Peritumoral allergic response in epithelial ovarian carcinoma

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Summary

Aims: Desmoplasia, intratumoral lymphocyte infiltration, and calcification within the tumor and peritoneum are quite common in advanced epithelial ovarian carcinoma. Peritumoral inflammatory reactions associated with hematologic paraneoplastic syndrome are extremely rare. *Materials and Method:* We describe in detail two cases of epithelial ovarian carcinoma associated with proliferation of Russell bodies and Mott cells in desmoplastic tumor stroma. *Results:* In the first case, monoclonal proliferation was diagnosed with intranuclear inclusions (Dutcher bodies) in plasma cells. Dutcher bodies were seen both in the tumoral tissue and bone marrow. Monoclonal gammopathy of undetermined significance (MGUS) was diagnosed with an IgM level less than 3 g/l and clonal paratrabecular lymphoplasmocytoid infiltrate less than 10% in the bone marrow. There were no light chain restrictions. Elevated beta 2 microglobulin level and anemia complicated the patients' survival. In the second case, because of desmoplasia the tumor volume did not decrease after the standard chemotherapy although a significant portion of the carcinomatous tissue disappeared. In this study, we checked the role of peritumoral allergic response prospectively in five epithelial ovarian carcinoma cases by actin, desmin, and lambda light chain immunohistochemical staining of the omentum. *Conclusions:* Further studies are necessary to show the relation between peritumoral hypersensivity reaction and HLA 1 antigen processing machinery to improve disease-specific survival in epithelial ovarian carcinoma.

Key words: Epithelial ovarian carcinoma; Beta 2 microglobulin; MGUS; Russel body; Dutcher body; Mott cell.

Introduction

Proliferation of non-fibrous connective tissue within the tumor and peritoneum is quite common in the cases of advanced stages of ovarian carcinoma. Paraneoplastic syndromes, including endocrinopathies, neurologic abnormalities, skin lesions, and coagulation abnormalities may occur with tumors as a result of hypersensivity reactions. The response to the therapy differs across patients despite the standardization of surgical therapy and chemotherapy. Epithelial ovarian carcinomas account for nearly 90% of all ovarian malignancies. Intratumoral lymphocyte infiltration varies significantly among benign, borderline, and malign epithelial ovarian tumors [1]. The absence of intratumoral T cell infiltration has a negative effect on the survival of patients with ovarian carcinoma [2]. Matrix metalloproteinases (MMP) are proteolytic enzymes implicated in ovarian cancer progression and metastases [3]. The overexpression of stromal MMP-9 and membrane type 1-MMP is found to be independently associated with shorter survival rate, which is specific to the type of the disease in epithelial ovarian carcinoma [4]. Hoskins *et al*. [5] demonstrated that the effect of secretory leukocyte protease inhibitor (SLPI) is amplified in serous ovarian cancer. SLPI and MMP-9 expression are strongly correlated in serous ovarian cancers. Degradation of tumor matrix and normal tissue result in the release of tumor-derived DNA into the circulation. Kamat *et al*. [6] demonstrated that preoperative plasma cell free DNA is an independent predictor of death from disease in ovarian carcinoma. Although the origin of cell free DNA is unclear, physiochemical investigations suggest that it may originate from internucleosomal cleavage of the chromatin, a hallmark of the apoptotic process. Ebstein-Barr virus DNA is also detected in the cell-free DNA of nasopharyngeal carcinoma patients' serum. In addition to all of these studies, actin bundling protein fascin expression patterns are found to be a tumor phenotype, which does not change despite standard treatment procedures in epithelial ovarian carcinoma [1-4].

The aim of the study was to evaluate peritumoral allergic responses by histopathologic examination of the omentum in seven epithelial ovarian carcinoma cases.

Case Report

Case 1

A 61-year-old woman was admitted to Osmangazi Hospital because of postmenoposal bleeding and a pelvic mass. Initial laboratory test results were as follows: hemoglobin; 11.9 g/dl, leucocytes 6940/ml, and platelets 220,000/ml. HbsAg, anti HCV and HIV tests were negative. Alpha fetoprotein: 3.19 U/ml, hCG: 2.69 mIU/ml, CA-125: 21.6 U/ml. The patient was diagnosed with advanced-stage ovarian carcinoma and she underwent surgical staging. Type II hysterectomy, bilateral salpingo-oophorectomy, lymphadenectomy, partial omentectomy and multiple biopsies from the peritoneum and Douglas pouch were performed. The postoperative course was uneventful and the patient was discharged from hospital. The pathologic examination revealed biphasic malignant tumoral involvement of the ovaries, lymph nodes, omentum, peritoneum, and Douglas pouch. Mixed pleomorphic tumoral infiltrate containing lymphoid cells, plasma cells, atypical pleomorphic large cells containing Dutcher bodies, clusters of Russell bodies and Mott cells, and focal serous ovarian carcinoma were seen in the ovaries, and six metastatic lymph nodes and peritoneum (Figure 1-2). Binucleated or multinucleated plasma cells were observed in the desmoplastic tumoral stroma. Multiple intranuclear eosinophilic inclusions were seen in the nucleus of atypical pleomorphic large cells. Kappa or Lambda light cell restrictions

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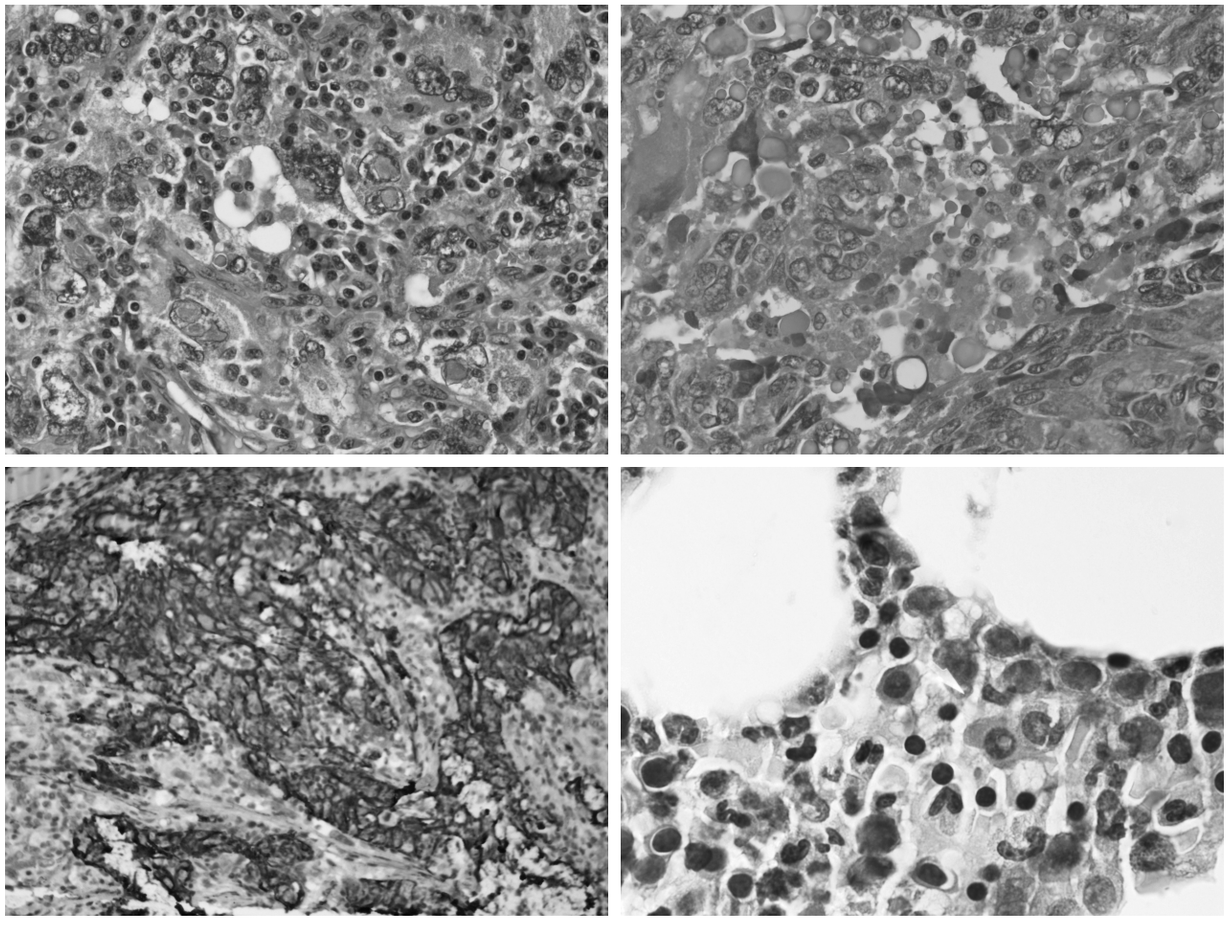

Figure 1. — Plasma cells and pleomorphic large cells containing eosinophilic intranuclear inclusions. Dutcher body containing plasma cells were seen (case 1 – hematoxylin-eosin x 400).
Figure 2. — Plasma cells, Mott cells, Russell bodies, and atypical pleomorphic tumoral cells which were not stained by cytokeratin 18 (case 1 – hematoxylin-eosin x 800).
Figure 3. — Cytokeratin 18 highlighting the high-grade serous carcinoma cells in the biphasic tumoral infiltrate (case 1 – CK18 immunohistochemical stain x 400).
Figure 4. — Dutcher body (arrow) in the nucleus of a plasma cell showing monoclonal proliferation of lymphoplasmocytoid cells in the bone marrow. The cells are less than 10% of bone marrow cells (case 1 – hematoxylin-eosin x 2000).

were not observed in plasma cells by immunohistochemical staining, however the plasma cells stained with kappa light chain were bigger than the plasma cells stained with lambda light chain. CK18 immunohistochemical staining highlighted serous carcinoma cells among the mixed pleomorphic tumoral infiltrate (Figure 3). The combined pattern of high-grade serous carcinoma and pleomorphic plasma cell tumor were also observed in the sections from ovaries and pelvic para-aortic lymph nodes. After the operation, laboratory test results were as follows: myoglobulin: 659.36 ng/ml (N = 10-92 ng/ml), troponin I: 0.11 ng/ml (N = 0-0.1 ng/ml), LDH: 539 U/l (N = 240-480 U/l). Bone marrow biopsy examination revealed paratrabecular lymphoplasmocytoid infiltrate and some atypical monocytoid cells. Dutcher bodies in plasma cells showed monoclonal proliferation of lymphoplasmocytoid cells in the bone marrow (Figure 4). The protein electrophoresis was as follows: gamma: 20.2 g/l (N: 7-12 g/l), alpha 1: 8.2 g/l (N: 2-3 g/l), alpha 2: 12.1 (N: 4-10 g/l), albumin: 48.2 g/l (N: 35-50 g/l), beta 1: 5.9 gr/lt (N: 5-11 g/l), beta 2: 5.4 g/l, immunoglobulin levels: IgG: 13.6 g/l, IgM: 0.777 g/l, IgA:0.29 g/l, beta 2 microglobulin: 4.22 mg/dl (N: 1.16-3.21 mg/dl). Histopathological classification and laboratory evaluation revealed high-grade, Stage IIIC serous ovarian carcinoma with MUGUS. Two months after the surgery the patient was readmitted to the hospital and was administered the standard adjuvant chemotherapy for serous ovarian carcinoma. The patient died of disease after the first dose of chemotherapy because of acute renal failure.

Case 2

A 62-year-old female patient was referred to Osmangazi Hospital with unresectable pelvic tumor. Needle biopsy was performed. Tumor cells had hyperchromatic pleomorphic nuclei, scant cytoplasm and formed irregular nests in the desmoplastic stroma. Plasma cells, clusters of Russell bodies and Mott cells were observed in the stroma. Plasma cells were partially positive for CD138, Kappa and Lambda immunohistochemical staining. After six doses of standard chemotherapy for serous ovarian carcinoma, the patient underwent cytoreductive surgery.

The right ovary was 18 x 13 x 8 cm in dimension. The left ovary was 3.5 x 1.5 x 1.2 cm in size. High-grade serous ovarian carcinoma was diagnosed in the right and left ovary, Douglas pouch and peritoneum. Infarction was observed in the right ovary. *Blastomyces hyphae* were seen in the necrotic areas of the right ovary. In the left ovary benign Brenner tumor focus associated with serous carcinoma was observed. The stroma of the tumor was desmoplastic. Actin and desmin positive myofibroblastic cells, and multinuclear giant cells were seen in the stroma and peritoneum. Cytokeratin 18 immunohistochemical stain revealed decreased tumor cell volume after chemotherapy. Collagen-1 binding proteoglycan, syndecan-1 (CD138) immunohistochemical staining decorated the surface of serous carcinoma cells with papillary architecture and plasma cells. There were no light chain restrictions by kappa or lambda immunohistochemical staining.

Control cases

The control patients' age ranged between 44-75 years. Omental biopsies of five cases of grade 3 epithelial ovarian carcinoma were examined prospectively to check the presence of hypersensivity reaction. Among the histopathologic types of cases, four were serous and one was endometrioid type. There were three patients in Stage IA, one patient in Stage 3C, and one patient in Stage 4. Among the cases with histopathologic examination of the omentum, two cases had tumoral involvement, one case had fat necrosis, the other cases had mild to moderate degrees of fibrosis with capillary proliferation and mononuclear inflammatory cells in the adipose tissue or around the vessels. Immunohistochemical stains were performed for actin, desmin and lambda light chain by using the avidin-biotin peroxidase complex method.

Results

Desmin immunohistochemical stain only stained periarteriolar myoid cells. Actin immunohistochemical stain highlighted desmoplastic fibrous tissue with small capillary proliferation in four patients. Lambda immunohistochemical stain was partially positive in plasma cells in three cases. The staining pattern highlighted the polyclonal composition of lymphoplasmocytic infiltrate. One case of Stage IA, grade 3 serous carcinoma had non-specific strong lambda light chain staining in the dense, homogenous and hyalinized connective tissue. The other case of Stage IA serous carcinoma had minimal inflammation and fibrous tissue proliferation in the omentum.

Discussion

Waldenström and Pedersen demonstrated the presence of large quantities of a high molecular weight globulin in the plasma of a group of patients and differentiated the electrophoretic patterns of monoclonal and polyclonal gammopathies. The patterns of gamma globulin in a chronic viral disease were very broad whereas in that of myeloma they were sharp with a narrow spike designated as monoclonal gammopathy [7]. The presence of monoclonal B-cell proliferation does not necessarily imply malignancy. Monoclonal gammopathies can be complicated as a variety of cutaneous diseases, Sjogren syndrome, scleromyxedema, necrobiotic xanthogranuloma with paraproteinemia and POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein and skin lesions) [7-9]. Waldenström's macroglobulinemia (WM) associated with hepatic carcinoma, lung carcinoma, conjunctival in situ carcinoma, mucinous carcinoma of urinary bladder, larynx carcinoma, and some other malignancies were reported [10-13]. Most of these solid malignancies were diagnosed during the course of paraproteinemia. The median survival is five years and approximately 10% of the patients are still alive after 15 years [14].

Lymphoplasmacytic lymphoma (LPL) is a rare low-grade lymphoma that is often associated with WM, which is defined as a subset of plasmacytoid lymphocytic lymphoma. The presence of a large IgM paraprotein in the absence of LPL is no longer considered as WM, and LPL in the absence of IgM paraprotein is not WM. Diagnostic criteria for asymptomatic myeloma are M-protein in the serum at myeloma levels less than 3 g/l and/or less than 10% of clonal plasma cells in bone marrow. This disease is called IgM MGUS (= monoclonal gammopathy of undetermined significance) and the patient has no signs of anemia, constitutional symptoms, lymphadenopathy or hyperviscosity [15]. Our first case had a pelvic mass, multiple abdominal lympadenopathies, anemia, and high levels of beta 2 microglobulin. However, other laboratory results and the bone marrow biopsy were compatible with MGUS. In this case, hematologic examination was performed ten days after the cytoreduction surgery for ovarian carcinoma. Our patient had two poor prognostic criteria (anemia and high beta 2 microglobulin level) for WM [15]. The presence of Dutcher bodies containing plasma cells and/or atypical cells in both bone marrow and peritumoral tissue demonstrated that the proliferation of plasma cells were monoclonal, however there was no light chain restriction.

Satoskar *et al*. [16] reported 24 patients with cardiac amyloidosis. Six patients in this series were diagnosed as MGUS related to AL amyloidosis. We could not find any case of amyloidosis associated with ovarian neoplasia. However, Han *et al*. [2] reported beta 2 microglobulin expression of 63.3% for epithelial ovarian carcinoma. In the first case, high levels of plasma beta 2 microglobulin and anemia were associated with poor prognostic factors for WM [15]. Defects in HLA class I antigen processing machinery (APM) might create a mechanism for tumor cells to escape from immune recognition. Han *et al*. [2] demonstrated heterogenous or positive expression of TAPI, TAPII, HLA-class I heavy chain and beta 2 microglobulin in epithelial ovarian carcinoma. Down-regulation of the APM component has been found to have a negative effect on the survival of patients with ovarian carcinoma.

Chronic inflammatory infiltrate in the peritoneum displays perivascular or diffuse patterns containing lymphocytes, macrophages, plasma cells, and eosinophils. The fibrous component is characterized by myofibroblasts within a type I collagen matrix. Metastatic tumor cells within the retroperitoneum may cause an exuberant

desmoplastic response. Plasma cells may be positive for IgG4 isotype [17-20].

In this study, we have presented two rare cases of serous ovarian carcinoma associated with special type desmoplastic reaction with peritumoral proliferation of Mott cells and Russell bodies. Mott cells, specific forms of plasma cells that contain multiple intracytoplasmic inclusions called Russell bodies, are occasionally observed in hematopoietic tumors with plasmacytic differentiation, as in plasma cell myeloma [8]. Shinozaki *et al*. [21] described two cases of Epstein-Barr virus associated-gastric carcinoma with prominent reactive Mott cell proliferation. The tumor volume did not decrease in our second case after six doses of standard chemotherapy and there were actin and desmin positive myofibroblasts in the tumoral stroma, however an important portion of carcinomatous tissue had disappeared. There were no Dutcher bodies in the peritumoral tissue. In the second case, Mott cell and Russell body proliferation were reactive. Rampisela *et al*. [8] described an unusual self-limited clonal Mott cell proliferation with lymphoplasmacytic lymphoma-like features in an inguinal lymph node of a child who was previously diagnosed with Wiskott-Aldrich syndrome and Von Recklinghausen's neurofibromatosis. The child spontaneously recovered in less than a year, however Burkitt's lymphoma developed in the parapharyngeal space four years later. Mott cell proliferation in this case was also reactive because there were not any Dutcher bodies containing plasma cells in the infiltrate.

The presence of monoclonal proliferation of Mott cells and Russell bodies are extremely rare peritumoral allergic responses in epithelial ovarian carcinoma. In the first case, we demonstrated the defective antigen processing machinery component by elevation of beta-2 microglobulin in the plasma [2]. All our cases were treated with standard therapy. The apparent differences in disease-specific survival among epithelial ovarian carcinoma cases showed the role of peritumoral allergic response in epithelial ovarian carcinoma. Further studies on defects of HLA class I antigen processing machinery are necessary for the improvement of disease-specific therapy in advanced stages of epithelial ovarian carcinoma.

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