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Case report

Placental-site trophoblastic tumor with bone metastasis: A diagnostic and therapeutic challenge

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ABSTRACT

Placental-site trophoblastic tumor (PSTT) is a rare pathological entity included in the spectrum of gestational trophoblastic neoplasia (GTN). It is a neoplasia with metastatic potential that, once metastasized, has poor prognosis because the tumor tends to be less sensitive to chemotherapy. We present a rare case of gestational trophoblastic neoplasia, in which hysterectomy for persistent gestational trophoblastic disease after hydatidiform mole, revealed a primary PSTT in the uterus. Subsequently, a slight persistent elevation of the beta fraction of human chorionic gonadotropin hormone (B-hCG) during follow-up revealed the presence of bone metastases. This location is not usual from this tumor, being even more rare the case of PSTT with isolated bone metastases. Metastasic foci were only identified with PET-CT since the usual diagnostic resources were not able to do it. Finally, it is also remarkable in our case that the treatment required the confluence of chemotherapy together with immunotherapy to achieve a favorable response.

1. Background

Gestational trophoblastic disease (GTD) encompasses a group of low-incidence entities such as hydatidiform mole (complete or partial) (80 % of cases), invasive mole (15 %), and gestational trophoblastic neoplasia (5 %). The latter can be diagnosed on the basis of persistent active trophoblastic tissue, which is typically identified by ongoing detection of B-hCG during the follow-up. Choriocarcinoma, PSTT, invasive mole and epithelioid trophoblastic tumor are all under the umbrella of GTN (Coronado et al., 2020).

PSTT is an uncommon GTN that originates in the intermediate trophoblast, with a more latent clinical course and only discrete elevations of B-hGC, unlike the more common trophoblastic neoplasm (choriocarcinoma). It is a slow-growing tumor that may appear months to years after gestational history. It accounts 0.2 % of trophoblastic diseases with an incidence about 1/100,000 births (Santaballa et al., 2018; Lukinovic et al., 2022) and with an age range of presentation from 20 to 63 years (Hui, 2019; Feng et al., 2019; National Cancer Institute, 2022). Its spread is lymphatic with a reported metastasic incidence of 5–15 %, and the most common foci are located in lung, liver, abdominal cavity and brain (Coronado et al., 2020; Santaballa et al., 2018).

Patients with GTN must be classified by FIGO-staging and besides by FIGO/WHO prognostic scoring system for GTN as low or high-risk. However, the latter does not correlate well with outcomes in PSTT and ETT due to less hCG production and different clinical behavior and response to chemotherapy, although it may be of value in guiding management (Santaballa et al., 2018; Lukinovic et al., 2022).

PSTT is generally less chemo-sensitive than other GTN and the treatment of choice in stage I (confined to uterus) is total abdominal hysterectomy with over 80 % cure rate. Pelvic and retroperitoneal lymphadenectomy is suggested, but some authors support this approach only when myometrial infiltration is greater than 50 %, and/or there are suspicious nodes. Besides, it is still unknown whether this procedure could influence overall survival (National Cancer Institute, 2022; De Nolaa et al., 2018; Gadducci et al., 2019).

Since PSTT is not very sensitive to single-agent chemotherapy with methotrexate or actinomycin D (unlike choriocarcinoma), patients with advanced disease (stage II-IV) or high-risk patients based on FIGO criteria (Table 1.), surgery might include lymphadenectomy and should be followed by adjuvant multi-agent chemotherapy (Coronado et al.,

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2020; Santaballa et al., 2018; Feng et al., 2019). The most widely used regimen is EMA-CO (etoposide-methotrexate-actinomycin D-cyclophosphamide-vincristine), but approximately 20 % of these patients suffer recurrences. For those women with high or very high-risk based on FIGO criteria, or with recurrence after EMA-CO (20 %), other regimens include PE/EMA (etoposide-cisplatin/etoposide-methotrexate-actinomycin D) or TE/TP (taxol-etoposide/taxol-cisplatin) (Santaballa et al., 2018; National Cancer Institute, 2022; Clark et al., 2021; Albright et al., 2023).

The PSTT specific mortality rate is estimated higher than for other GTN, due to its unpredictable biological behaviour and its limited response to chemotherapy (Feng et al., 2019). A retrospective study with 62 PSTT cases reported a 10-year survival rate of 90 % (range 77–100 %) in stage I patients treated with surgery, and 52 % in stage II and 49 % in stage III and IV, all those treated with surgery and chemotherapy (Hancock and Tidy, 2021).

The postulated pathogenesis for PSTT is that persistent small nodules of trophoblastic tissue in the myometrium, which are not reabsorbed, can proliferate transforming into atypical cells. This could be due to alterations in intracellular or intercellular signaling pathways, such as ERK, MAPK, mTOR, and/or transcription factors NF-kB, Kiss-1 and GATA3 (Hui, 2019; Feng et al., 2019; Hancock and Tidy, 2021).

Macroscopically, it may present as a well-circumscribed tumor, with focal areas of necrosis and/or hemorrhage. Deep invasion is common and could invade the perimetrium and parauterine tissues. Microscopically, neoplastic intermediate trophoblastic tissue is detected (mononucleated cells with variable shape, with an irregular nuclear membrane and thick, granular chromatin) infiltrating the myometrium, typically replacing the wall of the vessels with fibrinoid deposits. (Zampacorta et al., 2023). Immunohistochemically, it is characterized by the presence of hPL, MUC-4, HSD3B1, HLA-G, CD10, and Mel-CAM (CD146), cytokeratins (AE1/AE3 and 18) and Ki 67 (10–30 %) (Hancock and Tidy, 2021).

2. Case presentation

A 52-year-old patient presented with light spotting after a 3-months history of amenorrhea, and medical history was unremarkable. She had

Table 1
Clinical staging (FIGO 2000) and risk staging score of GTN (FIGO-WHO 2015). The items marked with ★ were present in our patient.

Clinical staging of GTN (FIGO 2000)

Stage I	Disease is only in the uterus
Stage II	GTD extends outside the uterus but is limited to the genital structures
Stage III	GTD extends to the lungs and may or may not involve the genital tract
Stage IV	GTD has extended to other distant sites, called metastasis

Risk staging score of GTN (FIGO-WHO 2015)

Risk Factor	0	1	2	4
Age (years)	<40	≥40 ★	–	–
Antecedent pregnancy	Mole ★	Abortion	Term	–
Interval (months)	4	4 to 6	7 to 12 ★	>12
Pretreatment serum hCG (mIU/mL)	$<10^3$ ★	10^3 to 10^4	10^4 to 10^5	$>10^5$
Largest tumor (including uterus)	<3 cm	3 to 4 cm ★	≥5 cm	–
Site of metastases	Lung	Spleen, kidney	GI tract	Brain, liver
Number of metastases	– ★	1 to 4	5 to 8	>8
Prior failed chemotherapy	–	–	Single drug	≥2 drugs

two previous uncomplicated deliveries and the last gestation was a miscarriage nine years before. Her menstrual period was regular and normal, and was using condoms as contraceptive method but irregularly.

Clinical examination was normal but transvaginal ultrasound showed a "snowstorm endometrium" of 45 mm (Fig. 1), with poor visualization of the fundus and posterior myometrial wall, and normal ovaries.

She had a positive urine pregnancy test and subsequent serum B-hCG was elevated to 614.256 UI/mL. Molar gestation was suspected, uterine aspiration-curettage was performed, and final pathology confirmed complete hydatidiform mole. Her remaining blood work and chest x-ray were all normal.

Her B-hCG was monitored closely and resolved to undetectable two months after curettage, with restart of regular menstrual periods. She continued with condoms because did not accept other methods.

Five months after her negative testing, her B-hCG was again positive, and progressively increased (from negative to 35 mIU/mL at 5th month, 64 mIU/mL three weeks later, and 97 mIU/mL after another week), being the patient asymptomatic. Clinical exam and pelvic ultrasound were completely normal. Subsequently, a CT scan was performed, which revealed a discreetly intramural hypodense lesion of 3.1 cm in the anterior myometrial wall (Fig. 2), which was reported as a fibroid. This diagnosis was ruled out due to the history of mole and the elevation of B-hCG.

Thus, we made a clinical diagnosis of GTN, at stage I (FIGO) and low risk (4 points by FIGO/WHO scale, table 1). At this stage, the indicated treatment is single-agent chemotherapy or surgical treatment for women without desire for childbearing, so, total laparoscopic hysterectomy and bilateral salpingoophorectomy were performed, without lymphadenectomy because there was not suspicious lymph nodes on CT scan.

Finally, pathology confirmed PSTT, with a tumor size of 3.5 cm, confined to the uterus with tumor-free surgical margins. No vascular invasion was identified, but some areas of hemorrhagic necrosis, proliferative activity of 15 mitosis/10 CGA were present (Fig. 3). Immunohistochemical study revealed: positive cytokeratin AE1-AE3 and E-Cadherine; focally positive EMA, Inhibin, B-hCG, and PLAP; and negative Vimentine, Actin, and P53. The MIB-1/Ki-67 was 20 %. DNA repair proteins (MSH6, MLH1, MSH2 and PMS2) conserved expression. PDL-1 was positive in high expression greater than 0.50 %, and the presence of intramural T lymphocytes was 10 %.

The strict follow-up confirmed normalization of B-hCG one month after surgery, but a new elevation of B-hCG was observed 7 months later (from negative to 20 mIU/mL), with very slow increase every two–three weeks (25, 33 mIU/mL) to 43 mIU/mL two months later. The patient remained asymptomatic and with completely normal clinical exam. New extension studies were carried out and total body CT scan did not find alterations and MRI showed normal brain. In spite of this, a PET-CT study was recommended and then two hypermetabolic lesions were detected in the seventh right costal arch and the tip of the right scapula, both suggestive of bone metastases (Fig. 4).

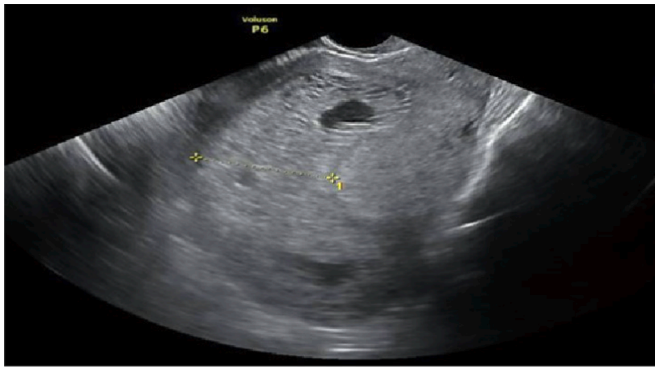

Fig. 1. Transvaginal ultrasound image in the gynecology outpatient clinic. A snowstorm endometrium of 45 mm is observed.

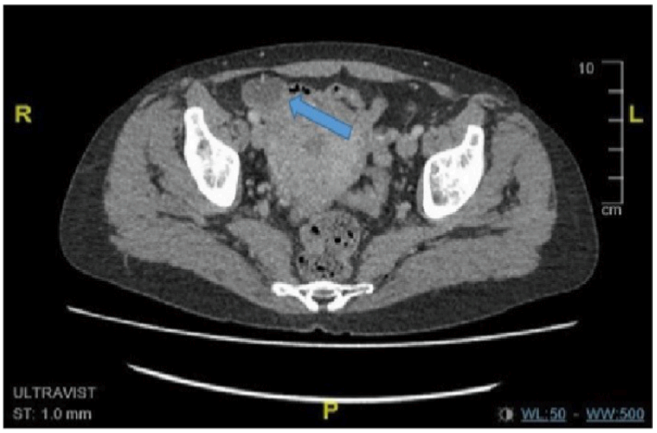

Fig. 2. Pelvic CT image. A hypodense lesion is shown in the anterior face of the uterus (arrow).

PSTT relapse was then clinically diagnosed and chemotherapy for high-risk-patients (EMA-CO) was started with a poor response after two cycles of chemotherapy (B-hCG weekly was 42–49-59 mIU/mL), and for this reason was decided to associate immunotherapy (pembrolizumab) with a plan of maintaining it until 6 months after normalization of B-hCG. The B-hCG levels achieved a favourable trend with negativization at 3 months. So, the patient received chemotherapy scheme for 7 cycles (every 2 weeks): 5 cycles to B-hCG normalization and 2 additional cycles post-normalization, and pembrolizumab (2 mg/Kg every 3 weeks) for 10 cycles (6 after normalization of B-hCG), with complete metabolic and biological response and total remission of bone metastases at the PET-TAC at the end of treatment. The patient is now without evidence of relapse (clinical, analytical nor PET-TAC) with a disease-free interval of two years at the moment.

3. Discussion

We describe a case of GTN, which was diagnosed approximately 7 months after surgical treatment for hydatidiform mole. Around 50 % of GTN appear after a previous molar gestation as in our case, 25 % after an abortion and 25 % after a normal gestation. Women at the extremes of reproductive life are at increased risk for mole and GTN, but the risk of developing GTN is especially higher in those older than 45 years, with very elevated B-hCG values (>100.00 IU/L) at diagnosis, previous molar pregnancy (principally complete mole, that becomes GTN in 15–20 % of the cases vs 0.5–2 % in the partial mole), all these factors present in our patient. And also, but not present in our case, uterine size greater than expected for gestational age, theca lutein cysts > 8 cm and hyperechogenic lesions in the myometrium with increased vascularity (Coronado et al., 2020; Santaballa et al., 2018; Lukinovic et al., 2022).

The usual clinical presentation of PSTT is abnormal uterine bleeding and/or amenorrhea, although less frequently with abdominal pain or symptoms that may also occur due to local extension of the tumor or distant metastasis. Other manifestations such as postpartum hemorrhage, nephrotic syndrome, galactorrhea, virilization, polycythemia and skin lesions have been also described (Gadducci et al., 2019). It is a tumor of slow growth with, in general, slight elevation of B-hCG (as was our case) or even absent. PSTT diagnosis is complicated due to lack of sensitive and specific tumor markers; the literature describes the elevation of placental lactogen hormone as a characteristic element, but this is not a sufficiently sensitive and reproducible diagnostic marker [5]. Even if there are no definitive immunohistochemical markers, the determination of human chorionic gonadotropin (B-hCG), human placental lactogen hormone (hPL) and cytokeratins are used to clarify

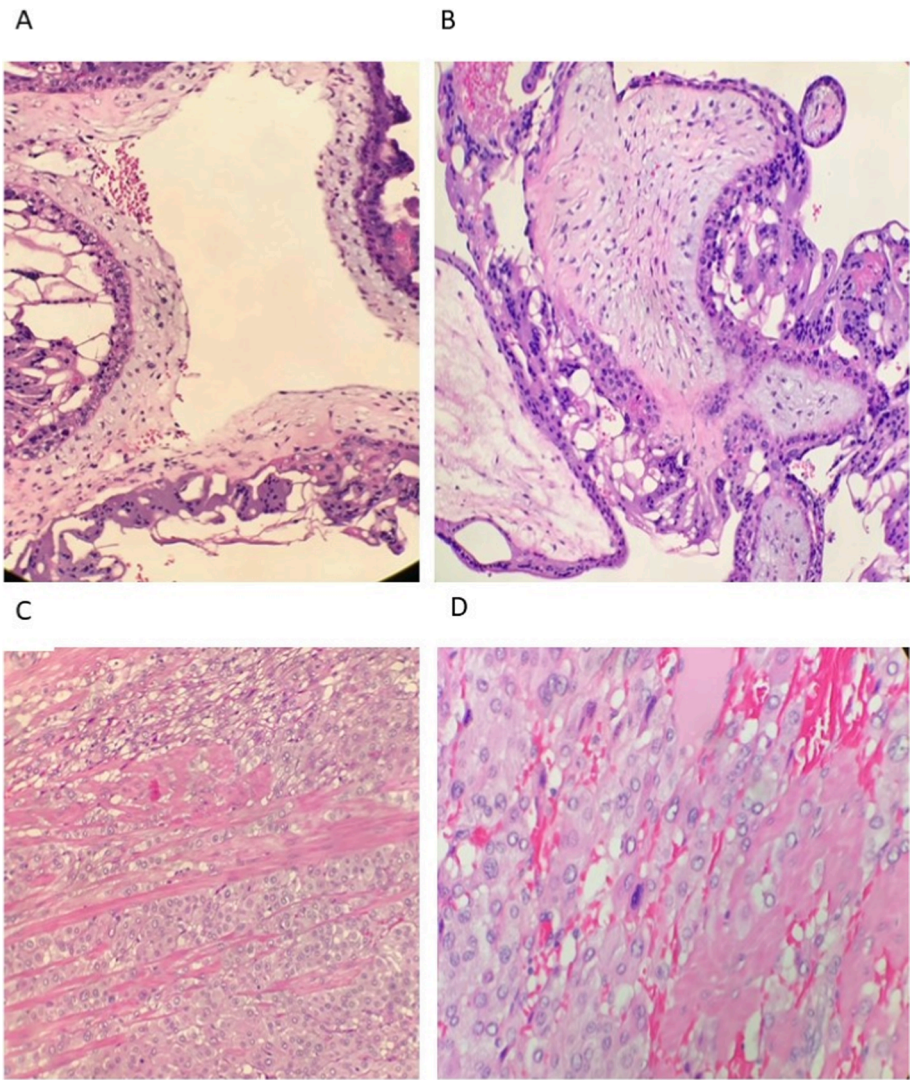

Fig. 3. . **A: Hydatidiform mole** with chorionic villi with hydropic degeneration and trophoblastic hyperplasia (cyto and syncytiotrophoblast) (HEx200); **B: PSTT**. There is a neoplastic proliferation of intermediate trophoblast at the placental site, without villi and without cytotrophoblast, with very occasional syncytiotrophoblastic plurinucleated cells; **C: PSTT:** Invasion of the myometrium by intermediate trophoblast (HEx200); **D: PSTT**. Cellularity with abundant eosinophilic cytoplasm and pleomorphic nuclei (HEx400).

the diagnosis (Hui, 2019; Clark et al., 2021). hCG and hPL are present in both the syncytiotrophoblast and intermediate trophoblast, but hCG is most strongly expressed in the first and hPL in the latter (Rhoton-Vlasak et al., 1998). PSTT have greater positivity to hLP and weak to hCG (as in our case), while in choriocarcinoma the opposite is observed. However, these markers are not useful for detecting differences between PSTT and exaggerated placental site reaction (a benign trophoblastic lesion, formerly called syncytial endometritis). But the number of mitosis by highly increased fields and anti-MIB1 antibodies might be used to establish the rate of Ki-67 proliferation, which only are altered in the PSTT (as in our case) and not in the exaggerated placental site reaction. To distinguish between PSTT and epithelioid Trophoblastic Tumor (ETT), p63 marker (a tumor suppressor from p53 family), hPL and vimentin are useful, showing PSTT positivity for hPL and negativity for p63 and vimentin (as we observed in our patient), being the opposite in ETT (Feng et al., 2019; Luiza et al., 2014).

This case that we report is very interesting due to the presence of isolated bone metastases, uncommon location in these tumors. We only have found in the literature a report from Japan of a 25-year-old patient with a simultaneous diagnosis of PSTT at uterus and right ovary coinciding with metastasis at the occipital subaponeurotic level, that was surgically resected and also received chemotherapy (Aoki et al., 2005). Afterwards, appeared cranial metastases in the left orbital bone and the parietal subaponeurotic level, with invasion of the underlying parietal bone and dura mater. She was then treated with radiotherapy and the patient died of multiple metastases in different organs. Another report described a case with an intramuscular mass superficial to the left frontal bone, but infiltrating it, in which histology was a mixture of choriocarcinoma and PSTT (Chatterjee et al., 2022).

Imaging studies (ultrasound, CT, and MRI) are useful to locate genital lesions and metastases as in other pathologies. Although ultrasound findings are not considered as a diagnostic criteria for PSTT according to FIGO, it is postulated that solid lesions with low blood flow (doppler) along with low levels of elevated serum B-hCG would be sufficient to diagnose PSTT (Albright et al., 2023; Yan et al., 2015, Santaballa et al., 2018). In our case, we were surprised by the detection by CT of the tumor, as it was not observed during prior ultrasounds, but we have found some other reports in which the lesions were not visualized on ultrasound (Gadducci et al., 2019). It could be due to intrinsic characteristics of the patient's tissular density or other factors. In any case, at the time of the possible fibroid diagnosis detected by CT, we suspected that it could be GTN due to the present low B-hCG levels.

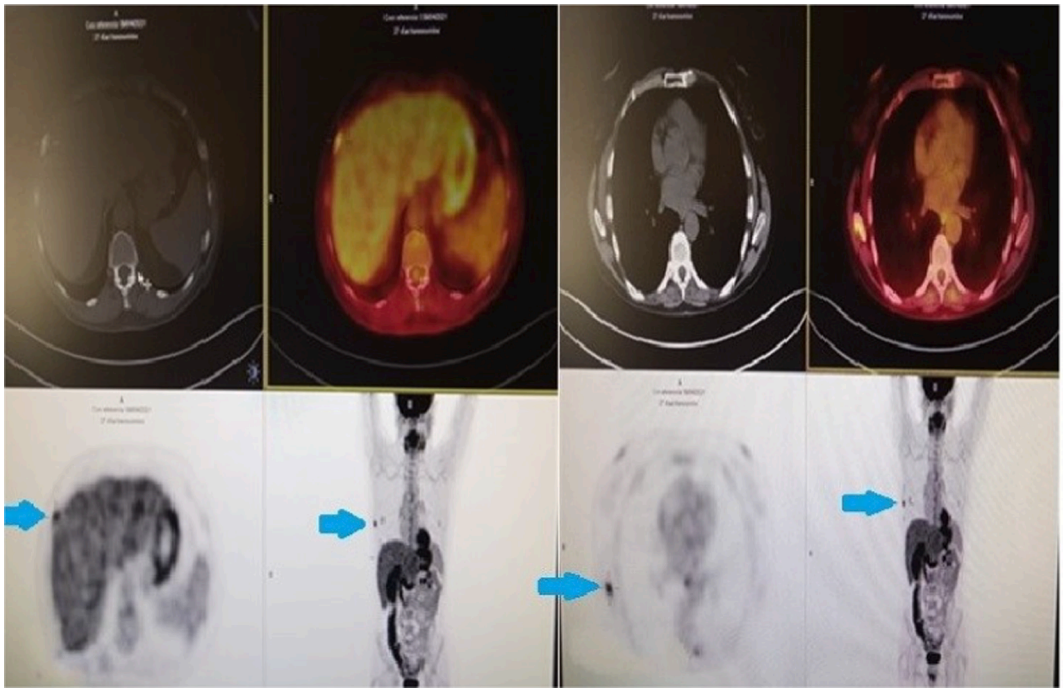

Fig. 4. PET/CT scan. Bone metastases in the seventh right costal arch and the right scapular tip are indicated by arrows.

Initial use of PET-CT is not recommended, since it has not shown to be superior to routine imaging tests, but it is believed that it has an important role in high-risk patients, in cases where there are diagnostic discrepancies, and also for monitoring of patients with recurrences and chemoresistance. This occurred in our case since there was a discrepancy between the persistence of slightly abnormal B-hCG levels and the absence of findings in usual imaging studies including CT. It was surprising that bone metastases in the rib and scapula were only detected by PET-CT and is another aspect of interest in the reporting of this case, since our approach that included PET-TC avoided an additional delay in the initiation of treatment. Another debatable question is wether or not a confirmatory biopsy of bone metastases is required. According to some authors, unlike what happens with other neoplasms, biopsy of metastatic lesions for histological confirmation is considered unnecessary for diagnosis and to allow start of appropriate treatment as soon as possible, as we did (Lukinovic et al., 2022).

The recent advances in immunotherapy after the introduction of immune checkpoint-inhibitors, have focused its target on PD1 (programmed-death-1). PD1 is a transmembrane receptor expressed on the surface of T and B lymphocytes, NK cells and antigen-presenting cells. After binding with their PD-L1 ligand, PD1/PD-L1 complex inhibits the lymphocyte T-activated production, taking place immunosuppression/immunotolerance which allows the tumor to evade the immune system, and thus achieve its expansion. Pembrolizumab and nivolumab are anti-PD1 monoclonal-antibodies, aimed at blocking the PD1 receptor on T-lymphocytes, thereby preventing binding to their ligand PD-L1, and avoiding the activation of the T-lymphocyte inhibitory pathway; that is, they promote the cytotoxicity of T-lymphocytes against the tumor cells. It is thought that, cause of the memory function of the immune system, once the PD-1 inhibitor works, patients will have a chance to achieve long-term cure. Pembrolizumab is well-tolerated with an acceptable toxicity profile (Feng et al., 2019; Clark et al., 2021; Ghorani et al., 2017; Choi et al., 2019).

Our patient's tumor was intensely expressing PD-L1 molecules, and was the reason why pembrolizumab was included in the treatment rapidly after an unfavourable course with the first two cycles of multiagent chemotherapy, and probably the cause of the good response observed when added.

The first report on the use of pembrolizumab to treat GTN was published in 2017 and described 4 patients (2 with choriocarcinoma, 1 with PSTT, and 1 with a mixed PSTT and ETT), with high-risk progressive disease after several lines of chemotherapy, and all received pembrolizumab (Ghorani et al., 2017). Three patients achieved a complete response and remained in remission. Unfortunately, one patient progressed and subsequently died from her disease. Since then, some other reports have been published about PD-1 agents use for the treatment of GTN, in cases with chemoresistance, relapse, or non-tolerance to chemotherapy (Choi et al., 2019; Baas et al., 2023). It has been generally used as monotherapy but, in our case, given the few reports of immunotherapy for PSTT at that time, the presence of infrequent bone metastases, and that its use was not approved for this entity (off-label use), we decided to introduce pembrolizumab added to chemotherapy. So, we do not know wether the effects had been the same avoiding chemotherapy.

In any case, both have been used in combination for other types of cancer (non-small cell lung cancer, metastatic triple-negative breast cancer, advanced endometrial cancer, etc.) with good results (Baas et al., 2023).

In our view, future research should clarify whether immunotherapy agents may have a role earlier in the course of the disease, their best use alone or in combination with chemotherapy, or at least whether combination therapy may result in a reduction in the duration of chemotherapy needed and thus potentially less toxicity.

In summary, we present a case of GTN derived from a complete molar gestation, in which total hysterectomy revealed to be a PSTT. Seven months after its negativization, a very slight persistent elevation of B-hCG required reevaluation and led to the diagnosis of bone metastases only detected by PET-CT. Treatment with multiagent chemotherapy had a poor response and addition of immunotherapy (pembrolizumab) achieved excellent results. New immunotherapy and chemotherapy regimens are being tested and may open new horizons in the future treatment of GTN.

4. Consent

The study was carried out in accordance with the guidelines of the

Declaration of Helsinki. The patient's informed consent was obtained before the publication of this study, and it was approved by the Ethics Committee of San Juan University Hospital of Alicante.

CRediT authorship contribution statement

Alfredo Ramirez-Espinoza: Conceptualization, Visualization, Investigation, Writing – original draft, Writing – review & editing. **Irene Vela:** Conceptualization, Visualization, Investigation. **Laura Server:** Conceptualization, Visualization. **Juan M. Rodriguez-Celdrán:** Conceptualization, Visualization, Investigation. **María T. Chuliá:** Visualization. **Francisco Quereda:** Conceptualization, Writing – review & editing, Supervision.

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.

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