Why do we miss Metastatic Renal Cell Carcinoma?

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Introduction

The initial diagnosis of renal cell carcinoma, has improved due to availability of imaging modalities [1]. While bone, lymph nodes and lungs constitute expected 'homing' sites, metastasis may turn up at unusual locations [2-7]. The failure to consider RCC as a source of a metastasis, can be attributed as much to 'missing' the nephrectomy scar, as not considering the possibility on a cytologic examination of the metastasis. This is compounded by a long time interval for metachronous metastasis.

Case Reports

Case 1

A 45 years old male patient was referred for Fine needle aspiration cytology (FNAC) of a multinodular goiter with a dominant left lobe enlargement. The aspirate was unusually haemorrhagic and showed papillary clusters of malignant cells anchored on to prominent vascular channels. The cells had moderate amount of cytoplasm with granularity. Focally, smaller groups of cells had a clear cytoplasm. There was evidence of nuclear pleomorphism with prominent nucleoli. No nuclear grooves or pseudoinclusions were identified (Fig 1). No normal thyroid cells were seen. The pattern did not conform to known primary thyroid malignancies. The possibility of a metastatic adenocarcinoma was considered. An ultrasound revealed a heterogenous, hypoechoic mass, occupying most of the left lobe of thyroid. The colour Doppler revealed multiple intralesional vascular channels with arteries showing low resistance flow (Fig 2). Leading questions and examination elicited history of operation for a renal tumor 4 years prior and a healed operative flank scar. The final diagnosis was metastasis of a renal cell carcinoma (RCC) to the thyroid.

Case 2

A 60 years old male presented with a cherry-red swelling on the lower lip diagnosed as 'epulis' in the OPD. Review at the Oncology Centre elicited history of a prior nephrectomy

for RCC with the lumbar scar on general examination. FNAC of the lesion confirmed a metastatic RCC.

Case 3

A middle-aged patient was operated for an aural polyp. The histopathologic diagnosis returned was a ceruminoma. On follow-up, the patient returned with a cutaneous lesion and on general examination the ubiquitous flank scar of nephrectomy was detected. The surgery had been performed 4 years before. Review of the original slides confirmed it to be a metastatic granular cell variant of renal cell carcinoma.

Discussion

Renal cell carcinoma often remains silent till it assumes a large size. Incidental detection rate at autopsy has fallen from 0.91 to 0.72/100 over the past 50 years. This is attributed to improvement in primary diagnosis by sophisticated imaging techniques [1]. At times, synchronous metastasis draws attention to it. However, even when the patient has the knowledge of a previous renal surgery for a tumor, metachronous metastatic lesions fail to be diagnosed as originating from a renal primary.

A significant contributor to the delayed diagnosis is poor patient recall of the primary surgery, because a considerable time may elapse before metastasis appear [6, 7]. This results in a vital 'missed link' of history and a cursory general examination may fail to note the large nephrectomy scar. Our cases amply illustrate this.

The predilection for haematogenous spread makes RCC notorious for metastasis: some usual sites are (lungs and lymph nodes), unusual (muscle, brain, thyroid and pancreas) [2-7]. Bones are a favoured target but small bones of the hands and feet are rarely involved. The CNS is an unusual site for metastatic RCC but rarely cases of spread to the choroid plexus and sphenoid sinus are reminders that no site is exempt [4]. Solitary masses, on imaging, are likely to be considered primary tumors

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Fig 1: Case 1. USG guided FNAC of the enlarged left lobe of thyroid showing cohesive, cellular papillary clusters of epithelial cells attached to vessels (Papanicolaou x 4). Inset A & B. The cells demonstrated moderate amount of granular and clear cytoplasm and marked nuclear pleomorphism (A. Papanicolaou x 10, B. MGG x 40)

of the organ eg. pancreas and thyroid. Thyroid metastases are rare, being detected in only 6 of a series of 941 thyroidectomies and RCC accounted for three of these [6]. This is complicated by the fact that tumors with clear cell appearance (which is the hallmark pattern of RCC) can also occur in these organs [7]. Attention to the rich arborising vasculature of a malignant epithelial tumor, with at least some areas showing a clear cell pattern, would ensure that RCC is not missed. This can be well visualized even on fine needle aspirates. Chromosomal aberration patterns specific for RCC (monosomies of chromosomes 3 and 14) can help in solving the issue.

Recent attempts to explore markers predictive of RCC's with a higher propensity for haematogenous metastasis have suggested that tumors with high microvessel density counts and high matrix metalloproteinase (MMP):E-cadherin ratio are especially prone [8]. Complimentary DNA microarray profiling can also identify subsets with higher metastatic potential [9]. The life expectancy even after distant metastasis can be anywhere from 10 months to several years [3, 4]. This is especially true in case of solitary metastasis when surgical resection with adjuvant chemotherapy offers a 77% survival at 1 year and 31% at 5 years [10]. Recognition of tumor subsets with high MMP: E-cadherin ratio not only has implications for close follow-up after primary surgery, but also provides opportunity for exploring therapeutic strategies targeting these molecules [8].

Conflicts of Interest

None identified

Fig 2: Case 1. USG of the thyroid showing a heterogenous hypoechoic mass in the left lobe. Inset: Colour Doppler of the mass showing multiple vascular channels indicating high vascularity.

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