Carcinoma of the Breast and Klinefelter's Syndrome

D. G. HARNDEN, N. MACLEAN, and A. O. LANGLANDS

Department of Cancer Studies, University of Birmingham, and the Departments of Pathology and Radiotherapy, Western General Hospital, Edinburgh

A number of associations have been suggested between neoplastic disease and conditions known to have abnormalities of the chromosomes. The association between Down's syndrome (trisomy 21) and malignancy is well documented (Stewart, Webb, and Hewitt, 1958; Holland, Doll, and Carter, 1962) and that between gonadal neoplasms and females with a Y chromosome in at least some cells is widely accepted (Teter and Boczkowski, 1967; Polani, 1968). An association between carcinoma of the breast and Klinefelter's syndrome has been suggested by isolated cases and by the findings of Jackson *et al* (1965), who in 21 cases of carcinoma of the breast in males found 3 to be chromatin positive and have an abnormal sex chromosome complement. Nadel and Koss (1967), however, found no chromatin positive males in 16 cases of carcinoma of the breast.

Material

We have surveyed 150 cases of carcinoma of the breast in males and have found 5 to be chromatin positive. The cases come from two sources. Ninety cases were located in the Birmingham Regional Cancer

Registry for the years 1957-68 and all but 2 were suitable for determination of sex chromatin in the histological specimens which were available. The remaining 62 cases were all the cases of male breast carcinoma known to the Registry of the Department of Radiotherapy, Edinburgh, and the Pathology Department of the Western General Hospital, Edinburgh, in which biopsy sections, buccal smears, or cultured blood leucocytes were available for carrying out sex-chromatin or sex-chromosome studies.

Results

Of the 88 Birmingham cases suitable for analysis three (nos. 1, 2, and 3) were chromatin positive (Table I). Cases 1 and 2 were already dead but further sections were cut from the original blocks and the presence of sex chromatin was confirmed in sections stained with cresyl violet. Case 3 was still alive and examination of 30 lymphocytes cultured from peripheral blood showed there to be 47 chromosomes including an extra C-group chromosome. Taken in conjunction with the presence of sex chromatin in the sectioned material this strongly suggests an XXY sex chromosome complement.

Two of the 62 Edinburgh cases (nos. 4 and 5) were

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TABLE I
AVAILABLE DETAILS OF THE 5 CASES

Case No.	Age at Diagnosis	Diagnosis	Sex Chromatin	Sex Chromosomes	Comments
1	61	Scirrhus carcinoma of right breast	+ ve	Not analysed	Married at 24; no children; normal intelligence; no clinical diagnosis of Klinefelter's syndrome
2	52	Infiltrating scirrhus carcinoma of right breast	+ ve	Not analysed	Married at 24; no children; normal intelligence; no clinical diagnosis of Klinefelter's syndrome
3	33	Spheroidal cell carcinoma of right breast	+ ve	XXY (blood)	Undergoing psychiatric treatment; no clinical diagnosis of Klinefelter's syndrome; married with 5 children
4	73	Adenocarcinoma of left breast	+ ve	XXY (skin and blood)	Penis and scrotum underdeveloped; neither testis palpable (case no. 229/60; Court Brown <i>et al</i> , 1964)
5	58	Poorly differentiated adenocarcinoma	+ ve	XX/XXY (skin and blood)	Penis and scrotum normal; testes small; no gynaecomastia; married at 36; no children; normal intelligence

found to be chromatin positive. In case 4, 68% of the buccal mucosal cells and 51% of the tumour cells contained single sex chromatin bodies. In 500 neutrophil polymorphs there were 12 drumsticks and 8 sessile sex chromatin appendages. The abnormal chromosome complement was confirmed by analysis of 100 cultured peripheral blood leucocytes and 88 cultured skin fibroblasts which showed him to have 47 chromosomes and an XXY sex chromosome complement. In case 5, 57% of buccal mucosal cells were chromatin positive; 500 neutrophil polymorph leucocytes were examined and 5 cells were found with drumsticks and 6 with sessile sex chromatin appendages. One hundred cells cultured from blood leucocytes and 30 fibroblasts cultured from skin were analysed. The majority of cells contained 47 chromosomes and had an XXY sex chromosome constitution, but a second line with 46 chromosomes and XX sex chromosomes was also present. The sex chromosome constitution of this patient is therefore accepted as 46,XX/47,XXY.

Discussion

While a definite diagnosis of Klinefelter's syndrome cannot be made in cases 1 and 2 the facts are compatible with such a diagnosis. The cytogenetic findings in case 3 make a diagnosis of this syndrome probable but he may be a chromosome mosaic. It proved impossible to get adequate data on his clinical status or on his family but his apparent fertility suggests that there may also be a 46,XY cell line. Cases 4 and 5 are confirmed to be cases of Klinefelter's syndrome on both clinical and cytogenetic grounds.

These data give a frequency of 33.3 chromatin-positive cases per thousand males with breast cancer. If these data together with previous data

(Table II) are grouped to give an overall estimate of frequency there are 7 chromatin-positive cases amongst 186 males with breast cancer (excluding the index case of Jackson *et al.*, 1965), an incidence of 37.6 per thousand, whereas chromatin-positive males occur with a frequency of 1.9 per thousand in newborn males (Court Brown, 1969). This is a highly significant increase.

It is not proposed to discuss possible mechanisms here but it could be that the hormonal imbalance which leads to gynaecomastia in a high proportion of cases of Klinefelter's syndrome (Overzier, 1963; Court Brown, 1967) also plays an important part in the aetiology of breast cancer in these patients.

Summary

Of 150 cases of carcinoma of the breast in males, 5 were found to be chromatin positive. Three were confirmed to have an XXY sex chromosome constitution.

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TABLE II

NUMBER OF CHROMATIN-POSITIVE
MALES AMONG EXAMINED CASES OF
MALE CARCINOMA OF THE BREAST

No. Examined	No. Chromatin Positive	Authority
21	3*	Jackson <i>et al.</i> (1965)
16	0	Nadel and Koss (1967)
62	2	Present study: Edinburgh cases
88	3	Present study: Birmingham cases
187	8*	

* One case is the index case and therefore not included in the calculation of frequency (see text).