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Metastatic Renal Cell Carcinoma: The Importance of Immunohistochemistry in Differential Diagnosis

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Key Words
Renal cell carcinoma · Lung carcinoma · Immunohistochemistry · Differential diagnosis

Abstract
Introduction: Clear cell carcinoma accounts for 75% of all types of renal neoplasms. Approximately one third presents with metastatic disease at diagnosis. Immunohistochemical studies play a significant diagnostic role.
Case Report: We report the case of a 48-year-old heavy smoker who presented with productive cough and progressive dyspnea. The study revealed a renal mass and lung alterations compatible with primary tumor of the lung. The patient underwent a right complete nephrectomy. The anatomopathological exam showed clear cell renal carcinoma (pT1bN0Mx). After transthoracic needle aspiration biopsy, the clinical diagnosis was stage IV adenocarcinoma of the lung. Initially, the patient received one cycle of chemotherapy (cisplatin/pemetrexed). Two weeks later, the immunohistochemistry tests revealed a secondary lesion with probable renal origin. Chemotherapy was stopped and the patient was started on sunitinib treatment. After two cycles the disease progressed. A second-line treatment with everolimus was proposed; however, the patient died 2 weeks later due to terminal respiratory insufficiency.
Discussion: Clear cell renal cell carcinoma remains one of the great mimickers in pathology. Immunohistochemistry is a valuable tool in the differential diagnosis of lung carcinomas. With the help of thyroid transcription factor 1, it is possible to distinguish a primary lung tumor from a metastasis with a reasonable degree of certainty. The present case report illustrates the challenge of making a definitive and adequate diagnosis. The immunohistochemistry added information that changed the whole treatment strategy. For the best treatment approach, it is fundamental that clinicians await all possible test results, before establishing a treatment plan.

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Introduction

Renal cancer accounts for 2–3% of all adult malignancies and is the third most frequent urological malignancy after prostate and bladder cancer. The incidence of renal cancer has been increasing during the last 30 years from approximately 7/100,000 to 11/100,000 in 2002. This rise is primarily due to the fact that renal masses are increasingly being diagnosed incidentally by routine imaging studies. Renal tumors occur more commonly in men than in women (ratio 2:1). Smoking is regarded as the single most important risk factor. Clear cell carcinoma accounts for 75% of all types of renal neoplasms [1].

Approximately one third of patients presents with metastatic disease at diagnosis. Additionally, 30% of all other patients develop metastasis at a later stage of their disease. The lungs are the most common site of clear cell renal cell carcinoma (CC-RCC) metastasis, comprising from 21 to 54% of metastases. Patients with metastatic disease have a median survival of 1 year and an expected 5-year survival of <20% [1].

Targeted therapies are now standard treatment for metastatic renal cell carcinoma, so the recognition and diagnosis of this carcinoma has become even more critical [2]. As advances in image-guided biopsies make a wide variety of body sites more accessible, we have encountered an increasing number of cases in which a diagnosis of renal cell carcinoma is being considered from an extremely small tissue sample. In this setting, adjunctive immunohistochemical studies often play a significant diagnostic role [2].

Case Report

We report the case of a 48-year-old man who worked in a cork factory and had a past history of heavy alcohol intake. In addition, he was a heavy smoker (45 pack-year) and suffered from chronic obstructive pulmonary disease (GOLD stage II).

He initially presented with productive cough and dyspnea after moderate efforts associated with anorexia and weight loss (6 kg) for the past 3 months. Physical examination showed palmar erythema, facial telangiectasia and a palpable right supraclavicular adenomegaly. There were no other lymphadenopathies. Heart sounds were normal and chest auscultation revealed basal inspiratory crackles. Abdominal examination was normal.

Thoracic computed tomography (CT) showed bilateral basal alveolar opacities, lymphatic permeation of some bronchovascular spaces, subcarinal lymph node enlargement, and right renal opacity, alterations compatible with bronquialveolar carcinoma, lymphangitis, and kidney tumor spread to the lung.

In this context, the patient was sent to a pulmonology consultation. He underwent a bronchofibroscopy with a transbronchial pulmonary biopsy, bronchial aspirate and lavage, which were negative for malignancy. A second bronchofibroscopy with transcarinal aspirative puncture was made. Cytology suggested a carcinoma with squamous differentiation stigmas. Thoraco-abdominal CT revealed a right renal mass of 6.2 cm in size in relation with the probable neoplasm (**fig. 1**). The mass was adjacent to the renal fascia. There was no involvement of the renal vessels and no retroperitoneal nodes. In the thorax, several mediastinal nodes with a maximum diameter of 1.5 cm were present. It was evidently an infiltrative process of the inferior lobes of the lungs (**fig. 2**).

Positron emission tomography showed a right renal mass with intense FDG uptake suggestive of malignant infiltration. Multiple lung foci with bilateral inferior lobes and left superior lobe involvement, bilateral paratracheal, pre-vascular space, bilateral hilar, subcarinal, and left interlobar

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nodes were present. Laboratorial tests were normal with the exception of nonspecific enolase (NSE), which was elevated (54.6 U/ml; N <12.5).

It was concluded that the patient presented two primary tumors: probable squamous cell carcinoma of the lung and kidney neoplasm. He underwent right complete nephrectomy. Anatomopathological examination showed CC-RCC, 5.5 cm in size (AE1/AE3+, vimentin+ CD10+; TTF1–), Fuhrman nuclear grade 3 with grade 4 focus, limited to the kidney, preserved capsule, without vascular and lymph nodes invasion (pT1bN0Mx). Staging bone scintigraphy was negative. To reevaluate the lung alteration, a CT scan was performed which revealed increased bilateral basal consolidations, some nodular small lesions, and an increase of mediastinal nodes. A transthoracic needle aspiration biopsy was done, and the histology was compatible with adenocarcinoma of the lung (stage IV – with lung metastasis).

It was decided to initiate chemotherapy with the doublet cisplatin/pemetrexed. The patient completed one cycle with good tolerance. Two weeks later, immunohistochemistry tests revealed negativity for vimentin and thyroid transcription factor 1 (TTF-1), which led to the conclusion that the lung lesions were secondary: lung metastasis of probable renal origin. Chemotherapy was stopped and the patient was started on sunitinib treatment (50 mg/day – 4 weeks on, 2 weeks off).

After two cycles of treatment, the patient presented with dyspnea at rest. Reevaluation CT scan showed pulmonary disease progression with several mediastinal nodes, bilateral pleural effusions and basal increased extensive consolidations.

Once we were confronted with disease progression a special authorization was requested for the use of everolimus for second-line treatment. Two weeks later, the patient was admitted to the internal medicine department due to terminal respiratory insufficiency for comfort measures and terminal illness care. He died 6 days later.

Discussion

CC-RCC remains one of the great mimickers in pathology. It can metastasize to virtually any body site and can have significant morphologic overlap with other nonrenal neoplasms and normal tissues [2].

The most basic method used by pathologists for the study of tumors is conventional histology. This technique involves processing representative tissue samples in a standard fashion to produce thin tissue sections that are stained with special chemical dyes and then examined under transmitted light in a microscope. The information obtained from this simple and basic technique will permit answering most routine questions in 70–80% of cases in most pathology laboratories [1, 3, 4].

Immunohistochemistry is the most widely used ancillary technique for the differential diagnosis of human tumors. A large variety of tumor-associated surface, cytoplasmic and nuclear antigens have been developed that are amenable to detection in routinely processed human tissue samples. Specific immunophenotypes of neoplasms help to characterize their properties and to identify their lines of differentiation. Although a few fairly specific markers have been developed over the years, no truly specific marker exists, and it is therefore better to call them tumor-associated markers for diagnosis. Because of this lack of absolute specificity, antibodies are best used in panels rather than singly. The selection of markers must always be guided by histological features of the tumor in concert with the clinical background [3, 4].

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With a panel of immunohistochemical markers, it is possible to distinguish or narrow down most lung neoplasms and separate them into meaningful therapeutic categories. It is a very valuable and often used tool in the differential diagnosis of lung carcinomas whether primary or secondary to the lung. The most useful application is distinguishing primary lung tumors from metastatic tumors to the lung from common sites (colon, breast, prostate, and kidney) [3].

Although there is no lung specific tumor marker, with the help of a relatively restricted marker, TTF-1, it is possible to separate a lung primary from a metastasis with a reasonable degree of certainty. TTF-1 is highly specific for lung tumors, particularly lung adenocarcinomas. Most primary adenocarcinomas are positive for 2 of the 3 markers, namely TTF-1 and CK7. Most non-lung adenocarcinomas are positive for either CK7 and CK20 or both and negative for TTF-1 [3].

The case report presented here illustrates the challenge of making a definitive and adequate diagnosis, particularly if the patient presents with two potentially synchronous cancers. That is the basis for all subsequent treatment decisions. Once incorrect, most probably the patient will not be treated adequately. The immunohistochemistry is an important tool which added information that changed all the treatment strategy in this case.

It is also fundamental that for the best treatment approach, whenever possible, the clinicians should wait for all feasible diagnostic and staging data, before proposing a treatment. It is better to postpone the treatment for some days or weeks, than starting one which is not appropriate, and moreover adding toxicity to the patient.

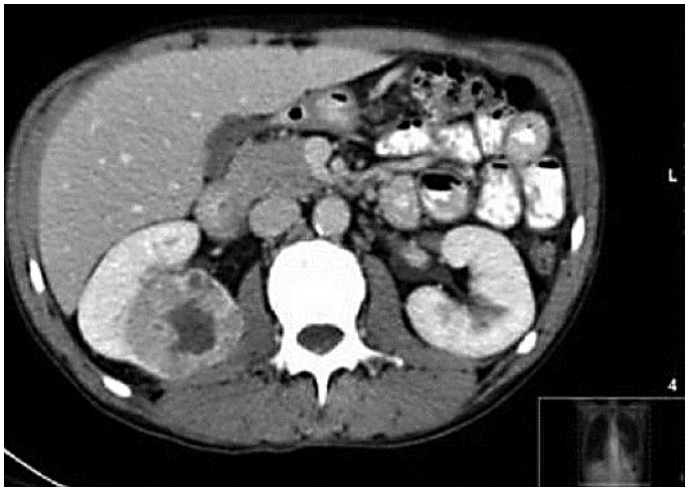

Fig. 1. Abdominal CT showing a renal mass.

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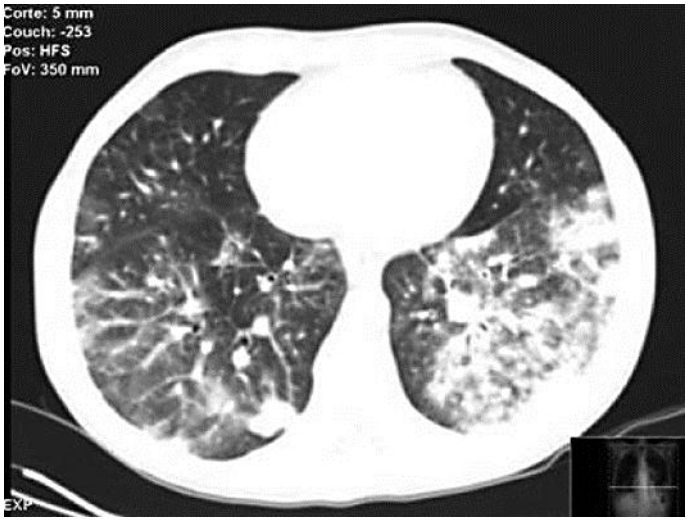

Fig. 2. CT showing lung infiltrative processes.

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