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LYMPH NODE CALCIFICATION IN HODGKIN'S DISEASE FOLLOWING IRRADIATION

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In a survey of patients who attended the Institute for Hodgkin's disease calcifications were observed following irradiation of lymph nodes which had been affected by the disease.

Previously, 18 cases of calcific deposits appearing after radiation therapy of Hodgkin's disease seem to have been published (Table 1). Similar lymph node calcifications have been observed in some other malignancies: cystadenocarcinoma of the ovary (CASTRO & KLEIN 1962), neuroblastoma, thyroid papillary and follicular carcinoma, reticulum-cell sarcoma, dysgerminoma of the ovary, and embryonal carcinoma of the testis (DOLAN 1963). Two cases of seminoma testis with calcifications developing after irradiation of lymph node metastases were found in a review of 124 cases from this Institute (CAPPELLINI). FISHER et coll. (1962) reported 2 cases of calcification following radiation therapy in a material of 154 cases of Hodgkin's disease, but they did not give any clinical information.

Different hypotheses have been advanced about the pathogenesis of these calcific deposits. The one most widely accepted is that they develop in a necrotic process. No significant relationship to abnormal serum calcium and serum phosphate levels has been found. SPEHL et coll. (1974) admit that the pathogenesis of the calcifications has not yet been clarified, but suggest that three factors may influence their occurrence: natural history of the disease, radiation therapy and chemotherapy.

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Table 1

Lymph node calcification in Hodgkin's disease following radiation therapy in 18 cases (from the literature)

References	Sex	Age at diagnosis (years)	Histologic subtype	Dose (rad)	Appearance of calcification Time after irradiation	Site of calcification	Survival (years)
WHITFIELD et coll. (1970)	F	36		2 500	9 years	Ant. mediast.	13 NED
GREBBEL & LYONS (1971)	F	11	NS	2 000	2 years	Ant. mediast.	12 NED
WYMAN & WEBER (1969)	F	36		6 000	11 years	Ant. mediast.	32 WR
	M	26		3 500	2 years	Ant. mediast.	5 WR
	M	20		2 000	4 years	Ant. mediast.	7 †WR
	F	29		5 000	1 year	Ant. mediast.	17 WR
	M	34		1 000	8 years	Ant. mediast.	23 WR
	M	37		3 000	21 years	Ant. mediast.	22 NED
	F	19		2 000	1 year	Ant. mediast.	5 WR
	F	32		3 000	11 years	Ant. mediast.	14 WR
	F	15		2 000	3 years	Ant. mediast.	26 NED
MCLENNAN & CASTELLINO (1975)	M	29	NS	4 000	2 years	Pelvis	5 †WR
	M	62	NS	2 025	5 years	Pelvis	9 NED
DOLAN (1963)	M	14		2 500	8 months	Pelvis	5½ WR
	F	11		4 500	20 months	Ileum and abdomen	3½ WR
	M	33		4 500	Not known	Neck and axilla	13 NED
	M	30		2 700	23 months	Abdomen	6 WR
NIBLETT (1975)	M	9		1 000	35 years	Neck and axilla	42 WR

NED = no evidence of disease, WR = with relapse, † = dead.

Material, Methods and Results

The survey included all patients with Hodgkin's disease (all stages) attending this Institute from Jan. 1, 1960 to Mar. 31, 1975, except those with chest films inadequate for evaluation.

The clinical notes and chest films of 481 patients were scrutinized; 8 cases were found with calcification at the site of lymph nodes previously involved and irradiated. In all but one case, the calcifications were evident; less evident ones may well have been unnoticed.

These patients had some characteristics in common; they were all females, young

Table 2

Lymph node calcification in the anterior mediastinum in Hodgkin's disease following radiation therapy in 8 females (present material)

Case No.	Age at diagnosis (years)	Stage	Histologic subtype	Dose (rad) at the site of calcification	Appearance of calcification. Time after irradiation (years)	Survival (years)	Appearance of calcification
1	15	II A	—	2 500	12	13 NED	Mulberry-like
2	27	II A	NS	3 600	2	11 WR	Mulberry-like
3	27	II A	—	2 600	6½	22 WR	Mulberry-like
4	16	II AE	—	3 850	6½	10 † NED	Mulberry-like
5	14	II A	LD	3 500	3½	16 (last relapse 1964)	Mulberry-like
6	20	II B	NS	3 600	10½	16 WR	Shell-like
7	38	II B	LD	4 400	5	6 NED	Mulberry-like
8	36	II A	LP	1 400	11	12 WR	Mulberry-like

NED = no evidence of disease, WR = with relapse, † = dead.

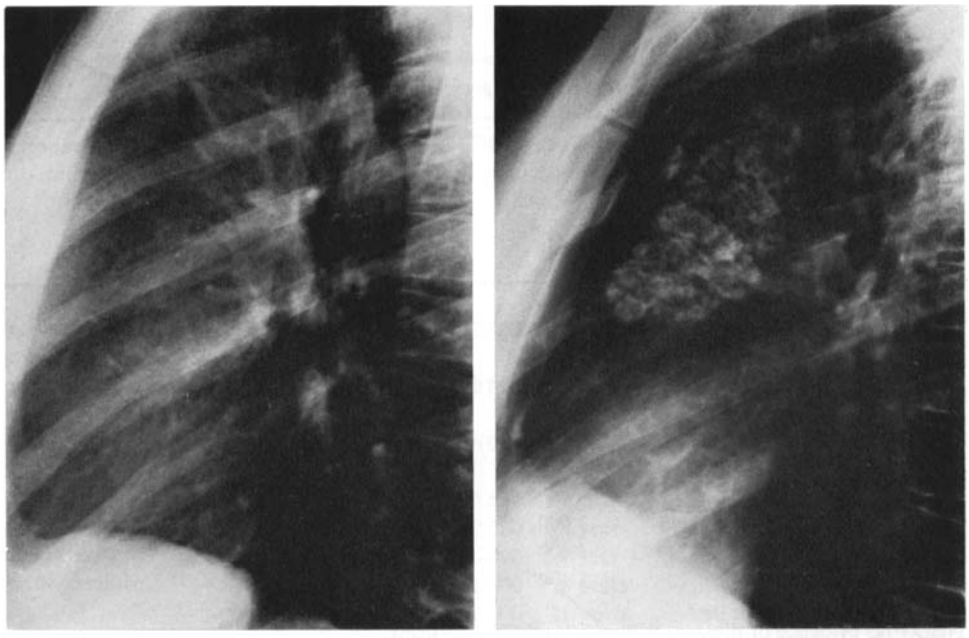
at the time of diagnosis, the anterior mediastinum was involved, and they all had a long survival (Table 2).

Nineteen females with involvement of the anterior mediastinum survived for more than ten years and in this group were all the cases that developed calcifications, except one treated 5 years ago (Table 3).

In all but one of the cases, the disease was diagnosed before 1966; 3 of the patients attending this clinic after this date were previously treated in other hospitals.

Chest films in 6 of the 8 patients clearly excluded the presence of calcifications before treatment; in the other 2 the evaluation was not conclusive, due to the contrast of the films.

The radiologic appearance in 7 cases was that of coarse, nodular calcific deposits, usually forming a stippled mulberry-like mass, circular or oval and 3 to 5 cm in diameter; neither an increase nor a reduction in size occurred during the observation period. In the 8th case, a thin, ring-like calcification appeared, that could be defined as an egg shell, thus quite different from the others. Reproductions and descriptions of the cases in the literature indicate that an egg shell appearance occurred in only 2 of the 9 patients described by WYMAN & WEBER (1969). This appearance, which is similar to what is found in silicosis, suggests a deposit of calcium in the marginal sinus. This seems impossible to explain on the basis of a post-treatment necrosis. In this patient the film taken before treatment was of such a quality that the presence of a thin calcification cannot be excluded with certainty. However, the history, age,



a b

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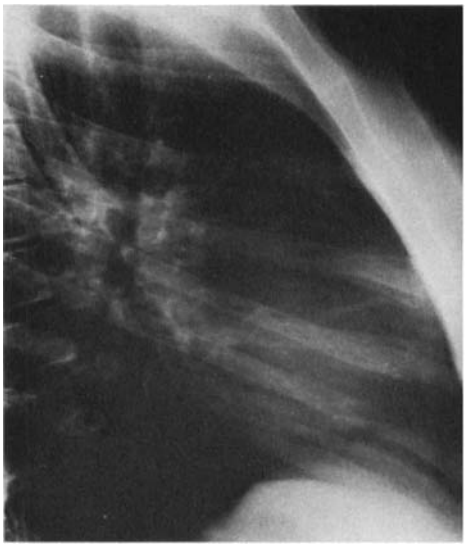
Fig. 1. Case 2. Lateral chest films. a) After completion of treatment for large left-sided mediastinal mass. b, c) 11 years later. Widespread calcification in the left anterior mediastinum.



a

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Fig. 2. Case 5. a) Lateral chest film. No calcifications. b) Lateral chest film and c) a.p. tomography. Calcification in the upper anterior mediastinum.

general appearance of the lungs, and site of the calcification did not suggest silicosis. The patient had a recurrence at the site of the calcification. In no other case were recurrences found in a calcified node. This is in agreement with the statements of WYMAN & WEBER. None of their 9 patients, except perhaps one, had a recurrence at the site of calcified nodes.

Six of the patients survived for more than 10 years from the time of diagnosis.

Fig. 3. Case 6. Tomography, lateral view. Shell-like calcification in the anterior mediastium close to sternum.

One died of cardiovascular failure after 10 years; at autopsy no evidence of Hodgkin's disease was found. The patient treated 5 years ago is alive, without relapse.

In all cases, at the site of calcification, a large mass had been present, which had shrunk markedly following irradiation.

Although other lymphatic nodes were involved and irradiated in all patients, the calcific deposits occurred only in the anterior mediastinum.

The diagnosis was confirmed histologically in all cases, but owing to the flood in

Table 3

Hodgkin's disease. All stages. Sex distribution, survival and involvement of anterior mediastinum in the present series

	Total case series		Survival time 10 years (patients at risk 149)	
	No. of cases	Involvement of anterior mediastinum	No. of cases	Involvement of anterior mediastinum
Males and females	481	201	37	22
Males	277	89	7	3
Females	204	112	28	19

Florence in 1966, only in 5 cases was it possible to classify the material into defined types: 2 LD, 2 NS, 1 LP.

Bone involvement developed in none of the patients, at any stage of the disease. The serum levels of calcium and phosphorus were not determined in all cases, but those recorded in the notes were all within normal limits.

The patients were in clinical stage II, A or B; when first treated, lymphangiography had not been performed in 4.

All patients had a low ESR, and a negative tuberculin skin test, except the patient with the shell-like calcification, whose test was positive.

All irradiations at this intstitute were performed with ^{60}Co teletherapy; 2 of the treatments in other hospitals were given with roentgen irradiation.

Discussion

Spontaneous calcification is not unusual in some tumours (neuroblastomas, psammomas, ovarian and colonic tumours), but in the literature only one case of spontaneous calcification in Hodgkin's disease seems to have been published (NIBLETT 1975).

Calcification in irradiated normal tissues is not common and the cases reported in the literature are questionable. Calcification of basal ganglia has been reported following radiation therapy (HARWOOD-NASH & REILLY 1970, NAMAGUCHI et coll. 1975), as well as in other conditions. DEETHS & STANLEY (1976) described parametrial calcifications in patients treated, before 1964, with ^{198}Au. The calcific deposits were found in the region of gold injections. They seem to reproduce a normal parametrium and are, in the authors' opinion, secondary to a direct radiation effect. In our opinion, a mechanical trauma cannot be ruled out with certainty.

Besides the calcifications described following irradiation of node metastases, few reports of calcification of primary tumours after irradiation or after chemotherapy have appeared (FLAMENT-DURAND et coll. 1975).

Most calcifications following irradiation of involved lymph nodes were found in cases of Hodgkin's disease with long survival.

Although data on the histologic subtype are scarce, 3 cases of 18 in the literature and 5 of 8 in the present series, nodular sclerosis (5 of 8) is predominant and is well correlated with the favourable development of the disease.

While in the cases reported in the literature males predominated (10 of 18), the patients in this series were all females and like those previously reported were young.

The calcifications appeared in the anterior mediastinum of females with long survival. They developed in 7 of 19 patients surviving for more than 10 years. An eighth patient, who was treated in 1971, is still living free of disease.

All but one of the patients with calcifications were first treated before 1966 and, as was then the policy for cases in stages I and II, all were given mantle treatment.

The patient treated 5 years ago received similar treatment owing to mental conditions. None of the patients underwent splenectomy.

In the enlarged lymph nodes in the lower part of the neck and in the axillae, calcific deposits never appeared after treatment in the present series; these regions are normally possible to evaluate on a chest film. Only 2 cases have been described (DOLAN, NIBLETT) as having calcifications in supraclavicular and axillary nodes.

Survey films of the abdomen are usually not taken as often as chest films, but in the present series abdominal films from lymphangiographic or urographic examinations performed during follow-ups were available. No calcifications were observed on these films. However, calcification of abdominal lymph nodes was reported in 3 patients by DOLAN and in 2 by MCLENNAN & CASTELLINO (1975). Two of DOLAN's patients were alive, with disease, more than 3.5 and 6 years after irradiation. One of two patients mentioned by MCLENNAN & CASTELLINO, a 62-year-old man, stage IV, with histologically documented liver involvement, was free from disease 9 years after treatment, which may be considered exceptional.

The fact that abdominal calcifications following irradiation are not commonly reported is probably not so much due to the circumstance that survey films of the abdomen are less frequently obtained than those of the chest, as to biologic factors. Healing of large abdominal masses is not frequent, and the general behaviour of the disease in such patients is usually less favourable.

The time for appearance of calcification following irradiation may be rather short; from 2 years in the present cases and from 8 months in the literature. Thus a long survival would not seem to be a sine qua non for the occurrence of calcific deposits. Biologic factors and the treatment policy seem to have significant influence on their development.

Conclusions. The development of calcifications in irradiated lymph nodes affected by Hodgkin's disease seems to be more common than is generally assumed. They often appear after a relatively short period and mainly in cases with a more benign course of the disease. Probably they develop in spontaneous or radiation induced necrosis but biologic factors seem to be of essential significance for their appearance.

SUMMARY

Calcification at the site of lymph nodes previously affected by Hodgkin's disease and irradiated was found in 8 patients in a series of 481 consecutive cases. The patients were all women, young at the time of diagnosis, and had a long survival. The calcific deposits developed in the anterior mediastinum.

ZUSAMMENFASSUNG

Eine Verkalkung am Platze der Lymphknoten, die von Hodgkinscher Erkrankung befallen waren, wurde bei 8 Patienten in einer Reihe von 481 aufeinandererfolgenden Fällen ge-

funden. Diese Patienten waren alle Frauen, die jung zur Zeit der Diagnose waren und eine lange Überlebenszeit hatten. Die Kalkablagerung entwickelte sich im vorderen Mediastinum.

RÉSUMÉ

Une calcification à l'emplacement de ganglions lymphatiques préalablement atteints par la maladie de Hodgkin et irradiés a été trouvée chez 8 malades sur une série de 481 cas consécutifs. Ces malades étaient tous des femmes, qui étaient jeunes au moment du diàgnostic et avaient une longue survie. Ces calcifications sont apparues dans le médiastin antérieur.

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