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Case Report

F-FDG^{18}PET/CT incidental detection of tumor-to-tumor metastasis in patients investigated for squamous cell lung cancer

Ghizlane Rais, MD[a,*], *Imad Ziouziou, MD*[b], *Soukaina Wakrim, MD*[c], *Hind Serhane, MD*[d]

[a] *Medical oncology department, Faculty of medicine and pharmacy of Agadir, University Ibn Zohr Agadir, 102, Res Yasmine, Rue Alikhlass, Quartier Najah, Agadir, 80000, Morocco*
[b] *Urology department, Faculty of medicine and pharmacy of Agadir, University Ibn Zohr Agadir, Morocco*
[c] *Radiology department, Faculty of medicine and pharmacy Agadir, University Ibn Zohr Agadir, Morocco*
[d] *Pneumology department, Faculty of medicine and pharmacy Agadir, University Ibn Zohr Agadir, Morocco*

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ABSTRACT

Tumor-to-tumor metastasis (TTM) is a well-known entity, although this is still an extremely rare phenomenon. The lung cancers are considered the most frequent metastatic donors while kidney cancers are the most common recipient. The finding of TTM is often incidental during a biopsy of metastases or on surgical specimens but never suspected on radiological assessment of tumor extension. The finding of an unexpected region of Fluorodeoxyglucose (FDG) uptake can occur when performing whole body Positron Emission Tomography/computed tomography (PET/CT) scan and potentially raises the possibility of a second primary tumor. However, PET/CT scan incidental detection of tumor-to-tumor metastasis has never been reported in English literature. We report here a case of clear cell renal carcinoma, receptor of metastases originating from an oligometastatic squamous cell lung cancer detected on the PET/CT scan performed as part of the extension workup. Morphological and immunohistochemical analysis of a percutaneous biopsy of the renal mass were consistent with the diagnosis of a metastasis of lung cancer into renal cell carcinoma. This is the first case of oligometastatic lung cancer with the occurrence of TTM suspected in PET/CT scan. Although this is a rare setting, it should be considered in daily practice, as it could potentially modify the oncological management offered to the patients.

Abbreviation: SUV, standardized uptake values; TTM, Tumor to tumor metastasis; ISUP/WHO, International Society of Urologic Pathologists/world health organization; FDG, Fluorodeoxyglucose; PET/CT, Positron Emission Tomography/ Computed Tomography.

* Corresponding author.
E-mail address: medghiz@gmail.com (G. Rais).

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Introduction

Multiple primary malignant neoplasms are not uncommon, but metastasis from 1 primary tumor to another is an extremely unusual event. This phenomenon is clinically called tumor-to-tumor metastasis (TTM). Since the publication of the first case by Berent in 1902, approximately 150 cases have been published [1–3].

Among the donor tumors, lung cancers are the most frequent primaries, followed by breast, prostate, and thyroid carcinomas [4,5]. Renal cell carcinomas and meningiomas are the most common malignant and benign metastasis recipients [1,4,5].

PET/CT scan is an imaging technique which plays an important role in the detection and staging of several malignancies (both in first diagnosis and follow-up). Incidental PET/CT findings consistent with a second primary are occasionally encountered during staging workup. Moreover, the incidence of double primary cancer is increasing as a result of the current significant development in medical diagnostic technologies [6]. However, the finding of an unexpected region of FDG uptake within a second primary suggesting tumor-to-tumor metastasis has not been previously reported in the literature.

We hereby present a very rare case of metastasis of a non-small cell lung carcinoma into a clear cell renal carcinoma, first suspected in PET/CT and then histologically confirmed, which we believe is the first case of this type of description.

Case report

We report the clinical case of a 52-year-old man, former well digger, with a long history of tobacco smoking (18-pack-years) and occasional cannabinol consumption, both quit 22 years ago, who consulted for a chronic dry cough and acute dyspnea of stage II (according to SADOUL classification) along with a recent history of chest wall, upper abdomen, and back pain.

Physical examination revealed only a slight pallor of the integuments. Chest X-ray showed an area of hyper density on the upper surface of the right lower lobe of the lung with enlarged mediastinal lymph nodes.

Chest CT scan showed an intra-parenchymal tumor process in the upper segment of the right lower lobe (Fig. 1A), measuring 7.2 × 4.9 × 5.1 cm, as well as several hilar and right mediastinal lymph nodes, classified as T3N2Mx according to the 8th TNM classification of lung cancer [7]. A CT-guided lung biopsy was performed, and pathological examination revealed poorly differentiated squamous cell carcinoma (SCC).

Immunohistochemical profile showed diffuse positivity for the P63 marker supporting this diagnosis.

A distant staging work-up, including thoracic, abdominal and pelvic CT scans, revealed a suspicious lower polar mass in the left kidney (Fig. 1B). A further abdominal ultrasound revealed an 8 cm lower pole left renal mass suspicious for metastasis.

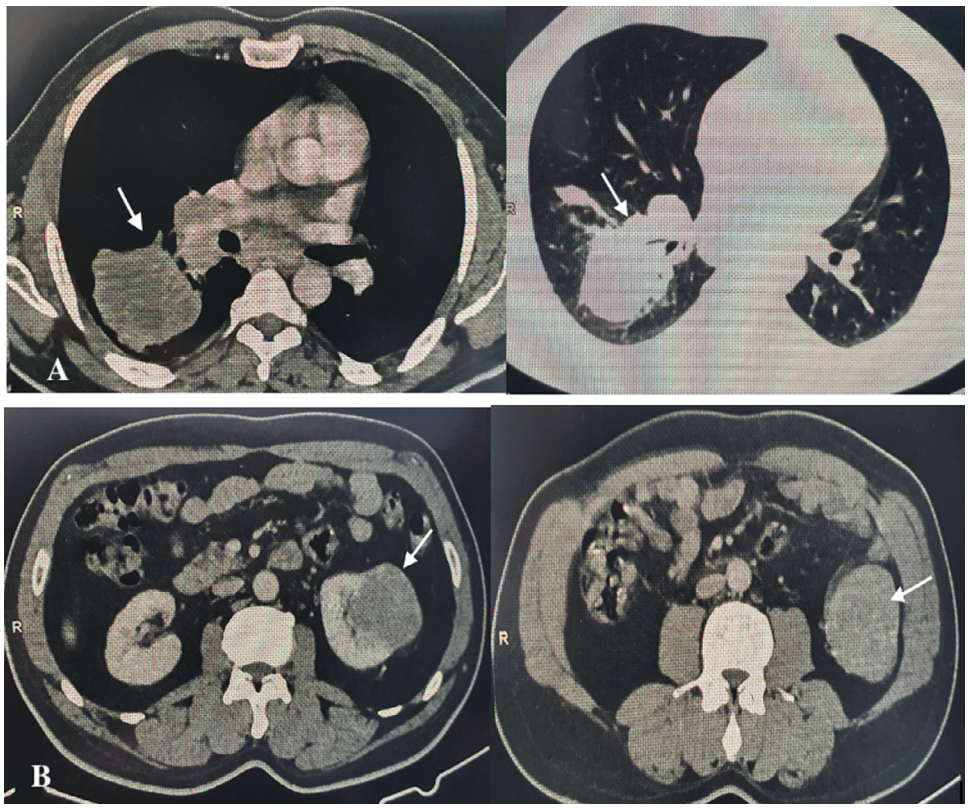

Fig. 1A – A thoracic computed tomography scan showing an intra-parenchymal tumour process in the upper segment of the right lower lobe with hilar and right mediastinal lymph nodes. Figure 1B Abdominal CT revealed a polar mass in the left kidney.

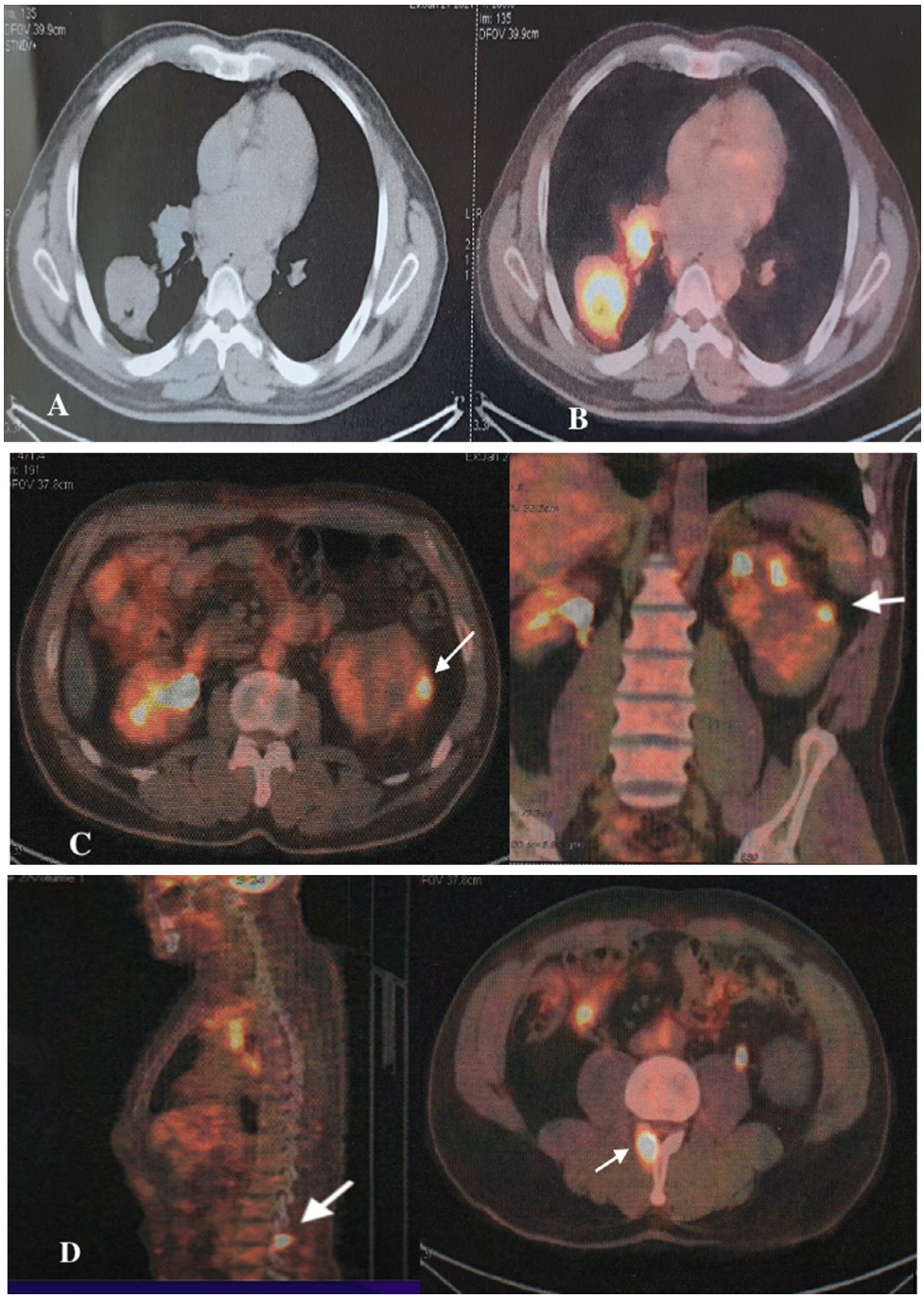

Fig. 2 – A and B PET/CT showed hypermetabolic mass of lower lobe (SUVmax of 9.8/large axis 63 mm) with ipsilateral mediastino-hilar and subcarinal metastatic lymph nodes (SUV max of 7.5). Figure 2C Inferior polar left renal mass of heterogeneous density and hypermetabolism measuring 8 cm in long axis with focal uptake on its superior-external side (SUVmax of 8). Figure 2D Inferior polar left renal mass of heterogeneous density and hypermetabolism measuring 8 cm in long axis with focal uptake on its superior-external side (SUVmax of 8).

A subsequent PET/CT scan was performed and showed an excavated hypermetabolic right lower lobar lung mass with spiculated contours and scissural attachments (SUVmax of 9.8/large axis of 63 mm) (Fig. 2A). Hypermetabolic right hilar (SUVmax of 10.7), mediastinal (right upper paratracheal (SUVmax of 7.2/small axis of 14 mm), right lower paratracheal (small axis of 16 mm/SUVmax of 7.5), subcarinal and pre vascular enlarged lymph nodes were found in the mediastinal field (Fig. 2B).

We also note the presence of an inferior polar left renal mass of heterogeneous density and hypermetabolism. It measures 8 cm in long axis and the most intense focus was on its superior-external side (SUVmax 8) (Fig. 2C).

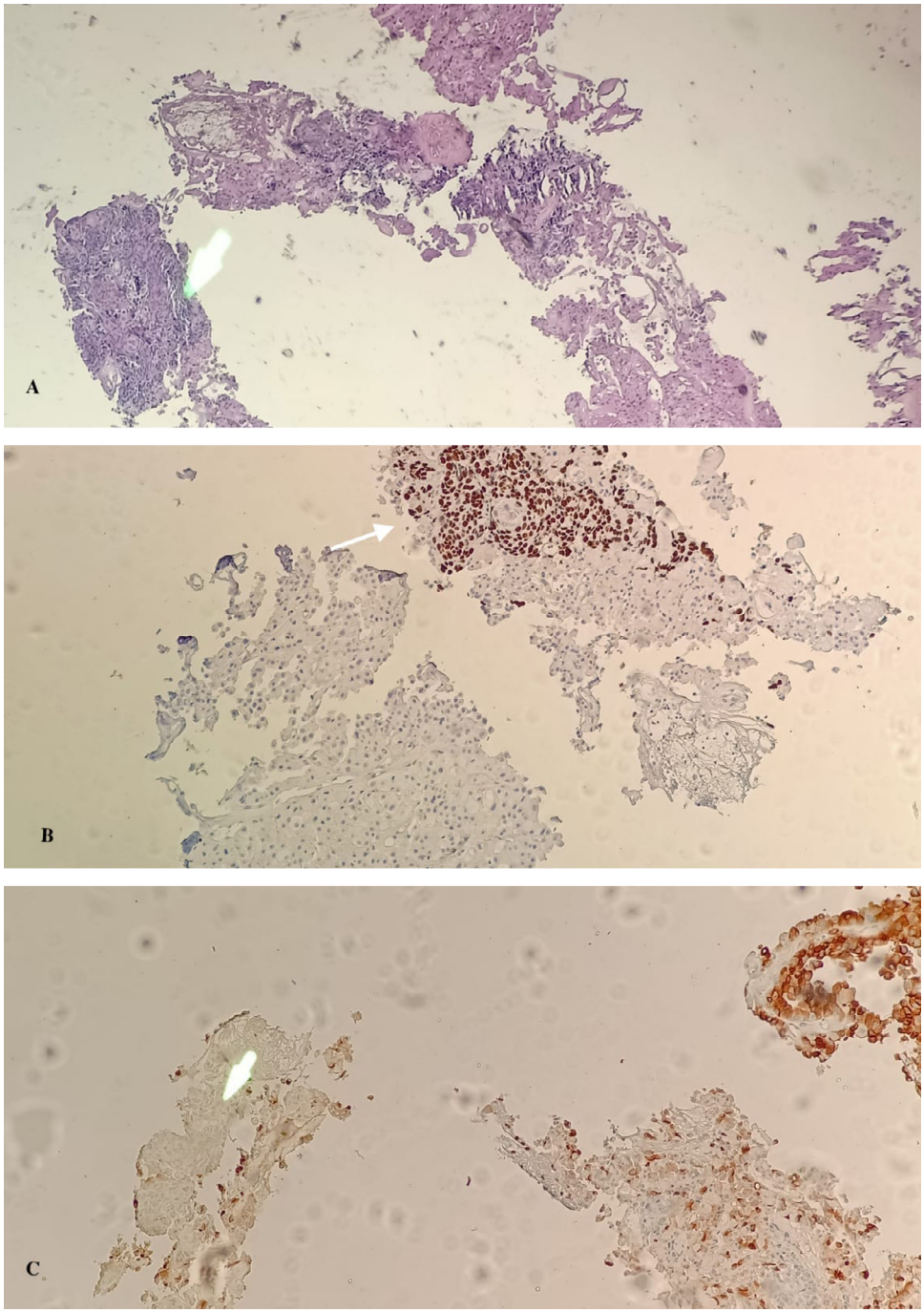

Fig. 3A – Renal cell proliferation (right side of the image) associated with an epidermoid-like differentiating contingent (arrow on the left side of the image) HEx10. Figure 3B Intense nuclear expression of P40 only in the squamous differentiation contingent (x10). Figure 3C CD10 expression only in the renal cell contingent (x10).

A hypermetabolic lytic lesion, on the right side of the spinous process of L3, was found as well (SUVmax 15.7) (Fig. 2D).

Biopsy of the suspected renal mass (directed to the area of hyper fixation) was indicated to differentiate a primary from a secondary process. Morphological and immunohistochemical profiles were compatible with a grade 2 clear cell renal carcinoma according to the WHO/ISUP 2016 nuclear classification system (Fuhrman's grade 2), associated with several microscopic foci evoking a metastasis of squamous cell carcinoma of the lung already known in this patient (Fig. 3A). Immunohistochemistry was performed to demonstrate the presence of a possible double tumor component. 2 components were found in both tumor areas: the clear cell areas were clearly positive for vimentin and CD10 (Fig. 3B), and negative for cytokeratin 7 and TTF1. The same clear cell component involved small foci

with a more atypical profile showing different reactivity characteristics with clear positivity for P40 (Fig. 3C). These morphological features and immunohistochemical findings along with the clinical history allowed the diagnosis of lung squamous cell carcinoma metastasis in renal clear cell carcinoma.

After discussion in a multidisciplinary meeting, it was decided to treat the patient as an oligometastatic lung cancer with a second clear cell renal cancer.

The patient was then started on a concomitant chemoradiation with curative intent, including conformal external beam radiation targeting the primary lung tumor as well as the regional lymph nodes up to the dose of 66 Gys in 33 daily fractions along with concurrent weekly Navelbin and Cisplatin chemotherapy regimen. The patient also received a stereotactic radiation to the single metastatic bone lesion of the third lumbar vertebrae with a total dose of 16 Gy in 1 fraction. Extended left nephrectomy was suggested by the multidisciplinary team, in case of good response to the primary treatment. Unfortunately, soon after completion of chemoradiation course, the patient contracted a severe COVID-19 infection. The prevalence of SARS-CoV-2 infection in our country at this time (July 2021) was about 180 cases per 100,000 inhabitants, and the predominant variant was Delta. The patient had received a single dose of vaccine and was infected with acute respiratory distress syndrome, and died in the meanwhile before surgery. The autopsy was not performed.

Discussion

The occurrence of a metastatic deposit of 1 malignant tumor within the substance of another, commonly known as tumor-to-tumor metastasis, continues to be an exceedingly rare phenomenon. However, these entities are thought to be more common than what is suggested by the approximately 150 cases, currently documented in the literature as case reports and series [1,8].

Renal cell carcinoma (RCC) is by far the largest recipient among malignant tumors for TTM (60%-80%) [1,4,5]. This was first noticed by Campbell et al in a series of 22 cases, where the RCC was the leading recipient with a rate of 65% of all cases [3]. Several facilitating factors have been suggested, including rich vascularity, abundant blood supply, rich vascular stroma and the presumed lipid and glycogen content of RCC. All these factors could potentially be preferential factors in the occurrence of metastasis from another carcinoma.

Although many physio-pathological mechanisms are still unknown, some theories have arisen to explain this phenomenon, including the « Seed and Soil » theory. The latter suggests that metastatic tumor cells (seeds) achieve successful growth and propagation in a hospitable environment (soil) [1–5].

Host tumors involve meningiomas, glioblastomas, gastric, pancreatic, and prostatic carcinomas, each representing 1% to 3% of cases depending on the series. In our case, the recipient tumor consisted in a typical case of RCC. Regarding origin cancer sites, the most common malignancies metastasizing into clear cell renal carcinoma are, in order of frequency, lung cancer, prostate cancer, and other isolated cancer cases reported occasionally in the literature.

Despite current developments in diagnostic, TTM diagnosis establishment still requires the fulfillment of criteria early described by Campbell in 1968 [3]. First, the patient must have 2 or more different tumors, and the recipient tumor is a true benign or malignant neoplasm. Second, the metastatic neoplasm should be a true metastasis, rather than a contiguous growth. Another additional criterion involves that the metastatic tumor must be compatible with the primary carcinoma by morphological or immunohistochemical means. The present case meets all these criteria.

Most importantly, TTM diagnostic possibility was never suspected on conventional imaging (including renal ultrasound or CT scan), in almost all cases reported in the literature, even when renal cancer was the recipient. In fact, most cases found in living patients with TTM, have been diagnosed incidentally in nephrectomy specimen for renal cancer, or more rarely, on renal biopsy. Occasionally, some cases of TTM were discovered during autopsy [1,2,8,9].

However, because of the widespread use of imaging modalities and the large improvement in treatment and follow-up of cancer patients leading to longer survival times, the possibility of encountering metastasis from one tumor to another could potentially increase in the near future.

FDG-PET/CT offers the unique opportunity to provide not only whole-body images, but also metabolic and functional information regarding tumor tissue. Moreover, the widespread availability of this imaging technique led to increasing the number of incidental findings [6,10]. It is well known that unexpected FDG uptake is frequent in patients having PET/CT investigation for lung neoplasms. However, before performing a biopsy with morphological and immunohistochemical analysis, TTM cannot be suspected even on PET/CT scan.

All malignancies need to be discussed at local multidisciplinary team meetings (MDTs). Increasingly, a well-trained PET/CT radiologist can provide advice on the probable significance of such findings, in conjunction with the clinical context. Thus, high suspicion index along with careful review of the imaging, and biopsy directed to the specific metastatic lesion are highly warranted to establish the accurate diagnosis when the metastatic lesions show unusual clinical presentations and/or metastatic patterns.

The renal mass in our presented case was 8 cm in size, single, unilateral, non-wedge-shaped, hyper vascular, and exophytic, a pattern consistent with primary RCC.

Retrospectively, after reviewing the clinical and imaging results, it would not be possible to suspect, in advance, the histological findings observed. However, the abnormal focal FDG uptake within the renal mass was suspicious for 2 different tumor components. To the best of our knowledge, this is the first case of TTM detected in PET/CT scan.

These findings outline the fact that when focal unusual FDG uptake is detected, high suspicion of malignancy should be raised warranting further investigations. That includes histological and Immunohistochemistry (IHC) studies, which could potentially modify the management offered to the patients [10,11].

Similar morphological and immunoreactivity features should be found in the primary and recipient tumors to retain

the diagnosis of TTM. The latter can be focal and small, requiring a wide sampling of the biopsied specimen, including all the heterogeneous areas. All that for the sake of avoiding any misleading of these metastatic foci, given their importance in making the accurate diagnosis, and for all the subsequent possible prognostic and therapeutic implications [1,9,12]. IHC is an essential part of the histological diagnosis of these cases and should be performed systematically as soon as the pathologist detects 2 different tissue components. Nevertheless, it is still important for the pathologist, who is faced to such cases, to be aware of the clinical history of any previous or coexisting neoplasms. This will ease the proper interpretation of morphologically unusual tumoral areas, inside a renal carcinoma, as metastatic from another tumor. Therefore, there will be a subsequent confirmation using the relevant immunohistochemical panel. In our case, it is important to underline that the diagnosis of TTM was performed on a percutaneous renal biopsy. Thus, based on histological and immunohistochemical features of squamous cell inside RCC, we concluded that squamous cell lung carcinoma metastasized to RCC.

TTM is an indicator of diffuse disease. Most reported cases in the literature had multiple metastases at the time of diagnosis. Notwithstanding, in our case, only a single bone metastasis was detected by radiological examination, in addition to the histologically confirmed renal one. Therefore, this occurrence was not in the context of generalized tumor spreading and thus, oligometastatic nature of lung cancer represents another aspect to highlight in this case.

Although the advanced stage and poor prognosis of the primary cancer should be kept in mind, some selected patients may benefit from aggressive treatment of incidental lesions and show survival benefit. Therefore, for patients with history of lung cancer, especially with limited multi-organ metastasis, resection of kidney tumor should be carefully considered.

Conclusion

The widespread availability of 18F-FDG PET/CT led to increasing the number of incidental findings. Further investigations are still necessary to better clarify their etiology. Tumor-to-tumor metastasis should be taken into consideration, especially if an uptake is detected in a renal mass, especially when encountering unexpected patterns in patients who have undergone PET/CT imaging for the investigation of lung cancer. Pathologists must also be alert in these situations, particularly if they find a renal tumor with a dimorphic or rare morphology. Immunohistochemistry plays a fundamental role in establishing the exact diagnosis.

Author contributions

GR was involved in the analysis of the data and the literature search and wrote the manuscript. IZ helped with the patient management and revision of the manuscript. SW and HS contributed to the preparation of this manuscript, and interpretation of the case. All the authors have read and approve the final version of the manuscript.

Declaration of figures authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

Competing Interests

The authors declare no conflict of interest.

Patient consent

Written informed consent was obtained from the patient's next of kin for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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