Hemorrhagic Invasive Ductal Carcinoma with Immunohistological Expression of β-subunit HCG : A Case Report

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Abstract : **A hemorrhagic breast mass was excised from a 27-year-old female. Microscopically, the tumor showed typical areas of invasive ductal carcinoma with intraductal component admixed with some trophoblast-like tumor giant cells in the hemorrhagic area. These cells exhibited β-subunit HCG by immunohistochemistry. The modified radical mastectomy was done after exclusion of the coexisting choriocarcinoma in breast cancer. Postoperatively, the HCG serum level was within normal limit and the gynecological check up showed no positive findings. The modified radical mastectomy specimen revealed that the residual tumor showed the same findings as seen in the previously excised mass.**

เรื่องย่อ : รายงานผู้ป่วยมะเร็งเต้านม 1 ราย ที่แสดงการตรวจพบทางอิมมูโนวิทยาของเบต้าเอชซีจี

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ได้ทำการตรวจก้อนเนื้อที่เต้านมขนาด 4 x 3.5 x 3.5 ซม. ที่ได้รับการผ่าตัด จากผู้หญิงไทย อายุ 27 ปี ซึ่งมีลักษณะเลือดออกมากภายในก้อน จากการตรวจทางจุลพยาธิพบว่าก้อนเนื้องอกมีลักษณะเป็นมะเร็งของท่อน้ำนมชนิดแทรกซึมร่วมกับชนิดที่อยู่ภายในท่อน้ำนม และยังพบเซลล์มะเร็งยักษ์ที่มีหลายนิวเคลียสที่คล้ายคลึงกับที่พบในเนื้องอกของเซลล์อ่อน ที่เรียกว่า โทรโฟบลาสติกเซลล์ (trophoblastic cells) ในบริเวณที่มีเลือดออก เซลล์เหล่านี้แสดงผลบวกทางอิมมูโนต่อเบต้าสับยูนิตเอชซีจี (β-subunit HCG) ผู้ป่วยได้รับการผ่าตัดเอาเต้านมและต่อมน้ำเหลืองออกหลังจากที่ได้รับการวินิจฉัยแยกโรคมะเร็งชนิดโดริโอคาร์ซิโนม่าที่อาจเกิดร่วมกับมะเร็งเต้านม ได้ออกไปก่อนโดยได้มีการตรวจหาระดับของเอชซีจีในซีรั่มหลังจากตัดเอาก้อนเนื้องอกออกไปตอนแรก ซึ่งพบว่าอยู่ในเกณฑ์ปกติ และตรวจทางนรีเวชวิทยาไม่พบมีความผิดปกติอื่นใด ผลการตรวจเต้านมและต่อมน้ำเหลืองพบว่าลักษณะทางจุลพยาธิวิทยาของมะเร็งที่เหลือคล้ายกับที่พบในก้อนเนื้องอกที่ตัดออกไปตอนแรก

INTRODUCTION

There were some previous reports of β-subunit HCG expression in breast cancer cells [1,2,3,4,5,6,7] and some of coexisting breast cancer and metastatic choriocarcinoma[8]. Several cases of breast cancer in our department showed no features of hemorrhagic mass or no evidence of syncytiotrophoblast-like giant cells in the microscopic findings. This report describes β - HCG expression in invasive ductal carcinoma with presence of syncytiotrophoblast-like giant cells in 27-year-old woman who presented with a markedly hemorrhagic breast mass, an unusual morphology of breast cancer.

CASE REPORT

A 27-year-old female presented with a left breast mass for 3 months without any symptoms except rapid growth within 2 months. The breast mass was excised. The formalin fixed and paraffin embedded section of breast mass was studied using routine histology and immunohistochemistry.

Grossly, the breast mass was a grayish white rubbery firm well-circumscribed mass measuring 4x3.5x3.5 cm. Cut surface was a large area of hemorrhagic, non homogeneous tissue rimmed by grayish rubbery firm areas of remaining breast tissue.

Microscopically, the tumor mass consisted of mainly invasive ductal carcinoma, grade III with part of intraductal component in the periphery and large hemorrhagic area in the center containing scattered tumor giant cells with large bizzare multiple nuclei looking like malignant trophoblasts (syncytiotrophoblast-like giant cells).

Immunohistochemical study using antibody to β-HCG (Rabbit Anti-human chorionicgonadotropin (HCG) DAKO, Glostrup, Denmark) dilution 1:40,000 was performed by using the labeled streptavidin-biotin peroxidase method on formalin-fixed and paraffin embedded section of the excised breast mass. The antigen retrieval was performed under microwave technique.The results showed that the tumor multinucleated giant cells marked with β–HCG whilst the intraductal and the invasive components of breast cancer showed no immunoreactivity.

The ultrastructural study was additionally performed. The viable tumor cells were difficult to find due to extensive hemorrhage and necrosis. They were scattered singly. Each cell contained one or more bizarre nuclei with finely dispersed chromatin. The cytoplasm did not contain significant number of organelles such as well developed rough endoplasmic reticulum, abundant polyribosomes, multiple Golgi complexes, mitochondria, cholesterol-rich lipid inclusions, and microvilli-lined intracellular lumens like that of syncytial trophoblasts. Phagocytized red blood cells and secondary lysosomes (phagosomes) which are often seen in the neoplastic trophoblastic cells were not present.[9] In this case the tumor giant cells did not harbour the ulltrastructures of the trophoblasts.

Serum HCG on the fifteenth postoperative day was 0.9 mIU/ml. (normal 0-1.4 mIU/ml). Gynecologic examination revealed no positive findings. The modified radical mastectomy was performed approximately one month after excision of breast mass. There was a residual ill defined hard mass with yellow necrotic appearance in the outer upper quadrant measuring 2.5 x 2.5 x 2 cm. The nipple was grossly free of tumor. Microscopically the tumor was invasive ductal carcinoma infiltrating into the adjacent quadrant with lymphatic permeation, and axillary lymph node metastasis in 9 out of 16 nodes. There was a few residual tumor giant cells expressing β – HCG by immunohistochemistry technique whilst the majority of the invasive ductal component did not.

In order to find out wheter the β-HCG expression of breast cancer was rarely or commonly found in our institution a preliminary study in 29 consecutive cases of breast cancers (28 invasive ductal carcinoma and 1 mucinous carcinoma) in the same series of estrogen and progesterone receptor expresssion study was performed using immunoperoxidase technique. There was one case with few cells expressing positive immunostaining for β-HCG and 2 cases with few cells expressing weakly positive staining (±). The remaining 25 cases of invasive ductal carcinoma and one case of mucinous carcinoma were negative for β-HCG. All tumors had no hemorrhagic appearance and the tumor cells including the HCG stained cells were not multinucleated giant cells.

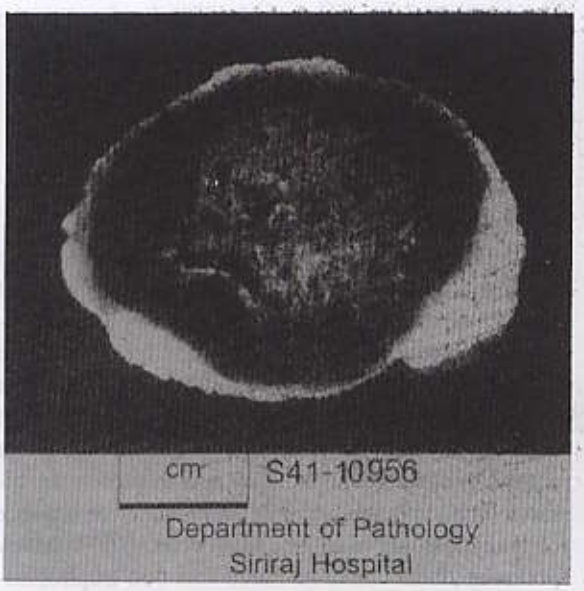

Figure 1. A breast mass with a large area of hemorrhagic, non homogeneous tissue rimmed by grayish rubbery firm areas of remaining breast tissue.

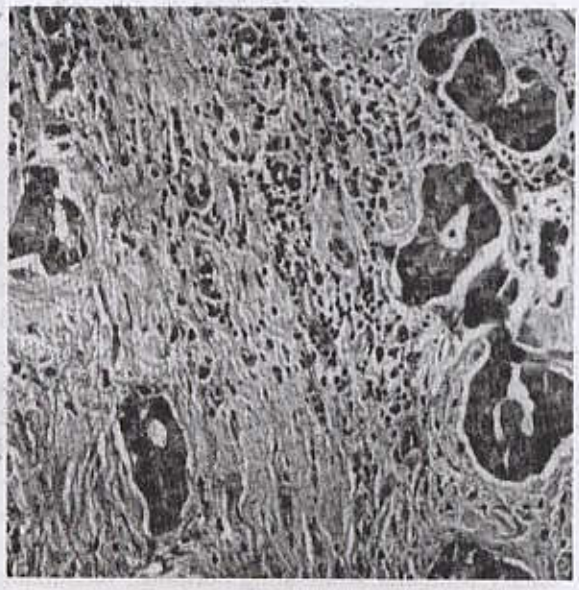

Figure 2. The representative field of invasive ductal carcinoma (H & E x 100.)

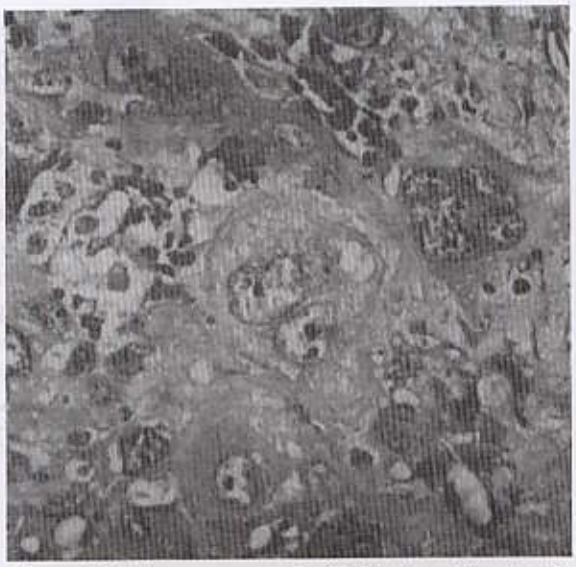

Figure 3. The representative field of multinucleated tumor giant cells around hemorrhagic cystic cavity which is seen at the right sided area. (H & E x 200.)

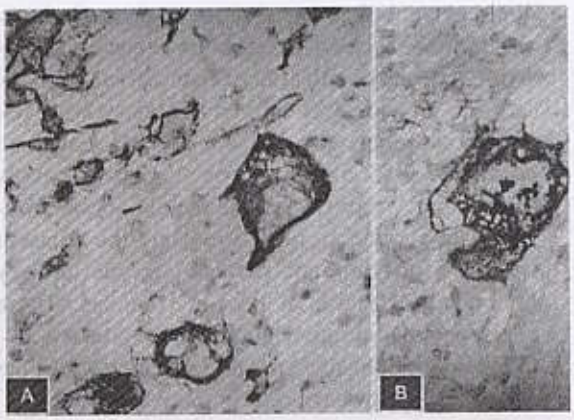

Figure 4. Positive staining for HCG confined to the tumor giant cells. (H & E x 200. A, B)

DISCUSSION

Human chorionic gonadotropin (HCG)[10,11] is a glycoprotein hormone with a molecular weight about 38,000. It is formed by 2 subunits, α and β which are themselves inactive. They are non-covalently linked in the active molecules. Although the syncytiotrophoblast is clearly the significant site of HCG synthesis, there is also some evidence that the villous cytotrophoblastic cells can also participate in the production of this hormone. The α subunits are identical or nearly identical to those of pituitary follicular stimulating hormone, luteinizing hormone and thyroid stimulating hormone.The β-subunits vary and provide biological specificity to each hormone so that the antibody against the beta subunit of HCG is used to detect trophoblastic differentiation in germ cell tumors. However HCG is not only the product of gestational trophoblastic disease, several cases of patients with ectopic production of HCG by nontrophoblastic neoplasms were also reported.[12] The associated neoplasms included bronchogenic carcinoma, pancreatic carcinoma, breast carcinoma, melanoma, hepatocellular carcinoma / hepatoblastoma, gastric carcinoma, multiple myeloma, and retroperitoneal sarcoma, etc. In that report[12] the ectopic production of HCG by nontrophoblastic neoplasms was investigated by a sensitive radioimmunoassay that measured the hormone in blood samples of the patients with well established neoplasms. There have been some documents about ectopic production of HCG by non trophoblastic tumors such as breast cancer in the presence or absence of syncytiotrophoblast-like giant cells.[1,2,3,4,5,6,7] Many previous studies have revealed that non trophoblastic tumors such as breast cancer with different patterns have an antigenic expression of HCG detected by immunohistochemistry.[1,2,3,4,5,6,7]

Agnantis[1] reported that 55.5% of breast cancer including lobular, ductal, medullary and mixed types and recurrence was strongly positive for β-HCG, 18.5% was weakly positive (±); 63.8% of the grade III tumors was negative whereas 81.21% of the grade II was positive, and the remaining was weakly positive (±). Lee et al.[2] reported in their immunohis-

tochemical study in a retrospective series of 233 invasive breast carcinomas that expression of tumor markers [carcinoembryonic antigen(CEA), human chorionic gonadotropin (HCG), placental lactogen, alpha-lactalbumin and pregnany-specific beta-1 glycoprotein (SP_1)] alone or in combination was not found to bear any significant relationship to prognostic indicators. They found that the frequencies of HCG reactivity in infiltrating duct carcinoma were 21% and 19% using the α-HCG and β-HCG antisera, respectively (Tufts University), and 15% using the β-HCG anti-serum (Memorial Hospital) while in in situ ductal carcinoma components, positively stained cells were found in 15%, 13% and 9% of cases, respectively.The positive reactivity in their cases was not associated with anaplasia or multinucleated cells. Wachner et al[5] found β-HCG reactivity in 16 carcinomas out of 129 carcinomas (12%). They described that the morphology of positive cells could not be distinguished from β-HCG negative cells, and only very few cells in most of the tumors contained β-HCG. These breast cancers included tubular carcinoma, mucinous carcinoma, lobular carcinoma and invasive ductal carcinoma. From the preliminary study of β-HCG expression in our 29 invasive breast cancers yielding 3.45% positivity, the positive cells were also tumor cells with single nuclei not multinucleated giant cells and the tumor did not exhibit hemorrhagic cut surfaces. In case of β-HCG expression with syncytial cell like tumor cells in invasive ductal carcinoma Saigo & Rosen[6] reported a case of 55-year-old woman who was treated 13 years previously for invasive ductal carcinoma of the right breast and presented with a new lesion in the left breast which showed histology of moderately well differentiated infiltrating ductal carcinoma merged with areas of anaplastic tumor having histological pattern of choriocarcinoma. The anaplastic areas showed positive immunostaining with β-HCG. Green[13] reported a case of mucoid carcinoma of the breast in which one of the axillary lymph nodes was infiltrated by tumor having the appearance of choriocarcinoma showing positive staining for HCG confined to the tumor giant cells (syncytial appearance).

Our case presented a breast mass with hemorrhagic cut surface, an uncommon macroscopic finding of breast cancer. These findings might raise a possibility of differential diagnoses of breast carcinoma with choriocarcinomatous features or coexisting breast carcinoma and metastatic choriocarcinoma or metastatic choriocarcinoma alone or vascular tumor. However the areas of the invasive ductal carcinoma in this case was distinct enclosing the area of HCG containing cells . The presence of merged areas between two cell types helped confirming the diagnosis of breast carcinoma with focal HCG expression. In case of coexisting breast carcinoma and metastatic choriocarcinoma, the typical area of breast carcinoma might be found and distinctly separated from the area of typical choriocarcinoma and there should be lack of transitional zone between these two neoplasms. In case of metastatic choriocarcinoma alone, the typical area of breast carcinoma would not be found. However, the combined breast cancers and metastatic choriocarcinoma could not be entirely excluded since there was a previous report about coexisting intraductal breast carcinoma and metastatic choriocarcinoma.[8] Gynecologic workup including prior history of having gestational trophoblastic disease, and serum HCG level in this case was done, to confirm the absence of coexisting choriocarcinoma. Follow up of this case should be done, any recurrence if present, serum level of β-HCG should be sought to see whether this tumor marker could be use as a prediction of recurrence in this particular case.

CONCLUSION

A hemorrhagic and poorly diffrentiated invasive ductal carcinoma with β–subunit HCG containing syncytiotophoblast-like giant cells in a 27-year-old Thai female was reported. Due to the hemorrhagic appearance of the tumor and the presence of β subunit–HCG expressing multinucleated tumor giant cells which were not common in invasive ductal carcinoma, metastatic choriocarcinoma should be excluded.

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