Severe thyrotoxicosis as initial presentation of gastric choriocarcinoma: a case report

Nicole M. Iñiguez-Ariza1,2*, Dalia Cuenca1,2, Juvenal Franco-Granillo1,3, Alberto Villalobos-Prieto4, Janet Pineda-Díaz2 and Javier Baquera-Heredia5

Abstract
Background: Extragonadal choriocarcinoma is rare and can be associated with hyperthyroidism when producing very high levels of human chorionic gonadotropin.

Case presentation: A 62-year-old Hispanic female presented with a 3-week history of shortness of breath, palpitations, extreme weakness, new-onset hot flashes, and right flank pain. Her physical examination was remarkable for tachycardia, hepatomegaly, hyperreflexia, and tremor; goiter was absent. Laboratory studies revealed increased lactate dehydrogenase, alkaline phosphatase, suppressed thyroid stimulating hormone, very elevated T4, and absent thyroid stimulating immunoglobulin. 18F-fluorodeoxyglucose positron emission tomography-computed tomography exhibited hepatomegaly with multiple large fluorodeoxyglucose-avid liver masses and a focus of fluorodeoxyglucose avidity in the stomach with no structural correlate. A thyroid scan (99mTcO4−) showed diffusely increased tracer uptake. She was started on propranolol and methimazole. Upon stabilization of severe thyrotoxicosis, upper endoscopy was performed, showing a ~5 cm bleeding lesion in the greater stomach curvature body; biopsy was consistent with choriocarcinoma; beta-human chorionic gonadotropin hormone was 2,408,171 mIU/mL. The patient received methotrexate followed by etoposide and cisplatin. Methimazole was titrated down, and upon liver failure the medication was stopped. The thyrotoxicosis was effectively controlled with antithyroid drug and concurrent chemotherapy. At ~1.5 months after initial diagnosis, the patient died due to bleeding/acute liver failure with coagulation defects followed by multiple organ failure.

Conclusions: Severe thyrotoxicosis can represent an unusual initial presentation of metastatic choriocarcinoma in the setting of extreme elevation of beta-human chorionic gonadotropin. Primary gastric choriocarcinoma is an aggressive malignancy with very poor outcomes. The co-occurrence of severe thyrotoxicosis with advanced primary gastric choriocarcinoma and imminent liver failure complicates management options.

Keywords: Hyperthyroidism, Paraneoplastic syndrome, Human chorionic gonadotropin, Germ cell tumor, Case report

Introduction
Choriocarcinoma is a human chorionic gonadotropin (hCG)-producing tumor observed in the setting of gestational trophoblastic disease (GTD) [1]. GTD entails a group of benign (hydatiform mole) and malignant (invasive mole, choriocarcinoma, and other) tumors arising from the uterus/placenta. Choriocarcinoma represents <5% of all GTDs and can be associated with very high hCG concentration capable of inducing hyperthyroidism due to cross-reactivity with the TSH receptor. GTD patients usually enjoy excellent prognosis in response to effective chemotherapy (long-term survival >95%), but
high-risk malignant GTD lessens 5-year overall survival (OS, 75–90%) [2, 3].

Choriocarcinomas rarely occur in extragonadal sites (e.g. lung, gastrointestinal tract, mediastinum, retroperitoneum, and other) with primary gastric choriocarcinoma (PGC) representing 0.08% of all gastric cancers [4, 5]. However, unlike gonadal choriocarcinoma, PGC is associated with very poor prognosis with median OS of < 2 months [5–7]. Herein, we present a case of a patient with metastatic PGC presenting with thyrotoxicosis.

Case presentation

A previously healthy 62-year-old Hispanic gravida 5 woman (2 spontaneous abortions), presented with a 3-week history of increasing shortness of breath, palpitations, extreme weakness, new-onset hot flashes, and right flank pain. Physical examination was remarkable for tachycardia (heart rate ~ 100 ×), temperature of 37.7 °C, speech compromised by shortness of breath, eyes with pale conjunctivae (with no erythema, chemosis, or exophthalmos), thyroid gland normal to palpation without nodules (~ 15 g), heart sounds increased in frequency with a systolic tricuspid murmur, basal lung breath sounds decreased to auscultation, hepatomegaly of ~ 5 cm below the right costal margin extending to the epigastrium (with hardness and tenderness to palpation in this area), as well as hyperreflexia and tremor. Chest X-ray and renal ultrasound demonstrated normal lung and renal findings but multiple liver nodules.

She was referred to our institution for evaluation and management. Laboratory tests indicated normocytic anemia (hemoglobin 8.1 g/dL), elevated lactate dehydrogenase at 3054 U/L (122–222), alkaline phosphatase 434 U/L (40–29), and elevated T4 with suppressed TSH consistent with thyrotoxicosis (Table 1). Her echocardiogram showed pulmonary hypertension (65 mmHg), dilated right atrium and ventricle, tricuspid regurgitation, adequate left ejection fraction, and a previously unknown atrial septal defect with inter-auricular communication with a right to left shunt and high risk for embolism. Contrast-enhanced 18FDG PET-CT showed hepatomegaly with multiple large FDG-avid liver masses, with a focus of FDG avidity in the stomach with no structural correlate (Fig. 1).

Her thyroid function tests and thyroid scan with technetium 99m pertechnetate (99mTcO4−) were consistent with thyrotoxicosis due to hyperthyroidism (Table 1; Fig. 1). Graves’ disease was ruled out in the setting of no signs of Graves orbitopathy, no goiter, and negative thyroid stimulating antibodies (TSI index < 1.0 and thyroid receptor antibody < 1.00 IU/L). At presentation, she also had mildly altered liver function tests [AST 137 U/L (10–50), ALT 70 U/L (8–54), total bilirubin 1.8 mg/dL (0.3–1.3)]

She was started on propranolol and antithyroid drug (methimazole 30 mg/day). Upon stabilization of severe thyrotoxicosis, upper endoscopy was performed, showing a ~ 5 cm bleeding lesion in the greater stomach curvature (Fig. 2). Gastric biopsy was consistent with choriocarcinoma with extensive necrosis with no evidence of concurrent conventional adenocarcinoma nor endodermal sinus component; immunostaining with antibodies against hCG, GATA3, LPH, PLAP, and CK7 was positive (Fig. 2). Neoplastic cells had strong and diffuse membranous reactivity to PD-L1 antibody.

Subsequently, beta-human chorionic gonadotropin hormone (β-hCG) was found to be extremely elevated at 2,408,171 mIU/mL. Other tumor markers (CA-125, CEA, and AFP) were measured and unrevealing. After this workup, an extragonadal germinal tumor (primary

| Table 1 Laboratory tests and treatment modalities |
|-----------------------------------------------|
| Upon presentation | At 10 days post MTX dose and 2 weeks post ATD initiation | At 4 weeks post ATD initiation | At readmission | At 10 days post EP |
|-------------------|----------------------------------------------------------|--------------------------------|----------------|-------------------|
| FT4 (0.71–1.85 ng/dL) | 4.1 | 1.5 | 1.1 | 1.1 | 1.1 | 1.1 |
| TT4 (4.5–12 mcg/dL) | 30.2 | 9.5 | 7.4 | 5.2 | – | – |
| TSH (0.45–5 mL/U/L) | 0.06 | 0.04 | 0.01 | 0.02 | 0.07 | – |
| β-hCG* (0–10 mL/U/mL) | 2,408,171 | 3,904,164 | – | 3,105,708 | 832,558 | – |
| Methimazole dose (mg/day) | 30 | 20 | 10 | Stopped | – | – |

TSH thyroid stimulating hormone, FT4 free thyroxine, TT4 total thyroxine, β-hCG* beta-human chorionic gonadotropin hormone, confirmed by serial dilution up to 1:100, MTX methotrexate, ATD antithyroid drug, EP etoposide-cisplatin

Concurrent with first chemotherapy (MTX) she received not only ATD but also Lugol’s solution for a couple of days due to threat of transient increase in β-hCG levels and consequent worsening thyrotoxicosis

During her readmission, she was treated aggressively in the intensive care setting, her AST and ALT trended down from 1346 U/L and 500 U/L, respectively, to 247 U/L and 110 U/L, respectively

At 11 days post EP, the patient died due to multi-organic failure, particularly liver failure (AST 7224 U/L, ALT 2026 U/L, total bilirubin 27.4 mg/dL) with disseminated intravascular coagulation and persistent gastrointestinal bleeding
gastric choriocarcinoma) with extensive liver metastases and paraneoplastic hyperthyroidism was deemed the most likely diagnosis.

The patient was treated initially with methotrexate (200 mg/m²) and subsequently with etoposide and cisplatin. Methimazole was titrated down from 30 to 10 mg/day, achieving euthyroidism. The thyrotoxicosis was effectively controlled with antithyroid drug and concurrent chemotherapy.

One month after initial diagnosis, the patient was readmitted with hemorrhagic hypovolemic shock due to gastrointestinal bleeding and acute liver failure with severe coagulopathy (AST 1346 U/L, ALT 500 U/L, total bilirubin 5.6 mg/dL, altered coagulation: INR 2.17, fibrinogen 111 mg/dL). Methimazole was discontinued upon liver failure onset. She required intensive care therapies with a multidisciplinary team, but unfortunately died ~ 1.5 months post presentation in the setting of multiple organ failure.

Fig. 1 Imaging studies upon presentation and upper endoscopy. A–E Contrast-enhanced ¹⁸⁸FDG PET-CT exhibited hepatomegaly (22 cm longitudinal axis) with multiple large FDG-avid liver masses, measuring up to 12 cm and SUV max of 13.5. A focus of FDG avidity in the gastric antrum had no structural correlate (red arrows), with an SUV max of 9.4. CT also showed mesenteric lymph nodes and small lung infiltrates. F Thyroid scan (¹⁹⁵mTcO₄⁻) with tendency to diffusely increased tracer uptake (radioiodine thyroid scan was not performed due to use of IV-iodinated contrast in the preceding two days). G Upper endoscopy showing a ~ 5 cm bleeding lesion in the greater stomach curvature body.
Discussion

Primary gastric choriocarcinoma (PGC) occurs more frequently in males (2.3:1) at a median of 63 years of age. The mean tumor size at diagnosis is 7 cm. The most common location is in the lower third of the stomach (40%), with almost all having macroscopic hemorrhage or necrosis [4]. Our case is consistent with this clinical presentation, with the exception of gender and gastric location. PGC is a very rare and extremely aggressive tumor that, unlike primary gastric adenocarcinoma (which usually metastasizes through lymphatics), is characterized by rapid proliferation and early distant hematogenous spread [5, 8]. In a pooled analysis of 53 PGC cases, most presented with metastatic disease, with liver metastases occurring in 45% [4]. In the present case, the primary tumor size was ~ 5 cm, while the liver had disseminated metastatic disease with some of the liver metastases as large as ~ 10 cm.

The etiology of PGC is debated. The less accepted theory is that PGC occurs de novo, since hCG-producing cells have been found in normal gastric mucosa and gastric adenocarcinoma; the existence of these cells might be the origin of pure forms of PGC, without preceding adenocarcinoma. Nonetheless, the most accepted theory is the “dedifferentiation theory,” with dedifferentiation of gastric adenocarcinoma to the embryonal ectoderm level, but with the ability to form trophoblasts. Supporting the latter theory is the fact that most PGC have a poorly differentiated adenocarcinoma component (~ 70%); moreover, PGC genetically has characteristics of both adenocarcinoma and gestational choriocarcinoma [4, 5, 9]. The dedifferentiation theory suggests that pure PGC occurs when overgrowth and elimination of the original adenocarcinoma has occurred [5, 10].

Our case is a histologically pure PGC, although we cannot with certainty exclude a possible adenocarcinoma component in unsampled tumor areas. Although definitive diagnosis by endoscopic biopsy is rare (8%), we were able to achieve a biopsy-proven diagnosis [5].

The differential appropriate diagnosis of the etiology of recent-onset thyrotoxicosis is of particular importance in the sense that it significantly impacts treatment choice strategies. Thyrotoxicosis can occur in the context of increased thyroid function, release of preformed hormones, or even because of factitious ingestion of thyroid hormones. History and physical examination (e.g., orbitopathy, goiter), measurement of thyroid stimulating antibodies, and nuclear medicine thyroid scans (radioiodine or 99mTc pertechnetate) are of aid in the initial approach to thyrotoxicosis [11].

Though β-hCG-mediated thyrotoxicosis is a well-known but infrequent cause of overt hyperthyroidism,
thyroid stimulation is directly proportional to hCG concentration, equivalent to 1 mU/L of TSH activity [14, 15]. The level of hCG is very high hCG concentration (~ 2 million). Serial hCG dilutions were accordingly performed, resulting in a concentration of > 11 million mIU/mL [16]. In our patient, the concentration was 193 mU/mL with a real value after serial dilutions of 193 mU/mL [16]. Our patient presented with symptomatic hyperthyroidism along with multiple liver masses, requiring treatment with methimazole and propranolol and briefly Lugol’s solution, with adequate response to therapy and resolution of thyrotoxicosis.

Hyperthyroidism can occur with hCG levels > 200 mIU/mL, but overt hyperthyroidism is usually seen in germinal tumors when hCG concentration is >50,000—100,000 mIU/mL [12, 15–19]. Roughly, 25,000 U/L of hCG is equivalent to 1 mU/L of TSH activity [14, 15]. The level of thyroid stimulation is directly proportional to hCG concentration, but not all patients with elevated hCG levels present with hyperthyroidism; this is thought to depend on secondary modifications of the hCG molecule, such as glycosylation and sialylation, that affect hCG bioactivity with differing TSH receptor sensitivity. hCG deglycosylation and desialylation may promote thyrotropic potency [12, 16, 20, 21]. Moreover, hCG produced by GTD is usually more potent than normal pregnancy hCG because of the lower sialic content of GTD hCG; < 3% of the oligosaccharide side chains of hCG derived from a choriocarcinoma contain sialic acid, whereas normally pregnancy-produced hCG is mostly sialylated [12, 21]. In some cases of extreme paraneoplastic hCG production, a “hook effect” leads to falsely low and misleading measured serum concentration. In a uterine choriocarcinoma case report, initial measurement of hCG concentration was 193 mU/mL with a real value after serial dilutions of > 11 million mIU/mL [16]. In our patient, serial hCG dilutions were accordingly performed, confirming very high hCG concentration (~ 2 million).

The 2016 American Thyroid Association (ATA) guidelines [11] acknowledge trophoblastic disease/choriocarcinoma as a cause of thyrotoxicosis, characterized by diffuse hyperactive thyroid. The guidelines, furthermore, recognize that thyrotoxicosis can occur in the setting of choriocarcinoma due to “the effect of tumor-derived hCG upon the TSH receptor. This cross-stimulation only occurs at very high levels of hCG, since hCG is only a weak agonist.”

However, it is perhaps underappreciated that hCG-induced hyperthyroidism may be life threatening if not recognized promptly. Treatment usually consists of correcting the cause, if possible. In the choriocarcinoma setting, effective cancer management decreases hCG concentration, palliating thyrotoxicosis. Nonetheless, overt hCG-induced hyperthyroidism requires medical therapy with antithyroid drugs and beta-blockers, with some patients requiring Lugol’s solution in parallel. The 2016 ATA guidelines suggest that treatment of hyperthyroidism due to choriocarcinoma should include both methimazole as well as treatment directed against the primary tumor [11]. There are, however, no specific recommendations on hyperthyroidism management in the setting of an extragonadal widely metastatic choriocarcinoma with imminent liver failure.

Our patient presented with very symptomatic hyperthyroidism along with multiple liver masses, requiring treatment with methimazole and propranolol and briefly Lugol’s solution, with adequate response to therapy and resolution of thyrotoxicosis.

A remarkable feature of our patient’s neoplastic cells was the strong and diffuse membranous reactivity for the programmed cell death ligand-1 (PD-L1) antibody (Fig. 2). This, although striking, is consistent with previous reports. In an immunohistochemical study of PD-L1, it was demonstrated that it was constitutively and strongly expressed in normal tissue placental trophoblast, choriocarcinomas, and trophoblastic components of germ cell tumors. Choriocarcinomas were uniformly positive for PD-L1 with a membrane pattern, suggesting that PD-L1 might be a supplemental marker for diagnosis of choriocarcinoma or trophoblastic features in other germ cell tumors [22]. A study assessing in detail the distribution of PD-L1 expression in human placentas and GTD showed that PD-L1 was highly expressed in syncytiotrophoblast in complete moles and choriocarcinomas [23]. High PGC PD-L1 expression suggests that cancer treatment with immune checkpoint inhibitors may be fruitful, with a case report showing a partial response to nivolumab as second-line treatment for poorly differentiated adenocarcinoma with choriocarcinomatous features [24].
Choriocarcinoma is usually chemosensitive and has excellent outcomes when gonadal in origin [2, 3]. However, PGC has dismal prognosis; an analysis of 53 patients showed that 19% died < 1 month postoperatively [4] with median OS of < 2 months [5–7]. There is no standard of care for PGC patients, but commonly used chemotherapeutic agents include, methotrexate, etoposide, folinic acid, actinomycin D, cyclophosphamide, vincristine, and others [2, 25]. Our patient received initially methotrexate with no response and later etoposide-cisplatin with biochemical decrease of hCG tumor marker but with structural progression and later etoposide-cisplatin with biochemical decrease of hCG tumor marker but with structural progression and ultimate liver failure–multiple organ failure. One wonders whether PGC location might be the main driver of poor prognosis, since a gastric location of a highly vascularized “placental-like” tumor with rapid growth and hematogenous spread entails easy access to hepatic seeding with consequent widespread liver metastatic disease upon diagnosis, many times with little normal liver reserve, with all the calamities associated with this context. Moreover, thyrotoxicosis treatment and need for chemotherapy in the setting of high tumor burden and hepatic failure is particularly challenging.

Univariate and multivariate analysis of PGC pooled data showed that the presence of residual tumor, synchronous liver metastasis, and absence of chemotherapy were significantly associated with increased mortality [4]. Our case had widespread synchronous liver metastases with high tumor burden. The most frequent causes of death in PGC are hepatic failure due to metastatic spread (29%) and bleeding from primary or metastatic disease (24%). Our patient died of both complications.

Conclusion
Primary gastric choriocarcinoma (PGC) is an aggressive malignancy with very poor outcomes. The co-occurrence of severe thyrotoxicosis with advanced PGC and imminent liver failure complicates management options. We believe that this case is of educational value and that it might aid future PGC patients and clinicians, favoring early recognition and expedited care, as well as to set expectations clear upfront of the prognosis of this terrible disease complicated by severe thyrotoxicosis. Finally, we hope that this report will lead to the design of research studies for future therapies that could improve the grim prognosis of this malignant disease.

Acknowledgements
We are grateful to our late patient and her family for entrusting her care to us; she was an exemplary human being and a beloved wife and mother. It was our privilege to know her. We are in debt to Dr. Keith Bible for editorial assistance.

Authors’ contributions
NMI-A: conceptualization, analysis, writing—original draft, writing—review and editing, supervision. DC: conceptualization, analysis, writing—original draft, writing—review and editing. JF-G: analysis, writing—review and editing. AV-P: analysis, writing—review and editing. JP-D: analysis, writing—review and editing. JB-H: analysis, writing—review and editing. All authors made meaningful contributions to the analysis and critical revisions to the writing, and approved the final version for submission for publication.

Funding
Not applicable.

Availability of data and materials
Data sharing is not applicable to this article as no datasets were generated or analyzed in this single-patient case report.

Declarations
Ethics approval and consent to participate
This case report complies with the guidelines for human studies and was conducted in accordance with the World Medical Association Declaration of Helsinki. It was exempt from Institutional Review Board (IRB) approval due to the single nature of the case report (n = 1) and adequate protection of identifiable patient information.

Consent for publication
Written informed consent was obtained from the patient’s next of kin for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

Author details
1Department of Medicine, American British Cowdray Medical Center, Mexico City, Mexico. 2Department of Endocrinology and Metabolism, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico. 3Critical Care Unit, American British Cowdray Medical Center, Mexico City, Mexico. 4Department of Medical Oncology, American British Cowdray Medical Center, Mexico City, Mexico. 5Department of Surgical and Molecular Pathology, American British Cowdray Medical Center, Mexico City, Mexico.

Received: 2 August 2021 Accepted: 21 February 2022

Published online: 21 April 2022

References
1. Walkington L, Webster J, Hancock BW, Everard J, Coleman RE. Hyperthyroidism and human chorionic gonadotrophin production in gestational trophoblastic disease. Br J Cancer. 2011;104(11):1665–9.
2. Abu-Rustum NR, Yashar CM, Bean S, Bradley K, Campos SM, Chon HS, et al. Gestational trophoblastic neoplasia; version 2.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2019;17(11):1374–91.
3. Seki M, Sebire NJ, Fisher RA, Golfer F, Massuger L, Sessa C, et al. Gestational trophoblastic disease: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24(Suppl 6):vi39-50.
4. Kobayashi A, Hasebe T, Endo Y, Sasaki S, Konishi M, Sugito M, et al. Primary gastric choriocarcinoma: two case reports and a pooled analysis of 53 cases. Gastric Cancer. 2005;8(3):178–85.
5. Martins VF, Moreno F, Vizzcaino JRP. Santos J. Primary gastric choriocarcinoma: a rare case. Int J Surg Case Rep. 2015;14:44–7.
6. Ajay VarunReddy TKR. Primary gastric choriocarcinoma with para-neoplastic hyperthyroidism: a rare case report. J Dental Med Sci. 2016;15(6):78–80.
7. Yoon JH, Kim MS, Kook EH, Ahn SH, Jeong SY, Han MS, et al. Primary gastric choriocarcinoma: two case reports and review of the literature. Cancer Res Treat. 2008;40(3):145–50.
8. Shastri A, Daver NG, Hayes TG. Primary gastric choriocarcinoma: a needle in a haystack. Rare Tumors. 2011;3(2):e19.
9. Liu AY, Chan WT, Ng EK, Zhang X, Li BC, Chow JP, et al. Gastric choriocarcinoma shows characteristics of adenocarcinoma and gestational choriocarcinoma: a comparative genomic hybridization and fluorescence in situ hybridization study. Diagn Mol Pathol. 2001;10(3):161–5.
10. Liu Z, Mira JL, Cruz-Caudillo JC. Primary gastric choriocarcinoma: a case report and review of the literature. Arch Pathol Lab Med. 2001;125(12):1601–4.
11. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American Thyroid Association Guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid. 2016;26(10):1343–421.
12. Hershman JM. Physiological and pathological aspects of the effect of human chorionic gonadotropin on the thyroid. Best Pract Res Clin Endocrinol Metabol. 2004;18(2):249–65.
13. Korevaar TL, Steegers EA, de Rijke YB, Schalekamp-Timmermans S, Visser WE, Hofman A, et al. Reference ranges and determinants of total hCG levels during pregnancy: the Generation R Study. Eur J Epidemiol. 2015;30(9):1057–66.
14. Meister LH, Hauck PR, Graf H, Carvalho GA. Hyperthyrotoxicosis due to secretion of human chorionic gonadotropin in a patient with metastatic choriocarcinoma. Arq Bras Endocrinol Metabol. 2005;49(2):319–22.
15. Sotello D, Rivas AM, Test VI, Lado-Abal J. Choriocarcinoma presenting with thyrotoxicosis. Proc (Bayl Univ Med Cent). 2016;29(1):42–3.
16. Hsieh TY, Hsu KO, Kuo PL, Huang SC. Uterine choriocarcinoma accompanied by an extremely high human chorionic gonadotropin level and thyrotoxicosis. J Obstet Gynaecol Res. 2008;34(2):274–8.
17. Morley JE, Jacobson RJ, Melamed J, Hershman JM. Choriocarcinoma as a cause of thyrotoxicosis. Am J Med. 1976;60(7):1036–40.
18. Odell WD, Bates RW, Rivlin RS, Lipsett MB, Hertz R. Increased thyroid function without clinical hyperthyroidism in patients with choriocarcinoma. J Clin Endocrinol Metab. 1963;23:658–64.
19. Soutter WP, Norman R, Green-Thompson RW. The management of choriocarcinoma causing severe thyrotoxicosis. Two case reports. Br J Obstet Gynaecol. 1981;88(9):938–43.
20. Yoshimura M, Hershman JM. Thyrotropic action of human chorionic gonadotropin. Thyroid. 1995;5(5):425–34.
21. Yoshimura M, Pekary AE, Pang XP, Berg L, Goodwin TM, Hershman JM. Thyrotropic activity of basic isoelectric forms of human chorionic gonadotropin extracted from hydatidiform mole tissues. J Clin Endocrinol Metab. 1994;78(4):862–6.
22. Inaguma S, Wang Z, Lasota J, Sarlomo-Rikala M, McCue PA, Ikeda H, et al. Comprehensive immunohistochemical study of programmed cell death ligand 1 (PD-L1) analysis in 5536 cases revealed consistent expression in trophoblastic tumors. Am J Surg Pathol. 2016;40(8):1133–42.
23. Veras E, Kurman RJ, Wang TL, Shih IM. PD-L1 expression in human placentas and gestational trophoblastic diseases. Int J Gynecol Pathol. 2017;36(2):146–53.
24. Ochi M, Miyamoto S, Terada Y, Furuhata Y, Awano N, Izumo T, et al. The significant antitumor activity of nivolumab in lung adenocarcinoma with choriocarcinomatous features. Intern Med. 2018;57(12):1773–7.
25. Raghavapuram R, Veerankutty FH, Anandakumar M. Primary choriocarcinoma of the stomach. A case report and review of the literature. Indian J Surg Oncol. 2016;7(1):119–23.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.