放射線治療後皮膚血管肉瘤

—病例報告暨文獻回顧—

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Cutaneous Post-irradiation Angiosarcoma

—A Case Report and a Review of the Literature—

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Cutaneous angiosarcoma (AS) is a rare malignancy arising from vascular endothelium, and occurs extremely rarely on the abdominal wall. Several predisposing factors, including external irradiation for another malignancy have been suggested. Few cases of abdominal-wall AS in patients previously treated with pelvic irradiation for gynecological malignancies have been reported hitherto. Herein, we describe a patient with squamous cell carcinoma of uterine cervix developed a cutaneous AS eight years after radiotherapy. The diagnosis was confirmed by histopathological and immunohistochemical studies, which showed positive staining for Vimentin, CD31 & CD34 while negative staining for Cytokeratin, S-100 & LCA. She received aggressive multi-modality therapy including total excision of tumor, skin flap and chemotherapy but died 6 months after the initial diagnosis of AS. The literature between 1960 and 2002 was also reviewed. (Dermatol Sinica 21 : 180-186, 2003)

Key words: Angiosarcoma, Abdominal wall, Irradiation / radiotherapy

皮膚血管肉瘤是源自於血管內皮細胞罕見的惡性腫瘤，極少發生於腹壁，其致病因子甚爲複雜，包括有因放射線治療其他惡性腫瘤所導致的皮膚血管肉瘤。目前只有數個病例報告是骨盆腔內惡性腫瘤接受放射線治療後，於腹壁上罹患皮膚血管肉瘤。吾人提出一位因子宮頸上皮鱗狀細胞癌接受體外放射線治療後八年，於腹壁上罹患皮膚血管肉瘤的病例報告。經由組織病理及組織化學免疫學 (包括 Vimentin，CD31 和 CD3 的陽性反應；Cytokeratin，S-100 和 LCA 的陰性反應) 的確診。雖然該病人於確診後接受手術全切除、皮瓣移植及化學等治療，仍不幸於六個月後因敗血症死亡。我們整理此病例並回顧自 1960 至 2002 年的相關文獻。(中華皮誌 21 : 180-186, 2003)

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Introduction

Angiosarcoma (AS), a rare malignant hemangioendothelioma, accounts for 1% to 2% of all soft-tissue sarcoma[1] and constitutes an exceedingly rare primary tumor in the abdominal wall. The etiology of AS is unclear. However, several predisposing factors, including external irradiation for another malignancy have been suggested. Herein, we report a patient with cutaneous AS at lower abdomen growing after radiotherapy for squamous cell carcinoma of uterine cervix and review the literature.

Case Report

A 76-year-old female patient presented with an eroded, easily touch-bleeding, deep-purplish huge mass (about 6 x 6 x 5.5 cm) on the left lower abdominal wall, and surrounded by some asymptomatic erythematous satellite nodules that developed rapidly for 2 months (Fig 1).

In 1994 the patient was diagnosed with a stage Ib squamous cell carcinoma of uterine cervix and bilateral ovarian cystoadenoma. Subsequently, she underwent a total hysterectomy and a bilateral salpingo-oophorectomy. In addition, she received adjuvant radiotherapy consisting of linac10 Mev-X-irradiate to the whole pelvis through the opposing anterior & posterior ports, up to 45 Gy / 6 weeks. She had regular follow-up at Gyn outpatient clinics

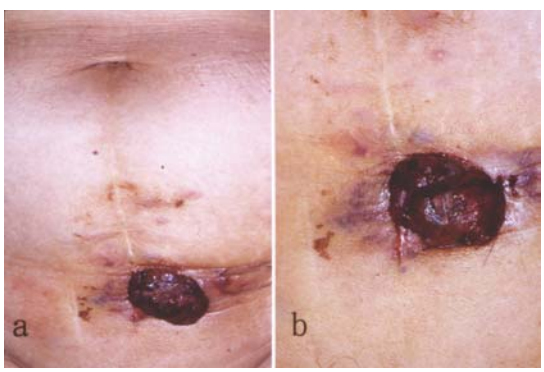

Fig. 1

One eroded, easy-touch-bleeding, deep-purplish huge nodule (about 6 x 6 x 5.5 cm) on the left lower abdominal wall, and surrounded by some asymptomatic erythematous satellite nodules that developed rapidly for 2 months.

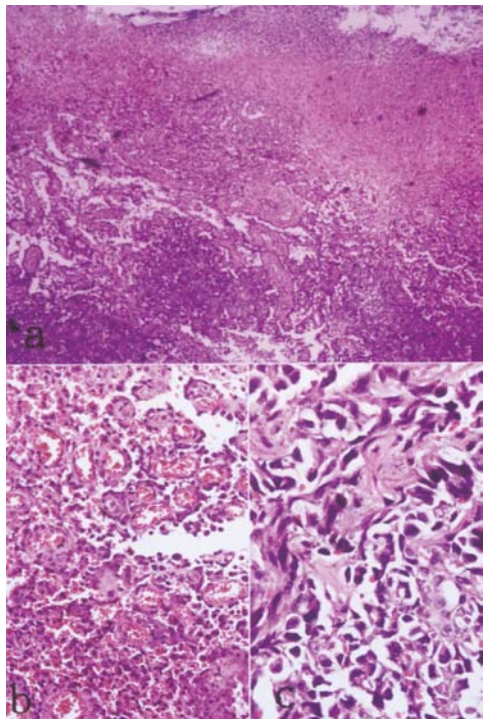

Fig 2a

The cross view showed necrosis & inflammation and interstitial hemorrahge. The pleomorphic cancer cells arranged in fascicles, solid sheets or micropapillae protruding into irregular clefs or slit. (H & E, 40x)

Fig 2b

There are numerous new proliferate vascular structure and multiple pleomorphic cancer cells with spindled or oval nuclei and scanty cytoplasm arranged in fascicles or solid sheets. (H & E, 100x)

Fig 2c

The protruding papillae lined with pleomorphic cancer cells and lots cancer cells form the intracytoplasmic lumina & extravasated erythrocytes or leukocytes adjacent to the cancer cells simulating hemophagocytosis. Mitotic activity and necrosis are noted. (H & E, 400x)

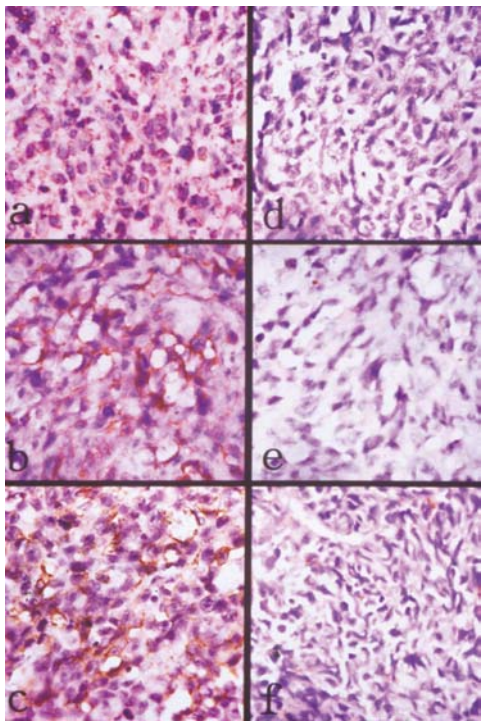

Fig. 3
Immunohistochemically, the cancer cells are diffusely positive stained with Vimentin (3a, 400x), CD31 (3b, 400x) and CD34 (3c, 400x); but negative stained with Cytokeratin (3d, 400x), S-100 (3e, 400x) and LCA (3f, 400x).

thereafter for 6 years. Neither lymphedema nor radiodermatitis had been noted, but she got lost follow-up 2 years ago.

Unfortunately, one hemorrhagic mass, initially sized about 2 x 2 x 1.5 cm, rapidly grew up near the previous abdominal surgical wound since December 2001. She went to our Dermatological outpatient clinics for help on Fab. 20, 2002. Physical examinations revealed no lymphadenopathy, lymphedema or vaginal bleeding. The initial clinical diagnosis was suspected that metastatic squamous cell carcinoma and an incisional skin biopsy was carried out.

Microscopically, the tumor is mainly composed of pleomorphic cancer cells with spindled or oval nuclei and scanty cytoplasm arranged in fasicles, solid sheets or micropapillae protruding into irregular clefs or slits (Fig. 2a, 2b). Brisk mitotic activity and necrosis are noted focally. There are numerous extravasated erythrocytes or leukocytes adjacent to the cancer cells simulating hemophagocytosis or intracytoplasmic lumina (Fig 2c). Immunohistochemically, the cancer cells are diffusely positive for Vimentin, CD31 and CD34 (Fig 3a, 3b, 3c, respectively), but negative for Cytokeratin, S-100, LCA (Fig. 3d, 3e, 3f, respectively). Therefore the histology of the tumor is consistent with angiosarcoma (AS) rather than squamous cell carcinoma.

Then she was admitted to our Gyn ward for further study. The complete blood counts with differential count and biochemistry examinations were within normal limits. Serous tumor markers including carcinoma antigen-199 (CA199), carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC), tissue-peptite antigen (TPA) were unremarkable. The abdominal sonography showed a hepatic cyst at S4 lobe. The pelvic CT showed an ill-defined soft tissue mass over cutaneous level of low abdominal wall without local recurrence in the pelvic cavity. The chest x-ray and KUB showed unremarkable findings. Pelvic sonography revealed only normal vaginal stump and the colonfibroscopy as well as cyctoscopy showed no evidence of tumor metastasis. The Tc99m MDP whole body bone scan showed probable bone metastasis to the spine and the ischium. Then she underwent wide excision of tumor and abdominal reconstruction. Nevertheless, four firm skin nodules near the operative wound were noted half a month later and incisional biopsy confirmed local recurrence. She then received another total excision and skin flap coverage followed by adjuvant chemotherapy (Epirubicin and Isofosmide). Unfortunately she still expired 6 months (due to leukopenia and sepsis) after the initial diagnosis of AS.

Discussion

Radiotherapy, in gynecological field, has been established as a primary or an additional

Table I. Site of Postirradiation AS in 87 cases between 1970 to 2002

Site	Cases	
Cutaneous tissue		68
Chest wall	37	
Abdomen wall	11	
Other skin	20	
Intestine		9
Spine		3
Lung		1
Pericardium		1
Popliteal fossa		1
Bladder		1
Vagina		1
Paravertebral		1
Uterus		1

therapy for cervical carcinoma of uterus.[2] With an increase of patients who are cured for their primary malignancies, a rise in the prevalence of radiation-associated sarcomas is considered.[3] As early as in 1948, Cahan *et al*.[4] proposed the following criteria for diagnosis of postirradiation sarcoma as: ① no microscopic or clinical evidence of antecedent malignant lesion, ② a history of irradiation, the tumor must arise in the field of radiation or on the directly adjacent skin, ③ a latent period of several years must elapse, and ④ a histological confirmation. Our case met all the above criteria and was therefore diagnosed as post-irradiation angiosarcoma (radiation-associated angiosarcoma).

Angiosarcoma (AS), a rare malignant tumor derived from vascular endothelium, presumed about 1% to 2% of all sarcomas[1] and originates through whole body such as skin, soft tissue, liver, breast, spleen, bone and heart. One third of angiosarcomas arise in the skin, where they have varied clinical presentations such as ecchymosis-like patches or plaques, dusky or ulcerating satellite nodules.[5] Cutaneous AS presents with three clinical patterns. The most common pattern occurs on the scalp and face in the elderly men. The second common pattern is those develop in areas of chronic lymphedema secondary to radical mastectomy (Stewart-Treves syndrome).[6] The least pattern develops in areas after radiotherapy, estimated only 0.09%-0.26% of all sarcomas.[7]

Table II. Thirteen cases of angiosarcoma following irradiation for cervical carcinoma

	Primary disease	Site	Lat (Mo)	Dose(Gy)	Age (y/o)	F/U (Mo)	R
1	Cervical ca	Abdominal wall	276	30	61	A	14
2	Cervical ca	Uterus	65	46	61	D 2	2
3	Cervical ca	Vagina	252	30	80	D op	11
4	Cervical ca	Intestine	240	50	80	D op	12
5	Cervical ca	Intestine	96	Ns	Ns	D 2	13
6	Cervical ca	Buttock	228	54	79	D 28	9
7	Cervical ca	Abdominal wall	130	51	63	A 24	10
8	Cervical ca	Suprapubic area	144	45	52		16
9	Cervical ca	Abdominal wall	300	Ns			15
10	Cervical ca	Suprapubic area	48	55			17
11	Cervical ca	Suprapubic area	96	60			17
12	Cervical ca	Perianal area	240	Ns			17
13	Cervical ca	Abdominal wall	96	45	76	D 8	pc

Abbreviation: Lat = latency interval from irradiation to diagnosis of angiosarcoma, Age = age at diagnosis of angiosarcoma, F/U = time to follow-up, Mo = months, R = reference, ca = cancer, Ns = not stated, d = dead, a = alive, op = post-operative death, pc = present case.

The postirradiation AS has similar clinical morphology to other types of AS.[8] Kim *et al*.[9] reviewed 66 cases of postirradiation angiosarcoma between 1970 and 1996 and found the most common primary disease was breast cancer (44%, 29/66), and the second one was gynecologic cancer (21%, 14/66). In addition, the vast majority of postirradiation AS developed in the cutaneous tissue (68 cases, see Table I). To the best of our knowledge, there has been 13 case reports of postirradiation AS after treating squamous cell carcinoma of uterine cervix (Table II)[9, 10, 11-17], including seven cases developed on the lower abdominal wall area (our case included).

The causative link between radiotherapy and AS is strongly suggested by the fact that tumor generally arises from the site of previous treatment, such as lower abdomen after treatment for carcinoma of uterine cervix, an area where AS rarely develops. However, the pathogenic mechanism remained debated. In 1908, Clunet *et al*.[18] induced a fatal sarcoma in a rat by cyclical irradiation. Talerman *et al*.[19] claimed the first experimental radiation-induced AS in a rat in 1972. In addition to the direct oncogenic effect of ionizing radiation, it has been assumed that prolonged stimulation aimed at repairing tissue damage resulting from radiation-induced ischemic change may also play a role in the development of AS.[20]

The correlation between the radiation dose and the latent period is not completely clear. Boice *et al*.[21] considered that even under a low dose radiotherapy, it is still a cause of secondary malignancy. Pizzarello *et al*.[22] demonstrated that tumor induction is dose-related and has a linear correlation of increase with doses exceeding 1 Gy. Experimentally, the latent period has been found to be directly related to radiation dose when above 40 Gy, which was a balance point between death of malignant cells and neoplastic transformation of nonmalignant cells.[23] In Kim's analysis,[9] the median latent interval was 84 months in eight patients who received more than 40 Gy, while it was 216 months in 32 patients who received less than 40 Gy. Goette and Detlefs *et al*.[14] also reported that if the initial indication for radiotherapy is a benign condition such as eczema, the latent period averages about 23 years. If the indication is for malignancy, however, the latent period may be shortened to an average of 12 years, reflecting that higher doses of irradiation may cause AS more easily.

The differential diagnosis depends mainly on tumor histology and its immunohistochemical studies. In our patient, the lesion was initially considered as squamous cell carcinoma but the immunohistochemical staining for cytokeratin was negative, whereas CD31 & CD34 were positive. The "dissection of collagen" pattern of AS may be similar to Kaposi's sarcoma and benign lymphangioendothelioma but the latter two have bland appearance of endothelial cells and absent moderate mitosis.

The choice for treatment includes wide excision, radiotherapy, chemotherapy, and interferon-α,[12] but the effective treatment of postirradiation AS depends on early diagnosis. Most postirradiation angiosarcomas present in advanced stages, and usually have more aggressive clinical courses with poorer prognoses. The reported overall median survival for patients with AS is 20 months,[17] but only 12 months for those with postirradiation AS.[9, 10] The recurrence rate is approximately 80% because of widespread microscopic invasion in surgical specimens and most recurrences appear within the first 12 to 24 months.[11, 17, 24] In our case, the patient had local recurrence within one month after the first operation and survived only 6 months although she had received wide excision twice. Early diagnosis and radical surgery may offer a chance of cure for rare long-term survivors. On the other hand, Buatti *et al*.[25] had reported a promising long-term survival of more than three years with radiotherapy. Therefore, radiotherapy may be considered when the tumor is unresectable.

Postirradiation AS is an aggressive malignancy arising as a possible late complication of irradiation. Its prognosis depends mainly on tumor grade and tumor size, and poor prognosis

is usually caused by delayed diagnosis, poor differentiation, and high rates of local invasion or distant metastasis. Although not proven, it is likely that radiation plays a role in the development of postirradiation AS. To the best of our knowledge, there had been only 13 cases of AS after irradiation treatment for cervical carcinoma reported, including seven developing on the abdominal wall. Because radiotherapy for cervical carcinoma is an essential part of therapeutic arsenal, this rare complication should be always kept in mind and long-term follow-up after irradiation is necessary.

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