LUTEINIZATION OF FOLLICLE CYSTS IN RAT OVARIES AS AN EFFECT OF POTASSIUM IODINE ADMINISTRATION

(UDC 618.11-006.2-06:618.19]-085.777.12-092.4/9)

I. O. Smirnova

Laboratory of Experimental Hormone Therapy (Head-Cand. of Biol. Sciences N. I. Lazarev) Institute for Experimental and Clinical Oncology (Director, Active Member AMN SSSR Prof. N. N. Blokhin) AMN SSSR, Moscow
(Presented by Corresponding Member AMN SSSR L. M. Shabad)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 57, No. 5, pp. 94-98, May, 1964
Original article submitted May 11, 1963

Recently there has clearly been established the dependence of the development of mastopathy on the presence of follicular ovarian cysts. Thus, in most rats, a dishormonal proliferation appears in the mammary glands three to five months after the appearance of follicle cysts in the ovaries [1].

The experimental data fully conform the clinical. In women, 10-15 years after the removal of a myomatous uterus where cystic changes were present in the ovaries, no pathologic processes are detected in the mammary glands, whereas after hysterectomy without removal of cystic ovaries, most women develop mastopathy after 10-15 years [3].

However, the deciding role for follicular cysts in the development of mastopathy was elucidated in experiments in which the removal of cystic ovaries not only prevented the development of mastopathy but led to its disappearance [2]. Moreover, we succeeded in proving that the appearance of mastopathy may precede the application of hormone therapy directed at the liquidation of ovarian follicle cysts in the organism. Thus, in our laboratory it has been established that short term effects of chorionic gonadotrophins, which possess luteinizing properties, evoke in most experimental rats luteinization of follicular ovarian cysts which precede the appearance of mastopathy.

It would seem that the application of chorionic gonadotrophins might be considered the method of choice of luteinizing follicular cysts and, correspondingly, a method for curing mastopathy. However, clinically, a number of authors [8, 9, 12, 13] have established that exogenous gonadotrophin often evokes rupture of the cysts, accompanied by various complications which demand operative intervention. Of course, this method cannot be recommended in clinical practice and other possibilities for luteinization of follicular ovarian cysts must be sought.

One such possibility comes from an analysis of the causes for the appearance of follicle cysts. According to contemporary views, persisting follicles and follicle cysts arise as a consequence of insufficient luteinizing function of the pituitary [2, 5, 10]. One must expect that an increase in the production of endogenous luteinizing hormone (LH) also may stimulate luteinization of follicle cysts. In distinction to the results of exogenous gonadotrophins in this case, the level of LH rises to the upper limits of the physiologic dose, which stimulates the normal ovarian cycle.

Thus, the goal of our investigation comes to the study of possible luteinization of follicular ovarian cysts as a result of stimulation by products of endogenous LH. To solve this problem we used data from zootechnic endocrinology [6, 7], according to which a microdose of potassium iodide (KI) may be used to increase the production of this hormone in the organism. By studying the problem of dryness in the cow, produced by the presence of persisting ovarian follicles, it was established that microiodotherapy markedly stimulated LH production and that an increased level of LH normalized the ovarian cycle and ended the cow's sterility. This method of stimulating LH production was used in these investigations.

METHODS

Forty rats with follicular cysts of the ovaries were placed under observation. In 25 of them the development of cysts had been stimulated by X-ray (300 R) treatment directed to the lumbar region, and in 15, by subtotal castration.

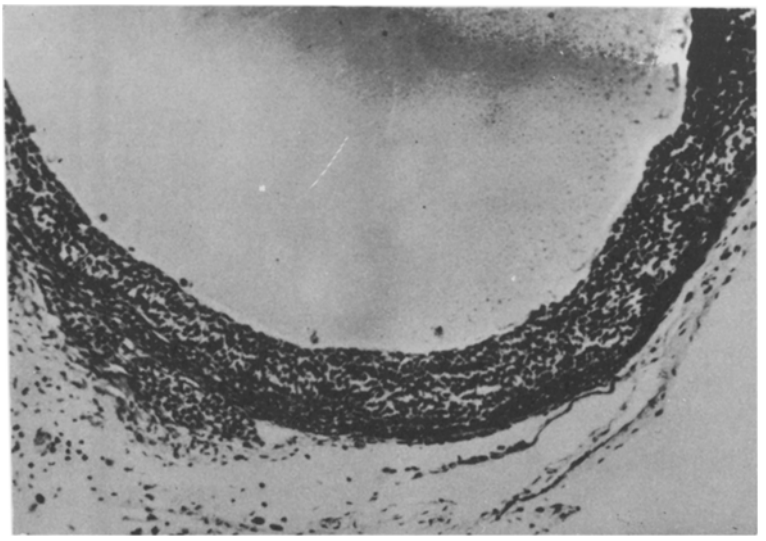

Fig. 1. Structure of a typical follicle cyst, produced after X-irradiation (300 R) in a rat ovary. The walls of the cyst consist of several rows of small granule cells next to which lie the theca interna and theca externa. Microphotograph. Magnification 130 ×.

In rats with follicle cysts constant estrus appeared, as detected by vaginal smears. During the study, the rats underwent laparotomy several times in order that the distribution of ovarian cysts might be recorded and the changes in them followed.

Potassium iodide was given orally to 27 rats in their drinking water at a dose of 500 micrograms daily for 7 weeks after which the rats were observed for another 5 weeks. The remaining rats served as controls.

In 5-10 days after beginning KI treatment, 15 out of 17 rats (88%) had a cessation of estrus, testifying to a decrease in levels of endogenous estrogen. At laparotomy during this time, it was established that the cessation of

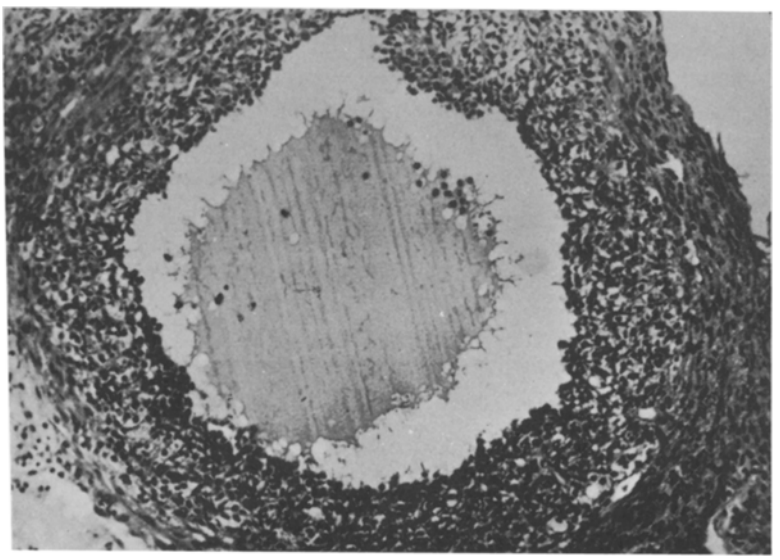

Fig. 2. Luteinization of the granular lining of a follicle cyst after treatment with KI. The regular distribution of cells is disrupted. Vacuolization of the cytoplasm is evident in many cells. Photomicrograph. Magnification 130 ×.

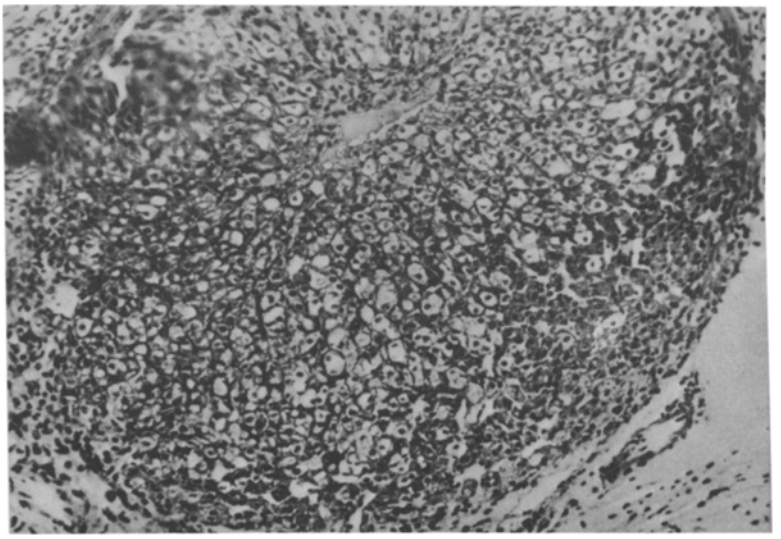

Fig. 3. Corpus luteum which developed from a follicle cyst under the action of KI. Photomicrograph. Magnification 130 ×.

estrus was accompanied by luteinization of the walls of the follicle cysts. A second laparotomy showed that the cyst walls grew thicker with time and that fully luteinized cysts were complete at the end of the second week after starting KI treatment.

To study the morphologic changes which were taking place in the follicle cysts under the influence of KI, 10 rats were sacrificed at different times, from 4-22 days after initiation of KI.

RESULTS

Upon morphologic study of the ovaries of the control rats we established that the thickness of the granular layer of the follicle cysts may vary with the location; however, most frequently the entire wall of the cyst consists of 5-15 rows of cells (Fig. 1). The cell nucleus is rather more compact than in granule cells of normal follicles. They have a round or oval shape and are surrounded by a comparatively small amount of basophilic cytoplasm. The theca interna usually consists of round epithelial-like cells and shades into the theca externa, which consists of stretched out, spindle-shaped cells.

In the ovaries of rats, sacrificed on the fifth day of KI treatment, the follicle cysts have changed noticeably: the nuclei of the cells in the cyst wall are distributed more sparsely, and are somewhat increased in size and part of the centrally positioned cells are desquamated (Fig. 2).

In rats which have received KI for 7 days cysts are frequently observed to have thicker epithelial linings. In cells from the walls of such cysts more or less straight-positioned nuclei, characteristic for follicle cysts, are not present; the nuclei have become even more compact and the amount of cytoplasm is greater; clear cytoplasmic vacuoles appear. In individual cells all the cytoplasm may appear as a large clear vacuole with a pyknotic nucleus pushed to the periphery. This vacuolization of the cytoplasm is related to the accumulation of lipid material and represents the process of luteinization of the follicle cyst [2, 11].

In parts of the cyst the luteinization is poorly apparent and affects only some granular cells; in other cysts the process is markedly expressed. Cells of the theca interna also grow bigger, round up and become morphologically indistinguishable from luteinized granule cells. In the ovaries of certain animals such an ovarian stroma is also involved in luteinization.

In parallel to the process of luteinization, the cavity of the cysts diminishes in size. Already by the seventh day of KI supplementation the ovaries of the rats have become corpora lutei and their central cavities have either shrunken markedly or have collapsed and have been replaced with connective tissue (Fig. 3).

Ovaries of rats which have received KI for 22 days contain in addition to the many corpora lutea, in several instances large cysts with their walls preserved; such cysts have been transformed into typical corpus luteum cysts.

The morphologic changes described indicate that the action of KI is to stimulate the production of LH in the rat.

After stopping the administration of KI the nature of changes in the estral cycle in the experimental animals varied during the five weeks of observation. In 4 rats the cycle became normal; in 6 it was irregular with changes in the stage of estrus, in 5 animals estrus ceased and in the others there was a prolonged diestrus. Estrus did not cease in two rats.

It is interesting to note that in our experiments, as in the effect of exogenous gonadotrophin, the estral cycle became normal in rats with small follicle cysts which were transformed into small corpora lutea. But in those animals whose large follicle cysts formed large corpora lutea, diestrus appeared, for a time, after which uninterrupted estrus resumed. Probably, in such instances, the presence of large corpora lutea prevented normalization of the estral cycle over a prolonged period (for their involution requires several weeks) by delaying ovulation in ripening follicles which have the capacity to form new follicle cysts.

In contrast to the experiments with application of chorionic gonadotrophin, in which luteinization of the follicle cysts began in 2-4 days and ended by the 10th day of treatment, our experiments with KI caused luteinization of the cysts from the fifth to fourteenth day. It is possible that the difference is explicable on the basis of the mechanism of action: application of CGT immediately has an action on the cysts directly whereas KI requires some time for stimulation of endogenous LH production.

Our results on iodine treatment of follicular ovarian cysts serve to recommend the use of this method on a clinical basis in our institute with the goal of treating mastopathy. In clinical investigations the therapeutic effect of KI is observed in the majority of severe mastopathies [4].

From the data presented, it follows that microiodotherapy produces luteinization in experimentally produced follicle cysts in rats and leads to a decrease in the estrogen level.

SUMMARY

Following X-irradiation or subtotal castration rats developed follicular cysts of the ovaries; this was accompanied by hyperestrogenism of the organism manifested in the appearance of a constant estrus. In connection with the fact that the development of follicular cysts was caused by insufficiency of the luteinizing function of the hypophysis an attempt was made to stimulate the luteinizing hormone production by microdoses of potassium iodine. The daily administration of KI in a dose of 500 γ provoked within 2 weeks luteinization of follicular cysts and their transformation into corpus luteum. Luteinization of the cysts was accompanied by a marked reduction of the body estrogen level, as manifested by the arrest of estrus with subsequent normalization of the estral cycle or a prolonged diestrus.

Under study were the morphological changes occurring in the follicular cysts during their luteinization under the effect of KI.

The process of gradual transformation of follicular cysts into corpora lutea was followed up.

LITERATURE CITED

1. E. A. Ird, Probl. endokrinol (1961), No. 4, p. 35.
2. E. A. Ird, Significance of Follicular Ovarian Cysts in the Development of Dishormonal Tumors (Experimental Investigation) [in Russian] Cand. dissertation, Moscow (1962).
3. Yu. N. Korepanov, Probl. endokrinol. (1963), No. 1, p. 95.
4. N. I. Lazarev, V. I. Yanishevskii, E. G. Bishnyakova, and others. Thesis proceedings of the 8th International Anti-Cancer Congress [in Russian], Moscow (1962), p. 347.
5. S. K. Lesnoi, In book: Principles of Clinical Endocrinology [in Russian], Moscow (1958), p. 221.
6. E. I. Smirnova, Uchen. zapiski 2nd Moskovsk. med. in-ta (1958), Vol. 16, p. 175.
7. E. I. Smirnova, Zhivotnovodstro (1960), No. 1, p. 86.
8. C. Beclere, Presse méd. (1960), Vol. 68, p. 31.
9. Idem, Sem. Hop. Paris (1962), Vol. 38, p. 3897.

10. D. Brian-Brachetto, Tex. Rep. Biol. Med. (1956), Vol. 14, p. 276.
11. E. Pederson, Am. J. Anat. (1951), Vol. 88, p. 397.
12. H. Stange and K. Schaumkell, Z. Geburtsh. Gynak. (1958), Bd. 151, S. 113.
13. I. Stein and M. Cohen, Am. J. Obstet. Gynec. (1939), Vol. 38, p. 465.

All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
