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Case Report

Pulmonary Enteric Adenocarcinoma Lung-Case Series and Approach to Diagnosis

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Abstract

Pulmonary enteric adenocarcinoma (PEAC) is a rare variant of pulmonary adenocarcinoma, recognized first in the year 1991. The subtype was included in the WHO in the year 2015. Because of the rarity and uncanny resemblance of this subtype with colorectal adenocarcinoma; it is generally misdiagnosed as a case of metastasis from the colorectal tract. At present there are only a limited number of cases reported as primary PEAC and the results are often inconsistent. Hence, prompt documentation and publication of such rare cases will help in creating awareness and avoiding detrimental misdiagnoses and subsequent mistreatment. Through this paper our intent is to provide a detailed diagnostic work up in cases of PEAC by application of relevant IHC such as CDX-2, SATB2, Calretinin, TTF-1, Napsin A, CK 7 and CK 20, so that they can be identified from their morphological mimickers.

Keywords: PEAC; Enteric; Lung; Colorectal; Adenocarcinoma; IHC; CDX-2; TTF-1; SATB2; Napsin; CK7; CK20

Introduction

Pulmonary enteric adenocarcinoma (PEAC) as recently described is an extremely rare variant of primary pulmonary adenocarcinoma which morphologically resembles metastatic colorectal carcinoma (MCC) both histomorphologically as well as on immunohistochemistry [1]. It was described originally in 1991 by Tsao et al as a primary pulmonary adenocarcinoma with enteric differentiation [2]. The entity gained its diagnostic criteria by World Health Organisation (WHO) in the year 2015 [3]. Only recently in 2011, PEAC was classified as a rare variant of invasive adenocarcinoma by the International Association for the Study of Lung Cancer/American Thoracic Respiratory Society (IASLC). IASLC defines Pulmonary Enteric Adenocarcinoma to exhibit so called "enteric pattern" resembling colorectal carcinomas in more than 50% tumour cells. It consists of glandular or cribriform structured lined by neoplastic columnar cells with nuclear pseudo stratification, luminal necrosis and prominent nuclear debris. Furthermore, expression of at least one marker of enteric differentiation (CDX2, CK20 or MUC2) is essential for diagnosis of this rare subtype [4]. Adenocarcinoma of lung presents with varied histomorphological patterns including acinar, lepidic, papillary, micropapillary, solid, pure intestinal and mucinous [1]. In 2005 Inamura et al described about seven cases [5], while Meada et al in 2008 described one case as pulmonary intestinal-type adenocarcinoma [6]. Currently, there have only been a limited number of reported cases but there has been recent emergence of interest in this subtype.

Case history

Adding to the list we present two cases of PEAC received at our setup,

CASE I: A 59 years old male patient had complaints of chest pain and difficulty in breathing with few episodes of haemoptysis since three months.

CT scan revealed subsegmental collapse of left lung involving the lower lobe with an ill-defined lesion in the collapsed

segment measuring approximately 42mm x 34mm with maximum SUV 4.0. Diffuse thickening with nodularity is seen along the costal, mediastinal and diaphragmatic surface of the left pleura with maximum SUV 3.1. The patient had colonoscopy and full body PET scan done and no other lesion was detected outside the lung or in the gastrointestinal tract. The case was initially reported as metastatic adenocarcinoma of likely colorectal origin. Histological examination of the tumour showed intestinal-type mucinous adenocarcinoma without a lepidic, clear cell or squamous component, not ruling out the possibility of a metastasis (Figure 1a). On Immunohistochemistry, CK7, CK20, TTF-1, SATB2, CDX-2, Napsin A and Calretinin were carried out; the tumsour cells demonstrated diffuse positive staining for CK7, CK20, CDX-2 and negative staining for TTF-1, SATB2, Napsin A and Calretinin, findings suggestive of PEAC over MCC (Figure 1b, c & d).

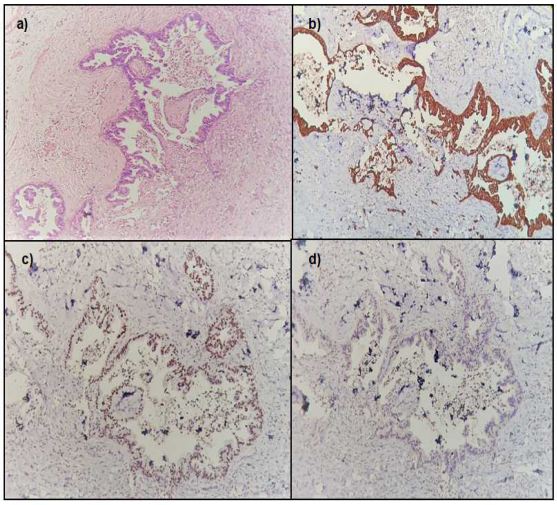

Figure 1: a) Neoplastic cells arranged in a glandular architecture with intestinal type morphology. The lumina shows debris resembling 'dirty necrosis'. b) CK7 immunostain- The neoplastic cells showed strong and diffuse positivity. c) CDX2 immunostain- The neoplastic cells were diffusely positive. d) SATB2 immunostain- No staining observed in the neoplastic cells.

This case was prototypical with findings completely matching the diagnostic criteria of PEAC.

CASE II: A 38 year old male patient presented with difficulty in breathing, coughing and haemoptysis and chest pain since 1 month. CT scan revealed an ill-defined lesion with internal specks of calcification and spiculated margins involving posterior segment of right lower lobe with surrounding collapse. Lesion measured 61 x 42 mm with a SUV of 10.1 encasing and compressing right lower lobe bronchus, descending pulmonary artery and inferior pulmonary artery. PET scan and other investigations including Gastro-intestinal (GI) scopy confirmed primary lesion in lung and gastrointestinal tract to be unremarkable. The case was initially reported as metastatic adenocarcinoma likely from colorectal origin. Tiny biopsy showed tumour arising from dysplastic bronchial epithelium, arranged in glandular pattern with nuclear pseudo stratification, luminal necrosis and nuclear debris (Figure 2a). On Immunohistochemistry, CK7, CK20, TTF-1, SATB2, CDX-2, Napsin A and Calretinin were carried out; the tumour cells demonstrated diffuse positive staining for CK20, CDX-2, SATB2 with weak focal staining for TTF1 while CK7, Napsin A and Calretinin were negative (Figure 2b, c & d).

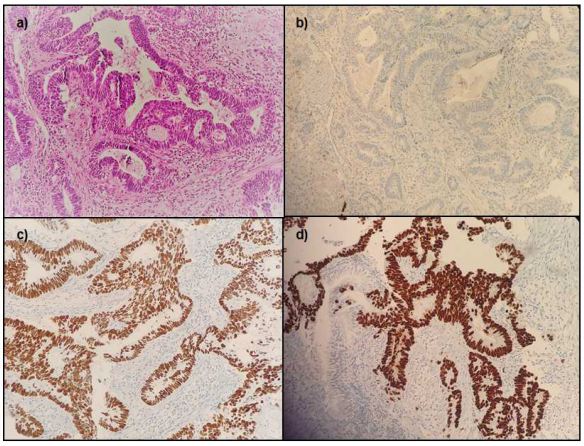

Figure 2: a) Neoplastic glands showing nuclear pseudo stratification and luminal debris. b) CK7 immunostain- The neoplastic cells did not show any staining. c) CDX2 immunostain- The neoplastic cells showed diffuse and strong staining. d) SATB2 immunostain- Strong and diffuse positivity observed in the neoplastic cells.

Furthermore, on molecular testing, EGFR was negative in exons 18,19,20 and 21. ALK and Ros 1 were found to be of wild type. PDL 1 was negative.

This case shows rare exceptions which can be seen in diagnosis of PEAC with CK7 being negative and SATB2 being positive. The diagnosis needed a detailed clinico-radiological evaluation in which the patient was not found to have any GI symptoms or any lesion in the GI tract.

Discussion

PEAC is defined as a primary pulmonary adenocarcinoma when a predominant component (>50%) of intestinal differentiation is present and the tumour cells are positive for at least one intestinal

marker (such as CDX2, CK20 and MUC2) [4]. Epidemiologically it is known to affect males more in comparison to females predominantly affecting the age group of 60-70 years. Haiyan li in their study found a male to female ratio of about 1.23 and most patients fell in the age group of 60-72 years with a median age of 65 years (7) [4]. Jie Zhang in their study found the average age for patients with PEACs to be 61.2 years, ranging from 45 to 69, with 7 males and 6 females [8]. In our case both patients were males, one was in 5th decade while other was in 3rd decade. In some previously documented cases smoking has been known to be consistently associated with PEAC. Like in the study done by Bian et al, it was found that 76.9% of the cases of PEAC had a strong association with smoking [9]. However, Haiyan li found this correlation to be present only in 46.1% [7], much less than Bian's study. In the paper published by Jie Zhang, 3 were smokers and 10 were non- smokers [8]. Inamura in their study found PEAC cases with history of smoking and also suggested that inhalation of toxic inhalants may have a contributory effect in the genesis of PEAC [4]. There are not enough studies done establishing the strong association of PEAC and smoking. In our cases as well, we did not find history of smoking. In the limited number of cases reported yet, PEAC had been described as a heterogeneous tumour containing a lepidic or clear cell component besides intestinal differentiation, thus offering a clue for its diagnosis. Inamura et al also describe primary pulmonary adenocarcinomas to have wide variety of histologic architecture like papillary, acinar (tubular), solid, bronchio-alveolar, and mucin-producing elements [4]. In most of the studies CK7 expression was found to be reliable and useful marker along with CDX-2 for diagnosis of PEAC, however, two CK7 negative cases have been reported in literature [7]. In our study both the cases expressed strong diffuse staining for CDX-2 and CK20, CK7 positivity with SATB2 negativity was seen in first case while in the second case SATB2 was positive and CK7 was found to be negative, making it eligible for the rarest of rare exceptions. With increase in expression of markers of intestinal differentiation, PEACs lose expression of pneumocytic markers. In a study by Nottegar et al more than half cases exhibited loss of TTF1 and Napsin A (4) [4]. Chen et al showed CK7 and TTF1 positivity was consistently seen in about 36% of cases [3]. Most of the previous literatures that have reported PEAC did not mention the utility of SATB2 as compared with CDX-2 except for few. Stefan M Brettfeld et al. advocated and found SATB2 to be more accurate marker of colorectal origin across a variety of expression levels compared with CDX-2 [10]. Bian et al also suggested that the use of SATB2 with CDH17 together can increase the sensitivity (76.92%) and specificity (100%) of the diagnosis of PEAC and this kind of combination could be used as the best marker to distinguish PEAC from MCC [9]. Nottegar et al expanded their immunophenotyping study by recruiting villin apart from CDX-2, CK20, CK7, TTF-1 and Napsin-A, and successfully demonstrated positive staining of villin as well with the typical enteric pattern in about 76.1% of the cases [4].

Extraintestinal CDX-2 immunoreactivity is not limited to lung, Inamura et al have reported CDX-2 immunoreactivity in other sites, including intestinal metaplasia occurring in the stomach and oesophagus, gastric carcinomas with intestinal-type differentiation, other intestinal- type adenocarcinomas occurring in different locations, mucinous carcinomas of ovary, pancreas, and lung, and pulmonary neuroendocrine carcinomas, making the use of other site specific markers such as SATB2 and CDH17 necessary [5]. Meanwhile, TTF-1 positivity has been documented in primary gastrointestinal malignancies too [11]. With regard to molecular profiling there are mixed findings due to limited literature, associating PEAC more with KRAS mutation than EGFR mutation. Like Wang et al in his study of 46 cases could evaluate only 9 cases for mutation analysis and found that they were EGFR-wild and KRAS -wild types [12]. Lazlo et al demonstrated KRAS mutation indistinguishable from MCC [13]. Contradictory to Wang et al, Nottegar and colleagues showed a higher rate of KRAS mutations. In literature no significant data has been found for BRAF mutation and EML4-ALK while EML4-ALK is one of the most important translocations in lung adenocarcinomas. In our study, molecular mutation of EGFR, ALK and ROS 1 were wild type.

Very rare cases of PEAC are absolutely identical to MCC with regards to morphology, immunohistochemistry and EGFR/K-RAS mutation testing and it is essential to emphasize the pivotal role of a detailed clinico-radiological correlation. Immunotherapy plays a vital role in cancer treatment in recent years, its efficacy has been confirmed in variety of tumour types. Total absence of EGFR mutation corresponds to inability to use tyrosine kinase inhibitors in these patients. Possibility of benefit from checkpoint blockade therapy was suggested by Chen et al; however, complications and immune related adverse events (irAEs) created skepticism [3]. Hiroyuki Tachi et al mentions that there is no standard treatment available for this rare variant [14]. At present the mainstay of treatment for PEAC are surgery and systemic chemotherapy and the most commonly used regimen is carboplatin combined with paclitaxel [7]. Several reports have demonstrated tumour control with traditional Non-Small Cell Lung Carcinoma (NSCLC) chemotherapy; whereas colorectal cancer regimens have not been useful. The study of Garajova et al and Lin et al reinforced this fact as all the patients who were started on capecitabine/oxaliplatin/bisphosphonate which is the standard combination therapy for colorectal carcinoma or it's metastatic foci failed to respond [15,16].

Conclusion

Since the incidence of PEAC is low and the fact that it

is a newly recognized entity, not a lot of literature exists about the finer details and the approach to its diagnosis. Because of the high resemblance, it is wrongly diagnosed as MCC, leading to catastrophic outcome as these tumours fail to show response against the chemotherapy offered for MCC. There will be serious and devastating implications in failing to differentiate between PEAC and MCC, particularly with respect to therapeutic strategies and prognosis, thus warranting proper knowledge and accurate diagnosis. Going through the literatures and through our cases as well; it is realized that a correct diagnosis is possible with the support of adequate clinico- radiological correlation and by employing minimum but relevant IHC markers namely CK7, CK20, TTF-1, Napsin A, SAT B2 and CDX-2. What is also seen is that while the diagnostic criteria which are mentioned in the literature are seen to be met in most cases, they are not sacrosanct and the knowledge about exceptions is a must, thus warranting a detailed clinicopathological approach in clinching the diagnosis.

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