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EFFECTS OF IRRADIATION ON GRAFTED SKIN — VASCULAR CHANGES AFTER IRRADIATION —

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ABSTRACT

Early changes in the vascularity of grafted skin after X-ray irradiation were evaluated using the microangiographic technique. There was a correlation betweeen the vascular density at the time of irradiation and the vascular density two weeks after irradiation. The grafts irradiated in the early hypovascular stage showed mild-moderate vascular reactions to irradiation, whereas those irradiated in the hypervascular stage showed severe vascular reactions. The grafts irradiated in the late hypovascular stage showed mild vascular reactions. There was also a relation between the skin reaction and vascular reaction to irradiation. It was concluded that primary consideration should be given to the vascular damage of grafted skin when determining the proper time for postoperative irradiation.

Keywords: Free Skin Graft, Irradiation, Vascularity.

INTRODUCTION

The previous study[1] showed that the reactivity of grafted skin to irradiation was closely related to the time at which irradiation was conducted after grafting. A close correlation was also suggested between the radiosensitivity and the vascularity of the graft. Also, the failure of grafted skin irradiated postoperatively was attributable to vascular damage due to irradiation. Although many studies[2-4] have been published on the histopathological changes of the vascular tissue of the skin after irradiation, there have been few reports in which the vascular changes of irradiated grafts were studied.

This communication describes how the vascular system of grafted skin changed after irradiation. The significance of vascular damage is strongly suggested when reconstructive surgery with free skin graft and postoperative irradiation are to be combined.

MATERIALS AND METHODS

The subjects of the study were 80 male Wistar rats, weighing 280–300 g (9 weeks old). The rats were given water and fed on a commercial diet ad libitum. Each rat was anesthetized with pentobarbital sodium, 50 mg/kg, intraperitoneally. The operative area was shaved and cleansed with 0.5% chlorohexidine gluconate. Grafting beds, 15 mm in diameter, were prepared to the level of the panniculus carnosus by careful dissection. Full-thickness skin grafts were removed from the abdomen and fixed to the recipient sites with biological adhesive. To prevent attempts to dislodge the grafts, a tube protector made of stainless steel was normally used for seven days after grafting.

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Microangiographic examinations of the non-irradiated graft were carried out two days, one week, three weeks and six weeks after grafting, which coincided with the time of irradiation, to analyze vascular change of the graft.

Irradiation was delivered by a Philips Superficial Therapy System (exposure factor: 37 kV, 0.3 mA with 0.4 mm Al filtration giving a half value layer of 0.3 mm Al). The X-ray dose at skin level was estimated with a standard dosimeter to be 719.5 rads/min. One thousand five hundred rads were given in a single dose to a field of 25 mm in diameter that included the graft in the center, two days, one week, three weeks and six weeks after grafting. Two weeks after irradiation, when the graft exhibited the maximum skin reaction under gross observations,[1] microangiographic observations of the irradiated graft were carried out to analyze the vascular reaction of the graft to irradiation. The microangiographic technique was as described in previous reports.[1,5]

RESULTS

Two days after grafting, microangiograms showed early capillary invasion into the graft from the recipient bed. New capillary formation was observed at the junction of the graft and the recipient bed. In some areas, especially in the center of the graft, there was no filling of the small vessels. The vascular density at this stage was summarized as hypovascularity (Fig. 1-A).

The microangiograms of grafts irradiated two days after grafting and examined two weeks after irradiation showed mild to moderate vascular reactions to irradiation. Hypervascular areas were observed in the marginal area, but were not observed over the entire irradiation field. In the center of the graft, a hypovascular area was noted. Morphologic changes such as vasodilatation, tortuosity and stenosis were observed in some grafts. Sporadic oozing of contrast medium was also noted. New capillary formation was seen, especially in the marginal area (Fig. 1-B). In cross sections, mild to moderate vascular reactions were also recognized. Few vascular reactions were observed in the bed (Fig. 2-A).

At the first week after grafting, there was considerable filling in the vessels all over the graft. The newly generated vessels were numerous and showed greater distension. Oozing of contrast medium was seen in some cases. Tortuosity and ramification of the vessels were also observed. The vascular density at this stage was characterized as hypervascularity (Fig. 1-C).

The microangiograms of the graft irradiated one week after grafting and examined two weeks after irradiation showed severe vascular reactions to irradiation. A hypervascular area was observed over the entire irradiated area. Vascular reaction was remarkable, especially in the marginal area. Vascular proliferation was noted in the radiation field and newly generated vessels were observed in a radial manner from the center of the graft. Striking dilatation and tortuosity were observed in all the grafts (Fig. 1-D). The cross sections showed severe vascular reaction to irradiation. In the bed, vascular response to irradiation such as vasodilatation and new capillary growth were observed (Fig. 2-B).

Three weeks after grafting, the vascualr pattern was almost normal, although there was still high vascular density in the marginal area. No sporadic vasodilatation and oozing of contrast medium were found, but there were some occasional, irregular vascular patterns. In some cases, the center of the graft contained hypovascular areas. The vascular density at this stage was summarized as marginal hypervascularity (Fig. 1-E).

The microangiograms of the grafts irradiated three weeks after grafting and examined two weeks after irradiation showed moderate vascular reactions to irradiation. In the irradiation field slight hypervascularity was observed and vascular reactions were noted in the marginal area. New capillary formations were noted to some extent, but their number decreased compared to

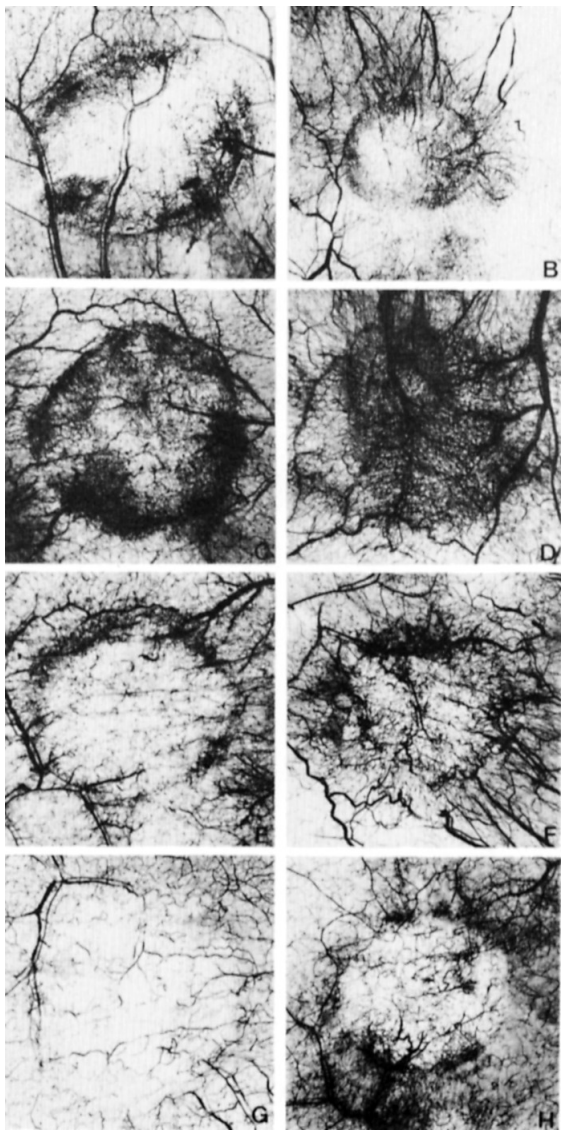

Fig. 1 Representative angiograms
A: Two days after grafting (x 3)
B: The angiogram of the graft irradiated two days after grafting, taken two weeks after irradiation, shows mild to moderate vascular reaction. (x 2)
C: One week after grafting (x 3)
D: The angiogram of the graft irradiated one week after grafting, taken two weeks after irradiation, shows severe vascular reaction. (x 2)
E: Three weeks after grafting (x 3)
F: The angiogram of the graft irradiated three weeks after grafting, taken two weeks after irradiation, shows moderate reaction. (x 2)
G: Six weeks after grafting (x 3)
H: The angiogram of the graft irradiated six weeks after grafting, taken two weeks after irradiation, shows mild vascular reaction. (x 2)

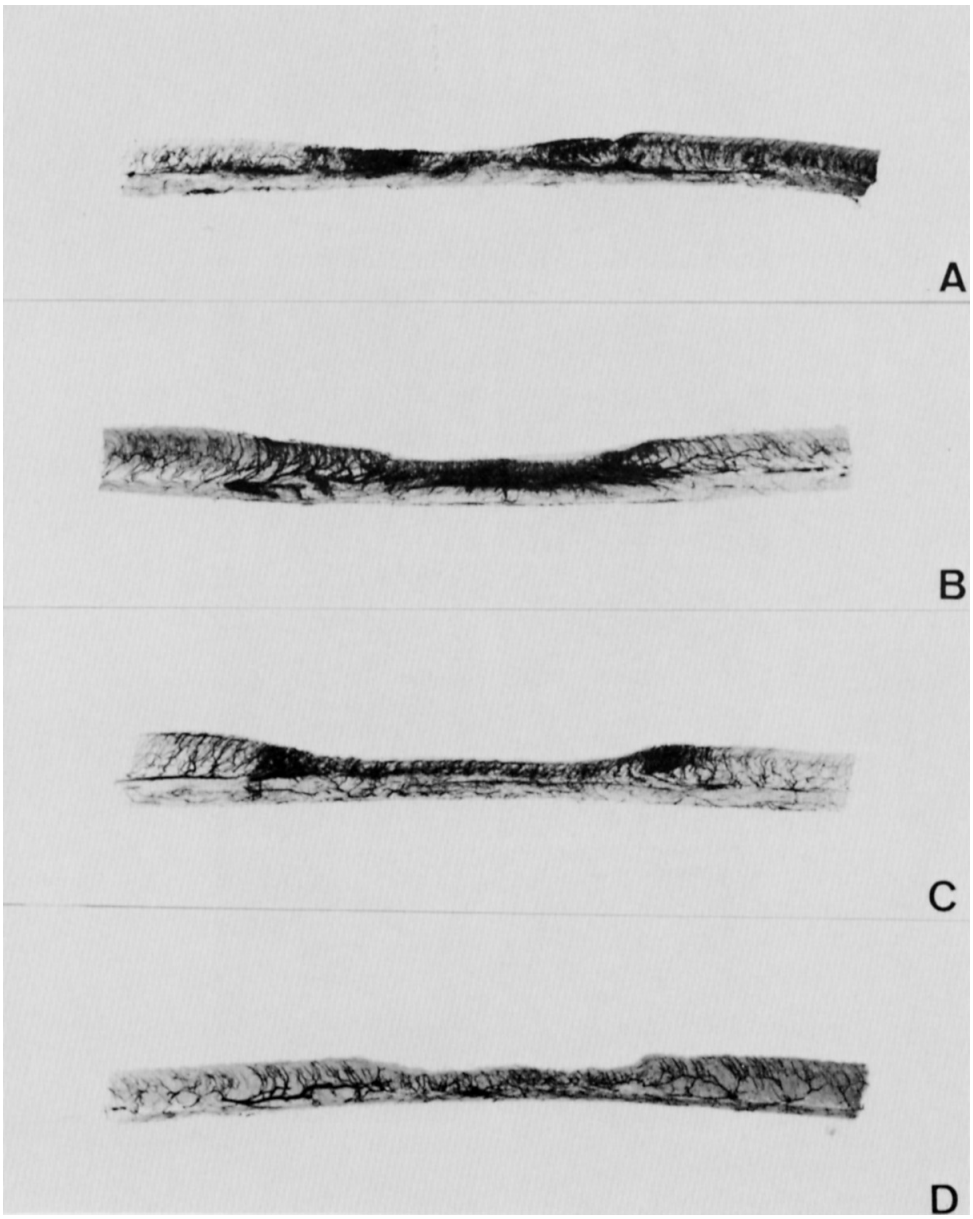

Fig. 2 Representative angiograms
(Cross sections: two weeks after irradiation)
A: Graft irradiated two days after grafting. (x 3)
B: Graft irradiated one week after grafting. (x 3)
C: Graft irradiated three weeks after grafting. (x 3)
D: Graft irradiated six weeks after grafting. (x 3)

the graft irradiated one week after grafting. Stenosis and tortuosity of the vessels were also observed (Fig. 1-F). In cross sections, moderate vascular reactions were also recognized. The bed showed slight new capillary formation (Fig. 2-C).

At the sixth week after grafting, no new capillary formatin was observed even in the marginal area and there were few vessels in the center of the graft. The vascular density at this stage was described as hypovascularity (Fig. 1-G).

The microangiograms of the graft irradiated six weeks after grafting and examined two weeks after irradiation showed mild vascular reactions to irradiation. In the irradiation field there was little vascular change due to irradiation. In some cases, marginal hypervascularity was noted but the degree was low. Stenosis was sometimes observed in the irradiation field (Fig. 1-H). In cross sections, mild vascular reactions were observed (Fig. 2-D).

DISCUSSION

Reinhold[6] classified the influence of radiation on the blood vessels into three stages: 1) early effects, 2) intermediate period, and 3) late changes. This study presents the early effects (two weeks after irradiation) of irradiation on the vasculature of free skin grafts. The reasons why the early effects were selected were 1) the skin reaction to irradiation reached a peak two weeks after irradiation in gross observations[1] and 2) Ueda *et al.*[7] reported that the vascular density after irradiation peaked in the second week in rat skin using microangiography. The dose of 1500 rads was selected because 1) in our preliminary experiment moderate vascular reactions were observed when the rat normal skin was irradiated with 1500 rads and 2) in gross observations, significant differences of skin reaction were recognized when the grafts were irradiated with 1500 rads at two days, one week, three weeks and six weeks after grafting.

Table 1 summarized the overall results of the study.[1] Grafts irradiated in the hypervascular stage showed severe vascular reactions and skin reactions, while those irradiated in the hypovascular stage showed mild vascular reactions and mild skin reactions. Moderate vascular reactions and skin reactions similar to those of normal skin were observed in grafts irradiated at about the normal vascular stage. In the early effects of irradiation, these facts demonstrated a correlation between the vascularity at the time of irradiation and the vascular reactivity after irradiation, and that there was also a relation between the vascualr reaction and the skin reaction in gross observations. The vessels in the graft at one week after grafting were considered to be newly generated ones. Therefore, it was suggested that newly generated vessels showed high reactivity to irradiation of 1500 rads, whereas old vessels in the graft at six weeks after grafting exhibited little reaction to irradiation. This observation coincided with the results of Takahashi.[8] In the course of graft healing, invasion of newly generated vessels into the graft is indispensable for the graft's survival,[9][10] so these observations were of paramount importance. There is now considerable evidence to suggest that radiation damage to the vascular system of free skin grafts is the primary target through which graft damage is provoked.

Recently, the importance of reconstructive surgery for a patient's full rehabilitation of life and work has been increasing, and therefore immediate reconstruction with resection of cancer is frequently carried out in oral and maxillofacial surgery. Although complete surgery should be the treatment of choice if the cancer is resectable, the cancer cannot always be extirpated totally, so residual lesions or recurrence of the cancer is not uncommon. In such cases, the site of reconstruction may well be included in the field of radiation therapy. When reconstructive surgery and postoperative irradiation are to be combined, the time of irradiation must be carefully decided. It is our conclusion that primary consideration should be given to vasclular damage of the reconstructive site when the proper time of postoperative irradiation is decided.

Table 1. Relationship among the vascularity at the time of irradiation, the radiosensitivity of the graft, and the radiosensitivity of the vascular system in the graft.

Time after Grafting	Vascularity	Skin Reaction to Irradiation*	Vascular Reaction to Irradiation*
2 days	Hypovascular	Reaction similar to that of normal skin	Mild-moderate reaction
1 week	Hypervascular	Severe reaction	Severe reaction
3 weeks	Marginally hypervascular to normally vascular	Reaction similar to that of normal skin	Moderate reaction
6 weeks	Hypovascular	Mild reaction	Mild reaction

*2 weeks after irradiation

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REFERENCES

1) Sumi Y, Ueda M, Kaneda T, Etoh K., Effects of irradiation on grafted skin. *J. Oral. Maxillofac. Surg.*, **41**, 586–591, 1983.
2) Ueda M, Torii S, Kaneda T, Oka T: Revascularization of autogenous skin grafts placed on irradiated tissue. *J. Oral. Maxillofac. Surg.*, **40**, 477–481, 1982.
3) Fajardo L F, Berthrong M: Radiation injury in surgical pathology. *Am. J. Surg. Pathol.*, 159–199, 1978.
4) Rudolph R, Arganese T, Woodward M: The ultrastructure and etiology of chronic radiotherapy damage in human skin. *Ann. of Plast. Surg.*, **9**, 282–292, 1982.
5) Ueda M, Torii S, Oka T: Microangiography in rat skin. *Jpn. J. Plast. Reconstr. Surg.*, **23**, 627–633, 1980.
6) Reinhold H S: The influence of radiation on blood vessels and circulation. *Curr. Top. in Radiat. Res. Q.*, **10**, 58–74, 1974.
7) Ueda M, Torii S, Oka T: An experimental study of skin autograft on irradiated tissue. *J. Oral. Maxillofac. Surg.*, **40**, 74–77, 1982.
8) Takahashi T: The action of radium upon the formation of blood capillaries and connective tissue. *Br. J. Radiol.*, **3**, 439–445, 1930.
9) Smahel J: The healing of skin grafts. *Clin. Plast. Surg.*, **4**, 409–424, 1977.
10) Sumi Y, Ueda M, Kaneda T, Oka T, Torii S: Dynamic vascular changes in free skin grafts. *J. Oral. Maxillofac. Surg.*, **42**, 382–387, 1984.