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Case Report & Review of the Literature

Co-Occurrence of Multiple Sclerosis & Ovarian Cancer: A Case Report and Literature Review

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ABSTRACT

Background: The possibility of an association between Multiple Sclerosis (MS) and cancer has not been thoroughly investigated.

Case Presentation: We present a case of ovarian cancer in 58-year-old woman with MS. Radical hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and pelvic and para-aortic lymph node dissection was performed. Pathohistological analysis and immunohistochemistry confirmed the diagnosis of a clear cell carcinoma of the left ovary, grade III, FIGO2014 stage IA. Adjuvant chemotherapy of paclitaxel-carboplatin regimen (paclitaxel 175mg/m², carboplatin AUC 6, at intervals of 3 weeks) was implemented for 4 courses.

Conclusion: The occurrence of ovarian cancer in MS patients may be coincidental. Nevertheless, the long-term use of immunosuppressive and/or immunomodulatory drugs in MS and the incidence of cancer may be associated.

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Background

Ovarian cancer is the third most common gynaecologic malignancy worldwide [1]. In China, ovarian cancer accounts for 7.95 cases in 100,000 women, and it remains the leading cause of death among Chinese women with gynaecological cancer [2]. The median age of onset is 62. The incidence of ovarian cancer appears to have slightly decreased over the last 10 years [3]. It has a lifetime risk of approximately 2% for women. Due to its insidious onset and vague presenting symptoms, over 70% of women present with late-stage disease (stage III or IV). This results in high mortality to incidence ratio as survival at 1 year drops from 93.5% at stage II to 71% at stage III [4].

Multiple sclerosis (MS) is a demyelinating disease involving the central nervous system, which is believed to be an immune-mediated disorder mediated by a complex interaction between a person's genetics and as yet unidentified environment insults [5, 6]. The possibility of an association between MS and cancer has not been thoroughly investigated. Although the overall risk for malignancies in MS patients does not seem to be increased, there have been suggestions for a possible increase for certain cancers such as breast cancer, cancers of the CNS, the urinary tract system and nasopharynx [7]. MS is not known to be a risk factor for the subsequent development of cancer, but a potential long-term complication of immunosuppressive drug and/or immunomodulatory treatment in MS on cancer development should be

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discussed. We present a case of co-occurrence of multiple sclerosis and ovarian cancer.

Case Presentation

This 58-year-old female patient of Han Chinese was diagnosed with MS and optic neuritis on the right eye in 2004 at age 43. The first manifestation of the disease was pain in the right eye and the paralysis of the right side of her body, dizziness. She was treated with a high dose of corticoids, interferon β and plasma exchange therapy. After such treatment for a month, her disease remained stable with no major signs of deterioration except for a temporary case of dysphasia. She was switched to prednisone 10 mg once a day for maintenance therapy which she had taken for nine years. For the past four years, she had taken laquinimod, an immunomodulator, in the dosage of 0.5 mg. She suffered from pain and visual impairment on her right eye in June 2017, diagnosed with a relapse of MS, optic neuritis. After high-dose corticoids pulse therapy, she was relieved and changed to low dose prednisone maintenance therapy. She maintained irregular outpatient follow-ups.

She had no smoking habit of tobacco and no family history of malignant tumors. In January 2019, she presented and was admitted to our hospital due to complaints of "abdominal distension for more than 3 months and progressive worsening." Transvaginal colour Doppler ultra-sound detected a 172 mm \times 162mm \times 141mm mixed cystic and solid pelvic mass with an irregular shape and little blood flow signals. An abdominal and pelvic magnetic resonance imaging (MRI) scan revealed an irregularly shaped cystic and solid mass in the pelvic measured approximately 170mm \times 160mm \times 140mm and a small proportion was solid. Enhanced MRI scanning demonstrated uneven enhancement of the solid part.

The serum cancer antigen 125 and 199 level were 58.40, 498.43U/mL, respectively. At that time, a malignant tumor was suspected, possibly originating from the reproductive system. On the recto-vaginal and abdominal examinations, a huge cystic-solid mass in the pelvis and abdomen was non-adherence to the intestine and no involvement of sacroiliac ligament. Three gynaecologic oncology specialists and imaging specialists evaluated the MRI scan images and the findings of recto-vaginal and abdominal examinations. They considered that it would be helpful to more accurately identify the patient with early epithelial ovarian carcinoma that was likely to undergo optimal primary cytoreductive surgery.

On 19 January 2019, she underwent a hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and pelvic and para-aortic lymph node dissection. During the surgical operation, the peritoneal lavage cytology was negative. The surgical outcome was satisfactory, with no residual cancer foci. The postoperative biopsy results demonstrated a clear cell carcinoma, grade III, of the left ovary, which did not involve the right ovary, the uterus, the bilateral fallopian tubes and bilateral pelvic walls, with no lymph node involvement. The postoperative pathological stage was IA, according to the 2014 International Federation of Gynaecology and Obstetrics (FIGO) staging criteria for ovarian. Immunohistochemistry confirmed the diagnosis of a clear cell carcinoma (CK pan positive, Glypican positive, P53 positive, P16 positive, PAX-8 positive, and ER, PR, SALL4, CD30, CD117, WT-1 negative).

Subsequently, adjuvant chemotherapy of paclitaxel-carboplatin regimen (paclitaxel 175mg/m², carboplatin AUC 6, at intervals of 3 weeks) was implemented for 4 courses. At present, the patient continues to follow up closely.

Discussion

Ovarian cancer is rare in women under 40-year-old of age and most cancers in this age group are germ cell tumors. Above age 40, more than 90% are epithelial tumors and the risk increases with age, peaking in the late 70s [8]. Our patient was diagnosed with ovarian cancer at the age of 58, which is the expected age for this type of cancer.

Since ovarian cancer is insidious in presentation with few sentinel symptoms and lacks effective screening test strategies, most of the women present with late-stage disease [4]. Its clinical presentation often is that prodromal symptoms tend to be vague and include distension, constipation, and vague pelvic pressure. Pain is minimal, and the progression to advanced disease is insidious. Without sentinel symptoms of early disease, patients frequently present with symptoms at distant sites to the ovary [9]. Although the patient has a huge ovarian tumor, she has no symptoms such as pain, vaginal discharge, and only abdominal distension caused by increased pelvic pressure. This might be associated with MS and lack of regular follow-up.

The association of autoimmune diseases with cancer has been explored for several years, and reports have appeared suggesting an increased cancer risk in some autoimmune diseases [10, 11]. The long-term exposure of patients suffering from these disorders to immunosuppressive therapy may have confounded the association with cancer [12]. A nationwide population-based cohort study by Sun L M *et al.* in 2014 revealed that Taiwanese patients with MS have a higher risk of developing overall cancer types and breast cancer in particular [13]. However, earlier researchers also found that MS patients were not at a higher risk of developing cancer overall or were even at a low risk than the general popular [14-16]. The researchers believed that the pathogenic mechanisms involved in MS are associated with the autoimmune response of autoreactive T cells against myelin peptides. As MS is a chronic autoimmune disease, the immunogenic process that leads to persistent immune stimulation may inhibit carcinogenesis [17].

Marrie R A *et al.* conducted a meta-analysis for population-based studies. 38 studies evaluated the incidence or prevalence of MS. They found that cervical, breast, and digestive cancers had the highest incidence. The risk of meningiomas and urinary system cancers appeared higher than expected, while the risks of pancreatic, ovarian, prostate and testicular cancers were lower than expected. They believed that the complexity of understanding cancer risk in MS is augmented by inconsistencies in study design and the relative paucity of age, sex and ethnicity-specific risk estimates from which the strong impact of age on the incidence of cancers can be assessed [18].

Our patient used a high dose of corticoids, interferon β in acute attacks in the initial stages of the disease, and she later had used prednisone for maintenance therapy for nine years, then laquinimod for four years. When she relapsed into MS two years ago, she was changed to corticoids maintenance therapy after relief by corticoids pulse therapy. Laquinimod

has been turned down two times by the European Medicines Agency's Committee for Medicinal Products for Human Use because of concerns about possible teratogenic effects and cancer in animal studies of long-term exposure to laquinimod. The latest research, however, showed that there was no increase in the incidence of malignancies in long term use of laquinimod [19].

The patient has a huge ovarian tumor in the pelvis, but the postoperative pathological stage was IA which is in the earlier stages. We speculate that the reason may be related to the pathological type of clear cells. Clear cell carcinomas account for 10% of epithelial ovarian cancers and are similar to endometrioid cancers in that they have a relatively good prognosis. This is because they, too, are often diagnosed in the earlier stages. If diagnosed late or once the disease has advanced, the prognosis will be similar to that of the serous or endometrioid type. This is partial because of the cells being less sensitive to platinum-based chemotherapy, as well as associated complications that are seen with this diagnosis (i.e., blood clots and paraneoplastic hypercalcemia) [20]. Because mortality is closely related to disease stage at diagnosis (the 5 year survival rate is higher than 70% in stage I or II, but decreases to 40 and 20% in stages III and IV, respectively), an early diagnosis and timely surgical and/or chemotherapeutic treatment are vital [21].

It is estimated that approximately 18% of epithelial ovarian cancers, particularly high-grade serous carcinomas, are caused by inherited mutations that confer elevated risk, the majority in the BRCA1 or BRCA2 gene. Mutations in BRCA1 and BRCA2 account for almost 40% of ovarian cancer cases in women with a family history of the disease [22]. Holzmann C *et al.* reported a case of ac.5266dupc (5382insC) frameshift mutation in 33-year-old woman with breast cancer, multiple malignant melanomas and MS, whose family shows further cases of MS in BRCA1 mutation carriers [23]. To our patient, except for ovarian cancer, she had no personal and family history of malignant tumors. Although BRCA1/2 mutation tests were not carried out, it was unlikely that she had BRCA1/2 mutation.

Conclusion

Patients with MS may require additional attention due to the effect of their therapy and lack of symptoms when ovarian cancers are considered. An early diagnosis and timely surgical and/or chemotherapeutic treatment are vital.

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Authors Contributions

DX (Xu) and YL conceptualized and designed the study; FH, CL (Luo), XL and CL (Lu) collected the data; XL, CL (Luo), DX (Xie), FH, DX (Xu) and YI wrote the manuscript; All authors contributed to data interpretation, read the final manuscript and gave the approval.

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Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Consent for Publication

Written informed consent was obtained from the patients for publication of this report and any accompanying images, according to the principles of the Declaration of Helsinki (Link). Copies of the written consent are available for review by the editor of the journal.

Ethics Approval and Consent to Participate

Ethical and regulatory approvals were sought and obtained from the First Affiliated Hospital of Hainan Medical University.

Competing Interests

None.

Abbreviations

MS: Multiple Sclerosis

CNS: Central Nervous System

MRI: Magnetic Resonance Imaging

FIGO: Federation of Gynaecology and Obstetrics

CK: Cytokeratin

PAX 8: Paired-box gene 8

ER: Estrogen Receptor

PR: Progesterone Receptor

SALL4: Spalt Like Transcription Factor 4

CD: Cluster of Differentiation

WT: Wilms Tumor Protein

AUC: Area Under the Plasma Concentration/Time Curve

BRCA: Breast Cancer Gene

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