Endocrinology, Diabetes & Metabolism CASE REPORTS

N E Hummelshøj and others | SLR in pregnant patient with metastasized NET

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First-generation somatostatin ligand receptor treatment in a pregnant patient with a neuroendocrine tumor with liver metastases

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Summary

This rare case describes the course of a pregnancy in a patient with a disseminated small intestinal neuroendocrine tumor. The patient received treatment with first-generation somatostatin ligand receptor (SLR) every 4 weeks and had stable disease for several years before her pregnancy. First-generation SLR treatment was initially paused after detection of the pregnancy. During pregnancy, the patient experienced moderate gastro-intestinal discomfort and fatigue, which was considered predominantly pregnancy related. However, since symptoms could be linked to the patient's cancer, treatment was resumed after the first trimester. Chromogranin-A measurements remained stable throughout pregnancy and was paralleled by the absence of diarrhea and only minor flushing. She gave birth by elective caesarean section in week 37 to a healthy baby. Subsequent follow up imaging immediately after and 10 months postpartum showed no disease progression. The safety profile of SLR treatment during pregnancy in the context of disseminated neuroendocrine tumors (NET) is discussed.

Learning points:

- Neuroendocrine neoplasms (NEN) are rare cancers often occurring in the gastro-intestinal tract or lungs.
- Many patients with NEN live for several years with disseminated disease.
- SLR treatment has been given to pregnant patients before; often patients with acromegaly. Pregnancies are reported uneventful.
- This patient completed an uneventful pregnancy while receiving SLR treatment for disseminated neuroendocrine disease and gave birth to a healthy baby.
- More research regarding long term effects and safety signals of SLR treatment during pregnancy are much needed.

Background

Neuroendocrine neoplasms (NENs), including neuroendocrine tumors (NET) and neuroendocrine carcinomas (NEC), are rare disorders with an incidence of 5.9/100 000 (1).

The neoplasms usually arise in the small intestine, pancreas, colon, and lung, and typically metastasize to local lymph nodes and the liver. NENs are graded according to the World Health Organization (WHO) 2017 and 2019 classifications, using morphology and proliferation and divided into well-differentiated NETs (G1–G3) and poorly differentiated NECs (always G3) (2).

Both the location and grading of the primary NEN are used for therapeutic decision-making. Curative resection is performed in patients with low-grade tumors (G1–G2) if possible. In metastatic disease, the treatment depends on primary tumor site and Ki67-index/grading (2).

First-generation somatostatin ligand receptor treatment is first-line medical therapy, and the treatment is in general well tolerated (2, 3).

Patients with NETs typically exhibit a less aggressive disease course (1) and may survive for several years with disseminated disease. Gastrointestinal NENs in pregnancy are rare and only sporadically reported and, accordingly, information about both pregnancy outcomes and SLR treatment are scarce (3, 4, 5).

We report a case of a patient with small intestinal NET, treated with SLR during the pregnancy.

Case presentation

This case concerns a 32-year-old Danish woman with disseminated small intestinal NET.

The patient was diagnosed in May 2013 at age 25 with a G1 small intestinal NET and multiple liver metastases (KI-67 <1%). She had experienced flushing (up to 20 times a day) and diarrhea accompanied by a partially intended weight loss of 43 kg for approximately 2 years prior to diagnosis.

SLR treatment was initiated in May 2013, and operative debulking with resection of 240 cm of the small intestine was performed in July 2014. Resection was performed due to a prolonged period with sudden but persistent abdominal pains, as the patient did not tolerate any morphine or morphine-like medication due to extreme nausea. The abdominal pains were not accompanied by nausea or other signs of obstruction by the primary tumor. Routine follow-up with regular imaging showed stable disease with several liver metastases up to 8 mm in diameter and enlarged retroperitoneal and mesenterial lymph nodes.

Treatment

The disease had been stable on SLR treatment with 120 mg of subcutaneously administered lanreotide (Ipstyl autogel) every 4 weeks for 6 years, when the patient became pregnant in October 2019. She received SLR treatment in pregnancy week 1, before the pregnancy was recognized. The treatment was paused after confirmed pregnancy. The decision to pause treatment during at least the first trimester was made in collaboration with the Department of Clinical Pharmacology as only sparse data on pregnancies and Ipstyl existed and were therefore based on a cautionary approach. Treatment was resumed in gestation week 16+6. Dosage was initiated with 60 mg of Ipstyl, subsequently increased to 90 and finally 120 mg every 4 weeks (Fig. 1). The dosage was initially set low, as physicians wanted to maintain a cautionary approach to treatment, but was increased to same dosage as before pregnancy, as the symptoms persisted until this dosage was reached. The physicians chose to treat with Ipstyl rather than octreotide since the patient was more comfortable with the drug she knew already and confer with the Department of Clinical Pharmacological yielded no apparent contraindications. Throughout the pregnancy chromogranin-A (CgA) measurements remained relatively stable (Fig. 2), accompanied by only minor flushing and no diarrhea throughout the pregnancy. The patient experienced moderate gastrointestinal discomfort and fatigue interpreted as being predominantly pregnancy related.

Investigation

During her pregnancy, the patient was managed at a tertiary center for high-risk obstetrics. Routine nuchal fold ultrasound with combined risk assessment was performed in week 12. Malformation scans were done by fetal medicine specialists in weeks 16 and 20 with normal biometrics and no detected anomalies. Growth and well-being ultrasound scans were performed in GW 23 and every 2nd week from week 28. There was normal growth with an apparent increase in growth velocity from week 33 to 34 onwards. Amniotic fluid index, biophysical profile, and Doppler flows (middle cerebral artery and umbilical artery PI) were normal at all scans. There were no obstetric complications including no gestational hypertension or pre-eclampsia, and routine screening revealed no gestational diabetes. Patients blood biochemistry remained completely normal with no serum alanine aminotransferase (ALAT) or estimated glomerular filtration rate (eGFR) measurements outside normative values. The patient's chromogranin-A values in relation to the pregnancy are shown in Fig. 2.

The patient gave birth by elective cesarean section on maternal request in GW 37+3/7 (June 2020). The postoperative period was uneventful, and the patient was discharged 3 days later.

The baby girl appeared normal with birth weight 2950 g (z-score −0.17), length 50 cm, head circumference 34 cm, and with normal Apgar (10/1 and 10/5) and normal umbilical cord pH (7.3). The baby showed no signs of adverse effects of the medication. Based on theoretical

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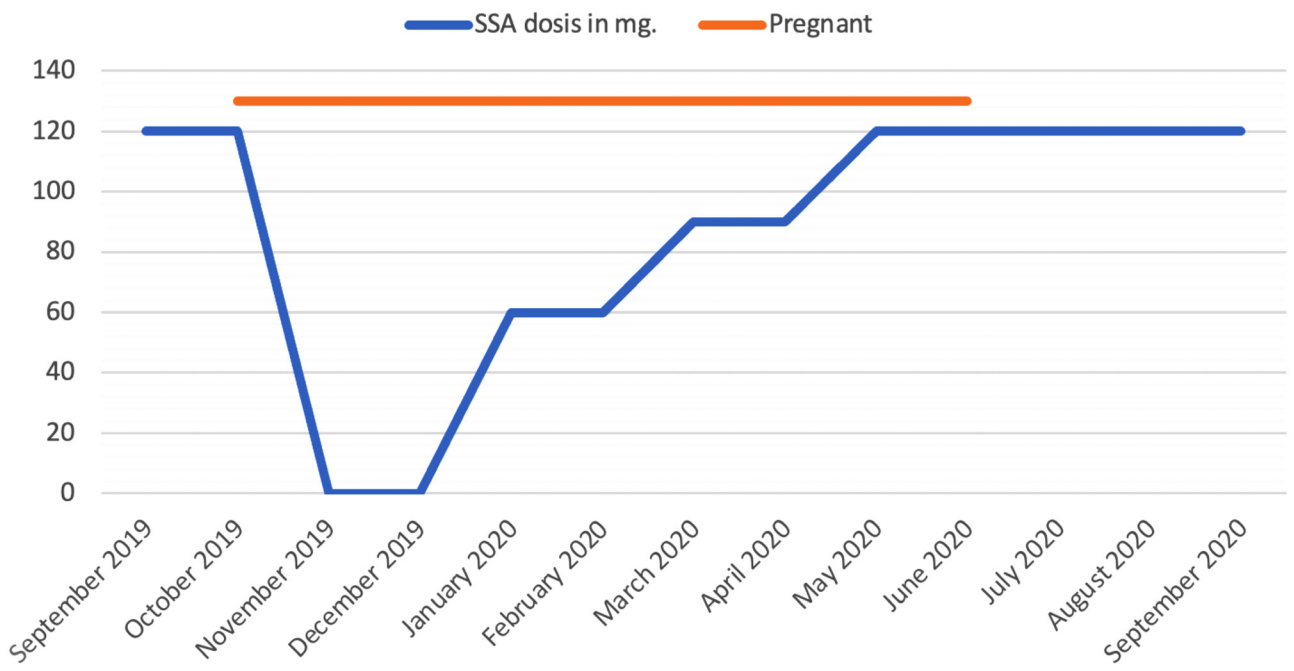

Figure 1
Shows the SSA-administration in a 1-year period in relation to the pregnancy.

considerations, repeated blood glucose measurements were taken 2 and 6 h postpartum and once per day the following 2 days; all blood glucose measurements were within the normal range. The baby was evaluated by a pediatrician within the first 24 h with a normal result, including no visible malformations, no tremor, normal reactions to the examination, and normal reflexes. The baby was bottle-fed based on physician's recommendation as Ipstyl autogel contraindicates breastfeeding based on lack of data, and also on maternal wishes.

Within the first year there has been one outpatient contact with the hospital system (coded as a viral infection, the baby received no treatment and was not admitted). We have no information on general practitioner contacts.

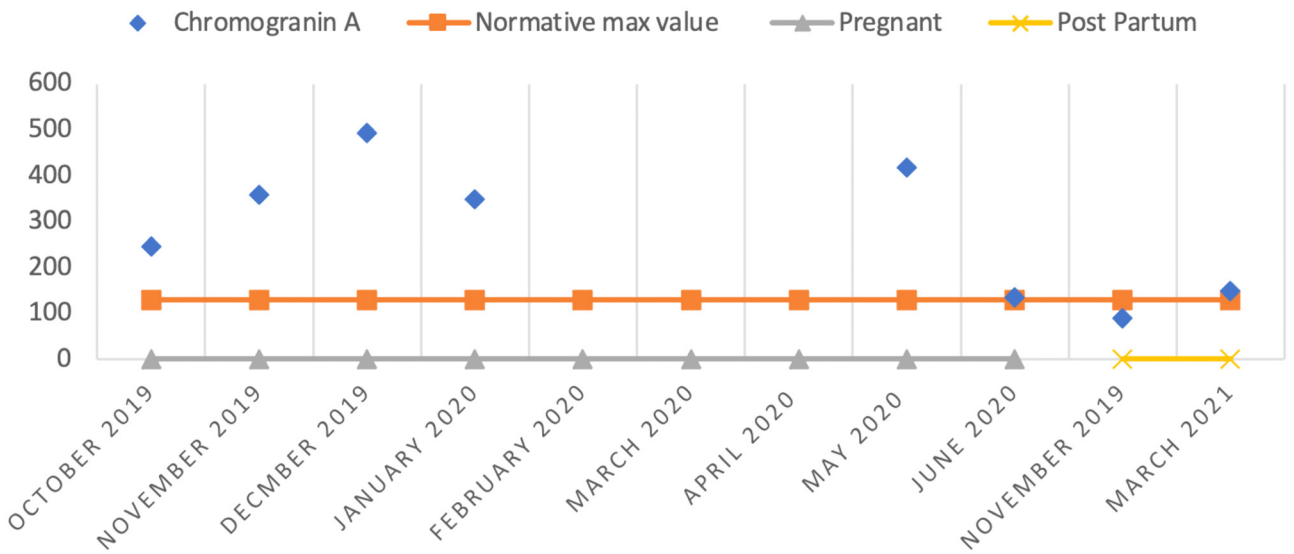

Figure 2
Shows serum-chromogranin A in pmol/L in relation to pregnancy and postpartum.

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The follow up program was resumed after birth and showed stable disease with no new metastases neither immediately postpartum nor after 6 or 10 months.

Discussion

This case describes a rare case of disseminated small intestinal NET treated with SLR during pregnancy.

To our knowledge, only two previous cases of patients with metastasized NETs receiving SLR during pregnancy are reported in the literature (4). Both women received SLR treatment throughout their pregnancies and were closely monitored, presenting with stable blood glucose and normal fetal development.

One patient, a 41-year-old overweight Nigerian woman, with nonfunctioning ileal NET G2 (Ki67 4%), and breast, axillary lymph nodes, and liver metastases, required a caesarian section (CS) at gestational week (GW) 35 due to preeclampsia and delivered a healthy child.

The second patient, a 37-year-old Japanese woman diagnosed with pNET G2(Ki67 11%) and liver- and bone metastases, delivered a healthy child by elective CSn at GW 39 (4).

A few (n= 39) cases of pancreatic neuroendocrine tumors during pregnancy have been published (3), however, information about SLR treatment is lacking (3). Some cases in pregnancies in NEN of the lung (n= 6), appendix (n= 7), and various others (ovary (n= 3), GIT (n= 2), pelvic, trachea, and uterus (all n= 1) are reported. But yet again, information on treatment is lacking, and only a few cases had metastasized disease (5).

First-generation somatostatin ligand receptor therapies are also used in the management of acromegaly, typically caused by growth hormone-secreting adenomas of the pituitary gland (6). Among patients with acromegaly treated with SLR, several pregnancies have been reported of which most have been uneventful (6, 7, 8).

A larger study reports information on treatment with SSA therapy in pregnant women with acromegaly (n= 62). However, multiple patients discontinue treatment during pregnancy (8). Among these cases only one malformation was reported (uteral stenosis). Due to an insufficient amount of data on pregnancy outcomes after perinatal treatment with SLR of any kind and volume (9) the guidelines state that SLR treatment of patients with acromegaly should be discontinued, if possible, upon diagnosis of pregnancy (9). Reasons for continuation of therapy is reported mainly to be persistent analgetic-resistant headaches, expanding tumor close to the optic chiasma, or severe signs of and symptoms of acromegaly (9).

In non-NET cancers, the outcomes are overall non-favorable for both the mother and the fetus in pregnant patients with disseminated disease (10). Most reported pregnancies have resulted in elective or spontaneous abortion, and maternal mortality is high (10). However, since low-grade (G1–G2) NET typically have a less aggressive behavior (1), many patients live with liver metastases for several years. In these patients, pregnancy outcomes(n= 42) are generally favorable (3, 4).

In conclusion, we report an uneventful pregnancy in a woman with known disseminated small intestinal NET, who was treated with SLR during pregnancy. The baby appeared healthy at birth with normal birth weight and no malformations, and development at 6 months of age was normal. The woman experienced acceptable symptoms and no new metastases were detected neither 6 nor 10 months postpartum.

The paucity of long-term fetal outcome data demands a conservative and cautionary approach even though no safety signals so far have been reported (4, 9).

Larger series including long-term follow-up of women and children are much needed.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Patient consent and consent from patient's guardian is obtained.

Author contribution statement
Nynne Emilie Hummelshøj: research year student conducting research regarding patients with NET is the first author of this article and has permission to obtain all information necessary for writing of this case report. Permission is granted from the patient's primary physician and this article's last author, Gerda Elisabeth Villadsen. Nynne is supported by a scholarship from the Danish Cancer Association. Gitte Dam: is Nynne's primary guidance counsellor and co-author of this case report. Lars Henning Pedersen: was the patient's physician during pregnancy and has co-authored the case report (specifically sections on pregnancy surveillance). Astrid Hjelholt: conducted assistance regarding pharmaceutical choices and planning of treatment during the full pregnancy. Has also co-authored the case report. Gerda Elisabeth Villadsen: Is the primary physician and has co-authored the case report.

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