Strongly suspected microangiopathic hemolytic anemia associated with radiotherapy in the treatment of advanced cervical cancer

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Introduction

The term "microangiopathy" was first proposed by Brain [1] in 1962. It designates a group of disorders characterized by the presence of schizocytes and thrombocytopenia associated with hemolytic anemia. Microangiopathy is caused by impairments in microcirculation. Such impairments in microcirculation may be induced by various causes including idiopathic, viral infection, malignant hypertension, pregnancy, connective tissue disease, or neoplasia [2-4]. In this report, we describe cancer-associated microangiopathy that emerged soon after radiation therapy for uterine cervical carcinoma.

Case Report

A 73-year-old Japanese nullipara single female was referred on April 25, 1994 to our hospital for treatment of uterine cancer. She had had a myomectomy at 40 years of age but had no history of any other disease. Abnormal genital bleeding began in Sept. 1993, and dysuria and pretibial edema were observed in the beginning of April 1994. She had severe pyometra which increased her white blood cell count (WBC) to 38,000/mm^3. Anemia (hemoglobin level (Hb) of 8.1 g/dl) due to genital bleeding for a long time, poor nutrition, and pretibial edema were manifest. The squamous cell carcinoma antigen (SCC Ag) tumor marker was also elevated. A pelvic examination revealed that the cervix of the uterus was deformed and occupied by carcinoma tissue. The tumor invaded up to the superior, two-thirds of the length of the vaginal column. The uterus was enlarged to fist size and elastic-hard as associated with pyometra (Fig. 1). Carcinoma invaded both the parametrium and the pelvic wall. Bilateral hydronephrosis was revealed by drip intravenous pyelography and the urinary bladder was invaded by tumor tissue. Chest X-ray before therapy was normal (no metastatic shadows). The patient was diagnosed as stage IVa carcinoma of the uterine cervix. Histological examination by the biopsy of the cervical tumor revealed large cell non-keratinizing squamous cell carcinoma.

The patient received a blood transfusion to restore depletion from anemia and then radiotherapy to the whole pelvis was initiated. After the completion of linear acceleration (linac) 30 Gy irradiation, genital bleeding ceased, pyometra was released, the uterus became normal size (from 13 x 9.8 x 9.6 cm to 7.6 x 7.2 x 3.3 cm) (Fig. 2) and SCC Ag level that was 3.2 ng/ml before radiation therapy recovered to a normal range of 0.8 ng/ml. Blood cell counts also improved (WBC count 7,600/mm^3, Hb 9.4 g/dl, platelet count 103,000/mm^3). After finishing external-beam irradiation of 50 Gy by linac and during radiotherapy of 20 Gy by a remote after-loading system (RALS), intermitent high fevers (39-40 °C) occurred. The WBC count elevated to 90,000/mm^3 and the serum lactate dehydrogenase (LDH) level increased to 2,159 WU from normal level. The platelet count decreased to 17,000/mm^3, severe anemia, and jaundice of the general body developed. A blood bacterial culture was negative, and sepsis was neglected. The laboratory findings confirmed the progression of disseminated intra-vascular coagulation (DIC) by signs such as prolonged prothrombin time and partial thromboplastin time, low fibrionogen, elevated fibrin degradation products-D-dimmer and thrombin antihrombin complex, and low antithrombin-III in comparison to normal laboratory findings at admission (Table 1). Interestingly, an automatic

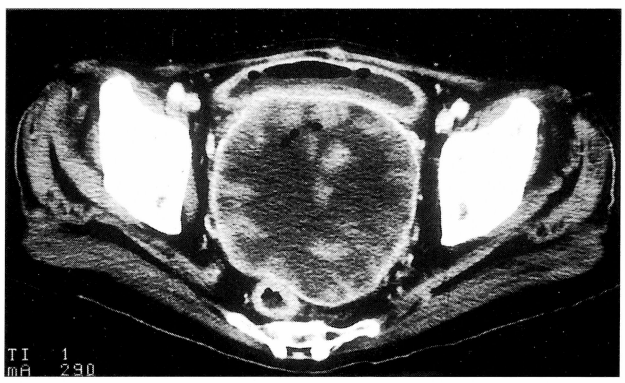

Figure 1. — Pelvic CT scan before radiation shows the uterus is enlarged whith pyometra.

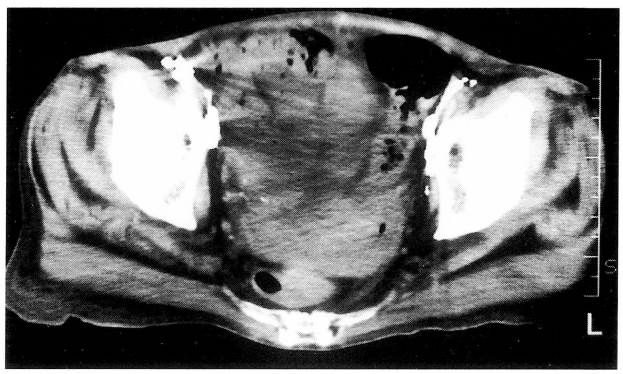

Figure 2. — Pelvic CT scan after the completion of Liniac 30 Gy irradiation showed the uterus became normal size.

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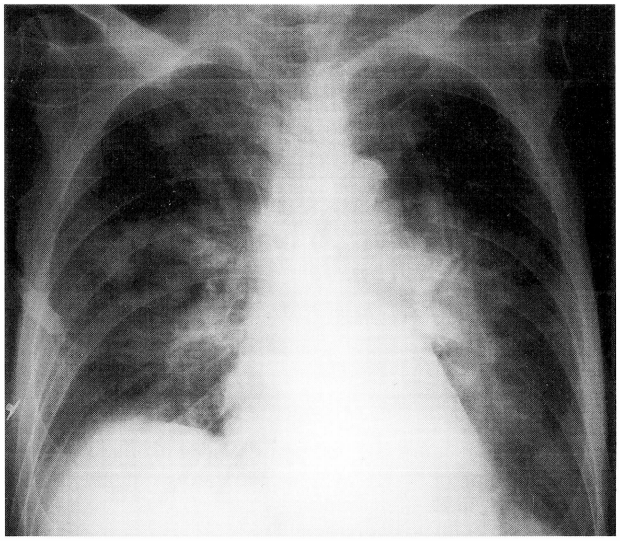

Figure 3. — Chest X-ray film shows diffuse abnormal shadows in bilateral lung fields.

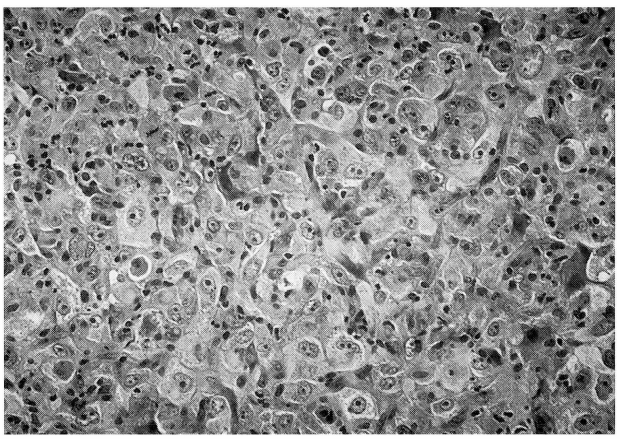

Figure 4. — The microscopical photography of cervix obtained by biopsy of pre-radiation therapy. It reveals large cell non-keratinizing squamous cell carcinoma.

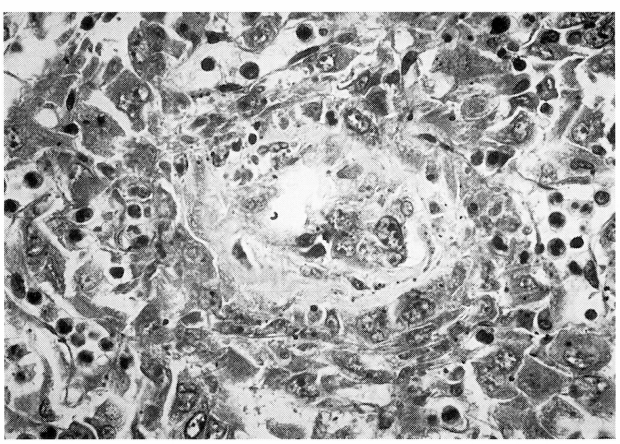

Figure 5. — Autopsy specimen reveals tumor cell emboli in the pulmonary arteriole with intimal proliferation.

Table 1. — *Characteristics of a patient with cancer-associated microangiopathic hemolytic anemia*

	(admission)	normal values
Hemoglobin (g/dl)	7.4 (8.7)	(12-16.5)
Platelets x 10^3	17.0 (121.0)	(120-280)
Fibrinogen (mg/dl)	222.0 (268.0)	(220-470)
Fibrinogen degradation products D-dimer (μg/ml)	2.0 (<0.5)	(less than 0.5)
Anti-thrombin III (%)	30	(75-125%)
Thrombin-antithrombin complex (ng/ml)	49.2	(less than 3.75)
Prothrombin time (%)	26 (61)	(70-130)
Activated partial thromboplastin time(s)	46.0 (34.7)	(less than 40.0)
Total bilirubin (mg/dl)	12.0 (0.9)	(0.2-1.2)
Indirect bilirubin (mg/dl)	4.1 (0.5)	(0.1-0.8)
Lactate dehydrogenase (WU)	2159 (309)	(50-400)

analysis of erythrocytes showed the existence of various sizes of everythrocytes that schizocytes seemed to be in the peripheral blood. An X-ray examination revealed an abnormal shadow on the bilateral lungs that was rapidly extending (Fig. 3). At this time, SCC Ag rapidly elevated again to 24.6 ng/ml. Despite transfusions of one unit of packed, total red blood cells which was administered every 4 days, the patient's hemoglobin and hematocrit did not improve. After 10 days of this acute change, she died due to respiratory insufficiency.

Upon microscopic examination of the cervix and vaginal wall before radiotherapy, large cell nonkeratinizing squamous cell carcinoma was observed (Fig. 4). However, a punched biopsy of the cervix after radiation therapy showed only degenerated and necrotic cells, proving a good radiation response of local carcinoma tissue.

Autopsy confirmed wide spread metastasis to various organs (bilateral lungs, bilateral pleura, liver, spleen, ribs, vertebrae, both adrenals, and lymph nodes). Histologic examinations of autopsy specimens revealed tumor cell emboli in the pulmonary arteriole with intimal proliferation (Fig. 5) and alveolar wall capillaries.

Discussion

It is very rare for neoplastic microangiopathy to appear as a secondary effect of cancer. Antman *et al.* [5] could find only 55 of these cancer-associated cases in their review of the literature. Hügli *et al.* [6] also reviewed 135 cases. Most of the cancers in which microangiopathic hemolytic anemia occurred were mucin-producing adenocarcinoma. The most common cases were gastric cancer. The uterine carcinoma case was only one out of 135 cases. A similar result was reported by Angiola *et al.* [7].

In this study, we have presented a case of microangiopathic hemolytic anemia associated with uterine cervical cancer confirmed by clinical and laboratory findings. But, we can not completely neglect the possibility of DIC due to sepsis which occurs in advanced cancer. 30Gy of radiotherapy to the whole pelvis healed the pyometra and leucocytosis, and so, it seems impossible that sepsis occurred under such conditions. Moreover, our patient had hemolytic anemia, jaundice, thrombocytopenia, DIC, elevated LDH, tumor emboli of the capillaries histopathologically proven, and a rapid course to death. We therefore think our case corresponds to complicated neo-

plastic microangiopathy. But, it remains to be seen if the mechanical procedure of RALS might induce sepsis. Early papers on neoplastic microangiopathy emphasized the importance of schizocytes [1, 6]. A smear of peripheral blood was not examined in our case, but the automatic analyzer always showed the existence of various sizes of erythrocytes and this suggests the existence of schizocytes in the peripheral blood.

The mechanisms which cause neoplastic microangiopathy are not yet understood. It seems that multiple factors are involved, such as mechanical, biochemical, circulating antigen-antibody complexes, procoagulants, and the secondary effects of anti-cancer agents [6].

In our case, SCC Ag reflected the patient's clinical course. After the completion of 30 Gy radiotherapy to the whole pelvis, vaginal bleeding stopped and the swollen uterus shrunk to almost normal size. The level of SCC Ag became normal- from 3.2 ng/ml to 0.8 ng/ml (normal value less than 2 ng/ml). However, when more radiation (RALS) was added the patient's condition rapidly became worse. The level of SCC Ag dramatically increased to 24.6 ng/ml within a month. This suggested that the cancer cells disseminated rapidly to the general body and it was speculated that neoplastic microangiopathy occurred within the last month.

Many reports claim that the histological type of cancer is almost always adenocarcinoma, but a case of squamous cell carcinoma has not been reported. Pathological examination of our case showed that the primary lesion was a large cell non-keratinizing squamous cell carcinoma. It should be distinguished from glassy-cell carcinoma with a poor response to radiation and histologic mucin content. This patient's tumor was very radiosensitive and did not contain mucin histologically. It is reasonable to believe that this case was squamous cell carcinoma.

Some clinicians [7, 8] report that neoplastic microangiopathy occurred during chemotherapy. In our case, it occurred during radiation therapy (RALS). It is possible that direct radiation or mechanical effects to the cervical cancer mass induced dissemination of tumor cells to many organs. It is probably linked to tumor lysis (liberation of factors toxic for the capillary endothelium, procoagulants) rather than to the effects of radiation. Clinicians should be careful in treating advanced cancer directly (such as with RALS treatment) avoiding dissemination of tumor cells by mechanical or tumor lysis. The prognosis of neoplastic microangiopathy is generally very poor [5, 6, 9-17] and the survival time of this case was only 10 days. No treatments, including chemotherapy, are effective against it. More studies on the pathophysiology and therapy of neoplastic microaniopathy are needed.

Conclusion

We have reported a case of microangiopathic hemolytic anemia strongly presumed to have occurred after a patient was diagnosed with uterine cervical carcinoma. A 73-year-old Japanese woman with stage IVa cervical squamous cell carcinoma of the uterus was treated with radiation therapy using linac and RALS. The radiation therapy using linac was effective enough to shrink the local tumor of the uterus. However, when radiotherapy by RALS started, the patient fell into hemolytic anemia and thrombocytopenia (14,000 platelets/mm^3) and her serum LDH elevated to 2,159 WU. The patient was diagnosed with microangiopathic hemolytic anemia according to these laboratory findings. In spite of intensive treatments, there was no response to the therapies. She died from respiratory insufficiency due to diffuse metastasis of the lung after the 10th day after the onset of these symptoms. This is the first report of uterine cervical squamous cell carcinoma presumed to have been accompained by microangiopathic hemolytic anemia during radiotherapy.

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