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Case Report

Expression of Beta-Human Chorionic Gonadotropin (Beta-HCG) in Transitional Cell Carcinoma

Yacur M[1], Marks EI[1], Sulseki J[1], Drabick JJ[3], Crist H[2] and Joshi M[3]*

[1]Department of Medicine, Penn State Milton S. Hershey Medical Center, USA

[2]Department of Pathology, Penn State Milton S. Hershey Medical Center, USA

[3]Division of Hematology-Oncology, Penn State Hershey Cancer Institute, USA

***Corresponding author:** Monika Joshi, Division of Hematology-Oncology, Penn State Hershey Cancer Institute, USA

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Abstract

This report describes the case of a 46 year-old woman with widely metastatic high-grade papillary transitional cell carcinoma of the bladder and very high concentration of circulating beta-human chorionic gonadotropin (β-HCG). The elevated level was incidentally detected on a preoperative urinary β-HCG test intended to screen for pregnancy approximately 15 months after her initial diagnosis. Follow-up testing of the patient's blood revealed marked elevation of serum β-HCG to approximately 24,000mIU/mL in the absence of an intrauterine pregnancy. Further review of a biopsy specimen obtained from a pulmonary lesion revealed prominent syncytiotrophoblastic elements that strongly expressed β-HCG, implicating it as the likely source. In this manuscript, we review the literature regarding β-HCG expression in urothelial carcinoma and other solid malignancies, paying particular attention to its possible roles as a growth factor and driver of immune tolerance for malignant cells. Potential implications for selecting treatment and monitoring response to therapy based on β-HCG levels, as well as possible directions for further research, are also discussed.

Introduction

Transitional Cell Carcinoma (TCC) or Urothelial Carcinoma (UC) is the most common primary malignancy of the bladder. Worldwide, bladder cancer is the 4th most common cancer in men but less common in women [1].

All TCC arise from the epithelial cells that line the urinary tract. Despite sharing this common cell of origin, these tumors are notoriously heterogeneous. Up to 25% display variant pathology, including squamous, glandular, sarcomatoid, or micropapillary features [2]. Rarely, TCC may also contain elements that strongly resemble choriocarcinoma. These cells appear macroscopically similar to the syncytiotrophoblastic cells ordinarily found in the placenta and may synthesize placental hormones, such as Human Chorionic Gonadotropin (HCG) [2].

HCG is a glycoprotein hormone that is comprised of an alpha and beta subunit. While the alpha subunit is common to several other hormones, such as TSH, LH, and FSH, the beta subunit (β-HCG) is entirely unique to HCG [3]. It is this subunit that is responsible for the specific functions of HCG in pregnancy, such as maintaining the endometrial lining via progesterone release and promoting immune tolerance of the developing fetus through the action of regulatory T cells [3]. Evidence also suggests that β-HCG facilitates angiogenesis through the transforming growth factor beta pathway [4].

While β-HCG is ordinarily produced in pregnancy, ectopic secretion has been observed in a variety of malignancies, including transitional cell carcinoma [5]. Despite this, we seldom monitor the levels of β-HCG in cases of TCC of the bladder. Below, we present a case of TCC of the bladder with syncytiotrophoblastic features that produced sufficient quantities of β-HCG to be measured in the urine and blood. This is followed by a review of the literature regarding ectopic β-HCG production in TCC with particular attention to its implication for treatment and prognosis.

Case Description

A 46 year-old woman with a past medical history of multiple sclerosis was diagnosed with high-grade papillary transitional cell carcinoma of the bladder in August 2013 as the result of a workup for lower urinary tract symptoms. She underwent Transurethral Resection of Bladder Tumor (TURBT) in September 2013. Pathology from this procedure revealed high grade TCC with micropapillary features. Extensive invasion into the muscular is propria and lymphovascular system was present. Tumor DNA sequencing by Foundation One revealed mutations of TP53, PIK3CA, and amplification of EGFR.

Shortly after undergoing the TURBT, this patient was referred to medical oncology for consideration of neoadjuvant chemotherapy prior to cystectomy. A staging CT was obtained and revealed a recurrent bladder mass in addition to diffuse lymphadenopathy and several pulmonary nodules that were later biopsy-proven as metastatic TCC. In December2013, she began combination chemotherapy with gemcitabine and cisplatin. Follow-up imaging after 3 cycles showed a mixed response to treatment, with partial response in the bladder but clear progression within the lung. She was then transitioned to dose-dense MVAC (methotrexate, vinblastine, doxorubicin, cisplatin), completing 4 cycles with radiographic improvement of pulmonary nodules and stable disease in the bladder. In September of 2014, the patient developed progression within the lung and was started on docetaxel as next line of therapy. After the first cycle, she developed metastatic foci in the brain, which was treated with gamma knife radio surgery. CT was obtained following the second cycle, showed concerns for progression in the liver and bone. Her systemic therapy was changed to pemetrexed. Shortly after receiving the first cycle, the patient developed worsening cough and dyspnea. To further evaluate

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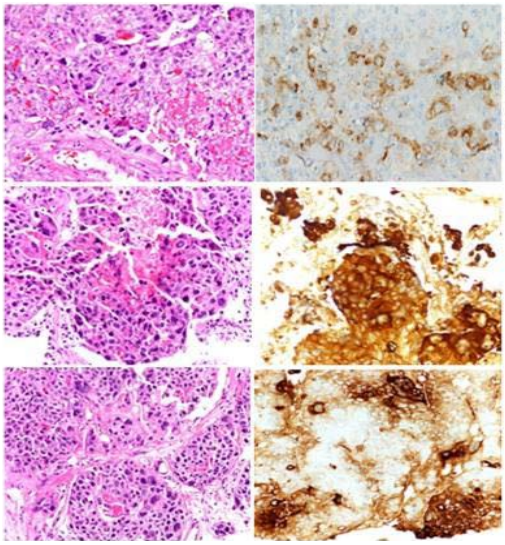

Figure 1: Image 1A- pathology slides: 1A Bladder trans-uretheral resection specimen showing mild HCG+ on IHC stain; Image 2A shows strong HCG+++ on IHC stain; Image 3A shows liver biopsy showing HCG++ stain.

this, CT imaging was obtained and showed substantial disease progression within the lung and large malignant pleural effusions. As a result, pemetrexed was discontinued in favor of irinotecan, and she was scheduled to undergo placement of a pleural drain. During the routine pre-procedure evaluation, the patient underwent urine qualitative β-HCG testing to screen for pregnancy. The test was positive, so a quantitative serum test was ordered. This demonstrated a markedly elevated level of serum β-HCG in excess of 24,000mIU/mL, with the reference range at our institution being 0-10mIU/mL for a non-pregnant patient. Pregnancy was ruled out by vaginal ultrasound. Seeking an alternative explanation for the elevated level of β-HCG, the patient's previous lung biopsy specimen was further evaluated. Under closer scrutiny, the presences of both mono- and multi-nucleated syncytiotrophoblasts were noted. These cells stained strongly positive for HCG on immune histochemistry, suggesting a transformation to choriocarcinoma like malignancy (Figure 1).

In light of these findings, the patient was started on VIP (etoposide, ifosfamide, cisplatin) with a dramatic decrease in serum-HCG to 1,028mIU/mL after 2 cycles (Figure 2). Radio graphically; her response to treatment was mixed, with roughly stable disease in the lung and mediastinum, but clear progression in additional metastatic sites, including the liver, bone, and brain. Due to this discordance, a liver biopsy was obtained, which confirmed the diagnosis of metastatic TCC. She also underwent repeat gamma knife radio surgery, treating six additional lesions. Next generation sequencing of her tumor was also obtained, showing mutations of PIK3CA E542K, TP53, and ARID1A.Retrospectively we did determine that she had tumor mutational burden of 66.597655193 mutations/Mb. Programmed Death –ligand 1 testing on the tumor was not done at that point. As this mutation profile suggested sensitivity to everolimus, we attempted to obtain this medication for the patient. Before the drug could be obtained, however, her quality of life deteriorated rapidly and she elected to discontinue chemotherapy in favor of hospice care. The patient died in the winter of 2015, approximately 18 months following her initial diagnosis. Given her history of multiple sclerosis, she was excluded from the immunotherapy clinical trials.

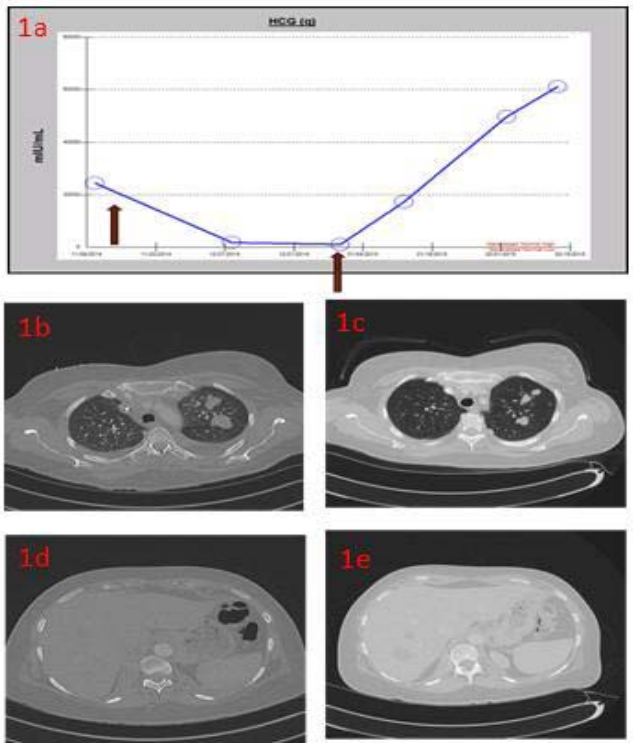

Figure 2: Correlation of HCG to radiological response: 1a represents graphical representation of levels of beta-HCG; 1st brown arrow represents -start of VIP (Nov 2014) and 2nd brown arrow represents -timeline after 2 cycles of VIP (Jan 2015). 1b and 1c represent CT scan depicting metastases in lung- pre (1b) and post 2 cycles of VIP (1c). 1d and 1e represents CT scan depicting liver pre (1c) and post 2 cycles of VIP (1e- showing liver metastases).

Discussion

This 46 year old woman was diagnosed with highly aggressive transitional cell carcinoma of the bladder that rapidly metastasized to the lung, liver, bone, and brain. She underwent multiple lines of systemic treatment before undergoing routine pre-operative quantitative urine and serum β-HCG testing to screen for pregnancy prior to pleural drain placement. This revealed an exceptionally high level of serum β-HCG. Once pregnancy was ruled out, we explored the possibility that her tumor was an ectopic source of serum β-HCG. Further analysis of this patient's pulmonary metastases demonstrated syncytiotrophoblastic elements and was strongly positive staining for β-HCG on immune histochemistry. Following this discovery, serum levels of β-HCG were trended as a tumor marker with mixed correlation to radiographic measures of disease burden.

The synthesis of β-HCG by malignant cells is a well-documented phenomenon. While most commonly associated with choriocarcinoma and other Gestational Trophoblastic Diseases (GTD), β-HCG production may be observed in a host of other cancers, such as prostate adenocarcinoma and urothelial cancer [6]. Venoy et al, demonstrated in their study that approximately 62% of muscle invasive urothelial cancers are positively stained for β-HCG, whereas only 24% of superficial urothelial cancers express β-HCG [5]. Mounting evidence suggests that the expression of β-HCG in

urothelial carcinoma indicates dedifferentiation towards a gestational trophoblastic phenotype. These tumors are often poorly differentiated and histologically similar to choriocarcinoma, containing cells that resemble syncytiotrophoblasts and cytotrophoblasts [7]. In addition to β-HCG, these tumors may also produce other trophoblastic substances, such as placental alkaline phosphates, human placental lactogen, and pregnancy specific beta 1 glycoprotein [7, 8]

While the role of β-HCG in cancer pathophysiology remains incompletely understood, it is thought to closely mirror the hormone's physiologic functions in pregnancy. During gestation, β-HCG promotes the development of immune tolerance to the fetus by expansion of T regulatory cells (Treg) which are immunosuppressive [9]. This is mediated, in part, by indoleamine-2, 3-dioxygenase-induced alterations in the activity of dendritic cells and recruitment of Treg cells to the maternal-fetal interface.

There is also evidence suggesting that β-HCG acts in an autocrine or paracrine fashion to stimulate the proliferation of bladder cancer cells [10]. This may occur through exploitation of the structural similarity between β-HCG, Transforming Growth Factor (TGF) and Platelet Derived Growth Factor (PDGF). In bladder cancer cell lines, exposure to HCG results in resistance to TGF-β-induced apoptosis, likely through HCG antagonism at the TGF-β receptor (TGF β-R) [11]. HCG is also believed to facilitate angiogenesis through activity at TGF-R [4].

Given these potential functions of HCG in blunting the immune response, resisting apoptosis, and facilitating angiogenesis, it is not surprising that HCG production in TCC often portends poor outcomes. Separate studies have found it to correlate with more advanced disease, early hematogenous spread, and decreased survival [5,12]. This relationship is robust and persists throughout the course of treatment for TCC. In a retrospective analysis of 235 patients with TCC, elevated serum β-HCG concentration following cystectomy and first or second line chemotherapy was found to be independently prognostic of reduced overall survival [12]. It is assumed that the intensity of β-HCG staining within tumors is greatest in areas of most rapid cellular proliferation.

Despite all of this, the survival data regarding germ cell tumors that secrete β-HCG is not quite as poor. However β-HCG secreting TCC cancers may be less sensitive to the traditional cisplatin-based chemotherapy treatments that are commonly employed against urothelial tumors, such as MVAC, gemcitabine plus cisplatin, or radiotherapy, and they may respond to regimens typically used to treat germ cell tumors. In one case report, combination therapy with etoposide and cisplatin followed by vincristine, methotrexate and bleomycin (EP + OMB) was utilized to good effect [13]. Recent studies have suggested that immunotherapy focused towards tumor associated antigens such as β-HCG may negate the ability of β-HCG to promote immune tolerance to cancer cells [14]. While this concept is still under investigation in β-HCG secreting tumors, the PD-1 (programmed death -1) directed monoclonal antibodies have already shown promise in TCC of the bladder and has gained Food and Drug Administration approval in metastatic bladder cancer [15,16]. Additionally, next generation sequencing of tumor can help identify targetable mutations, such as PIK3CA seen in our patient that may have therapeutic implications.

Furthermore, serial measurements of β-HCG may be a useful tumor marker in patients with hormone-producing TCC. Several case studies and a small observational study have documented that β-HCG levels often mirror radiographic measures of tumor burden [8,17]. It is therefore interesting that in this case, β-HCG measurements fluctuated independent of overall disease activity but reliably corresponded to the burden of metastatic disease within the lung. This could be the result of a founder effect, where the lung metastases were seeded by cells that produce β-HCG and other metastatic deposits arose from cells that did not synthesize the hormone. The presence of marked heterogeneity with respect to β-HCG expression within this patient's primary tumor makes such an explanation seem likely. A similar occurrence was noted by Cook et al. while evaluating the role of serum tumor markers as predictive biomarker in TCC [17]. While undergoing treatment, one patient experienced a complete response of pulmonary metastases and dramatic decrease in serum β-HCG levels despite progression elsewhere in the body. Although this may be a likely coincidence, future studies should seek to clarify possible reasons why peripheral levels of β-HCG may more accurately reflect tumor burden within the lung.

As this case illustrated, the expression of β-HCG in TCC is most commonly observed in tumors that are poorly differentiated. Such tumors are often highly aggressive and respond poorly to typical treatments that are used to treat TCC, but may be susceptible to regimens that are usually employed against germ cell tumors. In addition, newer treatment options such as targeted therapies or PD-1 pathway antibodies should be studied in this population. Additional studies are needed to further characterize β-HCG as a biomarker and to understand its use as a therapeutic target; however in patients with TCC of the bladder with tumors that secrete β-HCG, serially measuring its concentration within peripheral blood may be utilized in tandem with imaging to gain greater insight into the extent of disease activity, as well as prognosis of the disease.

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