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LETTERS TO THE EDITOR

Impact of EGFR and ALK deregulation in oral squamous cell carcinomas: a significant molecular landscape

Dear Editor,

Concerning lung carcinomas, especially adenocarcinoma and squamous cell carcinoma (both former non-small cell lung carcinomas-NSCLCs), epidermal growth factor receptor (EGFR, gene locus: 7p12) and anaplastic lymphoma kinase (ALK, gene locus: 2p23) are critical genes for handling patients based on targeted therapeutic strategies. Tyrosine-kinase inhibitors (TKIs) and also monoclonal antibodies (mAbs) have been already applied in subsets of patients that demonstrate specific molecular profiles (mutations, amplification in EGFR gene or translocation mechanisms in ALK gene).

EGFR and ALK inhibition strategies are relatively novel oncology approaches in the field of oral squamous cell carcinoma (OSSC). According to a recently published study [1], EGFR gene amplification but not protein expression seems to be an early genetic event during the malignant transformation in oral squamous epithelia. The authors observed that EGFR genomic gain was detected in a quarter of early-stage OSCC lesions called as oral potentially malignant disorders. Another study group analyzed EGFR at the protein expression level by immunohistochemistry. Interestingly, they concluded that EGFR expression in high-grade invasive cells was significantly downregulated compared with that of low-grade invasive cells. Furthermore, a significant observation emerged, comparing the expression levels of the molecule to epithelial-mesenchymal transition (EMT)-associated genes including N-cadherin, vimentin and Snail. All of them were found upregulated in the high-grade invasive cells. So, the study group suggested that loss of EGFR expression in OSCC was associated with EMT, and may modify critically tumor invasiveness and resistance to mAbs (ie. cetuximab) based treatment [2]. Expanding the knowledge regarding the efficacy of natural agents with potential chemotherapeutic, anticancer activity, another study explored the role of Lupeol. This is a natural triterpene (phytosterol) inside fruits and vegetables. Analyzing its influence in OSCC cell lines the authors of this study showed that the agent inhibited the proliferation of OSCC cells *in vitro* by inducing apoptosis. Interestingly, Lupeol suppressed the expression of COX-2, and also partially protein kinase B (PKB/AKT), I kappa B (IκB), and nuclear factor kappa B (NF-κB). The same anti-EGFR activity was observed by negatively modifying its ligand-induced phosphorylation [3].

Besides EGFR gene in OSCC, another significant molecule is ALK. Although translocation and fusion with EML4 is the most crucial ALK deregulation mechanism in carcinomas for applying TKIs, such as crizotinib, epigenetic silencing of the gene via DNA hypermethylation of promoter CpG islands is detected frequently in OSCCs. The role of this genetic mechanism in the biological behavior of OSCCs is currently unclear. A study showed that ALK promoter methylation was preferentially observed in OSCCs without node metastasis, whereas relatively lower methylation levels were present in metastatic tumors [4]. Additionally, the role of specific micro-RNAs (miRs) in ALK expression and oncogenic activity is under investigation. Based on recently published molecular experience, miR-1271 overexpression suppressed cell proliferation, colony formation, migration and invasion of OSCC cells. Furthermore, ALK was identified as a target miR-1271. In fact, ALK was inversely correlated with miR-1271 expression in OSCCs [5]. This is a very promising observation in handling patients by applying anti-ALK inhibitors and also future inducers of miR-1271 expression.

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Evangelos Tsiambas[1,4]*, Athanasios E. Athanasiou[2], Panagiotis P. Fotiades[3,4]*, Vasileios Ragos[5]

[1]*Dept of Immunohistochemistry & Molecular Biology, 401 General Army Hospital, Athens, Greece;* [2]*Dept of Medical Oncology, Metaxa Cancer Hospital, Piraeus, Greece;* [3]*Dept of Surgery, Leicester General Hospital, UK;* [4]*Dept of Pathology, Medical School, University of Athens, Greece;* [5]*Dept of Maxillofacial, School of Medicine, University of Ioannina, Ioannina, Greece*

* These authors equally contributed equally to this work

Correspondence to: Evangelos Tsiambas, MD, MSc, PhD.
E-mail: tsiambasecyto@yahoo.gr

Complete response to crizotinib in a patient with adenocarcinoma of the lung cancer harboring c- MET amplification

Dear Editor,

Lung cancer is the leading cause of cancer-related death worldwide [1]. In the past decade, lung adenocarcinoma, one of the major histological subtypes, has rapidly increased in incidence [2]. In recent years, the discovery of activating mutations in MET gene, which occurs in 3% of lung adenocarcinomas [3], has played an important role in the targeted therapy of the disease [4].

c- MET is a tyrosine kinase receptor, which is encoded in part by MET exon 14. Mutations in the MET gene can cause exon 14 dysfunction, which means increased c-MET signaling and oncogenic stimulation [5]. MET gene mutations can be detected either by fluorescence *in situ* hybridization (FISH) or immunohistochemistry.

Herein we present a 73-year-old man and former smoker who was diagnosed with a pT1aN2M0 stage IIIA lung adenocarcinoma in 2014. He received adjuvant treatment with 4 cycles of carboplatin and paclitaxel. He was examined every 3 months and last imaging showed multiple mediastinal and left pectoral lymph node metastases (Figure 1). A second histopathological examination was performed from the initial specimen for sequencing and molecular analysis. We evaluated EGFR, ALK and ROS1 gene mutations. However, we did not determine EGFR mutation and ALK, ROS1 amplification. Pathologic specimen of the patient was evaluated for c-MET gene mutation by FISH, which demonstrated strong (85%) amplification (met/cep7 ratio >5). The patient received crizotinib at a dose of 250 mg orally twice a day in March 2016. PET/CT imaging 12 weeks after initation of crizotinib showed complete response to therapy (Figure 2). The patient is still on treatment maintaining complete response.

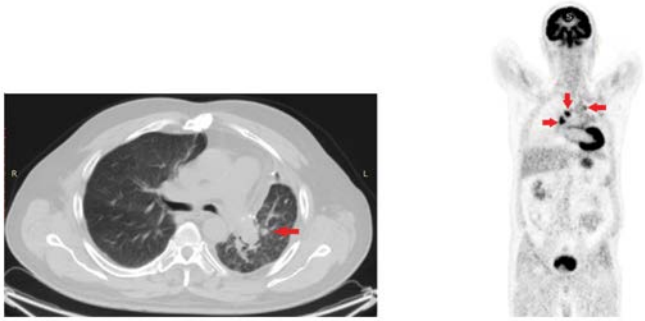

Figure 1. PET/CT after the first line chemotherapy demonstrates multiple metastatic lymph nodes (arrows).

Like well-known gene mutations, such as ROS1 and ALK, c- MET is also a potential target for crizotinib.

In conclusion, this case could suggest strong c-MET amplification in patients with advanced lung adenocarcinoma who should probably be treated with c-MET inhibitor such as crizotinib.

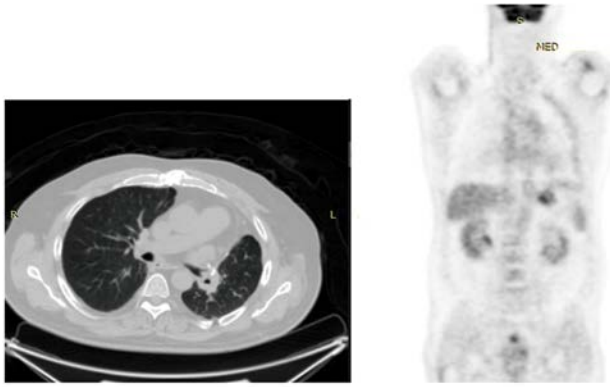

Figure 2. PET/CT shows complete response after crizotinib therapy.

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Ibrahim Cil[1], Alisan Zirtiloglu[1], Nurbanu Saydam[2], Deniz Tural[1]

[1]*Department of Medical Oncology and*
[2]*Department of Internal Medicine, Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Istanbul, Turkey*

Correspondence to: Deniz Tural, MD.
E-mail: deniztural@gmail.com

Challenging management of synchronous cancers presenting with dysphagia

Dear Editor,

A 69-year-old woman presented with progressive dysphagia to solids during the last 6 months. She had been an active smoker and used to have about one liter of wine consumption per day for 22 years. Her medical history was remarkable for total thyroidectomy due to papillary cancer in the left thyroid lobe 11 years ago. Initial esophagogastroscopy revealed a mild stricture with papillomatous appearance at 30-33cm from the incisors that was compatible with squamous dysplasia, and targeted biopsies were taken. Histological examination showed squamous polyps with elements suggestive of human papilloma virus (HPV) infection along with high grade dysplasia, but without any evidence of invasive disease. At a subsequent clinical examination, a palpable non-fixed mass in the left neck was found and fine needle aspiration (FNA) with ultrasound monitoring followed. FNA cytology showed lymph nodes invaded by metastatic disease of epithelial origin. During the staging workup, positron emission tomography – computed tomography (PET-CT) scan demonstrated increased fluorodeoxyglucose (FDG) uptake in the left piriform sinus, as well as in multiple left cervical lymph nodes (Figure 1a). Pathologic evaluation of the biopsies taken during endoscopy of the piriform sinus established the diagnosis of a solid, poorly differentiated, non-keratinized, squamous nasopharyngeal carcinoma with focal positivity in p16.

The oncologic council opted for initial administration of concurrent chemo- and radiotherapy against the hypopharyngeal neoplastic lesion. The therapeutic protocol was successfully completed and resulted in non-residual disease.

Furthermore, a re-evaluation workup for the esophageal dysplasia followed (Figure 1b). The pathologic examination of the endoscopic tumor biopsies showed elements of invasive squamous cell esophageal carcinoma. No evidence of metastatic disease was shown on CT scan. Subsequent surgical management included Ivor Lewis esophagectomy and inferior mediastinal lymph nodes resection. It is noticeable that the esophagogastric anastomosis was performed in the thorax instead of the cervix, due to the preceding radiotherapy in the cervical region. Histopathologic examination of the resected specimens indicated a poorly differentiated squamous esophageal cancer, stage T1b N0. Routine follow-up every 6 months was suggested to the patient, taking into consideration the risk of recurrence for both neoplasms as well as the possibility of developing a new malignancy.

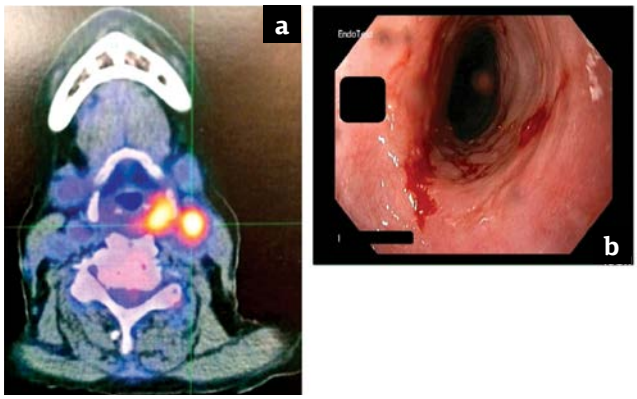

Figure 1. (a) PET/CT scan showing increased FDG uptake in the left piriform sinus and in multiple left cervical lymph nodes. **(b)** Endoscopy of the esophagus showing a stricture at 30cm from the incisors and ulcerated areas.

Management of synchronous malignancies constitutes a diagnostic and therapeutic challenge. The simultaneous incidence of esophageal and head & neck (H&N) cancer may be attributable to common risk factors such as smoking, alcohol consumption, while the role of HPV infection remains elusive [1-3]. FDG-PET/CT, which is commonly used for determining possible metastatic disease during the staging workup of esophageal cancer, has shown superiority compared to the conventional imaging modalities such as CT scan in detecting synchronous malignant neoplasms [1,4]. Conversely, rigid esophagoscopy has been suggested as screening method for patients diagnosed with H&N malignancies, who are at high risk for developing synchronous esophageal carcinomas [3]. Furthermore, it has been shown that the prognosis of patients with synchronous esophageal and H&N cancers is primarily dependent on the more advanced malignancy;

thus, a staged treatment strategy, giving priority to the more advanced and then treating the early cancer, is reasonable [2].

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Ioannis Ntanasis-Stathopoulos[1], Tania Triantafyllou[1], Nikolaos Sfougatakis[2], Dimitrios Theodorou[1]

[1]*Department of Foregut Surgery, 1st Propaedeutic Surgical Clinic, "Hippokration" General Hospital of Athens, National and Kapodistrian University of Athens, Athens;* [2]*Department of Gastroenterology, "Hippokration" General Hospital of Athens, Athens, Greece*

Correspondence to: Ioannis Ntanasis-Stathopoulos, MD.
E-mail: j.dan@windowslive.com

Lapatinib plus capecitabine in metastatic human epidermal growth factor receptor 2-positive breast cancer patients that received prior therapy with trastuzumab and pertuzumab: Better option than T-DM1?

Dear Editor,

Ado-trastuzumab emtansine (T-DM1) is currently approved for treatment in patients with human epidermal growth factor receptor 2 (HER2)–positive, metastatic breast cancer (MBC) who

previously received trastuzumab and a taxane. Approval was based on results of the phase III EMILIA trial that demonstrated increased progression-freesurvival (PFS) and overall survival (OS) in the T-DM1 arm compared with capecitabine and lapatinib in patients who experienced progression on one prior line of trastuzumab-containing therapy for metastatic cancer [1]. The standard first-line therapy for HER2-positive MBC has changed from trastuzumab and a taxane to trastuzumab and taxane plus pertuzumab [2]. Currently, there is no published clinical trial or observational data on the activity of T-DM1 in patients previously exposed to pertuzumab. A recent retrospective study by Dzimitrowicz et al. [3] dealt with the T-DM1 activity in metastatic HER2-positive breast cancer patients that received prior therapy with trastuzumab and pertuzumab. They reported that tumor response rates were lower than in prior reports of trastuzumab-resistant, HER2-positive MBC, but one third of patients received therapy with T-DM1 for ≥ 6 months. The authors suggested that T-DM1 provided a clinically relevant benefit in patients who had received prior pertuzumab. This was the first report to demonstrate the efficacy of T-DM1 in a contemporary patient population that has received pertuzumab. One might predict that this patient population having already received trastuzumab and peruzumab was no longer expected to be sensitive to anti-HER2-positive antibodies such as T-DM-1. In turn, I question that use of lapatinib plus capecitabine would be better option in these cases. Lapatinib plus capecitabine should be considered in further clinical trials in which HER2-positive MBC patients have already received pertuzumab and trastuzumab.

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Kadri Altundag,

Hacettepe University Cancer Institute, Ankara, Turkey

Correspondence to: Kadri Altundag, MD. E-mail: altundag66@yahoo.com

Negative CDX2 expression can be an important predictive and prognostic biomarker in stage II colon cancer

Dear Editor,

In the last decades, early-stage colorectal cancer (CRC) outcomes have improved with new adjuvant cytotoxic treatment strategies. Although such strategies are clear in patients with operated stage III colorectal cancer, they are controversial in patients with stage II colorectal cancer. In the randomized phase 3 QUASAR (Quick and Simple and Reliable) trial, 3239 (91% stage II) operated colorectal cancer patients were randomized to receive either chemotherapy with fluorouracil and folinic acid (FUFA) or observation [1]. The authors reported that adjuvant chemotherapy decreased the recurrence risk and improved overall survival (OS) in early-stage CRC (stage II and III) [1]. In the subgroup analyses of this trial, the relative risk of recurrence was 0.78 (p=0.004) in stage II CRC with chemotherapy compared to observation group. However, the relative risk of mortality from any cause with chemotherapy was 0.84 (p=0.049) with an absolute 3.6% improvement in OS in stage II CRC. There was no statistically significant survival difference with the high risk subgroup of stage II CRC patients compared with the low risk subgroup. Absolute mortality reduction was 5.4% and 3.6% in the high risk and low risk groups, respectively.

Another important trial that investigated the role of adding oxaliplatin to standard chemotherapy is the randomized phase 3, MOSAIC (Multicenter International Study of Oxaliplatin/5-Fluorouracil/ Leucovorin in the Adjuvant Treatment of Colon Cancer) trial [2]. In this trial, Andre et al. reported that adding oxaliplatin to fluorouracil plus leucovorin (FL) nonsignificantly improved the risk of relapse (28%) in stage II CRC patients who had at least one adverse prognostic factor (stage T4, obstruction, perforation, poorly differentiated tumor, venous invasion). There was a nonsignificant detrimental effect in the low-risk stage II group, and a nonsignificant benefit in high-risk stage II group with adding oxaliplatin to FL. According to the QUASAR validation study, with tumor samples from 1,436 patients with stage II CRC 12-Gene Colon Cancer Recurrence Score was significantly associated with recurrence risk after surgery and predicted recurrence risk beyond other risk factors. According to a prospective validation study of 12-Gene Colon Cancer Recurrence Score in NSABP C-07 trial, it was shown that stage II patients with high recurrence score may benefit more by adding oxaliplatin to FL compared to stage III patients with low recurrence score [3].

Microsatellite instability (MSI) is another predictive marker of adjuvant treatment in stage II CRC. MSI is a hypermutable phenotype caused by the loss of DNA mismatch repair (MMR) activity and detected in about 15% of all colorectal cancers. Ribic and colleagues reported that fluorouracil-based adjuvant chemotherapy benefited patients with stage II CRC with microsatellite-stable tumors or tumors exhibiting low-frequency MSI [4]. However, there was no benefit with adjuvant chemotherapy in the group with high-MSI. Sargent et al. also reported that provicient MMR (pMMR) is associated with improved outcome with adjuvant chemotherapy but deficient MMR (dMMR) was not. Andre et al. evaluated the addition of oxaliplatin to 5-FU based chemotherapy according to MMR status in the randomized phase 3 MOSAIC trial [2]. In that trial 902 patients with both BRAF and MMR statuses available, BRAFV 600E mutation was identified in 94 (10.4%) and DMMR was identified in 9.4% of the available specimens. The authors reported no benefit by adding oxaliplatin in the pMMR group (HR:0.87, p=0.185) while disease-free survival (DFS) and OS were improved in the dMMR group but without statistical significance (DFS; HR: 0.48, p=0.088; OS; HR: 0.41, p=0.069).

Currently, in a recently published trial, Dalerba and colleagues reported that lack of CDX2 expression may be a new marker to predict the benefit of adjuvant chemotherapy [5]. In this study, 87 of 2115 tumor samples (4.1%) lacked of CDX2 expression. In the validation group, the 5-year DFS rate was lower in patients with CDX2-negative CRC than in patients with CDX2-positive, independent of the patient's age, sex, and tumor stage and grade (12 vs 87 %, HR: 2.42, p=0.003). In addition, 5-year DFS rates were 49 and 87% in patients with stage II CDX2-negative and CDX2-positive CRC, respectively (p=0.004). In the subgroup analyses of all cohorts, the 5-year DFS was significantly improved from 56 to 91% in patients with stage II CDX2-negative CRC treated with adjuvant chemotherapy compared to those not treated with adjuvant

chemotherapy (p=0.006). This study showed that adjuvant chemotherapy has beneficial effect in the CDX2-negative CRC patients but there was no data about improvement of adjuvant treatment with oxaliplatin use.

In the light of the literature data, we know that adding oxaliplatin to 5-FU based chemotherapy may improve recurrence risk in high risk stage II CRC (stage T4, obstruction, perforation, poorly differentiated tumor, venous invasion, <10 lymph nodes examined) and high MSI status. Lack of CDX2 expression can be a new and absolute high risk marker for prediction of benefit from the addition of adjuvant chemotherapy with or without oxaliplatin in stage II CRC. However, it is not clear that adding oxaliplatin to treatment is effective or not, thus there is a need for confirmatory trials to determine the oxaliplatin effect in the CDX2-negative CRC patients. We suggest that it is necessary to collect a large CDX2-negative cohort to study the association of MSI and CDX2 as this is a very small subgroup of CRC patients.

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Burak Bilgin, Mehmet AN Sendur, Muhammed B.Akinci, Bulent Yalcin

Yildirim Beyazit University, Faculty of Medicine, Department of Medical Oncology, Ankara, Turkey;

Correspondence to: Mehmet Ali Nahit Sendur, MD. E-mail: masendur@yahoo.com.tr

Is preoperative smoking abstinence needed for terminally ill cancer patients?

Dear Editor,

I am preparing a Ph.D. proposal entitled Smoking Cessation Intervention Efficacy in Patients Undergoing Elective Surgery – a Randomized Clinical Trial. The research question is: Does a general practitioner's (GP) smoking intensive intervention increase biochemically validated cessation rates? In addition to pharmacotherapy with bupropion, additional measures will be tailored for pre- and postoperative phases. For example, patients will be required to sign a declaration of commitment in a contract to quit smoking, and a biochemical validation test (saliva cotinine detection) will be performed at the time of admittance to surgical facility. Cessation will be tested (1) at the time of surgery and (2) at 6 months post-surgery for a population of smokers scheduled for elective surgery. The proposed study will compare the effectiveness of usual care and intensive intervention facilitated by a family physician and by trained nurses.

The exclusion criteria will contain the following: pregnancy or lactation, serious illness associated with short life expectancy (advanced disease state, including advanced cancers, chronic obstructive lung disease, liver disease), severe heart disease (NYHA class IV), unstable history of seizures, recent psychiatric hospitalization (< 8 weeks), alcohol or substance abuse or dependence, and conditions causing cognitive impairment (e.g., dementia). One of my colleagues suggested that in the exclusion criteria segment I should not include patients with advanced cancers. His argument is the study from Sweden that GPs were more willing to offer an expensive treatment to a non-smoking lung cancer patient than to a smoking patient with the same disease [1]. The authors stated that oncologists were more inclined than GPs to offer the new, expensive treatment, regardless of the patient's smoking status. This may reflect the fact that because GPs seldom treat terminal cancer patients, they prefer to use available resources for prevention or treatment of curable diseases. My colleague also stated that it is a well known fact that carbon monoxide (CO) from inhaled cigarette smoke causes a 3-12% reduction in oxygen delivery to the tissues [2], and CO-hemoglobin formation damages the tissue oxygenation and contributes to shortening the life of terminally ill patients.

However, sudden nicotine withdrawal may cause delirium in terminally ill cancer patients during the post-operative period [3]. Therefore it is not clear if such patients should be asked to quit smoking before surgery and during the whole perioperative period. I would appreciate an input of oncologists on this subject; specifically, do they recommend smoking cessation of terminally ill cancer patients in the preoperative phase when submitted to surgery?

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Anto Domić, MD, M.Sci.

Zdravstveni centar Brčko, Brčko district, 76100 Brčko, Bosnia and Herzegovina.

Correspondence to: Anto Domić, MD, M.Sci
E-mail: anto.domic67@gmail.com

Role of stereotactic radiosurgery in the salvage treatment of leptomeningeal metastases

Dear Editor,

Leptomeningeal metastases (LM) are detected in 3-8% of patients with solid tumors, in 5-29% with non-Hodgkin's lymphoma (NHL) and in 11-70% with leukemia. The incidence rates increase in parallel with the life span [1]. There is no consensus in the treatment of LM because of lack of randomized studies evaluating optimal management and treatment. In order to decide the kind of treatment, factors such as patient age, performance status, widespread resistant systemic disease, type of cancer and neurologic symptoms are important. Whilst treatment options are quite limited, given treatments consist of radiotherapy (RT) and chemotherapy (systemic or intrathecal). Indications for RT are: symptom palliation due to LM, treatment of bulky radiographic disease, correction of CSF flow abnormalities and treatment of parenchymal brain metastases. For spinal lesions, focal RT and for cerebral lesions whole brain RT (WBRT) are given [2-4].

In recent years, stereotactic radiosurgery (SRS) has begun to be used in the treatment of LM. SRS is considered a good option in the treatment of selected cases. Lekovic et al. reported a patient with breast cancer who first underwent craniospinal RT and intrathecal trastuzumab for focal/nodular LM that proved resistant to this approach. Afterwards the patient was treated with SRS considering that this therapeutic method is safe and effective for treating nodular or focal recurrent and/or residual disease [5]. Bertke and colleagues studied a breast cancer patient and after multiple lines of systemic chemotherapy and WBRT, they reported that in the treatment of LM recurrence, intrathecal chemotherapy administration in combination with SRS was effective and safe [4]. After SRS has shown effectiveness in patients with LM, the concept of administration of SRS alone to avoid the disadvantages of WBRT was put forward. However, due to the short survival of patients with LM, randomized controlled trials have not been available yet.

When compared to WBRT, SRS is less toxic, with lower impact on the quality of life, provides long-term palliation and is a safe treatment option when used simultaneously with chemotherapy. In order to identify the group of patients who will benefit from this treatment, randomized controlled studies are needed.

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Yasemin Benderli Cihan

Kayseri Education and Research Hospital, Department of Radiation Oncology, Kayseri, Turkey

Correspondence to: Yasemin Benderli Cihan
E-mail: cihany@erciyes.edu.tr

A young woman with metastatic colon cancer presenting with elevated serum beta human chorionic gonadotropin

Dear Editor,

Serum β human chorionic gonadotropin (β-hCG) is generally connected with pregnancy and can be detected in gynecologic or rarely in non-gynecologic tumors [1]. In non-gynecologic tumors, elevated serum β-hCG is associated with poor prognosis and usually occurs in women in the reproductive age with lung tumors [1,2]. In the literature, urinary tract malignancies, sarcomas, gastric carcinoma and breast cancer are associated with high serum β-hCG [1]. To the best of our knowledge, there is only one case with metastatic colon cancer presented with elevated serum β-hCG [3].

A 35-year-old multiparous woman in good health had a right abdominal pain in the past 6 months. During her evaluation by a gynecologist, high serum β-hCG level was detected (600 miu/ml) but intrauterine and ectopic pregnancy had been ruled out. However, her serum β-hCG level had consistently increased and her abdominal pain had continued. A chest and abdominal computed tomography scans showed multiple masses in the liver and a solid mass in the right colon. Colonoscopy and biopsy of the mass revealed colon adenocarcinoma (CK-20+, CDX-2 +, CK-7-) with poor differentiation. Also high serum carcinoembryonic antigen (CEA) level (400 ng/ml) and KRAS 12th codon mutation were detected.

She was administered oxaliplatin 130 mg/m^2 and capecitabine 2000 mg/m^2 for 3 cycles without response and her β-hCG and CEA levels continued to increase (from 600 to 1400 mIU/ml and from 400 to 1200 ng/ml, respectively). The patient died of disease 3 months from diagnosis.

The most frequent high serum β-hCG producing non-gynecologic tumors in women of the reproductive age are lung tumors and detection of serum β-hCG indicates poor prognosis in the non-gynecologic tumors. Also serial serum β-hCG measurements may be useful to monitor the treatment response and progression of disease. The current case demonstrated that elevated serum β-hCG was not associated with a pregnancy and gynecologic tumors. We should be aware that increased serum β-hCG may be associated with conditions other than pregnancy and may be the first sign of a primary non-gynecologic tumor.

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Ozge Velipasalar[1], Hakan Kocoglu[1], Mehmet Hursitoglu[1], Deniz Tural[2]

[1]*Department of Internal Medicine and* [2]*Department of Medical Oncology, Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Istanbul, Turkey*

Correspondence to: Deniz Tural, MD. E-mail: deniztural@gmail.com