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Pulmonary adenocarcinoma with enteric differentiation: A distinctive histologic subtype

Tiago Biachi de Castria, Manoel Carlos Leonardi de Azevedo Souza

ABSTRACT

Introduction: Lung adenocarcinoma has a complex variety of different hystopathologic subtypes with distinct epidemiology, pathology and prognosis. Pulmonary adenocarcinoma with enteric differentiation is a rare variant defined as a tumor with more than 50% of colorrectal-like components, immunohistochemistry (IHC) positive for at least one marker of enteric differentiation (CK20, CDX-2 or MUC2) and no evidence of other malignancies. Case Series: Patients were identified in a review of a set of adenocarcinomas, apparently originated in colon, but posteriorly accessed as lung adenocarcinomas. Median age was 57.6 years, were all Caucasian subjects and presented with metastatic disease. The median size were 6.3 cm at the time of diagnosis and all had spiculated shape forms at CT scans. Microscopic description revealed a lepidic (mucinous) adenocarcinoma in all five cases. Immunohistochemistry were positive for CK20 or CDX-2 in all these cases and was negative for CK7 in one patient. Conclusion: The use of immunohistochemistry analysis can distinguish between metastatic colorectal carcinoma and primary pulmonary adenocarcinoma with enteric differentiation. This differentiation on the basis of morphological and immunohistochemical findings may be difficult in the case of CK7-negative and physical examination and image evaluation are essentials in this characterization.

Keywords: Adenocarcinoma, Enteric differentiation, Lung cancer, Pulmonary cancer

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INTRODUCTION

Non-small cell lung cancer (NSCLC) is the leading cause of cancer mortality worldwide and adenocarcinoma subtype is the responsible for at least half of these cases [1]. Lung adenocarcinoma (LAC) has a complex variety of different hystopathologic subtypes including acinar, papillar, micropapillar, solid and lepidic patterns. Each one of these subtypes has a distinct epidemiology, pathology and prognosis [2].

In 1991, Tsao and Fraser reported a case of a 40-year-old male that had had a pulmonary nodule resected. Microscopic examination (hematoxylin and eosin) revealed an enteric differentiation that consisted in the presence of typical epithelial colonic cells (absorptive, globet, Paneth and enterocromafin cells). The patient

was also submitted to an extensive screening for others neoplasms and negative results corroborated the diagnosis of a primary lung cancer with an enteric hystologic differentiation, posteriorly named pulmonary enteric adenocarcinoma (PEAC) [3].

After the publication of following cases and their better characterization, immunohistochemistry (IHC) has emerged as an important tool in differentiating these patients from those with metastatic colorrectal cancer (MCC). Yousem et al. pointed out that despite the similarities in H&E, those tumors have distinct patterns of IHC markers [4]. The thyroid transcription factor-1 (TTF-1), Napsin A, and cytokeratin 7(CK7) are often positive in LAC whereas cytokeratin 20 (CK20), CDX-2 and MUC2 are frequently positive in colorrectal cancer. Cytokeratin 7 is the most sensitive and specific marker for PEAC, and only two cases of CK7-negative patients are reported in literature [5, 6]. TTF-1 and Napsin A are positive only in 44–59% and 33%, respectively, according to latest series [7, 8].

In 2011, the new lung adenocarcinoma classification was published and supported by the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS): PEAC was first reconized as a rare variant of LAC. In this publication, a multidisciplinary team of experts defined this entity as a tumor with more than 50% of colorrectal-like components, IHC positive for at least one marker of enteric differentiation (CK20, CDX-2 or MUC2) and no evidence of other malignancies [2].

To date, fewer than 30 cases were described in English literature, all of them with resected localized lesion. The challenge is how to distinguish PEAC from MCC, since each one has distinct therapeutic strategies and prognosis. Here, five cases of metastatic PEAC are reported and we aimed to analyze the IHC panel, pattern of presentation and dissemination and response to different systemic treatment.

CASE SERIES

Five cases of PEAC were identified in a review of a set of adenocarcinomas previously thought to be originated in colon. But, when reaccessing the cases, we concluded that the patients had not had colon cancer. Therefore, the mass in their lungs was originated in the lung itself, with a IHC panel of enteric differentiation. The median age was 57.6 years, were all Caucasian subjects and presented at the time of diagnosis with metastatic disease. The median size of the tumors were 6.3 cm at the time of diagnosis and all had spiculated shape forms at tomography lung scans. Microscopic description revealed a lepidic (mucinous) adenocarcinoma pattern in all five cases (Table 1).

Patients 1 and 2 presented themselves with thoracic pain and dyspnea. After the clinical evaluation, CT scans of the lungs revealed a pulmonary mass associated with ipisilateral pleural effusion, posteriorly confirmed as neoplastic effusion. Endoscopy were performed in both patients and showed no lesions. Colonoscopy in patient 1 was normal and in patient 2 showed one tubular adenoma with low grade atypia in the sigmoid. Furthermore, bronchoscopy obtained fragments that were histologically analyzed and IHC revealed a panel with CK-20 positive and CDX-2 negative in both patients. CK-7 was positive in patient 1 and negative in 2 (Table 2).

Patient 1 is in chemotherapy with carboplatin (AUC 6) and gemcitabine (1000 mg/m², d1 and d8) every 3 weeks, with good tolerance and stable disease after 3 cycles.

Table 1: Clinicopathological characteristics of the patients analyzed in this study

Case	Age (years) / Sex / Race	Localization	Size (cm)	Visceral pleural invasion	Status
1	47 / F / W	LUL	7.3	+	DOD, 13 months
2	50 / F / W	HRR	5.2	+	AIT, 6 months
3	54 / M / W	RUL	2.8	-	AIT, 10 months
4	66 / M / W	LIL	3.4	-	DOT, 36 months
5	71 / M / W	Med and ILL	8	+	AIT, 6 months

Abbreviations: M: male; F: female; W: white; LUL: left upper lobe; HRR: horizontal right fissure; RUL: right upper lobe; LIL: left inferior lobe; Med: Midlle lobe; ILL: inferior left lobe; DOD: dead of disease; DOT: Deado f treatment; AIT: alive in treatment.

Table 2: Immunohistochemical results

Case	CK-7	TTF-1	Napsin	CK-20	CDX-2	Others markers
1	+	-	-	-	+	CEA+, CA19.9 -
2	-	-	NA	+	+	RE -
3	+	-	-	+	–	None
4	+	-	NA	+	+	Surfactant -
5	+	-	NA	-	+	None

Abbreviations: + = Positive; - = Negative; NA = non available.

Patient 2 was treated with mFOLFOX6 regimen (5-fluoracil, oxaliplatin and leucovorin) and progressed after third cycle. She developed a carcinomatous lymphangitis that culminated in respiratory failure and death of the patient in 6 months afterward.

Patient 3 presented lumbar pain associated with progressive paresis of lower extremities in a two-weeks period. Orthopedic evaluation and spinal CT scans showed invasion of the from D2 to D6 vertebrae. Laminectomy was performed and histological and IHC analysis showed metastatic adenocarcinoma compatible with colonic origin (positive for CDX-2 and CK-7 and negative for CK-20 and TTF-1) (Table 2).

After CT scans and head MRI scan, a pulmonary nodule of 3 cm in the right upper lobe and a cerebelar lesion of 2 cm in the vermis were detected. Furthermore, endoscopy was normal and colonoscopy detected a sessile polyp at the sigmoid that microscopic evaluation demonstrated a tubular adenoma with low grade atypia. He was submitted a whole brain radiotherapy and radiotherapy in sipne. He has not yet started the treatment with chemotherapy. Patients 4 and 5, on the other hand, had a past history of colonic adenocarcinomas.

Patient 4 had a moderately differentiated tubular adenocarcinoma treated with parcial colectomy and bladder resection (pT3 pN0 pM0) in 2009, after which lost clinical follow-up. He returned in 2011 with diagnosis of "pneumonia" which turned out to be a pulmonary mass. Follow-up revealed an indolent lesion and biopsy confirmed an enteric lepidic pattern (IHC positive for CDX-2 and CK-7 and negative for TTF-1 and CK-20). He received capecetabine and bevacizumab from June to November/2013, when started with dorsal pain secondary to neoplastic infiltration in D4. Chemotherapy with mFOLFOX6 and FOLFIRI regimens were attempted, but pulmonary lesion was growing nonstop despite of them. Finally, chemotherapy was changed to carboplatin and pemetrexed with a fleeting objective response, but patient presented with a pneumonia and died due to infectious complications.

Patient 5 had moderately differentiated stage II adenocarcinoma of the colon treated in 2003 with partial colectomy and adjuvant chemotherapy. He was disease free until 2014 when presented at the emergency room with disorientation and delirium. The CT scans and MRI scan of head showed a peri-hilar pulmonary mass of 8 cm in the right lung and a left frontal nodular lesion, respectively. Microscopic examination of the pulmonary lesion demonstrated metastatic lepidic mucinous adenocarcinoma and IHC was positive for CDX-2, CK-7 and CK-20 and negative for TTF-1.

While endoscopy was clear, colonoscopy revealed a sigmoid polyp, wich microscopic and evaluation confirmed as a tubular adenoma with low grade atypia.

He underwent treatment with chemotherapy based on 5-fluoracil, oxaliplatin and leucovorin, with partial response measured by RECIST 1.0 until this moment. Cerebral lesion was treated with radiosurgery with satisfactory follow-up.

The antibodies used to perform those studies are listed below (Table 3) and the tissue was fixed in 10% neutral-buffered formalin and paraffin embedded. Hystological descriptions were performed by experienced pathologists at the Pathology Department of Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil (FM-USP).

DISCUSSION

It is well known that primary pulmonary adenocarcinomas are typically very heterogeneous, showing a wide variety of histological features including papillary, acinar (tubular), solid, micropapillary, and leipidic (mucin-producing elements and no mucin-producing elements) [9].

Tsao and Fraser were the first ones to report a different type of adenocarcinoma differentiation in 1991. That new reported differentiation IHC had similar aspects of colon adenocarcinomas, therefore were called primary

Table 3: Antibodies utilized in the study of pulmonary intestinal-type adenocarcinomas

Antigen	Antibody (clone)	Source	Dilution	Antigen Retrieval
CA 19.9	116 NS 19.9	Dako	1/500	Yes
CDX-2	AMT28	DBS	1/400	Yes
Cytokeratin 20	KS 20.8	DBS	1/2000	Yes
Cytokeratin 7	OV.TL 12/30	Cell Marque	1/8000	Yes
Napsin	MRQ - 6	Cell Marque	1/12000	Yes
PSA	POLICLONAL (E2964)	Spring	1/10000	No
TTF-1	SPT - 24	Novocastra	1/5000	Yes
CD68	KP1	DBS	1/20000	Yes
Pan-keratin	AE-1/AE-3	Zeta	1/5000	Yes
Estrogen receptor	SP1	Spring	1/2000	Yes

lung adenocarcinoma with enteric differentiation. Since then, a few reports of pulmonary intestinal-type adenocarcinoma have occured in English literature, and in 2011 was reconized as a subtype of lung cancer [2].

The PEAC, or, more recently, pulmonary adenocarcinoma with enteric differentiation (PAED) is defined as a lesion containing more than 50% of cells with a similarity to intestinal epithelium, in other words, cells with columnar absortive, eosinophilic cytoplasm and an apical brush borders [4, 10]. In a serie with 430 patients with primary pulmonary adenocarcinoma only six (1.4%) fullfilled these criteria [10].

The use of immunohistochemistry (panel with CK7, CK20, TTF-1, and CDX2) may help to distinguish between metastatic colorectal carcinoma from PAED. Yousem et al. revealed that these patients were positive in IHC for TTF-1 and/or CK7, but not CDX-2 and CK20. Our data, presented in this paper, revealed that no patient was positive for TTF-1 and four patients expressed CK7. As Yousem et al., we concluded that PAED may show no enteric differentiation by an immunohistochemical study. This conclusion is also corroborated by another series of fifteen pacients described in english literature (Table 4) [4, 11].

Table 4: Immunohistological results of 15 reported cases of primary pulmonar adenocarcinoma with enteric differentiation. Adapted from K. Hatanaka et al. / Pathology – Research and Practice 207 (2011) 188–191.

Case (sex/age (year))	CK7	CK20	TTF-1	Napsin A	MUC2	MUC5AC	CDX-2
M/NA	+	-	+	-	-	NA	
M/NA	+	-	+	-	+[a]	NA	+
F/NA	+	+[a]	-	-	-	NA	+[a]
M/NA	+	+[a]	-	-	-	NA	+[a]
M/NA	+	+	-	-	+[a]	NA	+
M/NA	+	-	+[a]	-	-	NA	+[a]
M/NA	+	-	-	-	+[a]	NA	-
F/74	+	-	+	NA	-	-	-
F/70	+	-	+	NA	-	+[a]	-
M/82	+	-	+[a]	NA	-	-	-
F/63	+	-	+	NA	-	-	-
F/73	+	-	+	NA	+	+[A]	-
F/57	+	-	+	NA	-	-	-
M/69	+	-	+	NA	NA	NA	NA
F/51	-	+	-	NA	NA	NA	+
F/51	-	+	-	-	+[A]	-	+

NA, not applicable.
[a] +, partially positive.

CONCLUSION

There are few reports on primary pulmonary adenocarcinoma with enteric differentiation (PAED), and nearly all reported cases were positive for CK7. Here, we described the third case negative for CK7 in English literature. Distinguishing primary PAED from metastasis on the basis of morphological and immunohistochemical findings may be difficult in the case of CK7-negative PAED patients. Therefore, physical examination, Computed tomography scan, fiberoptic gastroenteroscopy, video capsule endoscopy, and FDG-PET may be important for detecting primary colorectal cancers. So, it is necessary to accumulate and evaluate these cases on the basis of immunohistochemical and genotypic studies.

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Author Contributions

Tiago Biachi de Castria – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Manoel Carlos Leonardi de Azevedo Souza – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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