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LETTERS TO THE EDITOR

Breast sarcoma: A rare malignancy

Dear Editor,

Primary sarcomas of the breast are extremely rare neoplasms with <0.1% of all malignant tumors of the breast and <5% of all sarcomas [1,2]. Since breast sarcomas are originated from connective tissue they have no connection whatsoever with breast adenocarcinomas. The aim of this communication was to retrospectively evaluate breast sarcoma cases. We searched the databases of 2837 patients who were diagnosed with breast cancer at Hacettepe University Oncology Hospital between 1989-2013. Ten patients with breast sarcoma were identified (0.035 % of all breast malignancies).

The median patient age was 47 years (range 26-76). Tumor histologic subtypes were 4 phyllodes tumors, 2 carcinosarcomas, 1 periductal sarcoma, 1 angiosarcoma, 1 spindle cell sarcoma and 1 malignant mesenchymal tumor. Fifty percent of the patients were premenopausal and 50% postmenapausal. Median tumor size was 6.5 cm (range 3-16).Only 2 patients had nodal involvement. Three of the 4 patients whith known hormone receptors and HER-2 status were triple negative and 1 was ER(-) PR(+) HER-2 (-). Only 1 patient had metastasis at diagnosis. Treatment was modified radical mastectomy (N=8), and breast conserving surgery (N=2). Eight of the 10 patients received adjuvant chemotherapy and only one patient received hormonal therapy because of PR positivity. Different adjuvant chemotherapy regimens including cyclophosphamide and anthracyclines were administered. Seven patients received adjuvant radiotherapy. Median follow up time was 14 months, during which 4 patients developed metastasis/recurrence and 3 patients died.

In conclusion, breast sarcomas are a rare form of breast cancer. Their size is greater compared with adenocarcinomas and rarely involve the lymph nodes.Treatment includes surgery and radiotherapy .The rarity of this pathology led to a lack of consensus on the optimal treatment approach [3]. Multi-institutional studies with larger numbers of patients are needed for understanding the biology and plan newer, more effective treatment modalities for these rare breast tumors.

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Is programmed cell death ligand-1 expression required for optimal response to anti–PD-1 antibody in cancer

Dear Editor,

Programmed cell death 1 (PD-1), an inhibitor checkpoint receptor which is expressed by activated T cells, strongly mediates immunosuppression. The PD-1 receptor binds to two ligands for activity: PD-L1, which is upregulated in many cancer types, is the main responsible ligand for immunosuppression; and PD-L2 which is only expressed by macrophages and dendritic cells. Thus, interference with PD-1 or its ligand PD-L1 can increase the antitumor immunity [1]. Both mature and ongoing studies reveal the importance of human monoclonal antibodies anti-PD-1 and anti-PD-L1. The aim of this communication was to emphasize which patients can benefit from targeting PD-1 receptor or PD-L1.

In a multicenter phase I trial, Topalian and colleagues reported that the anti-PD1 antibody nivolumab produced objective responses in non-small cell lung cancer (NS-

CLC), malignant melanoma and renal cell cancer [1]. In this study, response rates were 18, 28 and 27% in NSCLC, malignant melanoma and renal cell cancer, respectively. According to the intra-tumoral PD-L1 expression, objective responses were significantly higher in the PD-L1 expressing group compared to PD-L1 negative group with nivolumab in cancer patients (36 vs 0.0%, p=0.006). In another study, Hino et al. reported that overall survival (OS) rate of the high PD-L1 expression group was significantly lower than that of the low-expression group and multivariate analysis demonstrated that PD-L1 expression was an independent prognostic factor for melanoma [2]. Kronig et al. had found a positive correlation between PD-L1 expression on melanoma cells and OS [3]. Also in this study it was shown that PD-1 expression on melan-A-reactive T cells increased during progression to metastatic disease.

In contrast to these studies, Gadiot et al. reported no correlation between OS and high expression of PD-L1 in metastatic melanoma [4]. In this study also, no relevant PD-L1 correlation was found between the primary tumor and metastases. In a recently published study, Wolchok et al. reported that objective responses were not significantly different according to the PD-L1 positivity with nivolumab plus ipilumumab combination in advanced melanoma [5]. Since in this study the anti-PD1 monoclonal antibody nivolumab was used together with ipilimumab, no comment about the acitivity of nivolumab in relation with the PD-L1 positivity could be done. In another phase I trial, lambrolizumab anti-PD1 antibody, has shown impressive antitumor activity in advanced melanoma, but no biomarker analysis of PD-L1 was reported in this study. To better understand which patients will most likely benefit from lambrolizumab it is essential and critical to identify patients who are likely to benefit.

The role of PD-L1 expression by cancer cells remains controversial, and future clinical studies should focus on antibody validation in respect to disease progression. On these grounds, it would be interesting to know the tumor responses with anti-PD1 antibodies according to the PD-L1 expression.

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Prolonged use of bevacizumab may cause extensive coronary artery thrombosis

Dear Editor,

Bevacizumab, a recombinant monoclonal antibody against vascular endothelial growth factor (VEGF), is currently used to treat metastatic cancers of the colon, rectum, kidney, breast, lung and recurrent glioblastoma.

In 2009, FDA approved bevacizumab as a single agent for patients with glioblastoma, with progressive disease following prior therapy based on two single-arm studies. Today, bevacizumab is used in both metastatic colorectal cancers and progressive glioblastoma patients until disease progression or unacceptable toxicity. However, prolonged use of continuation of bevacizumab can cause life-threating side effects which includes proteinuria (35% of patients), hypertension (15-30% of patients), gastrointestinal perforation (5-7% of patients), and arterial emboli (0.5-1% of patients) [1].

We report herein a patient with extensive coronary thrombosis being on prolonged bevacizumab treatment, a possible side effect not frequently reported previously.

A 39-year-old male with no history of smoking and co-morbid diseases was diagnosed with a temporo-parietal glioblastoma multiforme. Gross total excision was performed in April 2010. He received adjuvant chemoradiotherapy with temozolomide. Unfortunately, the disease progressed in August 2010, and bevacizumab (10 mg/kg ; total 800 mg/day) was initiated on a bi-weekly schedule. He was lucky enough not to develop progression during 2.5 years on bevacizumab. However, he started having angina pectoris and was admitted to the department of

Cardiology in June 2013. Laboratory analyses revealed fasting blood glucose 88mg/dl (range 70-110), creatinine 0.98mg/dl (range 0.5-1.5), HDL 40mg/dl (range 35-65), LDL 146mg/dl (range 130-159), and uric acid 5.5mg/dl (range 4-7). Coronary angiography demonstrated severe and long stenosis of the intermediate artery and stenosis of the left anterior descending and diagonal branch. Right coronary artery was also found to be totally occluded. At the time of this writing, the patient was being prepared for bypass surgery.

Bevacizumab treatment has been associated with arterial thrombotic events (ATE). According to the meta-analysis of randomized controlled trials by Ranpura et al. [2] high grade arterial thromboembolic events occurred in 2.0% and cardiac ischemic events in 1.5%, with a relative risk of high grade cardiac ischemia of 2.14, compared to controls. Another meta-analysis conducted by Schutz et al. [3] showed that overall relative risk for ATE with bevacizumab-based therapy vs control was 1.46 (p=0.007).

As bevacizumab is used extensively in routine cancer treatment, it is important for physicians to recognize the risk of ATE including cardiac ischemia associated with bevacizumab therapy. Further studies are recommended to determine risk factors and underlying mechanisms for risk reduction.

Based on a significant clinical benefit, anti-angiogenic drugs such as bevacizumab, sunitinib, sorafenib, and pazopanib which target the VEGF receptor, are being used increasingly in cancer treatment. We think that, both oncologists and cardiologists may be facing more and more arterial complications of bevacizumab with its prolonged use. Even in the absence of risk factors for coronary artery disease, prolonged use of bevacizumab may cause thrombosis in coronorary arteries and this should be kept in mind.

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Radiosensitization effect of vemurafenib

Dear Editor,

A 32-year-old female patient with metastatic malignant melanoma applied to our clinic with severe pelvic and right shoulder pain. She was initially diagnosed with melanoma in 2011. After 4 cycles of temozolomide her disease progressed to stage IV, as a PET-CT scan showed multiple metastases in the liver, lung, abdominal lymph nodes and bones. She was found to have a mutated BRAF and vemurafenib, which is a selective BRAF inhibitor, was initiated at a dose of 960 mg. Because of pain unresponsive to analgesics, palliative radiotherapy was delivered to right shoulder and pelvic and femoral bones (8 Gy in one fraction). Photon energy of 6 MV was used with two parallel opposed fields.

Five days after radiotherapy the patient developed pruritic ertyhematous lesions limited to the skin of her irradiated areas (Figure 1). The lesions had an inflammatory appearance, however she did not have infection. Meanwhile, the patient was on dexamethasone (2mg/day) due to arthralgia. Her dermatitis subsided after topical moisturising lotion application without interrupting vemurafenib treatment. Three months later she was found to have both clinical and PET-CT metabolic response to treatment.

Our patient developed radiodermatitis while she was on vemurafenib. Cutaneous side effects of vemurafenib are well known [1] and are strongly associated with UV-A dependent phototoxicity. However, the radiosensitivity with the concomitant use of vemurafenib is very infrequent.

Camidge et al. emphasized the confusion between radiation recall, radiosensitization and acute radiation reactions [2]. Radiation recall is defined as an inflammatory reaction that is developed in a previously irradiated area after the administration of certain drugs [2]. They suggested that skin reactions caused by drugs administered less than 7 days after radiotherapy should be considered as radiosensitization.

Boussemart et al. reported dermatitis on previously irradiated skin areas in 2 patients that received subsequent vemurafenib one and 23 days after the last radiotherapy session [3]. Vesiculobullous skin reactions were observed 7-10 days after the administration of the drug. The patients continued their treatment with the addition of topical steroids.

Our patient started receiving vemurafenib one day before radiotherapy. She developed radiodermatitis 5 days after radiotherapy. We did not stop the oral treatment but add topical moisturising lotion to relieve the symptoms of the patient. The skin lesions responded well and subsided with the application of the lotion. However, she was also on low dose steroid treatment, thus this might also affect the calming down of the skin lesions. The use of Naranjo probability scale revealed it was probable that vemurafenib may indeed be responsible for erythematous lesions limited to the skin of her irradiated areas [4].

The radiosensitizing effect of vemurafenib should be known and the patient should be followed up for the possibility of radiation induced dermatitis after treatment. It is not a reason for discontinuing vemurafenib therapy.

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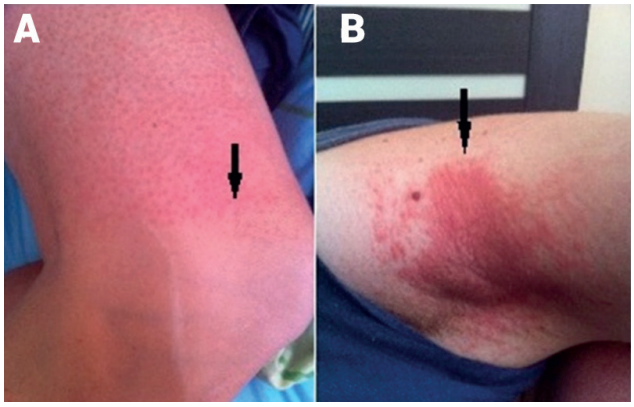

Figure 1. The patient's skin in the femoral (**A**) and axillary (**B**) region, 5 days after irradiation.

Being a medical oncologist near the war area

Dear Editor,

Syria is located in the south of Turkey, being its neighbor with the longest borderline. Syria has been frequently on the agenda both in Turkey and in the world due to the civil war for the last two years. A great number of Syrian citizens are being hosted in neighboring countries with security concerns because of the ongoing war. According to recent official reports Turkey is hosting more than 500,000 refugees who suffer with health problems along with the destructive economic, social, cultural problems of the war. The Turkish government provides healthcare services for refugees settled in southern cities close to Syria including Hatay, Adana, Urfa, Kahramanmaras, Gaziantep and those who stay in refugee camps in these areas. However, it is most difficult when it comes to providing healthcare services to cancer patients. Treatments of patients whose disease is newly diagnosed or known before are being provided in the oncology centers of the said cities. There are hundreds of Syrian patients under control in these centers. However, as cancer patient management becomes more sophisticated and sensitive today, treatment of these patients is getting more difficult since we try to provide support just within the capacities of the Turkish state for these patients who lack social security. We are making great efforts not to leave them helpless against their disease since they have already been desperately suffering from the war. We even have to provide cisplatin, the main cytotoxic agent to some of these patients, especially to those who entered the country illegally, from our own budget due to financial inability of these patients and their relatives. Most of the times, we can only administer basic treatment protocols, targeted and tailored therapy being nothing more than a dream. This problem poses troubles for the oncology experts who undertake the treatment. The desperation of these patients and their relatives in the 21st century saddens us first as human beings, then as physicians.

We believe that we can provide solutions to these problems by addressing them all together in a global sense and empathize with each individual's troubles and inabilities in our globalizing world. We would like to hear from our colleagues their ideas and recommendations for realistic solutions.

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Thymic carcinoma: what after disease progression?

Dear Editor,

Thymic carcinoma is a rare but lethal malignancy which accounts for 5% of all thymic neoplasms. It is more commonly seen in the 5th decade of life. The majority of thymic carcinoma patients present with locally advanced or metastatic disease at diagnosis, which confers a median overall survival of 2 years [1]. The commonest subtype of thymic carcinoma in Western countries is the poorly differentiated non-keratinizing squamous cell carcinoma [2].

No established treatment guidelines exist after disease progression. However, approximately 50-70% of patients with locally advanced or metastatic thymoma are candidates for second-line therapy [3]. The low incidence of squamous thymic carcinoma has precluded it from large phase II or III trials. Data on second-line chemotherapy derives, therefore, mostly from case series.

A phase II trial [4] evaluated the doublet capecitabine-gemcitabine in heavily pretreated thymoma patients. Among the 3 patients with thymic carcinoma (out of 12 included in the study) 1 experienced partial response, 1 stable disease and 1 progressive disease. The rationale behind using this doublet is the high efficacy of these drugs in squamous cell tumors and the cumulative experience gained from their effective use in cancers of other origins.

Herein, we present a 63-year-old Caucasian woman diagnosed with a grade II squamous cell thymic carcinoma with disease extending from the thymus to the manubrium, involving mediastinal lymph nodes and pulmonary nodules bilaterally. As such, it was assigned to stage IVb according to the Masaoka classification [5]. From June until October 2010 she received 6 cycles of first-line carboplatin and paclitaxel based chemotherapy, achieving a short-lasting partial response, at the cost of grade III peripheral neuropathy. She was then treated with 6 cycles of epirubicin with cyclophosphamide until February 2011, which stabilized the disease. Dramatic disease progression was observed in November 2011 during a regular follow-up with increased number and size of the pulmonary lesions, presence of bilateral pleural effusion, progression of mediastinal lymph node invasion and presence of liver metastases (Figure 1A). Taking into consideration the optimal performance status and the willingness of the patient to continue therapy we offered her third-line chemotherapy based on capecitabine 650mg/m^2 po bid for 14 consecutive days with a wash-out week, along with gemcitabine 1000mg/m^2 IV administered on days 1 and 8 in a 3-week cycle started in December 2011 [4]. A dramatic disease response was seen after the 3rd cycle with all lesions showing major regression in number and size. Further disease response has been constantly observed ever since (Figure 1B). Notably, the regimen was well tolerated. Due to financial constraints by the patient's insurance provider, though, therapy was discontinued in August 2012. The patient totally received 12 cycles of capecitabine with gemcitabine with major disease response. Not only was the regimen highly active and tolerable, but its efficacy was also long-lasting. We attribute the activity of this regimen to the squamous subtype histology of the neoplasm and stress the importance that therapies be tailored to histopathological subtypes.

Interestingly, the patient was subsequently treated with two more chemotherapy lines with etoposide-ifosfamide and docetaxel-gemcitabine doublets showing a partial response to the latter regimen. She is currently on sunitinib and is leading an active life.

Given the literature scarcity and clinicians' need for more data about this tumor subtype, we believe that information derived from each single case should be shared.

In conclusion, the combination capecitabine-gemcitabine was shown to be effective. We believe this gives scope for further studies in order to confirm its efficacy and potentially use this combination earlier in the treatment planning.

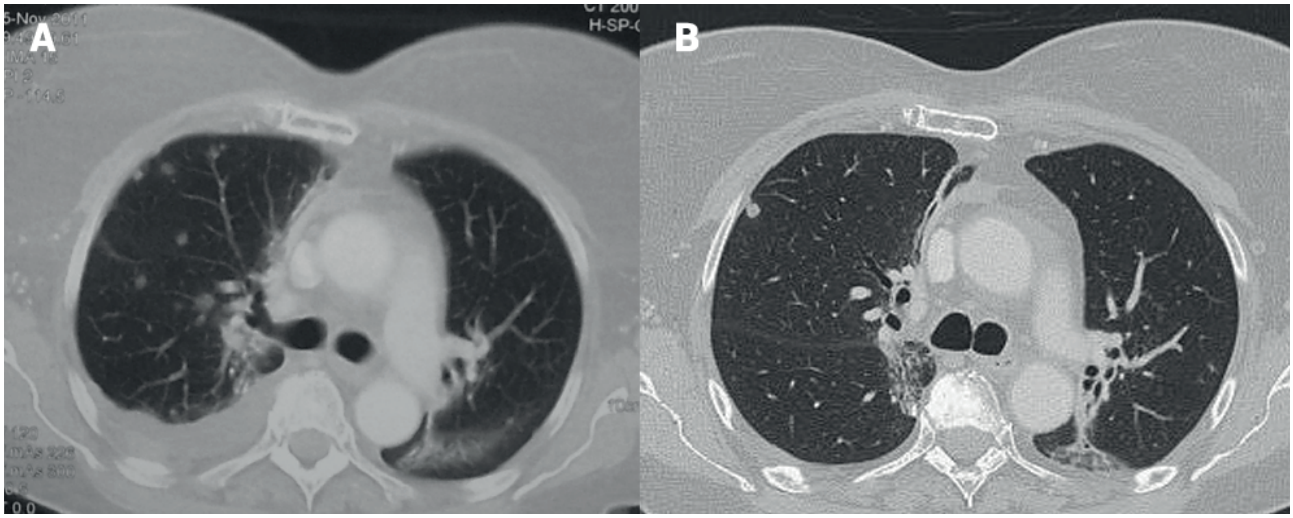

Figure 1. A: multiple lung metastases,mediastinal nodal disease,bilateral pleural effusion. **B:** impressive disease response.

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Amelanotic melanoma: a case with chr 9 monosomy

Dear Editor,

Melanoma is a common malignancy of melanocytes, the pigment-producing cells [1]. It is located predominantly on the skin, but it can also be found in the nervous system, the gastrointestinal tract, the eyes, the ears as well as the oral and genital mucous membranes [2]. The incidence of melanoma has increased (more than tripled) in the white population during the last 20 years, and melanoma currently is the 6th most common cancer in the United States. Melanoma accounts for only 4% of all skin cancers; however, it causes 79% of all skin cancer–related deaths worldwide and only 14% of the patients with metastatic melanoma survive for 5 years [3]. Amelanotic melanoma is not a common type, accounting for less than 5% of melanomas. Amelanotic melanoma is clinically presented as a nonpigmented, pink or flesh-colored nodule, occurring most commonly as nodular melanoma subtype, melanoma metastasis or rarely, lentigo maligna melanoma [4]. It is usually differentiated from basal cell or squamous cell carcinoma, pyogenic granuloma or hemangioma [5].

A 75-year-old male with Fitzpatrick's type-II phototype was admitted in our department because of the development of a giant mass on the left temporal area of the head. The lesion was a slowly progressive, neglected, giant, exophytic mass of 15-month duration (Figure 1). The tumor was approximately 10cm in diameter, well-defined, erythematous and was bleeding easily after minor trauma. His general health was good and no pain or pruritus was reported. The patient's physical examination was normal. According to his past medical history, he was a farmer with not known family history of skin cancer but with several past episodes of intermittent, intense sun exposure and sunburns. The patient also stated that he had used topical antibiotics unsuccessfully during the first weeks of the tumor development without medical advice. The clinical picture of this lesion was similar to a large squamous cell carcinoma.

An incisional biopsy was performed from the margin of the tumor and the histological examination revealed atypical melanocytes seen on the basal layer of the epidermis extending down the hair follicles. Focal ulceration was also present. The epidermis was atrophic with loss of rete ridges. There was cytologic atypia with presence of mitoses, especially deep in the dermis. The findings were compatible with a Breslow depth >4mm and Clark IV level amelanotic melanoma. Extended immunohistochemical analysis was also performed (Figure 1, inlet) and the diagnosis of amelanotic melanoma with loss of p16 protein expression and also with chromosome 9 monosomy (provided by chromogenic in situ hybridization) - a very rare genetic event in these malignancies. Serum tests including lactate dehydrogenase and liver function tests were within normal range. Chest radiography, brain MRI, CT scanning of the chest, abdomen, and pelvis and bone scanning were also normal. Melanoma was finally staged as II C (T4b N0 M0) [3]. The patient died of cardiac arrest 3 months after the final diagnosis.

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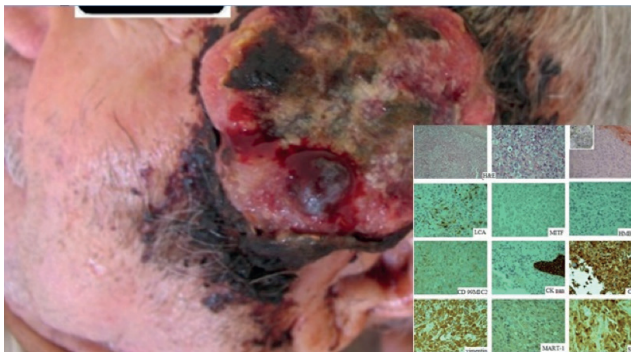

Figure 1. A giant exophytic mass of 15-month duration on the left temporal area of the head. The immunohistochemical analysis confirmed the diagnosis of amelanotic melanoma and chromogenic in situ hybridization detected chromosome 9 monosomy (inlet).

Extremely high level of CA 19-9 in a patient with metastatic pancreatic cancer: Second highest level of CA 19-9 in literature

Dear Editor,

Carbohydrate antigen (CA) 19-9 is a tumor marker used for the evaluation of several cancers such as colorectal, gastric, ovarian, hepatocellular and biliary tract; however, it has low sensitivity and specificity for the diagnosis of malignancies [1]. Also some benign conditions such as cholangitis, cholelithiasis, Hashimoto's thyroiditis, hydronephrosis and cystic fibrosis may increase the level of CA 19-9 [2,3]. Very high levels of CA 19-9 have been described in some benign and malignant conditions [3].

A 77-year-old male without any known chronic disease was admitted to our outpatient clinic with jaundice over the previous 10 days and 10 kg weight loss and epigastric pain over the previous 6 months. He was smoker (30 pack-years) and had no history of alcoholism. On physical examination, his sclera was intensively icteric and there were epigastric tenderness and palpable hydropic gallbladder in the right upper quadrant (Courvoisier's sign). Lab tests were normal except hemoglobin 12.9 g/dl (14-18), alanine aminotransferase 143 U/L (0-40), aspartate aminotransferase 191 U/L (0-40), alkaline phosphatase 831 U/L (30-120), gamma-glutamyl transferase 1030 U/L (0-50), total bilirubin 21 mg/dL (0.2–1.1), and direct bilirubin 15 mg/dL (0–0.5). Abdominal ultrasonography revealed a mass in the head of the pancreas and multiple hypoechoic solid masses in the liver, and also, intra and extrahepatic ductal dilatation and hydropic gallbladder. The levels of tumor markers were as follows: alpha fetoprotein: 3.03 ng/ml (0-8.78), carcinoembryonic antigen: 133 μg/L (0-5), and CA 19-9: 215,880 U/ml (0-37). After the diagnosis of metastatic pancreatic cancer, percutaneous catheter for biliary drainage was inserted. Only palliative care was planned because his performance status was so poor and the disease was inoperable.

It is usually believed that minimally increased values of CA 19-9 may be observed in cases of benign diseases, and quite high values in cases of malignancies [3,4]. Extremely high values of CA 19-9 have been observed in advanced and metastatic pancreatic cancer patients [5]. So far, the highest levels of CA 19-9 (19,516,020 U/ml) reported was in a patient with metastatic pancreatic cancer [5]. The other highest value was 187,000 U/ml, while no other values over 100,000 U/ml have been reported in pancreatic cancer patients [5]. In our case, severe cholestasis and metastasis to the liver may explain why the patient had very high level of CA 19-9. Determining the level of CA 19-9 helps get information about the prognosis and response to treatment of pancreatic cancer. In this malignancy high levels of CA 19-9 are associated with tumor size, tumor burden and advanced stage. CA 19-9 levels have limited sensitivity for the diagnosis of small-sized cancers and they are generally used in detecting disease recurrence and evaluating the effects of treatment after curative surgery or chemotherapy [1]. In conclusion, the highest level of CA 19-9 reported in the literature is 19,516,020 U/ml, and the second one is our case with of 215,880 U/ml.

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Can targeted programmed death-1 antibody be a new treatment approach in breast cancer

Dear Editor,

Programmed cell death-1 (PD-1) is a T-cell coinhibitory receptor with a structure similar to the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), but with very different mechanism of action [1,2]. The PD-1 receptor has different ligand specifity, and binds to two ligands, PD-L1 and PD-L2. The PD-L1 is upregulated in many cancer types and is the main ligand responsible for immunosuppression, whereas PD-L2 is only expressed by macrophages and dentritic cells [2]. Both completed and ongoing studies reveal the importance of human monoclonal antibodies anti-PD-1 and anti-PD-L1 .

The activity and safety of anti-PD1 antibody was investigated in advanced melanoma, non-small cell lung cancer, castration-resistant prostate cancer, renal cell cancer and colorectal cancer patients [3]. In this study, the majority of patients (47%) were heavily pretreated, with at least three prior regimens. Despite this, it was reported that anti-PD1 antibody produced objective responses in non-small cell lung cancer, malignant melanoma and renal cell cancer. The important point of this study was the immunochemical analysis for PD-L1. According to the intra-tumoral PD-L1 expression; objective responses were significantly higher in the PD-L1 expressing group (36%), whereas no responses were observed in the PD-L1 negative group (p=0.006). In another study, Hino et al. reported that overall survival rate of the high PD-L1 expressing group was significantly lower than that of the low expressing group and multivariate analysis demonstrated that PD-L1 expression was an independent prognostic factor for melanoma [4].

In a recently published study, Muenst and colleagues [5] showed that the presence of PD-1 was associated with significantly worse overall survival in HER-2 positive and negative luminal B subtypes and in triple-negative breast cancer (p<0.001 in all subtypes).

Recently published studies have shown the efficacy of anti-PD-1 antibodies lambrolizumab and nivolumab in metastatic or advanced melanoma. It was also reported that patients with positive expression of PD-1 had significantly worse survival compared to PD-1 negative group in breast cancer [5]. On these grounds, targeting PD-1 pathway can be a new treatment approach in breast cancer. Thus, future trials are needed to evaluate the safety and activity of anti-PD-1 antibodies in breast cancer.

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