HYPERNEPHROMA OF THE OVARY

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Some authors doubt the occurrence of a primary hypernephroma of the ovary and consider ovarian tumors resembling the classic renal hypernephroma as having arisen from lutein cells. Others, emphasizing the sharp differences between the development and arrangement of lutein cells and those of the so-called ovarian hypernephroma, accept the latter as a tumor entity, without reserve. At the present time the latter view has gained some precedence.

Peham (1), in 1899, published the first report of a hypernephroma of the ovary. This was in a multipara, aged forty-five, complaining of malaise, anorexia, and abdominal pain. The growth was a huge cystic tumor, composed of large vacuolated cells containing glycogen granules, and resembling the tissues in the zona glomerulosa of the suprarenal cortex. The tumor seems to have been benign, as there is no mention of recurrence. Although Peham introduced the term "hypernephroma of the ovary," Ulrich (2) in 1895 had described nodules of tissues in both ovaries which were similar to the accessory nodules of suprarenal gland tissues in the broad ligaments reported in 1883 by Marchand (3).

Pick (4), in 1901, described a tumor 9.0 by 7.5 by 7.5 cm. in the right ovary of a woman aged fifty-one. It was multicystic, seemed to arise in the hilum of the ovary, and was considered a primary hypernephroma. The post-mortem examination, twenty-one months later, demonstrated tumor tissue in the brain, both kidneys, and the left suprarenal gland. These tumors apparently were malignant and the conditions mentioned suggest the possibility that a renal or suprarenal tumor was the primary growth and the others, including the one in the ovary, were secondary.

Robert Meyer (5), in 1903, published an account of a tumor of the ovary which corresponded closely to the description by Pick, and in 1908 he reported another ovarian tumor as hypernephroid in structure. Sternberg (6), in 1906, recorded two tumors of hypernephroma structure in a patient aged eighteen, the larger in the left ovary and the other in the left parametrial tissues. Compressed ovarian tissue was seen about the periphery of the larger growth. This tumor probably began centrally and grew into the ovary, which formed a thin capsule. In 1907 Debevre and Riche (7) reported the presence of suprarenal tissues in the left ovary of a child, aged four, with precocious puberty, and in 1909 von Rosthorn (8) described a patient with tumors of both ovaries structurally similar to suprarenal gland tissue.

Vonwiller (9), in 1911, described a nodular encapsulated tumor as large as a man's fist in the right ovary. The cut surface showed yellow tissue alternating with gray and hemorrhagic areas. The ovarian stroma stretched over the tumor like a capsule. Vonwiller believed the hypernephrogenic nature of this tumor to be unquestionable. Alamartine and Maurizot (10), in 1912, re-
ported a tumor the size of an orange in the broad ligament and nodules in an enlarged ovary in a woman aged twenty-eight. The growth seemed to arise in the ovary and the mass in the ligament may have been metastatic.

Lévy du Pan (11), in 1924, described a tumor of the ovary in a woman aged twenty-eight, resembling the cortex of the suprarenal gland and containing large amounts of glycogen. He believed that the glycogen coefficient of a tumor indicated its malignancy. In the same year, Downes and Knox (12) described a similar tumor in a three-year-old girl. The autopsy, two years later, disclosed metastatic growths in the lungs, pleura, diaphragm, and liver.

The latest report, by Novak (13), includes tumors described by McCullagh and Graham, by Schattenberg, and Miller, and one previously published by Rottino (14). Rottino's patient was a Porto Rican girl aged twenty, with amenorrhea, deep voice, enlarged clitoris and hirsutism. The enlarged right ovary was removed and contained a nodule 3.0 by 2.5 by 2.5 cm., encapsulated by a thin layer of ovarian tissue. Histologic examination disclosed tissues similar to the cortex of the suprarenal gland. After six months the patient seemed well and had lost the masculine symptoms.

Other reports of primary ovarian hypernephromas are those of Scudder (15), Pfannenstiel (16), Delfourd and Lucien (17), Muller (18), Orrù and Volpe (19), Komocki (20), Reiners (21), Gough (22), Mathias (23), Büttner (24), Turco (25), Gardner and McCleary (26), Gaudier (27), and Saltykow (28).

The diagnosis of hypernephroma of the ovary in the reported cases was reached on the basis of the gross features, the general resemblance of cell structure to that in hypernephroma of the kidney, and the glycogen and fat content of the cells. The gross characteristics alone are inconclusive. In size the tumors varied markedly. Some were cystic, others solid, and the color was reported as gray or yellow with admixtures of brown. Recent and old hemorrhages were noted. Microscopically the tumors were seen to consist of groups or cords of large, pale, granular or vacuolated cells with vesicular, oval, or indented nuclei and definite cell membranes. A delicate vascular stroma formed the framework and separated the cell masses into alveoli or columns, resembling the structure of the suprarenal cortex. Pick (4), Peham (1), Sternberg (6), von Rosthorn (8), Bovin (29), Pfannenstiel (16), Lévy du Pan (11), Downes and Knox (12), Schwoerer (30), Miller (31), and Reiners (21) reported the presence of glycogen granules in the cells. Most of the descriptions mention fat droplets.

The tumors described by Pick (4), Meyer (5), Sternberg (6), Scudder (15), Downes and Knox (12) produced metastases. Pick's patient died twenty-one months after the ovarian tumor had been removed; many metastases were disclosed by the post-mortem examination. The subject of Sternberg's report had a recurrence six weeks after operation. The child with the tumor reported by Downes and Knox died after two years. Many of the other tumors appear to have followed a benign course. The recorded descriptions show no correlation between age and the occurrence of hypernephromas of the ovary. The ages ranged between three and sixty-five years.

The objections advanced against the occurrence of primary hypernephroma in the ovary include the denial of the displacement into the ovary of cortical
tissues of the suprarenal gland, the so-called accessory glands of Marchand. Glynn (32), Neumann (33), Pfannenstiel (16), and Miller (31) believed that these accessory nodules appear in the broad ligament but not in the ovary. In indirect support of their view, they cite the absence of such accessory nodules in the testis. Bovin considered the presence of suprarenal cortex tissues in the ovary possible, a view fully accepted by Downes and Knox (12), Sternberg (6), Schiller (34), Vonwiller (9), Reiners (21), and others. According to Miller (31), the few hypernephromas of the ovary reported cannot be accepted as primarily ovarian, but rather as growths of accessory suprarenal gland tissue in the broad ligament.

Those who oppose the hypernephroma concept believe that these tumors are derived from lutein tissues. Traut and Butterworth (35) consider the lutein-cell tumors a result of luteinization of granulosa-cell growths. The lutein cells, they state, are unable to differentiate further. This view was reached because some granulosa-cell tumors are partially luteinized, because completely luteinized granulosa cells resemble lutein cells, and because in the lutein tumors there are no undifferentiated (young) cells or cells in mitosis. Schiller (36), Geist (37), Brewer (38), and others agree.

Turnbull's (39) discussion of the differentiation between ectopic suprarenal cortical tissue, adenomas of the suprarenal cortex, and lutein bodies analyzes several disputed characteristics of cell arrangement and structure. The lutein body, he stated, has a central stellate core with centrifugal tapering trabeculae. Organization occurs rapidly at the periphery and tapering vascular trabeculae pass from the ovarian stroma to the center, thus arranging the lutein cells in folds. The centers of the accessory cortical bodies and cortical adenomas contain veins and one or more fibrous trabeculae. In aberrant suprarenal bodies the arrangement of the cells of the suprarenal cortex is duplicated. The cells of cortical adenomas are arranged usually in acini separated by a delicate vascular connective tissue. In contrast, the parenchyma of lutein tissues is traversed by a capillary network and there is no definite acinar structure. The cells of ectopic suprarenal bodies and cortical adenomas are acidophilic and granular, or spongy. Variations from the round or polygonal cells are rare. They are not so large, usually, as those of the lutein bodies, though the nuclei are larger. Most of the cells of the lutein bodies have a homogeneous cytoplasm, rarely spongy, and less acidophilic than the cytoplasm of the cells of the cortical bodies. Variations in shape are common, the cells often being elongated with axes radially directed to the center. The cells are larger than the average cell of the suprarenal cortex. Schiller (40) stated that the cells of a corpus luteum are never sharply demarcated from each other by walls and that they are connected by intracellular fibers, while the cells of hypernephromas are clear with sharp borders.

Corner, Bartelmez, and Hartman (41) described lipid inclusions in corpus luteum cells but did not mention glycogen. The hypernephroma cells, however, have generous quantities of glycogen. Glynn (42) believed that were examinations made in lutein growths glycogen would be found in some and perhaps all. According to Ewing (43), glycogen occurs in cells of embryonal tumors and is abundant in hypernephromas, teratomas, and choriomas.

Fat is mentioned in practically all reports as a constituent of the cells of
hypernephroma. Pick (4) reported large and small fat droplets; Scudder (15) described "fatty degeneration." Vonwiller (9) stated definitely that the vacuoles in the cells were fat. Orrù and Volpe (19), by the Ciaccio method, found that the peripheral portions of the droplets contained phosphorized fats (lecithin, etc.) and the central portions neutral fats (cholesterol, etc.). This distribution, they state, is analogous to the staining properties of the fats in the cells of the suprarenal cortex. In chloroform, ether, and alcohol extractions, Hochloff (44) recovered lecithin and cholesterol. Greenhill (45) found that the chemistry of tumor cells resembled that of the cells from which they arise, particularly in respect to lipid storage and chemical metabolism. He stated that suprarenal cortical rests in the ovary which have become neoplastic are frequently diagnosed as luteomas, luteinized granulosa-cell tumors, or hypernephromas of the ovary. In one such case an abundance of intracellular lipid crystals with certain morphologic staining and polariscopic properties was found. None was demonstrated in any of the other tumors examined nor in tissues of a corpus luteum or of a renal hypernephroma. Many were observed in a cortical adenoma of the suprarenal. The observations of Delamarre and Lécène (Lévy du Pan, 11) substantiate this.

At present, any conclusions concerning the effects of the so-called hypernephromas of the ovary upon the sex characteristics are overshadowed by the possibility that the diagnosis of the tumor may have been incorrect. The four-year-old child described by Debeyre and Riche (7) had hair on the mons pubis and hypertrophy of the vulva, as did Büttner's (24) ten-year-old patient. Menstrual irregularities are reported by Delfourd and Lucien (17), Scudder (15), Bovin (29), Gough (22), and Rottino (14). Marked hirsutism of the face and mons pubis was noted by Orrù and Volpe (19) and Hochloff (44). Glynn states that secondary sex changes are not produced by ovarian hypernephromas. Downes and Knox regard imbalance of secretions between the ovary and tumor cells as a possible cause of these symptoms. According to Orrù and Volpe a regression of ovarian fetal hormonal action may perhaps cause virilism. Schiller considers these theories merely a collection of unexplained facts. He believes that differentiation of the tumors should be on a morphological and chemical basis rather than on theoretic physiological grounds.

**REPORT OF A CASE**

A white woman, aged forty-two, entered the gynecological service of St. Luke's Hospital, Chicago, on May 9, 1937, in the care of Dr. E. A. Edwards. She complained of frequency of menstruation, a growing mass in the abdomen noticed for a year, nausea and vomiting, general gastro-intestinal distress for a few months, a cough of two months' duration, and chronic constipation. Her menstrual periods, beginning at sixteen, had occurred every twenty-eight days with a duration of seven days until two months before admission, when she began to menstruate every two weeks. The amount of flow and the duration of the periods had not increased. There had been no bladder symptoms.

The patient had been married nineteen years and had an eighteen-year-old son. She gave no history of tuberculosis, diabetes, goiter, or cancer, or of dysmenorrhea, leukorrhea or metrorrhagia. She had lost twenty pounds in the past few months. She had occasional tachycardia and palpitation, but no pain, hemoptysis, dyspnea, or ankle edema. Her appetite was fair. Constipation, present for years, had been severe in the past few months. There was no rectal bleeding. No changes in the secondary sex characteristics were observed.
The woman was fairly well nourished and not acutely ill. Her blood pressure was 140/90 mm. Hg. The abdomen was enlarged but not obese. A large, firm, fixed mass extended from the pelvis to above the umbilicus in the midline. It was nodular and apparently not cystic. There was no tenderness. The uterus was displaced to the right by the tumor. The clinical diagnosis was fibromyoma of the uterus or ovarian tumor. Two weeks before operation the erythrocyte count was 4,340,000, the leukocyte count 15,800 per c.mm., and the hemoglobin 65 per cent (Sahli).

On May 10, 1937, under ethylene and ether anesthesia, a supravaginal hysterectomy and left salpingo-oophorectomy were performed and a large multilocular, solid and cystic ovarian tumor was removed. The peritoneal cavity contained a small amount of fluid. There were no secondary nodules in the abdomen or on the surface of the liver. The tumor arose from the left ovary; the right ovary was not diseased. The patient received postoperative roent-

![Fig. 1. Photograph of a Broad Surface Made by Sectioning the Ovarian Hypernephroma](image)

Note the regions with colliquative necrosis and the lobulated gray and lighter colored (yellow) solid tissues.

gen therapy to the abdomen and after an uneventful convalescence was discharged from the hospital. Deep roentgen therapy was continued. An intravenous pyelogram made nineteen months after operation disclosed no deformity of the kidneys.

**Gross Pathology:** The ovoid, flattened mass, weighing six pounds and two ounces, measured 23.5 by 20.0 by 12.0 cm. It had a fibrous capsule torn in a number of places and stretched across at one end was a fallopian tube, about 18 cm. long and 3 to 4 mm. in diameter. The cut surface (Fig. 1) showed a solid tissue composed of yellow necrotic portions mixed with gray. There were also cyst-like pockets ranging from 3 to 6 cm. in diameter. Portions of the gray tissues taken for histological examination were soft and had the gross appearance of carcinoma.

**Histology:** Tissues from the tumor varied considerably in structure because of necrosis. The gray portions consisted of aggregates of cells, generally large, swollen, and pale, arranged in alveoli (Fig. 2). Between the alveoli were narrow, vascular, fibrous septa. Along the margin of some of the larger septa were a few aggregates of small cells. The cytoplasm was
granular, compact, and the nuclei were vesicular. These cells merged directly into the large swollen cells. Considerable fat was present in the cells of the necrotic portions, but the large pale cells in the intact tissues contained very little lipid material. In sections stained with osmic acid, a few scattered cells, some near the necrotic portions and more in the necrotic tissues, contained black granules. Sections of Zenker-fixed tissues embedded in paraffin were stained for glycogen. The cytoplasm of the large pale cells was laden with large and small globules of glycogen material, but this was lost in control preparations treated with saliva and then stained. Analysis of 240 grams of the moist formalin-fixed ovarian tissue showed a glycogen content of 1.78 per cent of the moist weight.

In cellular structure and the high glycogen content of the cells this tumor resembles more closely a hypernephroma than a tumor of the corpus luteum. Dr. Walter Schiller, who examined the histologic preparations, also expressed this opinion. The illustrations (Figs. 14, 15, and 16, especially Fig. 14) of adrenal tumors of the ovary in a recent report by Novak (13) show a structure duplicating that of the tumor in our patient. The growth seems to have been benign, since nineteen months after surgical removal there has been no recurrence.

SUMMARY

A solid and pseudo-cystic tumor of the left ovary, weighing 6 pounds and 2 ounces, was removed from a woman aged forty-two years, who had had increased menstruation and a pelvic mass for at least one year. Histologically the tumor consisted of large, pale, granular cells with distinct cell membranes, arranged in cords and alveoli, resembling the tissues in the cortex of the suprarenal gland. The cytoplasm of the cells contained numerous coarse and fine granules of glycogen. A chemical analysis of 240 grams of formalin-fixed

![Fig. 2. Photomicrograph showing large pale cells with granular cytoplasm, sharp cell membranes, and alveolar arrangement. × 198](image)
tissues demonstrated a glycogen content of approximately 1.78 per cent of the moist weight. The cytologic structure and the chemical analysis thus suggest a hypernephroma rather than a lutein-cell tumor.

BIBLIOGRAPHY

36. Schiller, W.: Personal communication.