

OVARIAN RETE CYSTS *

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Cysts of the ovarian hilus have been produced in experimental animals, but have not received much attention in human beings.¹ The normal human ovary has a cluster of small tubules and foci of interstitial cells resembling Leydig cells of the testis, both located in ovarian medullary tissue in the rete region where the mesovarium is attached (Fig. 1). Earlier embryologic opinion was that rete tubules were homologous to the male vas deferens, but according to Gillman² rete cords in the female are essentially sex cords developing from coelomic epithelium and not of mesonephric (wolffian duct) origin.³

In a review of ovaries from 740 women, obtained at necropsy, ovarian rete cysts were identified in 25 (3.4 per cent). Most of these cysts were small, and only 5 were described grossly as filled with clear fluid. These measured 0.4 to 2 cm. in diameter. Others were recognized microscopically. The site of origin in the abundant, tough, medullary, fibrous tissue of the rete would tend to interfere with the enlargement of rete cysts to sizes which could be recognized clinically.

Microscopically, most of the rete cysts ordinarily would be considered as "simple cysts." Their anatomical location and the resemblance of lining epithelium to the normal rete tubules served to distinguish this specific group. The epithelium was at times composed of tall columnar cells crowded together, with basal nuclei and with bulbous, irregular, free margins. In their lack of smooth, regular, cytoplasmic margins and arrangement they resembled wolffian urogenital epithelial structures rather than müllerian derivatives. Also, when stretched, the cells lacked a regular epithelial polarity and size, but instead showed variable size, overlapping or stratification, and rounded cytoplasmic projections such as characterize mesothelial, mesonephric, or paraovarian cysts. Simulation of the epithelium in immature human testicular tubules, rete of adult testes, and areas in some adenomatoid tumors of epididymis was observed also (Figs. 2 and 3).

The underlying stroma was composed of ordinary collagenous fibrous tissue. In some instances foci of calcification or ossification were observed (Fig. 4), similar to changes observed in the vas def-

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erens, particularly in diabetes mellitus.⁴ Comparable stromal metaplasias also are observed in some retroperitoneal neoplasms believed to originate from the urogenital ridge.⁵

The term ovarian rete cysts has been used mostly in animal pathology. It avoids the possible ambiguity of the term hilar cyst, since hilus cells of the ovary may refer also to the interstitial cells of Leydig type found in the ovarian hilus.

The 25 women with these cysts were from 27 to 84 years old, but all except 6 were over 55 years of age. In 5 cases the rete cysts were bilateral. In 8 of the women there was also ovarian cortical stromal hyperplasia⁶ present. Each of 2 patients had had one ovary removed surgically, and in another instance parts of both ovaries had been resected.

Eleven patients had cancer, including 2 cases of cervical and 2 of mammary carcinoma. There were also one case each of adenocarcinoma of endometrium, gallbladder, colon, and lung, one case of gastric carcinoma simplex, one of chronic leukemia, and one of lymphosarcoma. Five other patients had diabetes mellitus, 3 with hyalinized pancreatic islets. Seven had histories of hypertension, and 5 were obese. Two had biliary cirrhosis and one, cardiac cirrhosis secondary to rheumatic heart disease.

Hyperplastic changes were observed in some endocrine organs of 20 cases, usually limited to glands of one or two types. Adrenal cortical hyperplasia was found in 6 women and a demarcated adrenal adenoma in another case. Four others had abnormally nodular adrenal cortical architecture. In the pancreas, islets of Langerhans were increased in size and number in 6 instances. Papillary or adenomatous pancreatic duct hyperplasia was observed in 7 cases. Adenomatous goiter was found in 5 women, and 2 had diffusely hypertrophied glands. One thyroid fetal adenoma was identified. Parathyroid glands were examined in 6 of the necropsies. One mixed chief and oxyphil-cell adenoma was found, without osteitis fibrosa cystica; and 2 cases had oxyphil nodules identified.⁷ One thymus was enlarged.

Two of three pituitary glands examined showed an adenomatous increase of eosinophils, and in one gland the basophils also were hyperplastic. This latter patient was a 62-year-old diabetic woman with obesity, nodular adrenal cortical hyperplasia and adenoma, hypertension, hypertrophy of the thyroid gland, and hyperostosis frontalis interna. Evidently she represented an example of Morgagni's syndrome⁸ of hyperpituitarism.

Endometrial polyps were observed in 5 cases, one also with endometrial carcinoma. Four other women had endometrial hyperplasia, usually of cystic pattern. In 5 uteri, leiomyomas were found. Intestinal polyps were present in 3 cases, including 2 polyps of colon and one of duodenum.

Masculinization, with facial hirsutism or partial baldness, was present in one case each. One woman had Paget's disease of calvarial bone.

DISCUSSION

A majority of the women with ovarian rete cysts had morphologic evidences of endocrine imbalances. The abnormalities were not of any one particular type, but took the following patterns:

(1) Hyperestrinism, with endometrial polyps or cystic hyperplasia, 9 cases.⁹ In 4 of these, ovarian cortical stromal hyperplasia was present. Two others with atrophic ovaries had hepatic cirrhosis, and 2 demonstrated abnormal nodularity of adrenal cortices. The remaining case had had one ovary removed surgically.

(2) Gynecologic operations, 4 cases. Three patients had either one ovary removed, or parts of both ovaries resected. One had a supracervical hysterectomy.

(3) Masculinization, 2 cases. It is likely that other instances were overlooked, including the woman with Morgagni's syndrome. Adenomatous hyperplasia of rete tubules and stroma without cyst formation has been observed with arrhenoblastoma.¹⁰

(4) Adrenal cortical hyperplasia or adenoma, 7 cases. Four of these women were obese, and 3 had diabetes mellitus. The nodular hyperplasia involved chiefly the zonae fasciculata and reticularis.

(5) Hyperpituitary function, shown by hyperplasia of multiple endocrine glands and adenomatous pituitary architecture, 20 and 2 cases, respectively. The most frequent combinations were ovarian cortical stromal or pancreatic islet hyperplasia with adrenal cortical hyperplasia, 4 cases each. Obesity, diabetes, adrenal cortical hyperplasia, and thyroid hypertrophy occurred together in 2 women.

(6) Local factors, 3 cases. The remaining cases of this series lacked the above changes, but had abnormalities of pelvic circulation. In 2 cases this interference with blood supply was secondary to carcinoma of the cervix, and in one to regional ileitis. Perhaps local pressures occasionally may have predisposed mechanically to the formation of rete cysts.

In the series of human cases, etiologic factors suggested for rete

cysts corresponded closely to those already found in experimental animals.

(1) Estrogenic hormone injections have led to the development of ovarian hilar tubules, to cysts, or to adenomas in guinea-pigs, rabbits, or rats given large doses of estrin for at least 3 weeks.¹¹ Rats treated from early life with estrone benzoate, with or without equine pituitary extract, had these proliferations and also "syncytial tubules" resembling those of sterile testes.¹² Estradiol benzoate or propionate, or diethylstilbestrol similarly were effective in female guinea-pigs, their use being accompanied by a hyperplastic growth of ovarian germinal epithelium and some neoplastic derivatives.^{13,14} Implantation of testes into the necks of newborn, littermate, female mice was followed after 250 to 408 days by formation in their ovaries of rete cysts up to two thirds the size of the ovarian cross section. Pfeiffer¹⁵ attributed these cysts and other abnormalities observed to constant endogenous estrogen production by the persisting immature testicular implants.

(2) Surgical fragmentation of ovaries in guinea-pigs has been reported by Lipschutz¹⁶ to lead to a development of rete cysts in the ovarian remnant, and masculinization indicated by hypertrophy of the clitoris.

(3) Testosterone propionate treatment of newborn female rats for 30 days or ante-natal and post-natal testosterone in mice had similar effects on both the ovarian rete and clitoris.^{12,17}

(4) Adenomatous adrenal cortical nodules followed intrasplenic ovarian grafting in ovariectomized mice, associated with neoplastic proliferations of the granulosa cells.¹⁸ Tubular adenomatous rete nodules also were present, and the illustration provided by Furth and Sobel¹⁸ resembles those of Lipschutz.¹⁶

(5) Intrasplenic implantation of ovaries is a further experimental technique observed to produce abnormal medullary tubules and nodular hypertrophic rete growths of tubules and stroma.¹⁶ Induced ovarian-hypophysial imbalance in this situation is generally considered to involve a functional hyperpituitarism. It is not unlikely that the other experimental techniques depended also partly on induced pituitary dysfunction for their effectiveness in producing rete cysts.

Another morphologic stigma of hormonal imbalance is provided by the recognition of human ovarian rete cysts. They are not specific for any single hormonal abnormality, but are found in women who have endocrine dystrophies which appear to be similar to the experimental conditions leading to ovarian rete cyst formation in animals.

SUMMARY

Twenty-five human cases of ovarian rete cysts are reported. Only 5 were recognized macroscopically. Others were microscopic and lined with an epithelium characteristic of rete tubules. Women with these cysts usually had other tissue alterations at necropsy, classifiable as evidences of hyperestrinism, adrenal cortical dysfunction, or pituitary hyperfunction. Two women showed masculinization. Four had previous gynecologic operations. These are the same conditions found to be associated with ovarian rete cyst or adenoma formation in experimental animals.

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LEGENDS FOR FIGURES

- FIG. 1. Normal cluster of rete tubules in the ovarian hilus of a woman 56 years old. Hematoxylin and eosin stain. $\times 250$.
- FIG. 2. Rete cysts from the ovary of a 38-year-old woman who died of uremia secondary to carcinoma of the cervix. The cysts were bilateral. Of note is the abundance of interstitial hilus cells. Hematoxylin and eosin stain. $\times 150$.
- FIG. 3. Ovarian rete cysts, lined by flattened or columnar epithelium, from a woman 60 years old who died of cardiac failure. Cardiac cirrhosis, a mucosal polyp of the colon, and hyperplasia of pancreatic ducts and endometrium were present. Eosin and methylene blue stain. $\times 125$.
- FIG. 4. Calcification of the wall of a rete cyst from the ovary of a 63-year-old patient, dying of pulmonary embolism following resection of a colonic carcinoma. Prominent adrenal zona reticularis, hyperplasia of ovarian cortical stroma, and endometrial cystic hyperplasia were observed also. Eosin and methylene blue stain. $\times 250$.

