Autoimmune oophoritis: clinical presentation of an unusual clinical entity

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Abstract
Introduction
Autoimmune oophoritis is a rare condition, which provokes ovarian failure with either primary amenorrhea or secondary amenorrhea and a subsequent loss of fertility and ovarian hormonal function. The purpose of this report is to document the clinical findings from two patients with autoimmune oophoritis.

Cases report
Two cases of autoimmune oophoritis are presented whose histopathological findings were consistent with international literature. Both cases were histopathologically characterised by lymphocytic and plasmacytic inflammatory infiltrations around the cystic follicles. The inflammation was located both in the theca and granulosa layers.

Conclusion
Patients with autoimmune oophoritis should be recognised by the histopathology of the ovarian biopsies as they are at an increased risk of developing other autoimmune disorders.

Introduction
Premature ovarian failure (POF) is a condition characterised by amenorrhea, some hot flushes, elevated serum gonadotropin levels and hypo-oestrogenism with associated infertility in women before the age of 40 years1-4. The aetiologies of this condition include chromosomal anomalies (such as X chromosome monosomy, translocations or partial deletions), genetic predisposition (such as fragile X pre-mutations, BMP15 or DIAPH2 mutations), infectious diseases, complications of chemotherapy, pelvic radiotherapy, surgical interventions or surgery, enzymatic disorders and endometriosis. Premature ovarian failure might also be idiopathic or autoimmune. Among a total of 266 patients with spontaneous POF, 4% were diagnosed to have autoimmune oophoritis5,6. Ovarian autoimmunity was first reported and serologically documented by Vallotton and Forbes in 19665. Autoimmune oophoritis is a distinct clinical entity and one of the causes of POF, particularly in women with secondary amenorrhea5,6,8. Autoimmune oophoritis generally occurs in the setting of autoimmune polyendocrine syndromes and is associated commonly with other major endocrine failures such as diabetes mellitus, Addison’s disease, hypoparathyroidism or hypothyroidism7,9-10. A wide clinical spectrum has also been demonstrated11.

The aim of this report was to describe the clinical spectrum and the interesting pathological findings originating from small ovarian biopsies from two patients with autoimmune oophoritis.

Case report
Case 1
A 33-year-old woman presented with a 10-month history of secondary amenorrhea and hot flushes. Menarche had occurred at an age of 14 years, she had developed secondary sex characteristics appropriately and had regular menses on a 28-day cycle. She had five full-term normal pregnancies without any miscarriages.

On pelvic bimanual examination, an antverted uterus was palpated, while both fallopian tubes and ovaries were impalpable. Pelvic ultrasonography disclosed normal-sized ovaries with bilateral multicystic structures, with the largest follicle measuring 1.2 cm. The thickness of the endometrium was 3.5 mm. Initial investigation showed her serum gonadotropin concentrations to be elevated: follicle stimulating hormone (FSH) at 40 mIU/ml and luteinizing hormone (LH) at 56 mIU/ml. 17-beta oestradiol was at 30 pg/ml (normal range: 30–100 pg/ml). Serum prolactin levels were normal and there was no evidence of hypoparathyroidism. Thyroid function tests were normal. Also, kidneys and liver function tests were normal. Serum electrolytes were normal. Proteinuria was negative. Serum adrenocorticotropin hormone levels were normal. The progesterone challenge test was negative.

At exploratory laparoscopy, her ovaries appeared small and inactive. There were no signs of abdominal or pelvic inflammatory processes. Biopsies from both ovaries were obtained and endometrial curettage was performed as well.

Grossly, two specimens had been obtained from the right ovary with a whitish-grey colour, measuring 0.7 cm and 1.2 cm in their greatest dimension, respectively, and one specimen had been obtained from the left ovary with white tan to grey colour measuring 1.6 cm in its greatest dimension. Also, the specimen from the endometrial biopsy measured 3.5 × 3 × 0.2 cm. At micro-

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Case report

were in normal ranges. The patient underwent exploratory laparoscopy with an ovarian cystectomy and a wedge resection of the right ovary. The left ovary appeared small and inactive. There were no signs of abdominal or pelvic inflammatory processes.

Grossly, the largest specimen had dimensions of $6 \times 3 \times 0.5$ cm. Also, the other two histological pieces measuring $2.5$ cm and $3.5$ cm in their maximum diameter were sent for frozen biopsy. Cut sections revealed two cystic follicles measuring $0.4$ cm and $1.0$ cm in their maximum diameter, respectively.

Microscopically, the ovarian cyst was benign and the ovarian segments showed dense lymphocytic and plasmacytic inflammatory infiltrations around the cystic follicles. The inflammation was located both in the theca and granular layers (Figures 7–9). The secondary follicles showed layers of granulosa cells surrounding an unremarkable oocyte (Figure 10), while the primordial follicles were apparently and entirely spared from this process. The ovarian stroma was otherwise unremarkable. The scattered lymphocytes were positive for CD4, CD8, CD138 and CD45RO (PanT) (Figure 11).

After the pathology results, the patient was diagnosed as having POF due to autoimmune oophoritis and she was started on oestrogen and progesterone replacement therapy. During the one-month follow-up postoperatively, laboratory tests were negative for CRP, erythrocyte sedimentation rate, rheumatoid factor, anti–double-stranded DNA antibodies, C3 and C4, IgG and IgM alpha cardiolipin antibodies and surface antigen of the hepatitis B virus. Also, the serum Ig concentrations were negative for IgM (162 mg/dl; normal range: 46–304 mg/dl) and IgA (165 mg/dl; normal range: 82–453 mg/dl). Positive serum laboratory tests were found for antistreptolysin O (333 IU/ml; normal range: 0–116 IU/ml) and IgG (1730 mg/dl; normal: 751–1560 mg/dl). Also, the titres of ANA were positive.

During the six-month follow-up postoperatively, her serum gonadotropins were slightly elevated with FSH levels of 15.8 mIU/ml and LH levels of 18.4 mIU/ml. 17-beta oestradiol levels were 99 pg/ml. Prolactin levels were normal. High titres of anti-thyroglobulin antibodies (1/20; negative <1/20) and antimicrosomal antibodies (1/3.200; negative <1/100) were found. The thyroid-stimulating hormone levels were normal (0.54 microIU/ml; normal range: 0.3–0.6 microIU/ml). Also, the cortisol levels were normal (21.56 microg/dl; normal morning range: 10.4–26.4 microg/dl).

Discussion

Autoimmune oophoritis is caused by ovarian autoimmune inflammation resulting in ovarian destruction, atrophy and fibrosis. It provokes ovarian failure with either primary or secondary amenorrhea. There is a subsequent loss of fertility and ovarian hormonal function. The autoimmunity accounts for up of 30% of all POF cases. Also, coexistence of autoimmune POF with

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other autoimmune diseases such as those associated with the thyroid gland (e.g., Hashimoto's and Grave's disease) and adrenal gland (e.g., Addison's disease) is often observed, as in our case 2. Approximately 60% of POF cases without adrenal autoimmune disease lack ovarian follicles, and in these cases, fibrotic ovaries are found. Moreover, ANA and rheumatoid factors have been reported with a higher frequency in POF patients than normal. Moncayo-Naveda et al. reported the presence of anti-ovarian antibodies in 84% of the cases with system lupus erythematosus.

The patient of our case 2 presented with a large ovarian cyst measuring 8 cm in its maximum diameter and this is in agreement with the observations of other studies with autoimmune POF. The possible mechanism for the development of ovarian cysts in patients with autoimmune POF is due to the elevated gonadotropin levels because of the impaired negative feedback and the subsequent overstimulation of the ovarian tissues. Both of our cases were amenorrheic for 10 months (case 1) and three months (case 2) with increased FSH levels compared to women with regular cycles. In patients with autoimmune oophoritis, hormone replacement should be used as in our patients. During hormone-replacement therapy, elevated gonadotropin levels usually return to physiologically normal ranges. As a result, folliculogenesis may occur and less frequently is followed by ovulation and rarely by pregnancy. Both of our patients had completed their families. However, for patients who desire a child, there are multiple case reports in which corticosteroid treatment has resulted in pregnancies in women with autoimmune oophoritis and amenorrhea. Cowchock et al. described a patient who had been treated with oestrogen replacement therapy because of POF for more than 15 years. However, the patient developed Addison's disease and was treated with corticosteroid replacement therapy. An uneventful pregnancy was achieved one year after commencement of corticosteroid replacement therapy. Luborsky et al. described two patients with documented POF who became pregnant, and each patient delivered a healthy infant after treatment with high doses of corticosteroids. However, in both cases, POF has resumed after delivery. Also, Barbarino-Monnier et al. reported a pregnancy and delivery after in vitro fertilisation in a patient with anti-ovarian autoimmunity treated with corticosteroids. Apart from the case reports, Corenblum et al. studied 11 chromosomally normal patients with POF who received high doses of corticosteroids for 15 days and found that two of them had resumed ovarian function and became pregnant. In addition, Blumenfeld et al. studied 15 patients with autoimmune POF treated with human menopausal gonadotropins and corticosteroids after pituitary desensitisation with a gonadotropin-releasing hormone agonist. Eight of 15 patients had become pregnant at least once, and in total, 14 pregnancies were achieved. All of these pregnancies were completed within the first three months after the onset of treatment.

Conclusion

Autoimmune oophoritis is diagnosed by laparoscopic ovarian biopsy, which on microscopic examination reveals a folliculotropic, lymphoid infiltrate that affects developing follicles with a theca layer, corpora lutea and atretic follicles, and it indicates the patient's risk of developing other autoimmune diseases. Autoimmune oophoritis should be kept in mind by gynaecologists when treating women with POF. These patients should be treated with hormone replacement therapy. For young patients with autoimmune POF who desire a pregnancy, high doses of corticosteroids might help in the achievement of pregnancy.

Consent

Written informed consent was obtained from all patients for publication of this series study and accompanying images. A copy of the written consents is available for review by the Editor-in-Chief of this journal.

Abbreviations list

ANA, antinuclear antibodies; CA, carbohydrate antigen; CRP, C-reactive protein; C3 and C4, components 3 and 4 of the complement; FSH, follicle-stimulating hormone; Ig, immune globulin; LH, luteinizing hormone; POF, premature ovarian failure.

References


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**Case report**
