CASE REPORT

Treatment of succinate dehydrogenase B-associated renal cancer

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Accepted 25 July 2017

SUMMARY

Germline mutations in the succinate dehydrogenase B (SDHB) gene are associated with a rare renal cancer with a young age of onset. It is important to raise awareness of this condition as it is dominantly inherited and is associated with other neoplasms. The diagnosis should be considered in patients with renal cancers with distinctive histology. There is little guidance in the literature about how to treat metastatic SDHB renal cancers. We report a confirmed partial response to treatment with a vascular endothelial growth factor receptor tyrosine kinase inhibitor, pazopanib.

BACKGROUND

Succinate dehydrogenase B (SDHB) gene mutations are a rare but increasingly recognised predisposing factor for paragangliomas, pheochromocytomas, gastrointestinal stromal tumours and renal cancer. It is essential that patients and their families with these tumours are offered genetic screening. The associated renal cancers may be curable if detected early. There is little information on how to treat metastatic SDHB associated renal cancer; this is the second report of a response to pazopanib, a vascular endothelial growth factor inhibitor.

CASE PRESENTATION

A 42-year-old female doctor was referred to oncology with a diagnosis of a renal mass and multiple bone metastases. She had a 2-year history of multiple symptoms, including visual disturbance, orthostatic intolerance and weight loss, and had been seen by numerous specialists. Finally, she palpated a mass in her left flank and a renal mass was seen on ultrasound.

Relevant medical history included resection of a carotid body tumour 13 years previously; she had otherwise been fit.

Family history was positive for benign adrenal and pituitary tumours in her mother.

INVESTIGATIONS

A CT scan showed a 10×8 cm heterogeneously enhancing, exophytic left renal mass with areas of central low attenuation/necrosis and tiny flecks of calcification; there was no lymphadenopathy (figure 1). Widespread sclerotic bone metastases were present throughout the spine and pelvis (figure 2). The clinical picture was unusual; renal cancer typically causes lytic bone metastases.

Histology showed the morphological features of SDHB-deficient renal cell carcinoma (RCC), a rare type of renal cancer. The tumour had a predominantly solid architecture, although cystic areas were also present. The tumour cells were arranged in tubules or trabeculae, surrounded by a myxoid extracellular matrix. They had eosinophilic cytoplasm with, in some areas, the characteristic intracytoplasmic inclusions of this entity.¹ The overall nuclear grade was International Society of Urological Pathology (ISUP) grade 3 and there was brisk mitotic activity (3 per 10 high-power fields) and focal invasion of renal sinus fat (Union for International Cancer Control TNM 7th edition, pathological stage pT3a).² On immunohistochemistry, the tumour cells were reactive for EMA, vimentin, AMACR, PAX8 and Bcl-2 and lacked staining for RCC-Ma, CA-IX and CK7. Subsequent immunohistochemistry has also shown a loss of staining for SDHB in the tumour. Unusually for this entity, there was also diffuse staining for chromogranin A (although the tumour was negative for another neuroendocrine marker, synaptophysin). There was also weak patchy staining for c-KIT/CD117, which has previously been noted in only rare cases (<5%).^{3,4} The morphological features are consistent with those described for this entity in the 2016 WHO classification, with typical cytoplasmic vacuolation and inclusions.¹

Tertiary pathology referral confirmed the morphology of a succinate dehydrogenase (SDH)-deficient renal cancer and demonstrated a

Figure 1 CT showing left renal mass, sagittal section.

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To cite: Fife K, Warren A.
BMJ Case Rep Published
Online First: [please
include Day Month Year].
doi:10.1136/bcr-2017-
219626

Figure 2 CT showing sclerotic bone metastases.

germline mutation in the SDHB gene with the loss of the wild-type allele in the tumour (figure 3). DNA mutational analysis showed a cytosine-to-guanine transition at nucleotide C.79 (C.79 C→T) in exon 2 of the SDHB gene, leading to a premature

Figure 3 Histology showing the cytoplasmic inclusions (giant mitochondria) which characterise the tumour.

stop codon at codon 27 (p.Arg27*) confirming the diagnosis of SDHB-associated RCC.

DIFFERENTIAL DIAGNOSIS

Although the morphology was typical of this entity, other differential diagnoses considered were mucinous tubular and spindle cell carcinoma (because of the mucinous background) and oncocytoma because of the bland cytological appearance in many areas.

TREATMENT

She underwent a radical nephrectomy. Following nephrectomy, the visual symptoms abated and she felt mentally clearer.

She required palliative radiotherapy in the cervical and lower thoracic spine. There was a concerning lesion in the left neck of femur so she underwent a total hip replacement 5 months after presentation; the bone density of the metastasis was extremely high and histology showed malignant hyperchromatic cells set in a myxoid stroma similar to her renal tumour. There was a short period of observation to ascertain the growth behaviour of the cancer.

Six months after presentation, there was CT scan progression in both bone and a para-aortic lymph node so she was then commenced on pazopanib 800 mg. She had a RECIST 1.1 defined partial response to treatment in that the para-aortic node reduced from 19 to 6 mm and her bone metastases stabilised.⁵ Her pazopanib was poorly tolerated and the dose was reduced to 600 mg then 400 mg. She also had recurrent urinary tract infections which contributed to the fatigue. She continued this treatment with dose reductions for 10 months, until liver metastases and progression in her bones on MRI scanning were detected. As the cancer had shown some sensitivity to tyrosine kinase inhibitors, she was then treated with axitinib 5 mg two times per day. She coincidentally was found to have severe postural hypotension associated with fatigue; serum cortisol was low and Synacthen test was positive. The cause of her adrenal insufficiency was not confirmed; it was possibly secondary to short-term dexamethasone therapy. She improved on replacement hydrocortisone. She also had multiple pulmonary emboli found incidentally on a staging CT and was treated with dalteparin; there was slight progression in the liver and axitinib was increased to 7 mg two times per day. Although her CT remained stable after two further months of axitinib, she had clinical progression in both bones and liver and worsening pain and liver function. Palliative symptom control measures were instituted, and she died 19 months after presentation.

OUTCOME AND FOLLOW-UP

Her family members were screened for the SDHB mutation. Those testing positive are having regular screening for associated tumours.

DISCUSSION

Germline mutations in the SDHB gene are associated with paragangliomas, pheochromocytomas, gastrointestinal stromal tumours and rarely renal cancers. The latter were characterised in 2010.^{3 6 7} There is a spectrum of mutations which affect the SDH mitochondrial enzyme complex that catalyses the oxidation of succinate to fumarate in the Krebs cycle. The histology of these renal cancers is unique; dysfunctional mitochondria appear as large cytoplasmic inclusions.

Most (75%) SDH-deficient RCCs show indolent behaviour, with a metastatic rate of 11% at long-term follow-up,¹ but those

exhibiting coagulative necrosis, sarcomatoid change or high nuclear grade show more aggressive behaviour, with a metastatic rate of 70% in one reported series.⁴ The tumour showed high nuclear grade (ISUP grade 3) in some areas and exhibited invasion of renal sinus fat, which would be consistent with the aggressive clinical behaviour. No coagulative necrosis was identified histologically, but there were hypocellular, cystic and myxoid areas that might account for the CT appearances of a necrotic primary tumour.

Genetic referral is essential as these mutations are autosomal dominantly inherited; tumours are bilateral in 25% and mean age of onset is 39 years; early diagnosis is crucial as resection of small tumours may be curative.^{4–8} The diagnosis should be considered in younger patients who present with unusual renal tumours, particularly if multifocal or bilateral. There is little published on the management of metastatic SDHB-associated RCC. This report is the second to show that standard antiangiogenic tyrosine kinase inhibitor therapy can result in tumour response and control.⁹ Interestingly, in the case reported by Paik

et al, the bone metastases were lytic rather than sclerotic as in our case (A Gill, personal communication, 2017).

Contributors KF treated the patient, with the patient's knowledge and consent, then prepared the majority of the manuscript and figures. AW made the pathological diagnosis in this patient and contributed significantly to the manuscript and the pathology figure. Both authors conducted literature searches and approved the final manuscript.

Competing interests KF has received honoraria from GSK, Novartis, Pfizer, BMS and Roche.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Learning points

- Patients with paraganglioma need medical genetics referral to investigate for succinate dehydrogenase B gene mutations.
- Patients and families with such mutations should have kidney screening.
- The diagnosis should be considered in patients with unusual kidney tumours.
- Metastatic disease can be treated with vascular endothelial growth factor tyrosine kinase inhibitors, but prognosis is poor.

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