

CARCINOMA OF THE THYROID FOLLOWING IRRADIATION OF THE NECK

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It is 8 years since Duffy and Fitzgerald's important observation that there might be some relation between therapeutic irradiation of the chest in infancy and childhood and the subsequent development of cancer of the thyroid.¹ Since then a number of reports have appeared confirming their postulates. Stewart *et al.*² found an increased incidence of cancer, including leukaemia, in children whose mothers had had X-ray examinations of the abdomen during pregnancy. With evidence accumulating that carcinogenesis may result from exposure to X-rays, we report a case of papillary carcinoma of the thyroid in an African girl of 12 years developing 7 years after she had received irradiation for a lymphosarcoma of the neck.

CASE REPORT

M.M. a 12-year-old Bantu girl was admitted to the Johannesburg General Hospital on 9 January 1958 because of a swelling in the region of the thyroid which had gradually been increasing in size for 6 months (Fig. 1). Birth had been normal and the patient had been quite well until the age of 5, when she had developed generalized lymphadenopathy. A gland was biopsied at another hospital and the diagnosis of lymphoma was made.

The patient was hospitalized on 3 occasions between 1950 and 1952 and received irradiation to the following areas:

1950. Lateral aspect of neck: Right side, 2,000 r; left side 2,000 r; (field 10×8 cm.).

1951. Axilla: Right side, 2,000 r; left side, 2,000 r; (field 6×8 cm.).

1952. Submental region: 2,100 r (field 6×8 cm.).

In the intervening 6 years the patient had developed normally, both physically and mentally. Since the appearance of the thyroid swelling her mother had noticed that the child had become tired and lethargic. There was, however, no evidence in the history of either hyper- or hypofunction of the thyroid. No dyspnoea, dysphagia, cough, or voice change was recorded.

The patient was well developed. No clinical evidence of thyroid dysfunction was noted. The skin of the anterior aspect of the neck showed evidence of previous irradiation, with fibrosis and inability to extend the neck completely. The thyroid was easily palpable, particularly the right lobe, which was diffusely enlarged and contained a nodule $\frac{1}{2}$ inch in diameter; there was no fixation of the gland. The rest of the physical examination was not remarkable.

15 January 1958. Hb. 14.3 g.%, leucocytes 4,400 per c.mm. (N. 36%, L. 63.5%, E. 0.5%), ESR 26 mm. per hour, modified Ide test negative, serum protein-bound iodine 3 μ g.%, serum lipids 1,278 mg.% (repeated, 804 mg.%). Liver function tests: albumin 4.1 g.%, globulin 4.7 g.%, gamma globulin 2.95 g.%

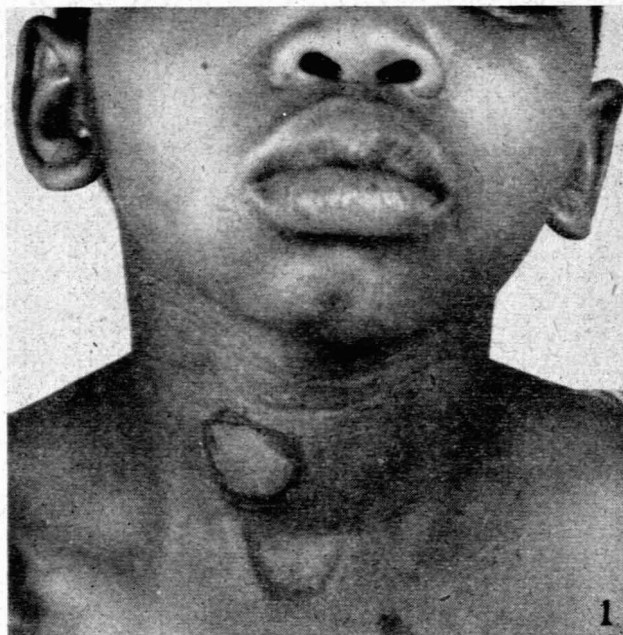


Fig. 1.

thymol turbidity 8.5, thymol flocculation +, alkaline phosphatase 31.4 K.A. units (repeated, 29.4), acid phosphatase 3.6 K.A. units (repeated 3.1). X-ray of chest normal. Skeletal survey normal.

A clinical diagnosis was made of thyroid carcinoma, and on 24 January a right hemithyroidectomy was performed (J.K.). The deep cervical lymph glands were not enlarged.

Pathological Report. The removed lobe shows numerous nodules, some of which have a colloid appearance on section, others showing firm white tumour tissue. No normal thyroid

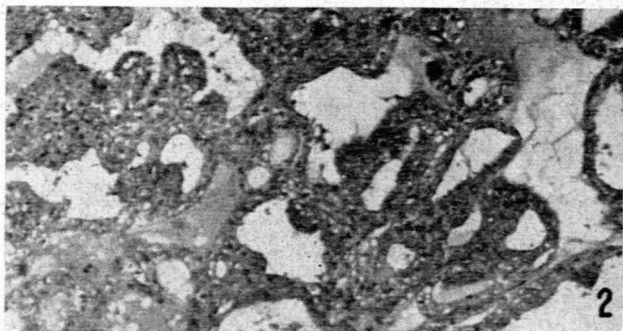


Fig. 2.

tissue is present. Sections of this lobe show the presence of a papillary adenocarcinoma of the thyroid, which occupies most of the lobe. Small islets of inactive thyroid tissue are present (Fig. 2).

The patient had a smooth post-operative course, and was discharged on 30 January 1958.

DISCUSSION

Duffy and Fitzgerald¹ reported 28 cases of thyroid carcinoma from the Memorial Hospital in New York in patients under 18 years old. Of these, 10 had been irradiated over the chest in infancy for symptoms thought to be due to an enlarged thymus. The irradiation dose was not recorded. These workers cautiously suggested a cause-and-effect relationship between thymic irradiation and thyroid cancer.

Clark³ reported 13 cases in which there was a history of previous irradiation; 3 had been irradiated on the upper chest for an enlarged thymus, 3 on the neck for cervical adenitis, 5 on the head and neck for enlarged tonsils and adenoids, 1 on the face and anterior chest for sinusitis and peribronchitis, and 1 on the anterior upper chest for pertussis. Clark presented statistics showing the increasing incidence of carcinoma of the thyroid in individuals under 15 years of age during the 50 years 1900-1950. This is correlated with the increasing use of X-irradiation in the treatment of benign conditions about the neck. He quotes Winshop,⁴ who found 8 cases of carcinoma of the thyroid in the literature in individuals under 15 years of age during the period 1900-1930, 34 cases in 1931-40, and 50 cases in 1941-51. Clark found that the interval between the irradiation and the development of cancer was 3-10 years, usually 6-9 years. A 'minimum carcinogenic dose' of 200 r was postulated.

The first controlled study on this problem, by Simpson *et al.*,⁵ added further evidence incriminating irradiation in the aetiology of thyroid cancer in childhood. These workers followed up 1,400 children who had received irradiation to the thymus gland in infancy, and noted the development of malignant neoplasia in 17, including 6 cases of carcinoma of the thyroid (4 within 9 years of the time of irradiation and 2 within 16 years) and 7 cases of leukemia. All the 17 patients who developed malignancy had received an irradiation dose of above 200 r to the chest. Follow-up of 1,795 siblings who had not received irradiation revealed no cases of carcinoma of the thyroid.

Duffy⁶ quotes Wilson and Asper,⁷ who reviewed 37 patients with thyroid cancer under the age of 25, and found that 17 had been given therapeutic doses of X-rays in childhood, 4 of them for thymic enlargement.

The case we are recording received an irradiation dose of 4,000 r about the neck, which is well above the so-called 'minimum carcinogenic dose' of 200 r, and developed carcinoma after an interval of 7 years. This brings the number of cases recorded in the literature to 47.

PATHOLOGY

The case reported showed the histological pattern of a papillary adenocarcinoma of the thyroid, which appeared to be confined to the thyroid gland. Of the 3 reported series of cases, Duffy *et al.*¹ and Simpson⁵ do not record the histological pattern of their cases. Clark's 13 cases³ were composed of (1) a papillary pattern in 4, (2) a follicular pattern in 6, and (3) a mixed papillary and follicular pattern in the remaining 3. Thus all 13 of his cases fell into the group of differentiated thyroid carcinoma, which has the best prognosis. Despite this, however, in only 1 case was the carcinoma limited to the thyroid gland. Metastatic deposits occurred most frequently in the deep cervical glands and in the lungs.

Biochemistry

Our patient consistently showed a raised serum alkaline phosphatase. The significance of this is not understood in the absence of any obvious cause for an increase of the enzyme concentration in the serum. Skeletal survey failed to reveal the presence of bony metastasis; whether the raised concentration of alkaline phosphatase is an indication of occult bony metastasis not at present discernible

on X-ray, is a question which will only be answered by continued follow-up.

Pathogenesis

Hall⁸ postulated two factors in thyroid carcinogenesis, viz.: (1) An initiating phase in which a carcinogen produces latent tumour cells, and (2) a promoting phase, mediated via endogenous thyrotropic hormone (TSH), which causes the cells to develop into visible tumours. Doniach⁹⁻¹¹ suggested that irradiation may act as the initiating factor and that subsequent growth and development of the thyroid from infancy to puberty, may be the promoting factor.

An alternative postulate emerges from the work of Lawson *et al.*¹² who showed that thymic tissue could inactivate TSH *in vitro* and, since TSH is known to play a part in the development of experimental cancer of the thyroid, it is conceivable that destruction of the thymus might in itself do something to provoke carcinoma of the thyroid by increasing circulating TSH in the blood. It is difficult to disprove this in humans, and present views are that the high incidence of thyroid cancer is due to irradiation of the thyroid itself.

Whether there is a minimum carcinogenic dose of 200 r is debatable; what is vastly more important is that the administration of radiation during infancy and childhood is extremely dangerous. By contrast the adult thyroid is reasonably resistant to the development of radiation cancer. Duffy⁶ reports a series of 328 cases who had received X-ray therapy for thyrotoxicosis more than 25 years previously, and of whom none developed thyroid cancer. Quimby and Werner¹³ state that in the adult the possibility of late malignant degeneration following roentgen therapy for toxic goitre is negligible. It should, however, be noted that 4 of their series developed carcinoma of other neck structures (larynx, trachea and oesophagus) 20 years after the X-ray therapy for thyrotoxicosis.

Duffy⁶ in addition to advocating restriction of unnecessary external irradiation also discourages the use of tracer ¹³¹I

in infancy and childhood. The *British Medical Journal* in an editorial¹⁴ points out that a dose of ¹³¹I resulting in a thyroidal uptake of 20 microcuries distributed equally throughout a 10-g. gland would deliver 200 r to the thyroid. Whilst this would be fraught with danger in the child, the effect on the adult thyroid is not nearly so hazardous. Radioiodine was first used in the treatment of thyrotoxicosis in 1940 and since that time reports of more than 5,000 adult patients treated with it have been published, without a single case of cancer of the thyroid definitely attributable to the treatment.

SUMMARY

A case is reported of papillary carcinoma of the thyroid in a girl of 12, following 7 years after irradiation to the neck; the literature of the association between irradiation to the neck in children and the subsequent development of cancer of the thyroid is reviewed. The possible pathogenesis is briefly considered.

Mention is made of the dangers of radio-iodine as a diagnostic tool in infancy and childhood in contrast to its apparent safety in adults.

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