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A teenager with lung mucinous adenocarcinoma harboring a *KRAS* mutation arising in type 1 congenital cystic adenomatoid malformation (CCAM)

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Abstract
A 14-year-old boy was referred to our hospital with a 1-year evolving productive cough and hemoptysis.A Positron-emission-tomography scan (PET/CT) revealed a 17cm hypermetabolic right lower-lobe lung mass in contact with mediastinal structures as well as multiple bilateral pulmonary nodules. Percutaneous lung biopsy identified an invasive mucinous adenocarcinoma (IMA; formerly mucinous BAC) associated with Type I Congenital Cystic Adenomatoid Malformation (CCAM).Genomic profiling was performed and detected a KRAS mutation (G12D).
NSCLC can be rarely seen in young patients. In the pediatric population, the incidence is approximately 0.0002% and it is usually associated with a congenital malformation.
CCAM is a group of rare lung congenital malformations. The estimated incidence is 1 in 25.000 to 1 in 35.000 pregnancies and it represents 25% of all congenital lung malformations. Type I is the most common subtype of CCAM. It is characterized by the presence of large cysts lined by pseudostratified ciliated cells that are often interspersed with rows of mucous cells.It has been largely recognized that some cases of type I CCAM show malignant transformation to mucinous adenocarcinoma.
Recent data clearly demonstrated that the occurrence of mucinous adenocarcinoma in type I CCAM is associated with KRAS mutation.
This case highlights the relationship between type I CCAM and lung mucinous adenocarcinoma/KRAS mutant. Moreover, demonstrated that the clinical outcome was consistent with the molecular feature of a KRAS mutant patient.

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1. Case report

A previously healthy, Caucasian, nonsmoker 14-year-old boy was referred to our hospital with a 1-year evolving productive cough and hemoptysis. He had undergone several antibiotic treatments before without symptom improvement. A positron-emission-tomography scan (PET/CT) revealed a 17 cm hypermetabolic right lower-lobe lung mass in contact with mediastinal structures as well as multiple bilateral pulmonary nodules [Figure 1]. Initial laboratory showed CA19-9 up to 3 × higher than normal value. Percutaneous lung biopsy revealed an invasive mucinous adenocarcinoma (IMA; formerly mucinous BAC) associated with Type I Congenital Cystic Adenomatoid Malformation (CCAM). Immunohistochemistry was positive for CK7, TTF-1 and MUC2, and negative for CK20 and CDX2 [Figures 2 and 3]. Genomic profiling was performed by next-generation sequencing and detected a *KRAS* mutation (G12D).

Patient underwent treatment with carboplatin and paclitaxel with stable disease but after 6 cycles developed clinical, radiological, and laboratorial (CA19-9 elevation) progressive disease. Docetaxel was initiated as a second-line treatment, but after 5 cycles of stable disease progression was detected. He was then exposed to Erlotinib for two months with rapidly worsening symptoms. A fourth-line treatment with Pemetrexed was started and despite radiological stable disease he had a good clinical response with improvement of symptoms and tumor marker decrease for 5 months. Finally, he was given Gemcitabine, developing a new pulmonary progression after two treatment cycles. He died from his disease 19 months after his original diagnosis.

2. Discussion

The median age of patients newly diagnosed with non-small-cell lung cancer (NSCLC) is 70 years. It is known that NSCLC in young people is not common and the incidence for under 40 s has been found to be approximately 1.2–6.2% [1]. In the pediatric population primary lung neoplasm is even rarer with an incidence of approximately one case per 2 million under 19 years of age [2]. Based on this data, neuroendrocrine tumors are the most common malignant pulmonary neoplasms found, corresponding to 50% of all cases. Adenocarcinoma is only the fourth most common neoplasm with a 6.5% frequency [2].

NSCLC can be rarely seen on children without congenital malformation. One of the most recognized abnormalities of the lung associated with lung adenocarcinoma is the CCAM. CCAM have been described since 1949 by Chin and Tang [3] as malformations of the lobes of the lungs characterized by cystic, composed of bronchial-like and bronchiolar-like structures in various 'hamartomatous' arrangements. In 2002 Stocker divided into five distinct subtypes on the basis of histopathologic appearance [4]. Type I CCAM is the most common subtype, accounting for 60–70% of all cases. It is characterized by involvement of one lobe (usually lower lobes) with single or multiple large cysts ranging 1–10 cm surrounded by often-underdeveloped alveolar parenchyma and variable number of smaller cysts. The largest cysts are lined by ciliated pseudostratified columnar epithelium and are often interspersed with rows of mucous cells whereas the smaller cysts resemble dilated bronchioles and are lined by cuboidal to columnar epithelium [4–5]. Although the diagnosis is typically made in early infancy, late presentation has been described. The association with malignant transformation, particularly with IMA, is well-described. Though the incidence of this phenomenon is low (1%) [5]. In 35–50% of type I CCAM cases, clusters of mucogenic cells are present and it has been held responsible for the malignant transformation [5–7]. Indeed, some authors identified an entire spectrum from type 1 CCAM to mucous cell/goblet cell hyperplasia to atypical adenomatous hyperplasia to mucinous BAC and IMA [6]. Lantuejoul et al. [7] not only reinforced this hypothesis but moved further by suggesting that a genetic alteration (*KRAS* exon 2 mutations) might be associated with this process as well. In their report, they

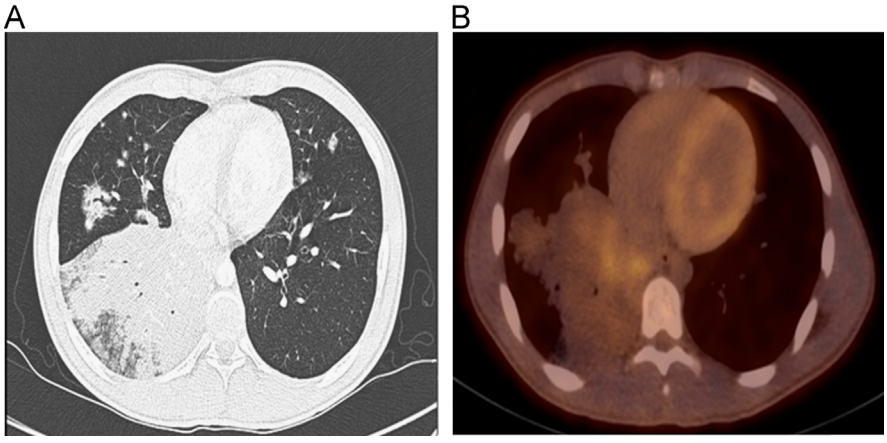

Figure 1 (A) Extensive mass with heterogeneous density and ill-defined borders, affecting almost all the right lower lobe, with air bronchograms, maintaining contact with the costal and mediastinal pleura. There are also areas of ground-glass opacity and multiple nodular opacities with soft tissue density and irregular contours in both lungs. (B) PET-TC showed a low uptake in the right-lower-lobe mass (SUV-2.8).