P2-27: High doses op'-DDD cause metrorragia in young girls

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Background

Gynecomastia is a well-known effect of treatment with op'-DDD in male adults. This side effect is related to an estrogenic effect of op'-DDD (1)

Metrorragia in young girls is a less known effect because only a few children receive this drug, mostly for bad prognosis adrenocortical carcinoma. Moreover, it has been reported that op'DDD causes precocious puberty, but cases are not well documented.

The only well documented and published case shows that estrogen and gonadotropins levels are low (2).

Methods

We report 2 cases of young girls receiving high-dose op'-DDD who presented recurrent metrorragia during this treatment.

Case 1

A 18 months old girl was diagnosed with virilizing adrenal mass of 6.5 cm. Surgical excision was complete but histology confirmed a bad prognosis adrenocortical carcinoma. It was decided to start an adjuvant chemotherapy with op'-DDD (Mitotane). She received 8g/m2 per day. 4 months after starting this drug, she presented gynecomastia and metrorragia. Ultrasound showed a uterine size of 55 mm, with swelling corpus, endometrial thickness 4 mm and prepubertal ovaries. Estradiol was low. Op'-DDD level was high 26 mg/l. The dosage was lessened to 6 and then 4g/m2. Gynecomastia raised progressively and intermittent metrorragia every 3 to 6 months persisted. At the age of 3.5 years old, treatment was stopped, a last event of metrorragia was observed 1 month after stopping op'-DDD. Then, gynecomastia and uterine size decreased until a prepubertal uterine size (34 mm) between 1 to 2 years after stopping treatment. Puberty started at 9.5 years old and first menses occurred at 11.5 years.

Case 2

A 18 months old girl was diagnosed with virilizing adrenocortical carcinoma. Microscopically incomplete surgical excision was done and an adjuvant op'-DDD therapy (Mitotane) was started, dosage 8 g/m2. 4 months after starting therapy, gynecomastia develops progressively and a first episode of metrorragia occurred at 15 months of therapy. Uterine size was 50 mm with swelling corpus, endometrial thickness and prepubertal ovaries. Androgens and Estradiol levels were low (2.2 pg/ml) and she was still in remission of the adrenocortical carcinoma. At that time, Op'-DDD level was high 23.5 mg/l. Unfortunately, she developed a few months later a choroid plexus carcinoma and died rapidly.

Conclusion

These cases show that gynecomastia and metrorragia can occur during high dosage op'-DDD treatment even in very young girls and are reversible when therapy is interrupted. Even if gonadotropins levels were not measured, the clinical course of the first case is more in favor of an estrogen-like effect of this drug than central precocious puberty, or estrogen secretion from the adrenocortical carcinoma.

References

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2- Oddie PD & al. Mitotane in the treatment of childhood adrenocortical carcinoma : a potent endocrine disruptor. Endocrinol Diabetes Metab Case Rep. 2018 Aug 23;2018:18-0059. doi: 10.1530/EDM-18-0059