Bilateral breast cancer in a male patient with hepatocellular carcinoma.
A case report

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Arianna Rubino*, Susanna Fissi**, Giorgio Secreto***

** Department of General Surgery, Istituto Clinico Humanitas, Rozzano, Italy*
*** Department of Surgical Oncology, "A. Manzoni" Hospital, Lecco, Italy*
**** Department of Experimental Oncology 'C' National Cancer Institute, Milan, Italy*

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Male breast cancer accounts for about 1% of all breast cancers and bilateral breast cancer in men is therefore a rare event*. Data in literature indicate that approximately 20% of these tumours are due to a probable alteration in the oestrogen metabolism*.*
Hepatocellular carcinoma (HCC) on the other hand, is a much more frequent tumour and in 70-80% of cases is associated with cirrhosis. The proven concomitance of cirrhosis and gynecomastia in HCC or previous intake of oestrogen in breast cancer, would indicate possible involvement of the hormonal metabolism in the appearance of the two neoplastic forms. To our knowledge a case with these two malignant diseases in the same male patient is an exceptional event, rarely reported in literature.
The fact that the breast cancer was bilateral in a male patient, the diverse histogenesis of the two breast cancers and the association with HCC in cirrhosis, led us to investigate into any common eziopathogenetic elements.

KEY WORDS: HCC, Male breast cancer.

Case report

On admission to hospital, a 61 year old male presented swelling of both breasts with palpable axillary adenopathy. The anamnesis showed a family predisposition for breast cancer; the patient was an ex-drinker and had suffered previously from hepatitis B infection. Due to the clinical characteristic of the bilateral breast mass a diagnosis of bilateral breast cancer was made. Biochemical data, the CEA markers and alpha-fetoprotein, chest x-ray and bone scintigraph were normal. CT scan[1] however, showed a non-capsulated area of 6 cms within segment VII. To resolve diagnostic doubt between hepatic metastasis from breast cancer and HCC in a cirrhotic liver, an echo-guided needle biopsy was performed (Tab. I). The histologic diagnosis was HCC.
On 4/1/1995 hepatic nodule was treated with transarterial chemoembolisation (TACE) with lipiodol (10 ml) and mitoxantrone (25 mg) despite the scarce vascularity evidenced by angiography and, five days later, the patient was submitted to simultaneous bilateral mastectomy according to Patey.

TABLE I - *Patient hormonal values before and two months after chemoembolisation of the liver tumour.*

Hormones	Initial	2 months after	Normal
Cortisol (ug/dL)	31.4	26.9	6-28
Prolactin (ng/ml)	3.8	10.2	2-20
LH	4.6	10.8	1-10
FSH (mIU/ml)	10.0	10.6	1-12
Estradiol (pg/ml)	33.4	68.5	5-35
Testosterone (ng/ml)	10.9	9.0	3-8
SHBG (nmol/l)	34.9	58.7	16-46
DHEA-S (ug/ml)	1416	924	700-5300
T/SHBG	0.31	0.15	
E2/SHBG	0.96	1.17	
E2/T	3.1\	7.7	

LH=luteinizing hormone; FSH=follicle stimulant hormone; SHBG= sex hormone binding globulin; DHEA-S=dehydroepiandrosterone sulphate; T/SHBG=testosterone/SHBG; E2/SHBG=estradiol/SHBG; E2/T=estradiol/testosterone.

The histologic examination of the two breast tumours showed: 1) infiltrating ductal carcinoma associated with infiltrating lobular carcinoma with metastasis at two

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For correspondence: Dr. Arianna Rubino, Istituto Clinico HUMANITAS, Via Manzoni 56, 20089 Rozzano (Milan), Italy (e-mail: arianna.rubino@humanitas.it).

lymph nodes at right axillary level I and II (pT4N1M0); 2) infiltrating lobular carcinoma (pT4N0M0) on the left side. The hormone receptors were: ERC positive and PgRc negative on the right and ERC positive and PgRc positive on the left side.
CT scan performed three weeks from the TACE (7/2/95), showed only Lipiodol ultra-fluid (LUF) with partial necrosis (30%) within the nodule. I.o. echography confirmed a solitary nodule within segment VII and segmentectomy was performed on March 1st 1995.
The postoperative course was uneventful. Definitive histologic examination confirmed the diagnosis of HCC in micro-macronodular cirrhosis, with necrosis equal to 30% of the nodule with no vascular invasion and infiltrated capsule.
Because of metastatic right axillary lymph nodes, six cycles of adjuvant systemic chemotherapy were planned according to the following scheme: epidoxorubicin (90-100 mg/m^2 i.v.) every three weeks for three cycles + cyclophosphamide (600 mg/m^2), methotrexate (40 mg/m^2), 5-fluorouracil (600 mg/m^2 i.v.) the 1st and 8th day every 4 weeks (4-6 cycles).
The patient underwent hormone treatment with tamoxifene.
HCC recurred in the left lobe of the liver in October 1996 and patient was submitted to left radical lobectomy (Dec. 96). No further chemotherapy or hormone treatment was prescribed.
In January 1998 another hepatic relapse was documented at CT scan.
The patient was treated with TACE and alcoholisation from February to September 1998 (5 TACE and 2 alcoholisation) with partial tumour response (reduction of 30-40%). Hepatic function levels remained acceptable during treatment, without complications. A close echographic follow up was made (2 months).
In February 1999 disease progressed and a new attempt at alcoholisation was made with stationary results up to November 1999.
Patient died for progression of disease and liver failure in February 2000.

Discussion

The case here reported deserves particular attention due to the simultaneous presence of uncommon characteristics: the bilateral situation of breast cancer in male patient (with different histogenesis of the two right and left nodules) and the simultaneous presence of HCC.
One hundred eighty eight male patients with breast cancer were admitted to the National Cancer Institute of Milan in the years spanning 1961-1994, of these only one had bilateral metachronous neoplasia.
Various hypotheses can be made as to which factors 'favour' these two different types of neoplasm. As far as breast cancer is concerned, a positive familiarity emerges from the anamnesis (the patient's mother had breast cancer) and previous potus and viral hepatitis B infection may have played an important role in HCC
This data must be stressed because research has proved the importance of alcohol abuse as a risk factor for breast cancer [11-12]. Despite the fact that such a risk becomes consistent only when a high level of alcohol is ingested and in association with other factors such as an excessively fatty diet.
We know however, that a chronic alcohol ingestion increases the protein connected to the sexual organs (SHBG) thus reducing the free fraction of plasmatic testosterone [13]. Furthermore, the patient in question is also carrier of chronic hepatopathy from progressive hepatitis B. It is well-known that the evolution into chronic hepatopathy and mainly into clear cirrhosis, leads to a change in the hormonal metabolism. In fact, in the plasma of male subjects, levels of estrone, estradiol and estriol appear increased and the concentration of oestrogen receptors is above average [14]. These alterations can cause an increase in the hormonal interception by the target organs and, consequently, a greater oncologic risk [15-18].
Based on hormonal evaluations made before and about two months after chemoembolisation of the hepatic tumour, (Tab. I) the following can be considered:
- The basic hormonal picture appears substantially normal. However, the above normal FSH levels could indicate an involvement of the seminal line of the testicle which, in cirrhotic patients is compromised earlier and in a more serious manner as regards the Leidig cell function. The observed rise in testosterone levels could indicate a reduced catabolic activity of the sexual steroids at hepatic level.
- After treatment a marked rise in estradiol concentrations and sex hormone-binding globulin (SHBG) is observed, the testosterone SHBG relationship (T/SHBG) drastically reduces indicating a reduction of the biologically active free fraction of the testosterone, responsible for the compensating increase of gonadotropina LH.

Altogether, the results of the hormonal study would suggest a decline in the hormone metaboliser of the liver after chemoembolisation, as indicated by the increase of the circulating concentrations of estradiol, by the reduction of the fraction of free testosterone and by the increase in estradiol/testosterone (E2/T) relationship. These results can be confirmed by larger case studies which should evaluate whether the presumed decline in the endocrine function of the liver induced by chemotherapy is acute or whether it is destined to progress. To our knowledge, no endocrinologic studies have been reported in literature to support this observation.
The occurrence of HCC is more understandable with the known succession of hepatitis-hepatopathy-cancer. The long natural history of chronic hepatopathy appears to be the dominant reason for the pathological events

presented in our patient. It could be hypothesised that the liver insufficiency, even though modest, determined by hepatopathy, acted as a pathogenetic factor both in the outcome of HCC and for the breast cancer. Therefore, in the reported case the hypothesis of a common etiopathogenetic factor rather than a coincidental combination of the two neoplastic forms would appear more valid.

Riassunto

Il cancro della mammella maschile incide per circa l'1% tra tutti i tumori mammari nella popolazione, ed è quindi da considerarsi un evento raro. Dati riportati nella letteratura riferiscono che circa il 20% di questi tumori sono dovuti ad una probabile alterazione nel metabolismo degli estrogeni.
Il carcinoma epatocellulare (HCC) indipendente dal sesso, è un tumore molto più comune e, nel 70-80% dei casi, concomita la genesi postepatitica o alcoolica. La provata concomitanza di cirrosi e ginecomastia nel maschio o la precedente assunzione di estrogeni nella femmina, potrebbero confermare un possibile coinvolgimento del metabolismo ormonale nella comparsa del carcinoma della mammella e dell'HCC. Un caso con ambedue queste patologie maligne nello stesso paziente maschile è un evento eccezionale e raramente riportato in letteratura.
La bilateralità del carcinoma mammario e dell'HCC nel paziente in oggetto ci ha indotto alla segnalazione del caso.

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