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Autoimmune Oophoritis

—A Case Report—

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A case is described of an autoimmune oophoritis that was diagnosed unexpectedly after a hysterectomy and bilateral salpingo-oophorectomy had been performed on the suspicion of ovarian cysts. The patient was a 43-year-old multiparous woman who presented with vaginal bleeding and lower abdominal pain which she had had for one month. Grossly, the ovaries were enlarged and multicystic. The cysts measured up to 3.0 cm. The major histological change was a lymphoplasmacytic infiltrate in close relation to the theca interna of developing, cystic and atretic follicles, but sparing the primordial follicles. The infiltrate increased in density with the follicular maturation and culminated against the corpus luteum. With involution of the developing follicles, the inflammatory infiltrate subsided to some extent. The proportion of the plasma cells increased with the density of the infiltrates. Immunohistochemical study of the ovarian mononuclear cell infiltrate revealed a mixture of B-and T-lymphocytes. The plama cells were polyclonal. These histological features of the present case are typical of autoimmune oophorits although the presence of autoantibodies and hormonal level in the patient's serum were unknown. This case may be identified as in the early active stage of autoimmune oophoritis.

Key Words: *Autoimmune oophoritis, Ovary, Autoimmune disease.*

INTRODUCTION

Autoimmune oophoritis is one of the autoimmune diseases characterized by the presence of both antisteroid-producing cell antibodies in serum and mononuclear cell infiltrates in the affected organs (Irvine, 1980). It provokes premature ovarian failure and is frequently associated with one or more autoimmune diseases (Irvine et al., 1968; Irvine and Barnes, 1975). More recently, pathologists have begun to define the morphologic features of autoimmune oophoritis (Russell et al., 1982; Gloor and Hurlimann, 1984; Sedmak et al., 1987). And its wide clinical spectrum has also been demonstrated (Bannatyne et al., 1990). However, little is still known about its natural history. To date, about thirty cases of autoimmune oophoritis have been reported in the world literature, but no such case has been described in Korea. This case was discovered incidentally on histologic examination following total hysterectomy and bilateral salpingo-oophorectomy for the suspicous ovarian cyst.

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CASE HISTORY

The patient was a 43-year-old woman with a history of vaginal bleeding and lower abdominal pain of 1 month duration. She had four previous pregnancies including two miscarriages. Menarche had occurred at age 15 years, and she had regular menses on a 28-day cycle until 5 years ago when her menses became profuse, painful, and irregular. The last menses occurred 9 days prior to admission. On pelvic examination the cystic mass was palpated in the right ovary, for which total hysterectomy and bilateral salpingo-oophorectomy were done.

Grossly, the right and left ovaries measured 5×5×3

cm and 5×4×1.5 cm, respectively. Both ovaries contained several cysts of various sizes, ranging from 0.4 cm to 3.0 cm in diameter. The cysts had smooth linings and were filled with bloody or clear fluid. The largest cyst was in the diffuse edematous and hemorrhagic right ovary (Fig. 1).

Microscopically, the ovaries contained primordial, developing, and atretic follicles. There were many luteininzed cystic follicles and a cystic corpus luteum. The most striking change was a lymphoplasmacytic cell infiltrate in close relation to the theca interna of developing follicles-the more advanced the follicles, the denser the inflammatory infiltrate and the greater the preponderance of plasma cells. But the primordial follicles remained intact (Fig. 2). In preantral follicles the inflammatory cells that consisted chiefly of lymphocytes were sparsely and focally noted in only the theca cell layer (Fig. 3). Antral and luteinized cystic follicles were surrounded by a denser inflammatory crown occupying the theca cell layer and invading focally the granulosa cells which appeared degenerate with focal disruption or sloughing into the antral fluid (Fig. 4). Atretic follicles were overrun by a dense infiltrate of mononuclear cells. The largest cyst was a cystic corpus lutem where both granulosa and theca lutein layers were heavily infiltrated by numerous plasma cells and a few lymphocytes. It resembled a narrow meandering ribbon and the granulosa was disorganized by severe degeneration and destruction (Fig. 5, 6). A regressing corpus luteum showed similar features to that of the cystic corpus lutum. With involution of the developing follicles, the inflammatory infiltrate subsided to some extent. Residual inflammation was noted around a corpora albicantia (Fig. 7). There was a sparse lymphocytic infiltrate, especially around the blood vessels in the medulla. An immunohistochemical staining against the monoclonal antibodies of MT1 (BioGenex, San Ramon, Calif), L26, and immunoglobulin kappa and lamda light chains (Dakopatts, Copenhagen, Denmark), using the peroxidase-antiperoxidase method, was done on the paraffin-embedded ovarian tissue. The ovarian mononuclear cell infiltrate revealed a mixture of B-and T-lymphocytes. The plama cells were stained against both anti-human immunoglobulin kappa and lambda light chain. The right ovary had findings of acute torsion such as diffuse stromal edema, congestion, and multiple hemorrhage. The uterus measured 8×6×4 cm and weighed 90 gm. It contained a 3 cm diametered endometrial polyp and adenomyosis. The endometrium was composed of narrow glands with mitosis and a dense stroma. The fallopian tubes displayed no inflammation.

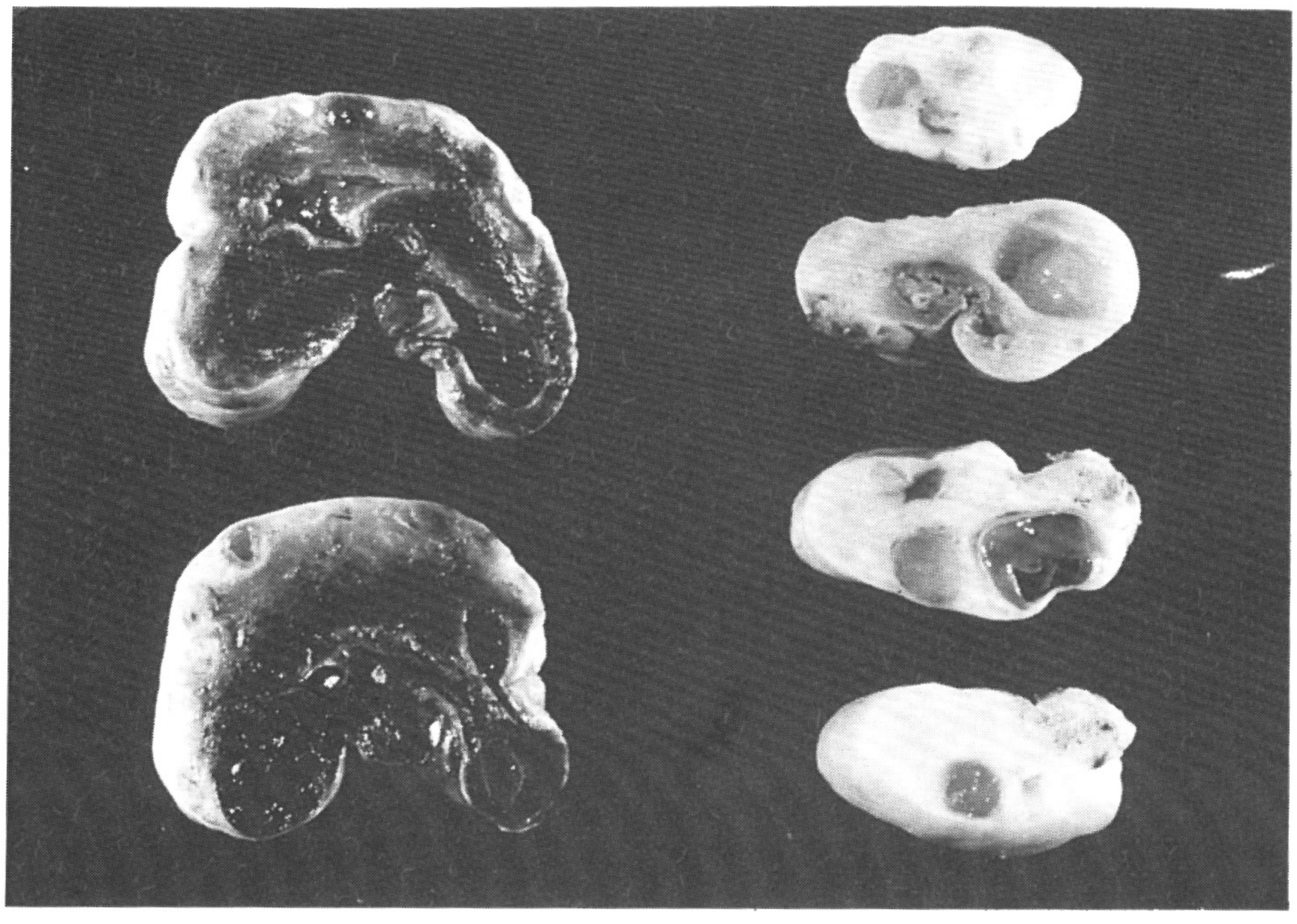

Fig. 1. Cut sections of both ovaries show several cysts of various size, measuring up to 3 cm in diameter. The right ovary is diffusely edematous and hemorrhagic.

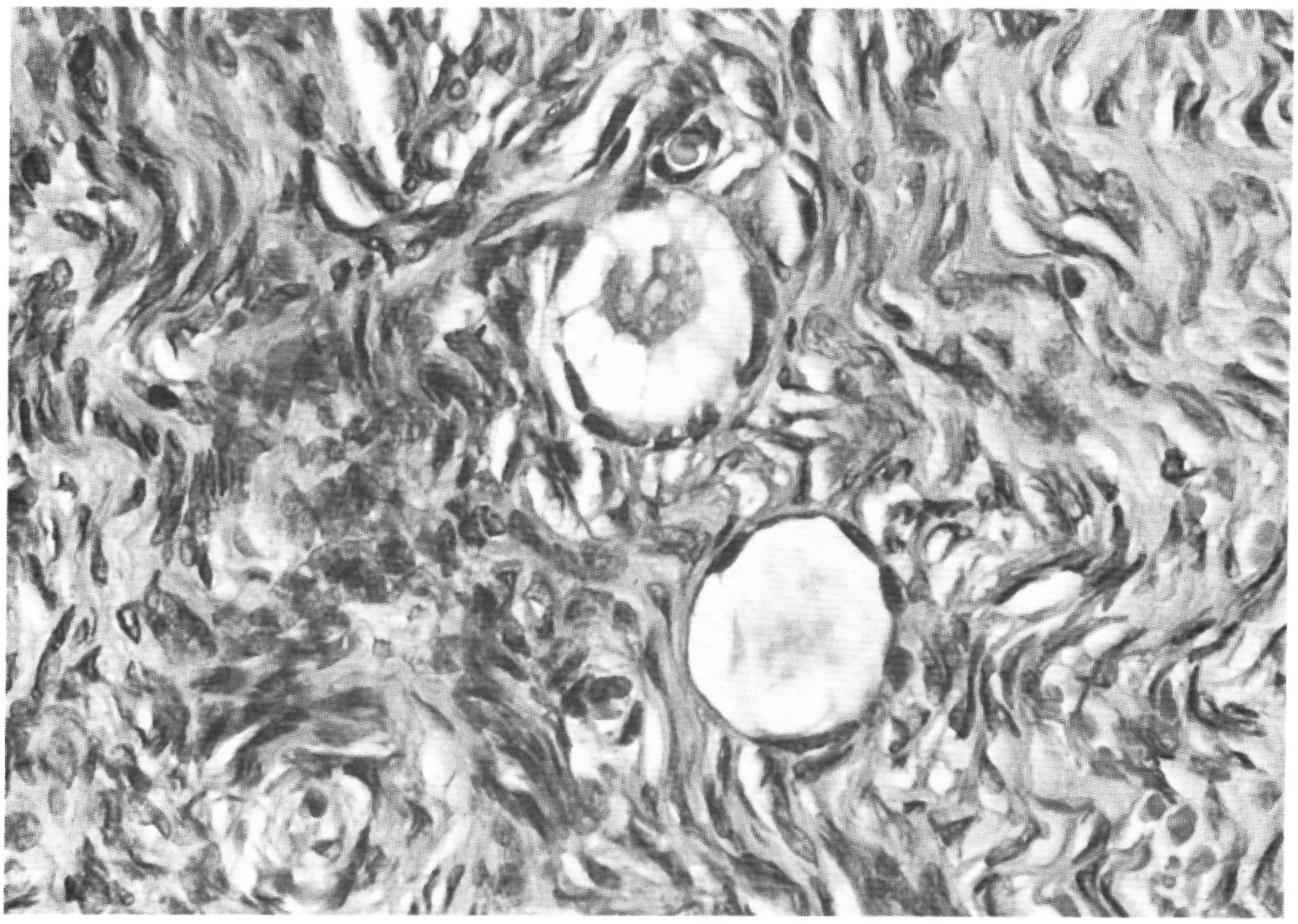

Fig. 2. Primordial follicles are unaffected by an inflammatory cell infiltrate (H&E ×400).

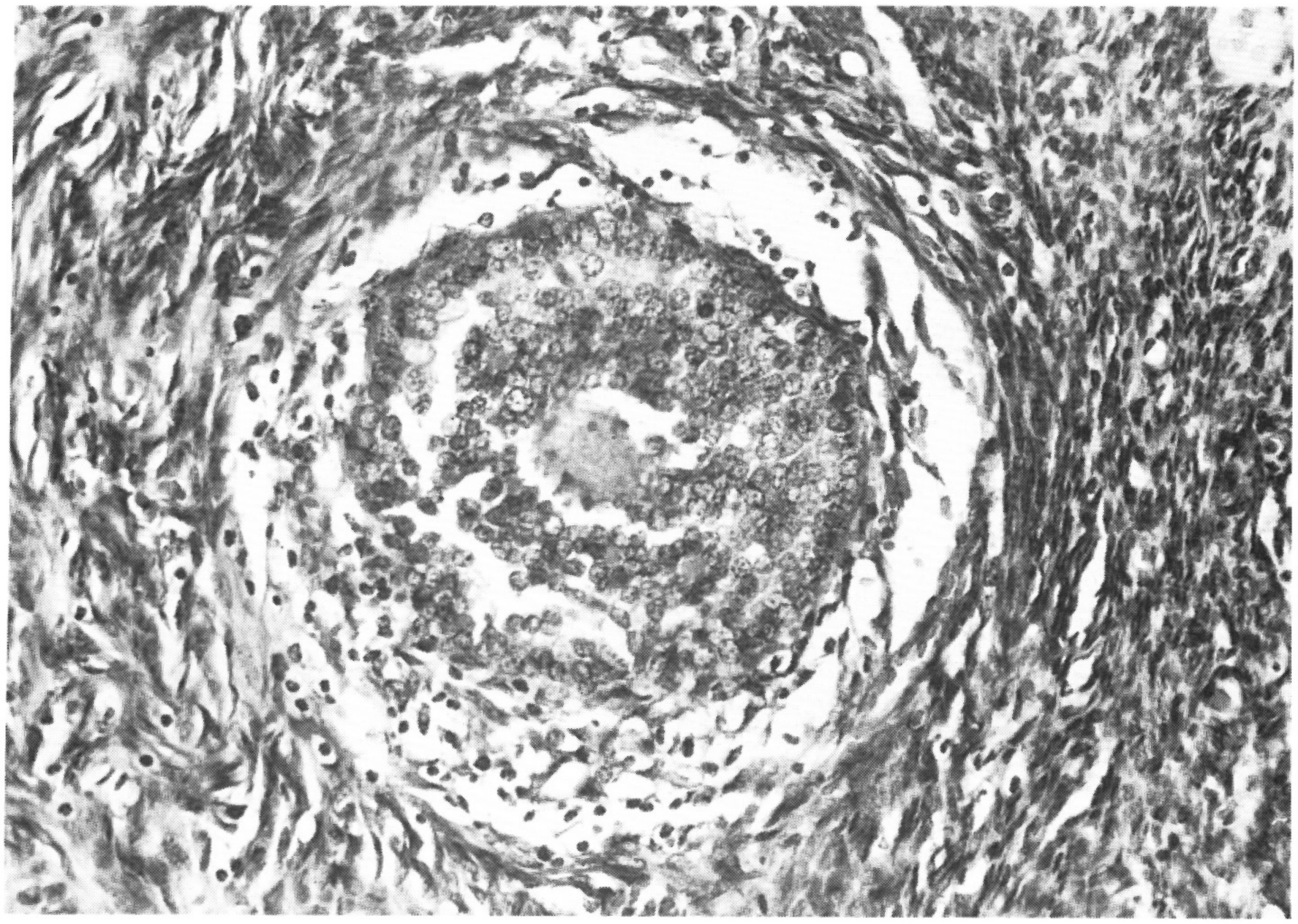

Fig. 3. A late primary or preantral follicle. A lymphocytic infiltrate is sparse and affects the theca cell layer but spares the granulosa (H&E ×200).

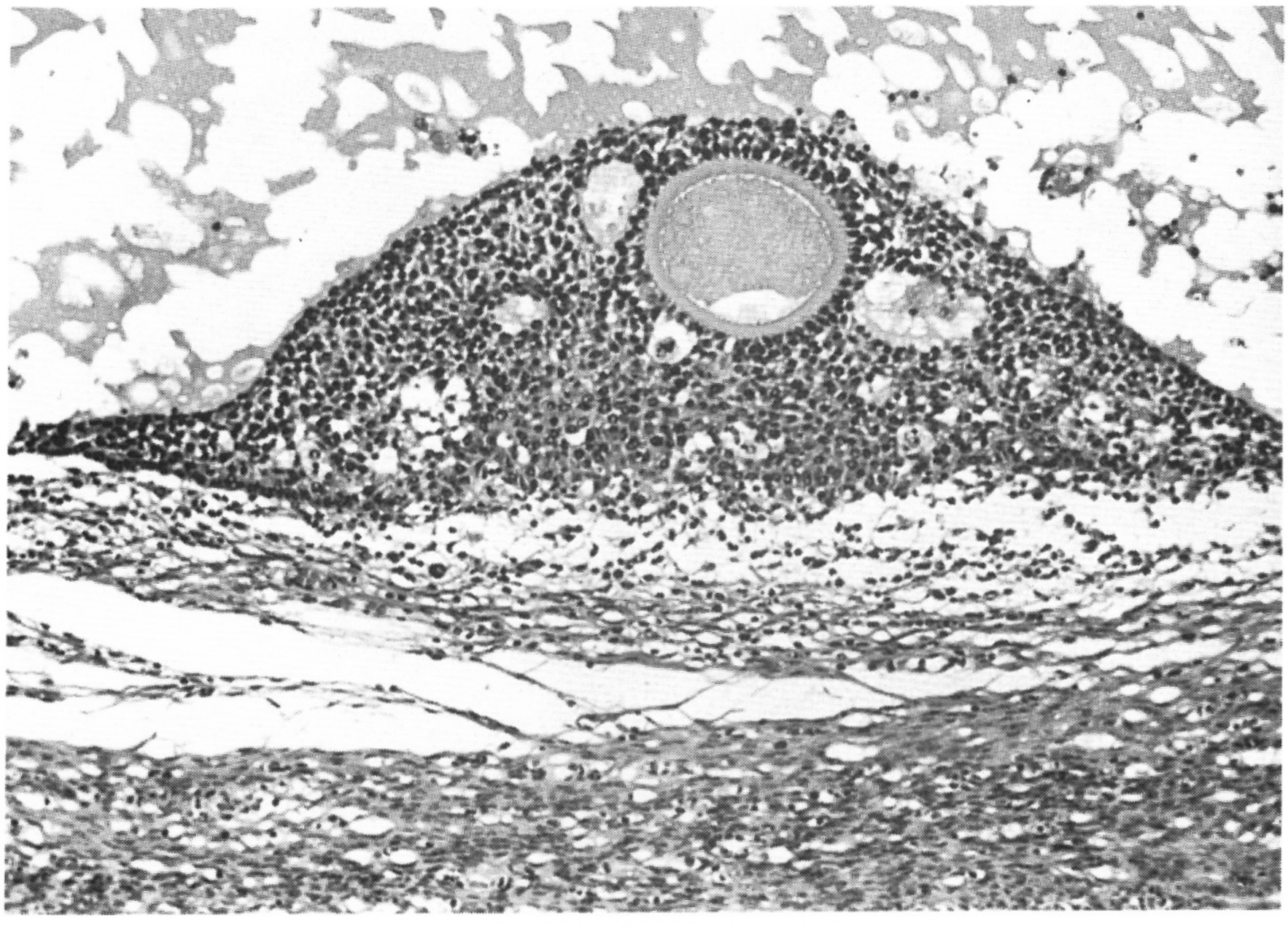

Fig. 4. An antral or graafian follicle shows an inflammatory cell infiltrate of the theca cell layer with proggressive invasion into the granulosa (H&E ×100).

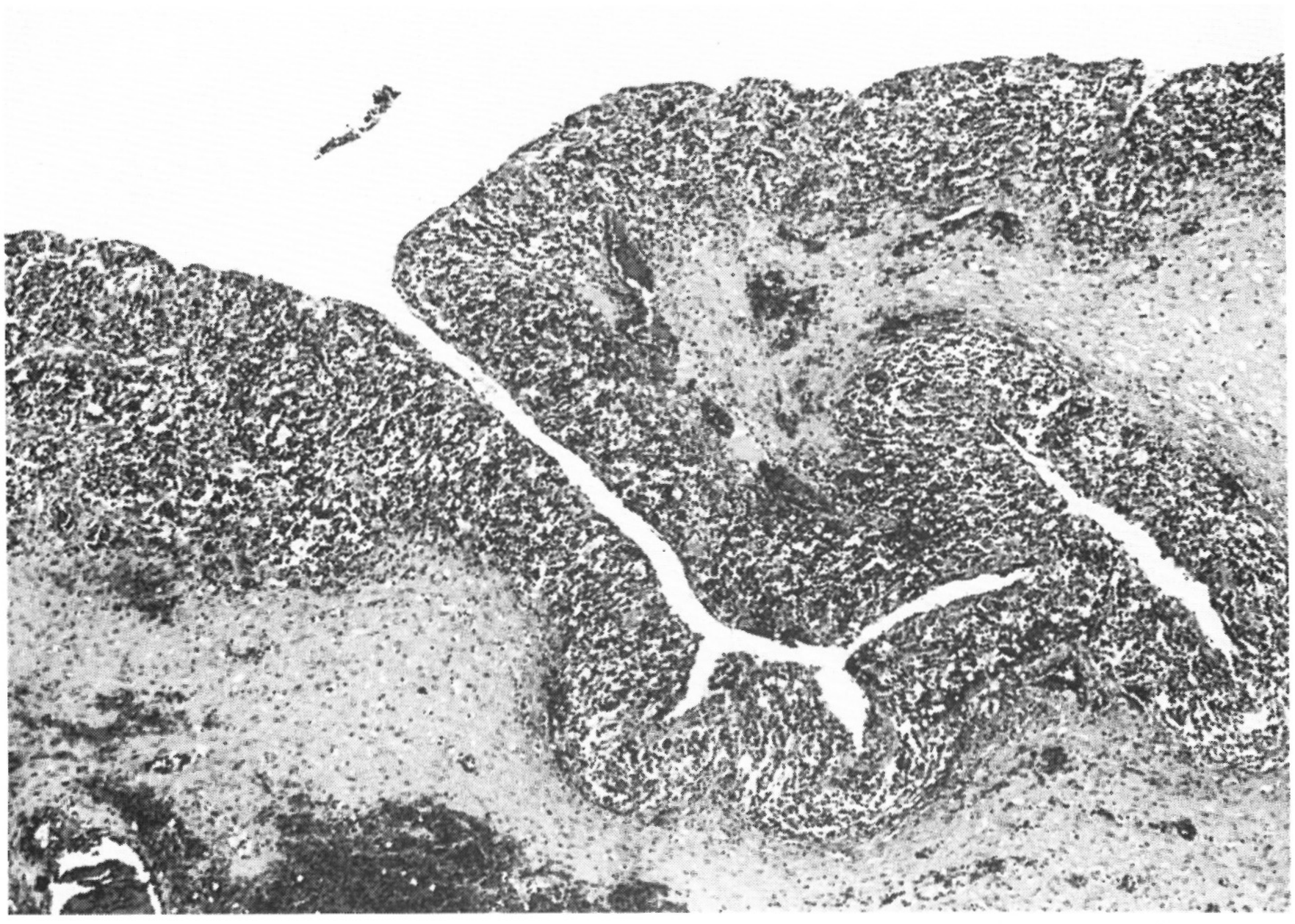

Fig. 5. A cystic corpus luteum is surrounded by an infiltrate of heavy inflammatory cells that is reduced to a narrow meandering ribbon (H&E ×40).

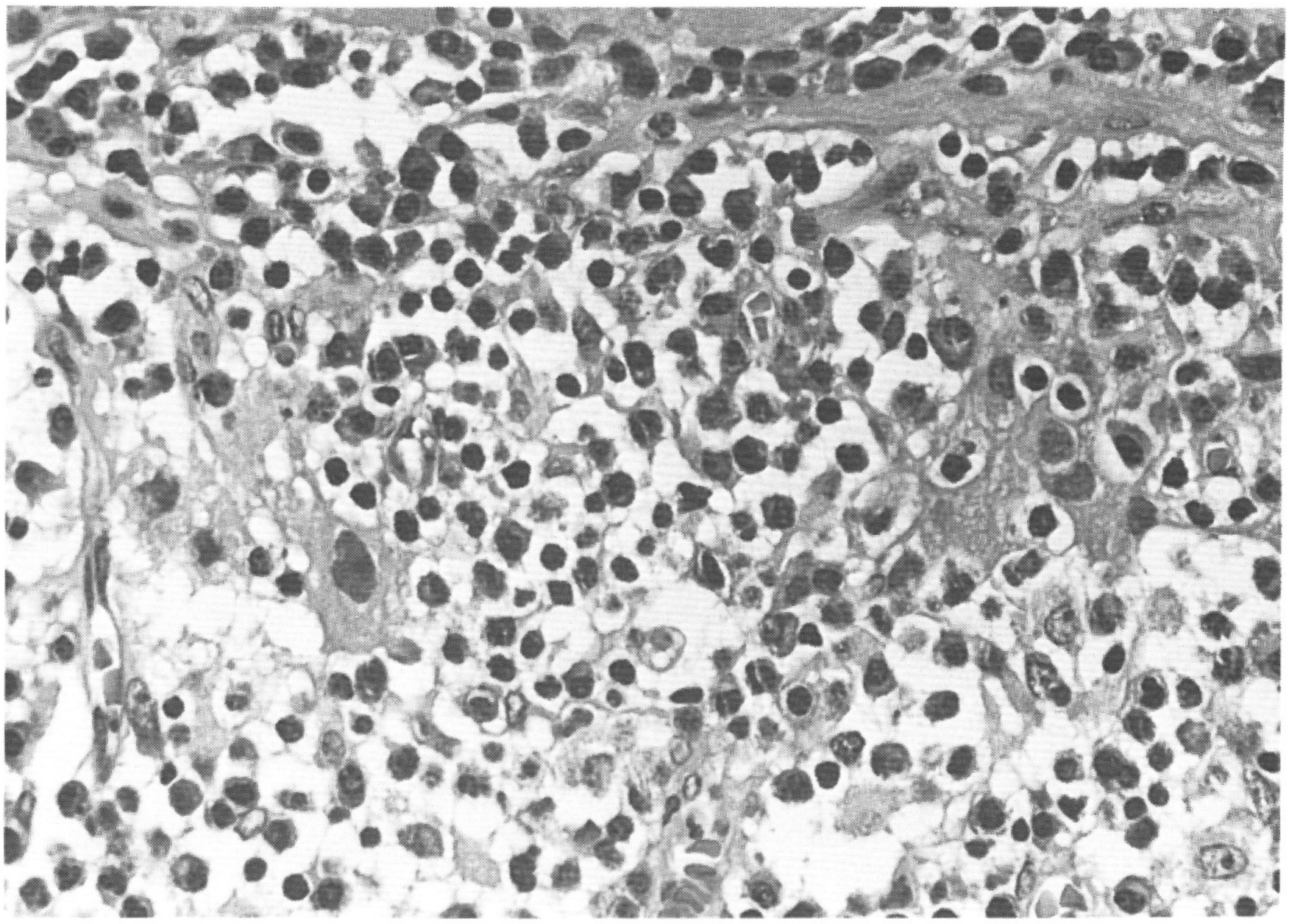

Fig. 6. High power view of Fig. 5 shows a severe inflammatory cell infiltrate in the granulosa with disorganized structure. The inflammatory cells consist mainly of plasma cells (H&E ×400).

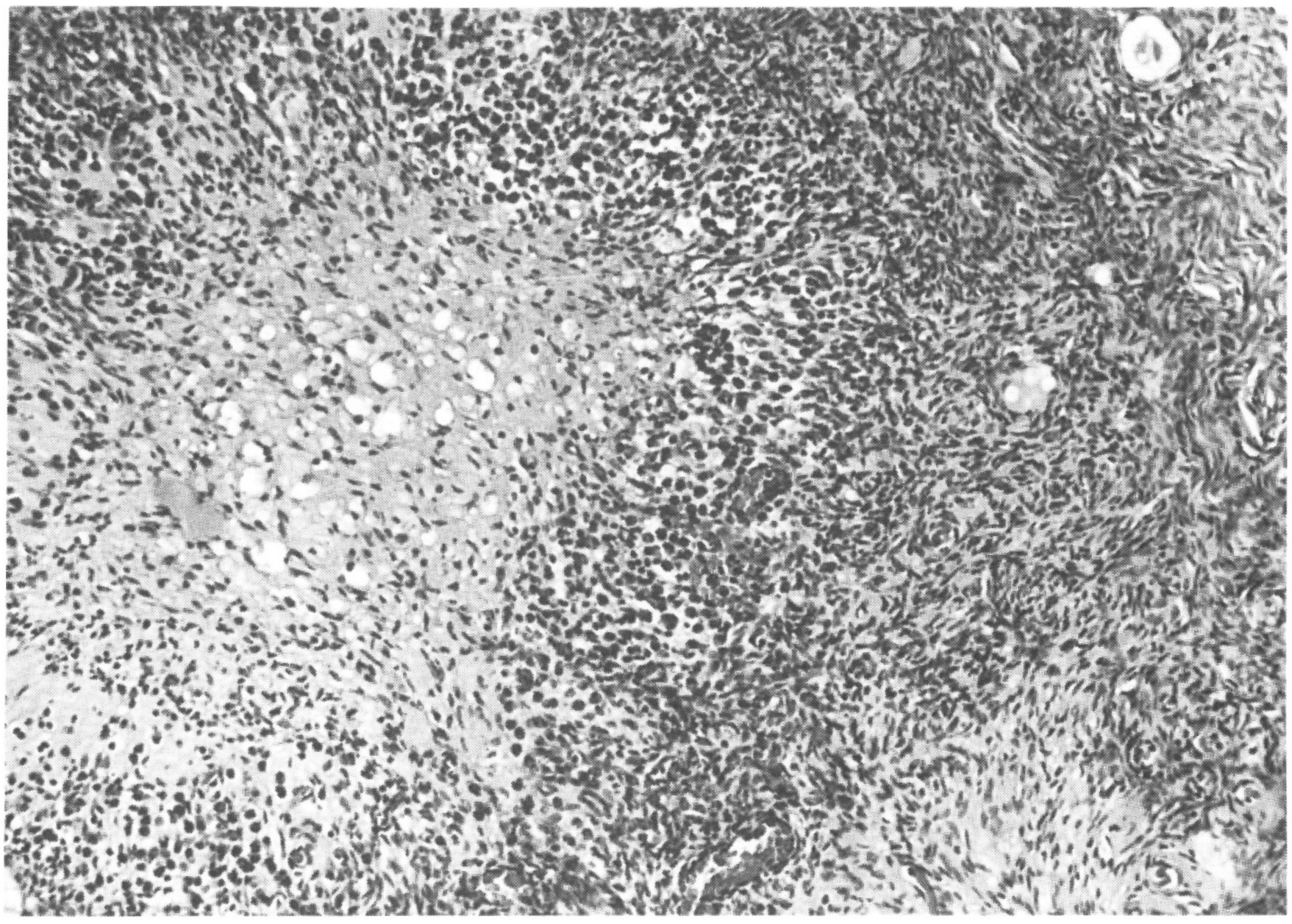

Fig. 7. A corpus fibrosum with a scanty inflammatory infiltrate (H&E ×200).

DISCUSSION

Both ovaries of this patient showed that the lymphocytic and plasma cell infiltrates had affected developing follicles, cystic,and atretic follicles but had spared primordial follicles. These histologic findings constitute the typical picture of autoimmune oophoritis. Unfortunately, this patient was lost to follow-up and the clinical study on the presence of circulating autoantibodies, hormonal levels, and the association of other autoimmune diseases could not be done. Histopathologic evaluations of the ovaries in autoimmune oophoritis have usually been incomplete because the diagnosis should be established on the basis of the presence of autoantibodies to the ovarian tissue in patients with premature ovarian failure and other autoimmune diseases rather than the histologic findings of the ovaries. There were limited histologic features obtained from small biopsy (Coulam et al., 1981; Sedmak, et al., 1987). The presence of circulating anti-ovarian antibodies in women with autoimmune disorders was first reported by Irvine and associates (1968). An ovarian biopsy in one of their patients showed a lymphocytic and plasmacytic infiltrate with destruction of developing follicles and sparing of primordial follicles. Since that first description of histologic findings was made, twelve cases recently reported by Bannatyne et al. (1990) have been the largest series in the study of histologically confirmed cases until now. According to them, 11 cases exhibited a lymphoplasmacytic infiltrate that spared primordial follicles but involved, with progressive intensity, early and late preovulatory follicles and corpora lutea. One case showed granulomatous oophoritis with a folliculotropic nature of inflammation. They and other investigators have stressed that a follicular distribution of the inflammatory infiltrates is an important histologic feature of autoimmune oophoritis although mild perineurial infiltration in the hilus has also been described (Gloor and Hurlimann, 1984; Case record of MGH, 1987). But in the present case as well as in 10 cases of the Bannatyne and associates series (10 biopsies included the medulla and hilar region of the ovary) significant extrafollicular infiltrates with chiefly medullary and perivascular distribution were observed. These observations have also been made by others (Coulam et al., 1981). Differences in these observations on the distribution of the inflammatory cells may be due to the limited biopsy specimens. The significance of the extrafollicular infiltrate is still unclear, but this distribution of the infiltrate may be related to the endocrinologically functioning stromal cells. Enlarged multicystic ovaries (2 to 5 times normal size), as shown in the present case are described to be an important gross feature of autoimmune oophoritis.

Autoimmune oophoritis has been regarded as a cause of premature ovarian failure. Most of the reported cases have presented with oligomenorrhea or secondary amenorrhea while this patient suffered from vaginal bleeding and abdominal pain. In this case abnormal bleeding may be due to two different causes. One is the result of an endometrial polyp or adenomyosis that was found in the patient's uterus, since this is a well-known organic cause of uterine bleeding. The other is caused by disordered ovarian function in relation to cystic ovaries. But it was impossible to evaluate the functional status of the patient's ovary. However, the presence of a regressing or cystic corpus luteum reflecting evidence of prior ovulation and the proliferative endometrium suggests that she was in normal ovarian function at the time of surgery. Therefore, this case may be detected early in its natural course before the symptom onset of premature ovarian failure. But the presence of ovarian follicles undergoing destruction indicates a high risk of subsequently developing impaired ovarian function.

The proportion of patients with premature ovarian failure who have autoantibodies to the ovarian tissue as evidence of autoimmune oophoritis has varied from 0% to 100% (Coulam and Ryan, 1979; Board, 1979; Fox, 1987). De Moraes-Ruehsen et al (1972) found antibodies to granulosa and theca cells in eight of 29 women (28%) with premature ovarian failure. Two cases reported by Russell et al. (1982) and Gloor and Hurlimann (1984) showed histologic evidence of autoimmune oophoritis and premature ovarian failure but no anti-ovarian antibodies in the serum. One of these patients had antibodies to the adrenal cortex in the serum, even in the absence of any clinical evidence of other autoimmune or endocrine disease (Gloor and Hurlimann, 1984). In addition to the initial 6 patients of Irvine and associates four more Addisonian patients were found with ovarian antibodies (Irvine et al., 1969). These 4 did not have apparent menstrual or gonadal problems. These discrepancies indicate that the presence of ovarian antibodies is not always associated with ovarian failure, at least at the time the antibodies are demonstrable.

The immunohistochemical study of this case is incomplete due to the absence of available frozen tissue. Immunohistochemical characterization of the infiltrate in one case reported by Sedmak et al. (1987) has revealed a mixture of B-cells and T-cells (T4+ and T8+), macrophage, and a few natural killer cells. In this case macrophages were scarce and natural killer cells could not be demonstrated. These immunohistochem-

ical findings suppot the hypothesis that a complex immune process with an interplay of humoral and cellular mechanisms is involved in the pathogenesis of autoimmune oophoritis (Russell and Bannatyne, 1989).

Although a rare disease, autoimmune oophoritis must be recognized histologically because it is a cause of ovarian failure and because it indicates that the patient is at risk of developing other autoimmune diseases. An important feature of autoimmune oophoritis is the frequent presence of enlarged multicystic ovaries, so much so that autoimmune oophoritis should be taken into consideration by radiologists, gynecologists, and pathologists. This should prevent the need for oophorectomy and give immediate treatment to young patients in hope of achieving a natural pregnancy, if desired, as recently reported by Biscotti et al. (1989).

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