CASE REPORT

Melanoma of unknown primary origin presenting as a rapidly enlarging adrenal mass

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SUMMARY

Metastasis to the adrenal can be seen in the context of metastatic melanoma, but primary adrenal melanoma is very uncommon. We present a case of a rapidly enlarging adrenal mass that mimicked non-functioning primary adrenal malignancies but later proved to be part of a widely metastatic melanoma of unknown primary origin. Careful physical examination of the patient led to the discovery of a subcutaneous metastatic focus that was not seen on [¹⁸F]-fluorodeoxyglucose positron emission tomography/CT imaging. The presence of subcutaneous metastases raised the suspicion for metastatic melanoma; however, pathological confirmation remained the ultimate tool to reach the final diagnosis.

BACKGROUND

In 2009, it is estimated that 68 720 patients were diagnosed with melanoma and 8600 deaths were attributed to melanoma in the USA.¹ The vast majority of melanomas have an apparent cutaneous primary lesion, but they can present as a metastatic disease without an obvious primary source.^{2–3} Metastatic melanoma to the adrenal gland is not uncommon, especially with advanced disease.^{4–5} However, primary adrenal melanoma (PAM) is rare, and fewer than 20 case reports have been documented in the English literature.^{6–20} We present a case of rapidly enlarging adrenal mass that was initially thought to be a primary adrenal malignancy but later proved to be melanoma of unknown primary origin. It remains unclear whether this case represents PAM or widely metastatic melanoma of unknown primary with a dominant large adrenal metastasis. It is very important to differentiate between metastatic disease to the adrenal gland and primary adrenal tumour because the treatment options are drastically different.

CASE PRESENTATION

A 70-year-old Caucasian woman presented with a sudden onset of pain in the left flank without experiencing other symptoms. She was evaluated at an outside facility, where CT of the abdomen revealed a 7×5 cm partially cystic left adrenal mass suspicious for malignancy (white arrow in figure 1). The patient denied having palpitations, anxiety, excessive sweating, hirsutism, weight gain or other clinical features that would indicate adrenal hormone overproduction. She had no history of other malignancies and reported having normal mammogram and colonoscopy results prior to her presentation. Otherwise, her medical history was

Figure 1 Axial CT image illustrating a heterogeneous left adrenal mass (white arrow) that measured 7×5 cm at presentation.

significant for essential hypertension that was well controlled with β -blockers alone, and family history was significant for her mother's colon and lung cancer.

A month later, the patient was referred to The University of Texas MD Anderson Cancer Center and had repeated CT imaging which showed that the left adrenal mass had increased in size, to 14×12 cm (white arrow in figure 2). Multiple pulmonary nodules (0.2–1.1 cm) were also noted, suggesting metastases. Laboratory test results showed a plasma free normetanephrine level of 0.43 nmol/L (reference range <0.90 nmol/L), plasma free metanephrine level of <0.20 nmol/L (<0.50 nmol/L) and serum testosterone level of 16 ng/dL (14–76 ng/dL). The levels of serum electrolytes, serum creatinine, serum cortisol, adrenocorticotrophic hormone, plasma aldosterone concentration and plasma renin activity were also within normal reference ranges. In light of these laboratory findings, the patient was

Figure 2 Axial CT image 1 month after presentation showing a partially cystic left adrenal mass (white arrow) that measured 14×12 cm.

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initially presumed to have a non-functioning primary adrenal malignancy with distant metastases.

Because the adrenal mass was partially cystic, biopsy of the presumed primary tumour was substituted with CT-guided biopsy of the largest nodule in the left lung. The specimen revealed extensive necrosis associated with haemosiderin-laden macrophages with few multinucleated giant cells and no clear evidence of malignant cells. [^{18}F]-Fluorodeoxyglucose positron emission tomography (FDG PET) with CT showed increased uptake in the left adrenal mass as well as in the peritoneum, thoracic nodes, subcutaneous tissue, muscles and brain, suggesting a widely metastatic disease (figure 3). MRI of the brain confirmed the presence of two metastatic foci: one in the inferior left lentiform nucleus, and the other in the superior left temporal gyrus with localised oedema but no midline shift. Because of the lack of a pathological diagnosis, and before we resorted to a biopsy of the left adrenal mass, another detailed physical examination was conducted in an attempt to identify an accessible subcutaneous nodule as seen on PET/CT for open surgical resection. On physical examination, small nevi (0.2–0.3 cm) were noted in the neck area, but none had a suspicious appearance or had changed according to the patient's report. Fundoscopic eye examination revealed a normal retina without

papilloedema or abnormal pigmentation. None of the subcutaneous lesions seen on FDG PET/CT were palpable; however, a 3 cm-deep subcutaneous nodule was felt in the left anterior thigh just below the cut-off margin of the PET/CT images. The patient reported progressive enlargement of this deep subcutaneous nodule 2 weeks preceding this visit. Excisional biopsy of this new subcutaneous nodule revealed a $3.2 \times 2.0 \times 1.5$ cm firm, solid mass with variegated (white, brown and red) cut surfaces admixed with fat. This tumour exhibited poorly differentiated epithelioid and spindle cells with prominent nucleoli and robust mitotic activity (figure 4).

INVESTIGATIONS

The subcutaneous metastasis excised from the thigh had focal areas of pigment accumulation, and the cells stained positive for S100, melan-A and vimentin but not for inhibin, calretinin or cytokeratin. The overall features of the tumour were most consistent with metastatic melanoma. Additional immunostaining was performed with these tumour cells, which stained positively for HMB-45 and MITF, further supporting a diagnosis of metastatic melanoma. Testing with molecular markers revealed a BRAF (V600K) mutation but no mutations in N-RAS, C-KIT, PIK3CA or EGFR.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of an enlarging and non-functioning adrenal mass includes adrenocortical carcinoma, non-functioning pheochromocytoma, adrenal metastases, adrenal lymphoma and sarcomatous tumour originating in the adrenal gland. Non-neoplastic causes include cystic adrenal masses and, rarely, infectious disease such as tuberculosis and histoplasmosis.

TREATMENT

The patient underwent stereotactic γ -knife radiotherapy for the two metastatic foci in the brain as well as systemic chemotherapy with temozolomide (300 mg/day). However, the disease continued to progress and the primary adrenal mass increased to 16×13 cm on CT imaging (white arrow in figure 5).

OUTCOME AND FOLLOW-UP

The patient was not considered for another treatment regimen or for research protocols because of her poor performance status. She died 6 months after her initial presentation.

Figure 3 Coronal whole body fluorodeoxyglucose positron emission tomography showing the left adrenal mass (large black arrow) with multiple subcutaneous metastases (black thin arrows) and lung metastasis (black arrow head).

Figure 4 Microscopic image showing poorly differentiated epithelioid cells with hyperchromatic nuclei, prominent nucleoli and rare pigment (H&E staining).

Figure 5 Axial CT image at last follow-up illustrating a 16×13 cm left adrenal mass (white arrow).

DISCUSSION

We presented a case of a rapidly enlarging adrenal mass with distant metastasis that was initially thought to represent a non-functioning primary adrenal malignancy but later proved to be part of a metastatic melanoma of unknown primary origin. It is impossible to know whether this case was a PAM that produced distant metastases or a metastatic melanoma of unknown primary source with a dominant adrenal metastasis. The detection of subcutaneous nodules helped to identify targets with which to establish a tissue diagnosis. Careful physical examination identified an enlarging subcutaneous metastatic focus that was below the cut-off margin of FDG PET/CT. Subcutaneous nodules are suggestive of metastatic melanoma and are reported in 8% of all melanoma cases.⁴

Melanoma is known to metastasise to the adrenal glands, probably because of their rich supply of sinusoidal blood supply. In contrast, PAM is so rare but could be explained by the common embryogenesis of medulla, chromaffin cells and melanocytes from neural crest cells.^{20–21} Divergent differentiation from neural crest cells derivative attributed to different neoplastic morphotypes and immunotypes has also been suggested.²²

Several authors have proposed criteria to differentiate between PAM and metastatic melanoma to the adrenal gland.^{10–21} Carstens *et al*¹⁰ proposed four criteria for a PAM diagnosis: the presence of primary malignant melanoma in only one of the adrenal glands, the absence of prior or current primary melanoma as primary elsewhere, no evidence of prior or current removal of pigmented skin or mucosal or eye lesions, and autopsy examination excludes the presence of a hidden primary source. Our patient satisfied the first three criteria. Autopsy was not performed because she had widespread metastases and there was limited expectation for additional information.

We were only able to find less than 20 cases of PAM reported in English literature and our case might be considered as another example of PAM in the light of the clinical presentation and disease course as well as the lack of obvious primary melanoma elsewhere. Flank pain was a common presentation in these reported cases of PAM and, except for one patient who was followed for 46 months,¹⁸ all died within 1 year of diagnosis.

Learning points

- ▶ Metastatic melanoma can mimic primary adrenal malignancies and histology is needed to clarify the diagnosis.
- ▶ Despite the availability of highly sophisticated investigational studies, careful physical examination remains invaluable.
- ▶ The presence of subcutaneous metastasis and an adrenal mass raises the possibility of melanoma.

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Competing interests None.

Patient consent Obtained.

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