CASE REPORTS

NOT ALWAYS A MIRACLE – THE CASE OF THE MISSING METASTASIS

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Abstract

Spontaneous regression of malignant neoplasms is extremely rare, but renal cell carcinomas (RCC) are most often associated with this phenomenon.

We report a case of a patient with personal history of RCC, who underwent nephrectomy and no other oncological treatment. One year after nephrectomy, a lung metastasis was detected and kept under follow-up for 3 years. Its size increased over time until a needle biopsy was performed, and its metastatic nature confirmed. Wedge resection of the lung nodule was performed, and no neoplastic cells were found, suggesting its spontaneous regression after biopsy.

Different theories have been proposed to explain this phenomenon and, in most cases, the mechanism seems to involve the activation of the immune system. This case supports the importance of reducing tumor burden and the impact of the disturbance of the tumor microenvironment caused by instrumentation, in improving immune system activation and its essential role in neoplasm regression.

Keywords: *Spontaneous regression; Renal cell carcinoma; Lung metastasis*

INTRODUCTION

Neoplasms may resolve without targeted treatment. Spontaneous regression is the regression of a malignant neoplasm, either in the absence of therapy or with treatment that is perceived as inadequate.[1]

The first case of spontaneous regression of metastatic renal cell carcinoma (RCC) was reported in 1928 by Bumpus.[2] RCC is the cancer most associated with spontaneous regression, which occurs in approximately 1% of cases and, most frequently, after excision of the primary neoplasm.[1,3] The site of the regression is most commonly the lung.[3,4,5]

CLINICAL CASE

We present a case of a 74-year-old female patient with personal history of clear cell RCC (Vim+, CD10+, Cam5.2+, CD117-, CK20-, CK7-) without invasion of the pelvicalyceal system, renal vein or its tributaries, but with vascular permeation (ISUP 3; pT2NxM0R0), and no other relevant personal medical history. The patient underwent right radical nephrectomy and no other oncologic treatment.

After one year of follow-up, the patient presented a hypermetabolic (SUVmax 2,7) 8 mm left lower lobe lung nodule (figure 1 A, B). Biopsy was inconclusive at the time, and the patient remained in follow-up for 3 years, when a CT scan showed its significant increase (3,5 cm) (figure 1 C, D). Transthoracic biopsy was repeated, and pathology reported a RCC lung metastasis (figure 2 A, B). In a follow-up CT scan 2 months after the transthoracic biopsy, the lesion measured 2,8 cm (figure 1 E, F). No other metastasis or locoregional recurrence was found. In the multidisciplinary team meeting it was decided to proceed with wedge resection of the metastasis. The patient was asymptomatic, had a performance status ECOG 1, and the physical exam and lung function were normal.

Wedge resection of the lung lesion was performed without complications and, surprisingly, after histological and immunohistochemical analysis, pathology reported only the presence of fibrosis and inflammatory infiltrate (figure 2 C).

No neoplastic cells were found. CT scan was repeated, and absence of the suspicious lesion was confirmed (figure 3).

DISCUSSION

RCC is a tumor of peculiar biological behavior characterized by great variations in its clinical course, varying from spontaneous regression or indolent course to rapidly fatal metastatic dissemination, paraneoplastic syndromes, or presenting metastases in unusual sites.[6]

The rarity of spontaneous regression of RCC precludes its systematic study, and thus its pathogenesis is still unknown. Different theories have been proposed and, in most hypotheses, the pathogenesis of spontaneous regression is thought to involve the activation of the immune system.[6] Melichar et al.[6] reported a case of simultaneous occurrence of RCC and autoimmunological disease, where spontaneous regression of RCC lung metastases was accompanied by exacerbation of psoriasis, and remission of psoriasis was associated with tumor progression, thus suggesting a direct relationship between the RCC spontaneous regression and the activation of the immune system.

The mutation or epigenetic changes in the Von Hippel-Lindau gene, that are present in most RCC, result in increased production of vascular endothelial growth factor (VEGF)

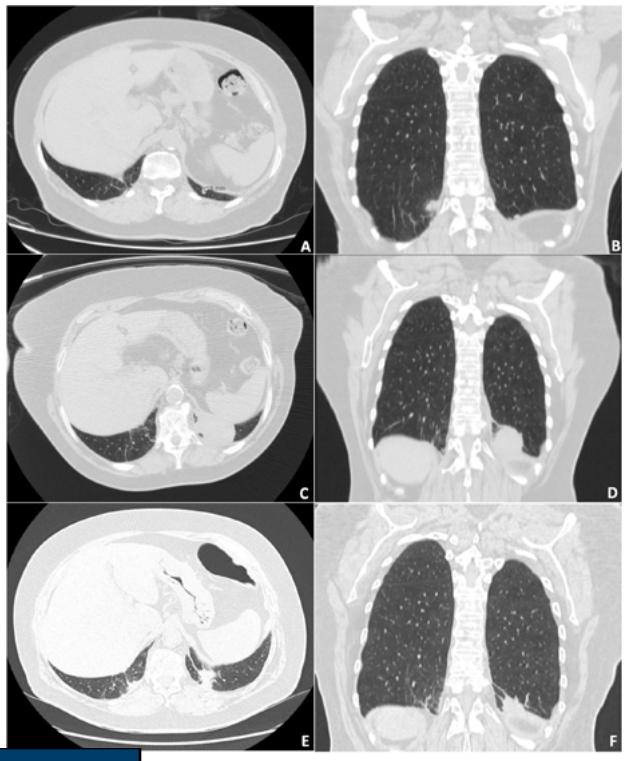

Figure 1

Thoracic CT scan (A – axial; B – coronal) showing an 8 mm (long axis) lung nodule in left lower lobe. CT scan (C – axial; D – coronal) 2 years later showing a 3,5 cm (long axis) left lower lobe lung mass. In the preoperative CT scan (E – axial; F – coronal), performed 2 months later, there is an unexpected overall decrease in size of the left lower lobe lesion, measuring 2,8 cm (long axis).

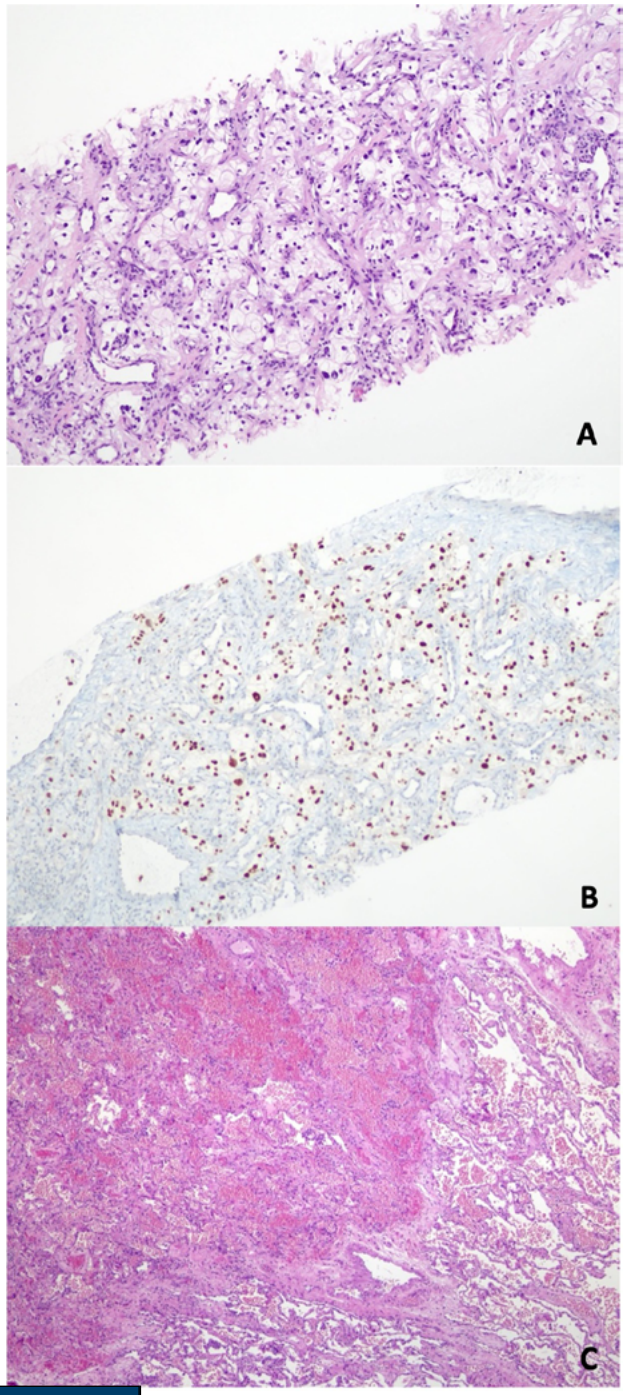

Figure 2

A – Tissue from the lung mass biopsy with H&E staining showing cells with marked cytological atypia and clarified cytoplasm, arranged in a richly vascularized stroma. B - Tissue from the lung mass biopsy with PAX8 immunohistochemistry study demonstrating a metastasis from previously diagnosed RCC. C – Surgical specimen after wedge resection, showing pulmonary parenchyma with areas of, fibrosis, degenerated elastic fibers, xanthelasma macrophages, predominantly mononuclear inflammatory infiltrate, and focal vascular congestion. No signs of neoplastic involvement.

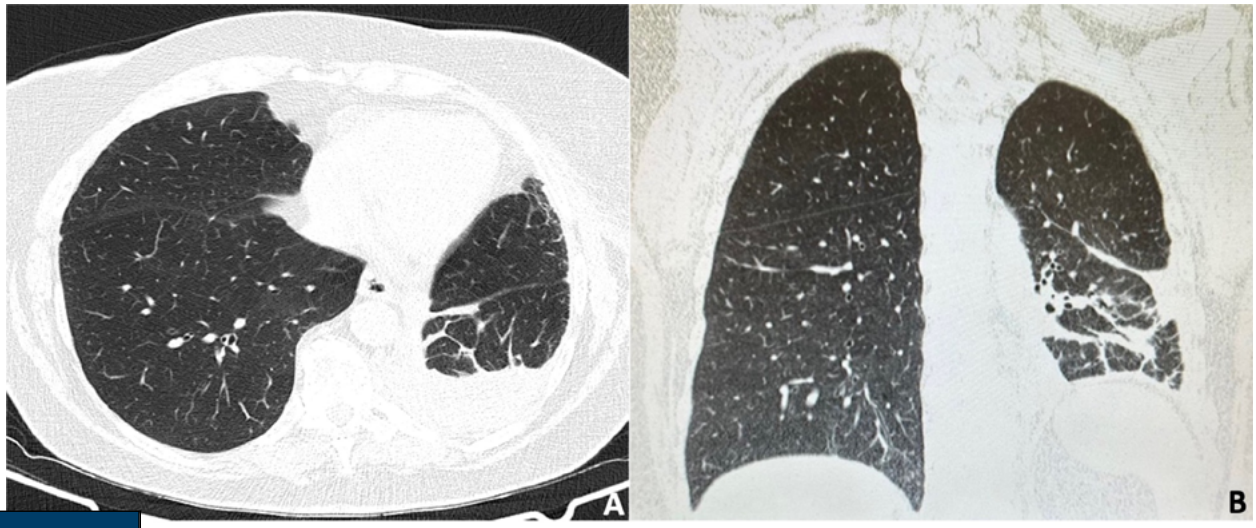

Figure 3 *Thoracic CT scan after surgery (A – axial; B – coronal) confirming the absence of the suspicious lesion. Presence of a small loculated pleural effusion at the left lower lobe adjacent to the surgical clips, with a maximum thickness of 2.3 cm.*

which results in higher tendency for cancer invasion and could be responsible for some of the biological peculiarities of RCC.[5] Most new therapeutic agents used in metastatic RCC also target the VEGF pathway, which has an inhibitory effect on adaptive immune response, and anti-VEGF therapy has led to augmentation of antitumor response in experimental animals.[7,6] Conversely, it has also been reported few cases of RCC spontaneous regression after and anti-VEGF therapy withdrawal.[8]

Nephrectomy is the gold standard treatment for RCC, and most cases of spontaneous regression are associated with kidney resection, resulting in elimination of substances secreted by the neoplasm (i.e. growth or antiapoptotic factors). Moreover, the dissemination of tumor cells which may occur during resection might lead to higher antigen exposure, which could amplify the immune response.[1,5] This theory is most often used to explain spontaneous regression of metastatic RCC that occur within 1 year of nephrectomy.[4]

However, in presented case, the lung metastasis was first detected 1 year after the nephrectomy and kept growing for 3 years until a needle biopsy was performed, after which the lesion started regressing.

Numerous reports detail spontaneous regression of RCC after biopsy.[9] One hypothesis is that biopsy leads to ischemia of the lesion due to physical disruption of its blood supply. This theory correlates strongly with the use of antiangiogenic agents in the treatment of advanced RCC. Tyrosine kinase inhibitors (TKI) and anti-VEGF drugs impede neovascularization and may improve overall survival.[10,1] It has been argued that the ischemic theory is inadequate because these tumors rely on complex vascular systems, rather than on a specific vessel.[9] It is more likely that instrumentation (biopsy) interferes with the tumor, increasing antigen exposure and triggering an immune response.[1] Another contributing factor may be that these tumors develop faster than their vascular network, causing central necrosis and subsequent antigen dissemination.[1,4]

The proposed mechanisms leading to higher antigen exposure and triggering of the host immune response result in higher levels of tumor-specific antibodies, cytokines, inflammatory cells, T-cells, and lymphocytes have been observed both in regressed neoplasms and in peripheral blood samples of patients.[9] Cessation of immunosuppressive therapies has also been seen to culminate in spontaneous regression of metastatic RCC.[10,1,5]

In conclusion, malignant neoplasm spontaneous regression remains a difficult phenomenon to fully characterize. Its rarity means that most of the literature consists of case reports and case series. Many case series lack histologic confirmation, thus allowing for misdiagnosis of spontaneous regression.[1]

In the presented case, 1 year after nephrectomy, our patient developed a pulmonary metastasis that spontaneously regressed after biopsy. Misdiagnosis was highly unlikely given the histologic confirmation of the primary RCC and the pulmonary metastasis. This case further supports the importance of reducing tumor burden and the impact caused by the disturbance of the tumor microenvironment caused by instrumentation, in improving immune system activation and its essential role in neoplasm regression.

Conflict of Interest

There are no conflicts of interest to report for any of the authors.

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