Local lymphocytic and epithelial activation in a case of autoimmune oophoritis

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Objective: To further define the immunological tissular modifications in premature ovarian failure (POF).
Method: The patient was followed up for premature ovarian failure and mild endometriosis associated with serum antiovarian antibodies. A laparoscopic ovarian biopsy was decided on to analyze the tissue and support the onset of immunosuppressive therapy. Immunohistochemistry was performed using monoclonal antibodies directed against T cell membrane markers, as well as activation molecules, to define the composition of the cellular infiltrate and the consequences on ovarian tissue.
Result(s): A dense infiltration of activated T lymphocytes was observed in close contact with follicular epithelium expressing HLA-DR and CD40.
Conclusion(s): This observation supports the role of cellular immunity in ovarian autoimmunity with features very similar to those reported in murine models and other human autoimmune endocrine pathologies. (Fertil Steril® 2008; 90:849.e5–e8. ©2008 by American Society for Reproductive Medicine.)

Key Words: Ovarian autoimmunity, premature ovarian failure, immunohistochemistry, autoimmune oophoritis, activated T lymphocytes infiltration

Ovarian autoimmunity was first reported and serologically documented by Vallotton and Forbes, four decades ago, in 1966 (1). The presence of antiovarian antibodies (AOA) in patients with various types of infertility has since been reported (2) with different technical approaches (3, 4).

The AOA are significantly associated with various gynecological diseases currently related to infertility such as endometriosis, idiopathic infertility, premature ovarian failure (POF), and polycystic ovary syndrome (PCOS) (5). The generation of such autoantibodies, according to the current understanding of autoimmune mechanisms, should also involve T cells, but this has been only seldom tackled (6–8), and then mostly in animal models of autoimmune oophoritis (9, 10).

Premature ovarian failure is a condition observed in about 1% of women before the age of 40 years. Clinical manifestations include amenorrhea and some hot flushes. Biologically, a typical hypergonadotropic–hypoestrogenic hormone profile is detected (3, 11). The etiologies of this syndrome are numerous and include chromosomal anomalies, genetic predisposition, infectious diseases, complications of chemotherapy, radiotherapy or surgery, enzymatic disorders, as well as endometriosis. Premature ovarian failure might also be idiopathic or autoimmune and the presence of autoantibodies should be investigated (12). In such cases, organ-specific antibodies can be detected, disclosing or confirming the context of a polyglandular autoimmune disorder, with adrenal failure, thyroiditis, or diabetes. These autoantibodies can be detected in up to 20% of POF cases (4, 13, 14). Kim et al. (15) and Hoek et al. (13) have summarized the arguments in favor of an autoimmune etiology of POF: circulating autoantibodies against ovarian targets, association with other autoimmune diseases, recovery of ovarian function after immunosuppressive therapy, and, in a few cases, ovarian lymphocytic infiltration seldom characterized immunophenotypically.

Here we report a case of extensive characterization of the ovarian infiltrate and adjacent ovarian tissue in a case of POF.

MATERIALS AND METHODS

Case Report

A 34-year-old woman, followed up for an infertility of 5 years duration in the Department of Reproductive Medicine, University hospital of Nancy, was diagnosed with POF associated to mild endometriosis. In her past history there was hypothyroidism treated by 100 μg/day of levothyroxine for 2 years. Her body mass index (BMI) was 20. The patient experienced spontaneous menarche at 16 years and presented with

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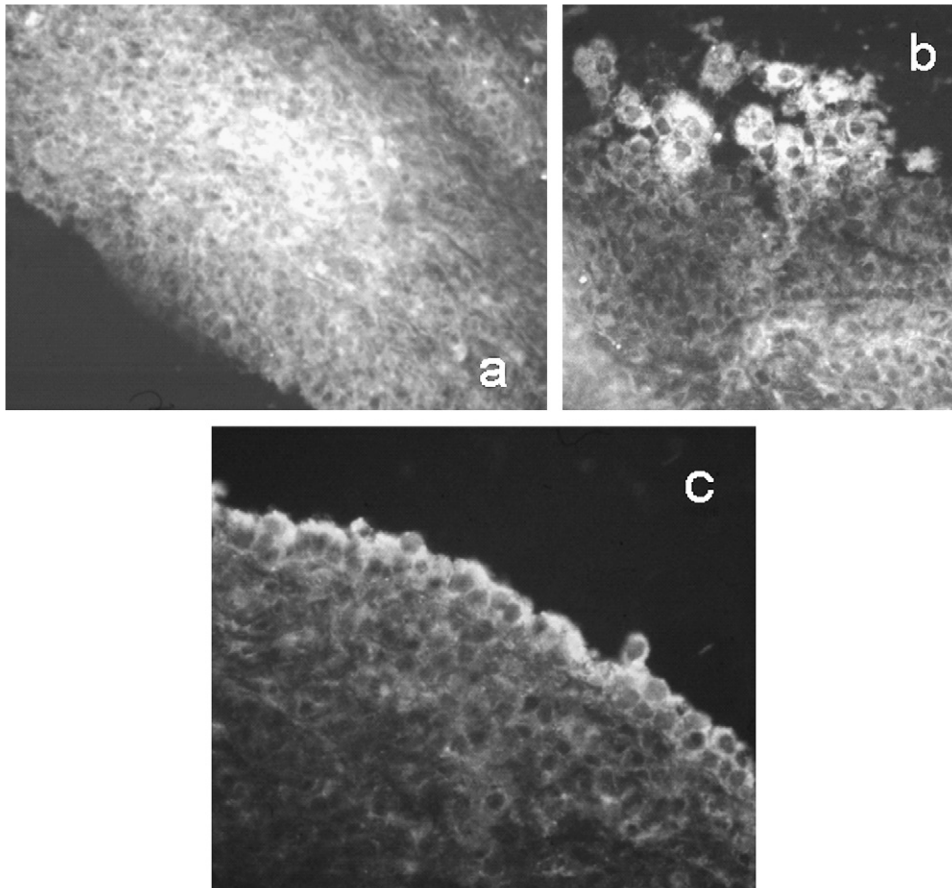
FIGURE 1

Immunohistologic staining of ovarian biopsy sections. (**a**) Lymphocytic infiltration brightly expressing MHC class II antigen DR; (**b**) CD40 staining of epithelial cells; (**c**) MHC class II antigen expression on epithelial cells.



Bats. Autoimmune oophoritis. Fertil Steril 2008.

regular menstrual cycles until the age of 32. She was amenorrheic since then. Ultrasound sonography disclosed ovaries of 22 mm and 28 mm. On the left ovary, six small antral follicles were observed. Serum FSH was at 21.2 UI/L, LH at 16.6 UI/L, 17b-E_2 at 33 pg/mL, and inhibin B at 132 ng/mL. The AOA were investigated and were initially highly positive for the IgM isotype but negative for IgG and IgA. Five months later, IgG AOA became also highly positive. She also had other autoantibodies directed to mitochondria, thyroglobulin, thyroperoxidase, adrenal, and cardiolipin. Because of the various signs of an ongoing autoimmune process, a laparoscopic ovarian biopsy was performed to detect an autoimmune oophoritis that could justify the onset of an immunosuppressive therapy. The present case was approved by an institutional review board and informed content was obtained from the patient.

Immunohistochemistry

The ovarian biopsy was snap frozen in liquid nitrogen, and then maintained at $-80°C$. Serial 4-μm sections were performed at $-30°C$ with a refrigerated microtome. The first section was stained with toluidine blue (Sigma, St. Louis, MO), for light microscopy examination of the tissue structure. A series of slides were incubated with fluorescein isothiocyanate conjugate (FITC_ rabbit antibodies to human IgG, IgM, IgA, C1q, C3, fibrinogen, and fibronectin (Dako, Glostrup, Denmark). The following sections were incubated with an appropriate dilution of the following monoclonal antibodies: CD2 (RPA-2.10; Beckman Coulter, Fullerton, CA), CD7 (M-T701; Beckman Coulter), CD3 (HIT3a; Beckman Coulter), CD4 (RPA-T4; Beckman Coulter), CD8 (RPA-T8; Beckman Coulter) to identify T-cell subsets, CD40 (5C3; Beckman Coulter), HLA DR (G46-6; Beckman Coulter) to assess the presence of costimulatory molecules, CD10 (HI10a; Beckman Coulter) for epithelial cells, CD9 (M-L13; Beckman Coulter) for B cells and endothelial cells, and CD82 for activated lymphocyte subsets. Incubations were carried out for 30 minutes in moist chambers at room temperature, followed by three washes in phosphate-buffered saline (PBS). For indirect staining, a second incubation was

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