SHORT REPORTS

Azoospermia after iodine-131 treatment for thyroid carcinoma

Male infertility from gonadal damage caused by irradiation and cytotoxic chemotherapy is seldom reversible,^{1 2} and therapeutic strategies include cryostorage of semen, gonadal shielding, and surgical oophorectomy. Thyroid carcinoma may occur at any age,³ and operation, thyroxine suppression, and treatment with radioiodine (¹³¹I) usually result in long-term survival. The efficacy and safety of ¹³¹I are well established, though leukaemia, marrow depression, and radiation pneumonitis are rare complications.³ Infertility after ¹³¹I for carcinoma of the thyroid has not been reported.

Case report

A 32-year-old man presented with secondary infertility for 20 months. His wife had delivered a healthy girl in 1976 (paternity confirmed by erythrocyte and HLA typing) but a second pregnancy begun in May 1978 had ended in miscarriage at 10 weeks. Subsequent attempts to conceive had been unsuccessful despite regular, apparently ovulatory cycles.

After the first pregnancy began (1975) the patient was found to have a mixed papillary-follicular thyroid carcinoma with metastases in cervical lymph nodes. Total thyroidectomy with en-bloc resection of diseased nodes was performed. In October 1975 residual thyroid detected by radionuclide scan was ablated with 100 mCi ¹³¹I by mouth. Thyroxine 300 µg daily was given continuously. Results of total-body scans with ¹³¹I remained negative until April and September 1978, when further uptake in the neck was treated with 100 and 150 mCi ¹³¹I respectively. In August 1979 the scan was negative. No medication other than thyroxine and radioiodine was given, and there was no history of orchitis.

Examination showed normal testes (18 ml each), full androgenisation, and no evidence of metastasis. Azoospermia was documented on three occasions. Serum luteinising hormone, testosterone, and prolactin concentrations and thyroid function values were normal. Mumps antibody was undetectable. Serum follicle-stimulating hormone concentration was greatly increased (32 IU/l; normal 0-7 IU/l) and remained so five and nine months later (16 and 18 IU/l respectively). Serum thyroglobulin was undetectable.

Details of patients

Case No	Age (years)	Sperm density (× 10 ⁶ /l)	Serum FSH	Total ¹³¹ I dose (mCi)
1*	32	0	32, 16, 18	350
2	34	17	3	100
3	22	1.5	14, 21	400
4	54	11	5	100
5	53	23	2	100
6	57	32	12	150
7	43	ND	12	130

FSH = Follicle-stimulating hormone. ND = Not done. *Present case. (No patient had a history of testicular disease and all had normal testicular volume and normal serum luteinising hormone, prolactin, testosterone, thyroxine, thyroid-stimulating hormone, and thyroglobulin concentrations. Patients with bilateral cryptorchidism (one) and over 60 years of age (one) were excluded.) Statistical: sperm density with total dose $r = -0.75$, $p < 0.05$; serum FSH concentration with total dose $r = +0.87$, $p < 0.005$.

Comment

This patient became azoospermic between April 1978 and October 1979 after three doses of ¹³¹I totalling 350 mCi for metastatic thyroid carcinoma. The pattern of azoospermia, near-castrate serum follicle-stimulating hormone concentrations, and normal-size testes were virtually diagnostic of toxicity to the seminiferous tubular germinal epithelium.

Radiation to the gonads after ¹³¹I derives from the blood and bladder urine containing ¹³¹I. When renal function is normal the dose from the blood is a constant fraction of the administered dose. Radiation from bladder urine, however, varies with hydration and the frequency of voiding and probably represents only a small fraction of the total testicular dose. Estimates of overall gonadal dose range from 0.09 rad/mCi in euthyroid men to 0.5-1.5 rads/mCi in hypothyroid patients with thyroid carcinoma.^{3 4} Higher gonadal dose is reported in hypothyroid states with lowered thyroidal ¹³¹I uptake, but testicular radiation dose after thyroidectomy is not specifically reported.⁴ Our

patient may therefore have received 175-525 rads to his testes. Reversible azoospermia may result from testicular doses of 50-600 rads. Factors increasing the effect of testicular irradiation include fractionation and postpubertal state.²

Radioiodine treatment for thyrotoxicosis reportedly has little effect on fertility. Doses for thyroid carcinoma, however, are on average 20 times higher and are often multiple. Sarkar *et al*⁵ followed up for over 14 years 13 men treated with radioiodine for thyroid carcinoma. Of these, 11 were subsequently fertile and two (treated after puberty) infertile, suggesting long-term reversibility of any early effects. Recall within five years after treatment (see table) disclosed evidence of possible toxicity to the testes in three out of six men. We therefore think that this is a regular though perhaps reversible feature of radioiodine treatment for thyroid carcinoma in men. Total ¹³¹I dose was correlated positively with serum follicle-stimulating hormone concentration ($r = +0.87$; $p < 0.005$) and negatively with sperm density ($r = -0.75$; $p < 0.05$). We suggest that this potential side effect should be considered when radioiodine treatment is initiated and appropriate advice given to patients.

We thank Dr H Bashir, of the New South Wales Red Cross Blood Transfusion Service, for the paternity test; Dr A Child for the gynaecological history; and Mrs T Bailey for seminal analysis.

¹ Roeser HP, Stocks AE, Smith AJ. Testicular damage due to cytotoxic drugs and recovery after cessation of therapy. *Aust NZ J Med* 1978; 8:250-4.

² Lushbaugh CC, Casarett GW. The effects of gonadal irradiation in clinical radiation therapy: a review. *Cancer* 1976;27:1111-20.

³ Werner SC, Ingbar SH, eds. *The thyroid*. 4th edn. London: Harper and Row, 1978.

⁴ Kaul A, Roedler HD, Hine GJ. Internal absorbed dose from administered radiopharmaceuticals. In: *Medical radionuclide imaging*. Vol 2. *Proceedings of a symposium, Los Angeles, 25-29 October 1976*. Vienna: International Atomic Energy Commission Agency, 1977:423-53.

⁵ Sarkar SO, Beierwaltes WH, Gill SP, Gowley BJ. Subsequent fertility and birth histories of children and adolescents treated with ¹³¹I for thyroid cancer. *J Nucl Med Allied Sci* 1976;17:460-4.

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Department of Medicine, University of Sydney, Sydney, NSW 2006 and Male Fertility Clinic, Department of Endocrinology, Royal Prince Alfred Hospital, Sydney, NSW 2050

DAVID J HANDELSMAN, MB, BS, NH and MRC research fellow

ANNE J CONWAY, MB, FRACP, staff endocrinologist

PETER E DONNELLY, MD, FRACP, visiting physician

JOHN R TURTLE, MD, FRACP, professor of medicine

Spontaneous abortion after hand-foot-and-mouth disease caused by Coxsackie virus A16

We report two cases of spontaneous abortion that occurred after proved Coxsackie virus A16 infection (hand-foot-and-mouth disease) in the first trimester of pregnancy. This association has not been noted before and highlights a potential hazard of this usually mild disease.

Case reports

Case 1—A 26-year-old woman experienced malaise, nausea, and tiredness beginning on 24 May. She developed mouth ulcers, and on 28 May some small vesicles appeared on hands and feet. Vesicle fluid was taken for culture. On 1 June she aborted a 7-week-old fetus. The products of conception were not available for examination. A virus was isolated from the vesicle fluid in MRC₂ cells and identified by neutralisation test in suckling mice as Coxsackie virus A16.

Case 2—A 24-year-old woman was admitted on 13 August with an incomplete abortion in the 12th week of pregnancy. She gave a history of chickenpox two weeks before, and the products of uterine curettage were

sent for virological examination. She described her illness, which had begun on 30 July with headache, fever, malaise, and tiredness followed by the appearance of mouth ulcers and several blisters on arms, legs, and trunk. This was clinically diagnosed as chickenpox. On admission she had several healing blisters on limbs and trunk (see figure). Her only child, a girl of

Case 2. Appearance of healing blister at time of admission.

16 months, had been unwell with a fever and papular rash on the buttocks the week before the patient's illness. Coxsackie virus A16 was isolated (in MRC₂ cells) from the products of conception and identified by neutralisation tests in suckling mice.

Case 3—A third patient reported that she had had a mild attack of hand-foot-and-mouth disease in the 14th week of pregnancy after contact with infected children. She described mouth ulcers and a few skin vesicles but no systemic upset. Her pregnancy was continuing normally to mid-term.

Pre-illness serum was available for these three patients, and convalescent samples obtained from each. Using an indirect immunofluorescence test for antibody to Coxsackie virus A16,¹ we showed a specific response in all three patients. Some IgG antibody was detectable in all pre-illness sera (titres 16, 8, 8), but there was a significant increase in each convalescent serum titre (128, 512, 512). The specificity of the pre-existing antibody remains to be determined.

Comment

Hand-foot-and-mouth disease caused by Coxsackie virus A16 was first described in Toronto in 1958.² Outbreaks of infection occur periodically in Britain, and there has been widespread activity this summer. The illness is generally mild and without complications.³ Clinical confusion with chickenpox is understandable when numerous larger blisters are present. Differential diagnosis relies on the absence of cropping and failure to pustulate or scab in hand-foot-and-mouth lesions. In our second patient we detected pre-existing immunity to varicella.

Isolation of Coxsackie virus A16 from placental tissue confirms the causative role of this virus in abortion. It is not known whether there is any long-term effect of infection in pregnancy with any Coxsackie A viruses. A report of the Toronto A16 outbreak, localised in a particular housing area, mentioned that four babies born there six months after the epidemic had "minor congenital defects."² We hope to identify other patients infected during early pregnancy and study any effects in their babies.

We thank Dr D R Gamble and colleagues, of the Epsom Public Health Laboratory, for identifying the Coxsackie A16 viruses.

¹ Brown GC, O'Leary TP. Fluorescent antibody response of cases and contacts of hand foot and mouth disease. *Infect Immun* 1974;**9**:1098-101.

² Robinson CR, Doane FW, Rhodes AJ. Report of an outbreak of febrile illness with pharyngeal lesions and exanthem: Toronto summer 1957— isolation of group A Coxsackie virus. *Can Med Assoc J* 1958;**79**:615-21.

³ Communicable Disease Surveillance Centre. *Communicable Disease Report* No 80/34 (in press).

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Department of Microbiology, Southampton General Hospital, Southampton SO9 4XY

MARIE M OGILVIE, BSC, MD, lecturer in medical virology

CHARLES F TEARNE, BSC, FIMLS, medical laboratory scientific officer

Deep vein thrombosis and anaesthetic technique in emergency hip surgery

In investigations of postoperative deep vein thrombosis (DVT) little importance has been attached to the anaesthetic technique used. We have studied by means of ¹²⁵I-fibrinogen scanning the incidence of DVT in elderly patients undergoing emergency hip surgery under either spinal or general anaesthesia.

Patients, methods, and results

We studied 74 patients (10 men, 64 women) aged 63-95 years (mean 82 years) who had compression-screw-and-plate fixation of a femoral neck fracture within three days of injury. Preoperative assessment included a full history, physical examination, and laboratory investigations. Sixty-eight patients had significant concomitant medical problems. DVT prophylaxis is not given to patients in this unit with hip fractures as it is of uncertain efficacy. Each patient was randomly allocated to either spinal or general anaesthesia. Spinal anaesthesia was achieved in a routine sterile fashion with hyperbaric amethocaine 0.5% (mean dose 7 mg) with adrenaline. Diazepam (mean dose 9 mg) was given intravenously for sedation. General anaesthesia was induced with diazepam (mean dose 9 mg) and fentanyl (mean total dose 200 µg) followed by nitrous oxide-oxygen and pancuronium (mean total dose 6 mg). Fluid and blood were replaced according to clinical state and blood loss. Post-operative management and preoperative and postoperative haematocrit values were essentially the same in both groups. The thyroid gland was blocked with potassium iodide 120 mg by mouth continued daily for two weeks. Consent was obtained for the intravenous injection of 100 µCi ¹²⁵I-fibrinogen (Radiochemical Centre, Amersham), which was given immediately before anaesthesia. Leg scans were performed daily for seven days using a Pitman 235N Isotope Localisation Monitor. Details of the technique, computer analysis, and diagnostic criteria have been described elsewhere.³ The scans were analysed sequentially according to Armitage.³

Scans showed DVT in 17/37 (46%) of patients given spinal anaesthesia and in 28/37 (76%) of patients given general anaesthesia (table). The difference was significant at the 5% probability level. The reduction in the former group was similar in both the operated and the non-operated limbs. Three patients given spinal anaesthesia and seven patients given general anaesthesia died in the first postoperative month. The difference in mortality was not significant (Fisher's exact test). Two patients given general anaesthesia were thought to have died from massive pulmonary embolism. Necropsy was performed on only one.

Results of ¹²⁵I-fibrinogen uptake scans in 74 patients undergoing hip surgery under spinal or general anaesthesia. Difference in incidence of positive scans significant at 5% level

	Positive scans				Negative scans
	Operated limb	Other limb	Bilateral	Total	
Spinal anaesthesia (N = 37)	11	4	2	17	20
General anaesthesia (N = 37)	13	5	10	28	9

Comment

Emergency hip surgery in the elderly places an ever-increasing load on hospital services in developed countries. The incidence of DVT in these patients exceeds 50%. Fatal pulmonary embolism occurs in 4-8% and the overall mortality is 10-30%.⁴ The effectiveness of prophylactic measures in emergency hip surgery has been widely investigated^{1,4} with considerably varying results. The anaesthetic techniques used in these studies have generally not been reported. ¹²⁵I-fibrinogen scan is an accurate way of detecting postoperative DVT originating in the calf² but it has some limitations in its application to hip surgery.⁴ A lack of standardisation of technique and interpretation has been criticised previously.² Despite that it remains a useful screening method.¹

Three major factors are thought to contribute to venous thrombosis—venous stasis, changes in blood constituents, and damage to the vessel wall. Spinal anaesthesia produces sympathetic blockade with vasodilatation and an increase in lower limb blood flow.⁵ It is not known whether the coagulation and fibrinolytic responses to surgery are altered by the use of afferent neural blockade of the site of injury. Hip surgery causes blood vessel damage at the site of operation, but this cannot account for the occurrence of DVT in the non-operated limb. On the evidence of ¹²⁵I-fibrinogen scanning spinal anaesthesia for emergency hip surgery reduces the incidence of postoperative DVT.