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A case of non-mosaic 47, XXX presenting as placental site trophoblastic, tumor secondary to partial mola

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ABSTRACT

Background: Placental trophoblastic tumor is a very rare form of gestational trophoblastic disease (GTD). There are some case reports in which some tumors have been associated with Trisomy X. Objective: is to inform and suggest a possible management for similar cases in a future. Material and methods: A systematic search was carried out in the bibliography and subsequent surgery. Case: Patient with karyotype 47, XXX and ETG. The associated phenotype consisted of a prominent forehead, epicanthal fold in both eyes, micrognathia with dental crowding. The biomarkers CKAE1/AE3, Ki75 were positive. The pathology report suggests an incomplete atypical mole. The final diagnosis was trophoblastic tumor of the placental site. Conclusion: We recommend hysterectomy with preservation of the ovaries if they are not involved.

***Keywords*:** *gestational trophoblastic disease; hydatidiform mole; trisomy; trophoblasts; trophoblastic neoplasms; hysterectomy.*

[1] Autor Principal

Un caso 47 XXX sin mosaico que se presenta con un tumor trofoblástico del sitio placentario secundario a mola parcial

RESUMEN

Antecedentes: El tumor trofoblástico placentario es una forma muy rara de enfermedad trofoblástica gestacional (ETG). Existen algunos informes de casos en los que algunos tumores se han asociado a la Trisomía X. Objetivo: es informar y sugerir un posible manejo para casos similares en un futuro. Material y métodos: Se realizó una búsqueda sistemática en la bibliografía y posterior cirugía. Caso: Paciente con cariotipo 47, XXX y ETG. El fenotipo asociado consistía en frente prominente, pliegue epicántico en ambos ojos, micrognatia con apiñamiento dental. Los biomarcadores CKAE1/AE3, Ki75 fueron positivos. El informe patológico sugiere una mola atípica incompleta. El diagnóstico final fue de tumor trofoblástico de sitio placentario. Conclusiones: Se recomienda la histerectomía con preservación de los ovarios si no están comprometidos.

Palabras clave: *enfermedad trofoblástica gestacional; mola hidatiforme; trisomía; trofoblastos; neoplasias trofoblásticas; histerectomía.*

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INTRODUCTION

Trisomy X (47, XXX) is a sex chromosome aneuploidy condition first described by Jacobs [1] in 1959. In 30% of cases an advanced maternal age is associated, along with greater probability of non-disjunction events in meiosis[2].

In girls with trisomy X, two of the three chromosomes are inactivated, and mosaicism occurs in the tissues, and this could be one of the possible explanations for the phenotypic different findings 2 such as learning disorders, language, development, motor delay, psychological problems, and kidney anomalies.[3,4]

Partial mola (PM) characteristically include the presence of two types of villi (one large, irregular, and hydropic, and the other small, fibrous, and immature), cisterns on some of the larger villi, highly irregular villi with scalloped edges, and usually mild to moderate trophoblastic hyperplasia. circumferential. There may be development of fetal structures.

Monochemotherapy with methotrexate is recommended as management in stage I gestational trophoblastic neoplasia (GTN, High evidence/Strong recommendation). Hysterectomy may be considered as an alternative to chemotherapy in selected cases when there is localized disease in the uterus and no desire to preserve fertility, good initial response to the decrease in hCG levels, but followed by stabilization or progressive or rapid elevation of new appearance, or poor response to decreased hCG levels.

Placental-site trophoblastic tumor (PSTT) arises from intermediate trophoblast (extravillous trophoblast), unlike choriocarcinoma, which arises from villous trophoblast. [5] The term “intermediate” trophoblast is commonly used to represent all types of extravillous trophoblast (Table 1). Scully evaluated the morphological aspects and malignant potential of the condition in 1981, naming it PSTT [6] but it had already been described since 1976 by Kurman, as syncytial endometritis, and who called it trophoblastic pseudotumor [7]

PSTT shows high invasion and deep infiltration into the myometrium and can penetrate the uterine wall. PSTT generally lacks extensive bleeding, although vascular involvement is common. The histologic morphology is often equivocal, and diagnosis depends on immunohistochemical staining. The

predominance of cytotrophoblastic cells is characteristic, and in immunohistochemistry many prolactin-producing cells and few gonadotropin-producing cells are found, for which the production of sub β hCG is variable or absent. It tends to remain confined to the uterus, with metastases appearing late in its evolution.

The treatment of these tumors is surgical, and Hysterectomy is the standard treatment for PSTT limited to the uterus. These tumors are relatively insensitive to chemotherapy and surgery to remove tumors have proven to be curative if chemoresistant.

Hereby, we report one of such cases.

CASE

Patient with a personal history of learning delay since childhood and with a family history of Diabetes Mellitus and Arterial Hypertension. Patient with 23 years old and personal history: menarche 17 years old, irregular menstrual cycles at a rate of 60-90/2-4 with days, dysmenorrheic bleeding, BASL: 17 years old, NOSP: 2, denies use of family planning methods, G1, date of last menstrual period: March 26, 2022: Pregnancy of 6 weeks of gestation. On physical examination there was comprehension problem, head with prominent forehead, epicanthic fold of the external angle of both eyes (figure 1), micrognathia with dental overcrowding, decreased oral opening, interincisors distance class II (3 cm), palatine mesh class III, Bellhouse Dore grade III, elongated and slender neck of 29 cm in diameter, cylindrical thorax, globose abdomen in hypogastrium at the expense of uterus 8 cm below the umbilical scar, integral limbs, and arachnodactyly.

Genitals corroborated as Tanner 3. Examination found a short vagina of approximately 3 cm, central cervix, lateralized to the left, of approximately 1 centimeter, closed, formed, finding uterus of approximately 14 centimeters by indirect hysterometry.

Among the complementary studies, there is evidence of elevation of HCG hormone (figure 2) and computed axial tomography of the abdomen with findings of well-defined 6 mm parapyelic cyst in right kidney Bosniak I and report of karyotype with 47 XXX interpreted as Trisomy X (figure 3).

Pathology: biopsy confirmed as a partial mole, surgical pathology reported arcuate uterus as well as a trophoblastic tumor of the placental site, confirmed by immunohistochemistry, probably the first reported case showing these findings. There was also found, within the PM, syncytotrophoblast

hyperplasia with chorionic villus edema, an effect described in moles many years ago but never reported as a histological phenomenon typical of moles among patients affected by mono-trisomies, what we just named Tienda-Estrada phenomenon [8] (figure 4)

MATERIAL AND METHODS

A systematic search was carried out in the bibliography. Given the rarity of these pathologies presented together, the recommendations for management, treatment and follow-up are null and there is no history of it, for which the objective of this article is to inform and suggest a possible management for similar cases in a future, trying to answer the question: Which would be most appropriate treatment, including morbimortality of the patients with these pathologies together.

Ethical aspects

An inter-institutional emergency meeting on ethical issues was held with the medical oncology, surgical oncology, and gynecology services, given the patient's age, the importance of the pathologies and looking after the patient's lack of desire to have children. The probable treatments and prognostics were informed to the patient and her couple, taking the final option of performing hysterectomy and subsequent follow-up with HCG.

DISCUSSION

Trisomy X presents a lot of phenotypic variability, from practically normality to severe affectations of the neurological sphere and other systems as we found in our patient[4.]

Tumors that have been reported in patients with trisomy X include the following: Ewing sarcoma (1999), Gastric non-Hodgkin lymphoma (2006), Neuroblastoma (2003), fibrous dysplasia (2019), and Dysgerminoma of the ovary (1995) (2021), among others [9-10].

PSTT is a rare tumor; the incidence of PSTT is approximately 1/100,000 of all pregnancies and approximately 1-2% of all GTNs, while its mortality is 25%. 10 As of 2015, almost 300 cases of PSTT have been reported worldwide. [11]

PSTT might follow any type of pregnancy event, not infrequently becoming clinically apparent even years later, and there is great variability in its malignant aggressiveness. [5] Approximately 60% will present after a term pregnancy. The remaining 40% will present after a mole or an abortion. Baergen et

al. found a history of full-term pregnancy in 57% of cases, miscarriage in 17%, and molar pregnancies in 26% of cases. [12]

While most NTGs are exquisitely amenable to chemotherapy, PSTT is relatively chemoresistant. Because hysterectomy is necessary for proper treatment, it is imperative that PSTTs be diagnosed correctly.

Histologically, PSTTs are monophasic proliferations of mostly medium to large mononuclear extravillous trophoblasts, although multinucleated extravillous trophoblasts may also be present. Extravillous trophoblast cells show marked nuclear atypia, prominent nucleoli, eosinophilic to clear cytoplasm, scattered mitoses, and occasional intranuclear inclusions. Characteristically, tumor cells permeate the myometrium, with prominent vasocentric proliferation and intravascular spread. High mitotic activity (>4 mitoses per 10 high-power fields) may indicate a poor prognosis. [13]

The syncytiotrophoblast expresses cytokeratin, human chorionic gonadotropin (B-hCG), human placental lactogen (hPL) and placental alkaline phosphatase (PLAP) as well as alpha-inhibin. In contrast, the intermediate trophoblast of the placental implantation site generally expresses the same antigens, although to a lesser extent, and instead expresses epithelial membrane antigen (EMA) and also alpha-inhibin. Tumor cells usually have a high level of expression of Ki-67 (about 10%-15%).

Immunohistochemical results for the PSTT: Antigen: CK (+++); hPL (+++); Ki67 (++); P53 (++); P63 (++); Calponin (++); HCG (+); PLAP (+); Vim (+); SMA (+); S-100 (+); Inhibin (-). (PLAP, placental alkaline phosphatase; hPL, human placental lactogen; SMA, smooth muscle actin) [14] (figure 5)

It is now accepted that placental-site trophoblastic tumors differ from other trophoblastic neoplasms in that the tumor load is not accurately correlated with the concentration of hCG, and that the tumor might be less sensitive to chemotherapy that is effective in the other types of trophoblastic neoplasia. [5]

The interval from the previous pregnancy to tumor development is usually less than 2 years, although PSTT has been reported almost two decades after the previous pregnancy. [15] PSTT is usually secondary to varieties of pregnancies and often follows full-term labor for a girl or after an abortion, molar pregnancy, or ectopic pregnancy. [16] PSTT has also been reported in association with a live twin pregnancy and was successfully resected during cesarean section. [17] Interestingly, PSTT can also

develop in patients with no history of pregnancy, and PSTT has been observed in the ovary of a young girl with isosexual precocious puberty [18] and in men. [19]

Metastases develop in 30% to 50% of PSTTs at presentation. 20,21 Recurrence occurs in more than 30% of cases.

The serum β-hCG level in 79% of the patients was below 1000 mIU/mL, 22 and below 400 mIU/mL in 97% of the patients. 23 The level of β-hCG in serum is not proportional to tumor burden 24 nor is it associated with malignant behavior. [20]

Histologic findings cannot distinguish benign or malignant features of PSTT. However, a high mitotic rate (greater than 10/10 hpf) and substantial hemorrhage and necrosis within the tumor are certainly indicative of malignancy.

Hysterectomy is recommended for women if it is not necessary to preserve fertility, as long as the disease is localized to the uterus. Furthermore, ovarian metastases are rare, and an oophorectomy cannot prevent postoperative extrauterine metastases or improve prognosis. Therefore, the ovaries and even fertility can be preserved in young women without ovarian metastases.

The type of antecedent pregnancy was normal term pregnancy in 7 (54%), elective or spontaneous abortion in 3 (23%), molar pregnancy in 2 (15%), and loss of the third trimester in 1 (8%). The median time from the last pregnancy to diagnosis was 13 months (range 0-240 months). Serum hCG levels at diagnosis ranged from 1 to 2606 mIU/mL (median 98 mIU/mL). [12]

Chen et al. found that among 20 patients with PSTT the history of pregnancy was term delivery in 88.2% and 1 miscarriage and 1 hydatidiform mole. [26]

Similarly, Baergen et al. reported a previous normal pregnancy rate of 57%, a miscarriage rate of 17%, and a hydatidiform mole of 26%. [13]

RESULTS

We present a case of 47, XXX female presenting with ultrasonography images showed normal external contour of uterus confirmed at laparotomy, which was successfully treated even with a dismal prognosis using simple and follow HCG.

CONCLUSIONS

In Gestational Trophoblastic Disease, patients with a poor prognosis like this patient, it is suggested to perform a simple hysterectomy to reach a cure, due to the aggressiveness of the tumor and resistance to other treatments, as well as rigorous monitoring of the quantification of the Gonadotropin Hormone Human Chorionic to assess follow-up on a weekly basis, for which this pilot care protocol is published for similar cases that may arise.

THANKS

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To Dr Sánchez for his support and guidance in this and in all my research.

REFERENCES

Jacobs, PatriciaA., Baikie, A. G., Court Brown, W. M., Macgregor, T. N., Maclean, N., & Harnden, D. G. (1959). EVIDENCE FOR THE EXISTENCE OF THE HUMAN “SUPER FEMALE.” The Lancet, 274(7100), 423–425. https://doi.org/10.1016/S0140-6736(59)90415-5

Hassold, T., Hall, H., & Hunt, P. (2007). The origin of human aneuploidy: where we have been, where we are going. Human Molecular Genetics, 16(R2), R203–R208. https://doi.org/10.1093/hmg/ddm243

Tartaglia, N. R., Howell, S., Sutherland, A., Wilson, R., & Wilson, L. (2010). A review of trisomy X (47,XXX). Orphanet Journal of Rare Diseases, 5(1), 8. https://doi.org/10.1186/1750-1172-5-8

Bender, B. G., Puck, M. H., Salbenblatt, J. A., & Robinson, A. (1990). Cognitive Development of Children with Sex Chromosome Abnormalities. In Psychoneuroendocrinology (pp. 138–163). Springer New York. https://doi.org/10.1007/978-1-4612-3306-0_10

Taylor, K., Bean, L. M., Anderson, K. M., Davis, M. A., McHale, M. T., Saenz, C. C., & Plaxe, S. C. (2016). A population-based study of rare malignant trophoblastic neoplasms: Epithelioid

trophoblastic tumor and placental site trophoblastic tumor. Gynecologic Oncology, 141, 105–106. https://doi.org/10.1016/j.ygyno.2016.04.286

Scully, R. E., & Young, R. H. (1981). Trophoblastic pseudotumor. The American Journal of Surgical Pathology, 5(1), 75–76. https://doi.org/10.1097/00000478-198101000-00010

Kurman, R. J., Scully, R. E., & Norris, H. J. (1976). Trophoblastic pseudotumor of the uterus.An exaggerated form of "syncytial endometritis" simulating a malignant tumor. Cancer, 38(3), 1214–1226. https://doi.org/10.1002/1097-0142(197609)38:3<1214::AID-CNCR2820380323>3.0.CO;2-J

Ezpeleta JM, López CA. Enfermedad trofoblástica gestacional Aspectos clínicos y morfológicos. Spain Journal of pathology. 2002; 35: 187-200. Corpus ID: 31997129. Available in: http://patologia.es/volumen35/vol35-num2/pdf%20patologia%2035-2/35-2-07.pdf

Lenroot, R. K., Blumenthal, J. D., Wallace, G. L., Clasen, L. S., Lee, N. R., & Giedd, J. N. (2014). A case-control study of brain structure and behavioral characteristics in 47,XXX syndrome. Genes, Brain and Behavior, 13(8), 841–849. https://doi.org/10.1111/gbb.12180

Wigby, K., D'Epagnier, C., Howell, S., Reicks, A., Wilson, R., Cordeiro, L., & Tartaglia, N. (2016). Expanding the phenotype of Triple X syndrome: A comparison of prenatal versus postnatal diagnosis. American Journal of Medical Genetics Part A, 170(11), 2870–2881. https://doi.org/10.1002/ajmg.a.37688

Luiza, J. W., Taylor, S. E., Gao, F. F., & Edwards, R. P. (2014). Placental site trophoblastic tumor: Immunohistochemistry algorithm key to diagnosis and review of literature. Gynecologic Oncology Case Reports, 7, 13–15. https://doi.org/10.1016/j.gynor.2013.11.001

Alexander, A. L., Strohl, A. E., Maniar, K. P., & Lurain, J. R. (2020). Placental site trophoblastic tumor: Successful treatment of 13 cases. Gynecologic Oncology Reports, 32, 100548. https://doi.org/10.1016/j.gore.2020.100548

Baergen, R. N., Rutgers, J. L., Young, R. H., Osann, K., & Scully, R. E. (2006). Placental site trophoblastic tumor: A study of 55 cases and review of the literature emphasizing factors of prognostic significance. Gynecologic Oncology, 100(3), 511–520. https://doi.org/10.1016/j.ygyno.2005.08.058

Zeng, X., Liu, X., Tian, Q., Xue, Y., & An, R. (2015). Placental site trophoblastic tumor: A case report and literature review. Intractable & Rare Diseases Research, 4(3), 147–151. https://doi.org/10.5582/irdr.2015.01013

NIGAM, S., SINGHAL, N., KUMARGUPTA, S., CHHABRA, D., & MANAKTALA, U. (2004). Placental site trophoblastic tumor in a postmenopausal female—A case report. Gynecologic Oncology, 93(2), 550–553. https://doi.org/10.1016/j.ygyno.2004.01.045

Küçük, Z., Ergün, Y., Işik, H., Kaya, F., Akgün, Y. A., & Çaydere, M. (2015). A rare case of uterine rupture due to a placental site trophoblastic tumour in the rudimentary horn. Journal of Obstetrics and Gynaecology, 35(1), 97–98. https://doi.org/10.3109/01443615.2014.940301

Liszka, L., Wilk, M., Wodolazski, A., Palen, P., & Sikora, J. (2009). Successful Treatment of Placental Site Trophoblastic Tumor in Twin Pregnancy without Hysterectomy. Tumori Journal, 95(1), 108–111. https://doi.org/10.1177/030089160909500120

Arroyo, M. R., Podda, A., Cao, D., & Rodriguez, M. M. (2009). Placental Site Trophoblastic Tumor in the Ovary of a Young Child with Isosexual Precocious Puberty. Pediatric and Developmental Pathology, 12(1), 73–76. https://doi.org/10.2350/08-05-0462.1

Suurmeijer, A. J. H., Gietema, J. A., & Hoekstra, H. J. (2004). Placental Site Trophoblastic Tumor in a Late Recurrence of a Nonseminomatous Germ Cell Tumor of the Testis. American Journal of Surgical Pathology, 28(6), 830–833. https://doi.org/10.1097/01.pas.0000126053.88174.b5

Feltmate, C. M., Genest, D. R., Wise, L., Bernstein, M. R., Goldstein, D. P., & Berkowitz, R. S. (2001). Placental Site Trophoblastic Tumor: A 17-Year Experience at the New England Trophoblastic Disease Center. Gynecologic Oncology, 82(3), 415–419. https://doi.org/10.1006/gyno.2001.6265

Chang, Y.-L., Chang, T.-C., Hsueh, S., Huang, K.-G., Wang, P.-N., Liu, H.-P., & Soong, Y.-K. (1999). Prognostic Factors and Treatment for Placental Site Trophoblastic Tumor—Report of 3 Cases and Analysis of 88 Cases. Gynecologic Oncology, 73(2), 216–222. https://doi.org/10.1006/gyno.1999.5344

Papadopoulos, A. J., Foskett, M., Seckl, M. J., McNeish, I., Paradinas, F. J., Rees, H., & Newlands, E. S. (2002). Twenty-five years' clinical experience with placental site trophoblastic tumors. The Journal of Reproductive Medicine, 47(6), 460–464.

HASSADIA, A., GILLESPIE, A., TIDY, J., EVERARDRGN, J., WELLS, M., COLEMAN, R., & HANCOCK, B. (2005). Placental site trophoblastic tumour: Clinical features and management. Gynecologic Oncology, 99(3), 603–607. https://doi.org/10.1016/j.ygyno.2005.06.054

Yalinkaya, A., Guzel, A. I., Kangal, K., Buyukbayram, H., & Firat, U. (2011). Two cases of placental site trophoblastic tumor. Taiwanese Journal of Obstetrics and Gynecology, 50(3), 372–374. https://doi.org/10.1016/j.tjog.2011.01.026

Saso, S., Haddad, J., Ellis, P., Lindsay, I., Sebire, N., McIndoe, A., Seckl, M., & Smith, J. (2012). Placental site trophoblastic tumours and the concept of fertility preservation. BJOG: An International Journal of Obstetrics & Gynaecology, 119(3), 369–374. https://doi.org/10.1111/j.1471-0528.2011.03230.x

Chen, Y., Zhang, X., & Xie, X. (2011). Clinical features of 17 cases of placental site trophoblastic tumor. International Journal of Gynecology & Obstetrics, 115(2), 204–205. https://doi.org/10.1016/j.ijgo.2011.06.008

ANEXOS

Tables and figures

Figure Legend: Patient phenotype showing characteristic facies. Front/Side

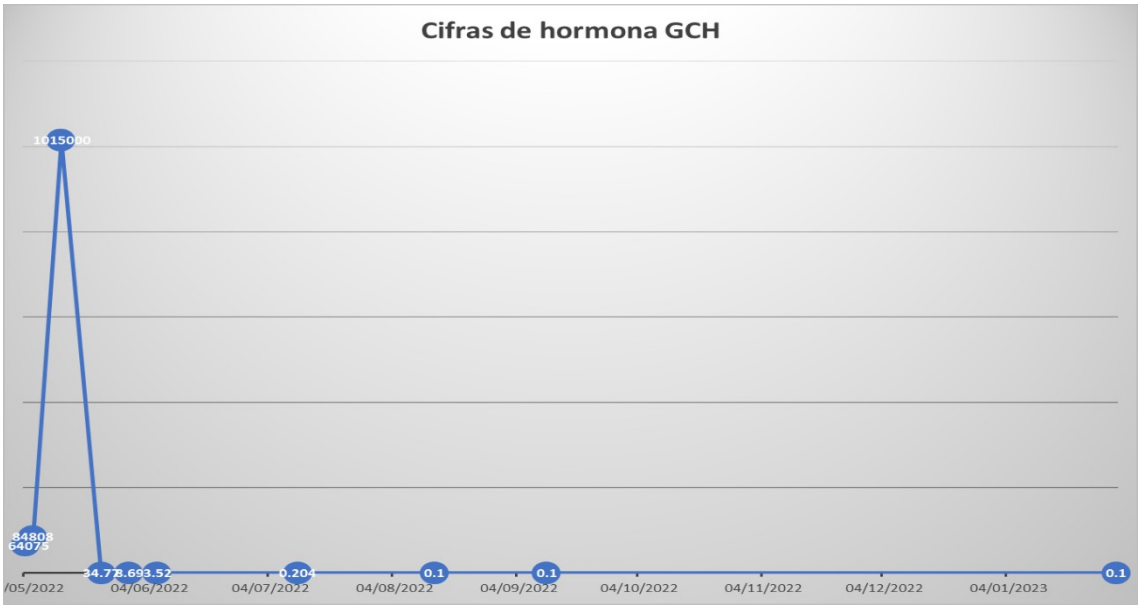

Figure Legend: Curve of serum beta HCG fraction control determination

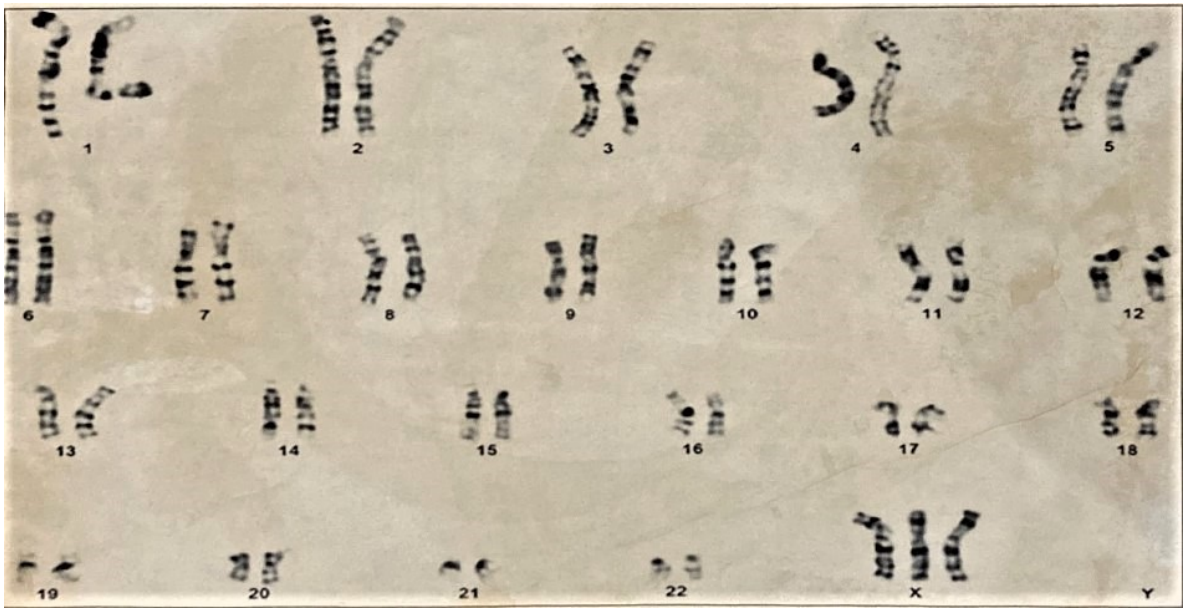

Figure Legend: Karyotype of the patient showing an extra copy of X chromosome, confirming the diagnosis.

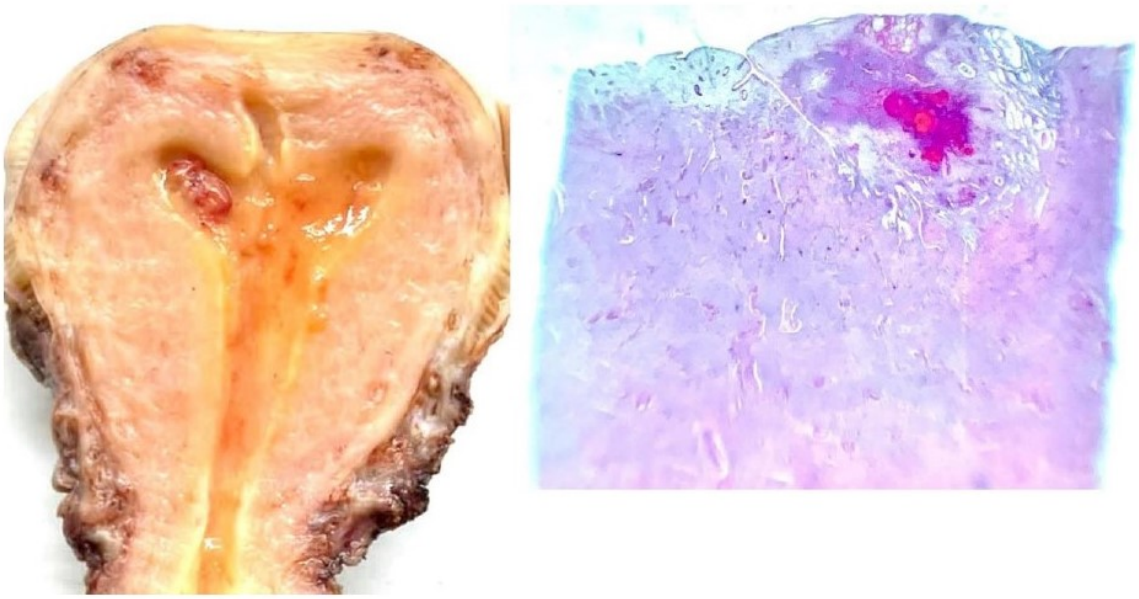

Figure Legend: Microphotographs showing the partial mole and placental site tumor (H&E, 100 X)

INMUNOHISTOCHEMISTRY:		
ANTIBODY	**RESULT**	**CONTROL**
CKAE1/AE3	POSITIVE	POSITIVE
HGC	NEGATIVE	POSITIVE
P16 PROTEIN	NEGATIVE	POSITIVE
P53 PROTEIN	NEGATIVE	POSITIVE
Ki67	POSITIVE REACTIV	POSITIVE
hPL	NEGATIVE	POSITIVE
p57 PROTEIN	NOT PERFORMED	N/A

Figure Legend: Immunohistochemical results

	Types	**Histological features**
A	Previllous trophoblast	Mononuclear trophoblast. It is not part of the villous lining. The pattern is dimorphic, similar to choriocarcinoma.
B	Cytotrophoblast	Small, polygonal or ovoid, uniform, mononucleate epithelial cells with clear, granular cytoplasm. Cell borders appear well defined. Conspicuous nucleoli and mitoses present.
C	Syncytiotrophoblast	Large cells that form masses with multiple nuclei and dense, vacuolated acidophilic cytoplasm. Nuclei dark and sometimes with pyknosis. There is no mitosis. Syncytial pattern.
D	Villous intermediate trophoblast	
	D1. Placental implantation site trophoblast	Its appearance varies depending on its location. In the endometrium: the cells are polygonal or round with abundant amphophilic cytoplasm similar to stromal cells with decidual reaction. In the myometrium (in decidua or around hypersecretory glands): the cells are spindle-shaped or ovoid with abundant and eosinophilic or amphophilic cytoplasm. Vacuoles can be seen and their nuclei exhibit granular chromatin and irregular contours. They may also be lobed or show pronounced indentations. The nucleoli are less prominent than those of the cytotrophoblast. They invade the wall of the spiral arterioles, replacing the muscle fibers but sparing the supporting structures.
	D2. Intermediate trophoblast of chorionic type	Uniform cells located lateral to the chorion of the fetal membranes, well cohesive with eosinophilic or clear (glycogen) cytoplasm. They are smaller than the trophoblast cells at the placental implantation site but larger than the cytotrophoblast cells. Occasionally they form islets or cords that insinuate themselves into the adjacent decidua.

Table 1. Types of trophoblast (histological features)