

Unusual Manifestation of Ectopic Human Chorionic Gonadotropin-Producing Cancers

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ABSTRACT

Elevated serum beta human chorionic gonadotropin (β -hCG) in a female usually indicates pregnancy or less commonly, gestational trophoblastic disease or gonadal germ cell tumors. Elevation of hCG exists in other conditions including malignant tumors of non-endocrine origin. The elevated β -hCG level can produce excessive amounts of estradiol via extra gonadal metabolism from androgen, and manifest as gynecomastia in males or vaginal spotting or suspicion of pregnancy in females. In either sex, β -hCG might serve as a useful tumor marker during therapeutic management for checking recurrence of the disease.

Introduction

Elevated serum beta human chorionic gonadotropin (β -hCG) in women generally indicates pregnancy, or less commonly, gestational trophoblastic disease, gonadal germ cell tumors, or extremely low levels from the anterior pituitary [1,2]. Elevation of hCG exist in several other states such as malignant tumors of non-endocrine origin (Figure1), and it has been suggested as possible tumor markers (Table 1). Some *in vivo* and *in vitro* studies have been shown that β -hCG acts as an autocrine growth factor within tumor [3,4]. Elevated expression of β -hCG may not be a reliable diagnostic marker, but it has been shown to serve as a strong indicator of poor prognosis for many non-endocrine tumors [1,3,4]. Elevated β -hCG might manifest as gynecomastia in male patients or cause vaginal bleeding as initial symptoms in postmenopausal female patients [5-8]. These signs associated with high β -hCG and subsequently increased level of estrogen may be attributed to paraneoplastic

syndrome due to non-endocrine tumors. We purpose to understand the unusual sign of the ectopic β -hCG producing malignancies as initial manifestation.

Gynecomastia in Males

Gynecomastia results from

- 1) Increased level of circulating estrogen, in particular estradiol,
- 2) Increased breast sensitivity to circulating estrogen, or
- 3) An altered balance of estrogen (stimulatory effect) and androgen (inhibitory effect).

Estrogen stimulates ductal epithelial hyperplasia, ductal branching and elongation, proliferation of the periductal stroma, and vascular distribution in the breast [5,6].

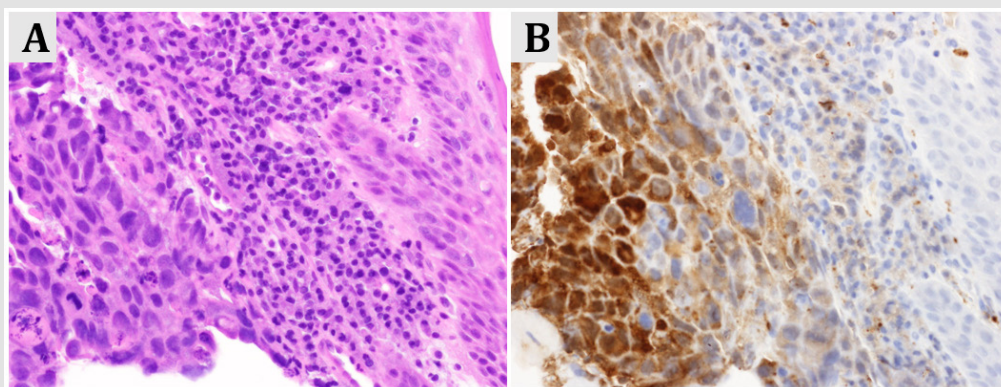


Figure 1: Stage IV gastric cancer in a postmenopausal woman presenting with intermittent vaginal bleeding
 (A) Microscopic image of gastric adenocarcinoma (hematoxylin/eosin staining, x400)
 (B) Tumor cells were diffusely positive for human chorionic gonadotropin (hCG, x400).

Estrogen production in postmenopausal females and males results mainly from the peripheral conversion of androgens (testosterone, androstenedione and dehydroepiandrosterone sulfate,) by the action of the enzyme aromatase to estradiol and estrone [7,8]. The extra gonadal formation of estrogen occurs mainly in adipose tissue, skin and muscle. The patients with malignant tumors characterized by ectopic production of β -hCG (Table 1) may be associated with excessive amounts of estradiol via the extragonadal metabolism of androgens.

Table 1: β -hCG-producing tumors.

Primary site	Histology	Ref.
Anus	squamous cell carcinoma	[10]
Bladder	urothelial carcinoma	[11-13]
Breast	malignant phyllodes tumor	[14]
Cervix	squamous cell carcinoma	[15]
Gallbladder	adenocarcinoma	[16,17]
Head and neck	squamous cell carcinoma	[18,19]
Kidney	renal cell carcinoma	[20]
Lung	non-small-cell adenocarcinoma	[21-25]
Ovary	mucinous adenocarcinoma	[26,25]
Stomach	gastric adenocarcinoma	[27,28]
Sarcomas	leiomyosarcoma, liposarcoma, rhabdomyosarcoma	[29-32]

Vaginal Spotting in Females

The reproductive organs undergo progressive atrophy due to a reduced circulating estrogen and progesterone. This physiologic process of aging is also found at an endometrial level. Without the cyclic hormonal actions of the menstrual cycle, the endometrium during menopause becomes atrophic [9-18]. Non-physiologically increased estrogen level may cause postmenopausal bleeding. In

a patient with unexplained vaginal spotting and no evidence of endometrial cancer or endometrial or cervical polyps, consideration should be given to the possibility of ectopic secretion of β -hCG from other tumors.

Suspicion of Pregnancy in Premenopausal Females

In reproductive-aged women with elevated hCG, when pregnancy, either normal or abnormal (e.g. missed abortion, ectopic pregnancy) is excluded, the malignancy should [18-24] be ruled out with imaging and surgical specimen immunohistochemically.

Comments

Pituitary hCG is naturally produced at extremely low levels in woman of reproductive age population. In peri- or postmenopausal state, levels of pituitary hCG increase because of the absence of feedback control by circulating estrogen and progesterone [2,25-32]. Elevated β -hCG level due to various cancers produce excessive amounts of estradiol by peripheral aromatase activation, which can manifest as gynecomastia in males or vaginal spotting in females. In either case estrogen and β -hCG might be useful tumor markers during therapeutic management for checking recurrence of the disease, alongside other examination.

Conflict of Interest

The authors declare that they have no conflict of interest.

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