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Postirradiation Malignant Mixed Mesodermal Tumor of the Uterus

— A case report —

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ABSTRACT

A case of malignant mixed mesodermal tumor (MMMT) developed after radiation therapy for a uterine cervix cancer is described. The patient was a 62-year-old female at the time of diagnosis of stage Ib squamous cell carcinoma of the cervix and a total of 12,000 rads of x-ray was administered on the pelvic area. Five years later she manifested vaginal spotting and rectal pain. Endomteial curettage and biopsy revealed carcinosarcoma. Radical hysterectomy was done and a 5×3×2 cm sized polypoid mass was noted in the uterine cavity. Microscopically, the tumor showed intimate admixture of adenocarcinomatous and sarcomatous areas. The sarcomatous stroma was compsed of compactly arranged atypical spindle cells with frequent mitoses, merging into a loosely textured reticular areas and abundant amount of heterologous elements such as skeletal muscle and cartilage. The rhabdomyosarcomatous element was confirmed by PTAH staining and immunohistochemical staining for myoglobin and desmin. Multiple metastases to the liver, lung, and lymph nodes appeared within one year of total abdominal hysterectomy and bilateral salpingo-oophorectomy. In spite of palliative radiotherapy, she expired one month later.

Key Words: Postirradiation, Mixed mesodermal tumor, Uterus

INTRODUCTION

Malignant mixed mesodermal tumors (MMMT) of the uterus are less infrquently encountered types of uterine sarcoma, and practically always occur to the postmenopausal women of mean age ranging between 62 and 68 years at the time of diagnosis[1-3].

Most of these tumors arise spontaneously, but a certain proportion is known to occur to women with a history of irradiation for benign or malignant diseases 5 to 40 years ago, the average latent interval being 16.4 years[1,4]. Although the mechanism remains obscure, the relationship between pelvic irradiation and the neoplastic potential of the uterine corpus is apparent[1,2,4-7]. As a rule, they are rapidly growing and lethal neoplasms composed histologically of epithelial and mesenchymal elements.

This report presents clinical and pathological findings in a patient with malignant mixed mesodermal tumor of the uterus developed after irradiation at the pelvic area for treatment of stage Ib cervix cancer and discusses about the malignant potential of the irradiation when treated on the uterus.

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CASE PRESENTATION

A 62-year-old female patient visited the Korea Cancer Center Hospital because of vaginal discharge and bleeding increasing from about one year ago. After colposcopic biopsy, she was diagnosed as invasive squamous cell carcinoma of the cervix of stage Ib (Fig. 1) and radiation therapy was started. She received 7000 rads of X-ray during first 7 weeks, and 2 weeks later, additional 5000 rads for 2 weeks on the pelvic area. Her post-therapeutic course was uneventful, but rectal pain and vaginal spotting appeared approximately 5 years after the irradiation. Endometrial curettage and biosy were done, showing carcinosarcoma. She received total abdominal hysterectomy, and the uterus showed a malignant mixed mesodermal tumor with myometrial invasion. About 10 months later, as defecation difficulty developed and progressed, colostomy was performed after abdominal CT was checked. The CT revealed enlarged para-aortic lymph nodes and she was again treated with 4000 rads of X-ray with palliative intent. As one month passed, the excisional biopsy was done for palpable left supraclavicular lymph nodes, which histologically demonstrated metastatic adenocarcinoma. Additionally, she was planned to be treated woth Co^{60} on the neck area but cancelled because follow up chest CT revealed multiple metastases in the lung, liver, and left lower cervical area. Thereafter, she developed leg edema during irradiation with elevated blood urea nitrogen and creatinine levels and expired on May 1989. Autopsy was not permitted.

PATHOLOGIC FINDINGS

The uterus was enlarged to a size of 9×7×5.5 cm as a result of a bulky mass, which was a 5×3×2 cm polypoid soft tumor protruding out of the uterine cavity. Cut surface was fish-fleshy, solid, and friable with areas of necrosis and hemorrhage. Cross section revealed the tumor invasion deep into the myometrium. Microscopically, the tumor consisted of intimately admixed adenocarcinomatous and sarcomatous components. The adenocarcinomatous areas showed well-differentiated malignant glands which did not differ in any way from the glandular

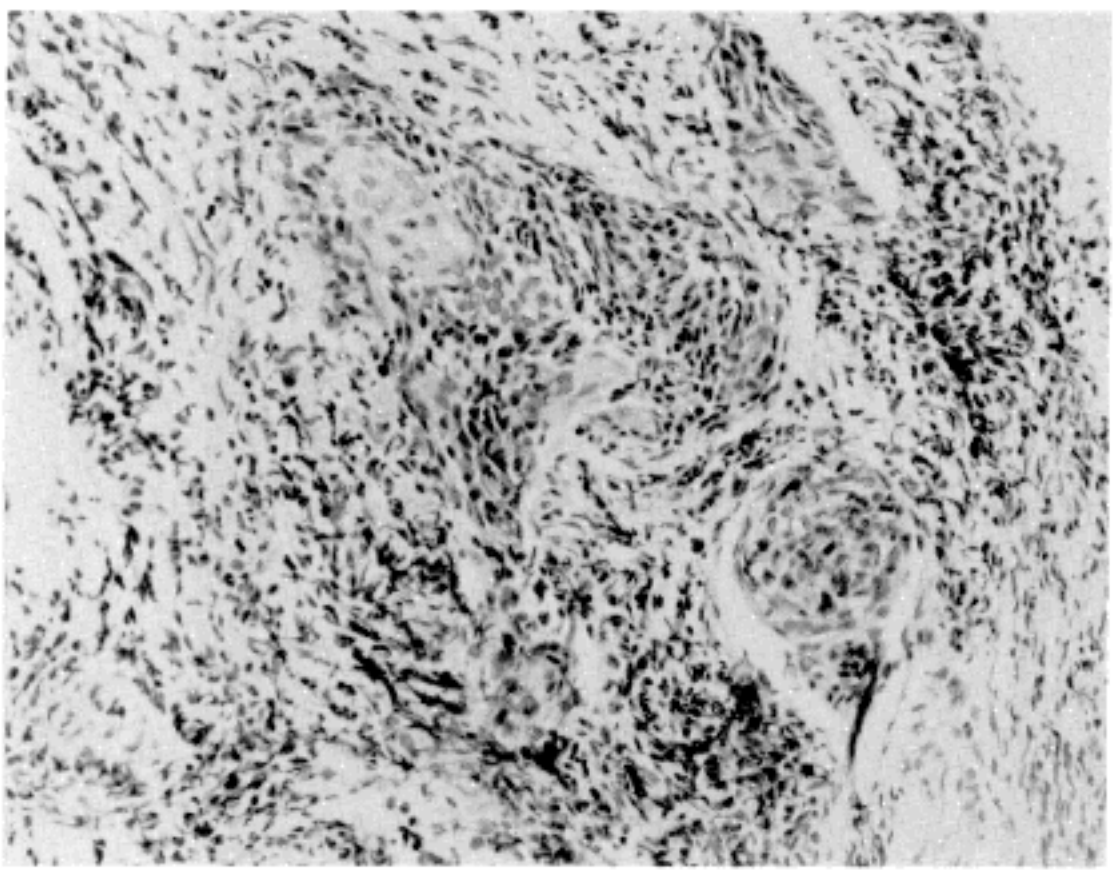

Fig. 1. Initial biopsy of uterine cervix showing invasive squamous carcinoma (H&E, × 50).

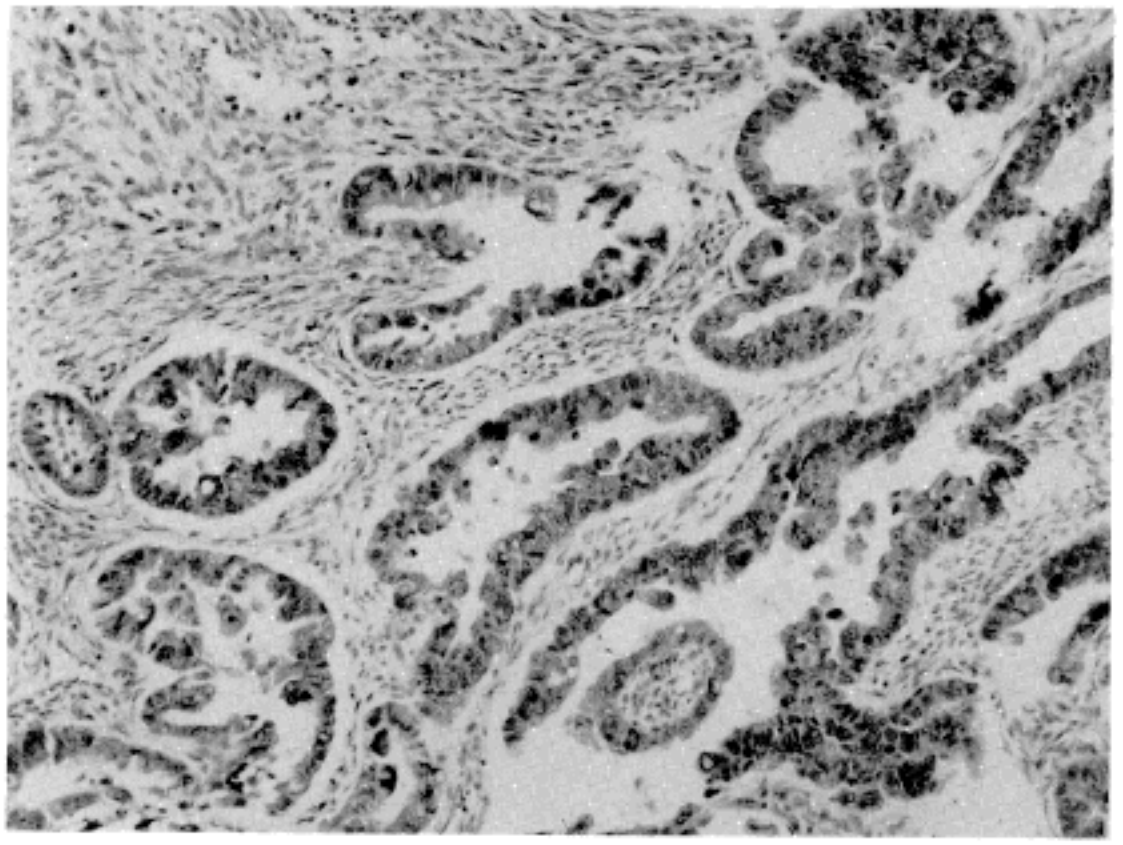

Fig. 2. Postirradiation MMMT showing areas of well differentiated adenocarcinoma (H& E, ×33).

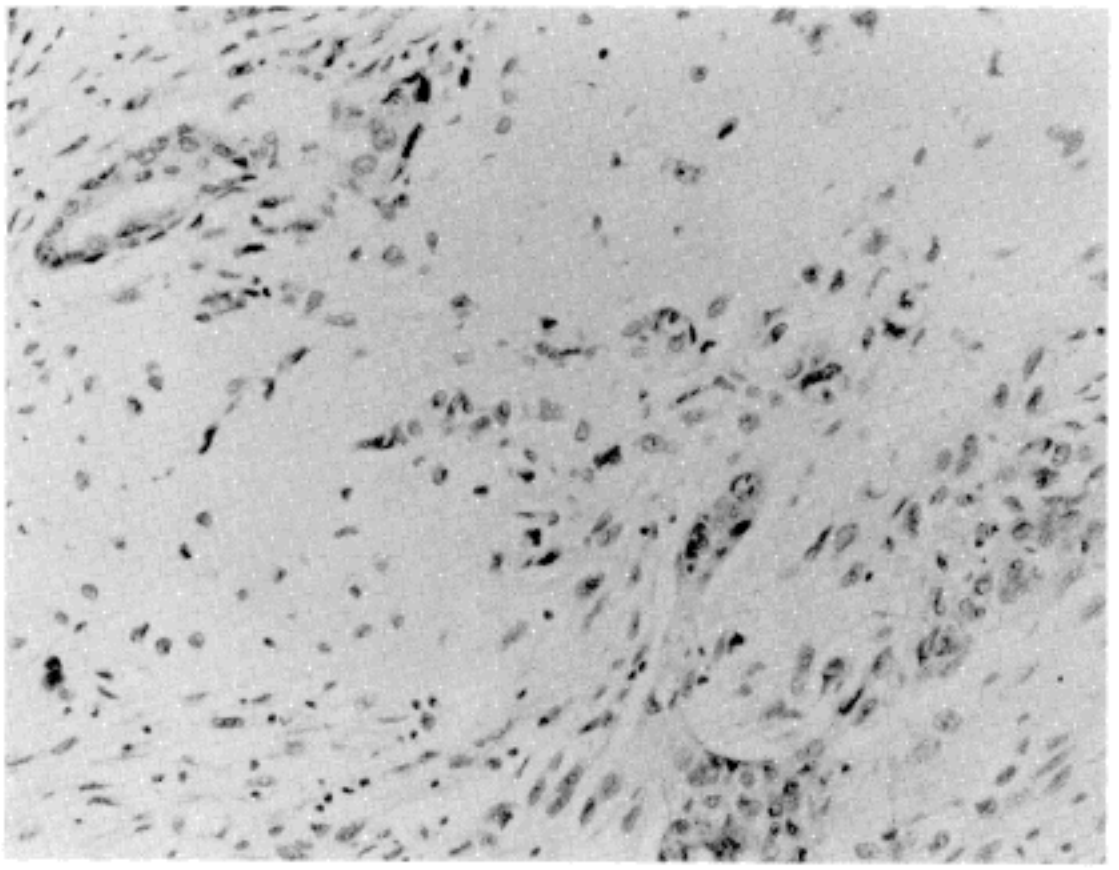

Fig. 3. Areas of adenocarcinoma admixed with chondrosarcomatous stroma (H& E, ×50).

component seen in the usual endometrial adenocarcinoma (Fig. 2). The sarcomatous stroma was composed of dense bundles of atypical spindle cells with frequent mitoses, merging into a more loosely textured reticular pattern and heterologous elements such as cartilage and skeletal muscle. The chondrosarcomatous component formed a few discrete neoplastic islands (Fig. 3). Rhabdomyosarcomatous differentiation was diffuse, prominent, and exhibited two patterns (Fig. 4). In one, Tte neoplastic rhabdomyoblasts were elongated and had abundant cytoplasm with conspicuous cross striations when stained with PTAH. The other pattern consisted of more immature, rounded cells with eccentrically

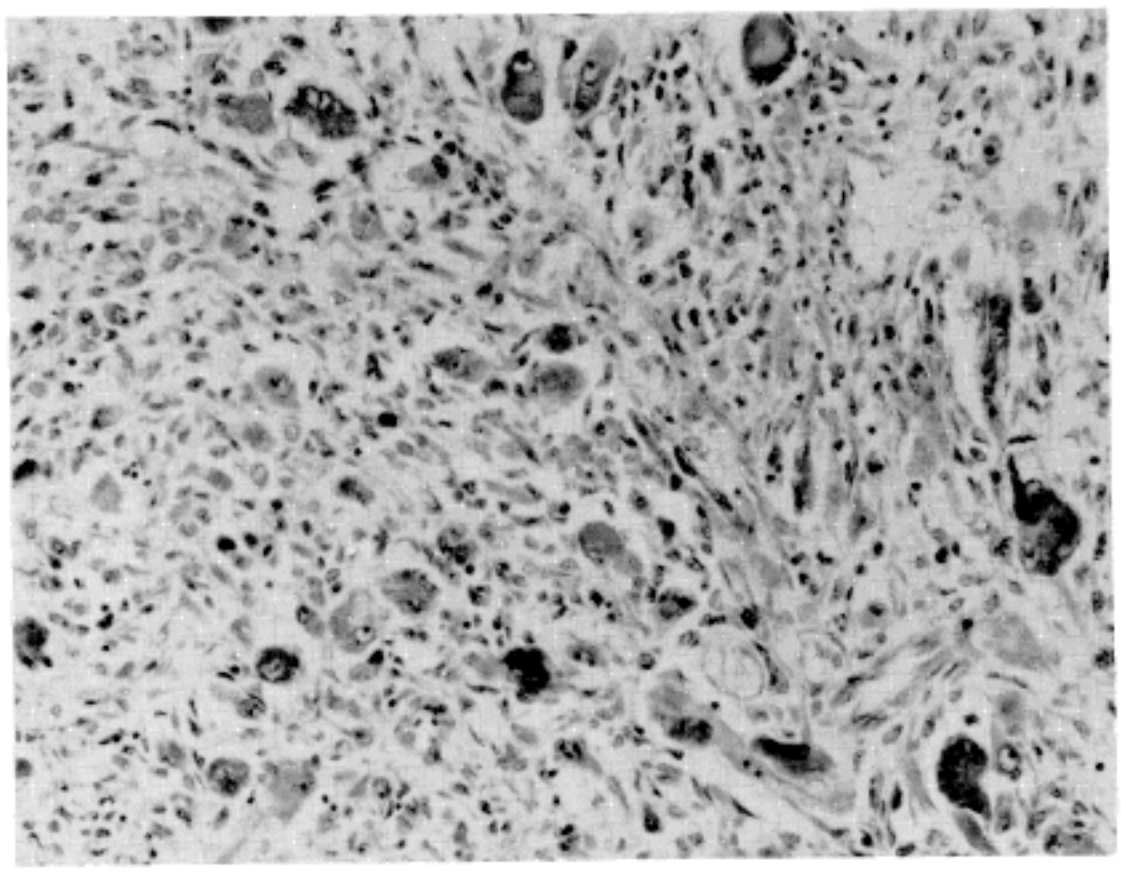

Fig. 4. Heterologous stromal components showing diffuse rhabdomyosarcomatous differentiation (H&E, ×50).

placed nuclei in an abundant eosinophilic cytoplasm without cross striations. Foci of necrosis were occasionally observed. Immunohistochemically, rhabdomyosarcomatous cells were stained positive for myoglobin and desmin but not for vimentin and CEA.

DISCUSSION

Most uterine sarcomas arising after irradiation are mixed mesodermal tumors or carcinosarcomas. In a review of 144 patients with histologically verified uterine sarcomas, 17 patients (12%) were found to have a history of irradiation on the pelvic area. The sarcomas consisted of 9 MMMTs, 4 carcinosarcomas, 1 stromal sarcoma, and 3 sarcomas of unclassified type. About one third of all MMMTs were shown to have developed after irradiation in this study[4].

In order to rule out the possibility that the tumor existed at the time of irradiation, a reasonable interval should elapse after the irradiation. A minimum asymptomatic interval of 4 years after irradiation is said to be sufficient to exclude the presence of the tumor at irradiation, because it is highly unlikely for the patient to be remain asymptomatic for this length of time. In general the latent interval between the initial radiation and the diagnosis of MMMT ranges from 5 to 40 years with the median of 16.5 years, and the best estimates of dosages are between 3000 and 5000 rads[1,4]. In the present case the tumor developed about 5 years after external radiation of x-ray of 12000 rads in total.

Although radiant energy is clearly oncogenic, the precise events responsible for neoplastic transformation are obscure. Two theories dominate current thinking: (1) The radiation directly ionizes critical cellular molecules, or (2) it indirectly acts through mediators such as oxygen free radicals. Finally the DNA sustains injury and results in inducing a somatic mutation. Indeed, the carcinogenecity of ionizing radiation (X-rays, gamma rays) appears to correlate best with its mutagenecity. Activation of protooncogenes resulting from radiation-induced mutation is an attractive hypothesis that is supported by some experimental evidences[9].

Clinically, the patients with irradiation-associated lesion presented at younger age (<55 years), much more frequently with abdominal distention and pain than with abnormal uterine bleeding alone, and had a greater propensity for rapid growth and intraabdominal spread of the tumor. The prognosis of MMMT of the uterus is generally considered quite poor and rapidly lethal[1]. our patient manifested symptoms such as rectal pain and vaginal spotting a few years after radiation therapy, foretelling a bad prognosis.

In regard to the pathologic findings, the heterologous mixed mesodermal tumor (MMT) is more friquent than homologous MMT as postirradiation sequelae and has an obvious feature that portends a poor prognosis, the deeply invasive nature[1]. Myometrial invasion in this case was seen nearly into the subserosal area. Recent reports, however, indicate that detection of the early superficial lesion improves the survival rate of the patients with these aggressive neoplasms. Accordingly, clinicians should consider a possiblilty of this disease entity in peri-or postmenopausal women with a history of radiation therapy and neoplastic endometrial tissue[2].

Finally, the hypothetical carcinogenic effects of radiation therapy upon the uterus and other pelvic structures should always be considered in postirradiation neoplasia since MMMT of the uterus strongly suggests the role of radiation energy on its development.

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＝국문초록＝

방사선 조사후 병발된 자궁의 악성 혼합 중배엽 종양 1예

원자력병원 해부병리과 및 산부인과*

명나혜 · 조경자 · 박상윤*·장자준

자궁경부암의 치료목적으로 방사선을 조사한후 발생된 악성 혼합 중배엽종양 1례를 보고하였다. 환자는 62세때 자궁경부의 상피세포암 제 1b기로 진단받고 골반강 부근에 총 12000 rads의 X-ray를 조사하였다. 5년후 그녀는 질 하혈과 직장통을 호소하여 자궁내막 소파술 및 생검을 실시한 결과 암육종으로 진단되었다. 현미경적으로 종양은 선암종과 육종이 혼합된 양상을 보였다. 육종성 기질은 흔히 유사분열을 보이는 비정형적인 방추상 세포들의 밀집된 배열로 구성되었으며 이는 점진적으로 느슨하게 조직된 망상 지역과 횡문근 및 연골과 같은 이형적 요소가 풍부한 지역들로 이행하였다. 횡문근육종의 요소들은 PTAH 염색과 myoglobin 및 desmin에 대한 면역 조직화학적 염색으로 확인되었다. 전자궁적출술 및 양측 난관 난소 절제술을 받은지 1년 이내에 간, 폐 및 림프절로 전이되어 고식적인 방사선 치료를 하였지만 그로부터 한달후 환자는 사망하였다.