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John Radcliffe Hospital Cryptorchidism Study Group

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Effect of rapid referral on thickness of melanomas

The prognosis of patients with malignant melanoma is made worse by delay in seeking help.[1] Therefore, in 1981 a pigmented lesion clinic was started in Southampton with the object of minimising the delay between patients presenting to their general practitioner with a malignant melanoma and the melanoma being excised in hospital. The patients' prognosis was determined by the accepted method of measuring tumour thickness.

Patients, methods, and results

When the clinic was established general practitioners were sent a colour pamphlet of the common pigmented lesions and encouraged to use the clinic as a rapid referral service for patients suspected of having a melanoma. The clinic was held once a week, and all patients referred that week with pigmented lesions were examined by a dermatologist whether or not their doctor had requested an urgent referral. The dermatologist screened out the benign lesions, and the potential melanomas were excised the same day.

During the next three years nine months 1230 patients with pigmented lesions were examined. Most had benign lesions, but some 7% had basal cell carcinomas and 75 melanomas were excised. The ratio of women to men with melanoma was 1·8:1 and the most common age of presentation 50-60. About 70% of the patients had blue or green eyes or burnt before tanning when exposed to sunshine, and 23% had lived in or near the tropics for more than one year. Twenty eight per cent had presented to their general practitioner within three months of first noticing their tumour, 38% had waited three to six months, 16% had waited six to 12 months, and 18% had delayed for more than one year. Forty eight per cent of the melanomas were on the leg, 20% on the trunk, 15% on the arms, 8% on the face, and 9% on the palms, soles, and genitals.

At the end of four years the histological findings were reviewed and the slides coded to enable tumour thickness to be measured without bias. The results (table) were analysed by non-parametric statistical methods. The melanomas excised in the pigmented lesion clinic were not significantly thinner than those excised in Southampton during the four years before the clinic started or those excised during the study period by other specialists in Southampton. Nor were there significantly more thin, good prognosis melanomas excised in the pigmented lesion clinic.

Mean thickness of melanomas excised by various agencies in Southampton during 1976-85

	No	Thickness (mm) Mean	SD
Melanomas excised after referral to pigmented lesion clinic 1981-5	75	2·42	2·57
Melanomas excised by other specialists in Southampton 1981-5	45	3·19	2·75
Melanomas excised in Southampton 1976-80	129	3·06	3·13

Comment

The results suggest that minimising the delay between the patient presenting to the general practitioner and the excision of the tumour in hospital does not improve the prognosis of malignant melanoma.

The prognosis of patients with melanoma examined in the pigmented lesion clinic was similar to the 62% five year survival rate found in a larger study in Scotland.[2] The aetiological role of sunlight in melanomas occurring in Britain was emphasised by the finding that most of the patients with melanoma examined in the pigmented lesion clinic were fair skinned, many of the lesions were on parts of the body habitually exposed to sunlight, and that one in five patients had lived in tropical or near tropical countries for more than one year.

We conclude that the prognosis of malignant melanoma in Britain is not significantly improved by rapid referral to hospital. Educating the public that enlarging pigmented lesions may be malignant and that early medical help can save lives may be more successful. This has been successful in Australia,[3] and a recent study from Glasgow suggests that a similar campaign would be successful in Britain.[4] The need for such preventive medicine in Britain will increase as the incidence of melanoma rises inexorably.[5]

The Southampton Melanoma Group comprises T Adams, A Chant, D W K Cotton, G M Fairris, P G Goodwin, V L Hall, M E Kesseler, N Kirkham, B J Leppard, A L McKenzie, and J E White.

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The neuropathy of the critically ill

An acute and often severe axonal neuropathy occurring at the peak of serious illnesses, with various causes but all complicated by shock and sepsis, has recently been recognised.[1] The only series reported has been from an intensive therapy unit in Canada, suggesting that this problem is overlooked elsewhere.[2,3] We report a further case to bring this complication to the attention of general physicians and surgeons caring for patients affected by it.

Case report

A 54 year old woman was admitted to the intensive therapy unit at this hospital in December 1985, having collapsed with abdominal pain. Her blood pressure was unrecordable. Pancreatitis was diagnosed when her serum amylase activity was found to be over 4000 IU/l. Secondary septicaemia was diagnosed when blood cultures grew *Escherichia coli*. She was treated with fluid replacement, infusions of dopamine and noradrenaline, and penicillin and gentamicin. She developed the adult respiratory distress syndrome and required ventilation. Apart from hypoxaemia, metabolic derangements included a moderate degree of renal failure, hyponatraemia, and later hypernatraemia, and for a while she had a high blood glucose concentration of around 25 mmol/l (450 mg/100 ml).

By the tenth day in hospital she was thought to be less responsive than her condition warranted, with no movement having been observed in her limbs. An electroencephalogram showed some generalised disturbances consistent with a metabolic encephalopathy. A few days later a neurological opinion was sought. She was now blinking in response to visual threat and trying to talk. She had been off the ventilator for two days, her cranial nerves were functioning normally, and there was no voluntary or reflex movement in her limbs. No muscle wasting was observed, reflexes were absent, and the plantar response was downgoing. Sensation was impaired in all four limbs distally. Electrophysiological tests showed no response in abductor pollicis brevis when the median nerve was stimulated at the elbow, but a small action potential (0·7 μV) was present in response to stimulation at the wrist. The lateral popliteal nerve was inexcitable, and no sensory action potential could be recorded from the median or sural nerves. Cell count in the cerebrospinal fluid was normal, as was the protein concentration (0·2 g/l). Urinary porphyrins were negative. Her chart was reviewed for any drug that is known to cause a neuropathy and to confirm that vitamin B complex and intravenous feeding had been given early in her illness. She did not abuse alcohol. We failed to obtain a biopsy specimen of the sural nerve, but a biopsy specimen of muscle taken at the same time contained small nerve fascicles that showed a lack of myelinated axons and a severe loss of non-myelinated axons with evidence of primary axonal degeneration. The muscle itself showed some neuropathic changes, but more striking was an inflammatory myositis.

Over the next three months, despite having been totally paralysed in her limbs for at least six weeks, she made an excellent recovery.

Comment

Although it is easy to understand how this neuropathy may be missed, it is important to recognise it, for if it passes unnoticed patients may be accused of having given up or are thought to be deteriorating and so less vigorous treatment may be instigated. Even in patients with complete paralysis recovery may be remarkable.[3] A neurological assessment will pick up most cases, but as this may be difficult electrophysiological confirmation of the neuropathy is advisable. Recognising the neuropathy (and the myositis and encephalopathy also seen in this patient) of severe illness is the first step towards finding an explanation; currently the aetiology is obscure because many metabolic, toxic, nutritional, and septic factors may be implicated. The condition to which it is most closely associated is shock lung.[2]

We thank Mr Malcolm Simms for referring the patient and Dr M P Carey for the interpretation of the muscle and nerve pathology.

ADDENDUM—We have recently seen another case of neuropathy in a critically ill patient. The primary disease in this case was uncertain, although the patient had pancreatitis and adult respiratory distress syndrome in conjunction with hepatorenal failure.

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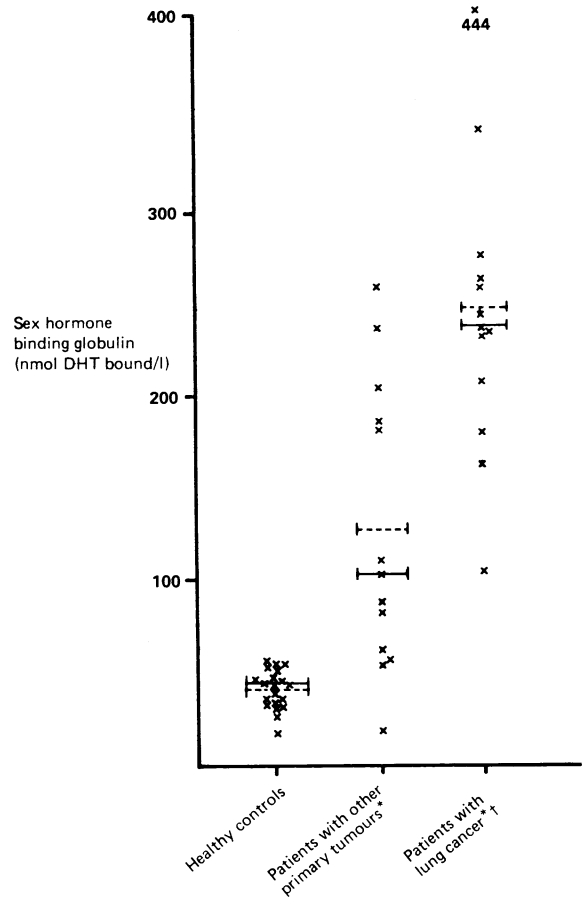
Serum concentrations of sex hormone binding globulin in lung cancer

The presence of low circulating total androgen concentrations in patients with lung cancer and of sex steroid metabolising enzymes and receptors in lung tumour tissue is well documented.[1,2] No previous study, however, has measured sex hormone binding globulin concentrations, which would allow the physiologically active fractions of sex hormones free from binding to sex hormone binding globulin and albumin to be calculated. We measured sex hormone binding globulin concentrations and circulating concentrations of testosterone, 5α-dihydrotestosterone and 17β-oestradiol in 13 men with lung cancer and two control groups matched for age.

Patients, methods, and results

We studied three groups of volunteers—namely, 13 men aged 45-76 (mean 55) with histologically confirmed carcinoma of the lung (squamous (five), adenocarcinoma (four), undifferentiated (four)), of whom nine had disseminated disease; 14 men aged 49-75 (mean 59) with primary malignancies of other sites (cholangiocarcinoma (four) and carcinoma of the colon (four), stomach (three), and urinary bladder (three)), of whom 10 had disseminated disease; and 20 healthy controls aged 45-75 (mean 57). Disability as assessed by the Karnofsky score was 50-80% in both groups of patients with tumours. No patient was receiving any treatment known to affect circulating sex steroid concentrations or had received radiotherapy or cytotoxic chemotherapy. Gynaecomastia and hypogonadism were not noted in any of the patients with tumours. Analysis of sex hormones was by radioimmunoassay, and assay of sex hormone binding globulin was by the method of Iqbal and Johnson.[3] The free fractions of the hormones were calculated by an interpolation method based on experimental data.[4] Statistical analysis was by the Mann-Whitney U and Student's *t* tests.

All of the patients with cancer had low total androgen concentrations ($p<0·02$) (median testosterone concentration 3·9 nmol/l (113 ng/100 ml) in the patients with lung cancer and 7·0 nmol/l (202 ng/100 mg) in those with other malignancies) and normal oestrogen concentrations (median oestradiol concentrations 135 pmol/l (3·7 ng/100 ml) in the patients with lung cancer) compared with the healthy controls (median testosterone concentration 14·5 nmol/l (418 ng/100 ml), oestradiol concentration 159 pmol/l (4·3 ng/100 ml)). Sex hormone binding globulin concentrations were also raised in all patients with cancer (figure), although those in the patients with lung cancer (up to 10 times normal) were significantly higher ($p<0·002$) than those in the patients with other malignancies. Because of the high affinity of sex hormone binding globulin for androgens the patients with lung cancer had extremely low free androgen concentrations (median free testosterone concentration 15 pmol/l (0·4 ng/100 ml)), which were significantly lower ($p<0·02$) than those in the patients with other malignancies (29 pmol/l (0·8 ng/100 ml)); the concentration in the healthy controls was 790 pmol/l (23 ng/100 ml). The usual negative correlation between sex hormone binding globulin and total 5α-dihydrotestosterone concentrations observed in the healthy controls and the patients with other malignancies was reversed in the patients with lung cancer (correlation coefficient 0·65, $p<0·01$).



Sex hormone binding globulin concentrations (expressed as nmol dihydrotestosterone (DHT) bound/l serum) in the three study groups. ——=Median value; - - -=mean value.
*$p<0·002$ compared with healthy controls. †$p<0·002$ compared with patients with other primary tumours.

Comment

Low total serum androgen concentrations, together with moderate increases in sex hormone binding globulin concentrations, have been observed in many patients with primary malignancies at various sites.[5] Extremely high concentrations of sex hormone binding globulin leading to extremely low free androgen concentrations have not been reported before in men with lung cancer. Normal total oestradiol concentrations in these patients together with the lower affinity of oestrogens for sex hormone binding globulin result in a profound alteration in the balance of sex steroids towards the oestrogens. We were unable to distinguish any difference in sex steroid or binding globulin concentrations between patients with lung tumours of different histological types, but a larger study might show such differences. The causes of this increase in sex hormone binding globulin concentration in patients with lung cancer are not clear. Normally sex hormone binding globulin concentrations are inversely correlated with total 5α-dihydrotestosterone concentrations, whereas in these patients a positive correlation was observed, suggesting that the normal homoeostatic mechanisms controlling circulating binding globulin concentrations were no longer operational.