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A Case of Uterine Cervical Cancer Presenting with Granulocytosis

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Granulocytosis occurs in 40% of patients with lung and gastrointestinal cancers, 20% of patients with breast cancer, 30% of patients with brain tumor and ovarian cancer and 10% of patients with renal cell carcinoma. Granulocytosis occurs because of production of G-CSF, GM-CSF and IL-6. Uterine cervical carcinoma with granulocytosis as a paraneoplastic syndrome, however, has been rarely reported. We recently witnessed a case of invasive squamous cell carcinoma of the uterine cervix with granulocytosis. Leukocytosis developed up to 69,000/μL, and then normalized after chemo-radiotherapy. There was no evidence of infection, tumor necrosis, glucocorticoid administration, or myeloproliferative disease by examination of a bone marrow aspirate when granulocytosis appeared. This phenomenon was probably associated with the secretion of hematopoietic growth factors such as G-CSF, GM-CSF and IL-6 by the tumor. We suggest that, like some other solid tumors, cervical cancer can present with granulocytosis as a paraneoplastic syndrome.

Key Words : Leukocytosis; Paraneoplastic syndrome; Cervical cancer

INTRODUCTION

About 30% of patients with a solid tumor have granulocytosis (granulocyte count > 8,000/μL). Moreover, in about half of these patients with granulocytosis and cancer, the granulocytosis has an identifiable non-paraneoplastic etiology (infection, tumor necrosis, glucocorticoid administration); however, the others have no identifiable etiology of granulocytosis.

It is well known that various types of nonhematopoietic tumors demonstrate granulocytosis of unknown cause without overt inflammation. Recently, studies have demonstrated that such granulocytosis is due to hematopoietic growth factors, including granulocyte colony- stimulating factor (G-CSF), which are produced by the tumor. A variety of nonhematopoietic malignant tumors, including bladder cancer, hepatoma, mesothelioma, oropharyngeal cancer, melanoma, and sarcoma, have been reported to produce G-CSF[1-4]. Granulocytosis occurs in 40% of patients with lung and gastrointestinal cancers, 20% of patients with breast cancer, 30% of patients with brain tumor and ovarian cancer and 10% of patients with renal cell carcinoma. However, carcinomas of uterine cervix producing these factors are extremely rare, although several cell lines producing IL-6, a pleiotropic cytokine, have been established from uterine cervical cancers[5].

We report a case of uterine cervical cancer presenting with granulocytosis as a paraneoplastic syndrome.

CASE REPORT

A 56-year-old woman was admitted to our hospital on December 22, 2002, complaining of vaginal spotting. The

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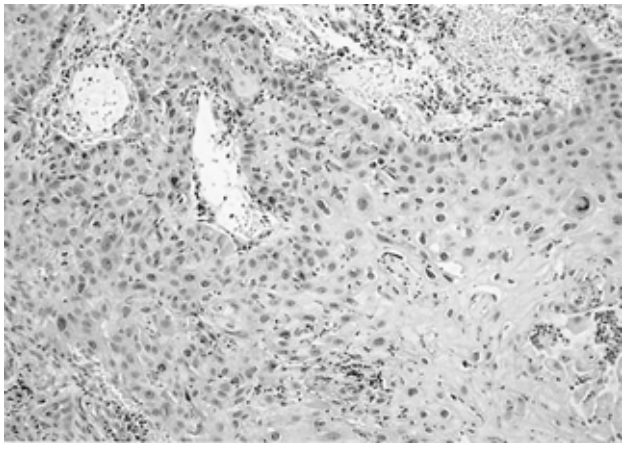

Figure 1. Uterine cervix punch biopsy shows invasive squamous cell carcinoma, keratinizing type. Hematoxylin and eosin stain (× 200)

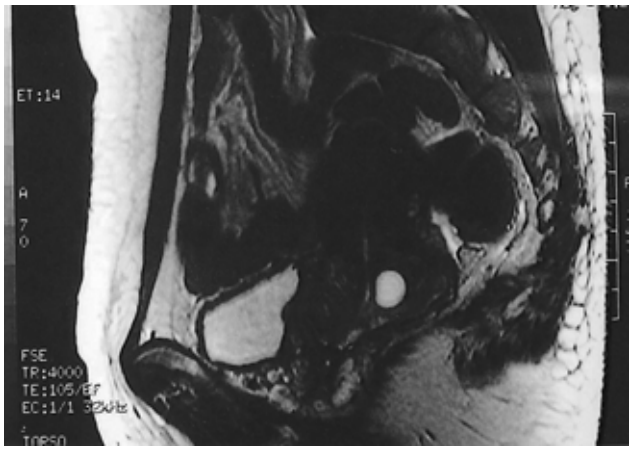

Figure 2. Abdomen and pelvic MRI scan shows 5.5×3.5 cm high signal intensity mass in the uterine cervix.

symptom developed initially about six months before admission. Colposcopic examination revealed a 5-cm sized cauliflower-like mass in the uterine cervix with upper vaginal invasion. A biopsy specimen was taken from the mass. Microscopically, the biopsy specimen revealed a keratinizing type invasive squamous cell carcinoma (Figure 1). There was a 5.5×3.5 cm high signal intensity mass in the uterine cervix with invasion of the left parametrium and a 1 cm lymph node in the left external iliac area on MRI scan (Figure 2). A chest X-ray revealed no abnormality. A blood sample showed the following findings: WBC, $12.7\times10^3/\mu L$ (78% neutrophils, 15% lymphocytes, 6% monocytes, 1% eosinophils); RBC, $3.54\times10^6/\mu L$, Hb, 8.7 g/dL, Hct, 34.6%, platelets, $413\times10^3/\mu L$, C-reactive protein, 7.0 mg/dL, blood urea nitrogen, 13 mg/dL, creatinine, 0.6 μg/dL, alkaline phosphatase, 207 IU/mL, AST, 29 IU/mL, ALT, 8 IU/mL, and total protein, 7.4 g/dL. There was no evidence of HIV and hepatitis infection by serological studies. The radiological diagnosis was uterine cervical cancer stage IIB, but physical examination revealed a movable cervix. Consequently, she was assessed as a potential candidate for radical hysterectomy.

Considering potential resectability, we treated the patient with neoadjuvant chemotherapy with MVC regimen (mitomycin-C 10 mg/m^2, vincristine 1.0 mg/m^2 and cisplatin 70 mg/m^2) every three weeks[6, 7]. After two cycles of treatment, the tumor size had increased as detected by a follow-up colposcopic examination. Simultaneously, the WBC count became markedly elevated to 69,000/μL. We performed a comprehensive evaluation of the newly developed severe leukocytosis, including blood culture, bone marrow aspiration and biopsy to rule out infection and hematological malignancy. No abnormalities were found.

The hematological diagnosis was a granulocytic reactive marrow. There was no evidence of bone marrow involvement of malignant tumor (Figure 3). Furthermore, there was no specific

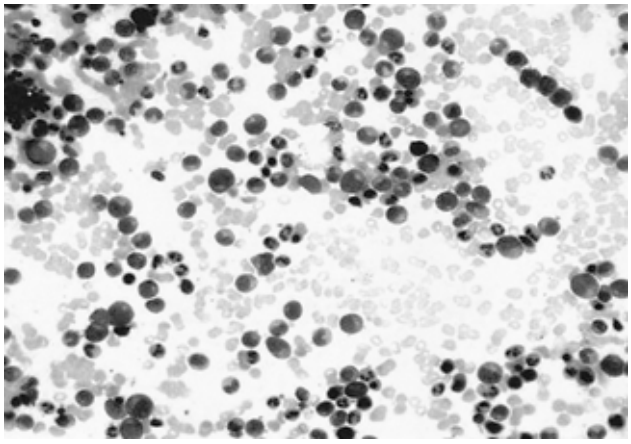

Figure 3. Bone marrow examination shows granulocytic reactive marrow. No evidence of bone marrow involvement of malignant tumor was detected. Wright, Giemsa stain (×400).

infection or drug intake history, including steroid and herb medication. Therefore, we considered the granulocytosis to be associated with the tumor itself. However, we could not determine the levels of G-SCF, GM-CSF, and IL-6 in serum because the patient refused these lab tests. Accordingly, we confirmed immunochemical expression of G-CSF and IL-6 by using paraffin block. Staining for G-CSF and IL-6 was mainly observed in the cytoplasm of cancer cells (Figure 4A, 4B).

After the diagnosis of granulocytosis, we changed the treatment plan. We started external radiation for six weeks (4000 cGy), six cycles of chemotherapy with weekly cisplatin administration (40 mg/m^2), and two cycles of sequential intra-cavitary radiation (ICR). After these treatments, the cervical mass was no longer seen in the follow up MRI scan (Figure 5). The WBC count returned to the normal range (4,100/μL) at that time. The follow-up complete blood count profile revealed: WBC, 4,100/μL

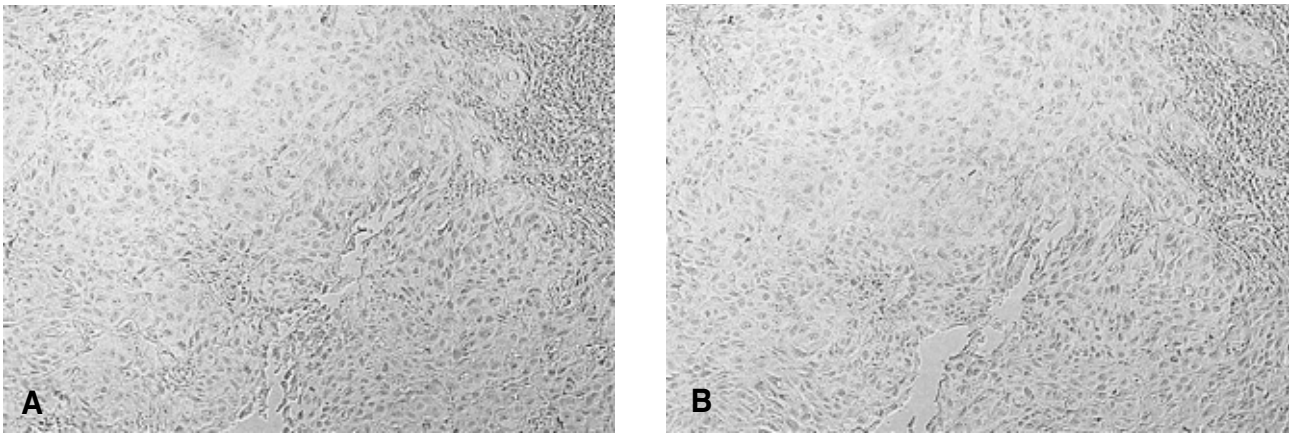

Figure 4. Immunohistochemical staining of G-CSF(A), IL-6(B) (×200).

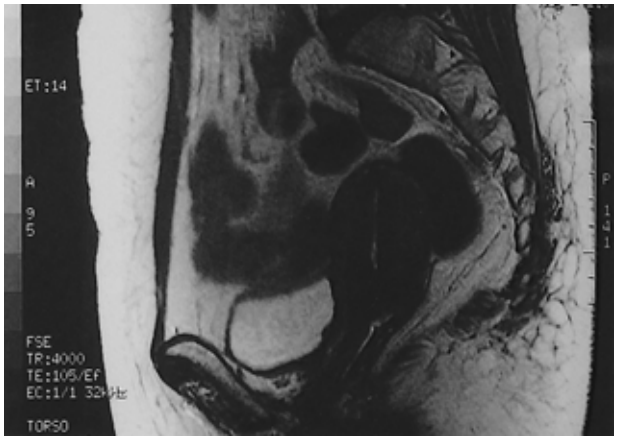

Figure 5. Follow-up abdomen and pelvic MRI scan shows no cervical mass.

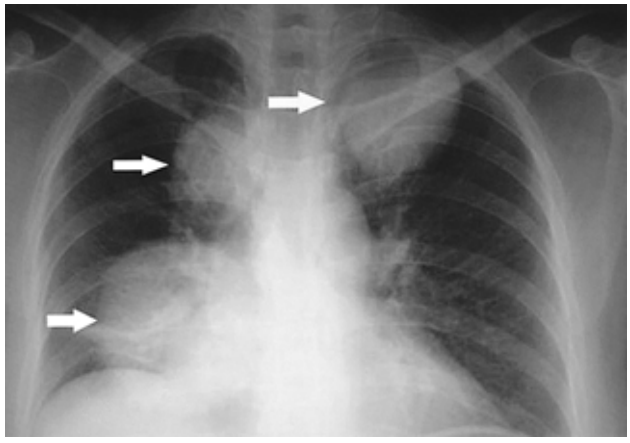

Figure 6. Follow-up chest X-ray shows markedly increased metastatic nodules of right lower lobe and left upper lobe and newly developed metastatic nodule in right upper lobe.

(65% neutrophils, 15% lymphocytes, 16% monocytes); RBC, $2.77\times10^6/\mu L$; Hb, 10.3 g/dL; and platelets, $366\times10^3/\mu L$.

One month later, a cavitary nodule was found in the left upper lobe of the lung in the chest X-ray, and a vulval mass was detected. Both lesions were confirmed pathologically as metastatic squamous cell carcinoma by percutaneous needle aspiration cytology. At that time, the WBC count became elevated again to 29,600/μL. Lastly, we changed the chemotherapy regimen to paclitaxel plus cisplatin. Over three months, four cycles of this combination chemotherapy were carried out. After four cycles of treatment, a marked increase in metastatic lung nodules was found on the follow-up chest X-ray (Figure 6), with severe granuocytosis (52,700/μL). The patient refused further chemotherapy and symptomatic management. She died three months later.

DISCUSSION

Granulocytosis is caused by an exaggerated myeloid response to several stimuli, including infection, allergies, burns, intoxication, acute hemorrhage, malignant neoplasms, and certain drugs, including corticosteroids and lithium[8-10]. Malignant tumor-associated granulocytosis likely involves the secretion of hematopoietic growth factors such as G-CSF, GM-CSF and IL-6 by the tumor.

Cervical cancer, like some other solid tumors, can also exhibit granulocytosis as a paraneoplastic syndrome. To rule out other causes of granulocytosis, extensive evaluation, including a careful assessment of patient history with particular attention to drug intake and a physical examination, should be performed.

Granulocytosis as a paraneoplastic syndrome usually involves carcinomas of the colon, lung, stomach, kidney, ovarian and bladder. The mechanism of ganulocytosis is possibly due to

the secretion of G-CSF by the tumor cells. G-CSF is a cytokine secreted primarily by monocytes, macrophages, endothelial cells and fibroblasts. Its target cells are late myeloid progenitors enhancing production and function. Therefore, cancer patients with marked granulocytosis and without infection may have cytokine-producing tumors, and aggressive treatment should be considered.

Our patient appeared to have paraneoplastic granulocytosis. Staining for G-CSF and IL-6 was mainly observed in the cytoplasm of cancer cells (Figure 4A, 4B).

The relationship between cervical cancer and extreme granulocytosis followed by rapid normalization of the leukocyte count after treatment supports the possibility of autonomous production of G-CSF by the tumor as the cause of marked granulocytosis in this case.

The most important characteristic of this case was rapid tumor progression, which has been reported to be frequently observed in cytokine-producing tumors. A variety of non-hematopoietic malignant tumors have been demonstrated to secrete G-CSF[1-4], and most of these patients had a poor clinical outcome. A few studies have shown that treatment of bladder cancer cell lines with exogenous G-CSF in vitro results in enhanced tumor growth stimulation[11, 12]. Therefore, we suggest that these malignant tumors should be regarded as aggressive and advanced disease, as they may have a high probability of poor response to treatment. Further studies are needed to define the biology of tumors with paraneoplastic granulocytosis. This will clarify the relation between paraneoplastic granulocytosis and disease severity. Furthermore, additional studies are needed to correlate the severity of paraneoplastic syndrome and disease progression or regression.

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