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Review Article

Histology of the normal ovary in premenopausal patients☆

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ABSTRACT

Detailed descriptions of ovarian histology are rare. We reviewed in detail 57 cases of normal ovaries in premenopausal patients, when the ovaries are active and primordial follicles are found. We also proposed updated definitions to more clearly distinguish inclusion cysts, which do not have a known relationship with any disease process, from endosalpingiosis, a lesion closely associated with low grade serous neoplasia of the ovary. The most interesting findings were the significant variation in the histologic features including the variation in the amount and the distribution of primordial follicles, follicular cysts, and endosalpingiosis, within the ovary and between both ovaries in the same patient, the frequent presence of primordial follicles in the medulla, specifically in cases of multiple follicular cysts, and the frequent presence of endosalpingiosis.

We believe that to confirm a pathologic process in the ovary, we need to become familiar with the histologic features of the normal ovary and their variations.

1. Introduction

There are studies describing the normal histology of the ovary, but we believe that these descriptions are incomplete, covering the histology only in general terms, without many details [1-4]. We decided to review the histology of healthy ovaries when they are active, in premenopausal women, rather than when their activity decreases after menopause.

During our review of primary ovarian neoplasms, we noticed that the residual ovary in some cases had features that could be abnormal; however, to our knowledge there are no detailed studies of the normal ovary with which to compare the abnormal findings. We believe that the study of the normal ovary will facilitate the understanding of the neoplastic ovary in cases of primary epithelial neoplasms.

2. Materials and methods

In this retrospective review of 57 cases from the various institutions of the authors, all patients were premenopausal. Most were younger than age 45 years. Patients older than 45 years were included when either the menstrual history confirmed premenopausal status or when a corpus luteum was histologically identified. For 32 cases, the ovaries were obtained from autopsy material of women who had died suddenly; in 25 cases, the ovaries were obtained from patients who had prophylactic resections. Six cases from autopsies were not included because of poor tissue preservation.

In 30 cases, we reviewed findings from both ovaries from an individual patient. In all cases, we reviewed from 1 to 12 slides, with an average of 4 slides per case. In every case, we evaluated changes in the

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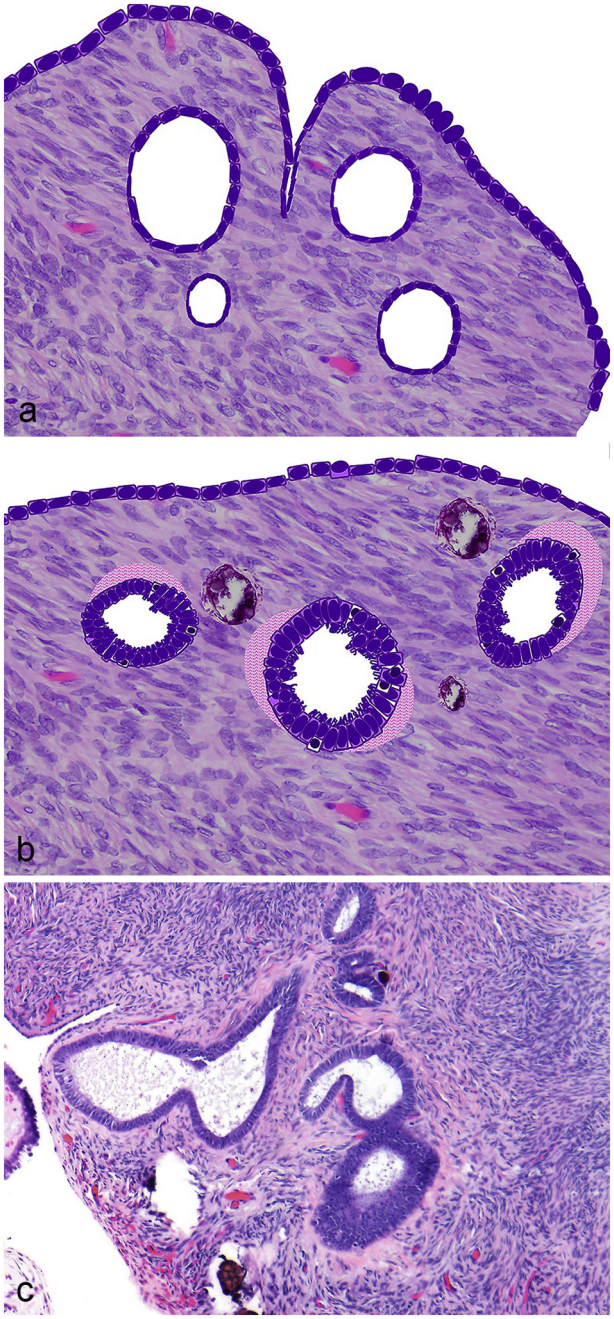

Fig. 1. A – Diagram - simple cysts lined by mesothelial cells. Note the invagination of the surface. B – Diagram - endosalpingiosis lined by tubal epithelium associated with calcifications, and focally, surrounded by a fibrous rim. C - Endosalpingiosis involving ovarian cortex with multiple glands, several of which are surrounded by an eosinophilic band of tissue, and calcifications.

ovarian cortex, including the albuginea and cellular cortex, and in the medulla. The number and location of the primordial follicles with oocytes and the presence of follicular cysts, endosalpingiosis, inclusion cysts, and simple cysts were documented. All of these histologic features were quantified with use of a low-power field (4× objective and an approximate 5-mm field diameter). On the basis of the definition of polycystic ovarian syndrome, a follicle was designated as cystic when it measured 2 mm or more [5].

Institutional review board approval was obtained independently from the multiple participating institutions.

The following definitions were used in this study:

Mesothelial inclusion cysts: Superficial cysts that are seen in ovaries with clefts, are primarily lined with flat mesothelial cells, although tubal metaplasia that is not associated with calcifications can be focally seen (Fig. 1A). These cysts are likely formed by invaginations of the mesothelial surface.

Endosalpingiosis: Endosalpingiosis is a condition in which glands or cysts, frequently multiple, can be found in any location, that is lined by fallopian tube–like epithelium, usually associated with calcifications. In most cases of endosalpingiosis, the ovaries have a smooth surface (without clefts). Endosalpingiosis might appear surrounded with a thin rim of fibrotic tissue (Fig. 1B–C).

3. Results

The ovarian parenchyma in premenopausal patients is composed of four different parts, the albuginea, the cellular cortex, the primordial follicles, and the medulla. Patients' ages ranged from 14 to 50 years, with a median of 34 years.

3.1. Albuginea

The most superficial part of the ovary is a hypocellular fibrotic layer known as albuginea, which has an average thickness of 0.3 mm. In 32 (56%) of 57 study patients, the albuginea was readily identifiable, at least focally (Fig. 2). In the remaining patients, the interface between the albuginea and the cellular cortex was blurred and indistinct.

3.2. Cellular cortex

Under the albuginea is a hypercellular cortex that is approximately 0.3 mm thick. All normal ovaries had a hypercellular cortex, very easy to distinguish from the hypocellular albuginea above or the medulla below. The cells in the cellular cortex are spindled with the axis parallel to the surface.

In 5 of 15 cases, small granulomas composed of lymphocytes, histiocytes, and reactive stromal cells were found in the cortex of patients older than 40 years. We could not find a relationship between these granulomas and other histologic features.

3.3. Primordial follicles and oocytes

In all cases, the distribution and frequency of the primordial follicles containing oocytes was not uniform. Foci of numerous oocytes were seen alternating with areas with very few oocytes (Fig. 3). Since the

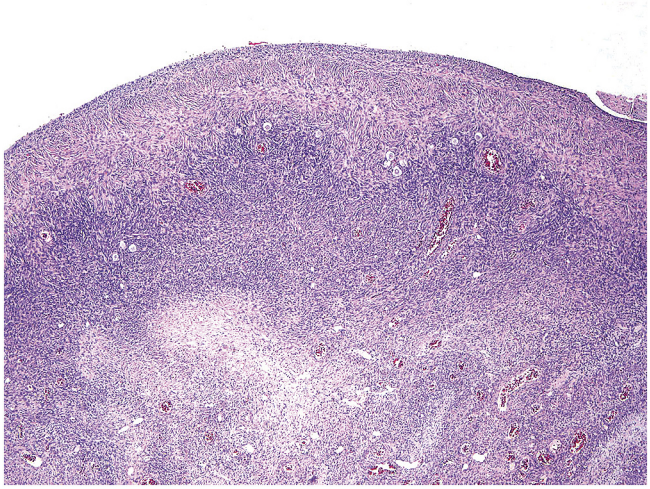

Fig. 2. Normal ovary. Fibrotic albuginea overlying cellular cortex. Numerous primordial follicles containing oocytes in the interface between the albuginea and the cellular cortex. Underlying the cortex is the medulla with vessels and a corpus albicans.

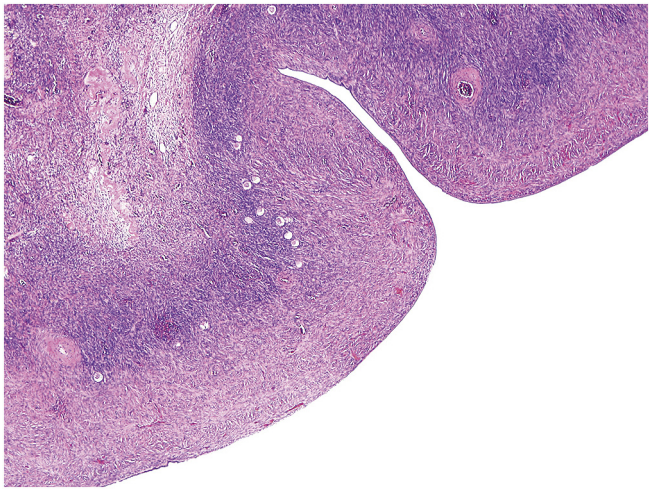

Fig. 3. Normal ovary. Irregular distribution of primordial follicles and oocytes. A deep cleft is seen in the ovarian parenchyma, which is not associated with cysts.

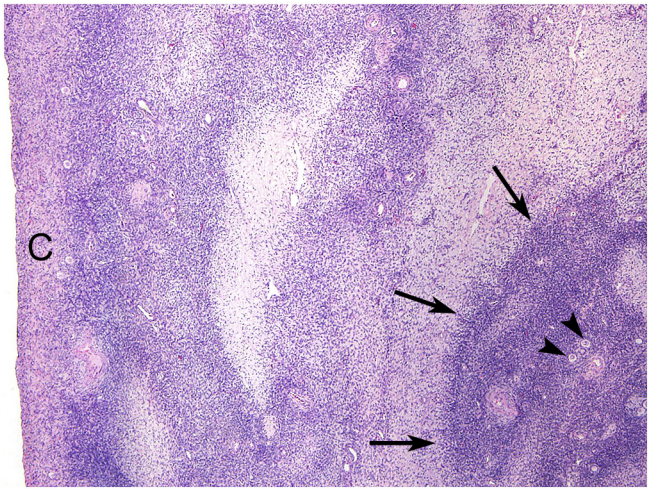

Fig. 5. Normal ovary with a nodule of spindle cells deep in the medulla (long arrows), C cortex. Arrowheads indicate numerous primordial follicles in the nodule.

number of primordial follicles containing oocytes varied according to patients' ages, we separated the cases into three arbitrary age groups as follows: 14 to 29 years, 30 to 39 years, and 40 to 50 years (Fig. 4). We arbitrarily chose 5 primordial follicles with oocytes visible on a low-power field to separate cases with abundant versus a low number of primordial follicles with oocytes.

In patients aged 14 to 29 years, there was a significant predominance of > 5 primordial follicles with oocytes. In those aged 40 to 50 years, there were more patients with fewer than 5 primordial follicles with oocytes than there were patients with > 5 primordial follicles with oocytes. In patients age 30 to 39 years, the number of patients with primordial follicles with oocytes was variable, but without the predominance of > 5 primordial follicles as seen in patients younger than 30 years or < 5 primordial follicles as seen in patients over 39 years.

A very interesting finding was observed in patients from whom both ovaries had been resected. In 16 of 30 of these patients, there was significant variation in the number of primordial follicles and oocytes between both ovaries; in 8 of the 16 patients with significant variation, one ovary had more than double the number of primordial follicles with oocytes than the opposite ovary had. In the remaining 14 patients from whom both ovaries had been resected, the number of primordial follicles containing oocytes was similar in both ovaries.

In all 57 study patients, the primordial follicles were located in the cellular cortex or in the interface between the cellular cortex and the albuginea. In addition, in 12 patients, primordial follicles were found in the medulla, in areas of nodular cellular proliferation similar to the cells in the cortex (Fig. 5). These nodular proliferations containing primordial follicles in the medulla are more frequent in cases with multiple follicular cysts.

Additional observations regarding primordial follicles and oocytes. In the developing corpus luteum, a cellular cortex near the corpus luteum was not seen, and only hypocellular areas with edema were present in these cortical areas. These findings are in keeping with the dynamic and adaptive state of the premenopausal ovary to cyclical hormonal changes.

The primordial follicles are lined by a single layer of flat granulosa cells. Early maturation was characterized by cuboidal granulosa cells. In most cases, the cytoplasm of the oocytes was not clearly visible. The nuclei were clear and granular with prominent nucleoli. In some cases, the oocytes had a basophilic appearance with chromatin condensation,

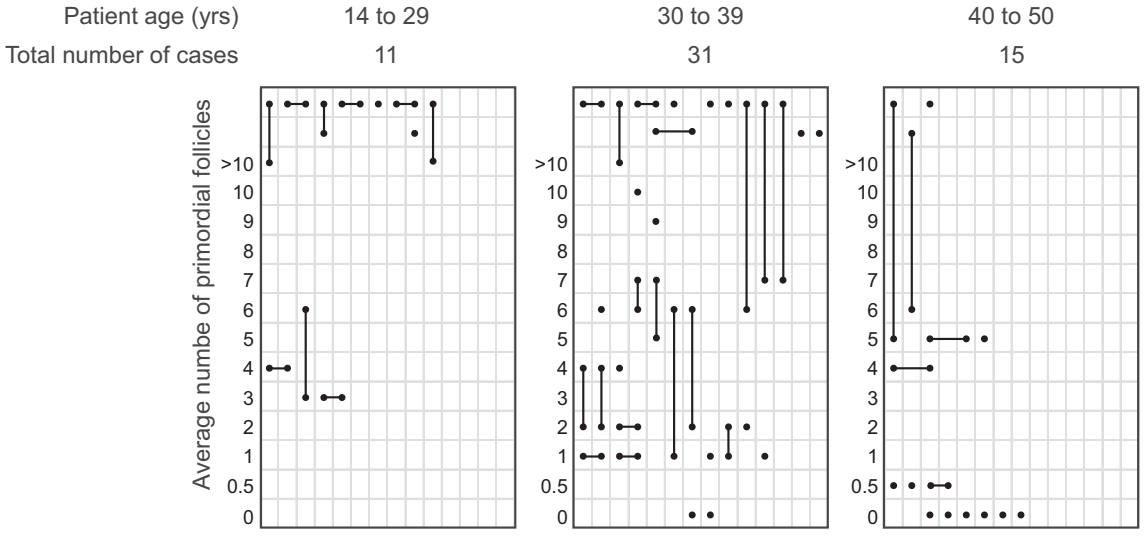

Fig. 4. 0 to > 10: average number of primordial follicles per low-power field. Each "•" symbol indicates the average number of primordial follicles with oocytes in each case. Two "•" symbols connected by a line indicate that both ovaries have been resected. A horizontal line indicates that both ovaries had a similar number of follicles. A vertical line indicates that both ovaries had a different number of follicles.

which could be due to a fixation artifact or a degenerative process. Rarely, the nuclei of two oocytes were found in one primordial follicle.

3.4. Medulla

Under the cellular cortex is a hypocellular medulla containing numerous vessels, which has the appearance of hydropic myxoid tissue. In 40 (70%) of 57 patients, groups of cells similar to the ones in the cortex were seen in the medulla, forming nodules in 15 patients and a diffuse proliferation in 25 patients. Of these 40 patients, 32 were older than 34 years. In 12 of the 15 patients in whom the cellular proliferation in the medulla formed nodules, primordial follicles were found between the spindle cells. In most patients, abundant blood vessels, usually small and thin-walled, were present in the medulla.

We have found two abnormal features that because of their frequency we believe should be included in the description of normal, healthy ovaries, follicular cysts and endosalpingiosis.

3.5. Follicular cysts

Follicular cysts were found in 46 (81%) of the 57 study patients. When both ovaries were resected, the number of follicular cysts was different between both ovaries. In 20 patients, the follicular cysts were single; 26 patients had multiple cysts. The size of the follicular cysts ranged from 2 to 9 mm, and they were located in the outer half of the ovarian parenchyma. In 13 patients, follicular cysts were also found in the medulla. In several patients with follicular cysts, one ovary had numerous cysts and the opposite ovary did not have any.

3.6. Endosalpingiosis

Endosalpingiosis was seen in 28 (49%) of the 57 study patients (Fig. 1C), and calcifications were found in the endosalpingiosis tissue of 24 (86%) of these 28 patients.

4. Discussion

Very few studies involving the normal histology of the ovary have been conducted, and we were unable to find detailed descriptions of this histology. However, if we are not familiar with the normal architecture of the ovary and the range of variations in patients without pathology, we would not be able to determine whether a lesion that develops in an ovary is associated with an abnormality in the ovarian tissue.

The fibrotic, hypocellular, most superficial part of the ovarian surface, the albuginea, described in most histology books was clearly seen in only 32 (56%) of the 57 study cases. In 25 (44%) of the 57 cases, it was not possible to identify the albuginea.

One of the most important parts of the ovary is the cellular cortex. The spindle cells of this area, recognized as the most enzymatically active cells [6], are very important in the metabolization of steroids that have estrogen as the final product. This may be the reason that primordial follicles are in the cellular cortex or between the cellular cortex and the albuginea, where the hormonal background of the spindle cells in the cortex is more important.

Regarding the primordial follicles, we have found significant variation in the distribution of the primordial follicles within an ovary and also between different ovaries. Fields without primordial follicles alternate with fields with numerous primordial follicles. In 8 of 16 patients in whom both ovaries had been resected, one ovary had more than double the number of primordial follicles with oocytes than the opposite ovary had. The significance of this variation is uncertain; however, it might be important in the development of follicular cysts and in the maturation of the follicles during fertilization.

The medulla is hypocellular, contrasting with the hypercellularity of the cortex, and has numerous vessels that sometimes even give the appearance of an angiomatous organ. The frequent presence of nodular or diffuse spindle cell proliferation in the medulla can have various explanations. Proliferations that are nodular or diffuse without primordial follicles probably represent a response to stimulation by follicle-stimulating hormone, which would be consistent with the age of the patients (most of whom in this group were older than 35 years). If hormone production by the ovary fails, a response could be the proliferation of cells to compensate the deficit [7]. However, the presence of nodular proliferations containing primordial follicles suggests that these proliferations are not a reactive change but could represent an abnormal development of the ovary, and they might explain the presence of follicular cysts in that medulla of the ovary, it is probably difficult for these follicles to reach the cortex. These stromal nodules have been recognized for a long time as active hormonal nodules because of the presence of oxidative enzymes in the cytoplasm [1–9].

Follicular cysts, similar to primordial follicles, again illustrate that the ovaries are completely independent organs since one ovary can show one or many follicular cysts while the opposite ovary can be devoid of these cysts.

Distinguishing endosalpingiosis from inclusion cysts is very important because endosalpingiosis has been associated with low-grade serous neoplasia. We reported this relationship in 1998 when we found that recurrence of stage I serous borderline tumors was associated with the presence of endosalpingiosis [8]. Other studies have shown that endosalpingiosis can be seen in lymph nodes and that if these lymph nodes are affected by low-grade serous tumors, the number of endosalpingiosis foci are typically doubled [9].

5. Summary

This detailed description of the histology of the normal ovary documents the distribution of the primordial follicles according to patient age and demonstrates the variation in the amount of primordial follicles, follicular cysts, and endosalpingiosis between both ovaries in individual patients. Recognizing that both ovaries are independent organs and that in a significant number of cases, one ovary can have different features from the opposite ovary would be the first step to understanding why some lesions and neoplasms are unilateral and some are bilateral.

Compliance with ethical standards

Funding

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Declaration of competing interest

None.

The authors do not have any conflicts of interest with the study.

Contributions

1. Elvio G. Silva, M.D. – Designed the study, re-reviewed all cases, wrote the paper.
2. Grace Kim, M.D. – Obtained and reviewed cases from USC. Participated in the design and the writing of the study.
3. Rania Bakar, M.D. – Collected and reviewed cases from CSMC.
4. Zehra Bozdag, M.D. – Collected and reviewed cases from Turkey.
5. Alexandra Shaye-Brown, M.D. – Collected and reviewed cases. Participated in the design and writing of the study.
6. Sanam Loghavi, M.D. – Participated in the design and writing of the study.
7. Simona Stolnicu, M.D. – Collected and reviewed cases from Romania.
8. Viorel Hadareanu, M.D. Collected and reviewed cases from

Romania.
9. Diana Bulgaru, M.D. – M.D. Collected and reviewed cases from Romania.
10. Lilian Isabel Cayax, M.D. – Collected and reviewed cases from Guatemala.
11. Martha Cecilia Tuñon Pitalua, M.D. – Collected and reviewed cases from Colombia.
12. Karen Pinto, M.D. – Collected and reviewed cases from Dallas.

It has been very difficult to obtain normal ovaries from premenopausal women. This is the reason for the large number of contributors.

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