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RADIATION INDUCED PERICARDITIS IN HODGKIN'S DISEASE

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The irradiation of Hodgkin's disease requires a sophisticated appreciation of normal tissue tolerance. Attention was focused upon the heart and pericardium when STEWART et coll. (1967) reported the first substantial series of patients with cardiac complications as a result of mediastinal irradiation. They showed that the tolerance of the heart and pericardium is closely related to the volume irradiated and the dose delivered to the mediastinum. The incidence of irreversible cardiac damage increases sharply as the dose exceeds 4 000 rad in four weeks in the customary regime of treating five days each week (STEWART & FAJARDO 1971). The authors have pointed out and demonstrated experimentally that cardiac fibrosis and constrictive pericarditis are both delayed manifestations of irradiation and that the symptoms of pericarditis usually do not appear until 6 to 30 months after irradiation.

A review of the series of patients treated at the University of Virginia Hospital disclosed two cases of pericarditis, probably attributable to irradiation. Certain features were present in these cases which bear directly on the dose required to produce pericarditis and the latent period before symptoms develop.

Materials and Methods. The records of all 235 patients with Hodgkin's disease from January 1956 through June 1971 were reviewed. Of those registered, 137

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Table 1*Treatment techniques in mediastinal irradiation of 87 patients*

Group	No. of patients	Years	Radiation quality	Dose /time relationships	Daily treatment regime
A	16	1961—65	⁶⁰ Co	3 000—3 500 rad, 20—25 fractions 5 days per week	All fields treated daily
B	18	1965—68	⁶⁰ Co	4 000 rad, 20 fractions 5 days per week	Opposed fields treated on alternate days
C	14	1968—69	⁶⁰ Co	3 500 rad, 15—18 fractions 5 days per week	All fields treated daily
D	19	1969—70	8 MV	3 500 rad, 15—18 fractions 5 days per week	Shaped mantle fields both fields treated daily
E	20	1970—71	8 MV	4 000 rad, 20 fractions in six weeks split course*	Shaped mantle fields both fields treated daily

* Two courses of 2 000 rad, in 10 days separated by two-week rest interval

received radiation therapy; 115 of these received radical irradiation to all known areas of involvement. The mediastinum was treated in 87 of these 115 patients and all received in excess of 3 000 rad. The remaining 28 patients received radiation therapy to head and neck areas only or below the diaphragm. The average age of these 115 patients was 33 years and there was an almost even split between the sexes.

Treatment techniques. The first Cobalt-60 teletherapy unit was installed in 1956 and provided a convenient date to commence this review. All patients were treated by Cobalt-60 teletherapy or in the more recent years by 8 MV roentgen therapy. Five periods in the evolution of treatment techniques can be identified (Table 1).

Results

Two patients developed cardiac complications which were attributed to irradiation. Both of these patients demonstrated clinical, radiographic and ECG evidence of pericardial disease. The first case occurred in treatment group B and presented as a classical case of pericardial effusion many months following treatment. The second case occurred in group E and is considered to represent an example of acute radiation pericarditis in view of the extremely short interval between completion of the treatment and onset of symptoms.



Fig. 1. Case 1. a) Mediastinal adenopathy before radiation therapy. b) Three months following irradiation with regression of adenopathy.

Case 1. An 18-year-old white male with a painless swelling in the left lower cervical region of two months duration. No other symptoms were present. Physical examination disclosed bilateral, cervical and supraclavicular lymphadenopathy. On chest films significant mediastinal adenopathy was apparent (Fig. 1 a) but phlebography of the inferior vena cava and lymphangiography were negative. All other laboratory values were within normal limits. Employing the Rye Recommendations, he was staged II A on the basis of neck and mediastinal involvement and absence of symptoms. Subsequent review has shown the histologic cell type to be nodular sclerosis. Three weeks after diagnosis, treatment was started to the nodal areas above the diaphragm employing a Cobalt-60 teletherapy unit. Limitations of the machine and the size of the patient necessitated the use of three pairs of anterior and posterior fields directed to (1) the right neck and axilla, (2) the left neck and axilla, (3) the mediastinum. The mediastinal fields measured 10 cm \times 15 cm and encompassed over 50 per cent of the cardiac silhouette. 4 000 rad were delivered to the mid-plane of the chest in an overall time of four weeks treating five days per week. Only one field of each pair was treated daily. The mediastinal interfield distance measured 27 cm and the maximum subcutaneous dose was calculated to be 5 100 rad. Thus, that portion of the heart irradiated received from 4 000 to 5 100 rad during this course of treatment. In particular, it should be noted that the increments received by the anterior part of the heart on alternate days was 450 rad and this was repeated 10 times at a rate of 2 or 3 fractions per week.

During treatment the patient experienced symptoms of moderate esophagitis which rapidly subsided on completion. A chest film three months after treatment demonstrated complete regression of the hilar adenopathy but perihilar fibrosis was noted (Fig. 1 b). The patient remained asymptomatic until 13 months following treatment when he developed moderate dyspnea on exertion and radiographic evidence of a pericardial effusion. Based on his symptomatology, radiographic appearance and electrocardiographic findings, a diagnosis of pericarditis with pericardial effusion was made (Fig. 2). He was placed on Prednisone, no pericardial aspiration or surgery being considered necessary. Over the ensuing

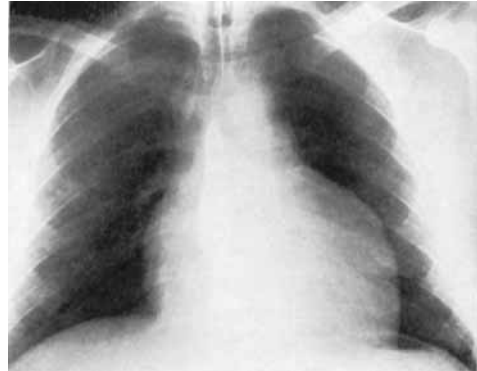


Fig. 2. Case 1. Thirteen months after completion of irradiation with pericardial effusion.

six months, he made an apparent uneventful recovery and his steroids were gradually discontinued. The patient has been followed regularly and is now four years post treatment and remains well, free of Hodgkin's disease.

Case 2. A 43-year-old white male with a one-year history of an asymptomatic left lower cervical mass. There were no other symptoms present and his past history was unremarkable with no suggestion of cardiac disease. Initial physical examination disclosed two small left lower cervical lymph nodes. Biopsy of one of these was reported as Hodgkin's disease, mixed cellularity type. The chest film was normal but a lymphangiogram was reported as equivocal. The remainder of his laboratory and radiographic investigations was negative. Staging laparotomy and splenectomy was performed with the findings of a positive para-aortic lymph node and a positive spleen. Liver biopsy was negative. He was staged III A and total nodal irradiation advised. Radiation therapy was first directed to all disease above the diaphragm and he received 4 000 rad to the mid-plane delivered by an 8 MV linear accelerator employing opposed mantle fields. The mediastinal portion of the field averaged 10 cm in width and included approximately 60 per cent of the heart. Treatment was administered over a six-week period utilizing a split course as described in Table 1, group E. He experienced nausea and symptoms of mild esophagitis and lost 4.5 kg in weight during this treatment. Two weeks following completion of this phase of treatment, irradiation was started to all disease below the diaphragm employing an inverted Y-field. Three weeks after completion of the mantle field, the patient began to complain of a vague anterior chest pain sometimes radiating to his shoulders. There were no physical findings, and films of the chest were negative but the discomfort persisted requiring the intermittent use of Codeine for relief. Because of a precipitous bone marrow depression when his platelet count fell from 280 000 to 40 000 per mm^3 , this phase of treatment was protracted over a seven-week period. Eight weeks after completion of the mantle field irradiation, while still under treatment, the patient developed severe substernal chest pain requiring admission. Several examiners noted a transient pericardial friction rub and serial electrocardiograms demonstrated low voltage and flat T waves suggestive of acute pericarditis. The patient was placed on Prednisone and over a seven day-period his symptoms subsided and all clinical evidence of pericardial disease disappeared. Over the following four months, the Prednisone was gradually discontinued and the patient appeared to make an uneventful recovery.

Table 2*Nominal standard dose determinations in rel for cases 1 and 2*

Position of NSD determination	Case 1 (Group B)			Case 2 (Group E)	
	NSD as treated (alternate fields daily, ⁶⁰ Co)	Hypothetical NSD (both fields daily, ⁶⁰ Co)	Hypothetical NSD (alterna- te fields daily, 8 MV)	NSD as treated (split course both fields daily 8 MV)	Hypothetical NSD (split course alternate fields daily, 8 MV)
Point of maximum dose	2150	1820	1812	1334	1580
1/4 interfield distance (heart dose)	1792	1518	1707	1317	1555
Mid-plane (tumor dose)	1368	1368	1368	1295	1295

Dosage calculations. Case 1 received a mid-plane dose of 4 000 rad in an overall time of 25 days delivered through opposed fields, each field being treated on alternate days, five days per week. Case 2 also received a mid-plane dose of 4 000 rad but in an overall time of 41 days delivered through opposed fields treating each field daily five days per week. The 4 000 rad was delivered in two courses of 2 000 rad in 10 treatments, separated by a rest interval of 2 weeks. Although the stated tumor dose is the same in both cases, the biologic effects are different due to the different treatment regimes. In order to facilitate comparison, the nominal standard dose (NSD) was calculated in each case utilizing the formula (ELLIS 1969).

$$\text{Total dose} = \text{NSD} \times (\text{fractions})^{0.24} \times (\text{time in days})^{0.11}$$

The results of these calculations are listed in Table 2. In case 1, considerable inhomogeneity in NSD is noted comparing the mid-plane dose with the point of maximum dosage (subcutaneous dose). The 'heart dose' is intermediate between these values. The reasons for the inhomogeneity are (1) treating one field on alternate days and (2) the large interfield distance (patient thickness) and (3) small percentage depth dose. For comparison, the NSD has been calculated treating both fields daily. The inhomogeneity is less but not eliminated reflecting the effect of patient thickness on depth dose.

The results for case 2 show a lower mid-plane NSD due to the prolonged overall treatment time consequent on the 'split', but this is not great. The

homogeneity is very satisfactory reflecting the better depth dose achieved with 8 MV roentgen rays. For comparison, the effect of treating one field on alternate days has been calculated. The homogeneity is less satisfactory but not as poor as with cobalt-60 radiation.

Discussion

Case 1 would appear to be acceptable as a case of radiation pericarditis with effusion as classically described. At first sight, the dosage of radiation would seem to be within the tolerance level defined by STEWART & FAJARDO (1971). However, the biologic effect of treating one field on alternate days has been shown to be greater than treating all fields daily (WILSON & HALL 1971). The magnitude increases as the interfield distance increases. The nominal standard dose in the region of the heart was, in fact, estimated to be 1792 ret, about 30 per cent greater than the mid-plane dose. This is considerably higher than the 1 600 ret described by STEWART & FAJARDO as critical for the production of cardiac complications and compares with the 1 800 to 2 000 rad single dose he showed would produce an 87 per cent incidence of pericarditis in animals. Table 2 shows that even with megavoltage equipment, treating one field on alternate days, especially in a stout patient, could raise the cardiac dosage to levels above tolerance. Various methods such as shielding the heart, limiting total dosage to 3 500 rad or utilizing split course radiation therapy are all used to circumvent excessive irradiation to the heart. All these methods have merit, but when high doses are utilized, treating all fields daily will offer an additional safety measure.

Case 2 is a typical example of Hodgkin's disease involving the abdomen and left neck but not the mediastinum. The dosage of 4 000 rad was delivered by 8 MV roentgen rays with a lower RBE than cobalt-60 and because of the split course, the biologic effect on the normal tissues was considered to be less. The NSD throughout the treatment volume was rather low (Table 2). However, within three weeks of completing treatment, he was experiencing chest pain and subsequently a diagnosis of acute pericarditis was made. Those cases in the series of STEWART et coll. (1967) who developed pericarditis during or shortly after treatment all had Hodgkin's disease in the mediastinum. In this case, there was no evidence of mediastinal or pericardial disease and so the latent period of three weeks seems unusually short. The shortest latent period in STEWART's material when there was no mediastinal disease was six months. There is some evidence that our patient was very sensitive to irradiation. He lost a considerable amount of weight during treatment and developed an erythematous skin reaction with some areas of moist desquamation. Symptoms of a moderate esophagitis were noted and he developed a marked and prolonged bone marrow depression.

Although no other etiologic agents could be implicated in this case, that possibility must be kept in mind. However in their absence, we accept this as an acute radiation pericarditis in an unusually sensitive individual.

Two cases of pericarditis in 87 patients with a minimum of six months follow-up represents an incidence of 2.3 per cent. It should be noted, however, that the incidence of cardiac complications was zero in the 47 patients in treatment groups A, C, and D who received a maximum of 3 500 rad. This would concur with the observation reported by STEWART & FAJARDO that pericarditis is extremely rare when the mediastinal dose is limited to 3 500 rad in 3.5 weeks. However, it should also be noted that all of these patients received irradiation to all fields daily.

Conclusions

Any technique such as alternate field therapy which inadvertantly increases the biologic effects of irradiation should be avoided. Sensitive individuals may exist who have a decreased normal cardiac tolerance to irradiation. 3 500 rad administered from opposed fields with all fields treated daily has not produced cardiac complications in this series of patients.

SUMMARY

In a series of 87 patients who received mediastinal irradiation for Hodgkin's disease, two patients developed pericarditis which was attributed to the radiation therapy. Both patients received 4 000 rad mid-plane tumor dose, one from a cobalt-60 unit to mantle fields treated on alternate days and the second by means of 8 MV roentgen rays utilizing a split course of treatment and treating both fields daily. Employing nominal standard dose determinations, case 1 was shown to have received a heart dose in excess of tolerance, the treatment of one field on alternate days contributing to the excessive dosage. The heart dose in case 2 was within tolerance but acute pericarditis developed within six weeks of radiation therapy. The possibility of individual sensitivity to irradiation is considered.

ZUSAMMENFASSUNG

In einer Serie von 87 Patienten, die eine Bestrahlung des Mediastinums wegen einer Hodgkin'schen Erkrankung erhalten hatten, entwickelten zwei Patienten eine Perikarditis, die der Strahlentherapie zuzuschreiben war. Beide Patienten erhielten eine Mittelplan Tumordosis von 4 000 rad, bei dem einen wurden jeden zweiten Tag mit einer ^{60}Co Einheit Mantelfelder bestrahlt und der zweite wurde mit 8 MV Strahlen bestrahlt, wobei eine „Split course“-Behandlung mit täglicher Behandlung beider Felder vorgenommen wurde. Bei Anwendung normaler Standarddosis-Bestimmungen zeigte sich, dass der erste Fall eine über der Toleranzgrenze liegende Herzdosis erhalten hatte, wobei die Behandlung eines Feldes jeden zweiten Tag zu der zu hohen Dosis beigetragen hatte. Die Herzdosis beim

zweiten Fall lag innerhalb der Toleranzgrenze, dennoch entwickelte sich eine akute Perikarditis innerhalb von 6 Wochen bei der Strahlentherapie. Die Möglichkeit einer individuellen Empfindlichkeit gegenüber Strahlung wird erwogen.

RÉSUMÉ

Sur une série de 87 malades ayant subi une irradiation médiastinale pour maladie de Hodgkin, 2 malades ont présenté une pericardite attribuée au traitement par les radiations. Ces deux malades avaient reçu 4 000 rad dans le plan moyen de la tumeur, l'un par cobalt thérapie sur des champs en mantelet traité un jour sur deux et le second par 8 MV des rayons de roentgen utilisant un traitement fractionné et traitant les deux champs chaque jour. La détermination de la dose standard normale a montré que le cas 1 avait reçu une irradiation cardiaque dépassant la dose tolérable; le traitement d'un champs un jour sur deux contribue au dosage excessif. La dose au cœur dans le cas 2 était dans les limites de tolérance mais une péricardite aiguë est apparue dans les six semaines qui ont suivi le traitement par les radiations. L'auteur envisage la possibilité d'une sensibilité individuelle à l'irradiation.

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