EJGO European Journal of Gynaecological Oncology

Endometrial cancer in a patient with rheumatoid arthritis

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Summary

Background: Rheumatoid arthritis is a chronic, systemic, and autoimmune disease. In patients with rheumatoid arthritis, there is increased risk for site-specific malignancies. The authors present a case of endometrial cancer in a patient with rheumatoid arthritis and a review of the current literature. *Case:* The patient, a 60-year-old, postmenopausal Greek woman suffering from rheumatoid arthritis, presented with a complaint of abnormal uterine bleeding. She underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy. Histopathology revealed endometrial cancer. The final diagnosis was Stage Ib endometrial cancer endometrioid type. She underwent postoperative adjuvant radiotherapy. She remains without evidence of disease, 16 months after initial surgery. *Conclusion:* Although the present patient was diagnosed at early-stage disease and remains well 16 months after initial surgery, she needs a multidisciplinary treatment approach in order to achieve prolonged survival.

Key words: Rheumatoid arthritis; Endometrial cancer; Surgery; Radiotherapy.

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, and autoimmune disease [1]. It is characterized by symmetrical joint swelling, joint tenderness, and destruction of synovial joints, leading to severe disability and premature mortality [1-3].

It affects approximately 0.5-1% of the population worldwide, including all ethnic groups [2]. However, it is more common in women (female/male ratio is 2.5:1) [2].

The etiology of RA is thought to be a complex with both genetic and non-genetic (hormonal, immunologic, and environmental) factors influencing susceptibility, severity, and response to therapies [2,4].

In patients with RA, there is increased risk for site-specific malignancies [5]. Also there is a concern whether the inflammatory disease or its treatment might increase the risk of cancer [5,6].

The authors' aim was to present a case of endometrial cancer (EC) in a patient with RA and a review of the current literature.

Case Report

The patient, a 60-year-old, gravida 5, para 2 postmenopausal Greek woman presented to the Department of Obstetrics and Gynecology of the University of Patras Medical School, with a complaint of abnormal uterine bleeding. She was suffering from RA for the last three years and received leflunomide, corticosteroids, and methotrexate. Her surgical history was unremarkable. She had no history of hormone replacement therapy and her family history revealed no evidence of cancer among the first-degree relatives.

On gynecologic examination there were no findings. Preoperative computer tomography (CT) of the abdomen and pelvis, and abdominal ultrasound (U/S) revealed irregular endometrial thickening. Chest X-ray, intravenous pyelography (IVP), colonoscopy, and urethrocystoscopy were normal. Dilation and curettage revealed EC. Preoperative CA-125 was normal.

She underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy.

The histopathology revealed EC endometrioid type, grade 2 (Figure 1). The endometrial tumor invaded more than half of myometrium. The ovaries, pelvic and para-aortic lymph nodes were normal. The peritoneal washing smear was negative for malignant cells. Immunostaining revealed that tumor cells were positive for ErbB-2 receptors (Figure 2). The final diagnosis was Stage Ib EC endometrioid type according to the FIGO staging system 2009 [7].

The patient underwent postoperative adjuvant radiotherapy. She received 5,000 cGy of external pelvic radiotherapy. Moreover, she continues medication with hydroxychloroquine and corticosteroids in order to achieve control of RA.

Follow up 16 months after initial surgery, with CT of the chest, abdomen and pelvis, abdominal U/S, chest X-ray, IVP, colonoscopy, and urethrocystoscopy, revealed no evidence of recurrence.

Discussion

RA is a common autoimmune disease with dysregulated lymphocytes reacting against self-antigens by producing autoantibodies and the normal immune function is suppressed [8]. Dysregulation of the host's immune surveillance is a recognized cause of human cancer [8,9]. The subsequent risk of cancer after diagnosis of RA has been studied extensively.

In patients with RA, there is increased risk for site-specific malignancies [5, 8, 10, 11]. The most common malignancies are: Hodgkin lymphoma (SIR 4.06), non-Hodgkin lym-

Revised manuscript accepted for publication November 14, 2013

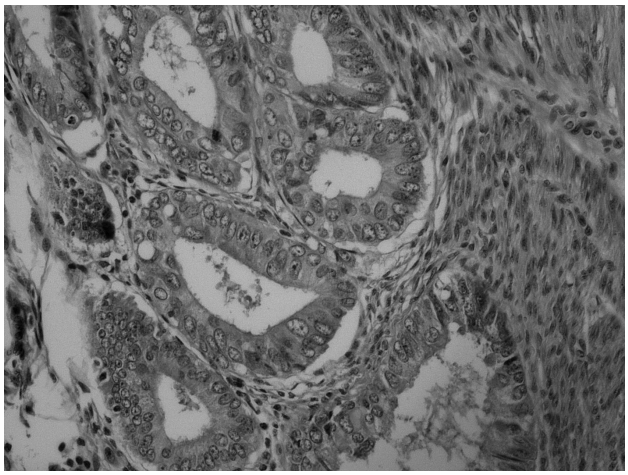

Figure 1. — The endometrial cancer was endometrioid type (HEx40).

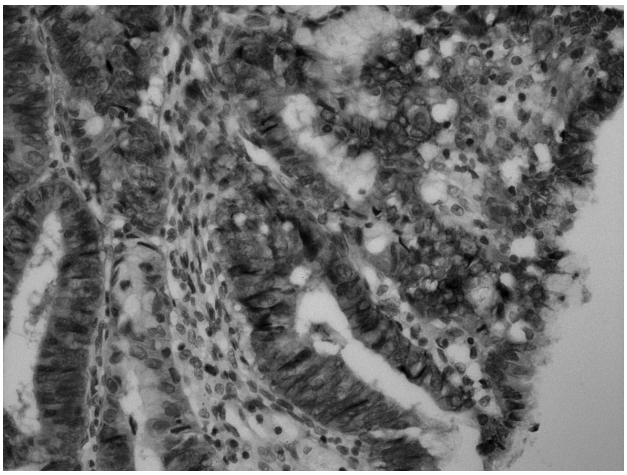

Figure 2. — Tumor cells were positive for ErbB-2 receptors (x40). For ErbB-2 receptors immunostaining, we used anti-ErbB-2 polyclonal antibody A0485 (Dako Denmark A/S, Glostrup, Denmark) in a dilution 1:300.

phoma (SIR 2.34), squamous cell skin cancer (SIR 1.89), lung cancer (SIR 1.73), non-thyroid endocrine glands cancer (SIR 1.62), kidney cancer (SIR 1.53), leukaemia (SIR 1.44), and prostate cancer (SIR 1.44) [5, 8, 10, 11].

The increased risks for lymphomas and squamous cell skin cancer are in accordance with the spectrum of cancers observed after immunosuppression [8, 10]. Moreover, EC is relative uncommon in patients with RA [5,8,11].

There is a concern whether RA or its treatment might increase the risk of cancer [5,6]. There are known associations between autoimmune diseases, chronic inflammatory diseases, and cancer [9, 12, 13]. Immunosuppression is a known risk factor for many cancers, as noted after organ transplantation and infection by immunodeficiency viruses [8]. Moreover, patients with RA are often subject to prolonged treatment with disease-modifying antirheumatic drugs (DMARDs) [5]. These drugs act by directly modifying the immunologic pathways involved in the pathogenesis of RA [5]. Perhaps, the immunosuppressive effect of DMARDs in patients with RA may predispose to the development of malignancies [5, 10].

Although EC is relative rare in patients with RA, the present patient developed EC three years after initial diagnosis of RA. During that period she received leflunomide, corticosteroids, and methotrexate in order to achieve control of RA. Perhaps immunosuppressive treatment for RA predisposed her to develop EC.

Surgery is the primary treatment for patients with EC [14]. For most of them, systematic surgical staging is the baseline therapy and allows clear decision for stage related postoperative adjuvant therapy [16]. Systematic surgical staging includes: total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, and complete resection of all disease [16, 17].

Appropriate surgical staging provides prognostic and therapeutic benefits for women with EC [14, 16, 17]. It facilitates targeted therapy to maximize survival and to minimize the effects of undertreatment (recurrent disease, increased mortality) and potential morbidity associated with overtreatment (radiation injury) [16, 17]. The present patient underwent systematic surgical staging according to current treatment protocols for EC [14-20].

In EC patients at increased risk for recurrence or with advanced stage disease, required more aggressive management with postoperative adjuvant radiotherapy and/or chemotherapy [14, 15, 17, 19]. Postoperative adjuvant radiotherapy includes external pelvic radiotherapy and/or brachytherapy.

External pelvic radiotherapy in EC patients with early stage disease, reduces the risk of local recurrences but has no impact on overall survival [16, 17, 21-23]. However, it is associated with significant morbidity and a reduction in quality of life [17, 21, 23]. It is used only in high-risk EC patients or at advanced stage disease [17, 24, 25]. The present patient underwent postoperative external pelvic radiotherapy [15, 18-20].

Vaginal brachytherapy in EC patients with early stage disease, also reduces the risk of local recurrences but has no impact on overall survival [17, 23]. Moreover, it is well tolerated and associated with less side effects than external pelvic radiotherapy [17, 23]. It is the adjuvant treatment of choice for high-intermediate risk EC patients [17,23,24].

Adjuvant chemotherapy is the mainstay of treatment for EC patients with locally advanced or metastatic disease [14, 15, 17, 26]. The most active chemotherapeutic agents are: taxanes, anthracyclines, and platinum compounds [26, 27]. Although they achieve high response rates, they have only

modest effect in progression-free survival and overall survival [17,26].

Molecular targeted therapies have still shown modest effect in unselected EC patients [26]. They usually target the inhibition of EGFR, VEGFR, and PI3K/PTEN/AKT/mTOR signal pathways [28]. Perhaps they may be clinically active as adjuvant therapy in well-defined subgroups of type II EC patients with EGFR and ErbB-2 overexpression [17, 29-32].

Prognostic factors for EC are: age at diagnosis, stage, grade, histologic type, ploidy, and receptor status [20, 33]. However, cancer patients with RA have dismal prognosis compared with patients without RA [34]. The high mortality rates are independent of age at diagnosis and stage of the disease [34]. It is obvious that those patients need a multidisciplinary treatment approach in order to achieve prolonged survival.

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