Radiation-Induced Skin Ulceration A Study of Five Patients.

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放射線皮膚潰瘍の5症例に関する検討

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放射線治療においては，超高圧放射線等の採用により，急性の皮膚障害は比較的軽減された．しかし低皮膚線量における慢性皮膚障害に関してはまだ日が浅い為，はつきりした結論が得られていない．我々は慢性放射線皮膚障害としての皮膚潰瘍の5症例を経験したので，これらについてEllisの提唱したNSD（nominal single dose）を用いて線量と発現時間との関係を検討した．線量と発現時間との間には両対数グラフ上で直線関係の傾向があり，日常の治療における皮膚照射線量（NSD：1,500ret以下）にても，10年以上経ると皮膚潰瘍の発現する可能性のある事を認めた．

Introduction

Skin damage is one of the most common side effects of radiotherapy, because, with few exceptions, all the radio-teletherapy techniques include some skin in the treatment field. Normal tissues usually respond to irradiation in bimodal phases. These responses are called early and late reactions.

The degree of each reactions is in proportion to the dose-time volume factor. Skin ulceration is known as one of the most severe late reactions of normal tissue. Five patients recently found to have radiation-induced skin ulceration without any evidence of malignancy are descrived in this paper.

Case Report

CASE 1

M.K. This 42 year-old Woman with a complaint of genital bleeding was found to have carcinoma. colli uteri (first stage). After a radical panhysterectomy on August 23, 1955 in the Department of Gynecology, she received postoperative irradiation therapy from September 13 to October 20, 1955.

Her irradiation program was as follows: The irradiation field consisted of four portals on the lower half of the trunk (two anterior and two posterior). Each field was 10×10 sq. cm.

The conditions of irradiation were: 200 KVP, 25 mA, HVL 1.0 mm Cu, FSD was 50 cm, (X-ray therapy apparatus: KXC-18, Toshiba).

The X-ray beams from both anterior and posterior portals had the same dose-time relationship. The skin dose was 300 rads/day (eight times) for a total skin dose of 2,400 rads. The period of irradiation was nine days and the skin dose (NSD) was 1,150 ret.

Eight years later she developed itching of the irradiated skin, which became increasingly severe. In October, 1965 (about 10 years after treatment), she developed a fist-sized skin ulceration of the right buttock (right anterior irradiated skin surface).

The circomference of the ulceration was red and in the center there was a yellowisch crust with oozing. The left buttock showed a relatively sharply defined redness. She received chemo- and ointment therapy, but on June 18 1970, the lesion showed severe ulceration, with erythema and capillary dilatation of the adjoining surface. A split-thickness skin graft was taken from the extensor

Fig. 1. Photograph of case 1.

surface of the left thigh. On September 19, 1970, a second graft was attempted from the extensor

surface of the right thigh.

On September 21, 1970, the lesion formed bullae, but by October, 1970, there was good fixation. She is now alive and well.

CASE 2

S.M. This 53 year-old woman was thought to have myoma uteri, but at operation (November 13, 1959) an ovarian tumor was resected, and postoperative histological diagnosis was thecoma. Postoperative irradiation was performed from November 27, 1959, to January 14, 1960, at our clinic.

Her irradiation program was as follows: The irradiation field consisted of three portals (one anterior and two posterior) over the lower trunk. Each field was 10×10 sq. cm. The condition of irradiation were: 200 KVP, 25 mA, HVL 1.0 mmCu, and FSD was 50 cm, for each portal, (X-ray apparatus: KXC-18, Toshiba).

The skin dose was 333 rads/day (10 times) for a total dose of 3,330 rads. The overall treatment time was 49 days, and the skin dose (NSD) was 1,250 ret. She complained of itching and redness of her right buttock in March, 1960, and she was treated with ointment and peroral drugs. In March, 1962, the irradiated skin showed induration with telangiectasia (poikiloderma), and chemotherapy was given.

In January, 1969, she developed ulceration of the skin of her right buttock. The base of the ulcer reached bone and a bloody secretion was present. The histological diagnosis was radiodermatitis.

The circumference of the ulcer showed capillary dilatation with brownish pigmentation. An E. coli infection was present.

In September, 1969, the lesion was covered with thick granulation tissue, but itching persisted. She received a skin graft and still alive.

Fig. 2. Photograph of case 2.

CASE 3

S.U. This 59 year-old houswife complained of a mass on the left side of her neck. It was resected on May 10, 1955, and the histological diagnosis was lymphosarcoma. The region was treated by X-ray irradiation from June 3 to July 24, 1955. The irradiation program was as follows:

The conditions of irradiation were: 200 KVP, HVL 1.0 mmCu, and FSD 50 cm, the irradiation field was 10×10 sq. cm (X-ray therapy apparatus: KXC-18, Toshiba). The skin dose was 300 rads/day (33 times) for a total dose of 9,900 rads, and 2,600 ret (NSD). The irradiation period was 106 days.

In 1961, she suffered from swelling of her whole face (especially the right side) and was treated in the Department of Orthopedics Still developed dyspnea and a thorachotomy was performed.

In May, 1964, she complained of ulceration of the irradiated region. This was diagnosed as a radiation induced ulcer, the size of a man's fist surrounded by severe dermatitis. The center of the ulcer was covered with a noted yellowish crust.

Erythema and pigmentation with induration and telangiectasia were on the margin of the ulcer. The ointment and peroral drug therapy was continued. In March, 1967, she became hoarse, the lesion showed deterioration, and itching continued.

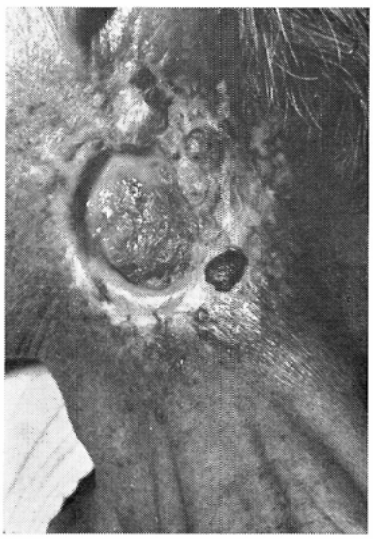

Fig. 3. Photograph of case 3, (case 4 was not photographed).

CASE 4

Y.S. This 31 year-old man received radiotherapy for carcinoma of the right lung from September 7 to December 24, 1960.

Since June 10, 1960, he had suffered from attachs of cough and bloody sputum, and a lung tumor was noted in his chest roentgenogram.

On admission to our clinic his cervical and axillary lymphnodes were not palpable, blood pressure was 118/55 mmHg, and ECG was within normal limits. Hb was 15.8 g/dl and leucocyte count was 5,380/mm^3.

The Wassermann reaction was (++).

On September 2, 1960, a bronchial biopsy confirmed malignancy, probably adenocarcinoma. On October 13, 1960, pigmentation and oppressive pain were noted in the irradiated field, and on December 7, 1960, bronchography showed narrowing and irregularity of the bronchial wall at segment

10a. His irradiation program was as follows:

1) Co-60 irradiation; irradiation field was 10×10 cm, from one posterior portal; skin dose: 250 rads/day (40 times)

2) 200 KVP X-ray irradiation with a sieve (X-ray therapy apparatus: KXC-18, Toshiba), irradiation field 13×13 cm, posterior; skin dose: 500 rads/day (13 times).

The total skin dose was 13,250 rads. With irradiation therapy, the tumor gradually became smaller on the chest roentgenogram.

The tumor dose was 9,610 rads with 53 fractions.

The overall treatment time was 109 days, and fractures of the ribs appeared in October, 1962 (two years and three months after treatment).

Skin ulceration appeared in December, 1969 (nine years after treatment), and a skin graft was performed.

He is still alive, a 10 year survivor.

CASE 5

S.S. From May 8 to June 17, 1959 this 57 year-old man received Co-60 and X-ray sieve therapy for carcinoma of the right lung (segment 6). Since December 27, 1958, he had a productive cough which was diagnosed pulmonary tuberculosis, and was given chemotherapy (SM, PAS, INAH), but further roentgenograms raised the suspicion of malignancy, so he was admitted to our clinic. The chief findings on admission were: cervical lymphnodes not palpable, blood pressure 130/80 mmHg, sputum culture: tbc. bacillus(−), staphylococcus aureus(+), tomography showed cavity formation in the center of the tumor mass; WBC 3,600/mm^3, and RBC 340×10^4/mm^3.

His irradiation program was as follows;

1) 200 KVP X-ray irradiation with sieve; irradiation field was 10×15 cm, posterior; skin dose:

Fig. 4. Photograph of case 5.

1,600 rads/day (twice).

2) 200 KVP X-ray irradiation with sieve; irradiation field was 10×15 cm, posterior; skin dose: 800 rads/day (15 times).

3) Co-60 irradiation; irradiation field was 10×15 cm, anterior; skin dose: 300 rads/day (11 times).

The total dose (tumor) was 5,385 rads with 30 fractions, and the overall treatment time was 40 days. The total skin dose was 10,500 rads and 3,200 ret (NSD). In 1963 he complained of itching of the irradiated skin surface, and an ulcer developed. This was 6×20 cm and infiltrated with a thick induration. In the upper half of the lesion, a tumorlike mass about 2 cm in diameter was present. The circumference showed pigmentation, depigmentation and telangiectasia. The base of the ulcer was covered with a yellowish-red necrotic mass. On August 31, 1966, a local biopsy showed no malignant changes. On September 14, 1966, staphylococcus aureus was isolated from the lesion. By February 3, 1967, the base of the ulcer had communicated with the parietal pleura. He is still alive.

Discussion

Many cases have been reported of radiation-induced skin ulceration (skin necrosis). Lackner (1959)[8] studied skin ulcerations occurring after radiation therapy for the skin cancer of the hand and suggested that each dose should not exceed 300–400 R and the total dose should not rise above 6,000 R.

Tanoue[10] reported one of radiation necrosis which followed radiation therapy for left cervical lymphnode tuberculosis. The irradiation program was: 120 KVP, 100R/fraction (once a week) for a total dose of less than 5,000 R. The irradiation period was about one year, and skin ulceration occurred 14 years after completion of the treatment.

He advocated that more cases should be reported of late radiation injuries of the skin, and that radiation necrosis of the skin is a very important hazard in the course of radiation therapy.

Ueno et al.[7] reported three cases among 50 patients who received radiation therapy with sieve. The treatment program was: 180 KVP, 20 mA, FSD was 40 cm, and 500–1,000 R/fraction; the average dose-time relationship was 11,000 R/12 days. Skin ulcerations occurred 55 days (case 1), two months (case 2), and 12 months (case 3) after completion of treatment. He attributed the cause of these injuries to the unsuitable open rate of the sieve and the uncertainty of positioning, and also scratching after therapy. Ellis (1942)[2] noted that the radiation tolerance of all tissues depends on that of their vasculo-connective tissues. Many attempts to prevent radiation injuries of the skin were tried, and it was found that excessive irradiation must be avoided and smaller irradiation portals used.

A more logical analysis of radiation injuries was undertaken by Traenkle (1955, 1960)[11][12]. He treated (on 1955) 935 patients with skin cancer by X-ray radiotherapy in four treatment schedules (1,000R×4 times/10–11 days, 1,000R×5 times/10–12 days, 500R×9 times/11 days, 400R×12 times/14 days) and reported 55 cases (14%) of skin necrosis. In 1960, he tried another treatment schedule (500R/time, 400R/time, 300R/time with a longer overall treatment time than before); this resulted in skin necrosis in only 3%.

The interval between final treatment and the appearance of skin ulceration was from four month to six years (in 50% it was more than two years), and he concluded that the most important factor is the dose of each irradiation, other factor being the field size, anatomic site and seasons of the year.

We tried to analyse our five patients with respect to their dose-time schedules and to correlate these with the time of appearance of the skin ulcerations.

The details summarized in Table 1. It was not easy to correlate total skin dose, number of fractions, overall treatment time and time of appearance of skin ulceration, so we used the Nominal Single Dose (NSD) (normal tissue). NSD (unit: ret) is recommended by Dr. F. Ellis, et al.[2)3)4)], and is a very usefull concept in fractionation, making it possible to compare radiation reactions even when total doses, nomber of fractions and overall treatment time differ.

The formula of NSD (normal tissue) is given as follows;

$$D = D_0 \times N^{0.24} \times T^{0.11}$$

where, D = total dose in rads

D_0 = NSD (normal tissue) in ret

N = No. of fractions

T = overall treatment time in days

Table 2. and Fig. 5. show the relationship between skin dose in ret and the time of appearance of

Table 1. Details of Five Patients with Radiation-Induced Skin Ulceration.

	case 1.	case 2.	case 3.	case 4.	case 5.
sex	female	female	female	male	male
age	42 years	53 years	59 years	31 years	57 years
disease	ca. colli uteri	thecoma	lymphsarcoma	lung cancer	lung cancer
therapy apparatus	X-ray	X-ray	X-ray	Co-60	X-ray (sieve)
total skin dose (rads)	2,400 rads	3,330 rads	9,900 rads	13,250 rads	10,500 rads
No. of fractions	8	10	33	53	30
overall treatment time	9 days	49 days	106 days	109 days	40 days
time of appearance of skin ulceration	10 years	10 years	9 years	9 years	7 years
skin dose in NSD	1,150 ret	1,250 ret	2,600 ret	3,000 ret	3,200 ret
result	alive	alive	not known	alive	alive

Table 2. Relationship between Skin Dose (NSD) and Time of Appearance of Skin Ulceration.

case	skin dose in NSD (ret)	time of appearance of skin ulceration
case 1	1,150 ret	10 years
case 2	1,250 ret	10 years
case 3	2,600 ret	9 years
case 4	3,000 ret	9 years
case 5	3,200 ret	7 years

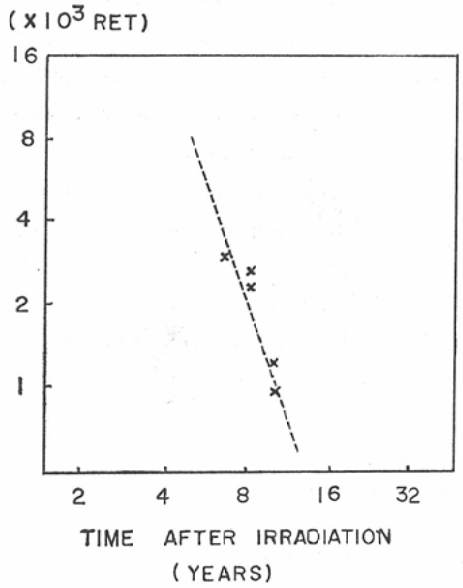

Fig. 5. Log—Log Diagram showing the Relationship between Skin Dose in ret and Time of Appearance of Skin Ulceration after the Completion of Irradiation.

radiation-induced skin ulceration.

In case 1 to 5, NSD was 1,150 ret, 1,250 ret, 2,600 ret, 3,000 ret, 3,200 ret respectively, and the time of appearance of skin ulceration was 10 years, 10 years, 9 years, 9 years and 7 years, respectively.

There is a tendency that the larger the dose (NSD) is, the shorter the time until the appearance of skin ulceration. This tendency coincides with the hypothesis of Rubin and with several reports concerning the late effect on the heart. Because of the small number of our patients with skin ulceration and the unknown incidence of radiation-induced skin ulceration, we could not do a statistical analysis so drew the dotted negative straight line in Fig. 5. which strongly suggests the dose dependence of the time of appearance of skin ulceration.

It is important to note that even a small dose (less than 1,500 ret) to the skin resulted in skin ulceration more than 10 years later.

Therefore, late skin ulcerations as well as early skin reactions must be taken into consideration in planning treatment schedules.

Summary

Five patients with radiation-induced skin ulceration are descrived. Skin ulceration is one of the most severe late skin reactions. The larger the dose the sooner it developes. A linear relationship was observed between the logarithm of the time of appearance after irradiation and the dose expressed in ret, although the number of cases used to determine this relationship was small. NSD as reported by F. Ellis is thought to be a useful parameter to express the radiation effect in normal tissues. Even in patients receiving low doses (NSD less than 1,500 ret), skin ulceration developed more than 10 years after radiation therapy.

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