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Letter to the Editor

The successful treatment of metastatic androgen receptor–positive tumours of parotid origin with androgen receptor blockade and immunotherapy

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Dear Editor,

Malignant parotid tumours are heterogeneous and diverse, ranging from indolent slow-growing adenoid cystic to rapidly progressive salivary duct carcinoma [1]. The current treatment is surgery eventually followed by radiotherapy to prevent local recurrence [2]. Metastatic disease outside the draining lymph nodes often includes numerous and widespread bony metastases. Standard chemotherapy includes platinum-based regimens and bisphosphonates in case of bone metastases. The response rate is in the range of 30% with a very limited life expectancy, with most of the patients not being alive within a year from the diagnosis of metastatic disease [3].

A 36-year-old man presented in December 2015 with a right axillary mass, which was biopsied and turned out to be a metastatic oncocytic tumour. In January 2016, he had a right axillary dissection, followed by adjuvant radiotherapy and, in June 2016, a complete clearance of the lymph nodes in the right neck for further recurrence. Three months later, he presented with multiple lytic lesions throughout his bony spine and pelvis (Fig. 1A). Three samples from the left iliac wing confirmed small deposits of apocrine/oncocytic carcinoma consistent with metastases. The specialist multidisciplinary team (MDT) recommended a platinum-based first-line treatment, and he was commenced with carboplatin and paclitaxel in November 2016. At the same time, he was started on zoledronic acid.

After four courses of chemotherapy, a reassessment showed marked increase in both the number and size of his original bone lesions (Fig. 1B).

A review of the literature showed that some of these tumours were noted to be (AR) positive [4], and a review of his pathology confirmed that he had very strong AR expression. Having found a case report of a response to abiraterone in a patient with a similar condition [5], he was commenced on abiraterone in April 2017. After 2 months on treatment, a disease reassessment showed a partial response with marked healing of all his bone lesions (Fig. 1C).

As he was a very young man, there was concern that abiraterone might not be a long-lasting treatment. Based

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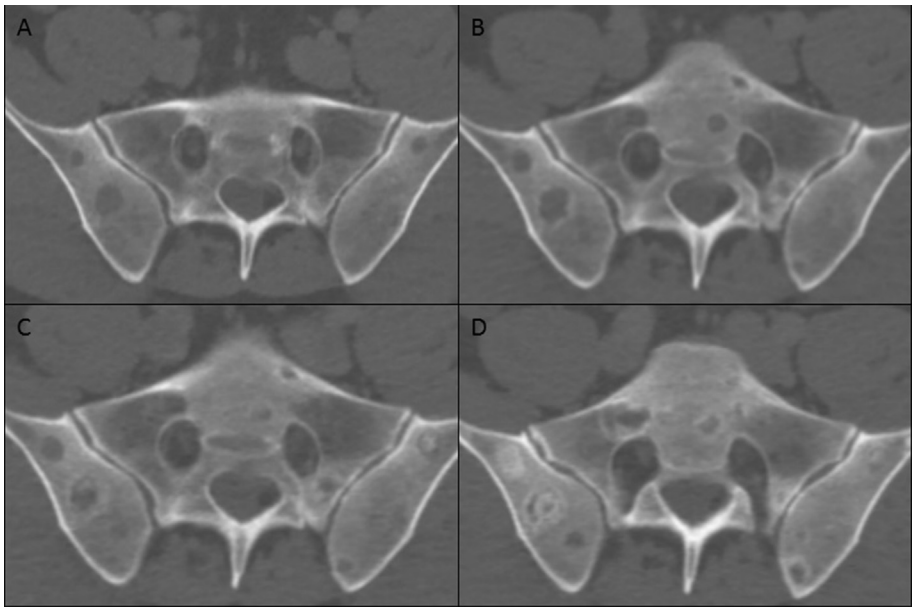

Fig. 1. Serial CT assessment of lytic skeletal metastases. Initial assessment (A) demonstrates multiple lytic skeletal metastases demonstrated in the iliac bones. Six months later, after four courses of carboplatin and paclitaxel, the interval CT assessment (B) demonstrates progressive disease with increase in size of lytic skeletal metastases and a new lesion in the sacrum in this image. First postassessment CT (C), after 2 months of abiraterone therapy, demonstrates stable size of bony metastases with internal and marginal sclerosis seen reflecting the early features of bone healing. An assessment study at 1 year (D) demonstrates further increased sclerosis of bone lesions, reflecting bone healing and sclerosis of prior subtle/occult metastases. CT, computed tomography.

on a case report [6], pembrolizumab was therefore introduced. The original report does not document programmed death-ligand 1 (PD-L1) expression, and this patient was essentially negative on testing. He received pembrolizumab for approximately 9 months before stopping because of toxicity. Abiraterone was continued and eventually stopped in February 2018 when the scans suggested a complete response (Fig. 1D).

A 69-year-old gentleman presented with a right parotid mass in January 2016 which was fully resected and shown to be an adenocarcinoma. In July 2017, he presented with a right trigeminal nerve metastatic deposit, and a restaging scan showed that he had multiple bone metastases and retroperitoneal lymph nodes. The bone metastases were biopsied and confirmed to be adenocarcinoma, in keeping with metastatic salivary gland tumour. He was started on zoledronic acid, gemcitabine and the investigational immunotherapeutic agent IMM-101 on a Named Patient Program [7]. His original histology was reassessed for AR expression and found to be strongly positive. He was not approved for abiraterone, but he was considered eligible for bicalutamide which he commenced in October 2017. This led to a significant clinical improvement and a complete response to treatment which is ongoing 9 months later (Fig. 2).

A 30-year-old gentleman first presented in 1976 with a pleomorphic adenoma of the left parotid which was treated with surgery. He recurred 33 years later in 2009 with a left-sided adenopathy, which was again treated with surgery. Two years afterwards, he presented with a thick melanoma on his left shoulder and had adjuvant Bacillus Calmette-Guerin (BCG) within a clinical study. In September 2016, a computed tomography scan showed widespread bone metastases with early cauda equina compression at L2 (Fig. 3 A, D). He had radiotherapy to L1–L3 for 20 Gy in 5 fractions and a L2 vertebroplasty afterwards for ongoing pain. A left iliac crest lesion was biopsied, and the result showed metastatic pleomorphic adenoma. The tumour was found to be strongly positive for AR (Fig. 4), and he was therefore commenced on bicalutamide in May 2017. Within 2 months of starting bicalutamide, a positron-emission tomography scan showed an initial response to treatment (Fig. 3 B, E). Because of ongoing back pain, which required further radiotherapy to T12, he was also commenced on 3-monthly leuprorelin acetate. After this, a recent scan showed further evidence of bone healing (Fig. 3 C, F).

This 54-year-old man presented in October 2015 with a lump in his right axilla which was found to be consistent with a metastatic ductal carcinoma likely of parotid origin. In April 2017, he was found to have secondaries in the brain as well as in the lungs and bones. He was given whole brain radiotherapy in May 2017 and carboplatin and paclitaxel afterwards, which he completed in August 2017, with some minor response to treatment. He was started at the same time with zoledronic acid. A reassessment in December 2017 showed ongoing benefit in the brain, but a significant progression of the lung (Fig. 5A and D) and bone.

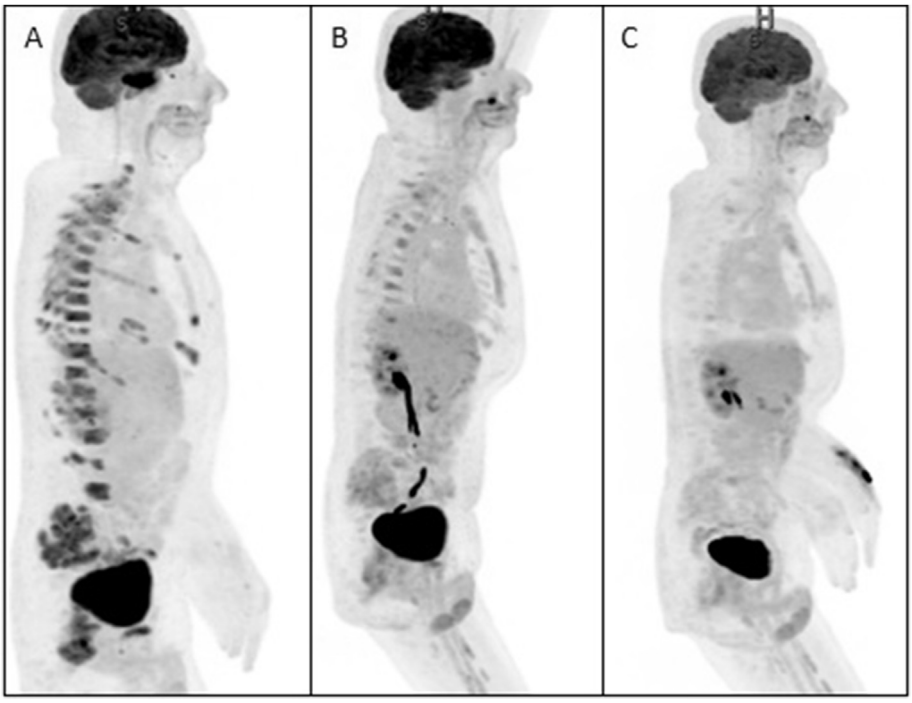

Fig. 2. Baseline 18F-FDG PET/CT assessment (A) demonstrating widespread skeletal metastases in the vertebra, ribs and pelvis on a sagittal maximum intensity projection of the PET component. This demonstrates a partial metabolic response at 3-month post-treatment assessment (B) with a complete metabolic response at 6-month post-treatment assessment (C). CT, computed tomography, PET, positron-emission tomography, 18F-FDG, 18F-fluorodeoxyglucose.

Once again, the histology was reassessed and found to be strongly positive for AR expression. He was therefore started with bicalutamide in January 2018, with regression in the number and size of pulmonary and brain metastases and healing of the bone metastases (Fig. 5B and E). The benefit is still ongoing after a year on treatment (Fig. 5C and F).

The main point from these cases is that a specialist MDT in a leading cancer centre recommended a platinum-based chemotherapy as recognised therapy. This is

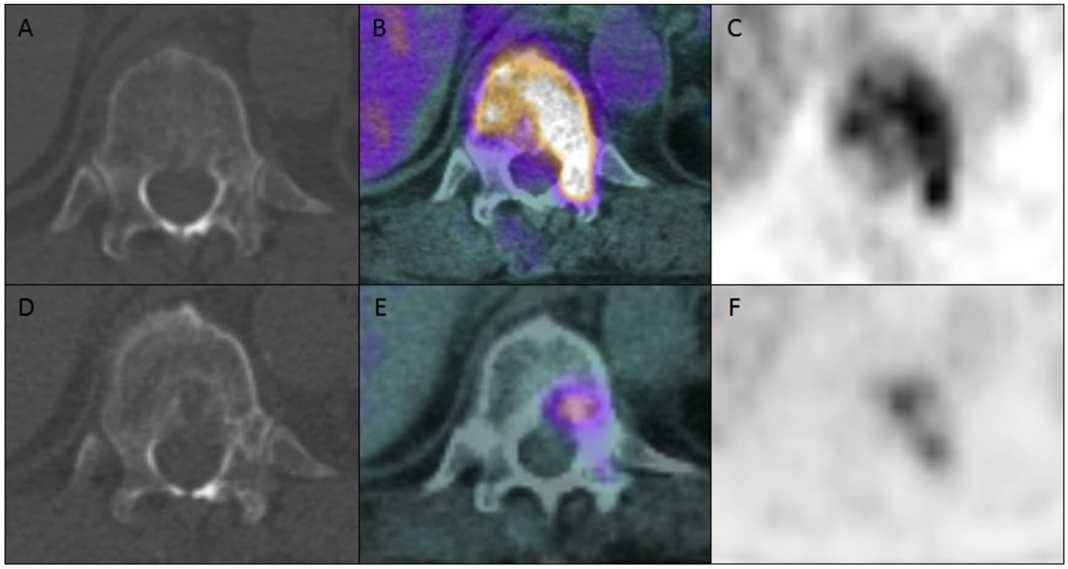

Fig. 3. Pre-treatment (A–C) and 6-month post-treatment (D–F) assessment 18F-FDG PET/CT studies (A and D, 3-mm axial CT; B and −3-mm fusion axial PET/CT and C and F, axial PET) demonstrating a partial response after commencement of bicalutamide. FDG avid disease is seen within the T12 vertebral body extending into the left pedicle on pre-treatment study with very subtle lucency on the CT study. The post-treatment scan demonstrates a marked reduction into FDG activity with patchy marginal sclerosis on the CT scan. CT, computed tomography, PET, positron-emission tomography.

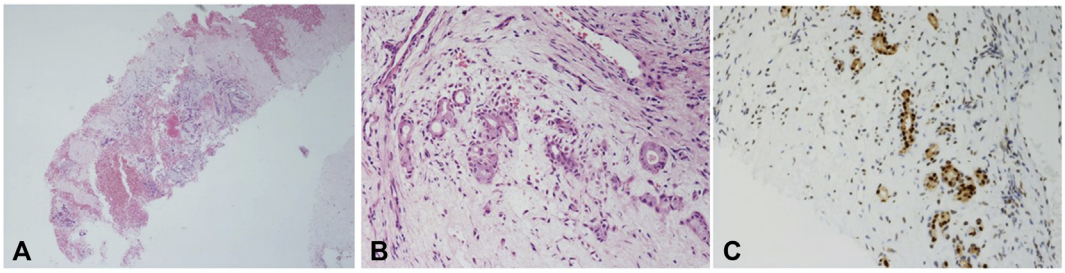

Fig. 4. Core biopsy of the left iliac crest showing (A) a myxoid and epithelial tumour with characteristic features of metastasising pleomorphic adenoma (MPA). Low-power view, 10x. (B) Higher magnifications showing small-sized ducts lined by cells with ample and eosinophilic cytoplasm, indicating oncocytic differentiation. 40x. (C) Immunohistochemistry for androgen receptor. Strong nuclear staining is seen in most ductal cells. 40x.

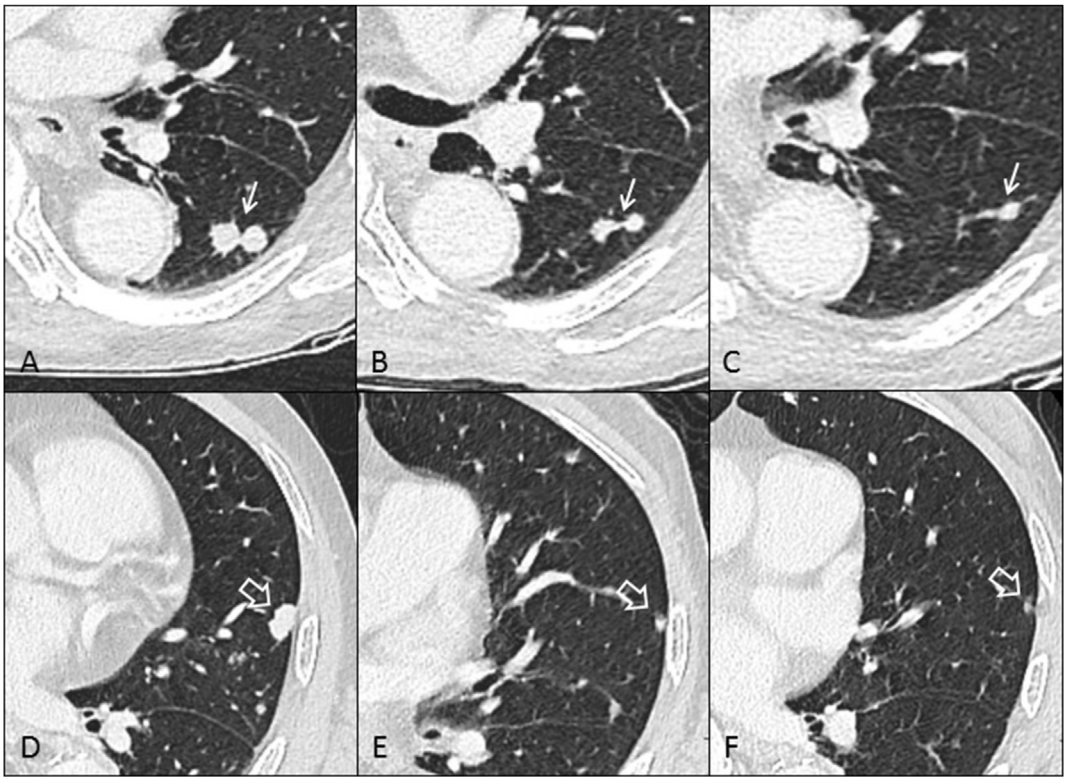

Fig. 5. Baseline CT (A and D) demonstrates pulmonary metastases in the left lower lobe (solid arrow) and left upper lobe (open arrow). After 4 months of bicalutamide therapy, (B and E) there has been a partial response to treatment. Continued response is seen at 10 months after bicalutamide therapy (C and F). CT, computed tomography.

despite the literature reporting an association with AR positivity for several years [4], together with the anecdotal response to anti-AR therapy including abiraterone [5].

A sole case report of a response to pembrolizumab in a patient with metastatic apocrine carcinoma with similar distribution of the disease led to it being added to abiraterone, with further reduction in disease progression. A cohort of patients with advanced PD-L1–positive salivary gland carcinoma was enrolled in the non-randomised phase Ib trial and treated with pembrolizumab. Three patients achieved a partial response (there were no CRs), and additional 12 patients had a stability of disease (SD) for a disease control rate (CR+PR+SD) of 58% [9].

It is of interest that the second patient was already on a non-specific immunotherapy (IMM-101) and that the third patient had received a BCG-based protocol for his metastatic melanoma. This raises the possibility that AR blockade may be even more effective when combined with immunotherapy.

Conflict of interest statement

The authors declare no conflict of interest.

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