CASE REPORT

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A Novel Tumor Marker for Anaplastic Lymphoma Kinase (+) Lymphoma: Beta-Human Chorionic Gonadotropin

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ABSTRACT Beta-human chorionic gonadotropin (beta-hCG) is an important tumor marker for germ cell tumors. Interestingly in some cases with lymphoma increased beta-hCG levels were detected. The association of beta-hCG expression and mortality in those rare cases isn't well established. We will present a 40-year-old male who was diagnosed with anaplastic large cell lymphoma with increased beta-hCG levels. Brentuximab-Vedotin monotherapy was started. The beta-hCG level decreased tremendously after initiating of chemotherapy and remained so in the follow up with consecutive chemotherapy cycles. After the treatment 18F-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) showed showed tremendous decrease in FDG uptake in comparison to previous PET-CT findings. These findings are correlant with the beta-hCG levels before and after treatment. A brief report of the possible pathophysiological mechanism of beta-hCG expression in lymphoma patients will be presented further.

Keywords: Lymphoma; beta-human chorionic gonadotropin; brentuximab; prognosis

Beta-human chorionic gonadotropin (beta-hCG) expression is usually observed in germ cell tumors with trophoblastic differentiation. Serum beta-hCG level is a well-established marker for the follow-up of patients with germ cell tumors.[1] To our knowledge, beta-hCG expression in anaplastic large-cell lymphoma has only been reported once in a pediatric patient without elevation of serum beta-hCG.[2] In addition, there have been a few cases of primary mediastinal large B-cell lymphoma with increased serum beta-hCG levels.[3] Several studies have suggested that beta-hCG expression and increased serum beta-hCG levels are related to poor prognosis. Herein, we present a case of a patient diagnosed with anaplastic large-cell lymphoma with increased serum beta-hCG levels. Informed consent was obtained from all patients.

CASE REPORT

A 40-year-old male with an unremarkable medical history was admitted to the hospital because of left scapular pain and dyspnea. Clinical examination revealed pretibial edema and bilateral rales. The patient had dyspnea and tachypnea. Chest computerized tomography (CT) revealed consolidation and nodular infiltration of the lungs. Subsequently, a positron emission tomography-CT (PET-CT) confirmed the presence of extensive metastatic infiltration of the lungs and showed the involvement of multiple bones and lymph nodes (above and below the diaphragm). Transthoracic lung biopsy was concordant with anaplastic lymphoma kinase (ALK) positive anaplastic large cell lymphoma (ALK+ALCL). Upon diagnosis, cyclophosphamide-doxorubicin-vincristine-prednisolone chemotherapy was initiated. Because of vertebral bone metastasis, the patient underwent radiotherapy. A partial response was documented on interim PET after 4 cycles. At the end of 8 cycles of chemotherapy, a control PET-CT revealed extensive maxillary, mandibular, hyoid bone, bilateral supraclavicular and infraclavicular, right axillar, right paravertebral, mediastinal, and abdominal lymph node

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infiltration. Furthermore, liver, subcapsular spleen, and bone infiltration were detected. In the lungs, multiple lymph nodes with enhanced 18F-fluorodeoxyglucose (FDG) uptake and increased reticulonodular infiltration were observed. The patient was admitted to the hospital with dyspnea and fever. Blood cultures showed no bacteriemia; however, elevated levels of acute-phase reactants were observed. Therefore, preemptive moxifloxacin treatment was initiated. Although the chest CT was not suggestive of pulmonary thromboembolism or pneumonic infiltration, pathologically increased mediastinal and hilar lymph nodes, bilateral multiple metastatic nodular infiltration, bilateral pleural effusion, and lymphangitic infiltration were detected. To confirm the diagnosis, a bone marrow biopsy was performed, which revealed no infiltration. In addition, an axillary lymph node biopsy revealed no evidence of lymphoma. Two consecutive coronavirus disease-2019-polymerase chain reaction tests yielded negative results. The initial serum beta-hCG level was 17.39 mIU/mL (Figure 1). Pituitary function test results were within the normal range; hence, the elevation of beta-hCG level due to hypogonadotropic hypogonadism was excluded. Scrotal ultrasonography revealed no testicular tumor. During the follow-up, the patient developed hypotension, tachypnea, need for supplemental oxygen, and elevated lactate levels. Moxifloxacin was broadened to piperacillin-tazobactam and clarithromycin therapy, and intermittent non-invasive mechanical ventilation (NIMV) was performed. Methylprednisolone therapy (100 mg) was administered for 3 days to alleviate dyspnea and tachypnea related to metastatic infiltration. The serum beta-hCG level increased to 43.68 mIU/mL. After the pulmonary symptoms resolved, brentuximab-vedotin monotherapy was administered because of the clinical progression of the lymphoma. The patient's clinical status improved rapidly, and the need for NIMV and oxygen supplementation ceased. Serum beta-hCG level decreased to less than 120 mIU/mL. The pathological specimen of the lung biopsy was stained for beta-hCG; however, aberrant beta-hCG expression was not detected. Control PET-CT was performed immediately after the treatment. FDG uptake in the mediastinal and axillary lymph nodes and spinal vertebrae was decreased (Figure 2). The patient was discharged after complete relief of symptoms. Autologous bone marrow transplantation was planned after 3 cycles of brentixumab-vedotin.

DISCUSSION

Beta-hCG is a glycoprotein consisting of 2 subunits: alpha and beta. As a tumor marker, it is primarily produced by germ cell tumors with trophoblastic differ-

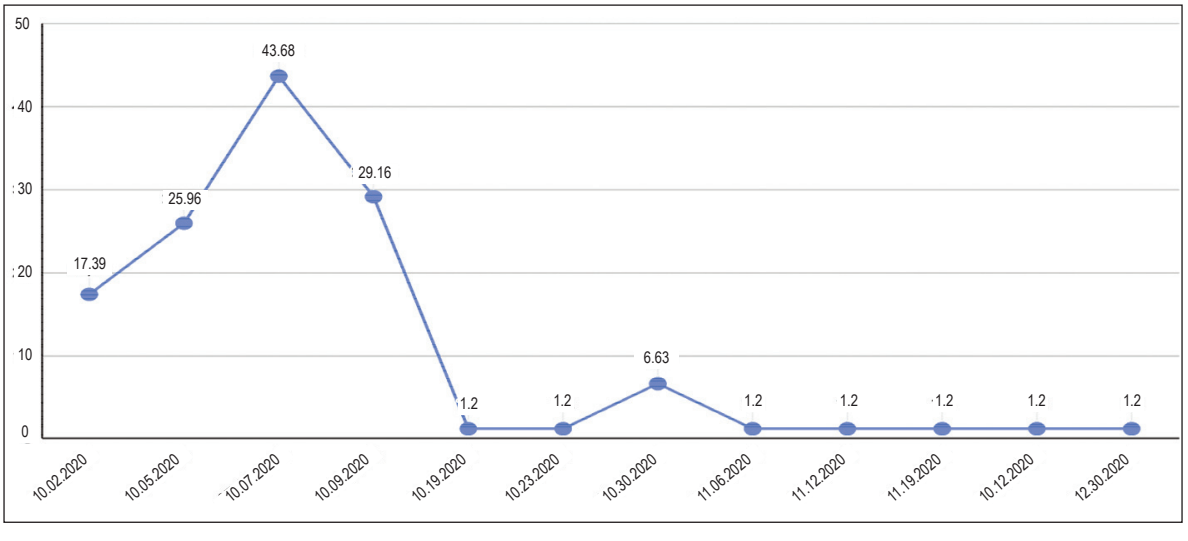

FIGURE 1: The beta-hCG level decreased tremendously after initiating of chemotherapy and remained so in the follow up with consecutive chemotherapy cycles. Beta-hCG: Beta-human chorionic gonadotropin.

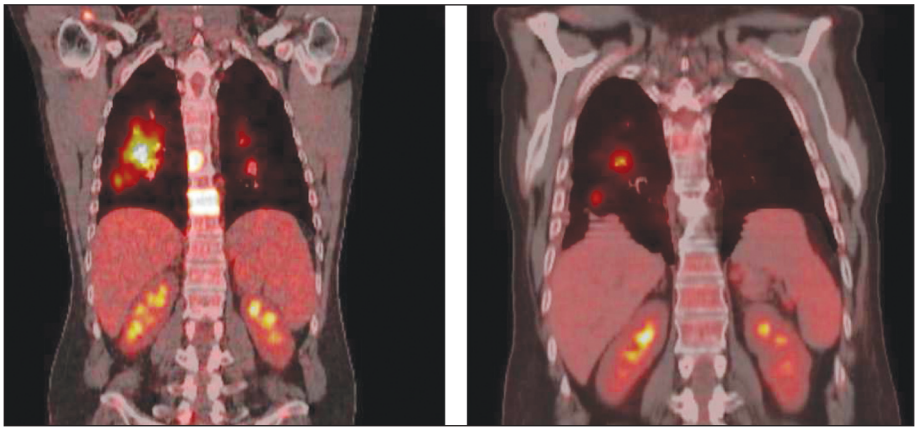

FIGURE 2: PET-CT before treatment (left) and after treatment (right). The FDG uptake decreased significantly after treatment. These findings are correlant with the beta-hCG levels before and after treatment.
PET-CT: Positron emission tomography-computed tomography; FDG: 18F-fluorodeoxyglucose; Beta-hCG: Beta-human chorionic gonadotropin.

entiation and is associated with poor prognosis.[4] Secretion of beta-hCG has also been reported in the colon, stomach, small intestine, breast, lung, bladder, prostate, and thymus cancers.[5-8] Beta-hCG is rarely expressed in hematologic malignancies.[3] However, some cases of lymphoma, such as primary mediastinal large-cell lymphoma, anaplastic large-cell lymphoma, adult T-cell lymphoma, and elevated serum levels of beta-hCG have been reported.[2,3] ALK+ALCL is a rare subtype of non-Hodgkin's lymphoma with CD30 + positivity. ALK+ALCL exhibits translocation in chromosomes involving the expression of a protein called ALK. The t(2;5) translocation aligns ALK to a largely expressed gene, nucleophosmin.[9] ALK+ALCL is usually observed in young adults, with male predominance. ALK+ALCL usually has a satisfactory outcome after appropriate chemotherapy. A pediatric patient with ALK+ALCL, who presented with an inguinal mass and raised beta-hCG levels, died 8 months after diagnosis, with no response to chemotherapy.[2] Furthermore, one of the two cases diagnosed as primary mediastinal large B-cell lymphoma with beta-hCG expression showed a poor response to the intensive chemotherapy regimen.[10] The main mechanism underlying beta-hCG expression in patients with lymphoma remains unclear. One explanation is that it might occur due to chromosomal translocation or aberration of the gene that encodes beta-hCG, which is located on the long arm of chromosome 19. Some ALCL cases express t(2,19) mutations; therefore, this gene can be overexpressed, resulting in increased beta-hCG production.[11] However, there is a need to determine the underlying mechanism.

In conclusion, increased serum beta-hCG levels or beta-hCG expression is associated with a worse prognosis in ALK+ALCL patients. Our patient had elevated serum beta-hCG levels before treatment. After treatment with brentuximab-vedotin, serum beta-hCG levels returned to normal. Careful and extensive investigations must be performed in patients with aberrant expression of beta-hCG to differentiate it from germ cell tumors and other malignancies. Our report suggests that there is a need for further research on ALK+ALCL to clarify whether there is a correlation-between increased serum beta-hCG levels with or without beta-hCG expression and poor prognosis.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Serkan Akın;* ***Design:*** *Kenan Moral;* ***Control/Supervision:*** *Kenan Moral;* ***Data Collection and/or Processing:*** *Dilan Yağmur Kutlay, Esra Seyhan;* ***Analysis and/or Interpretation:*** *Kenan Moral;* ***Literature Review:*** *Dilan Yağmur Kutlay, Esra Seyhan;* ***Writing the Article:*** *Kenan Moral, Dilan Yağmur Kutlay, Esra Seyhan;* ***Critical Review:*** *Serkan Akın.*

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