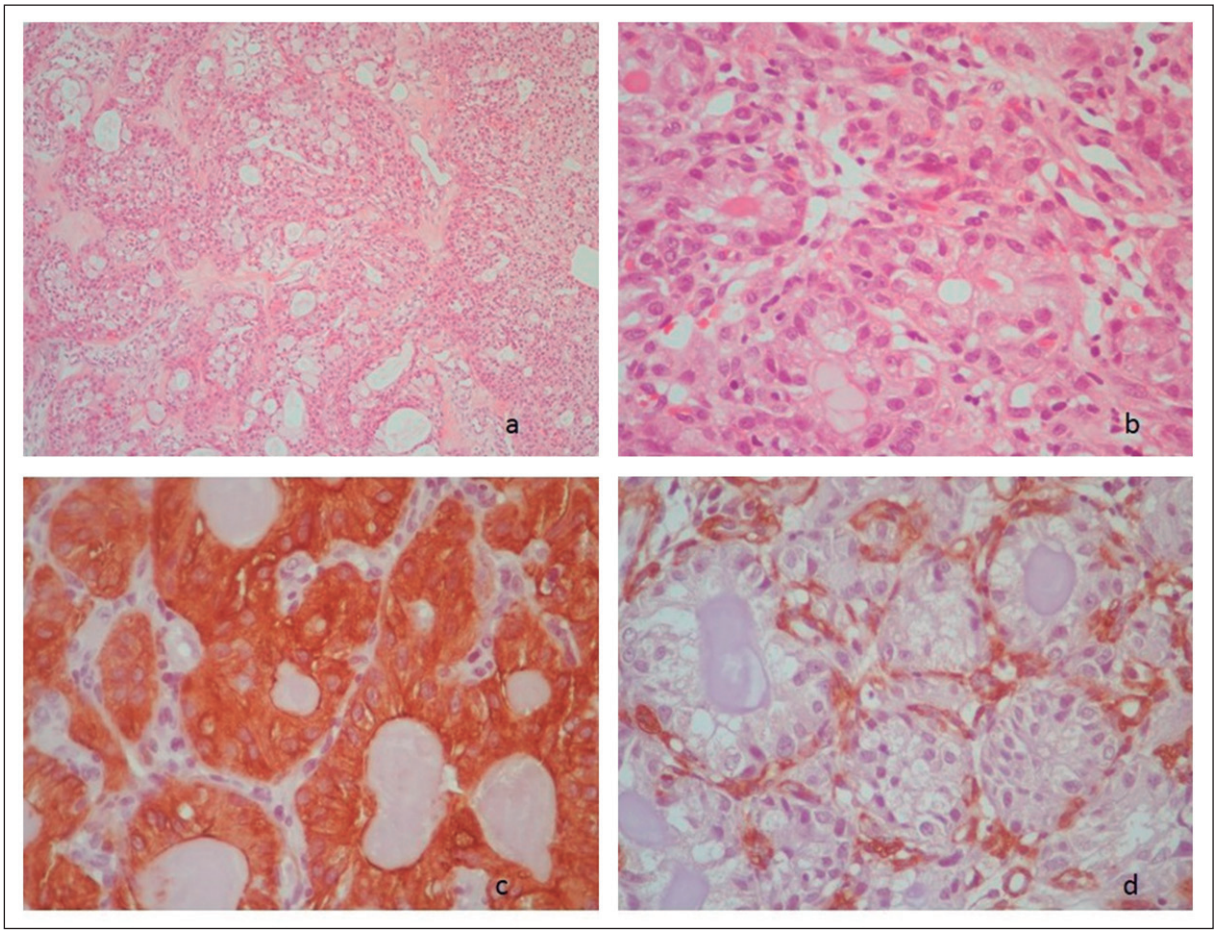


**Figure 3.** Mucoepidermoid carcinoma. **A.** and **B.** Epithelial lesion composed of sheets of mucinous and intermediate cells. **C.** Immunohistochemistry for CK7 is positive in most epithelial cells. **D.** Immunohistochemistry for CK5/6 is positive for some cells with epidermoid phenotype.

common to other diseases, which makes its diagnosis difficult[16]. In our patient, it appeared as a picture of frequent symptoms both in patients presenting this tumor and in respiratory infections, asthma, cystic fibrosis, immunodeficiencies, among others[17,18]. Differential diagnoses, such as ABPA can present with these symptoms in patients with history of asthma and increased IgE, reporting confusion with tuberculosis in up to 21% of cases[19,20].

In most cases, the diagnostic imaging tests show bronchial obstruction[11,16], as in this case, where we observed bronchial obliteration in the right lower lobe with volume loss. Frequently, MEC presents as an exophytic mass that can be observed in bronchoscopy, allowing the diagnosis through a transbronchial biopsy[17,21]; however, in this case, no lesion was evidenced, only a concentric reduction of the bronchial lumen. In the transbronchial biopsy, the presence of inflammatory tissue or results without alterations have been described, which delays the diagnosis. In our case, the transbronchial biopsy did not have good diagnostic performance since it did not show characteristics of malignancy, which agrees with the literature[17].

After reviewing 204 cases of lung tumors in children, Dishop et al. found that most of them were of metastatic origin, followed by benign tumors and finally primary malignant lesions[6]. Among the latter, carcinoid tumor, bronchogenic carcinoma, MEC, and pleuropulmonary blastoma were most frequently present[6,12]. Other authors have reported malignant lesions in 64% of the cases[22].

Jaramillo et al. describe predominantly left localization in cases of MEC in the pediatric population, as opposed to the patient presented. 41% of the cases were located on the right, out of which 23% were in the lower lobe bronchus[12]. The diagnosis of low-grade MEC is predominant in pediatrics[14], however, in this patient, it was classified as intermediate grade, which represents 6% of the cases reported in children under 18 years of age[12]. The prognosis in the pediatric popu-

lation is good, with a survival close to 100% at five and ten years of follow-up[23].

The main therapeutic measure for MEC is surgical resection with the removal of adjacent lymph nodes in order to verify its dissemination[24]. It is usually curative without the need for complementary therapies in low histologic grade[14,24]. The most common technique is lobectomy with the best results, but to preserve most of the lung parenchyma, however, alternatives such as segmentectomy and sleeve resection have been used[14]. Endoscopic removal is an alternative treatment, however, it has been considered an unreliable technique due to the difficulty for the complete resection of the tumor and other complications such as bleeding control[12]. Even so, the use of laser surgery has allowed the complete resection of some tumors, reducing complications and tumor recurrence in a follow-up of up to three years[25].

In the histological evaluation of this neoplasm, three characteristic cell types can be identified (luminal mucinous, squamous, and intermediate). The immunohistochemical studies include markers such as cytokeratins CK7, CK5/6, CK8 in addition to p53 and p63[26]. The MEC is negative for napsin A, TTF-1, S100, and alpha-actinin[21,26], which is in line with the immunohistochemical markers performed in this case.

## Conclusions

The pulmonary nodule in pediatrics requires a broad diagnostic approach, the most frequent etiologies such as infection and malformations must be ruled out, and then we must include the search for metastatic and primary malignancy of the lung. Among the latter is lung MEC, which, despite it is a very uncommon neoplasm in pediatrics, should not be underestimated, since its early diagnosis and timely treatment allow a good prognosis in children and adolescents.

## Ethical Responsibilities

**Human Beings and animals protection:** Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

**Data confidentiality:** The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

**Rights to privacy and informed consent:** The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

## Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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