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RADIATION CANCER OF THE PHARYNX

Case reports

by

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Radiation cancer of the skin was first reported at the beginning of this century (FRIEBEN 1902). Radiation-induced tumours in the pharynx on the other hand have been recognised only comparatively recently. Most of these tumours have occurred in patients previously irradiated for thyrotoxicosis or tuberculous lymphadenitis. A characteristic feature has been the long latent interval. We report here four further cases. Two of these patients are of particular interest because of a remarkable similarity in their case histories and because the latent interval even for this type of tumour was unusually long.

Case reports

Case 1. A woman was given roentgen therapy for a toxic goitre in 1916, at the age of 31. After she had finished treatment she developed an ulcer on the front of the neck which eventually healed. In 1957 she developed an ulcer, about 1 cm in diameter, on the anterior surface of the neck. The ulcer was situated just above the suprasternal notch in an area of atrophic and telangiectatic skin (Fig. 1).

Submitted for publication 5 January 1965.

Fig. 1. Atrophy and telangiectasis of the skin of the neck. A small area of ulceration may be seen just above and to the right of the suprasternal notch.

In March 1958 the affected skin was excised and the defect closed with a full thickness graft rotated from the chest. Histologic examination showed well-marked chronic radiodermatitis in the excised skin. There was a basal cell carcinoma at one edge of the specimen and in another area the epithelium at one margin of the ulcer was atypical and had the appearance of a squamous carcinoma.

In July 1961, at the age of 76, she presented with a history of four months dysphagia and pain in the chest. She had lost one stone in weight. Oesophagoscopy revealed a tumour in the upper oesophagus extending as high as the crico-pharyngeus muscle. Material removed for biopsy showed a moderately differentiated squamous carcinoma. She was treated on the linear accelerator receiving a mean tumour dose of 6 650 rad over a period of six weeks. After the treatment, her swallowing improved and became almost normal. Radiologic examination showed some persistent smooth narrowing of the oesophagus.

In March 1964 she developed clinical evidence of hypothyroidism. This diagnosis was confirmed by thyroid function tests and she was started on l-thyroxine 0.1 mg daily. She died suddenly eight days after starting thyroxine.

Autopsy revealed a white fibrous scar 1 cm in length almost encircling the oesophagus 1.5 cm below its origin. The regional lymph nodes were not enlarged. Histologic examination showed no evidence of residual tumour. There were minor irregularities of the epithelium consistent with previous irradiation. Over a length of 1 cm the oesophageal muscle was completely replaced by dense fibrous tissue which contained a few cells resembling radiation fibroblasts. The thyroid was small, weighed 10 g and appeared to be largely replaced by fibrous and fatty tissue. Histologic examination showed surviving islets of thyroid tissue surrounded by very considerable fibrosis.

The latent interval in this case was 45 years.

Case 2. A woman was treated by roentgen therapy for a toxic goitre in 1916 at the age of 29. Treatment was given once weekly for a period of one year.

In 1956 she developed a rodent ulcer on the anterior aspect of the neck. This was treated by a β-ray radium applicator.

In May 1962, at the age of 75, she presented with a history of six months pain in the right ear, soreness on the right side of the throat and more recently, a lump at the angle of the jaw. On examination she was found to have a warty tumour in the right pyriform fossa. There was a firm gland about 2 $\times$ 4 cm in the middle third of the cervical chain on the right side. The skin on the anterior aspect of the neck was thin, atrophic and telangiectatic. The rodent ulcer had healed without scarring. Material obtained for biopsy showed a moderately differentiated squamous carcinoma.

She was treated on the linear accelerator in June 1962, receiving a mean tumour dose of 6 700 rad in six weeks. Two months after completing treatment there was no visible tumour in the pyriform fossa, and the gland on the right side of the neck had resolved. When last seen, two and a half years after treatment, the pyriform fossa appeared to be clear. There were no lymph nodes palpable in the neck and no other evidence of recurrence. The latent interval in this case was 45 years.

Comments. Both the above patients were seen and treated in the Radiotherapy Department at Hammersmith Hospital. The other two patients have not been seen by us. They were referred to the Radiotherapy Department in Dublin but were not given any further radiotherapy (O'HALLORAN 1958).

Case 3. A woman was given a course of roentgen therapy for a goitre in 1915, at the age of 40. She was given a further course of treatment in 1916. She is said to have had a total dose of 14 pastilles.

In 1957, at the age of 81, she presented with a three months history of dysphagia and loss of weight. There was a considerable amount of scarring of the skin and subcutaneous fibrosis on the right side of the neck. A barium swallow showed narrowing of the cervical oesophagus and oesophagoscopy revealed complete obstruction in the lower part of the hypopharynx. Material removed for biopsy at that time did not show any evidence of malignancy but further material obtained two months later showed a squamous cell carcinoma. The latent interval in this case was 42 years.

Case 4. A woman was given a course of roentgen therapy for an exophthalmic goitre in 1929, at the age of 35. Four further courses of treatment were given during the subsequent two years. She is said to have had a total dose of 31 pastilles. In 1957, at the age of 63, she complained of dysphagia. Oesophagoscopy revealed an obstruction in the lower part of the hypopharynx and a small granulating area below the arytenoids. Material taken for biopsy showed the histologic changes of carcinoma in situ. The latent interval in this case was 28 years.

Discussion

It is difficult to be certain about the diagnosis of radiation cancer in a particular individual because the development of a tumour in an area previously subjected to irradiation may be coincidental. There is, however, fairly strong circumstantial evidence to support the diagnosis of radiation cancer in these patients.

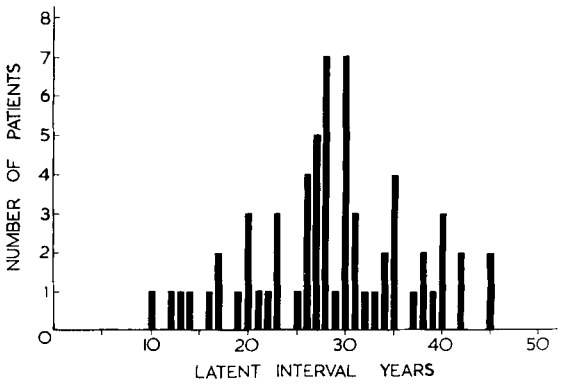

Fig. 2. The latent interval in radiation cancer of the pharynx.

There have been a number of reports of tumours developing in the pharynx many years after irradiation of the neck for benign conditions. We have found a total of 67 cases recorded in the literature (Bablik 1959, Beekmans 1960, Boette 1960, Cade 1957, den Hoed 1946, Garrett 1959, Goolden 1951, 1957, Holinger & Rabbett 1953, Kindler 1944, Krahl 1960, Kruchen 1937, Ogilvie 1951, Ombrédanne, Poncet & Gandon 1954, Raven & Levison 1954, Slaughter & Southwick 1957, Tsukamoto & Tazaki 1954, Vosteen 1959, Wlodyka 1962). Examination of the records shows that the patients who developed this type of radiation cancer have many features in common. Some patients were treated for tuberculous lymphadenitis but the majority were treated for thyrotoxicosis. By about 1920, roentgen rays were being widely used for the treatment of hyperthyroidism. At that time the surgical treatment of thyrotoxicosis carried a high mortality rate and it is not surprising that irradiation was frequently preferred to surgery. Treatment was often protracted, being continued over a period of a year or more, and, although information about the details of treatment is usually scanty, it is evident from subsequent events that radiation dosage must often have been excessive according to present-day practice. Patients who have developed radiation cancer of the pharynx usually have fairly severe radiation stigmata in the skin and subcutaneous tissues, but in some cases the changes have been minimal. It is not uncommon to find carcinoma of the skin in patients previously irradiated for thyrotoxicosis (Petersen 1954). Both basal and squamous cell tumours have been described. Other patients have developed necrotic ulcers which have required excision and sometimes extensive plastic repair of the irradiated area. Some of the patients with radiation cancer of the pharynx

have also had radiation cancer of the skin, the latter condition preceding the pharyngeal cancer by a number of years. Most radiation tumours of the pharynx are situated in the hypopharynx, the post-cricoid region being by far the commonest site. Several patients have developed tumours in the pyriform fossa. There appear to be only two other instances of neoplasms arising in the oesophagus (GOOLDEN 1957, SLAUGHTER & SOUTHWICK 1957) but the disease is often rather advanced at the time the diagnosis is made and it may be very difficult at that stage to decide whether it originated in the oesophagus or hypopharynx.

A characteristic feature of these tumours is the long latent interval. This varies between 10 and 45 years and has a peak at about 30 years (Fig. 2). It is very unlikely that such a large proportion of the patients would develop cancer after an interval of about 30 years if there were no relation between cancer and irradiation. There is, however, an alternative explanation which has to be considered. It might be argued that patients irradiated for thyrotoxicosis or tuberculous lymphadenitis would most probably be in the age group 20—30, and that cancer of the pharynx commonly occurs between the ages of 50 and 60. This being so, the majority of the patients might be expected to develop cancer after an interval of about 30 years. Analysis of the patients with respect to age, however, does not support this hypothesis. Both the age at the time of irradiation and the age at the time cancer was diagnosed vary over a wide range. It may be concluded, therefore, that the frequency distribution for the latent interval provides additional support for the diagnosis of radiation cancer in this group of patients.

The two patients seen in Dublin, whose case histories are presented above, resemble in most respects other patients who have developed radiation cancer of the pharynx. Both the patients seen at Hammersmith Hospital developed radiation cancer of the skin after an interval of about 40 years. After a further interval of four years, tumours developed in the pyriform fossa and oesophagus, respectively. It is unusual to encounter cancer in either of these sites in women of this age, a point in favour of the diagnosis of radiation cancer. The similarity between the two Hammersmith cases is perhaps another indication of a common aetiological factor. A latent interval of 45 years is longer than any so far recorded in radiation cancer of the pharynx.

It may seem irrational to treat by irradiation radiation-induced tumours but many of the patients with radiation cancer of the pharynx have in fact been treated by radiotherapy. Radiotherapy is usually preferred to surgery for tumours in the laryngo-pharynx and many of the radiation-induced tumours were in any case considered to be beyond the scope of surgery. Radiation changes in the skin and subcutaneous tissues have added to the difficulties

of radiotherapy, but the technical advantages of supervoltage therapy may be utilised to overcome some of these difficulties.

The prognosis in hypopharyngeal cancer is in general rather poor. It is of some interest to note that radiation-induced tumours apparently respond to irradiation at least as well as spontaneous tumours (GARRETT 1959), and the prognosis may perhaps be rather better for the patients with radiation cancer. Several patients have survived for two or three years without any evidence of recurrence (GOOLDEN 1957). The results of treatment in the two patients reported here were rather better than might have been expected. One is well without any evidence of disease two and a half years after treatment. The other patient who died two and a half years after treatment had no evidence of residual tumour at autopsy.

Information about radiation cancer in man derives mainly from cases reported in the literature. These probably represent only a small proportion of the total number which have occurred. The patients with radiation tumours in the pharynx now form quite a large group and it is appropriate to consider whether they contribute anything to our knowledge of radiation cancer.

Comment has already been made about the latent interval which seems to be longer and more clearly defined in this type of radiation cancer than in other types. Radiation cancer of the skin typically supervenes in an area of radiation dermatitis, and radiation-induced tumours in bone have developed in pre-existing radiation osteitis. These observations have led to the belief that radiation tumours develop only in tissues which have suffered gross radiation damage. It is not possible to estimate the radiation dose delivered to the pharynx as a result of irradiation of the neck carried out many years ago for thyrotoxicosis or tuberculous lymphadenitis, but it was probably considerably less than the dose to the skin and unlikely, therefore, to have produced changes in the mucous membrane of the pharynx comparable to those seen in the skin. This supposition is supported by the fact that a number of these patients, when submitted to further radiotherapy, were able to tolerate without any ill effect a lethal tumour dose in the region of the hypopharynx. It would seem, then, that radiation tumours may arise in tissues which have not been subjected to excessive irradiation in the usually accepted sense although tumours occurring in such circumstances may take longer to develop.

Little is known about the mechanism of radiation carcinogenesis. It is difficult to comprehend the process whereby ionising radiations initiate changes in the tissues which result in the appearance of a tumour after an interval of thirty years or more. Prolonged or repeated irradiation has been regarded as being more likely to induce cancer than a single exposure but the effect of fractionation on tumour production has yet to be clearly defined.

Little is known about the dose-response relationship or the factors which determine the latent interval. Some of these problems may be solved by experimental work in animals but the liability of man to develop cancer in response to irradiation can only be determined by observations in man. For these reasons the collection of data on radiation cancer is of more than historical interest.

Acknowledgements

We wish to thank Dr M. J. O'Halloran for kindly supplying details of the two patients seen in Dublin and Dr D. Evans who did the post mortem examination in Case 1.

SUMMARY

Cancer of the pharynx in four female patients, who had received radiotherapy of the neck for thyrotoxicosis, is described. In two of them, tumours in the pyriform fossa and in the oesophagus, respectively, developed 45 years after the irradiation, while in the two other patients tumours in the hypopharynx developed at 28 and 42 years, respectively, after the irradiation. The main features of radiation cancer of the pharynx are briefly reviewed. The latent interval for this type of tumour ranges between 10 and 45 years, with a peak at about 30 years.

ZUSAMMENFASSUNG

Es wird über Pharynxcancer bei 4 Frauen berichtet die wegen Thyreotoxikose eine Strahlenbehandlung des Halses erhalten hatten. Bei zwei von ihnen bildete sich 45 Jahre nach der Strahlenbehandlung ein Tumor in der Fossa pyriformis respektive im Ösophagus aus; in den zwei übrigen Fällen jedoch entwickelten sich Tumore im Hypopharynx 28 resp. 42 Jahre nach der Bestrahlung. Es wird über die Grundzüge der Strahlenbehandlung des Pharynxcancers berichtet. Das latente Interwall erstreckt sich für diesen Tumortyp auf 10 bis 45 Jahre mit einer Spitze bei etwa 30 Jahren.

RÉSUMÉ

Les auteurs rapportent quatre cas de cancer du pharynx chez des femmes traités par radiothérapie cervicale pour thyrotoxicose. Chez deux de ces malades la tumeur est apparue, dans le sinus piriforme ou l'œsophage, 45 ans après l'irradiation, alors que chez les deux autres la tumeur de l'hypopharynx est apparue 28 et 42 ans après l'irradiation. Les auteurs rappellent brièvement les principaux caractères du cancer radiothérapique du pharynx. L'intervalle de latence de ce type de tumeur va de 10 à 45 ans avec un maximum de fréquence autour de 30 ans.

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