EP-1145

Mitotane treatment for metastatic Leydig cell tumour

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Introduction

Testicular Leydig cell tumors (LCTs) are rare stromal tumors often associated with androgen excess. Metastatic malignant LCTs tend to progress rapidly and typically show resistance to radiotherapy and cytotoxic chemotherapy, calling for alternative management options. Here we describe our recent experience with treatment of two patients with metastatic LCTs and severe androgen excess with the adrenolytic drug Mitotane.

Patients

Patient 1: A 51-year-old patient presented with a 6-month history of restlessness, aggressiveness, facial plethora and increasing hirsutism, 15 years after successful orchidectomy for malignant LCT. Imaging by computed tomography revealed disseminated metastatic deposits. Biochemical work-up revealed severe androgen excess underpinning his clinical symptomatology, with a plasma testosterone of 93nmol/L and a 20-fold rise in urinary excretion of active androgen metabolites (androsterone and etiocholanolone), as well as high urinary cortisol.

Patient 2: A 65-year-old patient presented with disseminated disease three years after orchidectomy for LCT. This was also associated with steroid hormone excess, including exceedingly high testosterone (104 nmol/L) and oestradiol. Both patients were commenced on palliative chemotherapy with mitotane.

Results

In both cases, introduction of mitotane led to prompt control of the underlying hormonal excess, with a precipitous decrease in circulating testosterone and oestradiol levels, diminution of the excretion rate of all urinary androgen metabolites and substantial inhibition of 5a-reductase, as demonstrated by serial urine steroid profiling by gas chromatography/ mass spectrometry (Fig. 1, 2). Clinically, this resulted in a rapid alleviation of the debilitating clinical symptomatology of hyperandrogenism. Radiologically, stabilization of the rapidly progressive disease was documented on follow-up imaging for 6 months in case 1, while partial response was noted in case 2.

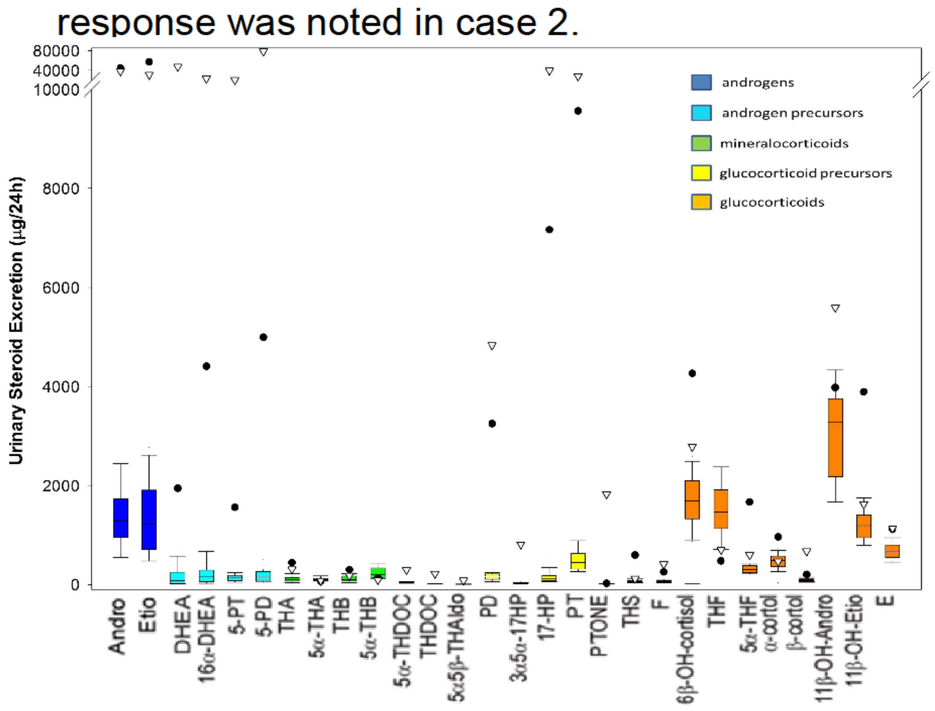

Fig. 1 24-h urinary steroid metabolite profiles (black dots: Patient 1; white triangles: Patient 2) before introduction of mitotane. Box plots represent medians and interquartile ranges from a group of 22 healthy male volunteers; whiskers represent the 5th and 95th percentile

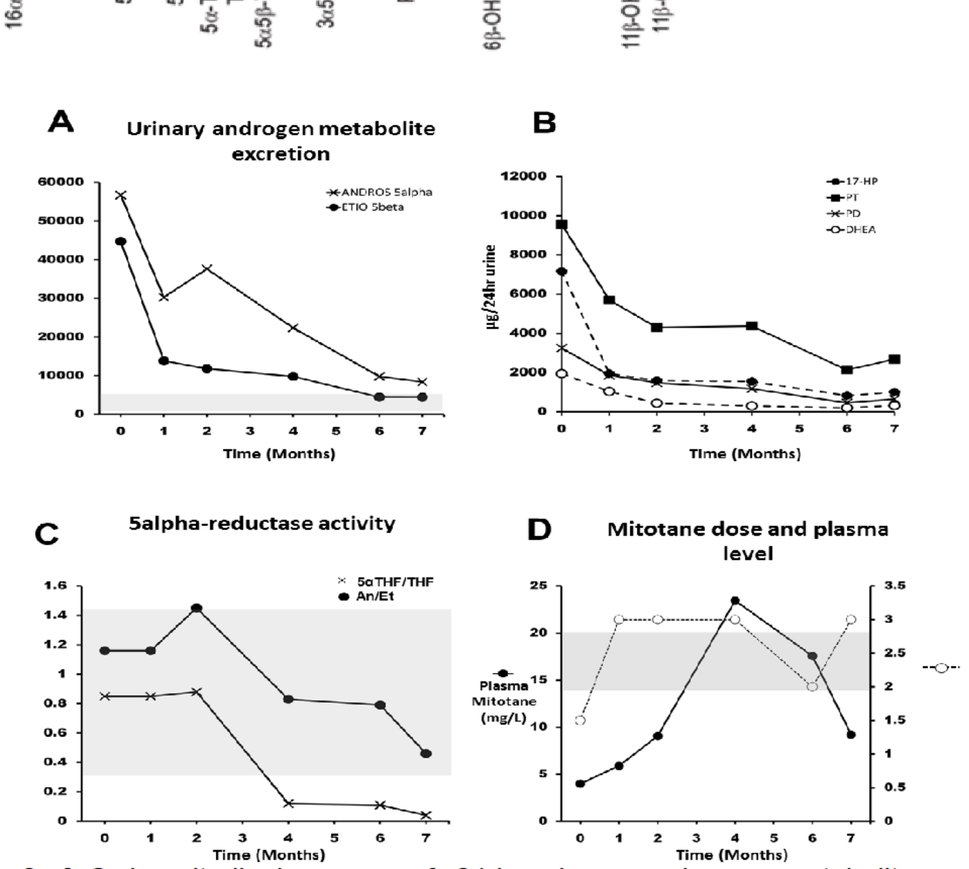

Fig. 2 A-C Longitudinal course of 24-h urinary androgen metabolites androsterone and etiocholanolone **(A);** 17-OH-Progesterone, pregnanediol, pregnanetriol and dehydroepiandrosterone **(B);** and 5α-reductase activity **(C)** during the course of mitotane treatment in Patient 1. **D** Mitotane daily dose and plasma levels over the same period

Discussion and Conclusions

Only 8 cases of patients with metastatic LCT treated with mitotane exist in the literature, and treatment lasted more than 2 months in only half of them. Prolonged treatment was associated with good symptomatic control and biochemical response; temporary disease stabilisation was noted in some of these patients. This is the first case series characterising the biochemical response of androgen producing LCTs using the powerful analytical tool of urinary steroid profiling by gas chromatography/ mass spectrometry. We suggest consideration of mitotane as a first-line treatment option in inoperable cases of LCTs associated with significant androgen excess, with the primary aim of good biochemical control and symptomatic palliation.

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17 ECE 1145--EP

Endocrine tumours

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DOI: 10.3252/pso.eu.17ece.2015

Poster presented at: ECE2015 16-20 May 2015 DUBLIN, IRELAND 17th EUROPEAN CONGRESS OF ENDOCRINOLOGY

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