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Primary hepatic metastatic epitheloid trophoblastic tumor of the uterus treated with multimodal therapy including pembrolizumab and thermoablation. Case report of an extremely rare disease and review of the literature

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ABSTRACT

Epithelioid trophoblastic tumor (ETT) is a rare gestational trophoblastic tumor, first described by Shih and Kurman in 1998. ETT often present as abnormal vaginal bleeding in women of reproductive age, but unlike more common forms of GTN tend to produce much less human chorionic gonadotropin (hCG) for the volume of disease present. ETT can occur after any gestational event and can occur in both intrauterine and extrauterine sites. We present a case of a 46-year-old female patient incidentally diagnosed with ETT and hepatic metastasis. Therapy was multimodal and involved chemotherapy, operation, thermoablation of liver metastases and immunocheckpoint inhibitor. The patient remains disease free for almost four years now. ETT presents a diagnostic challenge due to their rarity and histologic resemblance to other pathologies. ETT can be relatively chemo resistant and are therefore often treated surgically. Misdiagnosis might delay effective treatment and affects survival.

1. Introduction

Uterine epithelioid trophoblastic tumors (ETT) are very rare, accounting for approximately < 0.2% of all gestational trophoblastic diseases (GTD) and 1–2% of GTN (Shih and Kurman, 1998; Froeling et al., 2019; Frijstein et al., 2019; Yang et al., 2019).

GTD comprise a cytogenetically and clinically heterogeneous group of syndromes characterized by misdifferentiation and/or proliferation of the trophoblastic epithelium (Lurain, 2010; Gestational and Non-gestational Trophoblastic Disease. Guideline of DGGG, OEGGG and SGGG). A distinction can be made between hydatidiform moles (contain villi) and other trophoblastic neoplasms (lack villi) (Lurain, 2010). The non-molar or malignant forms of GTD are called gestational trophoblastic neoplasia (GTN). They include the invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor (Walker et al., 2004) (see also Fig. 4). These malignancies can occur weeks or years following any pregnancy but occur most commonly after a molar pregnancy (Bruce et al., 2023). The epithelioid trophoblastic tumor, usually originating from the intermediate trophoblast, belongs to the group of malignant GTD (GTN) (Fig. 4). Benign lesions include placental site nodule, exaggerated placental site, and hydatidiform moles. Malignant lesions, termed gestational trophoblastic neoplasia (GTN), include choriocarcinoma (CC), placental site trophoblastic tumor (PSTT), ETT, and invasive moles that do not spontaneously resolve (Scott et al., 2012). Macroscopically, ETT usually occur as a solid-cystic tumor with occasional calcifications and hemorrhages. Microscopically, intermediate trophoblasts with eosinophilic cytoplasm, eosinophilic map-like necrosis and blood vessels with a regular wall structure within tumor cell nests are characteristic (Stevens et al., 2015). Establishing an accurate diagnosis based on morphological and immunohistological features allows to differentiate between non-neoplastic lesions and neoplastic lesions such as PSTT and ETT, which might become locally invasive or trigger metastases (Fig. 5) (Scott et al., 2012). Literature reports that ETT tumor cells typically express HCG, inhibin-

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alpha and p63 (Yuan et al., 2023; Brodsky et al., 2022). The expression of p63 is helpful for the differential diagnosis of ETT and PSTT, as the latter is negative and ETT is positive (Houghton and McCluggage, 2009). Most reports have found a Ki-67 proliferation index greater than 10 % (Yuan et al., 2023; Ngan et al., 2021).

Approximately 120 cases have been published worldwide (see also supplemental table) (Brodsky et al., 2022; Gadducci et al., 2019), whereas it is very likely that there are other cases that have not (yet) been reported in literature. Often misdiagnosed as choriocarcinoma (CC), placental site trophoblastic tumor (PSTT) or cervical squamous cell carcinoma, ETT are characterized by specific histologic and immunophenotypic patterns, such as p63 and Ki67 (Scott et al., 2012). Affected patients are generally of reproductive age. In 67% of the cases, the first manifestation is preceded by any gestational event within an interval of 1–18 years (Shih and Kurman, 1998). One of the most common symptoms is a bleeding disorder, with elevated hCG levels in most cases, although levels are still lower than in other gestational trophoblastic neoplasia (GTN). In cases of primary pulmonary metastasis, however, patients may be noticed due to respiratory symptoms. In 40% of cases, metastases can already be detected at diagnosis. These cases have an extremely poor prognosis and a high mortality rate. The most common site of metastases in ETT is the lung. The two adverse prognostic factors are a long interval of more than 4 years to the antecedent or causative pregnancy and also advanced stage (Frijstein et al., 2019; Froeling et al., 2019; Gestational and Non-gestational Trophoblastic Disease. Guideline of DGGG, OEGGG and SGGG).

Although the International Federation of Gynecology and Obstetrics (FIGO) system is used to stage ETT, the WHO Risk Score, used for choriocarcinoma (CC), is not applicable (Yang et al., 2019; Ghorani et al., 2017). FIGO helps to help predict the risk of resistance to single agent chemotherapy and does not apply in the management of ETT/PSTT (Frijstein et al., 2019; Burkett and Soper, 2022). ETT produces less hCG, grows slower, has later metastases, and is less sensitive to chemotherapy compared to choriocarcinomas (Frijstein et al., 2019; Yang et al., 2019).

The aim of therapy in ETT is complete surgical removal. Chemotherapy whilst active is not as effective when compared to treating choriocarcinoma. This is why platinum-based chemotherapy such as EP/EMA is preferred by many investigators rather than EMA/CO and if residual lesions are present after treatment they should be resected. For localized disease, a complete resection of the uterus should be performed. The types of treatment and when to deploy them has recently agreed in international guidelines (Lok et al., 1990). For patients with advanced disease or for those with poor prognostic indicators, such as a previous pregnancy interval of more than 48 months, a multimodal treatment paradigm of surgery and chemotherapy using a high-risk GTD platinum-etoposide containing regimen is recommended including high dose chemotherapy (Ngan et al., 2021; Burkett and Soper, 2022; Liu et al., 2022; da Silva et al., 2021). The value of immunotherapy with pembrolizumab in avoiding the need for high dose chemotherapy in such poor risk cases is currently being explored with promising early data (Lok et al., 1990).

2. Case report

First presentation of a 46-year-old female patient (GII/PII) with an ETT confirmed externally by hysteroscopy and curettage in October 2017 at an outpatient clinic. Patient history showed two uncomplicated pregnancies and births (in 2007 and 2009). Staging examination performed at out clinic revealed a distended uterus, enlarged right pelvic lymph nodes and several liver metastases (Figs. 1 and 2). The initial hCG level was 142 mU/ml (Fig. 3). After four cycles of primary chemotherapy according to the EMA-EP regimen (Table 1), the liver metastases were resected in January 2018, followed by longitudinal laparotomy in February 2018, hysterectomy with bilateral salpingo-oophorectomy and right pelvic lymphonodectomy. Chemotherapy was completed to a total

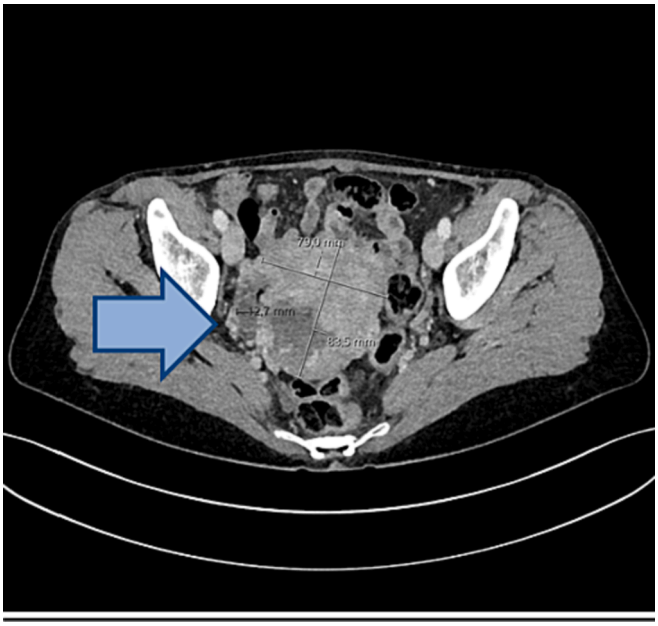

Fig. 1. Uterine ETT in staging computer tomography upfront therapy, October 2017.

of 8 cycles according to the EMA-EP regimen. During this course, staging revealed two small size progressive lesions and one new lesion in the liver. Histological examination confirmed metastases and showed PD-L1 positivity with a combined positive score (CPS) of 1. With stable hCG levels at 1,3 mU/ml, the indication for thermoablation of the liver metastases and initiation of therapy with the immunocheckpoint inhibitor pembrolizumab was given. After 6 cycles, no liver metastases were found. Since then, there has been no abnormal imaging and stable hCG levels around 2.5 mU/ml (Fig. 3a und 3b). In February 2020, there was a new onset of struma, most compatible with a subacute thyroiditis, presumably as a side effect of the pembrolizumab therapy. An autoimmune thyroiditis was excluded by differential diagnosis. Laboratory showed latent hyperthyroidism with normal thyroid parameters and suppressed TSH (0.06 µIU/ml). Simultaneously with the start of a therapy with prednisolone per os, the therapy with pembrolizumab was concluded after a total of 24 cycles in February 2020. Since this time, the patient has been in complete remission with hCG serum check-ups. Additionally, computertomography was performed twice a year for almost two years following treatment.

3. Discussion

Shih and Kurman first distinguished between epithelioid trophoblastic tumor (ETT) as a diagnosis distinct from placental site trophoblastic tumor (PSTT) and choriocarcinoma (CC) in 1998 (Shih and Kurman, 1998). ETT are extremely rare with only a limited number of case reports. The interval between prior gestation and diagnosis for our patient was 8 years, which is consistent with literature reporting a range of 1–18 years (Shih and Kurman, 1998). In two thirds of the cases, patients present with abnormal uterine bleeding as did our patient. Our patient was treated with the standard first line chemotherapy regimen of EMA-EP (Table 1) followed by hysterectomy, bilateral adnexectomy and resection of liver metastases. During the second course of chemotherapy staging revealed two small size progressive lesions and one new lesion of the liver metastasis. Given that histological testing showed high PD-L1 positivity, Tumor board consensus was to conduct thermoablation of the liver combined with a therapy of pembrolizumab. During therapy our patient was diagnosed with a new onset of struma, most compatible with a subacute thyroiditis, most likely as a side effect of the

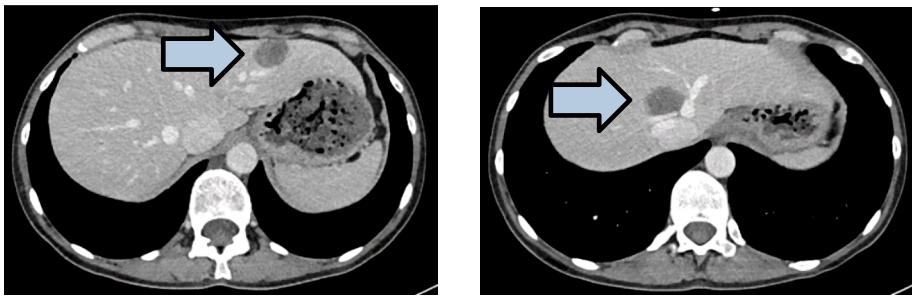

Fig. 2. Hepatic metastasis in staging computer tomography upfront therapy, October 2017.

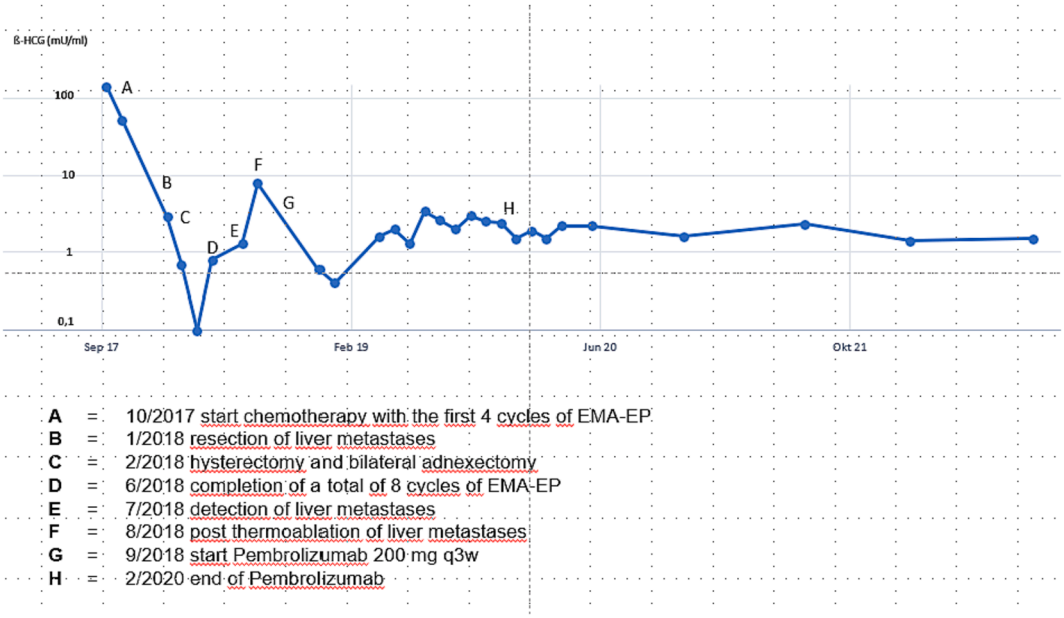

Fig. 3a. Levels of hCG during time course.

pembrolizumab therapy. After a total of 24 cycles therapy was therefore concluded. Although endocrine side effects are known for pembrolizumab, the fact that this subacute thyroiditis occurred after about 18 months is unusual since it usually develops sooner (few months) after initiation of therapy (Ghorani et al., 2017; Merck & Co, 2023).

Immunohistochemistry, in this case, showed that the ETT tumor cells typically expressed p63 and a Ki-67 nuclear labeling index greater than 10%, this is consistent with literature reports (Yuan et al., 2023; Ngan et al., 2021; Ngan et al., 2018).

Although the International Federation of Gynecology and Obstetrics (FIGO) system is used to stage ETT, the WHO Risk Score, used for choriocarcinoma, is not applicable (Yang et al., 2019; Ghorani et al., 2017). FIGO helps to help predict the risk of resistance to single agent chemotherapy, but does not apply in the management of ETT/PSTT (Frijstein et al., 2019; Ngan et al., 2021; Burkett and Soper, 2022).

Due to the risk of relapse, patients with ETT should be followed closely for at least 12 months with monthly hCG monitoring (Ngan et al., 2021; Ngan et al., 2018; Ahamed et al., 2012; Clark et al., 2021). During this period realiable contraception must be used. Follow up can be a burden for patients and high in costs, therefore identifying those patients at highest risk of relapse could permit a more targeted follow-up approach. However there is yet not routine follow up based on risk stratification and authors discuss follow up for years post treatment or even lifelong (Clark et al., 2021; Eiriksson et al., 2021).

Although to date there is still little known about the long-term impact of anti-PD-L1 therapy, Patrinely et al. recently described that - among patients on long term anti-PD-L1 therapy –19.5% had a grade 3, 4, or 5 event and 43% had a chronic immune-related adverse event that continued 12 weeks beyond discontinuation of therapy (Patrinely et al., 2021). Since a significant amount of trophoblastic cells express the PD-L1 receptor (Veras et al., 2017), there has been an interest in using immunotherapy in patients with trophoblastic diseases (Bell et al., 2021). Additionally, Pembrolizumab has been reported as a successful treatment in various forms of gestational trophoblastic diseases (Bell et al., 2021; Clair et al., 2020; Goldfarb et al., 2020).

Besides our case report there has been one further published case report of a patients with metastatic ETT having significant decrease of disease under treatment with pembrolizumab (Bell et al., 2021). Treatment of metastatic placental site trophoblastic tumor with a multimodal treatment including pembrolizumab was recently described by Porter et al (Porter et al., 2021). Another case series of four patients highlighted regression of disease for three patients on pembrolizumab (two with metastatic choriocarcinoma and one with metastatic placental site trophoblastic tumor). The fourth patient had a mixed placental site trophoblastic and epithelioid trophoblastic tumor; but disease progression was noted on pembrolizumab (Ghorani et al., 2017).

To the best of our knowledge, this is the first case report of a patient with ETT and liver metastases who remains disease-free after treatment with pembrolizumab. In line with Bell et al. and others (Liu et al., 2022; Bell et al., 2021); these findings suggest that pembrolizumab might be a reasonable option for therapy of ETT in patients with PD-L1 positivity. With the NHS approval in January 2018 for therapy with pembrolizumab in GTN, treatment of ETT and other gestational trophoblastic diseases appears to be advancing (Bell et al., 2021).

date	hCG (mU/ml)	event
10/2017	**142,5**	**start chemotherapy with the first 4 cycles of EMA-EP**
11/2017	51,5	hCG value after one cycle of EMA-EP
01/2018		**resection of liver metastases**
02/2018	**2,9**	**hCG value after hysterectomy and bilateral salpingo-oophorectomy**
03/2018	0,7	
04/2018	0,1	
05/2018	0,8	
07/2018	**1,3**	**hCG value when detecting suspicious liver lesions after completion of a total of 8 cycles of EMA-EP**
08/2018	**7,8**	**hCG value after thermoablation of recurrent liver metastases**
09/2018		**start Pembrolizumab 200 mg q3w**
12/2018	0,6	
01/2019	0,4	
04/2019	1,6	
05/2019	2	
06/2019	1,3	
07/2019	3,4	
08/2019	2,6	
09/2019	2	
10/2019	3	
11/2019	2,5	
12/2019	2,4	
01/2020	1,5	
02/2020	**1,9**	**end of Pembrolizumab due to a subacute thyroiditis**
03/2020	1,5	
04/2020	2,2	
06/2020	2,2	
12/2020	1,6	
08/2021	2,3	
03/2022	1,4	
11/2022	1,5	

Fig. 3b. Levels of hCG during time course.

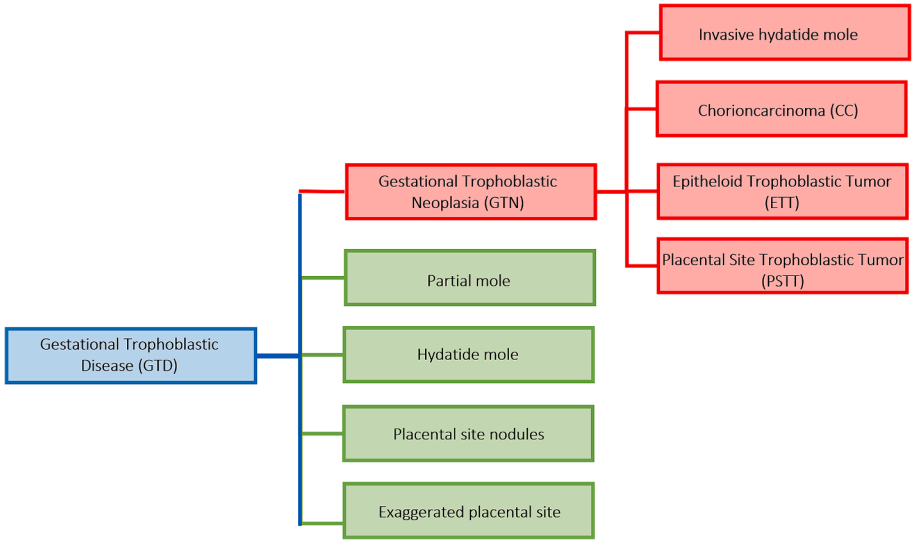

Fig. 4. Overview of Gestational Trophoblastic Diseases ((scheme modified after Stevens et al. 2015 (2015)) green = benign, red = malign).

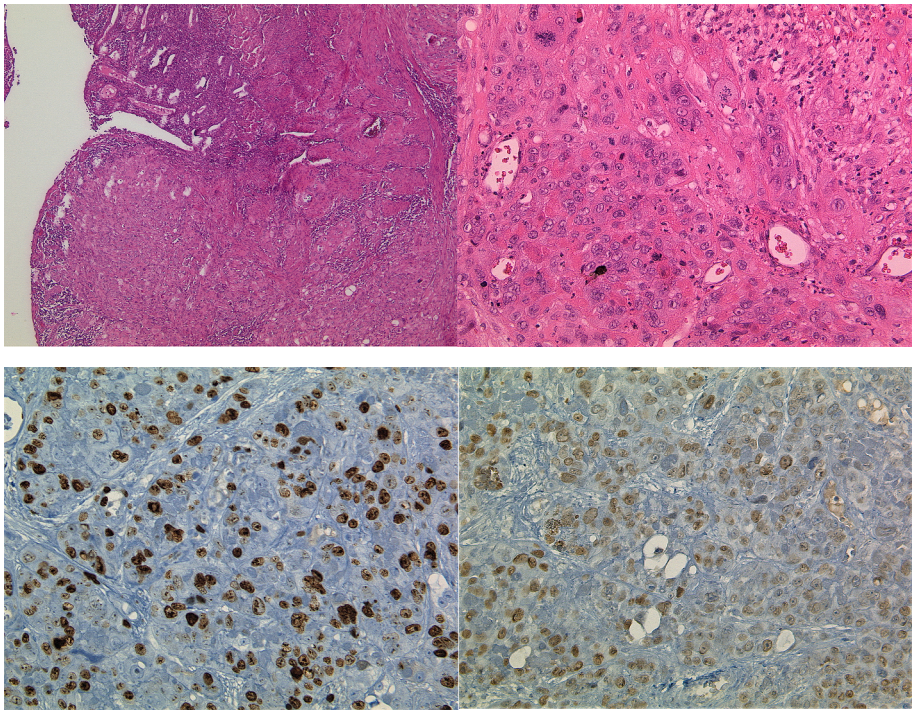

Fig. 5. Histopathological images of the tumor. a: Endometrium in the upper part with associated tumorcells in the lower half of the picture (HE, 10×). b: Neoplastic tumorcells with round to ovoid nuclei and mitosis, sourrounded by inflammation and fibrosis and blood vessels (HE, 20×). c: Tumorcells show with increased Ki67 proliferation index (IHC Ki67, 20×). d: Tumorcells show positive nuclear expression for p63 (IHC p63, 20×).

Table 1
EMA-EP scheme of therapy (modified after Cyriac, 2011) and Alazzam et al. 2016 (da Silva et al., 2021; Merck & Co, 2023).

EMA-EP (etoposide + methotrexate + actinomycin D → etoposide + cisplatin) interval of therapy: q3w duration of therapy: 2 cycles beyond normalization of hCG levels		
etoposide	100 mg iv	d 1, 2
methotrexate	100 mg/kg of body weight iv as bolus	d 1
actinomycin D	0,5 mg iv	d 1, 2
etoposide	100 mg/m^2 iv	d 8
cisplatin	50 mg/m^2 iv	d 8

4. Conclusions

Epithelial trophoblastic tumor is a rare type of gestational trophoblastic neoplasia. Clinical features vary. The diagnosis of ETT is mostly possible using immunohistochemistry (Fig. 5). Increased diagnosis accuracy helps clinicians in opting for the most appropriate disease management approach. Surgery remains the mainstay of treatment in ETT. For patients with advanced disease or for those with poor prognostic indicators, a multimodal treatment of surgery and chemotherapy is recommended. Pembrolizumab is an option for treatment for patients with significant PD-L1 positivity.

Informed consent statement

Written informed consent was obtained from the patient for publication of this case report and the accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Authors contribution

MH, AKV and WM had the idea of publishing this case. MS has seen the patient in the first place. SJ provided histopathology images. MH took the lead in writing the manuscript, supported by AKV and MW. MJS provided critical feedback and helped to shape the manuscript. MW and TF supervised the project.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2023.101281.

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