An advanced case of double primary malignancy involving the breasts and uterine cervix: satisfactory response to non-surgical management

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Summary

Double primary cancers are fairly rare. We report here a case of metachronous lesions; advanced cancer of the breasts and squamous cell carcinoma of the cervix. What is peculiar in this case is the rather unusual positive response to conservative treatment. Despite widespread metastases even to the liver, the patient is well and active more than six years after breast cancer was first diagnosed. Treating such advanced cases may be rewarding at times.

Key word: Advanced double primary malignancies; unusual response to conservative management.

Introduction

Double primary carcinomas are fairly rare though we have had such associations for the breast and cervix before [1]. We believe this is a coincidence since both pathologies are common in our environment. What is peculiar in the case reported here is the unsually good response to chemotherapy, even for the cervical lesion.

We report a case in which non-surgial management involving the use of chemotherapy, radiotherapy and hormonotherapy has resulted in complete remission (or cure) of both cancer of the breasts and the uterine cervix. Even liver metastases have disappeared.

Case report

Mrs G.E., a 49-year-old medical laboratory technician, first consulted a colleague in 1992.

On that occasion she had a right breast lump. She at first refused biopsy of the mass. Six months later on 29 January, 1993 an excision biopsy of a 4 cm mass was performed which revealed a lobular adenocarcinoma of the right breast.

She preferred treatment from a traditional herbalist and refused surgery. She presented a year later (i.e. January 1994) with another lump, this time in the left breast. The lesion in the right breast had recurred with significant axillary lymphadenopathy. She still refused surgery.

She was first seen by our team on 31 July, 1996 with the results of a Pap smear performed a week earlier. A punch biopsy revealed squamous cell carcinoma of the cervix. She had noticed post-coïtal bleeding for the first time on 15 January 1996. Post-coïtal bleeding had become more regular during the past three months. The menstrual pattern had not changed and she had 30-day cycles with a moderate flow lasting for 5 days. The referring physician made no mention of the breast lesion, which was only discovered by us on physical examination.

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She is a grand multiparous patient (G9P7027). She breast-fed all her children for at least a year. She is a non-smoker and also does not drink alcohol and was taking anti-inflammatory drugs occasionally for joint pains.

On physical examination on 31 July, 1996 her blood pressure was 140/90 mmHg; she weighed 69 kg, with a height of 168 cm. The heart sounds were normal and the lung fields clear. Both breasts were "inflamed", exhibited peau d'orange and contained huge lumps of about 8 cm in diameter. The nipple of the right breast was pointing towards the axilla. There were satellite skin nodules in the right axilla. Abdominal examination revealed normal findings. A speculum examination revealed an ulcerative tumour on the posterior lip of the cervix, which bled easily on contact and measured about 3 cm in diameter.

The uterus was of normal size, anteverted and mobile. No pelvic mass or tenderness was detected on bimannual examination. Rectal examination revealed that there was no parametrial extension.

Full blood count, coagulation screen, urine analysis, blood glucose, serum electrolytes and blood urea were all within normal range. The HIV test was negative. However, the vitesse sedimentation rate was 110 during the first hour and 128 during the second hour.

Most of the liver function test values were at the upper limit of the normal range, but the total bilirubin level was 20 ng/l (normal value is less than 10 ng/l). Research for Australian antigen and antibody was negative. A pelvic ultrasound was normal but an abdominal ultrasound revealed the liver was increased in size with secondary tumour deposits. There was an iso-echogenic mass of 10 cm in diameter in segment IV and another of 2.5 cm in segment VII of the liver. The gall bladder and other organs of the upper abdomen were of normal size. There were no enlarged retro-peritoneal lymph nodes and no ascites.

Her chest X-ray was normal. An ECG trace was also normal. The carcino-embryonic antigen value was 20 mg/l, (normal < 5 mg/l for non-smokers), and the CA 15-3 was 944 units/ml (normal = 0-30).

In view of the advanced nature of her breast cancer, we decided to start her on chemotherapy. She had 6 courses of a 3 weekly cycle of CAF (Cyclophosphamide 500 mg/m^2, Adriamycine 50 mg/m^2, 5-Fluorouracil 500 mg/m^2) with Prednisolone 20 mg daily x 7 days.

She became moderately jaundiced even before the first course of chemotherapy. When she returned for the second course, the jaundice was less intense and she felt slightly stronger but had developed ascites. There was marked diminution in the breast masses, the axillary lymph nodes had reduced in size, and had become mobile.

After the third course of chemotherapy, the axillary skin nodules disappeared and the ascites was scanty. After the fourth course of chemotherapy in November 1996, the liver function test values were also normal after an initial rise in alkaline phosphatase, transaminases and bilirubin after the first course.

The blood counts remained within the normal range throughout this period. By December 1996 she had developed amenorrhoea. The cervical lesion was also found to be disappearing. She finished the 6th course of chemotherapy in January 1997. The liver size had returned to normal but the secondary deposits persisted, though reduced in size. The 10 cm mass had reduced to 8 cm and the 2.5 cm mass to 2.2 cm. She was put on Tamoxifen, 20 mg daily, in February 1997 and she has been on it since. She had radiotherapy to both breasts and axillary areas in March 1997. The blood counts were normal and the vitesse sedimentation 20 mm in the first hour. She received 50 grays to the breasts and axillary bed. She was last consulted in February 1999 for a routine follow-up visit.

She looked well but had put on a lot of weight (11kg). The breasts had markedly reduced in size though were still hard. The axillary nodes were no longer palpable and the axillary skin nodules had disappeared. The abdominal and pelvic findings were normal and speculum examination revealed a healthy cervix. The laboratory results were all within normal range and a Pap smear was normal. Ultrasound examination of the breast revealed only fibrosis. The liver metastases had completely disappeared and pelvic echographic findings were also normal; Colposcopy evaluation of the cervix was normal.

Discussion

Double primary malignancy is not a common association. We have already published a paper on double primary gynaecological malignacies [1].

This patient refused mastectomy in 1993. Delay in seeking treatment is not uncommon [2]. The referring physician never knew that she had metastatic cancer of both breasts and had referred her only because of the newly acquired cancer of the uterine cervix. The double cancer in this patient only further strengthens the hypothesis that a patient with one cancer should be considered a potential candidate for another cancer. The patient should therefore be examined completely.

Despite the advanced stage of the breast cancer she responded favorably to a chemotherapy – hormonotherapy – radiotherapy regimen. She had complete regression of the primary and metastatic disease. Lobular adenocarcinoma may have microscopic foci in both breasts and systemic therapy is indicated [3]. The disappearance of huge liver metastatic lesions is however peculiar. Squamous cell cervical cancers have shown positive response to regimes containing cis-platinum [4]. Our patient's cervical lesion has disappeared completely on FAC protocol used primarily to treat the breast cancer.

The role of tamoxifen in controlling metastatic breast disease and radiotherapy for control of the local breast lesions are also important in this case. Recent studies have shown the benefit of tamoxifen in the management of patients with breast carcinoma [5].

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In the work of J. Bouda, O. Hes *"An unusual case of malignant Brenner tumor in association with low-grade urothelial carcinoma of the urinary bladder. A case report"* published in vol. XX, 4, 318 1999, due to a computer error Figure 2 was printed 2 times and Figure 3 was not printed. The following figures are correct. Please excuse the printer's mistake.

Considering the pathological diagnosis and almost no mitotic activity of tumor cells, radical irradiation of the pelvis was indicated (30 Gy for the whole abdomen with an increased lethal dose in the pelvis). As the patient poorly tolerated the treatment, it was discontinued. The following chemotherapy (cisplatin + cyclophosphamide + doxorubicin) had to be reduced because of hematotoxicity. During the treatment a growing resistance was found with bimanual examination and ultrasonography. CT showed an infiltrate 11x11x6 cm in size on the right side of the pelvis and also tumorous masses prominent into the urinary bladder. Cystoscopy and biopsy from large prominent masses were performed. CT also showed osteolytic deposits in the right acetabulum, which were not histologically examined, therefore it is not possible to make a statement about their origin.

Histology II

Samples from the urinary bladder contained a well-differentiated malignant tumor composed of small, uniform cells arranged on delicate fibrovascular stalks (Figure 3). No signs of invasion of the muscle layer were found. The diagnosis of primary urothelial carcinoma (grade I by Ash) was established.

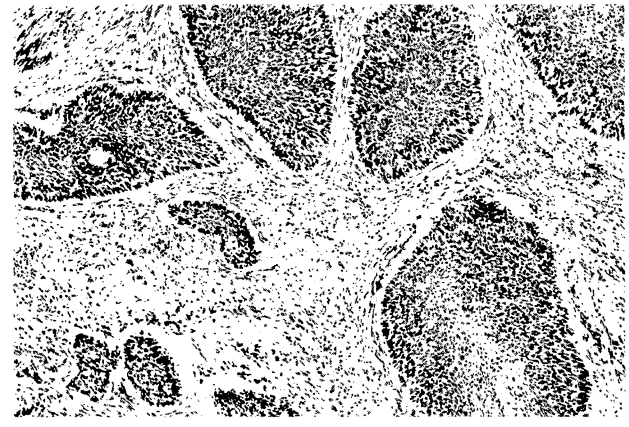

Figure 1. — Proliferating Brenner tumor with papillary fronds and nuclear atypia. Hematoxylin-eosin, 100x.

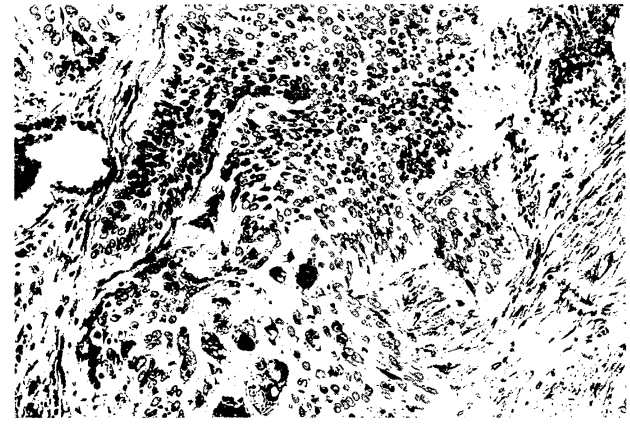

Figure 2. — Stromal invasion and squamous metaplasia present in a part of malignant Brenner tumor. Hematoxylin-eosin, 200x.

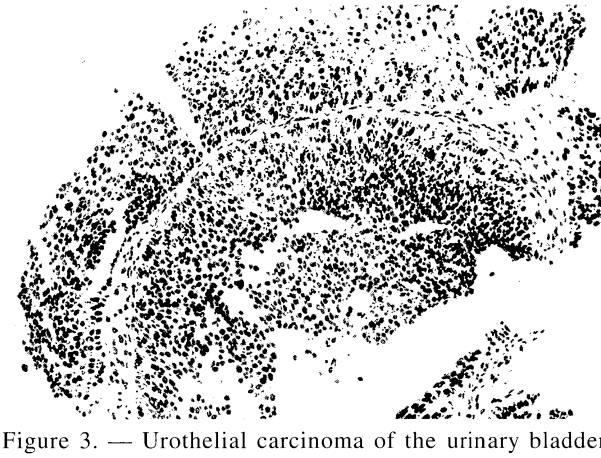

Figure 3. — Urothelial carcinoma of the urinary bladder; uniform cells arranged on a delicate fibrovascular stalk without signs of stromal invasion. Hematoxylin-eosin, 100x.

Discussion

BT represents about 1-2% of all ovarian tumors. It can often be seen in association with mucinous cystadenoma of the ovary, exceptionally with urothelial tumors, endometrial carcinoma, and struma ovarii [5, 6].

Histologically, BT is divided into several types. The first type is represented by **benign BT** with no cell atypia and without stromal invasion. **Metaplastic BT, proliferating BT**, and **borderline or low malignant BT** form an **intermediate group of BTs** [7]. The last type represents **malignant BT**, which is characterized by nuclear polymorphism and stromal invasion. It is usually found together with a component of benign, proliferating, metaplastic, or borderline BT.

Miles and Norris assume [8] that a better prognosis is expected of MBT, which also contains a benign and proliferating component of BT. The presence of these components is an important sign which differentiates MBT from **transitional cell carcinoma (TCC or non-Brenner type).**

The histogenesis of BT is not completely clear. Most authors assume the origin of BT derives from surface epithelium or from coelomic cysts through a process of transitional cell metaplasia [5, 9-11]. The other possible sites of origin include remnants of embryonic coelomic epithelium, displaced mesothelium, Walthard cell nests and remnants of mullerian, mesonefric, or wolffian ducts [3]. Extraovarian Brenner tumors in women are extremely rare and in a detailed search we found only 8 cases in the literature, all benign (4 in the vagina, 2 in the broad ligament, 1 in the uterine cervix and 1 in the uterine wall) [3, 4].

So far about 100 MBT and about 50 proliferating BT have been reported in the literature with the mean age of patients between 55-68 years [5, 6, 8]. The most frequent clinical symptoms are, similarly to other ovarian tumors, abdominal pain, abdominal "fullness", nausea etc. Menometrorrhagia or postmenopausal bleeding associated with endometrial hyperplasia is present in 12-20% of the patients with MBT. A minor part of the patients are asymptomatic, and a pelvic tumor can be found on routine examination. Most MBTs are clinical Stage I or II at the time of the presentation and ascites is very rare [5, 6, 12].