Treatment of metastatic invasive moles in two husband-side sisters-in-law. Case reports and review of literature

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Summary

Purpose of investigation: The treatment of "high risk" persistent trophoblastic disease (PTD) consists of poly-chemotherapy. This policy probably will lead to overtreatment of some patients. Also, familiar molar pregnancies through the paternal line are unknown in the literature up till now.

Methods: We describe two cases of "high risk" PTD in two husband-side sisters-in-law, in which poly-chemotherapy was stopped after histology became available and showed invasive metastatic mole.

Conclusion: It should be stressed that treatment decisions should be made based on the concept of "high" or "low" risk PTD, but if histology becomes available, chemotherapy might be less aggressive in cases of invasive mole. If invasive mole could be familiar through the paternal line remains unclear with the current knowledge of genetics in trophoblastic disease.

Key words: Persistent trophoblastic disease; Metastatic invasive mole; Familiar invasive mole.

Introduction

Persistent trophoblastic disease (PTD) is diagnosed strictly on persistent or rising human chorionic gonadotrophin (hCG) levels and patients with PTD are currently divided into a "low risk" or "high risk" category. Several scoring systems have been developed to divide patients into different risk categories to predict the prognosis. Nowadays treatment is based mainly on these scoring systems. After the initial diagnosis of a molar pregnancy further histology is seldom available because of the risk of severe haemorrhage after biopsy or excision. Therefore histology is not considered in the scoring systems, because it may lead to overtreatment as is demonstrated by the following cases. The scoring systems currently used are based on clinical features, blood levels of hCG and imaging techniques. PTD is defined as "low risk" if it is preceeded by a molar pregnancy or a spontaneous or missed abortion which was evacuated less than 12 months before the start of chemotherapy, if metastases are limited to vagina, or lungs or if the patient did not already receive chemotherapy. PTD is of "high risk" if already given mono-chemotherapy did not sufficiently decrease hCG levels or was given more than 12 months previously; if there are metastases in more than one organ outside the uterus; if there are metastases in the liver, spleen, kidneys, intestines, bones or brain or if the preceeding pregnancy was fully developed. If a patient has a PTD of "low risk", mono-chemotherapy with methotrexate is advised (methotrexate 1 mg/kg i.m. on days 1, 3, 5 and 7 with a leucovorin rescue scheme of 15 mg orally on days 2, 4, 6 and 8). If a patient has a PTD of "high risk", it is advised to treat her with poly-chemotherapy conforming to the EMACO regimen, which even in grossly metastatic disease can still be curative [1] (etoposide 100 mg/m^2 i.v. on days 1 and 2; methotrexate 100 mg/m^2 i.v. and 200 mg/m^2/24 hours i.v. on day 1, followed by a leucovorin rescue scheme of 30 mg twice daily on days 2 and 3; actinomycin D 0.5 mg on day 1 and day 2; and cyclophosphamide 600 mg/m^2 i.v. and vincristine 2 mg i.v. on day 8). Treatment usually is started as soon as possible because of the clinical experience that "high risk" PTD can be life-threatening due to haemorrhage in various metastases.

Because poly-chemotherapy is very potent in "high risk" PTD, it is not necessary to remove tumor bulk upfront. Thus, often the underlying histological diagnosis, either invasive mole or choriocarcinoma, is not clarified. Since the concept of PTD covers both invasive mole and choriocarcinoma, it sometimes can lead to overtreatment and cause confusion in everyday clinical practice.

Also, it is known that a molar pregnancy is the result of proliferation of a purely paternal conceptus [2]. To our knowledge, familiar molar pregnancies in the paternal line have not been described in the literature as yet.

We describe two husband-side sisters-in-law with "high risk" PTD whose poly-chemotherapy schedules were changed to mono-chemotherapy with methotrexate or stopped altogether respectively, when histology became available and showed invasive metastatic mole.

Case Reports

Case 1

A 29-year-old woman was diagnosed with a molar pregnancy in March 1996. She previously gave birth to a healthy daughter after a fully developed pregnancy in November 1994. When the molar pregnancy was diagnosed, a chest X-ray was negative for metastases and serum hCG levels were 1.2 million IU/l. The

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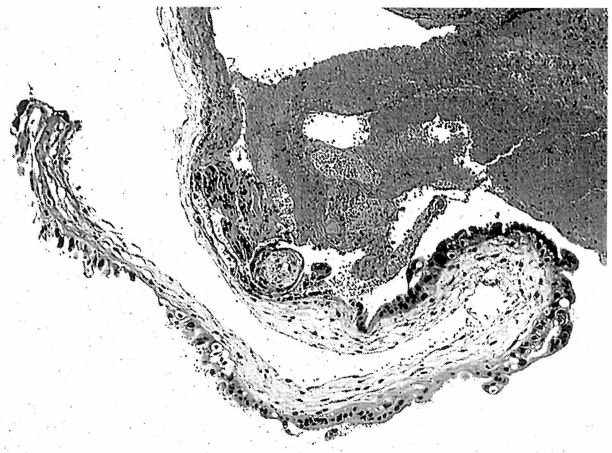

Figure 1. — Biopsy of the vagina of case 1 showing metastasis of an invasive mole. The photograph shows an enlarged villus with a central acellular cistern and minimal circumferential trophoblastic proliferation.

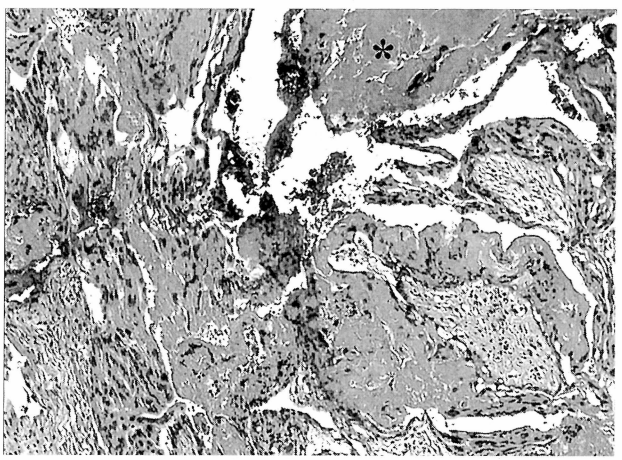

Figure 2. — Histology of case 2 of the perforation opening through the uterine wall with molar tissue consisting of villi with fibrosis and trophoblastic proliferation. The opening is bordered by necrotic myometrium indicated by an asterix.

molar pregnancy was evacuated by suction curettage and histology showed it to be a complete mole. After evacuation serum hCG levels initially dropped but after four weeks leveled off at 4,500 IU/l. The patient was diagnosed with a "low risk" PTD and started mono-chemotherapy with methotrexate. Eight days after the first course of methotrexate she was urgently admitted with severe vaginal bleeding caused by a 1 cm in diameter, new, vaginal lesion, which was excised. At that time she was re-evaluated. A chest X-ray was suspicious for multiple small pulmonary metastases, which were confirmed with a chest CT scan. The serum hCG level was 264 IU/l.

Although the hCG level had fallen from 4,500 to 264 IU/l after one course of mono-chemotherapy with methotrexate, it was concluded that the newly diagnosed vaginal lesion and the progression of pulmonary lesions justified the diagnosis "high risk" PTD and warranted poly-chemotherapy with an EMACO regimen which was started the next day. However, after the first course of EMACO, histological examination of the vaginal biopsy showed it to be molar tissue (Figure 1). With this histological diagnosis, together with the fact that hCG levels were dropping while methotrexate mono-chemotherapy was given, the treatment schedule again was changed back to mono-chemotherapy with methotrexate.

Because serum hCG levels had been normalised after the first EMACO course, three further consolidation courses of methotrexate were given. Follow-up showed a normal chest CT scan in July 1996 and normal serum hCG levels for one year. Thereafter the patient became pregnant spontaneously and gave birth to two healthy children in June 1998 and in June 2000.

Case 2

The husband-side sister-in-law of the patient described in case 1 was diagnosed elsewhere with a complete molar pregnancy in October 1997. The molar pregnancy developed in the beginning of her fourth pregnancy after two missed abortions and a term delivery of a healthy boy in 1993. After the first two missed abortions the couple consulted a clinical genetic centre because of the habitual abortions. Chromosomal analysis of both the patient and her husband were normal. As to the molar pregnancy, she originally was diagnosed with a missed abortion in October 1997 but the curettings were not sent for histological confirmation. In December 1997 she again consulted her gynaecologist because of heavy vaginal bleeding. Ultrasound showed pregnancy remains with a molar aspect. Again a suction curettage was performed and histological examination confirmed it to be a complete molar pregnancy. A chest CT scan showed multiple, small pulmonary metastases. She was diagnosed with "low risk" PTD and started three courses of methotrexate. Initially serum hCG levels dropped, but after the second course of methotrexate they leveled off. This was the reason she was referred to our hospital in January 1998. On admission the hCG level was 526,000 IU/l. Transvaginal ultrasound examination showed an 11 cm intrauterine mass, with typical molar and dense aspects. She was diagnosed with "high risk" PTD and the EMA part of the first EMACO course was started after a brain CT scan was negative for metastases and liver metastases were excluded by ultrasound. One week after the EMA part of the first EMACO course she presented with acute abdominal pain. Intra-abdominal blood loss was strongly suspected and emergency laparotomy revealed a perforated uterus which was extirpated. There were no further intra-abdominal abnormalities on inspection or palpation. Six days after the laparotomy she received the CO part of the first EMACO course. Histological examination of the removed uterus showed a 12 cm intrauterine invasive mole perforating the fundus (Figure 2). So again the final histological diagnosis was an invasive mole. This histopathological diagnosis, the fact that the molar tissue was removed with the uterus, and the fact that her serum hCG levels had dropped dramatically after the hysterectomy and one course of EMACO (to 411 IU/l one week after the CO part of the EMACO course), were arguments to stop her chemotherapy altogether. Thereafter serum hCG levels continued to decrease and were in the non-detectable range in May 1998. Serial chest CT scans showed a gradual disappearance of the lung lesions. In Janunary 1999 a chest CT scan was negative. Serum hCG levels were negative upto the submission of the manuscript in May 2001.

Discussion

In our view there are two remarkable features in the two described cases.

Firstly, the clinical management of patients with PTD on the definition of "high" and "low risk" as well as on

the hCG levels. Our first patient, with a known "low risk" PTD started treatment with mono-chemotherapy after hCG levels leveled off (molar pregnancy and possible metastases confined to the lungs). After a vaginal metastasis was found she was placed in the "high risk" category (metastases in more than one organ outside the uterus) and started on her first course of EMACO the next day.

In the second case the patient was diagnosed with "high risk" PTD because of the leveling off of hCG levels while on mono-chemotherapy for a "low risk" PTD after a molar pregnancy. Due to bleeding complications in both patients the bleeding sites were excised and thus histology became available showing metastatic invasive moles in both cases. The concept of PTD is based on the levels of a tumor marker, hCG, and covers a variety of underlying histological entities (both invasive mole and choriocarcinoma). This can cause confusion and can lead to overtreatment.

The histology result in both our patients made us reconsider the necessity for poly-chemotherapy. It has been suggested that so-called pulmonary metastases in a molar pregnancy are not true metastases but rather implant-like reactions which decrease in time after the molar pregnancy has been removed [3]. Also, invasive moles rather cause hemorrhagic complications and seldom change into choriocarcinoma [4]. Furthermore, in large series of treated cases, invasive moles have not caused deaths due to disease, in contrast to choriocarcinoma [4, 5].

Thus in our patients, the histology result showing invasive molar tissue, together with the fact that no bulky tumour was left and hCG levels had dropped dramatically after one EMACO course, were arguments to stop poly-chemotherapy. Another reason for this decision was the preservation of ovarian hormonal function and fertility, which are likely to be more diminished after EMACO therapy compared to mono-chemotherapy with methotrexate [6].

In Japan, where PTD is of more frequent occurrence compared with Western countries, there is a general consensus that patients with invasive moles need less aggressive chemotherapy compared with choriocarcinoma patients. Since histology is often not available, a diagnostic scoring system for patients with a PTD has been developed which differentiates between choriocarcinoma and invasive moles in the absence of histology, the so-called choriocarcinoma diagnostic score [7]. This scoring system is based on the underlying histological diagnosis more than on hCG levels and imaging techniques, which are the discriminating factors in the scoring systems used in Western countries. With the Japanese scoring system our two patients would have had a very low probability having choriocarcinoma, and hence would have received less aggressive chemotherapy. In our view, this Japanese scoring system should be studied in a prospective way for its use in the management of patients with PTD.

The second remarkable feature in these cases is the family relationship between the women. To our knowledge these are the first two cases of invasive moles described in two husband-side sisters-in law. Although it is known that women who have had one molar pregnancy have an increased risk of a second mole in the following pregnancy of 1:76, which increases to 1:6.5 after two molar pregnancies, molar pregnancies are not known to be familiar [5]. Since invasive mole is a relatively rare condition and since molar pregnancies are known to be of paternal origin, this warrants the possibility there might be a genetic defect in the family of the two brothers in the cases described above, which contributes to the development of a molar pregnancy with invasive potential. Because of habitual abortions, the chromosomes of one of the patients and her husband were screened and found to be normal. However, this is merely a numerical chromosomal screening. Recently, a candidate tumor suppressor gene, DOC-2/hDab2, has been described which might be involved in the development of trophoblastic disease [8]. Possibly, some other genetic defect makes the described family more prone to inactivation of the DOC-2/Dab2 tumor suppressor gene. For now, this is mere speculation, but hopefully the rapid developments in human genetics will clarify genetic implications in trophoblastic disease in the near future.

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