








Primary pulmonary enteric adenocarcinoma: A case report and review of literature

Janat M Alsaif¹ , Zainab S Alali¹ , Tarek El Sharkawy¹ , Ayesha Ahmed¹ , Awadia S Awadalla^{1*} ,
Methal I AlBayat¹ , Wejdan N Almotairi¹ 

¹Department of Pathology, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, SAUDI ARABIA

*Corresponding Author: awawadalla@iau.edu.sa

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ABSTRACT

Primary pulmonary enteric adenocarcinoma (P-PEAC) is an unusual subtype of invasive lung adenocarcinoma. The significance of such tumor lies in its similar histopathological and immunohistochemical characteristics to colorectal adenocarcinoma. Therefore, a detailed investigation is crucial to establish a definitive diagnosis. This paper reports a case of a 51-year-old Saudi female, diagnosed with a rare variant of lung carcinoma, P-PEAC.

Keywords: CK-7, CDX2, lung adenocarcinoma, colon carcinoma

INTRODUCTION

Lung adenocarcinoma is the second most common type of cancer in both females and males that falls under the umbrella of non-small cell lung cancer (NSCLC) [1]. 218,520 individuals were newly diagnosed with lung cancer in the United States and was estimated to cause 142,080 deaths in 2018 [2]. Primary pulmonary enteric adenocarcinoma (P-PEAC) is an unusual subtype of invasive lung adenocarcinoma that was recently recognized by the World Health Organization (WHO) in 2015 [3]. The first case report was published in 1991, when a 40-year-old smoker presented with a persistent productive cough. Chest X-ray revealed a two cm nodule located at the right upper lobe, which did not resolve despite extensive antibiotic and anti-tuberculous therapy. Ultimately, the patient underwent surgical resection of the nodule. Post-operative histological examination revealed lung cancer with intestinal differentiation. Additionally, systematic investigation, including ultrasonography and computed tomographic (CT) of the abdomen, contrast enema, gastroscopy, and colonoscopy did not show any evidence of extra-pulmonary tumor [4].

According to International Association for the Study of Lung Cancer (IASLC), P-PEAC has been defined by the following findings: the presence of pulmonary adenocarcinoma with an enteric differentiation greater than 50.00%, as well as the expression of one or more immunohistochemical markers of enteric differentiation by tumor cells [5]. Consequently, the histological and immunohistochemical characteristics of P-PEAC resembles that of metastatic colorectal adenocarcinoma (MCAC) and reaching a definitive diagnosis requires thorough investigation [3, 5]. Differentiating P-PEAC from other diagnoses primarily relies on a careful history, physical examination, laboratory investigation, imaging modalities, and more importantly, biopsy. Furthermore, the use of CT scan,

positron emission tomography, and colonoscopy is crucial to exclude metastasis of colorectal cancer [6-8]. Due to the rarity of P-PEAC, the current available literature on epidemiology, etiology, diagnosis, and treatment is scarce and further studies are mandated.

CASE DISCUSSION

This paper is reporting the case of a 51-year-old, Saudi female, diagnosed with a rare variant of lung carcinoma, P-PEAC. The patient's sole manifestation was dry cough precipitated by a flu-like illness in the preceding year. The patient had reported a negative impact of the cough on her sleep and daily activities. Associated symptoms such as chest pain, shortness of breath, hemoptysis, fever, night sweats, anorexia, and unintentional weight loss were denied. Physical examination only revealed coarse lung crepitations, otherwise unremarkable.

The patient is a known case of bronchial asthma, thereby her complaint was interpreted as an asthmatic exacerbation every time she sought medical advice. In her last visit to the primary health care, a chest X-ray revealed a left lung apical infiltration. As a result, she was advised to follow up in a secondary health care center for further investigation. The secondary health care center performed multiple virology testing for the patient including Human immunodeficiency virus, hepatitis profile, coronavirus disease of 2019, fortunately, none of the mentioned viruses were positive. Furthermore, the apical infiltration was further investigated by a CT scan in which the radiologist reported a mass like consolidation in the apico-posterior lung segment, in addition to multiple solid nodules and nodular opacities noticed in the upper segment bilaterally (**Figure 1**).

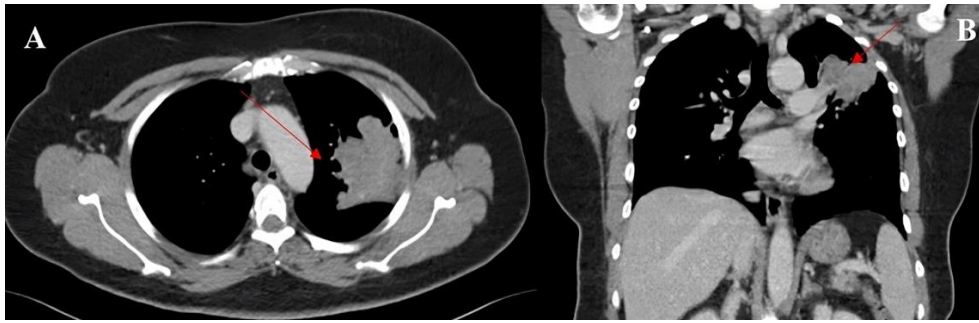


Figure 1. Image of CT scan of a 51-year-old representing an apical infiltration: (A) image of CT scan, visualized in an axial view representing an apical infiltration; (B) image of CT scan, visualized in a coronal view representing an apical infiltration (Source: Electronic data / pathology archives, reprinted with permission of the Department of Pathology of authors' institution)

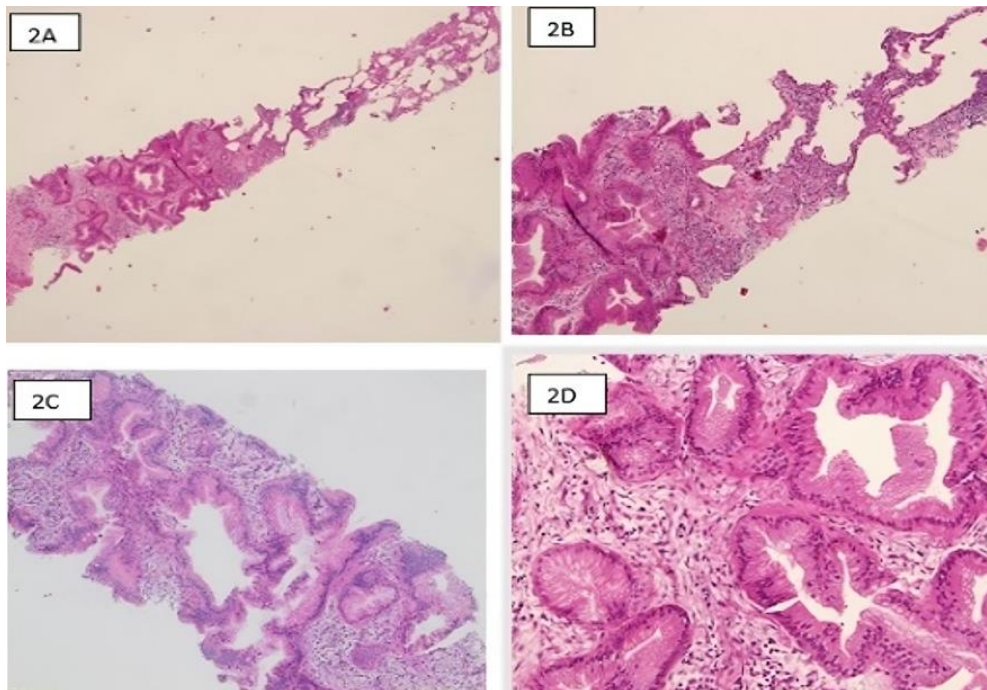


Figure 2. Hematoxylin & eosin stain (H&E) of core needle biopsy showing invasive carcinoma of lung parenchyma with intracellular mucin & desmoplastic reaction: (A) low power; (B) X10; (C) X20; & (D) X40 (Source: Electronic data / pathology archives, reprinted with permission of the Department of Pathology of authors' institution)

Moreover, left hilar lymph nodes and aortopulmonary lymph nodes were noted to be 0.7 cm and 0.8 cm in size, respectively. The radiologist suggested the diagnosis of bronchogenic carcinoma, however, could not totally rule out tuberculosis.

Furthermore, the patient underwent bronchoscopy in which it revealed normal airways, except for mucosal erythema of the left main bronchus associated with multiple nodularity. During the procedure bronchoalveolar lavage samples were obtained for cytology, gram stain, and other investigations.

The pathology report stated that the sample was clear of malignant cells, and included ciliated columnar cells, polymorphs, and macrophages. Tuberculosis was ruled out due to three negative acid-fast bacilli cultures.

Sequentially, an upper left lung core biopsy was obtained, and the pathologist reported presence of an invasive mucinous adenocarcinoma (**Figure 2**) in which the immunohistochemical and histopathological reports were suggesting the presence of a primary lung tumor.

According to pathology report, tumor cells were showing positivity of CK-7, CDX-2, and TTF-1 (**Figure 3**). Such a finding is highly suggestive of rare variant P-PEAC. Nonetheless, tumor cells were negative for CK-20, Ki-67, CK5/6, P63.

DISCUSSION

P-PEAC is an uncommon subtype of NSCLC that histologically resembles those arising in the colorectum [6]. In 2011, this malignancy has been declared as a variant of invasive adenocarcinoma of the lung by IASLC, American Thoracic Society, and European Respiratory Society [5]. Subsequently, the classification was recognized formally by WHO in 2015 [3]. The estimated prevalence of P-PEAC is 0.50% in NSCLC and 0.68% in primary lung adenocarcinoma [9]. Moreover, P-PEAC was found to be significantly higher in males relative to females, and more commonly seen in elderly with a mean age ranging from 60 to 63.2 years old [6-9].

The etiology of P-PEAC has not been established, however, several factors have been suggested to contribute to its

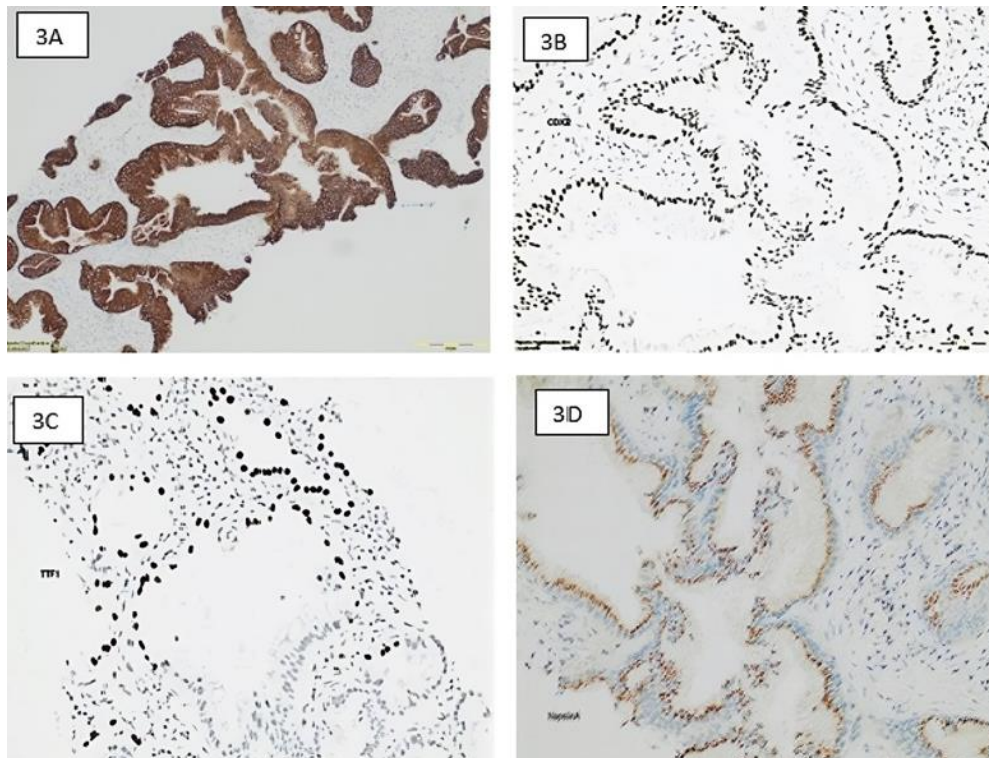


Figure 3. Immunohistochemical staining of tumor cells: (A) CK7 strong positive; (B) CDX2 positive; (C) TTF-1 focally positive; & (D) napsin-a positive (Source: Electronic data / pathology archives, reprinted with permission of the Department of Pathology of authors' institution)

pathogenesis. Several studies posed tobacco smoking as a risk factor for P-PEAC, however, the suggested correlation remains controversial and further studies are required [7, 8, 10]. In addition, genetic mutations have been suggested to play a role in the pathogenesis of P-PEAC. Epidermal growth factor receptor, B-raf proto-oncogene, and anaplastic lymphoma kinase, however Kirsten rat sarcoma viral oncogene homolog was reported as the most common genetic mutation observed in this malignancy [6, 11, 12].

Patients diagnosed with P-PEAC typically present with respiratory symptoms, with cough being the most commonly reported symptom. The cough is characterized by being non-productive, with a duration ranging from several weeks to years. Moreover, patients may present with hemoptysis, dyspnea, and/or chest pain, in addition to constitutional symptoms associated with malignancy [7, 9, 10, 12]. Furthermore, unfortunate patients may initially present with metastasis, most commonly the anterior chest wall, dorsum of the trunk, abdomen, and scalp. Other sites of metastasis have been reported in which a case report regarding skin metastasis as the initial manifestation was published [13].

The clinical approach and diagnosis of P-PEAC must involve clinical presentation, laboratory workup, imaging modalities, histopathology, and immunohistochemistry (IHC). Detection of serum tumor markers is often one of the initial steps when suspecting lung cancer. Serum tumor markers: carbohydrate antigen (CA19-9) and carcinoembryonic antigen (CEA) were found to be markedly elevated in P-PEAC than cytokeratin 19 fragment and neuron-specific enolase (NSE). As a result, the expression of CEA and CA19-9 is closely associated with P-PEAC rather than other subtypes of pulmonary adenocarcinoma [6, 8, 9]. Furthermore, the detection of the tumor by various forms of imaging is of paramount importance. Previous case reports have illustrated that the most common site for P-PEAC

visualized by chest X-ray and CT scan is the right upper lobe [6, 7, 9].

Upon microscopic examination, tumor cells revealed common structural features of colorectal adenocarcinoma, including tall columnar cells forming irregular acini. These cells contain an abundant cytoplasm that is characteristically eosinophilic, oval nuclei, prominent nucleoli, brush-borders, and central necrosis. Moreover, the cells lining the tumor tend to be weakly to moderately cohesive and contain a chromatin pattern that is finely granular to reticular [6, 7, 10, 11, 14]. This supports IASLC definition of P-PEAC, which is the presence of pulmonary adenocarcinoma with an enteric differentiation greater than 50.00% [5].

IHC plays an essential role in the diagnosis of P-PEAC as it cannot be completely distinguished from other malignancies based on its morphology. According to IASLS, at least one of the colorectal adenocarcinoma markers must be expressed to confirm the diagnosis of P-PEAC. The most widely used markers of enteric differentiation are caudal type homeobox transcription factor 2 (CDX2), cytokeratin 20 (CK20), mucin 2 (MUC2), and villain. Simultaneously, tumor cells express one or more of the typical markers of lung adenocarcinoma, such as cytokeratin 7 (CK7), thyroid transcription factor-1 (TTF-1), as well as novel aspartic proteinase of the pepsin family-A (Napsin-A) [5, 7]. It was reported that the most commonly expressed markers in P-PEAC are CK7 by 89.90% and CDX2 by 79.10% [8]. It was also reported that out of 129 cases diagnosed with P-PEAC, 92 patients were positive for both CDX2 and CK7 [8]. This suggested that a concomitant positive CDX2 and CK7 improved the sensitivity and specificity in the distinction of P-PEAC from MCAC by 71.30% and 82.00%, respectively [8, 11]. Moreover, CK7 and TTF-1 were demonstrated to be expressed in 50.00% of the cases diagnosed with P-PEAC [5]. Another

study revealed that Napsin-A is a marker that could support the diagnosis of primary adenocarcinoma of the lung [15].

Like P-PEAC, the detection of a primary lung adenocarcinoma that has common cellular characteristics with colorectal adenocarcinoma but does not express markers of intestinal differentiation is termed as pulmonary adenocarcinoma with enteric morphology [5]. The histological and immunohistochemical findings detected in P-PEAC are difficult to distinguish from MCAC. As a result, a complete systemic workup is recommended to rule out metastasis from an extrapulmonary site [6-8].

Treatment options for P-PEAC include surgical resection, which may be in the form of pneumonectomy, lobectomy, or the excision of a lung segment. The type of surgery is determined by the extent of the malignancy. Chemotherapy, radiotherapy, as well as targeted therapy can also be used as an additional treatment [9].

CONCLUSIONS

The establishment of the diagnosis of P-PEAC, specifically in its early stages, is of paramount importance. However, to our knowledge, the literature has mainly focused on establishing the diagnosis of P-PEAC in which studies concerning P-PEAC targeted therapy are scarce. Thus, the authors of this report highly recommend conducting high quality research for the sake of forming specific and effective treatment regimens for P-PEAC that will be utilized in national and international guidelines with the aim of improving the patient's outcome and survival rate.

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