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Endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of mediastinal metastases of clear cell renal cell carcinoma

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ABSTRACT

Evaluation of mediastinal lymphadenopathy in patients with a previous diagnosis of renal cell carcinoma (RCC) is critical for the determination of further treatment. A minimally invasive method of cytology sampling of mediastinal lymph nodes using endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has emerged as a useful tool in diagnosis. Between January 2010 and April 2018, we performed 1744 EBUS-TBNA studies of mediastinal and hilar lymph nodes for a variety of clinical indications including mediastinal malignancy. Sixteen patients (93.7% males, mean age 59.1 years, range 44–81 years) were diagnosed by cytological and cell block study to have metastatic clear cell RCC. Twelve patients had been diagnosed with clear cell RCC in the past (mean 39 months, range 4–89 months) while in four, the tumor was primarily diagnosed in the staging phase on the basis of EBUS-TBNA. The EBUS features of the mediastinal nodal masses included increase of size (mean 2.5 cm, range 1.6–3.8 cm), irregular, inhomogeneous, hypervascular, and hyperechoic echotexture. EBUS-TBNA is a procedure safe and effective for evaluating mediastinal lymphadenopathy in patients with clear cell RCC. Immunohistochemistry in the cell block is decisive for proper diagnosis. The cytologist plays a key role in the diagnosis of metastatic clear cell RCC due to the treatment implications that this neoplasm encompasses.

1. Introduction

Renal cell carcinoma (RCC) is the third most common urologic neoplasm and accounts for about 5% of adult cancers in men and 3% in women [1]. The most common metastatic sites in order of frequency are lung, bone, lymph nodes, liver, adrenal, and brain [2].

Patients treated for RCC can subsequently develop one or several mediastinal lymphadenopathies. Furthermore, it has been demonstrated that RCC may metastasize to mediastinal lymph nodes without any abdominal lymph node involvement [3,4]. Exceptionally, mediastinal disease can be the initial manifestation of RCC [5–7]. Accurate pathological diagnosis of such mediastinal lesions is critical for effective treatment. Mediastinoscopy and open thoracic surgery are standard methods for mediastinal lymph node staging. However, they are invasive and costly, require general anesthesia, and complications cannot be ignored. Endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) biopsy of mediastinal lymph nodes is a minimally invasive modality for tissue sampling of the mediastinum [8]. However, in terms of accessibility to some lymph nodes and of the amount of tissue that can be obtained, the procedure is limited.

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) cytology is a minimally invasive, safe and feasible procedure that can be used for diagnosing mediastinal lymphadenopathy [9]. There are reports of isolated cases [10,11] or small series [9] in the literature using this technique to detect metastatic RCC to the mediastinal lymph nodes.

In this study, we investigated the feasibility of EBUS-TBNA for evaluating mediastinal lymphadenopathy in clear cell RCC. Mediastinal lymph node metastases presented as a recurrence or a primary diagnosis in a series of 16 patients diagnosed with clear cell (conventional) RCC.

2. Materials and methods

Between January 2010 and April 2018, we performed 1744 EBUS-TBNA studies of mediastinal lymph nodes for a variety of clinical indications including mediastinal malignancy. In this study, EBUS-TBNA

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Table 1
Immunohistochemical antibodies used in the study.

Antibody	Source	Clone	Dilution	Retrieval solution pH (Dako)
Renal cell carcinoma marker	Dako	SPM314	FLEX RTU	Low
CD10	Dako	56C6	FLEX RTU	Low
PAX8	Dako	Polyclonal	1:400	Low
TTF-1	Dako	8G7G3	FLEX RTU	High
Cytokeratin	Dako	AE1/AE3	FLEX-RTU	High
Epithelial membrane antigen	Dako	E29/EP1	FLEX-RTU	High
CAIX	Abcam	Polyclonal	1:1000	Low
Vimentin	Dako	V9	FLEX-RTU	High
Cytokeratin 7	Dako	OV-TL 12/30	FLEX-RTU	High
p63	Dako	DAK-p63	FLEX-RTU	High
p40	Biocare Medical	BC28	1:50	High

Dako (Agilent Technologies, SL, Las Rozas, Madrid, Spain); Abcam, Cambridge, United Kingdom; Biocare Medical, Alcalá de Henares, Madrid, Spain.

was used to assess mediastinal and hilar lymph nodes for the presence of metastatic clear cell RCC. All the cases were seen in-house. The lymph nodes sampled were enlarged (short axis > 1 cm) according to computed tomography (CT) scans, and they were associated in some cases with nodular lesions in the lung.

Tumor staging was established according to the 7th edition of the AJCC Cancer Staging Manual [12]. Nuclear grade in the renal surgical specimens was established according to Fuhrman et al. [13].

The determination of the suitability of the patient was made based on the location of the suspected nodal metastasis.

EBUS-TBNA was performed under local anesthesia and midazolam and fentanyl sedation as an outpatient procedure, using a flexible bronchoscope Olympus BF-UC160F-OL8 (Olympus, Tokyo, Japan) and an ultrasound image processor Olympus EUS Exera EU-c60 (Olympus, Tokio, Japan). Specimens were obtained with a 22-gauge needle. The average number of needle passes from each location was 3 (range 1–6).

An on-site evaluation was performed in all the cases and the specimen was deemed adequate. Each case had aspirate smears that were stained with Diff-Quick and Papanicolaou method. In all the cases we had cell block preparations. Sections of the cytoblocks were stained with hematoxylin and eosin. Immunopathological study was carried out on formalin-fixed 4-μm-thick paraffin-embedded tissue sections using the EnVision FLEX Visualization System (Dako, Agilent Technologies, SL, Las Rozas, Madrid, Spain). Antibodies used in the immunohistochemical study are detailed in Table 1. The immunohistochemical reactions were performed using appropriate tissue controls. Automatic staining was accomplished on a Dako Omnis autostainer (Agilent Technologies, SL). Because of limited material and variation of the staining panel over the years, not all tumors were stained with the same series of antibodies.

3. Results

Over the study period (8 years and four months), we analyzed the data from 16 patients who underwent EBUS-TBNA with cytoblock. The patients underwent EBUS-TBNA because of suspected mediastinal metastasis according to CT. Twelve patients had been diagnosed with clear cell RCC in the past (mean 39 months, range 4–89 months) while in four, this tumor was primarily diagnosed in the staging phase by means of EBUS-TBNA (Table 2). At CT scan these four cases showed large, expansile, polylobulated, heterogeneous lesions due to internal necrosis and occasional calcifications. The peripheral areas were solid with mean density at the pre-contrast phase and intense contrast uptake at the cortico-medullary phase (Fig. 1). Perirenal adipose tissue invasion or renal sinus invasion was observed in all cases.

Table 2
Clinical details of patients with mediastinal metastases caused by clear cell renal cell carcinoma.

Case No	Age at metastases(y)/ Sex	Thoracic imaging	Mediastinal lymph node máximum diameter (cm)	Previous tumor staging	Interval to metastasis (months)
1	50/M	Mediastinal lymph nodes Pulmonary nodes	2.9	pT2aN0M0,g3	16
2	62/M	Mediastinal lymph nodes Pulmonary nodes	2.5	pT3bN0M0,g2	72
3	49/F	Mediastinal lymph nodes Pulmonary nodes	2.0	pT2bN2M0,g3	4
4	69/M	Mediastinal lymph nodes Pulmonary nodes	3.5	pT4N0M1	26
5	57/M	Mediastinal lymph nodes	3.0	pT3bN0M0,g3	47
6	51/M	Mediastinal lymph nodes	1.6	pT3aN0M1,g3	0
7	74/M	Mediastinal lymph nodes	1.7	pT3aN0M0,g4	7
8	64/M	Mediastinal lymph nodes	2.4	T3N0M1	0
9	81/M	Mediastinal lymph nodes Pulmonary nodes	2.5	pT2aN0M0,g3	89
10	63/M	Mediastinal lymph nodes	3.5	pT2bN0M0,g3	55
11	44/M	Mediastinal lymph nodes	2.3	pT2aN0M0,g3	39
12	56/M	Mediastinal lymph nodes Pulmonary nodules	3.8	T3N2M1,g4	0
13	46/M	Mediastinal lymph nodes	2.0	pT3aN0M1,g4	0
14	56/M	Mediastinal lymph nodes	2.4	pT1bN0M0,g2	22
15	59/M	Mediastinal lymph nodes	1.7	pT3aN0M0,g2	24
16	65/M	Mediastinal lymph node Pulmonary nodules	2.0	pT1bpN0pM1,g3	67

g, Fuhrman grade.