

Uterine Bleeding: a Rare Side Effect of Mitotane Treatment for Recurrent Adrenal Carcinoma

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INTRODUCTION

Mitotane is an adrenal-specific agent available for treatment of residual adrenocortical carcinoma (ACC) after surgery. It exerts a specific, direct cytotoxic effect on adrenal cell mitochondria and impairs adrenal steroidogenesis and it has been associated with increased SHBG and modulates their disposal for target cell. We report a rare case of uterine bleeding during mitotane in a girl with recurrent ACC.

CASE REPORT

- A 2.6 year-old girl was diagnosed with underlying right ACC Stage II disease (completely resected tumor with more than 100 g).
- TP53 mutational analysis was performed and R337H and P72R were detected in both primary tumor and peripheral blood.
- Her mother was also tested and the same mutations were identified in her maternal peripheral blood.

Oncology Follow up

- At 3,5 years old, after 9 months from surgery – tumor recurrence (DHEA-S ↑) – second total resection.
- Chemotherapy (Cisplatin, Etoposid, Doxorubicin and Mitotane) was initiated with normal DHEA-S levels for 12 months
- Second recurrence of the tumor observed due to elevation of DHEA-S, in contiguity with the inferior cava vein was observed due to a raise in DHEA-S 14 months after.
- Radiotherapy was indicated followed by a third surgery with total resection of the tumor.
- Since then the patient is on Mitotane only (2 g/m²/d) since the last surgery - with normal DHEA-S blood levels.
- Glucocorticoid (Prednisone: 15 mg/day) and mineralocorticoid (Fludrocortisone: 0,15 mg/day) were used as replacement.

Endocrine Evaluation

- At 6 y old she was referred due to, bilateral breast enlargement and pigmentation of areola, without pubic hair, followed shortly after by persistent uterine bleeding.
- Physical Exam:
 - Height: 117 cm (z: 0.42) NCHS 2000
 - Weight: 21.3 kg (z: 0,21)
 - BMI: 15.3 kg/m² (z: 0.09)
 - Tanner Stage: M2P1 (areola pigmented)
- Laboratory exams:
 - LH: < 0.1 UI/L
 - FSH: < 0.1 UI/L
 - Estradiol: < 0.1 UI/L
 - Cortisol: 14.8 µg/dL (5.4 - 25.0)
 - ACTH: 3.0 pg/mL (3.0 - 60.0)
 - DHEA-S: < 3.0 µg/dL (3.0 – 85.5)
 - β hCG and α fetal protein: negative
 - Sodium: 130.0 mEq/L and Potassium: 4.8 mEq/L (normal)
 - Glucose: 71.0 mg/dL

- Imaging exams:
 - Pelvic Ultrasound:
 - ✓ Uterus: 6.6x2.1x3.6 cm – volume: 26.0 mL
 - ✓ Endometrium: 1.0 cm
 - ✓ Body/cervix ratio: 2/1
 - ✓ Ovaries: R – volume 1.9 mL
L – non visualized
 - Brain MRI: normal

- LHRH Test: (100 µg I.V.)

Time	LH (UI/L)	FSH (UI/L)
zero	< 0.1	< 0.1
15 min	0.77	0.11
30 min	0.92	0.13
45 min	0.93	0.14
60 min	1.0	0.15

- SHBG: 482 mmol/L (22 – 130)

Follow-up

- Treatment:
 - Medroxyprogesterone Acetate Depot (MDAd)– 200 mg IM, was started, with initial cessation of uterine bleeding
- Evolution:
 - At 7 y old:
 - ✓ Height: 120 cm z: - 0.28
 - ✓ Weight: 23,8 kg z: 0,28
 - ✓ BMI: 16,5 kg/m² z: 0,59
 - ✓ Tanner Stage: B2P1 (less pigmented areola)
 - Medication:
 - ✓ MDAd due to uterine bleeding relapses
 - ✓ Mitotane: 4 g/m²/d PO 4 times a day
 - ✓ Prednisone: 20 mg/day + Fludrocortisone: 100 µg/d

COMMENTS

Mitotane exerts a specific, direct cytotoxic effect on adrenal cell mitochondria and impairs adrenal steroidogenesis and it has been associated with increased SHBG^{1,2} and modulates their disposal for target cell.

This is a very rare situation and was described once previously³.

In other case, the girl had vaginal bleeding during the use of mitotane, elevation of SHBG, prepubertal levels of LH, FSH with no rise after LHRH stimulation test, and the bleeding was ceased with the use of MDAd.

In our case, the girl presented a little improvement of her pubertal stage, is still receiving Mitotane and Prednisone and Fludrocortisone, but still has relapses of uterine bleeding that resolves not completely with MDAd, which is a challenge to improve her clinical condition.

References

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