IMMUNIZATION DURING PREGNANCY TO THE KIDD (Jk^a) RED-CELL ANTIGEN

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The production of anti-Jk^a as a result of pregnancy is rare. Simmons, Graydon, Jakobowicz, Santamaria, and Garson (1957) have reviewed the literature and described a case of their own. This note reports the finding of a further example of the antibody produced in this way, and demonstrates the importance of using suitable anti-globulin sera in compatibility tests.

Case Report

During her first pregnancy, Mrs. H. was found to be group O, rhesus negative, and her serum was free from immune antibodies; none were detected 10 days after delivery. The techniques used would have detected anti-Jk^a if this had been present. During her second pregnancy the only investigations of her blood were carried out 10 days before delivery. The sample submitted was too small for a full investigation, and on the limited amount of serum available we detected anti-D and anti-C active in saline and albumin. The serum was not tested by the indirect anti-globulin test against known rhesus-negative cells. As Mrs. H. had never been transfused the possibility of yet a third antibody was not considered.

She was delivered of a group O rhesus-positive child. The direct antiglobulin test was positive, and the haematological and clinical findings indicated that transfusion was necessary. Group O, rhesus-negative donor blood was matched against the mother's serum by saline, albumin, and antiglobulin techniques, and the cells of one donor were found incompatible by the antiglobulin technique. Other donors were compatible, and the baby was treated and progressed well. The blood samples of the parents and their baby were submitted for further investigation.

Further Serological Investigations

Red cells.—Mrs. H.: O, MNS, P₁-ve, cde/cde, kk, Le(a+b-), Lu(a-), Fy(a+), Jk(a-), Wr(a-). Mr. H.: A₁, M_sN_s, P₁-ve, CDe/cde, kk, Le(a-b+), Lu(a+), Fy(a-), Jk(a+), Wr(a-). Baby H.: O, CDe/cde, direct antiglobulin test positive. (Examined at a later date and found to be Jk(a+) when the antiglobulin test was negative.)

Serum.—The presence of anti-D and anti-C active in saline and albumin was confirmed, and examination against a panel of cde/cde cells suggested that the serum contained the immune antibody anti-Jk^a active by the antiglobulin technique, but completely inactive in saline and albumin media (see Table).

		Rhesus-negative Cells		
		Jk(a+)	Jk(a-)	
Mrs. H.'s serum	Positive	13	0	$P = \frac{1}{8568}$
	Negative	0	5	

Further examination of the anti-Jk^a showed it active with ficinized cells, weakly active with trypsinized cells, but completely inactive with papainized cells. Where enzyme-

treated cells did react the degree of reaction was not as great as in the antiglobulin test.

As anti-Jk^a has been reported (Stratton, 1956) as occurring in the non-gamma-globulin fraction, Mrs. H.'s serum was further examined. To anti-human-globulin serum was added a solution of gamma-globulin (1 in 50) so that the serum would no longer agglutinate rhesus-positive cells coated with incomplete anti-D. With this prepared anti-human-globulin serum it was possible to demonstrate that this anti-Jk^a was not a gamma-globulin. Prepared anti-human-gamma-globulin showed Mrs. H.'s anti-D and anti-C to be a gamma-globulin. Tests with a series of commercially available anti-human-globulin sera used at the dilutions recommended by the manufacturers were most unreliable for detecting the anti-Jk^a. Some of these reagents were reliable only for detecting gamma-globulin-type antibodies.

In all the tests the serum had complement present, or this was added to it as fresh human serum, as it was found that the reactions were stronger with complement than without.

Summary and Conclusions

A case is reported in which anti-Jk^a was present as well as the rhesus antibodies anti-C and anti-D. The only stimulus was pregnancy.

The anti-Jk^a was in the non-gamma fraction, and, unless the anti-globulin serum used had antibodies against globulins other than gamma-globulins, the anti-Jk^a could not be detected.

The presence of complement enhanced the reactions of the antibody. Similar experiences have been found with anti-K, anti-Le^a, and anti-Fy^a, and demonstrate the importance of using fresh serum for compatibility tests and of using antiglobulin serum capable of detecting the non-gamma-globulin-type antibodies.

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EIGHT FURTHER CASES OF RADIATION-INDUCED CANCER

BY

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In 1902, six years after the discovery of x rays, the first report of a radiation-induced cancer appeared in the literature (Friebe, 1902). It concerned an x-ray technician who developed a squamous-celled carcinoma on the dorsum of the hand.

At first, radiation-induced carcinoma was seen only in x-ray or radium workers, but in recent years most cases have occurred in patients who have had radiotherapy for malignant or benign conditions, and especially the latter. This is so because these patients live long enough to allow malignant change to take place; young developing tissue seems more susceptible to the carcinogenic effect of ionizing radiation (Clark, 1955), and the method often used in treating those conditions, by protracted multiple exposures, is accepted as the most potent method of inducing radiation carcinoma. Thyrotoxicosis was one of the conditions treated in this fashion (Barclay and Fellows, 1927).

Other benign conditions commonly treated by radiotherapy were haemangiomas, psoriasis, prurigo, pruritus, and lupus vulgaris.

Skin is the commonest site for radiation-induced carcinoma. Other sites reported include bone (Jones, 1953), mediastinum (Pettit *et al.*, 1954), thyroid (Duffy and Fitzgerald, 1950; Simpson *et al.*, 1955), stomach (Olson *et al.*, 1956), pharynx and larynx (Goolden, 1951, 1957), and tongue (Deller, 1951). The induction of leukaemia following x-ray therapy for ankylosing spondylitis is a special problem and has been fully reviewed by several authors, including Court Brown and Doll (1956).

Most radiation-induced growths are squamous-celled carcinoma, but osteogenic sarcoma, fibrosarcoma, and basal-celled carcinoma have all been reported.

The latent interval for radiation-induced carcinoma varies enormously; two years (Dunlap, 1957) is the shortest, and 49 years (Mitchell and Haybittle, 1955) the longest interval on record.

A description of eight further cases of radiation-induced carcinoma is given.

Case Reports

Case 1.—The patient was a married woman aged 66. From 1924 to 1926 x-ray therapy was given for thyrotoxicosis. The treatments were multiple and were given at frequent intervals. In 1948 a warty growth was

Case 1. Showing degree of post-radiation atrophy of the skin.

removed from the neck. Histological examination showed it to be a squamous carcinoma. In 1957 she complained of a lump in the throat—this was more noticeable during swallowing, but there was no real obstruction. She was referred to hospital on May 8, 1958. Examination revealed atrophy of the skin on the anterior aspect of the neck (see Fig.). The mucous membranes of mouth and tongue were normal. There was no koilonychia. The blood count was normal. A direct laryngoscopy revealed a haemorrhagic fleshy mass in the post-cricoid region 15–18 cm. from the incisor teeth. Biopsy showed squamous carcinoma. A soft-tissue x-ray film showed a mass in the post-cricoid region consistent with carcinoma. The patient was treated on the

linear accelerator. The treatment was well tolerated and the reaction was not unduly severe. Five months after completion of treatment she was symptom-free. Indirect laryngoscopy showed oedema of cords.

Case 2.—A married woman aged 54 had x-ray therapy to the neck in 1930 for over-active thyroid. She attended for treatment three times weekly for 18 months. She was referred to hospital on June 10, 1958, with a five-months history of pain in the left side of the throat made worse by swallowing, and of dysphagia for solids. Examination showed bilateral exophthalmos. The skin on the anterior neck was grossly atrophic. There was no evidence of anaemia or other suggestion of Plummer-Vinson syndrome. Direct laryngoscopy disclosed a fungating ulcerating growth in the post-cricoid region extending round the right lateral wall. Biopsy showed an epidermoid carcinoma, grade II. A soft-tissue x-ray film demonstrated the lesion. The blood count was normal. The growth was treated by megavoltage therapy. At the end of treatment a brisk erythema of the skin was present. The patient was able to swallow solids. An x-ray film showed marked regression of the growth. Four months later she was symptom-free and could swallow ordinary food.

Case 3.—The patient was a married woman aged 59. In 1913 and again in 1924 x rays had been applied to the neck for thyrotoxicosis. In 1928 a further course of radiation was applied over 10 months. The final course consisted of two exposures a week for two months, once weekly for two months, and then once monthly for six months. In 1950 she complained of a feeling of irritation on the right side of the neck. Later the skin of the neck broke down and subsequently developed into a squamous-celled carcinoma. The lesion was excised and grafted. Histological examination verified the diagnosis. At that time direct laryngoscopy did not show any growth in the pharynx or larynx. She was referred to hospital in March, 1957, complaining of huskiness of voice for two years; over the previous three months her voice had become definitely hoarse. There was a marked telangiectasia of the skin of the neck. A carcinoma was present on the right vocal cord. Biopsy of the cord showed a non-keratinizing well-differentiated squamous-celled carcinoma. On March 14, 1957, a right hemilaryngectomy was performed. The patient's progress continued to be favourable. At the time of writing she was alive and well, apart from huskiness of voice.

Case 4.—A married woman aged 50 had x-ray treatment for thyrotoxicosis when aged 25—at first weekly for three months, the course then being repeated. In April, 1949, she complained of pain on swallowing; the pain was referred to the right ear and up the right side of the head. By May difficulty on swallowing was present, and by August she could swallow only fluids. Pain was then constant. On examination her general condition was quite good. Marked telangiectasia and atrophy were present on anterior neck. A mobile gland was found in the right upper cervical group. Direct laryngoscopy showed extensive carcinoma in the post-cricoid region involving the entire right side of the oesophageal inlet and right arytenoid. Biopsy showed carcinoma. On September 14, 1949, an adenoma of the thyroid gland was removed and the tumour in the post-cricoid region was treated by implanting radon seeds. A secondary gland of the neck was excised. Histological report on the gland stated that it was a keratinizing squamous-celled carcinoma. Thyroid tissue showed hyperplasia only. The response to therapy was poor and there was a downhill course—swallowing became impossible and a gastrostomy was performed. The patient died in February, 1950.

Case 5.—A married woman aged 87 had x-ray treatment for Graves's disease in 1920; the treatment continued until there was no further evidence of toxicity. She was referred to hospital in July, 1958, with a three-years history of dysphagia. On examination her general condition was bad. A hard fixed gland was present in the right upper deep

cervical region. The skin of the anterior neck showed radiation stigmata. On indirect laryngoscopy there was swelling of the left side of the larynx and pharynx. A soft-tissue radiograph showed in the post-cricoid space a swelling almost certainly a neoplasm. No treatment was given.

Case 6.—A married woman aged 77 had a long course of x-ray treatment to the neck for thyrotoxicosis in 1930; she could not recall details. On February 13, 1958, she was referred to hospital. There was a history of six weeks' hoarseness—nothing else. Examination under anaesthesia showed a growth in the right pyriform fossa encroaching on the arytenoid cartilage and right false cord. Vocal cords were normal. The skin of the neck showed minimal changes. A palliative dose of x rays was given. In September, 1958, six months after therapy, she was symptom-free.

Case 7.—A married woman aged 69 had x rays to the neck for thyrotoxicosis in 1921; the course lasted 18 months—at first twice weekly and then once weekly. In April, 1956, she was referred to a general hospital because of recent loss of weight. Investigations revealed nothing to account for her symptoms. In August she complained of blood-streaked sputum, difficulty on swallowing solids, and cough after food. She was referred to hospital again in November, 1956, when her general condition was found to be bad. An indirect laryngoscopy did not show any growth, but pooling of mucus was present in the interarytenoid space. Both vocal cords were oedematous but mobile. A soft-tissue x-ray film of the neck showed what was almost certainly a carcinoma in the post-cricoid region.

Case 8.—When a young girl this patient, a married woman aged 57, was treated for overactive thyroid by x-ray therapy. She was referred to hospital in March, 1951, with a seven-months history of increasing difficulty on swallowing solids. The skin of the neck over the thyroid gland showed telangiectasia and atrophy. Oesophagoscopy revealed an infiltrating growth in the post-cricoid region. A radiograph showed a post-cricoid swelling in keeping with the diagnosis of neoplasm.

Discussion

Petersen (1954) reviewed the literature and found references to 200 cases of radiation-induced carcinoma, and he himself added another 21 cases of skin carcinoma to the list. This probably bears no relation to the true incidence of this type of malignancy.

Up to 1956 23 cases of cancer of the larynx and pharynx had been reported as being due to irradiation—five of these had occurred in the larynx and 18 in the pharynx. In 1957 Goolden reported another 18 cases, all in the pharynx, and Cade (1957) reported another four previously unpublished cases—all in the pharynx. The patients were previously treated by x rays for thyrotoxicosis, tuberculous adenitis, or syringomyelia. The vast majority were treated for thyrotoxicosis. Only four of the published cases occurred in males—an expected finding, since thyrotoxicosis is mainly a disease of women (8 females to 1 male).

In the present series the longest latent interval was 44 years, the shortest 20: the interval of 44 years is probably the longest on record for a radiation-induced carcinoma of the larynx (Case 3). Previous reports suggested that the latent interval for carcinoma of the larynx was shorter than for pharyngeal growths. For the five cases previously published the mean interval was 13 years.

The number of radiation-induced carcinomata is increasing, mainly owing to the fact that the latent interval has passed and the neoplasms are becoming

manifest. Carcinoma of the larynx and pharynx is not a common disease in women, and when a female patient presents with the lesion it is perhaps wise to inquire regarding the application of x rays many years before. This is especially to be recommended when a patient presents with a post-cricoid carcinoma without accompanying koilonychia, glossitis, or anaemia.

Not all patients with post-radiation carcinomata show skin stigmata, and seldom does the patient volunteer the information, as she does not connect her symptoms with the previous irradiation.

It will be noted that some of the patients have been treated by radiation—two on the 4 MeV linear accelerator. Perhaps at first sight it would seem hard to reconcile the fact that ionizing radiation is used to treat a radiation-induced growth, but radiosensitivity is not dependent on the causative agent. It is something inherent in the growth itself. Whether or not treatment by irradiation is possible depends on the degree of damage present in the surrounding tissue. Usually it is the skin that has suffered greatest damage, but, even when it is grossly altered, radiation in the 4 MeV range can still be applied, as the physical properties of this energy of radiation cause the maximum dose to be delivered below the skin with little energy absorption at the surface.

Summary

Another eight cases of radiation-induced laryngeal and pharyngeal carcinomata are reported.

All the patients were previously treated for thyrotoxicosis.

Among the eight cases is a carcinoma of the vocal cord, bringing to six the number of true laryngeal carcinomata assumed to be radiation-induced and reported in the literature.

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Commonwealth Perspectives (publication No. 8 of the Duke University Commonwealth - Studies Center) is a collection of essays on various aspects of the British Commonwealth. It includes an account of the development of health and welfare programmes in Australia, contributed by Professor B. U. Ratchford of Duke University, Durham, N. Carolina. *Commonwealth Perspectives* (214 pp., 1958) is obtainable in Great Britain from the Cambridge University Press, London, price 34s.