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Aberrant Hormone Production from Ovarian Neoplasms: Strategies for Diagnosis and Therapy

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Syndromes involving peptide or nonsex steroid hormone secretion due to aberrantly located tumors are rare. We report a collected series of 16 patients with ectopic hormone production from ovarian neoplasms, including 3 patients recently encountered at our institution as well as 13 additional cases identified in the recent literature. These tumors included 2 insulin-producing ovarian carcinoids, 1 ACTH-producing pituitary adenoma within a benign ovarian cystic teratoma, 2 cortisol-producing ovarian neoplasms, 8 gastrin-producing ovarian cystadenomata or cystadenocarcinomata, and 3 thyroxine-producing ovarian strumal carcinoids. All patients presented with syndromes of hormone excess. Only 62% of all tumors were localized preoperatively. Following ovarian resection, 87% of patients remained disease-free with a median follow-up period of 1.5 years. In addition to ovariectomy, 8 additional unnecessary ablative procedures were performed in 7 patients. These included distal pancreatectomy, pancreaticoduodenectomy, adrenalectomy, total gastrectomy, selective vagotomy, and subtotal thyroidectomy. Failure to localize the ovarian neoplasm preoperatively was associated with a significantly higher risk of subsequent unnecessary ablative procedures. Because of the potential for the ovary to act as a source of aberrant hormone secretion, we recommend complete preoperative evaluation of the pelvis in female patients presenting with nonlocalizable endocrine tumors.

Although relatively rare, clinical syndromes arising from ectopic or anatomically aberrant eutopic hormone production present formidable challenges in diagnosis and tumor localization. Various imaging modalities, including computed tomography, angiography, and selective venous sampling have facilitated tumor localization in a large number of cases [1], but frequently fail to identify small or aberrantly-located tumors. For example, approximately 10% of insulinomas [2] and up to 30% of gastrinomas [3] are not localized preoperatively. In this setting, the endocrine surgeon is faced with the specter of "blind" laparotomy in an attempt to identify the source of hormone production. Recently, increasing attention has been focused on the ability of ovarian neoplasms to synthesize a wide array of hormone products [4, 5]. This report seeks to define basic strategies regarding the diagnosis and treatment of aberrant hormone-producing ovarian neoplasms, based on 3 recent cases encountered at our institution as well as from a survey of the recent literature.

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Methods

In a retrospective review of the period from 1980 to the present, 3 patients at Yale-New Haven Hospital were identified with clinically overt syndromes due to peptide or nonsex steroid hormone production by ovarian neoplasms. Data were gathered regarding age, pre- or postmenopausal status, attempts at preoperative tumor localization, details of surgical therapy, tumor size and pathology, duration of follow-up, and clinical status at last evaluation. Only patients with overt clinical syndromes related to ectopic aberrant production from an ovarian source were included in the study.

In addition, a survey of the recent literature identified 13 previously reported patients with clinical syndromes related to ectopic peptide or nonsex steroid hormone production of ovarian origin. Selected statistical analysis between groups was performed using chi-square analysis.

Results

Yale Patients

Data for the 3 Yale patients are presented in Table 1. Patient 1 presented with recurrent seizures which abated during a noneventful pregnancy. Two weeks postpartum she suffered a grand mal seizure associated with profound hypoglycemia; seizure activity resolved following glucose administration. Both serum insulin and C-peptide levels were elevated. Preoperative attempts at insulinoma localization including abdominal computed tomography, magnetic resonance imaging, and celiac and superior mesenteric angiography were unrevealing. The patient underwent laparotomy where a left ovarian mass was resected. The differential diagnosis generated at the time of frozen section

Table 1. Summary of patients encountered at Yale-New Haven Hospital with syndromes of ectopic hormone secretion due to ovarian neoplasms.

Patient no.	Age (yr)	Clinical presentation	Pathology	Disease-free?	Duration of follow-up
1	27	Hyperinsulinism	Insulin-producing strumal carcinoid	Yes	2 yr
2	24	Cushing's syndrome (ACTH excess)	Pituitary adenoma within benign cystic ovarian teratoma	Yes	5 yr
3	35	Cushing's syndrome	Cortisol-producing ovarian carcinoma	No	17 mo

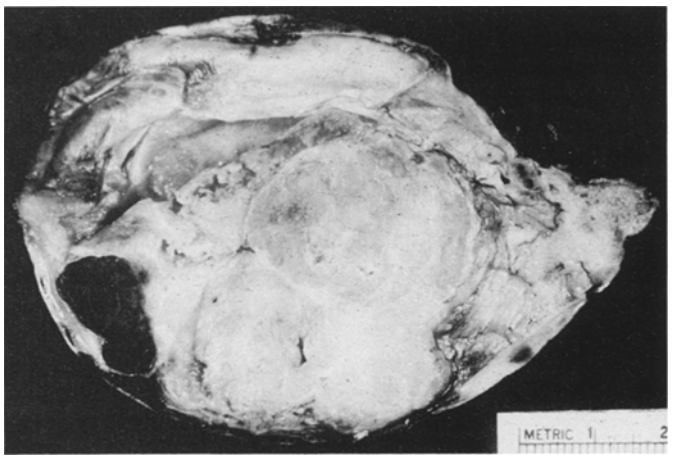

Fig. 1. A lobulated, solid neoplasm is surrounded by a thin rim of normal ovary.

included both carcinoid tumor and granulosa cell tumor (Fig. 1). Intraoperative ultrasound of the pancreas failed to demonstrate a neoplastic lesion. A distal pancreatectomy was performed. Postoperatively, the serum glucose returned to normal and she has subsequently suffered no symptoms of hypoglycemia during 24 months of follow-up. Histopathologic examination of the resected ovary demonstrated a strumal carcinoid tumor (Fig. 2). The carcinoid component of this tumor contained cells which demonstrated insulin immunoreactivity (Fig. 3). The resected distal pancreas was grossly and histologically normal.

Patients 2 and 3 have been previously described in isolated case reports [6, 7]. Briefly, patient 2 presented with rapidly progressive Cushing's syndrome and was found to have an ACTH-producing pituitary adenoma within a benign ovarian cystic teratoma. Her symptoms resolved and have not recurred during the 5 years following resection of the involved ovary. Patient 3 also presented with Cushing's syndrome and was found to have a cortisol-producing ovarian carcinoma with involvement of the contralateral ovary, uterus, cervix, urinary bladder, and omentum. Her symptoms resolved following an extensive debulking procedure, but recurred shortly prior to death 17 months later in the setting of diffuse abdominal carcinomatosis.

Literature Survey

A total of 13 patients with clinical syndromes due to peptide or nonsex steroid-producing ovarian neoplasms were identified. This included 8 patients with Zollinger-Ellison syndrome resulting from gastrin-producing ovarian tumors [8–14], 3 patients with hyperthyroidism due to thyroxine-producing ovarian strumal carcinoids [15, 16], 1 patient with Cushing's syndrome due to aberrant cortisol production from a lipoid cell tumor [17], and 1 additional patient with an insulin-producing ovarian carcinoid [18].

A summary of the data obtained from all 16 patients is presented in Table 2. The average age at diagnosis was 47 years, and 44% of patients were premenopausal at the time of diagnosis. Two tumors (one insulin-producing, one ACTH-producing), presented within 2 months postpartum. Although the average tumor size was 16 cm in diameter, preoperative detection of the ovarian neoplasm was accomplished in only 62% of patients.

Following ovarian resection, 87% of patients remained free from recurrent disease at last observation, with a median follow-up of 1.5 years. In addition to ovariectomy, 8 unnecessary ablative procedures were performed in 7 patients, including distal pancreatectomy, pancreaticoduodenectomy, adrenalectomy, total gastrectomy, selective vagotomy, and subtotal thyroidectomy.

Discussion

Syndromes of aberrant or ectopic hormone production are relatively rare. The frequency of ectopic loci ranges from 1% to 2% for insulinomas [19, 20] to approximately 10% for gastrinomas [3]. In spite of recent technical advances allowing increasingly frequent preoperative tumor localization, there still remains the occasional need for abdominal exploration and even "blind" resection in the case of nonlocalizable tumors.

In the past 2 decades, it has become increasingly clear that the ovary may act as a source of clinically significant ectopic or anatomically aberrant eutopic hormone synthesis and secretion. The current series clearly demonstrates the potential for ovarian neoplasms to produce diverse clinical syndromes including hyperinsulinism, Cushing's syndrome, Zollinger-Ellison syndrome, and hyperthyroidism.

Several points regarding the data deserve further consideration. Ovarian neoplasms producing peptide or nonsex steroid hormones can occur at any age following the onset of puberty, with an age range in this series of 20–81 years. Although definitive conclusions are difficult to make in view of small sample size, there appears to be a tendency for cortisol- and ACTH-producing tumors to occur in relatively younger women, while gastrin- and thyroxine-producing neoplasms more frequently present in the postmenopausal period. Two patients presented in the early postpartum period; the possibility that gestation and delivery may contribute to the induction of ectopic hormone-producing ovarian tumors remains intriguing but unproven.

Thirty-eight percent of the identified neoplasms occurred

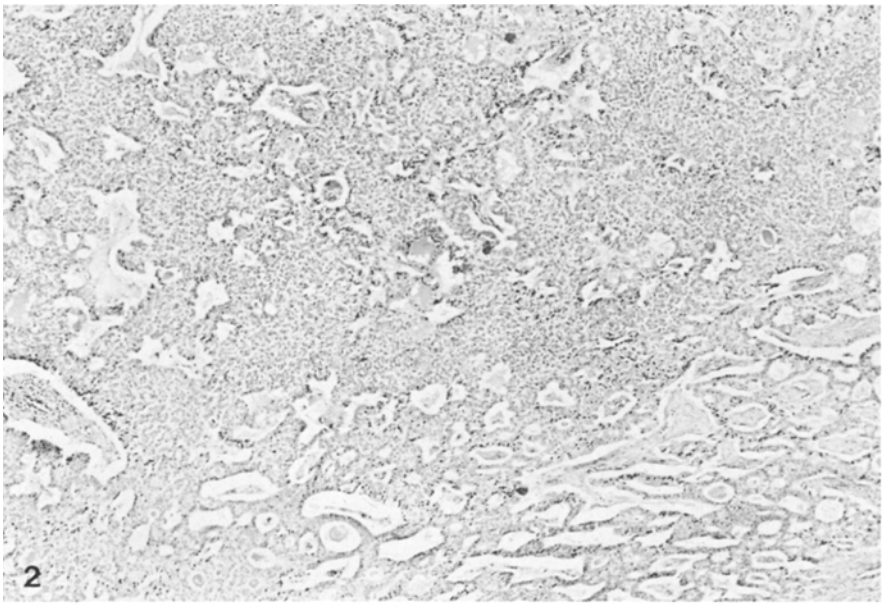

Fig. 2. The strumal carcinoid is composed of thyroid follicles which contain colloid intimately associated with the more cellular areas of colloid (hematoxylin and eosin, × 160).

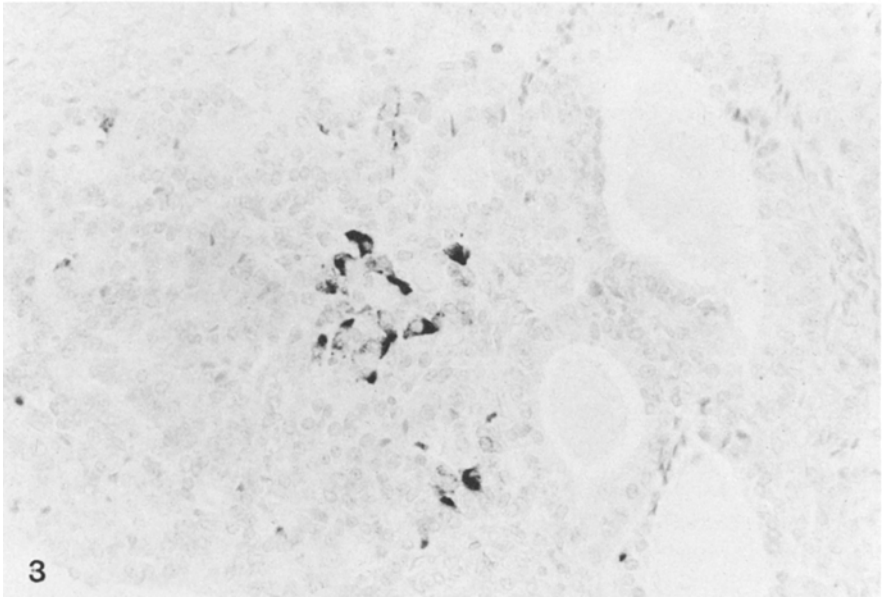

Fig. 3. Scattered cells immunoreactive for insulin are present in the areas of the carcinoid (ABC immunoperoxidase, × 40).

Table 2. Summary of data from collected series.

Hormone product	No. of patients	Mean age (yr)	Pathology	Preoperative localization	Disease-free	Median follow-up
Insulin	2	45	Strumal ovarian carcinoid (2)	0/2	1/2	2 yr
ACTH	1	24	Pituitary adenoma in benign ovarian cystic teratoma	0/1	1/1	5 yr
Cortisol	2	28	Ovarian carcinoma (1), lipoid ovarian tumor (1)	2/2	1/2	0.8 yr
Gastrin	8	50	Cystadenoma (4), cystadenocarcinoma (4)	5/8	6/6[a]	1 yr
Thyroxine	3	61	Strumal ovarian carcinoid (3)	3/3	3/3	2.5 yr
Total	16	47		10/16	12/14	1.5 yr

[a]Follow-up data unavailable for 2 patients.

within a benign ovarian cystic teratoma. This occurred in the case of 2 insulinomas, one ACTH-producing pituitary adenoma, and 3 thyroxine-producing strumal carcinoids. Ovarian strumal carcinoids are often associated with teratomatous elements, and are characterized by thyroid parenchyma interspersed with carcinoid cells [16]. These tumors rarely metastasize. When

immunohistochemically examined, almost one-half of these tumors contain cells within the carcinoid component which express a wide variety of neurohormonal peptides, including insulin, glucagon, pancreatic polypeptide, enkephalin, calcitonin, and somatostatin [4]. Only rarely, however, is immunoreactivity for a specific hormone associated with clinical features attributable to hormone excess. Within the thyroid component, typical thyroid follicles containing immunoreactive thyroglobulin are present, and while symptoms of thyroxine excess accompany less than 5% of these tumors, the true incidence of functioning thyroid tissue within these neoplasms remains unknown [16].

The other predominant group identified in the current series is characterized by ectopic hormone production within a mucinous cystadenoma or cystadenocarcinoma. This pathology was noted in 56% of identified neoplasms, including all gastrin-producing tumors as well as one insulin-producing tumor. One-half of these tumors were classified as malignant based on histologic criteria. Like cystic teratomata, ovarian cystadenomata and cystadenocarcinomata exhibit a propensity to express neurohormonal peptides [5]. Thirty percent of these neoplasms contain cells which are argyrophilic and felt to be of neuroendocrine origin [5]. Immunoreactivity for a number of neuropeptides, including gastrin, cholecystokinin, somatostatin, and enkephalin is frequently observed, with a higher percentage of immunoreactive cells in the setting of histologic malignancy. The vast majority of these peptide-producing neoplasms do not induce syndromes of hormone excess, although the true incidence of clinically-significant hormone production remains unclear.

Regardless of benign or malignant histology, the current series demonstrates the high rate of cure which results from resection of hormonally-active ovarian neoplasms. Eighty-seven percent of patients in this collective series had no evidence of either tumor or symptom recurrence following surgical therapy, with a median follow-up period of 1.5 years. The 2 treatment failures in the current series included 1 patient with a cortisol-producing ovarian carcinoma widely metastatic at the time of presentation [7] as well as 1 patient with an insulin-producing ovarian tumor discovered at postmortem examination following unsuccessful distal pancreatectomy and subsequent completion pancreaticoduodenectomy [18]. Clearly, ectopic hormone syndromes of ovarian etiology offer an opportunity for long-term cure following simple tumor resection.

In spite of the expected high rate of therapeutic success with ovarian resection, 8 additional unnecessary ablative procedures were performed in 7 patients. These procedures included distal pancreatectomy, pancreaticoduodenectomy, adrenalectomy, total gastrectomy, selective vagotomy, and subtotal thyroidectomy. The majority of these resections were performed concomitantly with simple ovariectomy for ovarian tumors which were initially felt to be incidental. In all cases, pathological examination of the additional resected tissue presumed to be responsible for excess hormone secretion revealed no evidence of hyperfunction.

In several cases, unnecessary resection was prompted by the perceived need for definitive therapy in the setting of rapidly progressive symptoms. This was apparent in patient 1 from the Yale series who suffered from recurrent hypoglycemic seizures and persistent hypoglycemia even while receiving high concentrations of intravenous dextrose. The recent availability of a long-acting somatostatin analogue may allow for medical rather than surgical control of refractory symptoms until a full preoperative evaluation can be carried out. This analogue has been shown to decrease insulin secretion from metastatic islet cell tumors [21], and also to inhibit gastrin release from ovarian cystadenomata [13].

Another factor contributing to the high rate of unnecessary resection in the current series may be the relatively low rate of preoperative tumor detection. In only 62% of all patients was an ovarian tumor identified prior to laparotomy. This rate is surprising given the fact that the subsequently identified neoplasms tended to be relatively large, with an average diameter of 16 cm. Indeed, preoperative failure to detect an ovarian tumor was statistically associated with subsequent unnecessary ablative surgery ($p < 0.05$, chi-square).

Several factors may enable an improved rate of preoperative tumor detection in the future. Clearly, a higher majority of these neoplasms might have been detected preoperatively had adequate pelvic examination been routinely performed. Bimanual examination remains a relatively simple way to detect ovarian masses as small as 4–5 cm, although its sensitivity is markedly diminished in obese patients. This may be especially relevant in the setting of truncal obesity due to Cushing's syndrome.

In several patients, preoperative detection was unsuccessful even though detailed abdominal imaging (ultrasound, computed tomography, or magnetic resonance imaging) was performed. In these patients, imaging was not extended into the pelvis and, thus, did not detect the tumor. Similarly, selective venous sampling frequently failed to include both ovarian veins. In 1 patient with a cortisol-producing tumor in this series, ovarian vein sampling did provide preoperative confirmation of an ovarian source [17].

One additional approach to preoperative tumor localization in this setting involves 99Tc-pertechnetate localization of functioning thyroid tissue within ovarian strumal carcinoids. While the true rate of technetium uptake by thyroid tissue in this ectopic position remains unknown, this method was successfully used to identify an ovarian tumor in 1 patient in the present series [15].

In spite of these strategies to improve the probability of preoperative localization, it remains likely that ovarian tumors will occasionally be discovered only at the time of exploratory laparotomy. Unless an ovarian source is confirmed by preoperative venous sampling, the finding of an ovarian neoplasm does not rule out the possibility of a hormone-producing neoplasm in a more typical location. Careful examination of the entire abdomen, therefore, remains mandatory. If not accomplished preoperatively, samples of ovarian venous blood should also be obtained for subsequent analysis.

The ideal surgical approach to the hormonally-active ovarian neoplasm is simple resection. This can often be accomplished by simple ovariectomy with histologic examination by frozen section. In the case of either strumal carcinoids or benign cystadenomata, no further therapy appears to be necessary. Although the incidence of bilaterality in cystic teratomata is approximately 10%, the current series suggests a low rate of contralateral recurrence following unilateral resection of benign disease. Certainly, the patient's future reproductive plans may

guide the extent of resection. If, on the other hand, there is pathologic or clinical evidence of malignant disease, an extensive debulking procedure should be performed including radical hysterectomy, lymph node dissection, and omental and diaphragmatic biopsies. Ideally, this procedure should be performed by a pelvic surgeon experienced in the treatment of gynecologic malignancy.

In summary, we present a collected series of 16 patients with clinical syndromes of peptide or nonsex steroid hormone excess attributable to ovarian neoplasms. The series confirms the ovary as a potential site of ectopic or aberrant eutopic hormone production. For female patients presenting with nonlocalized endocrine tumors, we advocate complete preoperative evaluation including careful pelvic examination, detailed imaging of the pelvis, and selective venous sampling including the ovarian veins when possible. In patients presenting with ectopic hormonal syndromes known to be associated with ovarian strumal carcinoids (i.e., hyperinsulinism, hyperthyroidism), consideration should also be given to 99Tc-pertechnetate scanning. Whether or not an ovarian tumor is identified preoperatively, complete abdominal exploration is mandatory at the time of laparotomy. If an ovarian tumor is encountered, it should be resected and sent for frozen section evaluation following sampling of the ovarian veins bilaterally. If no additional abdominal pathology is encountered and frozen section of the tumor indicates benign histology, the procedure may be terminated. If clinical or pathologic evidence of malignant disease is encountered, a more extensive debulking procedure may be required. In either case, blind resection of more classical hormone-producing tissue should be avoided.

Résumé

Les syndromes concernant la sécrétion d'hormones peptidique ou stéroïde nonsexuelle due à des tumeurs ectopiques sont rares. Nous rapportons une série de 16 patientes avec une production d'hormone ectopique provenant de néoplasmes ovariens, comprenant 3 patientes récemment soignées dans notre établissement ainsi que 13 cas supplémentaires relevés dans la littérature récente. Ces tumeurs comprennent 2 tumeurs carcinoïdes ovariennes productrices d'insuline, 1 adénome hypophysaire producteur d'ACTH à l'intérieur d'un tératome cystique ovarien bénin, 2 néoplasmes ovariens producteurs de cortisol, 8 cystadénomes ou cystadénocarcinomes ovariens producteurs de gastrine, et 3 carcinoïdes ovariens strumaux producteurs de thyroxine. Toutes les patientes avaient des syndromes d'hyperproduction hormonale. Soixante-deux pour cent seulement des tumeurs avaient été localisées en préopératoire. Après ovariectomie, 87% des patientes étaient apparamment sans récidive avec un suivi médian d'un an et demi. Cependent, outre l'ovariectomie, 8 interventions supplémentaires non nécessaires ont été accomplis chez 7 patientes. Celles-ci comprenaient: pancréatectomie distale, duodénopancréatectomie, surrénalectomie, gastrectomie totale, vagotomie sélective, et thyroïdectomie subtotale. L'impossibilité de localiser le néoplasme ovarien en période préopératoire était associée à un risque notoirement plus grand de faire une résection inutile. Compte tenu de la possibilité pour l'ovaire de se comporter en producteur de sécrétion ectopique d'hormone, nous recommandons un examen complet préopératoire du bassin chez les femmes se présentant avec des tumeurs endocrines non localisables.

Resumen

Los síndromes relacionados con la secreción de péptidos o de hormonas esteroideas no sexuales por tumores de ubicación aberrante ocurren infrecuentemente. En este artículo reportamos una serie de 16 pacientes con producción hormonal ectópica por neoplasmas ováricos, la cual incluye 3 pacientes vistos recientemente en nuestra institución y 13 identificados en la literatura médica de los últimos años. El grupo incluye 2 carcinoides ováricos productores de insulina, 1 adenoma pituitario productor de ACTH, 2 neoplasmas ováricos productores de cortisol, 8 cistadenomas o cistadenocarcinomas ováricos productores de gastrina, y 3 carcinoides ováricos estrumales productores de tiroxina. Todas las pacientes se presentaron con síndromes de exceso hormonal. En sólo el 62% de los tumores se pudo establecer la ubicación anatómica en la fase preoperatoria. Después de realizada la resección del ovario, 87% de las pacientes permanecieron libres de enfermedad en el período de seguimiento, que fue de 1.5 años en promedio. Además de la resección ovárica, se practicaron otros 8 procedimientos adicionales innecesarios en 7 pacientes. Estos incluyeron pancreatectomía distal, pancreatoduodenectomía, adrenalectomía, gatrectomía total, vagotomía selectiva, y tiroidectomía subtotal. La falla en la localización preoperatoria del neoplasma ovárico apareció asociada con un riesgo aumentado de ulteriores procedimientos quirúrgicos innecesarios. En vista de la potencialidad del ovario de actuar como fuente de secreción hormonal aberrante, nosotros recomendamos una completa evaluación de la pelvis en las pacientes femeninas en quienes se diagnostiquen tumores endocrinos no localizables.

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Invited Commentary

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This article draws our attention to a rare but important biological phenomenon—the production of hormones from ectopic sites. Aberrant hormone production can occur from one endocrine gland to another. Pheochromocytomas, for example, can secrete calcitonin [1]. Ectopic production of hormones (calcitonin, ACTH, and β-MSH) occurs more frequently in tumors derived from APUD cells [2]. The biosynthesis of hormones in nonendocrine tumors is acknowledged and the review by Rees of this subject remains the starting point for studies in this field [3].

The clinical detection of endocrine hyperfunction initiates a search for the source. This is sometimes as obvious as the goiter and other signs of Graves' disease, but in Cushing's syndrome due to ectopic ACTH production, for example, the primary neoplasm may never be uncovered until postmortem. The most important message from the present article is—"Difficulty with locating an obvious source of excess hormone production—think of the ovaries." The ovaries must then be examined clinically and by scanning techniques—ultrasound, magnetic resonance imaging, or computed tomography scanning. The detection of a tumor should then be followed by pelvic vein blood sampling to confirm hormone production, and this can be done relatively easily and with low morbidity.

If ovarian ectopic endocrine hyperfunction cannot be confirmed, is there justification for other ablative procedures carried out at laparotomy? Probably not. Most of the additional procedures carried out in patients in this series were major, unnecessary, and could be associated with significant morbidity (permanent in the case of total pancreatectomy) and mortality.

Intraoperative ultrasound is now able to detect tumors of less than 1 cm in diameter and selective venous sampling can often define areas of interest within the pancreas [4]. Vinik and associates [5] have said that "blind pancreatic resection can no longer be justified" and "the procedure not only increases the operative morbidity but may fail to remove the tumor."

The detection of an ovarian tumor in the presence of ectopic hormone production demands appropriate therapy for this neoplasm. Frozen sections may provide some assurance that "endocrine cure" is likely, especially if a teratoma or carcinoid tumor is reported.

Postoperatively, the syndrome is likely to regress if the ovary were the source of hormone production. If not, there are adequate medical therapies which should be instituted during the subsequent further investigation of the patient. The effects of hypergastrinemia can be controlled by the use of H_2-receptor blockers [6] or proton pump blockers such as omeprazole [7]. Excess insulin production can be treated with diazoxide [8]. Excess cortisol production is blocked by metyrapone and somatostatin analogues may block peptide and amine production from carcinoids [9] and many other tumors [10].

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