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GASTRIC SIGNET-RING CELL CARCINOMA WITH HYPERSECRETION OF β-HUMAN CHORIONIC GONADOTROPIN AND REVIEW OF THE LITERATURE

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β-Human chorionic gonadotropin (β-HCG) is an embryonic protein secreted by the syncytiotrophoblast of the placenta. The determination of the plasma β-HCG level is routinely used for the diagnosis and the follow-up of germ cell tumors. Some adenocarcinomas have been described as being rarely associated with β-HCG hypersecretion. We report a case of gastric signet-ring cell carcinoma with β-HCG hypersecretion and propose hypotheses to explain the pathogenesis of such hypersecretion.
***Key Words*: β-Human chorionic gonadotropin, gastric signet-ring cell carcinoma.**

β-Human chorionic gonadotropin (β-HCG) is an embryonic protein secreted by the syncytiotrophoblast of the placenta. The determination of the plasma β-HCG level is routinely used for the diagnosis and the follow-up of germ-cell tumors. Some adenocarcinomas have been described as being rarely associated with β-HCG hypersecretion. Amongst these adenocarcinomas, gastric and pulmonary origin was the most frequent. Its incidence ranges from 10.9% to 16.7% and 12% to14%, respectively, in gastric adenocarcinoma and lung cancer [1]. We report a case of gastric signet-ring cell carcinoma with β-HCG hypersecretion and we propose to analyze hypotheses to explain the pathogenesis of this hypersecretion.

OBSERVATION

A 52-year-old man was admitted for hematemesis with dysuria. Clinical examination showed an ascites. Oesogastroduodenal fibroscopy revealed an ecchymotic funditic gastropathy with bulbo-duodenitis. Histopathological study of gastric biopsy concluded to a signet-ring cell carcinoma of the fundial mucosa with non-atrophic and non-active chronic antro-fungal gastritis (Fig. 1). Duodenal biopsy was normal. A thoraco-abdomino-pelvic computed tomography showed a thickening of the gastric wall with a regular thickening of the anterior wall of the bladder of 10 mm (Fig. 2) and multiple osteo-condensing lesions of the iliac bone, sacrum, dorsolumbar spine and sternum. Cystoscopy showed a budding lesion of the anterior wall of the bladder. The patient had an endoscopic resection of the bladder tumor. Histologically, there was an undifferentiated tumor cells infiltration with isolated round-sized cells crushed with a cytoplasm. The nuclear pleomorphism was low and the tumor stroma was fibrous and abundant (Fig. 3). This proliferation extended to the muscularis. At immunohistochemical study, the tumor cells were positive for anti-keratin, ACE and HCG (Fig. 4). This study concluded to a bladder infiltration by signet-ring cell carcinoma of gastric origin. Testicular ultrasound was normal. β-HCG level was 458 mIU/ml. The patient had received palliative chemotherapy with EOX protocol (epirubicin, oxaliplatin, capecitabine) and biphosphonate. Control β-HCG level was 4 mIU/ml.

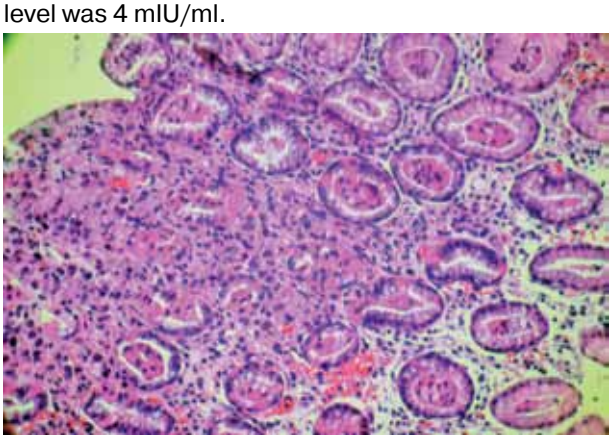

Fig. 1. Histological study of gastric biopsy. Infiltration of the fundic mucosa by tumor cells. Hematoxylin-eosin, × 400

Fig. 2. Pelvic CT: regular thickening of the anterior wall of the bladder

DISCUSSION

β-HCG is a glycoprotein hormone consisting of two subunits: α and β which are joined by noncovalent bonds. Since the α-subunit of HCG has a sequence homology similar to other pituitary hormones, including luteinizing hormone, thyroid-stimulating hormone and follicle-stimulating hormone, the β-subunit of HCG is assayed. HCG is physiologically produced

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Abbreviation used: β-HCG – β-human chorionic gonadotropin.

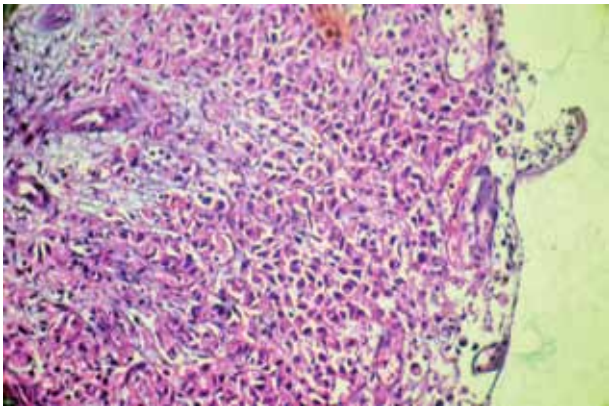

Fig. 3. Histological study: infiltration of the vesical mucosa by carcinoma cells. Hematoxylin-eosin, × 400

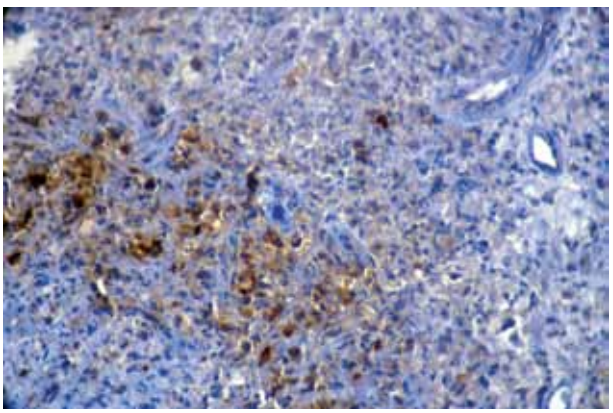

Fig. 4. Immunohistochemical study: positive staining for HCG, × 400

by syncytiotrophoblasts of the placenta and in increased amounts by germ cells tumors, particularly choriocarcinoma. β-HCG production have been previously described in oropharyngeal squamous cell carcinoma [1], urothelial carcinoma of bladder [2], clear cell renal cell carcinoma [3], leiomyosarcoma [4] and malignant phyllodes tumor of the breast [5]. Expression of serum β-HCG is not associated with any specific histological subtypes, although some authors have found that this phenomenon is more characteristic of adenocarcinoma [3]. A rare subset of tumors with hyperexcretion of β-HCG has been identified in nontrophoblastic cells, amongst gastric adenocarcinoma. The β-HCG-positive cells were located mainly in the antral mucosa and were generally restricted to a low portion of the pyloric and fundic glands [6] such in our case. The β-HCG-immunoreactive cells were found more often in advanced carcinomas that were histologically poorly differentiated than in early carcinomas or in well-differentiated tumors [6]. To our knowledge, our case represents the second report of a gastric signet-ring cell carcinoma producing β-HCG. This patient had also multiple osteo-condensing lesions of the iliac bone, the sacrum and the dorsolumbar spine. By reviewing the literature, bone metastases are five times more frequent in β-HCG secreting gastric adenocarcinoma than in nonsecreting tumors [7, 8].

β-HCG production is correlated with a poor prognosis in a multivariate analysis of 290 gastric adenocarcinoma patients [9]. Tomita and Kuwajima [10] reported that patients with gastric cancer and high levels of HCG in the serum or a high density of HCG-positive cells in the tumor tissue had a poor prognosis. Also, Ito and Tahara [11] who found β-HCG-positive tumor cells in 8.2% of the advanced cancer cases reported that gastric cancers with HCG immunoreactivity tended toward a poorer prognosis.

The mechanism of β-HCG secretion is poorly understood. It can be explained by a trophoblastic metaplasia within the carcinomatous tissue. Other hypotheses have been proposed to explain the origin of β-HCG-producing cells and include the following: displaced totipotential or gonadal cells (extragonadal choriocarcinomas); metastasis from an intrauterine or gonadal lesion and the presence of β-HCG-specific mRNA and the possibility of reactivation of β-HCG gene transcription in the malignant transformed cells, leading to ectopic β-HCG protein expression [12–14]. To date, few published reports have attempted to address this issue by exploring ectopic β-HCG production at the molecular level. Besides their important biological role in promoting progesterone production and angiogenesis in the uterine vasculature during pregnancy, free β-subunit and hyperglycosylated HCG were recently found to play a major role in the tumorigenesis of nontrophoblastic tumors. They acted as an autocrine antiapoptotic and angiogenic growth factor that inhibits the TGF- β apoptosis signaling pathway, resulting in cancer cell growth [15, 16]. This may also explain the chemoresistance and aggressiveness of β-HCG secreting tumors.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

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