CASE REPORT

Molar pregnancy after tubal ligation in a patient with neuroendocrine tumour: when a rare condition coincides with an unexpected diagnosis

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Accepted 8 April 2014

SUMMARY

A 40-year-old woman with a history of bilateral tubal ligation and a recent diagnosis of metastatic neuroendocrine tumour in the liver presented with severe nausea, vomiting, diarrhoea and dehydration. She had an inconclusive urine pregnancy test in the emergency department that was followed by an extremely high serum β -human chorionic gonadotropin. Transvaginal ultrasound, MRI and subsequent pathology from a dilation and curettage (D&C) revealed that the patient had a complete molar pregnancy. This is a case of an unusual patient who reminds us that one person can have a rare diagnosis and an unexpected obstetrical outcome. We could find no evidence in the medical literature of a causal link between these two diagnoses but present this case report of a reproductive age woman with neuroendocrine tumour and complete molar pregnancy. This case also serves as an example of the phenomenon of the 'hook effect.'

BACKGROUND

This case highlights the occurrence of an unexpected obstetrical disorder in a patient with a rare gastrointestinal disorder. In addition, it reminds us that surgical sterilisation is not a fail-proof method of sterilisation and more importantly in any woman of reproductive age, you must consider pregnancy and pregnancy-related complications in the differential diagnosis.

CASE PRESENTATION

A 40-year-old woman with a known history of biopsy proven metastatic neuroendocrine tumour (NET) in the liver from an unknown primary source presented to her primary care physician with a 4-month history of diarrhoea and abdominal pain and 3 days of intractable nausea and vomiting. She was sent to the emergency room due to concerns of worsening symptoms from her NET. Her medical history was significant for five pregnancies (one-term delivery and four miscarriages) and a bilateral tubal ligation in 2007. She had regular menstrual cycles every 28–30 days and her last menstrual period was 3 months prior to presentation. She was sexually active but reported only one episode of intercourse between tubal ligation and diagnosis.

INVESTIGATIONS

Initial biochemical and haematological investigations were normal. The urine pregnancy test was

indeterminate, and a subsequent β human chorionic gonadotrophin (hCG) was 428 680 U/L (normal range <5.0 U/L).

Urinalysis showed evidence of dehydration with ketonuria and hyaline casts.

A transvaginal ultrasound revealed a 7.76×11.44 cm intrauterine mass with a stormy echogenic appearance. MRI, compared with MRI performed 2 months ago, showed a new complex multicystic uterine/endometrial mass with internal haemorrhage and regions of soft tissue, compatible with gestational trophoblastic disease (GTD) without evidence of extraserosal extent or metastatic disease and unchanged appearance of hepatic metastases.

Faecal studies for *Clostridium difficile*, ova and parasite, faecal leucocytes and stool culture (*Yersenia*, *Campylobacter*, *Salmonella* and *Shigella*) were all negative.

DIFFERENTIAL DIAGNOSIS

We thought the most likely diagnosis of her nausea, vomiting and diarrhoea was complications from her NET. Carcinoid syndrome occurs in approximately 10% of patients with metastatic NET due to the secretion of vasoactive substances such as serotonin. It is characterised by episodic flushing (63–94%), diarrhoea (68–84%) and abdominal pain (10–55%).^{1–4} Nausea and vomiting can occur in patients with non-functioning NET and have been reported in 36% of such patients.⁵

We also considered an infectious aetiology for her nausea, vomiting and diarrhoea. Negative stool cultures and the persistence and severity of symptoms made infectious gastroenteritis less likely.

The possibility of pregnancy or a pregnancy-related complication was low on our differential due to the patient's history of a tubal surgical sterilisation. However, a urine pregnancy test is obtained as part of a standing order set for women of reproductive age presenting to our institution's emergency department with abdominal pain and nausea or vomiting. The result of the urinary β hCG was indeterminate, so a serum quantitative β hCG was ordered and found to be excessively high at over 400 000 U/L. β hCG secreting NETs have been reported but are rare, with mean β hCG levels of 198.7 U/L, so significantly lower than in our patient.^{6,7} Peak normal pregnancy levels of β hCG are typically below 100 000 U/L, whereas 40% of complete molar pregnancies are associated with hCG levels >100 000 U/L.⁸ At this stage, we decided to expand our differential diagnosis and

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To cite: Semanya AM, Roberts C, Mounsey A. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-203588

evaluate her for GTD with a transvaginal ultrasound. Ultrasound revealed a 7.76×11.44 cm intrauterine mass with a stormy echogenic appearance. Ultrasound has a low sensitivity (44%) and specificity (74%) for detection of a hydatidiform mole of any type, so MRI of the abdomen and pelvis was obtained.⁹ This showed a new complex multicystic uterine/endometrial mass with internal haemorrhage and regions of soft tissue, compatible with GTD without evidence of extraserosal extent or metastatic disease. This uterine/endometrial mass was not present on the MRI or Single-photon emission CT imaging that the patient had 2 months previously.

TREATMENT

Obstetrics/Gynaecology (OB/GYN) was consulted for treatment and management of molar pregnancy and on hospital day 3, she was taken to the operating room for dilation and curettage (D&C). Pathology showed complete hydatidiform molar pregnancy, confirming GTD as the cause of the patient's intractable nausea and vomiting.

OUTCOME AND FOLLOW-UP

After the D&C, the patient had an almost immediate resolution of her nausea and vomiting, although she does continue with mild abdominal pain and diarrhoea presumed secondary to her NET. Ten days after the patient's D&C, her β hCG was 1691 U/L and continued to decrease to a nadir of 187 U/L at 6 weeks postoperatively. However, at 8 weeks postoperatively, the β hCG had increased to 248 U/L and the decision was made to start chemotherapy with methotrexate. She had an excellent response to chemotherapy, with current β hCG levels below 5 U/L, 6 weeks after starting methotrexate.

Further evaluation for primary location of the NET revealed an elevated gastrin level of 621 pg/mL. Flexible sigmoidoscopy and upper endoscopy were normal and she will now undergo intraoperative evaluation for the site of the probable primary gastrinoma to evaluate the pancreas, small intestine and appendix with surgical resection of the liver metastasis. She has been started on omeprazole for peptic ulcer prophylaxis from her probable primary gastrinoma.

DISCUSSION

This case highlights the importance of maintaining a broad differential diagnosis and not assuming that a patient's symptoms are associated with a recent new diagnosis. The excessively increased β hCG indicated the possibility of an unexpected outcome, GTD, so that even though she had had a tubal ligation, this possibility had to be pursued.

Our case was first confounded by the patient's original 'indeterminate' urine pregnancy test. When considering a broad differential, it is important to question why the original urine β hCG results were resulted as indeterminate. In a review of the literature, this has been seen in other conditions where a large amount of β hCG is produced, which can cause a false negative result due to an oversaturation of the assay system, known as the 'hook effect'. Current urine pregnancy tests use antibodies directed against β hCG for immunological identification; two antibodies are directed against different parts of the β chain and when β hCG is present, the two antibodies form a 'sandwich' around the antigen and are interpreted as positive. However, falsely low or negative results can occur with a high level of the β -subunit core fragment (a breakdown product of β hCG). This high amount of the subunit can overwhelm the assay system and blocks the formation of 'sandwiches' between the two antibody-antigen sites. This phenomenon has been observed in

several cases where β hCG is made in excess, such as molar pregnancy, multiple gestations or cancer.^{10 11} With our patient, the suspicion for an obstetrical related disorder was low, but given the uncommon report of an indeterminate urine assay, we followed our institution's laboratory recommendation of following up with a serum β hCG. Given the report of 'indeterminate' but then resultant elevated serum β hCG in a patient with trophoblastic disease, this confirms that our findings demonstrate an example of the 'hook effect'.

Tubal ligations are not a guaranteed method of sterilisation. The US Collaborative Review of Sterilization (CREST) study followed 10 685 sterilised women for up to 14 years following their tubal ligation and found that the cumulative 10-year probability of pregnancy following tubal ligation was 18.5/1000 procedures (95% CI 15.1 to 21.8).¹² There are many risk factors for GTD including extremes of age, with the risk significantly increased in those over 35 years, previous GTD, current smoking (>15 cigarettes/day), maternal blood type AB, A or B, history of infertility, nulliparity and use of oral contraceptives.¹³ Despite a thorough literature review, we could not find any data that tubal ligation increases the risk of molar pregnancy. Thus, in our patient's case, the only risk factor she had for GTD was her age of 40. This patient's case demonstrates that pregnancy-related complications must be considered in a differential diagnosis in a potentially fertile woman despite a history of tubal ligation.

In addition, this patient was found to have two synchronous tumours, one of which was rare and the second of which was not expected; the prevalence of complete molar pregnancy is 1:1000–1500 persons in North America,¹³ and the prevalence of NET is 2:100 000 persons and accounts for 0.5% of all malignancies.¹⁴ Initially, we believed that there had to be a correlation between the patient's nausea, vomiting, diarrhoea and elevated β hCG with her NET, as it is known that NETs can secrete hCG. Further workup confirmed that the patient had a metastatic neuroendocrine hepatic tumour from an unknown primary origin with a synchronous non-metastatic primary molar pregnancy. Given the rarity of having two synchronous tumours, we performed a literature review to determine the link between NETs and trophoblastic tumours and could find no previous reports of both conditions in a single patient. This leads us to the conclusion that as clinicians, it is vital to always keep our differential broad and consider that patients can have a rare and an unexpected diagnosis.

Learning points

- ▶ Some patients may have a rare disease and a different unexpected disorder diagnosed within a short time span.
- ▶ Obstetrical conditions must always be considered in the differential diagnosis of a woman of reproductive age despite contraceptive status.
- ▶ The value of an order set that includes a urine pregnancy test for women of reproductive age presenting with abdominal pain or nausea and vomiting and the knowledge of the 'hook effect phenomenon'.
- ▶ Although the literature review did not show a link, could there be an association between neuroendocrine tumours and trophoblastic disease?

Contributors AMS was involved in the conception, literature search, data gathering, drafting of the manuscript and giving final approval. CR was involved in

the literature search, data gathering, drafting of the manuscript and giving final approval. AM was involved in the conception, critical revision of the manuscript and giving final approval.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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