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CASE REPORT / OLGU SUNUMU

Serum β-human chorionic gonadotropin as a tumor marker for malignant mesothelioma

Malign mezotelyomada bir tümör belirteci olarak β-human koryonik gonadotropin

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ABSTRACT

Peritoneal mesotheliomas are aggressive tumors arising from the peritoneal mesothelium. Tumor markers are biochemical substances produced by tumor cells due to the effect of malignant process. They can be used for screening, diagnosis, and predicting the prognosis. β–human chorionic β–human chorionic gonadotrophin (β-hCG), is a marker of germ cell tumors and trophoblastic diseases. In some reports, a relationship between β-hCG and other malignant diseases has been described. Hereby, we present a case of malignant peritoneal mesothelioma associated with elevated serum β-hCG levels. A 49-year-old man was admitted to the hospital with ascites. Peritoneal mesothelioma was diagnosed with peritoneal biopsy. During the treatment period, serum β-hCG levels were elevated together with disease progression and tissue samples stained positive for β-hCG. Rising levels of serum β-hCG due to disease progression can predict the response to treatment. If these levels were elevated at the beginning of the treatment, it may be a prognostic marker for peritoneal mesothelioma. Thus, β-hCG may be an important marker for prognosis or prediction of treatment for peritoneal mesothelioma patients.

Keywords: Mesothelioma, Human chorionic gonadotrophin, Tumor marker

ÖZ

Peritoneal mezotelyomalar, peritoneal mezotelyumdan köken alan agresif tümörlerdir. Tümör belirteçleri, malign olayların etkilerinden dolayı üretilen biyokimyasal maddelerdir. Kanser taramasında, tanısında, ya da kanser prognozunu belirlemek için kullanılabilir. β–human koryonik gonadotropin (β-hCG), germ hücreli tümörler ve trofoblastik hastalıklarda kullanılan bir belirteçtir. Bazı yayınlarda yazarlar, β-hCG'nin diğer malignitelerle de ilişkili olabileceğini belirtmişlerdir. Biz burada, serum β-hCG yüksekliği ile seyreden malign peritoneal mezotelyomalı hastamızı sunduk. 49 yaşında bir erkek hasta hastaneye assitle başvurdu. Peritoneal mezotelyoma tanısı periton biyopsisiyle kondu. Tedavisi devam ettiği sırada hastalık progresyonuyla birlikte serum β-hCG seviyesi yükseldi ve doku β-hCG ile pozitif olarak boyandı. Hastalık progresyonuyla artan serum β-hCG seviyeleri tedavi yanıtını predikte edebilir. Eğer peritoneal mezotelyomalı bir hastada serum β-hCG seviyesi tedavi başlangıcında yüksek olarak saptandıysa, prognostik bir belirteç olarak kullanılabilir. Tüm bunlardan dolayı, β-hCG'nin peritoneal mezotelyomalı hastalarda tedaviyi predikte edebilecek ve prognozu belirlemede yardımcı önemli bir belirteç olarak kullanılabileceğini düşünüyoruz.

Anahtar kelimeler: Mezotelyoma, Human koryonik gonadotropin, Tümör belirteci

Introduction

Mesotheliomas are rare and aggressive tumors arising from the mesothelium which derive from the lining of the coelomic epithelium in the embryo, the embryonic mesoderm. The pleura is the most commonly involved site (65-70%), while the peritoneum (30%), testicular tunica vaginalis and the pericardium (1-2%) are other sites of origin [1].

Tumor markers are biochemical substances produced mostly by tumor cells. They can be used for screening a healthy or a high risk population for the presence of cancer, to support the diagnosis of an already diagnosed patient with a specific type of cancer or to determine prognosis of an asymptomatic patient receiving cancer treatment [2]. β-human chorionic gonadotropin (β–hCG) and human placental lactogen (hPL) are

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the most common markers used for diagnosis and follow-up of germ cell tumors and trophoblastic diseases. In some studies, it was shown that β-hCG could also be used as a marker for tumors other than germ cell and trophoblastic origins. In a comprehensive review published in 1987, high β-hCG levels were detected in 20% of cancer patients whose tumors were not of trophoblastic or germ cell origin [3].

Malignant peritoneal mesotheliomas are aggressive tumors with no known tumor markers either for diagnosis or treatment. This case report presents a patient with malignant peritoneal mesothelioma who was admitted to our center with high serum β-hCG levels that increased with progression of the disease.

Case Report

A 49-year-old male patient was admitted with abdominal discomfort, pain and loss of appetite. His history was unremarkable. Physical examination of the abdomen revealed ascites and there were palpable masses in the abdomen. Except for an increase in blood urea nitrogen and creatinine, biochemical tests were normal. All tumor markers other than an incidentally detected increase in β-hCG (441mIU/ml) were within normal limits. Lactate dehydrogenase (LDH) and thyroid stimulating hormone (TSH) were also normal. His Eastern Cooperative Oncology Group performance status (ECOG PS) was 1.

Scrotal ultrasound revealed normal findings, and chest computed tomography (CT) did not demonstrate any mediastinal pathology. Abdominal magnetic resonance (MRI) imaging showed ascites with two papillary and irregularly shaped mass lesions around the descending colon, 6.5x3 cm and 3x3.5 cm in size. They appeared hypointense at T1W and hyperintense at T2W sequences. Diaphragmatic surfaces and paracolic areas also appeared to have some irregularities, probably due to minute lesions. Omental cake formation was also identified (Fig. 1).

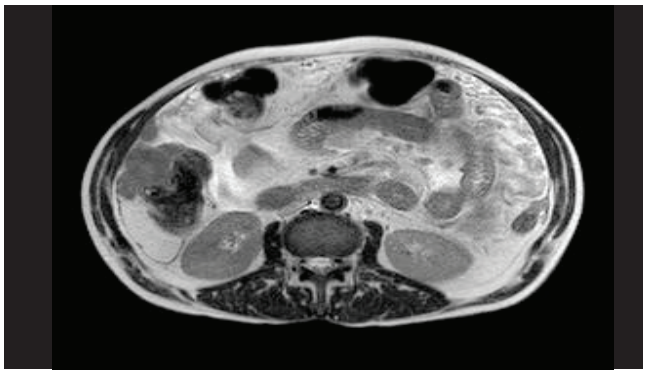

Fig. 1. Axial T2W MRI image of malignant peritoneal mesothelioma

Peritoneal biopsy under ultrasound guidance was performed and identified the lesions as a biphasic, epithelioid and sarcomatoid malignant mesothelioma. There were loosely bound, atypical epithelioid cells which had large polygonal cytoplasms, oval-round shaped nuclei and remarkable nucleoli, as well as atypical mesenchymal cells, scarce cytoplasms and spindle-like nuclei. Epithelioid cells stained positive with CK5-6 (cytokeratin), epithelial membrane antigen (EMA) and calretinin and negative with P53 and desmin. Partial membraneous staining was observed with Hector Battifora mesothelial cell antibody (HMBE-1) at the epithelioid side of the tumor. Both components of the tumor were stained positively with Wilm's tumor 1(WT1), with the stain being more prevalent in the epithelioid parts.

With these findings of deteriorating renal function and unfavorable ECOG PS, the patient was considered inoperable and chemotherapy with carboplatin AUC5, q21was considered. After the first cycle, the patient's ECOG PS increase to 2, his ascites increased and chemotherapy was ceased. At this stage, β-hCG level was 3944mIU/mL. Paraffin blocks were reconsidered for staining with β-hCG and human placental lactogen (hPL). Cytoplasms of the sarcomatoid components stained positive with β-hCG (Fig. 2) but there was no staining with hPL. The patient was deceased within five weeks of the diagnosis.

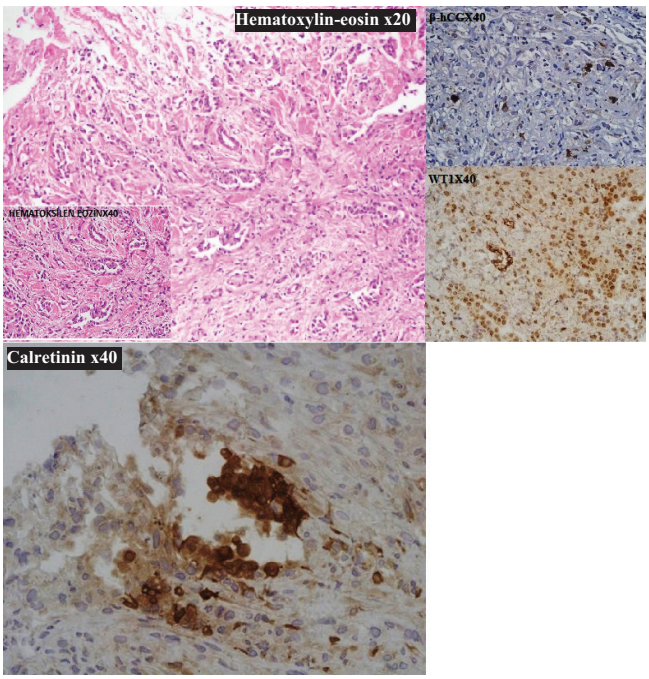

Fig. 2. Immun-stains; hematoxylin-eosin (H&Ex20), H&Ex40, β-hCGx40, WT1x40, Calretinin x40). Cytoplasmic immune reactivity with beta human chorionic gonadotropin (β-hCG) of peritoneal mesothelioma (magnification X4).

Discussion

Peritoneal mesothelioma is a rare tumor characterized by diffuse or locoregional involvement of peritoneal surfaces. In industrialized countries, the incidence is currently estimated to be between 0.5-3 cases per million for men, and 0.2-2 cases per million for women [4]. Currently, no biomarkers have been identified for use in the diagnosis and/or to follow-up of this entity. However, there are studies searching for a tumor marker, β-hCG in particular. In a study by Rich et al., high β-hCG levels were found in the ascitic fluid of malignant peritoneal mesothelioma patients, while their serum β-hCG levels were normal. It was hypothesized that β-hCG synthesized and secreted by the tumor cells into the ascites was rapidly cleared from the serum [5]. In another study, two patients with epithelioid pleural mesothelioma demonstrated elevated serum β-hCG levels and giant trophoblast-like cells in the tumor also stained positive for β-hCG. The authors suggested that this finding occurred as a result of 'disdifferantiation' of tumor cells into trophoblast-like cells [6]. Moreover, in their report concerning 201 cancer patients including four cases with malignant mesothelioma, Zimmerman et al., reported that serous effusions from two out of four mesothelioma patients (50%) and twenty-eight patients out of forty-four adenocarcinoma patients (64%) stained positive for hCG and mucin. They concluded that β-hCG was not clinically useful for effusion cytology because of a low specificity [7]. In another study by Ugurman et al., pleural and serum β-hCG levels and their ratio were evaluated for discriminating benign and malignant pleural effusions. Although there were no significant differences between benign and malignant groups in terms of β-hCG levels, the ratio of pleural fluid/serum β-hCG was significantly higher in the malignant compared to the benign group. Six mesothelioma patients of 27 cancer cases had the highest amount of fluid/serum β-hCG ratio (325 mIU/L in mesotheliomas compared to 55 mIU/L in other cancers) [8]. In his study, Gibbs et al., compared 29 mesotheliomas (12 epithelioid, 14 mixed epithelioid-sarcomatous, 3 sarcomatous) with 27 pulmonary adenocarcinomas and searched for immune staining with six different tumor markers including β-hCG and hPL in formalin-fixed pathology specimens. Only one out of 27 pulmonary mesotheliomas stained positive with β-hCG, but none with hPL. No information about the staining pattern in mesotheliomas was provided in this study [9].

Our patient had high serum β-hCG levels at presentation and his levels increased with disease progression. Biopsy specimen from the sarcomatous component with a spindle-like cytoplasm of the tumor also stained positive with β-hCG. Our patient was the first case with all of these findings (Table I).

Table I. Immune-staining and laboratory features of patients from various studies.

Author	Number of cases	Mesothelioma type		Serum β–hCG levels		Tissue staining			Fluid βhCG levels
		Pleural	***Peritoneal***	***Presentation***	***Disease progression***	β–hCG	α–hCG	***hPL***	
Rich, et al. [5]	1	_	1	<1μg/ml	_	_	_	_	+
Okamoto, et al. [6]	2	Epithelial	_	_	>9000IU/L	(+) cytoplasmic	(+) Cytoplasmic	(+)cytoplasmic	_
		Epithelial	_	22.670IU/L	7220IU/L with chemotherapy	(+)diffuse staining at giant cells	(+)diffuse staining at giant cells	(+)diffuse staining at giant cells	_
Zimmerman, et al. [7]	4	Pleural	_	_	_	_	_	_	(+) in 2 patients (% 50 positive)
Ugurman, et al. [8]	6	Pleural	_	55.67±132.84 (mean)	_	_	_	_	325±3.8
Gibbs, et al. [9]	29	12 purely epithelial 14 mixed Epithelial and sarcomatoid 3 purely sarcomatoid	_	_	_	26/1+	_	27/0	_
This study	1	_	Peritoneal mixed epitheliod and sarcomatoid	441mIU/mL	3944.55mIU/mL	+	Unknown	_	_

β-hCG (beta-human chorionic gonadotropin), α-hCG (alpha-human chorionic gonadotropin), hPL (human placental lactogen), IU/L (international unit per liter)

The increase in serum β-hCG levels (from 441 to 3944 mU/mL) during disease progression could be a predictor for treatment response and/or a prognostic marker for mesothelioma since the marker was high also at presentation. High β-hCG levels were found to be correlated with a poor prognosis of the disease [10]. Okamoto et al., observed a decrease in β-hCG levels after chemotherapy [6].

We hypothesize that mesothelioma cells differentiate into cells which secrete β-hCG or β-hCG-like glycoproteins. There are some studies concerning mesothelial cell differentiation, in support for our hypothesis. In one of these studies, mesothelial cells were observed to have a pluripotent stem cell-like feature with the capacity to differentiate into cells of different phenotypes, and progenitor-like mesothelial cell lineages were also demonstrated. As an example, mesothelial cells were shown to express increasing levels of alkaline phosphatase and form bone-like nodules [9]. In our case, even though the sarcomatoid component of the tumor did not contain choriocarcinoma cells, it stained positive for β-hCG.

Conclusion

Considering that nontrophoblastic tumors might stain positive for β-hCG in up to 20% of the patients [[3], our case is the first case in whom serum β-hCG levels increased with disease progression and the peritoneal mesothelioma stained positive for β-hCG. This is possibly related to the sarcomatoid component of the tumor.

β-hCG may be a marker for treatment prediction, and disease prognosis for mesothelioma patients. The low correlation between serum/tissue β-hCG levels may be due to tumor subtype (epithelioid or sarcomatoid), transfer problems from tissue to blood (endothelial barrier or clearance before transfer to blood), or destruction at blood. As a result, it is clear that more studies are required to determine the relation between β-hCG and mesothelioma.

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