PATHOLOGICA 2023;115:111-116;
DOI: 10.32074/1591-951X-873

Case report

Placental site trophoblastic tumor (PSTT): a case report and review of the literature

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Summary

Placental site trophoblastic tumor (PSTT), also known as atypical choriocarcinoma, syncytioma, chorioepitheliosis or trophoblastic pseudotumor, is a rare gestational trophoblastic disease (0.25-5% of all trophoblastic tumors) and it is composed by neoplastic proliferation of intermediate trophoblasts at placental implantation site. It consists of aggregates or sheets of large, polyhedral to round, predominantly mononucleated cells with a characteristic vascular and myometrial invasion. Main differential diagnoses are gestational choriocarcinoma (GC) and epitelioid trophoblastic tumor (ETT). We present a case of PSTT in a 25-year-old woman. Neoplastic cells showed moderate/high nuclear pleomorphism, abundant amphophilic, eosinophilic and clear cytoplasm, numerous mitotic figures (10 mitoses/10 HPF), and myometrial invasion. Other features are necrosis, vascular invasion with replacement of myometrial vessels by tumor cells and hemorrhage. The patient showed typical low serum β-hCG levels and high serum humane placental lactogen (hPL) levels.

Key words: gestational trophoblastic disease, placental site trophoblastic tumor, Intermediate trophoblast, HPL

Received: April 15, 2023
Accepted: April 17, 2023

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How to cite this article: Zampacorta C, Pasciuto MP, Ferro B, et al. Placental site trophoblastic tumor (PSTT): a case report and review of the literature. Pathologica 2023;115:111-116. https://doi.org/10.32074/1591-951X-873

Case report

We report the case of a young Ukrainian woman, aged 24, without significant surgical history, who entered labor (gave birth to a child), after physiological pregnancy, in December 2020 and gave birth to a normal child with a weight of 3300 g. The patient was discharged from hospital in good health state. In January 2021, she started the assumption of progesterone-based contraceptive. In February 2021, the patient has presented to the emergency room for abnormal mild uterine bleeding and proliferative endometrium was diagnosed. This report was discordant with progesterone-based therapy, so the woman was tested for a new pregnancy resulting in a positive test. Since the patient kept having mild uterine bleeding, she was submitted for ultrasound that showed a heterogeneous images evocative of placental remnants, but a new abortion could not be excluded. At this point β-HCG levels were 198 mIU/ml. In March 2021, scraping biopsies were performed to settle the diagnostic query and multiple irregular fragments were analyzed. We observed a cellular proliferation of intermediate trophoblast cells, characterized by huge hyperchromatic nuclei, eosinophilic/amphophilic cytoplasms and occasional mitosis (1-2 mitosis in 10 HPF). These elements tend to separate myometrial fibers and infiltrate vessel walls causing breakage,

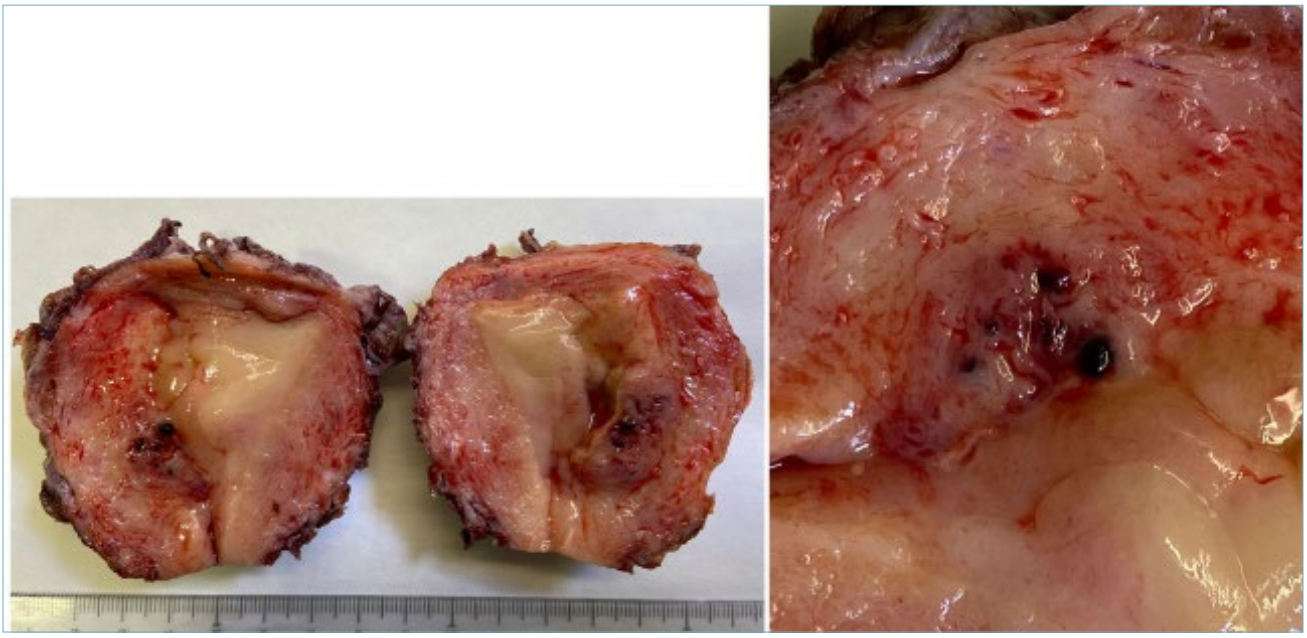

Figure 1. (A-B) Opened hysterectomy specimen containing placental site trophoblastic tumor (PSTT). The cut surface shows a pale-tan fleshy and hemorrhagic mass arising from the endomyometrium.

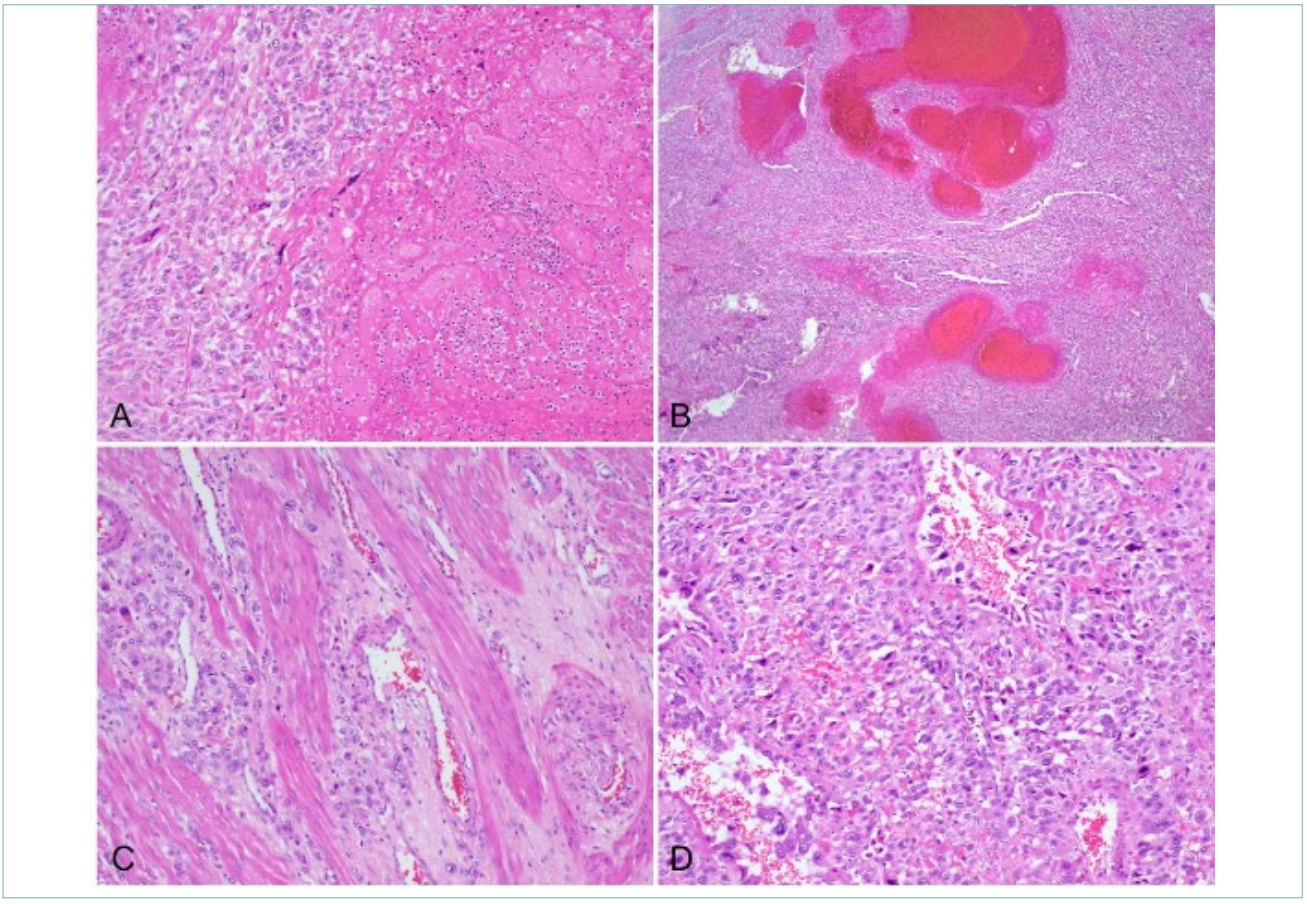

Figure 2. (A-D) Microscopic analysis reveals coagulative tumor cell necrosis (A), hemorrhagic areas (B), neoplastic intermediate trophoblasts infiltrating myometrium by separating individual muscle fibers (C) and vascular invasion with replacement of myometrial vessels by tumor cells (D).

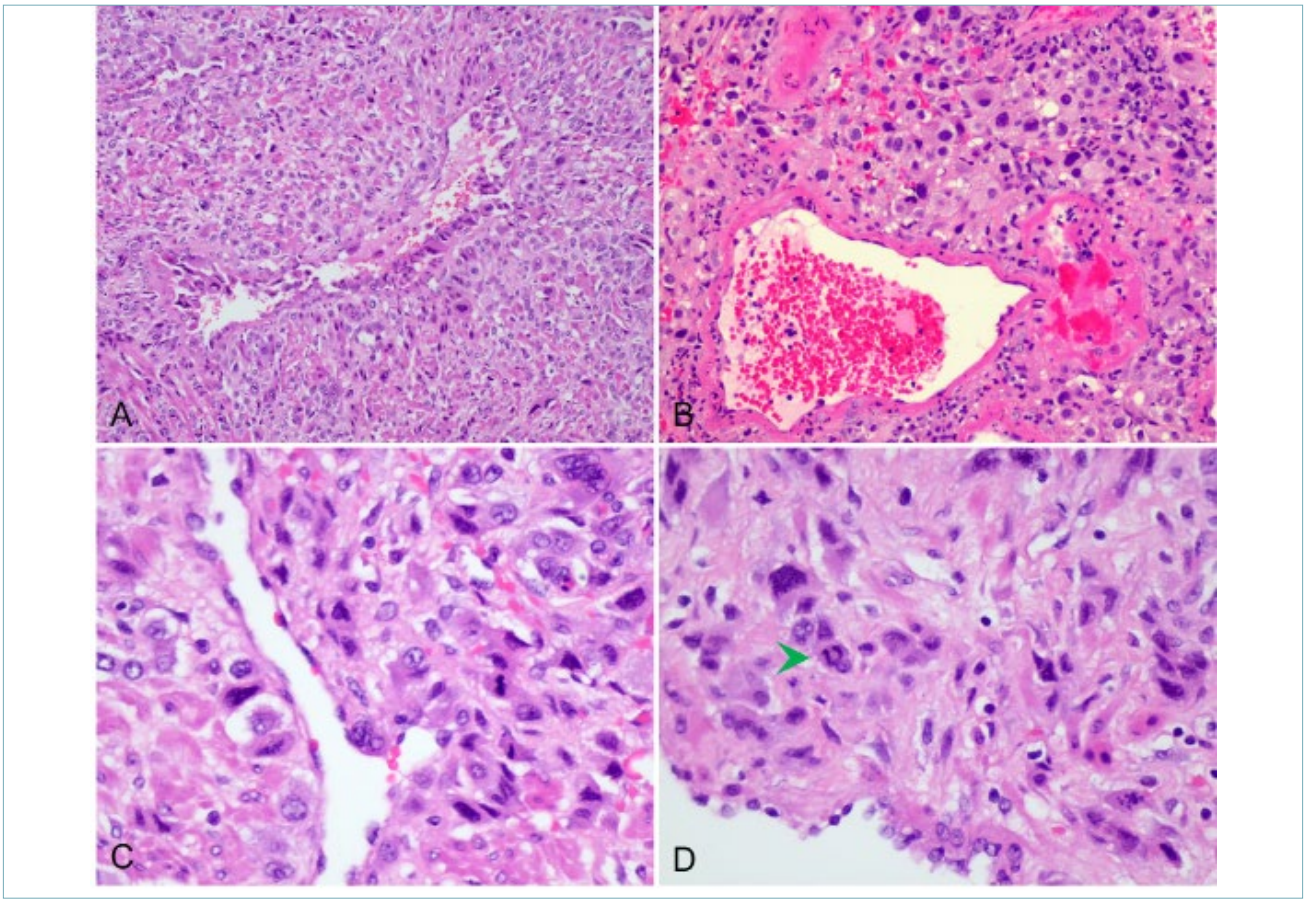

Figure 3. (A-D) Vascular invasion pattern recapitulates that of normal implantation trophoblast: the tumor cells replace the wall of myometrial vessels and these transformed blood vessels allowed PSTT diagnosis (A,B). At higher magnification, there is a cellular proliferation of neoplastic intermediate trophoblast cells, characterized by abundant amphophilic, eosinophilic or clear cytoplasm, variable nuclear size and shape with marked hypercromasia, nuclear grooves, pseudoinclusions, prominent nucleoli and several mitoses (green arrowhead) (C,D).

hemorrage and necrosis. No chorial villi were identified. β-HCG levels were now 105 mIU/ml and no hPL was detected in blood analysis.

We diagnosed these findings as PSTT, a malignant proliferation with good outcomes if hysterectomy is performed, even if recurrence is observed in 15% of cases, especially in the presence of extensive necrosis, several mitoses, clear cell differentiation, deep myometrial invasion, and Ki-67 expression > 50%.

The patient was submitted for MRI and no extrauterine lesions were detected.

Total hysterectomy and salpingectomy were performed, and at the opening, we observed a 20 mm irregular area at the left side extending to endometrium and internal myometrium (Fig. 1).

At histological examination, we observed a placental site trophoblastic tumor infiltrating myometrial wall for 10 mm. The proliferation was made of crowded and nested intermediate trophoblastic cells infiltrating blood vessels walls and determining noticeable vascular ectasia. Hemorrage and tumor necrosis were observed (Fig. 2). Neoplastic cells exhibited moderate to severe nuclear pleomorphism, eosinophilic/amophophilic cytoplasms, at times clear cell features, and several mitoses (10 mitoses in 10 HPF) (Fig. 3). Immunohistochemical profile showed a high proliferative index (Ki-67 > 30%) and diffuse and strong cytoplasm staining for hPL (Fig. 4). No chorial villi were observed. Five lymph nodes were examined with no pathological alterations.

After diagnosis, the woman was submitted for a first therapeutic line with metotrexate, with no clinical response. For the detection of lung nodules, new treatment was performed with four chemotherapy drugs

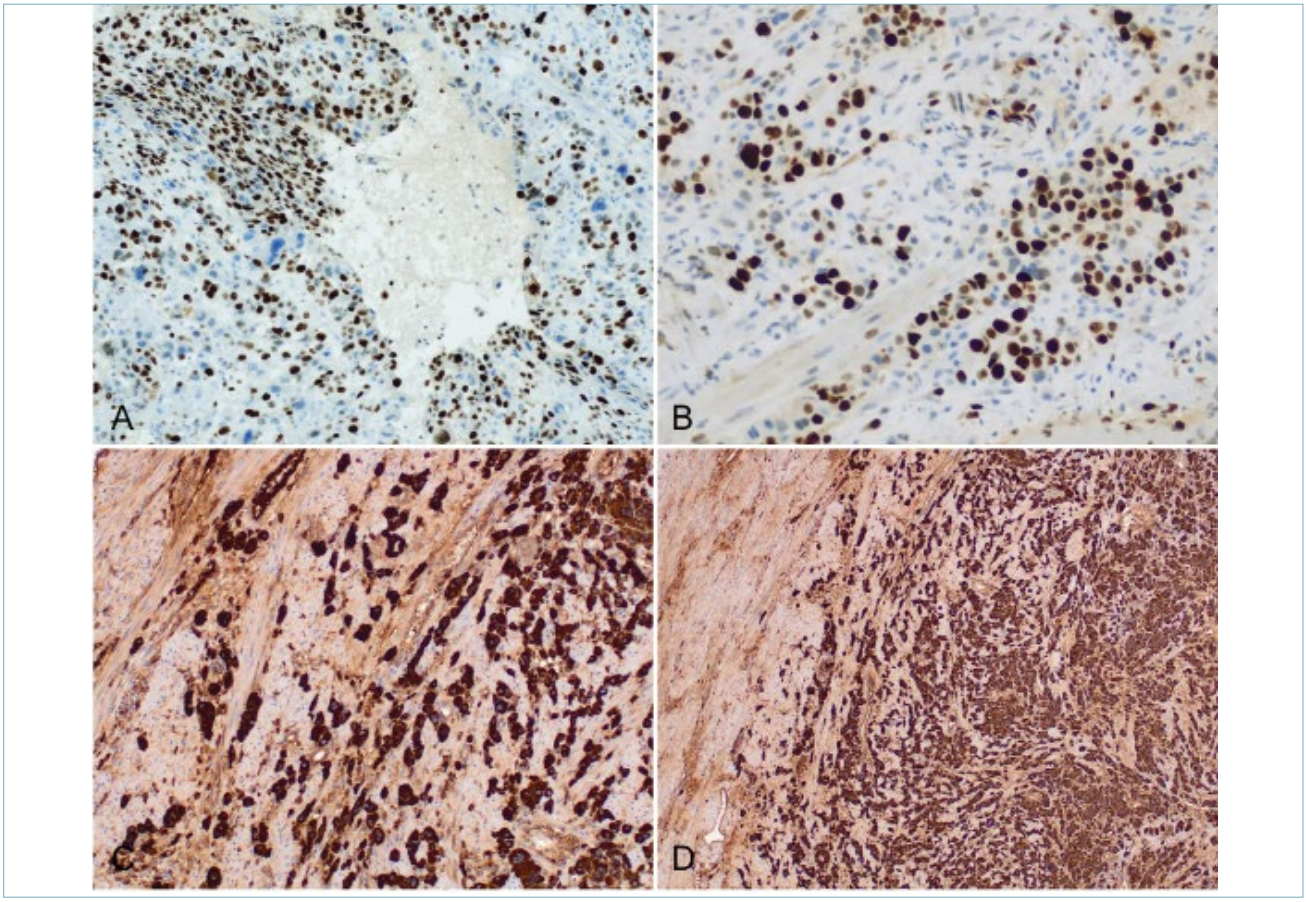

Figure 4. (A-D) Immunohistochemical profile shows a high proliferative index (Ki-67>30%) (A,B) and diffuse and strong cytoplasm staining for hPL confirming PSTT diagnosis (C,D).

and, currently, the patient has almost gained complete clinical response except for a single small lung nodule [2].

Discussion

Gestational trophoblastic neoplasia (GTN) is a group of malignant neoplasms that arise from the placenta and mainly consisting of gestational choriocarcinoma (the most common), placental site trophoblastic tumor and epitelioid trophoblastic tumor (1-2% of all trophoblastic tumor). All these diseases mainly occur in the reproductive years, with a mean age of 30 years, except for a significant percentage of ETT observed in premenopausal and postmenopausal patients [1,4].

Antecedent gestations include full term pregnancy (50-67%), spontaneous abortion (16-25%), and hydatidiform moles (16-50%) and the interval-time between antecedent pregnancy and clinical manifestation ranges from a few months to 20 years. These shared features make differential diagnosis more difficult.

Most common symptoms are vaginal bleeding and uterine enlargement, followed by amenorrhea and abdominal pain; both PSTT and ETT in 80% of the cases present mild to moderate elevation of serum human chorionic gonadotropin (hCG) (values ranging from 5 to 26000 mIU/mL), while GC has typical high levels of this hormone in all patients. Another difference between GC and the others concerns rates of recurrence and metastasis: while only 25-30% of the patients with PSTT or ETT show recurrence or metastasis, GC can present early metastases that can involve lung, liver, spleen, kidney, bowel, and brain.

Clinical suspicion may arise from symptoms, serology, pelvic ultrasound examination and/or other radiological examinations; hysterocolposcopy and biopsy are required for the diagnosis of certainty [5].

Grossly, PSTT is a well circumscribed, nodular, round, solid mass of 1 to 10 cm in size with cut surface usual-

ly solid and fleshy and a white-tan to light yellow color. Generally, involves the endomyometrium but deep myometrial invasion is seen in 50% of cases, transmural myometrial invasion and involvement of sierosa is seen in 10% of the cases, rarely with extension into the broad ligament and adnexa. Focal hemorrhage and necrosis are seen in nearly 50% of cases. On the other hand, GC and ETT present a deep invasion of surrounding structures, especially GC that is a bulky, dark red, solid, friable, destructive uterine mass with hemorrhage, necrosis, and deep myometrial invasion up to uterine perforation.

Microscopic analysis in PSTT reveals implantation site neoplastic intermediate trophoblasts, i.e., large, polyhedral to round, often mononucleated cells predominately aggregated into cords, nests and sheets with infiltrative growth pattern: characteristically these cells infiltrate the myometrium by separating individual muscle fibers and their vascular invasion pattern recapitulates that of normal implantation trophoblast. In fact, in more than two-thirds of cases tumor cells replace the wall of myometrial vessels and these transformed blood vessels are unique among all human solid tumors and allow PSTT diagnosis. Therefore, PSTT has a characteristic monophasic cell population consisting of neoplastic intermediate trophoblasts unlike triphasic GC that presents syncytiotrophoblast, cytotrophoblast, and intermediate trophoblast components. Furthermore, GC shows greater cytologic pleomorphism, higher mitotic index and more extensive hemorrage and necrosis than PSTT with infiltrative or solid destructive growth and common lymphovascular tumor thrombi.

In PSTT, neoplastic trophoblastic cells have abundant amphophilic, occasional eosinophilic or clear cytoplasm, variable nuclear size, and shape with marked hyperchromasia, nuclear grooves and pseudoinclusions. Nucleoli are generally prominent and mitotic count is usually between 2 and 4 per 10 high-power fields.

Other features are absence of villi, variable coagulative tumor cell necrosis, areas of hemorrhage and presence of scattered multinucleated implantation site trophoblastic cells resembling syncytiotrophoblasts.

ETT can be differentiated from PSTT through some unique pathologic features like the presence of eosinophilic hyaline-like material in the center of some tumor nests (simulating keratin formation), extensive or “geographic” necrosis, scattered decidualized benign stromal cells at the tumor periphery, calcification and, when involving the cervix, mucosal surface or glandular epitelium colonization by ETT tumor cells simulating high-grade squamous intraepithelial lesion. Immunochemistry can be useful for definitive diagnosis and exclude other gestational trophoblastic neoplasms.

Table I. Immunohistochemical profile.

	PSTT	GC	ETT
CKAE1/AE3	+++	+++	+++
hPL	+++	+ (intermediate trophoblast)	- / focal+
Inhibin	- / focal+	+ (syncytiotrophoblast)	+++
B-hCG	- / focal+	+++ (syncytiotrophoblast)	+ (syncytiotrophoblast)
p63	-	focal +	+++
MEL-CAM	+++	+ (intermediate trophoblast)	- / focal+
Ki-67	8-50%	> 90%	10-25%

In PSTT, immunohistochemical stainings for epithelial markers (CKAE1/AE3 and CK18), hPL, MUC4, HSD3B1, HLA-G, MEL-CAM (CD146), CD10, GATA3 and PDL1 are positive. Inhibin and hCG are positive only in scattered multinucleated tumor cells and the proliferative index evaluated with Ki-67 is equal to 10-30% of the neoplastic cells. On the other hand, in ETT, MEL-CAM and hPL are expressed only in individual cells while inhibin is diffusely positive in tumor cells; lastly, GC presents several staining patterns based on different types of neoplastic cells (syncytiotrophoblasts, cytotrophoblasts and intermediate trophoblasts), but the diagnostic key is the high mitotic index (Ki-67 > 90%) with a diffuse positivity for hCG [3] (Tab. I).

Conflicts of interest

The authors declare no conflict of interest.

Funding

None.

Ethical consideration

The information contained in this manuscript complies with the journal’s ethical standards.

Author contributions

All authors gave their approval for publication of the final version of the manuscript.

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