Spontaneous regression of renal cell carcinoma metastases

KC Chang, KL Chan, CW Lam

Spontaneous regression of some tumours is known to occur. We report here on a patient who developed lung and scalp metastases from renal cell carcinoma approximately 1 year after undergoing a radical nephrectomy. The lung metastasis was documented by computed tomography and histological examination. A spontaneous complete regression of the lung and scalp metastases occurred. Shortly after, however, a brain metastasis developed in the absence of any radiographic evidence of recurrence in the primary site or the lung.

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Introduction

Although renal cell carcinoma (RCC) is not common, it is one of the few tumours that have been reported to spontaneously regress.[1] A review of the literature by Everson and Cole[2] showed that RCC constituted approximately 20% of the 176 cancer cases that had spontaneously regressed. Other tumours that frequently undergo spontaneous regression include melanoma, neuroblastoma, and choriocarcinoma.

The standard treatment for RCC is surgical resection, as immunotherapy, hormone therapy, and chemotherapy have minimal efficacy.[1] Approximately 30% of patients with RCC have overt metastases at presentation and a 5-year survival rate of less than 10%.[1] The lung is the most common site of metastasis (50%-60%) followed by bone (30%-40%), liver (30%-40%), and brain (5%).[3]

The true incidence of spontaneous regression of metastatic RCC is believed to be less than 1%.[4] Kavoussi et al[5] found only 80 cases of spontaneous regression of metastatic RCC in their review of the literature in 1986. The majority of these cases involved metastatic pulmonary disease.[6] Most reported cases of metastatic RCC lack histological proof; of the 80 cases reviewed by Kavoussi et al, only 15 had acceptable histological documentation.[5] In a review of cases of spontaneous regression of lung metastases from RCC in 1989, Davis et al[7] identified only 10 instances of regression of pulmonary metastases from RCC that were histologically documented, and only four were unrelated to any therapy. Most reports involve regression following nephrectomy, hormonal therapy with progestational agents, and occasionally, the use of corticosteroid treatment.

We report a case of RCC metastases in the lung and scalp occurring approximately 1 year after a radical nephrectomy. The lung metastasis was proven histologically while the scalp metastasis was diagnosed clinically. The clinical course was discordant, with spontaneous regression of the lung and scalp metastases occurring within a few months of diagnosis, followed by the growth of a brain metastasis.

Case report

A 67-year-old Pakistani man was seen in the Wanchai Chest Clinic of the Tuberculosis and Chest Services, Department of Health in September 1996, complaining of a cough of a few weeks' duration. The patient did not have haemoptysis, fever, or weight loss. He had undergone a left radical nephrectomy because of RCC in November 1995. Histological examination showed

Pneumoconiosis Clinic, Tuberculosis and Chest Services, Department of Health, 4/F, 8 Chai Wan Road, Shaukeiwan, Hong Kong
KC Chang, MB, BS, MRCP
Ruttonjee Hospital, 266 Queen's Road East, Wanchai, Hong Kong:
Department of Pathology
KL Chan, MB, BS, FRCPA
Department of Respiratory Medicine
CW Lam, MB, BS, FRCP (Glasg)

Correspondence to: Dr KC Chang

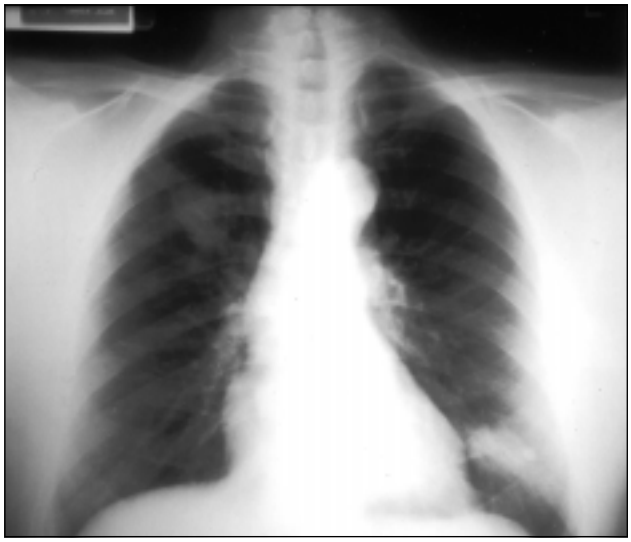

Fig 1. Chest radiograph showing opacities due to lung metastases in the upper and lower zones of the right and left lung, respectively

a grade IV sarcomatoid-type tumour. There was no evidence of a distant metastasis before surgery. He also had hypertension, non–insulin-dependent diabetes mellitus, and mild renal impairment. The results of the physical examination were unremarkable, but the chest radiograph showed two opacities: one in the upper zone of the right lung and another in the lower zone of the left lung (Fig 1). Previous chest radiographs taken before the nephrectomy on 28 February 1995, 27 June 1995, and 7 November 1995 showed no abnormality except a small calcified nodule approximately 0.5 cm in diameter in the lower zone of the left lung, which was compatible with the presence of a granuloma.

The patient was given a course of antibiotics, which gave symptomatic relief but no radiographic improvement. The cytological examination of his sputum on 18 October 1996 showed atypical cells present. A fibre-optic bronchoscopy was performed on 29 October 1996. No endobronchial lesion was seen, but a trans-bronchial biopsy from the apical segment of the right upper lobe showed a lesion that possibly was a tumour. The bronchial aspirate contained atypical cells.

The patient complained of a scalp mass on 6 November 1996, which had grown in size over the previous 2 months. Examination confirmed the presence of a soft non-tender mass over the vertex of the scalp. A skull X-ray was arranged, pending further investigation of the lung masses.

Computed tomography (CT) scans of the thorax and upper abdomen were performed on 14 November 1996. The two lung masses were located in the right upper lobe and left lower lobe. They had lobulated outlines and no significant contrast enhancement. Calcified foci were noted in the pretracheal, left para-tracheal regions, and near the left hilum, which were compatible with calcified lymph nodes. A small calcified granuloma was also detected in the left lower lobe. There were no enlarged lymph nodes in the mediastinum. Sections through the upper abdomen showed that the left kidney had been resected and that radio-opaque surgical clips were present. There was no evidence of local recurrence and no adrenal mass was seen.

Fine-needle aspiration of the right upper lobe mass was performed under CT guidance on 4 December 1996. The smears and cell block showed clusters and aggregates of loosely arranged tumour cells and features of an adenocarcinoma compatible with metastatic RCC (Fig 2). A skull X-ray taken on 5 December 1996 showed a lucent lesion with an irregular border in the parietal bone near the midline. Because the lesion was probably a metastatic tumour, a biopsy was not done.

The patient was followed up without any treatment being given for the metastases. On 11 December 1996, the scalp mass was approximately 3 cm across, soft, and non-tender. On 24 December 1996, the scalp mass was noticed to have shrunk and there was concomitant partial resolution of the right upper zone opacity. On 14 January 1997, the chest radiograph showed further resolution of the right upper zone opacity and the left lower lobe opacity also appeared to have shrunk. One month later, the right upper zone opacity could hardly be seen and the left lower zone opacity had further resolved. On 8 April 1997, the only conspicuous

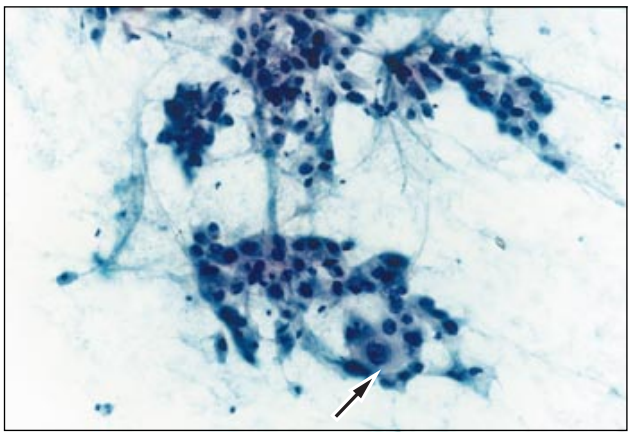

Fig 2. Direct smear of the fine-needle aspirate obtained from the right upper lobe mass showing an adenocarcinoma
Note the clusters of tumour cells featuring hyperchromatic, pleomorphic nuclei, and granular cytoplasm. Macronucleoli are present in some of the cells (arrow) [Papanicolaou stain, x250]

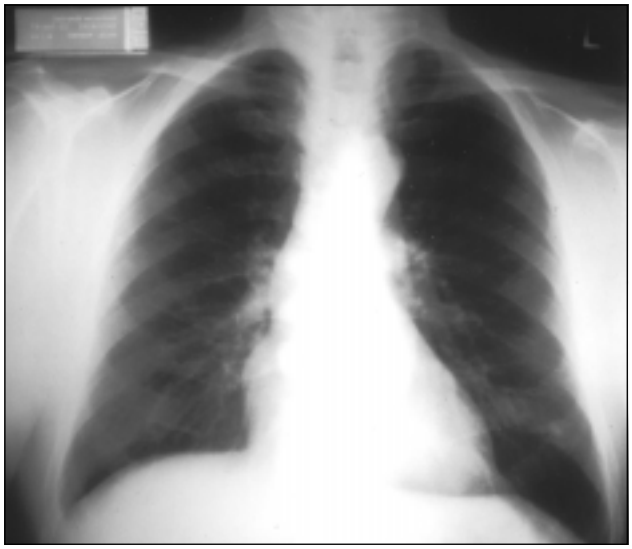

Fig 3. Chest radiograph showing resolution of the lung metastases
A calcified nodule is present in the lower zone of the left lung, which is compatible with granuloma formation

abnormality on the chest radiograph was the left lower zone calcified nodules, which had been present since 28 February 1995 (Fig 3). A chest X-ray taken on 3 June 1997 showed static progress. The scalp was last palpated on 8 April 1997 and no mass could be felt.

The patient reported that he had received no treatment for his malignant disease. He had only taken the calcium channel blocker, metformin, a few courses of antibiotics, and two doses of pre–CT-scan oral prednisolone.

On 24 June 1997, the patient complained of a sudden onset of mild right-hand weakness of 2 days' duration. Contrast CT scans of the brain, thorax, and abdomen were performed on 8 July 1997. A hyperdense mass with contrast enhancement measuring approximately 1.2 cm across was noticed in the left centrum semiovale. No metastatic lesion was noted in the thorax or abdomen. Systemic steroid was given and palliative radiotherapy for the brain metastasis was arranged.

Discussion

The natural course of RCC is puzzling and several intriguing features are apparent: (1) the unpredictable spontaneous regression of metastases after nephrectomy occurs[6]; (2) late relapse after nephrectomy is known, with the median time of post-nephrectomy relapse being 15 to 18 months[8]; (3) prolonged survival and stable disease in the absence of systemic treatment also occurs[9]; and (4) there is a poor long term prognosis, despite the spontaneous regressions.[7]

Recent molecular genetics studies have identified a number of abnormalities present in RCC, the major one being a deletion or mutation of the gene for von Hippel-Lindau disease at chromosome 3p, which occurs in most cases of sporadic RCC.[10,11] The gene is a tumour suppressor gene, inactivation of which contributes to tumour development. Mutations of the p53 gene, which is also a tumour suppressor gene,[12] and angiogenic growth factors may contribute to the development of metastasis.[13]

There is evidence from the in vitro assessment of cell-mediated immunity in RCC patients that those who have undergone a nephrectomy show a greater inhibition of tumour cell growth.[14] If the immune system is responsible for this phenomenon, the critical mediators are probably $CD8^+$ cytotoxic lymphocytes (CTLs), which are capable of recognising tumour cells when in a tumour antigen and major histocompatibility complex (MHC) class I molecule mixture; normal renal cells have relatively low levels of expression of MHC class I molecules.[15] Having more MHC class I molecules theoretically renders RCC cells more vulnerable to immune surveillance by CTLs. This theory has been partially borne out clinically by the use of interferon alfa (IFN-α) in patients with RCC.[16] The expression of MHC class I molecules on RCC cells increases when IFN-α is present.[17] Unfortunately, the response to this treatment was only 12%; however, patients who had undergone prior nephrectomy and who had predominantly lung metastases had a better response and lived longer.[16,18]

Most cases of spontaneous regression of metastatic RCC tumours occur in the lungs and this may be partly explained by the fact that the lungs are the most common sites of metastasis or by the fact that the lungs are exposed to constant antigenic stimulation.[19] Although this patient did not receive immunotherapy, most of the tumour bulk resided in his lungs, which could possibly have responded to his production of interferon as a result of a self-limiting minor respiratory tract infection. Unfortunately, immunological tests were not performed at the time of the tumour regression, so we do not have any objective evidence of an increase in interferon level.

The occurrence of the brain metastasis can also be explained immunologically. The brain is one of the few body sites that do not communicate with the conventional lymphatic system. Tumours in the brain are much less accessible to CTLs. In addition, the brain is capable of producing a cytokine called transforming growth factor beta, which inhibits T lymphocytes

including CTLs. As a result, a brain metastasis can evade the immune surveillance system.

Although it is possible that the spontaneous regression of metastases after a nephrectomy could arise as a result of reduced tumour bulk (which can then be overcome by the immune system), performing a nephrectomy for this purpose cannot be recommended because the associated morbidity and mortality from surgery (5%) are greater than the incidence of regression (under 1%).[20] Moreover, spontaneous regression is apparently an unpredictable event and is not necessarily related to nephrectomy.

Conclusion

This case report adds to the scarce literature regarding histologically documented pulmonary metastatic RCC undergoing spontaneous regression unrelated to any therapy. Our case report is probably the sixth of its kind. Although the immune system may be involved, we did not gather any objective evidence of this from the patient. The discordant behaviour of RCC in this patient probably reflects the complicated interactions that occur between malignant cells and the body's immune surveillance system.

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