

# Ectopic Hormone Production from Ovarian Tumor: A Review

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## Abstract

Although ectopic hormone-production is uncommon complication, certain tumors can produce symptoms due to the secretion of various bioactive substances accompanied by the aberrantly located tumors. Because of the potential for the ovary to act as a source of aberrant hormone secretion, in the literature, ectopic hormone production from ovarian tumor includes granulocyte-colony stimulating factor (G-CSF), parathyroid hormone-related protein (PTHrP), adrenocorticotrophic hormone (ACTH), peptide-YY, gastrin and insulin. All patients may present with syndromes of hormone excess. Failure to localize the ovarian tumor preoperatively may be associated with a significantly higher risk of subsequent unnecessary ablative procedures. Better characterization of hormonal forms relatively specific for neoplasia may enhance the clinical value of ectopic hormones as tumor markers, especially in malignancies that are commonly associated with ectopic hormone production. These circumstances may recommend complete preoperative evaluation of the pelvis in female patients presenting with nonlocalizable endocrine tumors.

## Keywords

Bioactive Substance Production, Ectopic Hormone Secretion, Ovarian Cancer, Ovarian Carcinoid, Benign Ovarian Tumor

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## 1. Introduction

The endocrine tumors may or may not be functional and have clinical manifestations according to the hormone secreted. Ectopic hormone syndrome can be caused by peptide or nonsex steroid hormone secretion due to aberrantly located tumors. Numerous types of endocrine and non-endocrine tumors acquire the ability to secrete sub-

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stances that are not normally secreted from the tissue where they originate. During the process of cellular differentiation, most of the genes of the hormone are inactivated. Neoplastic transformation, however, may activate repressed genes, thus producing hormones that are not produced by differentiated cells [1] [2]. It is now well recognized that ectopic bioactive substance secretion can be associated with various solid tumors, mostly of malignant or neuroendocrine origin. After biochemical confirmation of the ectopic hormone syndrome, optimal management includes localization and removal of the hormone ectopic source. Because of the potential for the ovary to act as a source of aberrant hormone secretion [3], we attempt to a comprehensive computer-based search for the unusual or rare ectopic hormone-producing ovarian tumors (Table 1).

## 2. Granulocyte-Colony Stimulating Factor (G-CSF)

G-CSF-producing tumor arises from various organs (e.g. lung, stomach, esophagus, gall bladder, thyroid, urinary bladder, liver, uterine cervix, colon) [4]-[9] including ovary [10] [11]. This type of tumor produces various cytokines such as G-CSF, and induces severe granulocytosis as a paraneoplastic syndrome. The diagnostic criteria for G-CSF-producing tumor are the following; 1) extreme granulocytosis; 2) elevated serum G-CSF levels; and 3) proof of G-CSF production within the tumor cells in an analogous manner with other ectopic hormone [12].

G-CSF-producing tumors are considered to have a poor prognosis, due to the effects of G-CSF on proliferating tumor cells and enhancement of metastasis. G-CSF may therefore accelerate the clinical progression of the disease [5] [13]. Tachibana *et al.* showed that G-CSF production by transitional cell carcinoma of the bladder augments autocrine growth, which may in part explain the poor prognosis [14]. Savarese *et al.* reported that 56.5% of primary ovarian carcinoma co-expressed G-CSF and the G-CSF receptor; potential autocrine and/or paracrine loops involving G-CSF and its receptor occur in over 90% of primary ovarian carcinomas [11]. Furthermore, Natori *et al.* reported that G-CSF stimulates angiogenesis and promotes tumor growth [15]. The production of G-CSF by squamous cell carcinoma cell lines was closely related to their *in vitro* invasiveness [16]. For these reasons, G-CSF-producing cancer has a very poor prognosis, and at the present time, there is no specific approach for G-CSF-producing cancer.

## 3. Parathyroid Hormone-Related Protein (PTHrP)

Hypercalcemia is one of the important paraneoplastic syndromes, mostly occurring in patients with advanced cancer. This complication can become life threatening and requires appropriate and immediate management. Hypercalcemia accompanied by malignancy can be divided into two broad categories based on its etiology: humoral hypercalcemia due to the malignancy itself, and local osteolytic hypercalcemia by the tumor metastasized to bone. Various human malignancies have been reported to be associated with the former type of hypercalcemia, all of which have been shown to produce PTHrP [17] [18]. PTHrP induces hypercalcemia by the same mechanism as PTH.

The ovary is the most common site and there have been reports of various histological subtypes with hypercalcemia being found on this site. Small cell carcinoma and clear cell carcinoma are the most frequent subtypes, followed by serous carcinoma, squamous cell carcinoma and dysgerminoma [19]. We experienced an interesting case in which the patient's serum levels of Ca and PTHrP was elevated only at the recurrence of the cancer,

**Table 1.** Ectopic hormone-producing ovarian tumors.

Hormone	Histologic type	Ref.
Granulocyte-colony stimulating factor	Squamous cell carcinoma, serous and mucinous adenocarcinoma	[10] [11]
Parathyroid hormone-related protein	Clear cell adenocarcinoma, small cell adenocarcinoma	[19]-[21]
Adrenocorticotrophic hormone	Serous adenocarcinoma, granulose cell tumor, mature cystic teratoma	[30]-[32]
Peptide-YY	Carcinoid	[40]-[45]
Gastrin	Mucinous cystadenocarcinoma	[49] [50]
Insulin	Carcinoid	[51]-[54]

although the primary tumor specimen was immunopositive for PTHrP [20]. Kitazawa *et al.* [21] also reported a case in which the patient's serum Ca level was elevated only at the recurrence of the cancer, although PTHrP was localized at both the primary and metastatic tumor. The clear cell carcinoma in this patient seemed to acquire the ability to over-express PTHrP with the recurrence, in the absence of CA125 and CA19-9 levels influence. PTHrP has growth factor-like properties that promote tumor progression [22], and PTHrP can be a potent tumor angiogenic factor [23]. In ovarian clear cell carcinoma, PTHrP production might be an indicator of prognosis. Several reports indicate that carcinoma which has potential of PTHrP production is predicted as their poor prognosis in certain malignancies [17] [18] and as their poor response to antihypercalcemic therapy by bisphosphonate [24]. PTHrP may be the major cause of hyperglycemia in primary or recurrent clear cell carcinoma [25].

#### 4. Adrenocorticotrophic Hormone (ACTH)

Adrenocorticotrophic hormone (ACTH)-producing tumor arises from various organs. Although small cell lung cancer and medullary thyroid cancer are the most frequent, ovarian tumors can cause this syndrome [26]-[32]. This type of tumor induces the inappropriately high levels of the hormone cortisol and subsequent Cushing's syndrome as a paraneoplastic syndrome [33]. The ectopic ACTH secretion is responsible for approximately 15% of cases of Cushing's syndrome [34] [35]. The diagnosis of ectopic Cushing's syndrome involves three steps: confirmation of hypercortisolism, differentiation between ACTH-independent and -dependent causes of Cushing's syndrome, and differentiation between pituitary and ectopic sources of ACTH.

Various benign and malignant tumors have been associated with ectopic ACTH. In most cases, when ectopic ACTH is produced by malignant tumors, circulating ACTH and cortisol levels are extremely high, the duration of symptoms is short and the clinical phenotype is atypical, in comparison with pituitary dependent Cushing's syndrome. Conversely, ectopic ACTH secretion is often associated with a number of mainly neuroendocrine tumors with differing aggressiveness which produces the typical sign and symptoms of Cushing's syndrome, with a biochemical resemblance to pituitary Cushing's disease [35].

Symptoms include rapid weight gain, particularly of the trunk and face with sparing of the limbs (central obesity). Common signs include the growth of fat pads along the collarbone, on the back of the neck or "buffalo hump" and on the face "moon faces" (see Refs. [36] [37]). Suzuki *et al.* [30] reported an interesting Cushing's syndrome due to ovarian serous adenocarcinoma secreting multiple endocrine substances. The patients presented with facial swelling and skin pigmentation. She manifested hypercortilemia, high plasma ACTH, vasopressin and a-fetoprotein, and lack of dexamethasone suppression.

#### 5. Peptide-YY

Carcinoid tumors are rare, slow-growing neoplasms that arise from the neuroendocrine cells and produce biogenic amines and various polypeptides [38]. However, carcinoids of the ovary are uncommon, especially primary ovarian carcinoids, which form approximately 0.3% of all carcinoid tumors [39]. Women with carcinoid tumors may present with clinical carcinoid syndrome characterized by amine-related symptoms such as skin changes (facial flushing, telangiectasia), abdominal pain and constipation, pulmonary and cardiovascular effects [40]-[45]. Certain symptoms of the carcinoid syndrome could be induced by a gastrointestinal hormone called as PYY (the peptide (P) having an N-terminal tyrosine (Y) and C-terminal tyrosine (Y)) that has a strong inhibitory effect on intestinal motility [41]. Additionally, PYY and its analogs have been shown to inhibit the growth of various cancer cells *in vitro* and *in vivo* [46]. Matsunami *et al.* [42] have described a carcinoid syndrome, mainly severe constipation, produced by ovarian carcinoid tumor of stromal component. It is important to be aware of this entity in the pathological diagnosis of ovarian tumors, in the presence of any clinical indicator of carcinoid tumor/syndrome, as it carries a markedly better prognosis and clinical outcome in comparison with most other malignant ovarian tumors.

#### 6. Gastrin

Gastrin is a peptide hormone that stimulates secretion of gastric acid (HCl) by the parietal cells of the stomach and aids in gastric motility. In the Zollinger-Ellison syndrome, gastrin is produced at excessive levels, often by a gastrinoma (gastrin-producing tumor) of the duodenum or the pancreas. Patients with Zollinger-Ellison syndrome may experience abdominal pain and diarrhea. The diagnosis is also suspected in patients without symp-

toms who have severe ulceration of the stomach and small bowel, especially if they fail to respond to treatment [47] [48]. There have been 11 cases of gastrin-producing ovarian tumors (benign and malignant) reported in the literatures [49] [50]. All of them present with the Zollinger-Ellison syndrome.

## 7. Insulin

As mentioned before, carcinoid tumors are slow growing and originate most frequently from gastrointestinal tissue [38] [39]. They may also appear in genital tissue like the ovaries. The primary tumors are divided into insular, trabecular, strumal, or mucinous subgroups [38] [39].

There are, in literature, 5 previous reports of verified insulin production in primary carcinoid tumors of the ovary [51]-[54]. Two of these were clinically silent tumors [54]. The remaining three appeared with episodes of severe hypoglycemia [51]-[53]. Morken *et al.* [53] reported the first case of insulin producing primary carcinoid tumor of the ovary, initially presented with amnesia and hypoglycemia and subsequently successfully treated with surgery.

## 8. Conclusion

In addition to the potential for the ovary to act as a source of aberrant hormone secretion, malignant transformation may acquire the ability to secrete substances that are not normally secreted from the tissue where they originate. Syndromes involving peptide hormone or bioactive substance secretion due to aberrantly located tumors can become life threatening and require appropriate and immediate management. Once ectopic hormone producing-tumor is suspected, high-resolution cross sectional imaging is now to localize the source of ectopic hormone. Selective vein catheterization and radionuclide imaging are helpful only in selective cases. Rather than finding the source of ectopic hormone syndrome, their role is to provide additional informational information on the nature of the lesions identified with cross-sectional imaging. Failure to localize the ovarian tumor preoperatively may be associated with a significantly higher risk of subsequent unnecessary ablative procedures.

## Conflict of Interest

The authors have no conflict of interest to disclose.

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