Failure of mitotane and metyrapone combination to control Cushingoid symptoms

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Background

Adrenocortical carcinoma (ACC) is a rare, aggressive and functional malignancy that produces elevated levels of cortisol resulting in Cushing's syndrome.

First-line therapy of adrenocortical carcinoma is surgical resection.
Incomplete resection of the primary tumour can result in metastasis and more severe symptoms of Cushing's syndrome.

Further management with metyrapone and/or mitotane for controlling the cortisol levels has been trialed in such cases, but their limited efficacy and adverse effects can limit their use.

Mitotane

Directly suppresses the adrenal cortex by cytotoxic atrophy of adrenal cells and alters the peripheral metabolism of steroids

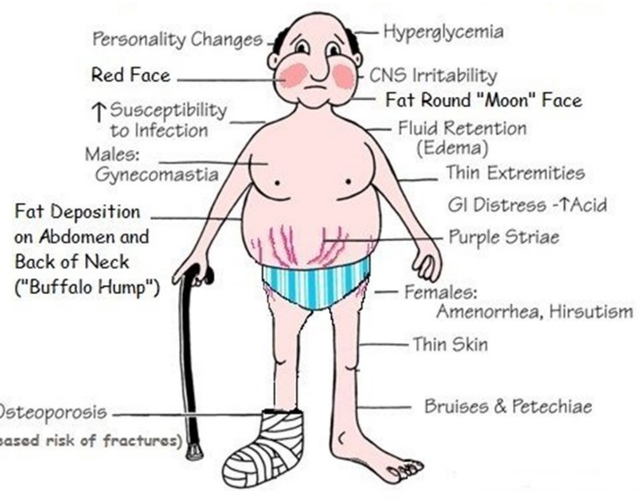
- First line for the treatment of inoperable adrenocortical carcinoma
- Adjuvant therapy for adrenal carcinoma in combination with chemotherapy (etoposide/ doxorubicin/cisplatin)

Metyrapone

Inhibits cortisol biosynthesis by inhibiting 11-beta-hydroxylation of precursors in the adrenal cortex.

- Diagnostic evaluation of hypothalamic-pituitary ACTH function
- Off-label use for treatment of Cushing's syndrome

Symptoms of Cushing's Syndrome[1]



Clinical Features

A 35 year old Caucasian female was diagnosed with stage 4 adrenocortical carcinoma which resulted in Cushing's syndrome. She underwent an adrenalectomy and was commenced on hydrocortisone.

Three months post surgery the patient presented to the Emergency Department (ED) with shortness of breath (SOB) and oedema. It was determined the surgical resection had failed to control the malignancy.

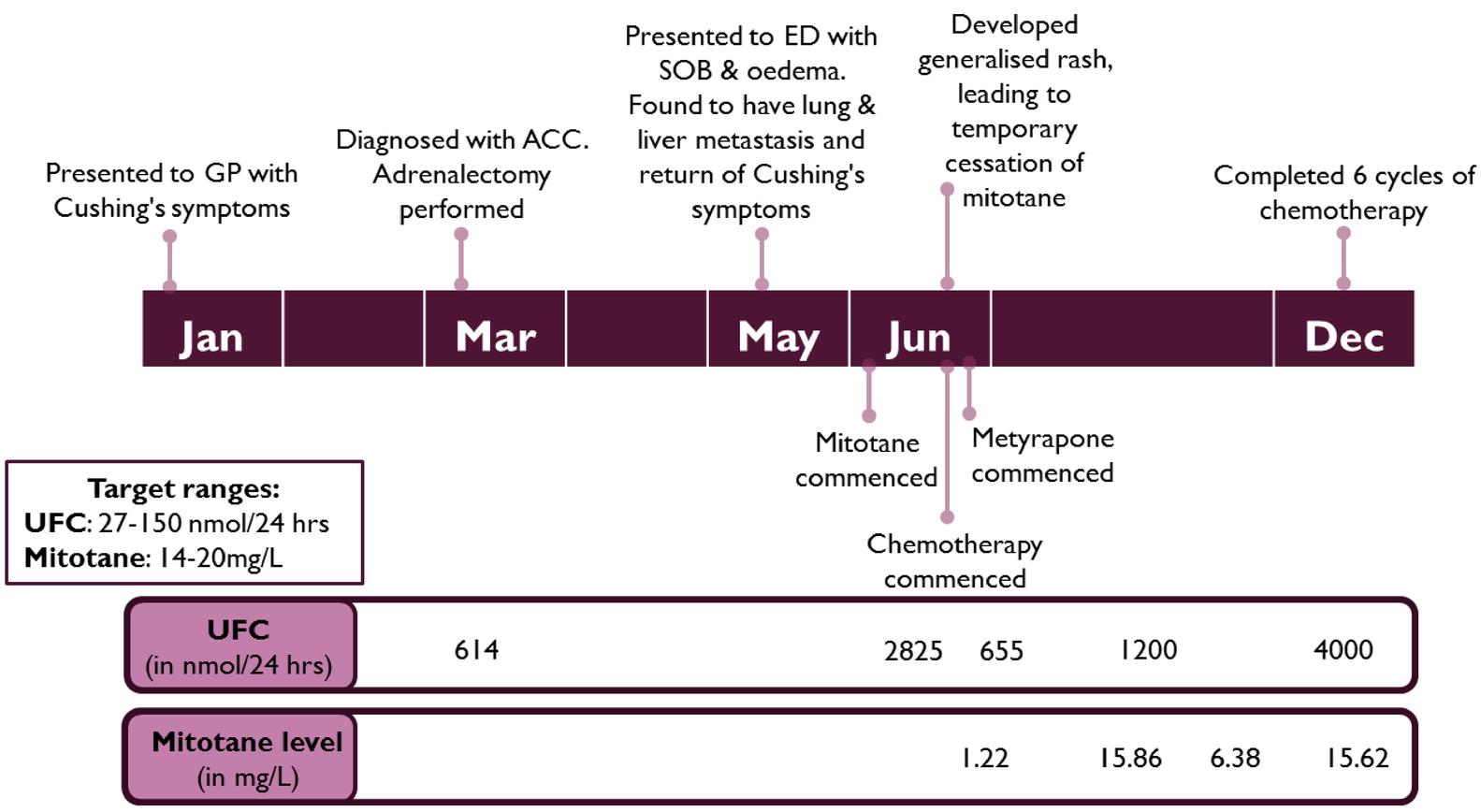
Metastasis in the lungs and liver were found and the patient had worsening symptoms including irregular periods, facial flushing and oedema.

She was given a prognosis of 6 to 18 months. Given her age, further medical management was considered.

Clinical Progress

Mitotane was commenced in combination with etoposide, doxorubicin and cisplatin chemotherapy.
Metyrapone was added three weeks later.
Monitoring included weekly urinary free cortisol (UFC) and electrolytes, and review of clinical symptoms.
Therapeutic drug monitoring for mitotane, aiming for a level of 14 to 20 mg/L was undertaken and the patient was observed for signs of adverse drug reactions.

Case Timeline



Outcome

Despite ongoing treatment with metyrapone and mitotane, the patient had elevated urinary free cortisol levels of > 4,000 nmol/24hrs and experienced severe cushingoid symptoms, including hypokalaemia, abdominal cramps, pitting oedema and unsteady gait related to proximal myopathy.

Nausea and vomiting, a generalised erythematous rash and lethargy were assumed to be adverse drug reactions to mitotane despite mitotane level maintained within the target range.

Objective

To report on the use of mitotane and metyrapone in the management of refractory Cushing's syndrome secondary to end-stage adrenocortical carcinoma.

Conclusion

The combination of metyrapone and mitotane failed to alleviate cushingoid symptoms associated with metastatic adrenocortical carcinoma in this patient, and led to significant adverse effects. We are not able to determine if the addition of mitotane and metyrapone to chemotherapy successfully delayed the progression of the disease. The patient was lost to follow up after completion of her chemotherapy.

Reference

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