

LETTERS TO THE EDITOR

Tyrosine kinase inhibitors may change the metastatic pattern

Dear Editor,

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) (erlotinib, gefitinib) were initially developed to be used as second-line therapy after failure of cytotoxic chemotherapy in non-small cell lung cancer (NSCLC) patients [1]. In patients with stage IIIB or IV NSCLC, erlotinib has been proven to prolong survival after failure of first-line or second-line chemotherapy. Almost all patients who initially respond to an EGFR TKI subsequently develop disease progression. The most common cause of acquired resistance to EGFR TKI is a secondary mutation in EGFR. TKI might initiate stromal and microenvironmental defense mechanisms that contribute to eventual drug loss of activity and may lead to a more aggressive and invasive tumor with an increased ability to metastasize [2].

A 61-year-old non smoker woman presented with chronic cough, weight loss and shortness of breath. Physical examination revealed decreased breath sounds in right lower lobe. Laboratory evaluation showed only mild anemia and chest x-ray showed pleural effusion on the right lower lobe and a mass on the right middle lobe. Thoracic and abdominal computed tomography (CT) showed a 44 x 57 mm mass on the right middle lobe with massive pleural effusion and ipsilateral hilar and mediastinal lymph nodes. Pathological examination of transbronchial biopsy of the mass and cytology of the pleural effusion confirmed lung adenocarcinoma without distant metastases (T4N2M0, stage IIIB). Then the patient was treated with gemcitabine-cisplatin chemotherapy. After 3 cycles of chemotherapy, due to progression of the pleural effusion and shortness of breath, erlotinib 150 mg/d was administered. The symptoms resolved in about 3 months and radiological evaluation showed very good partial response. After 19 months on erlotinib, disease progression was noticed (increase in size of mass and pleural effusion volume). Erlotinib was stopped and the patient opted not to have any treatment, but 2 months later she was readmitted with pain and erythema in the right breast. Physical examination showed peau d'orange in the right breast without palpable mass. Mammography and breast ultrasonography showed subcutaneous edema without mass. Thoracic and abdominal CT showed stable mass and effusion in the right lung without distant metastases. Then, skin biopsy of the breast was performed, which showed metastatic lung adenocarcinoma with negative estrogen and progesterone receptors and positive thyroid transcription

factor-1. The patient was put on single-agent pemetrexed for two months.

NSCLC accounts for more than 85% of all lung cancers, and adenocarcinoma is the most common type of lung cancer in nonsmokers [3]. Bone, adrenals, liver and brain are most common sites of metastasis in NSCLC patients [4]. Isolated cutaneous metastasis from lung cancer is very rare. In general, lung cancer that tends to metastasize to other organs also involves the skin. Terashima et al. reported that 3.1% of lung cancer patients developed cutaneous metastases whereas only 20% of these patients had isolated cutaneous metastases [5].

Preexisting somatic mutations in k-ras are associated with primary resistance to TKI [2]. Acquired resistance to TKI may increase the ability to metastasis, but changes on the metastatic pattern of the primary tumor was not still known. As in our case, rare isolated cutaneous metastases to the skin after erlotinib treatment support that TKI may change the metastatic pattern, but large trials are needed to reach a clearer picture.

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Vemurafenib-induced hypertension: is it real?

Dear Editor,

Vemurafenib is an inhibitor of the BRAF V600E mutation that was approved by the Food and Drug Administration of USA in August 2011 for the treatment of metastatic melanoma. In phase I, II, and III clinical studies involving melanoma patients with tumors having V600E BRAF mutations, vemurafenib was associated with consistent efficacy and improved survival [1,2]. Although it was generally well tolerated, common side effects of vemurafenib have been reported in the phase III study [2] such as arthralgia, rash, fatigue, alopecia, keratoacanthoma or squamous-cell carcinoma, photosensitivity, nausea, and diarrhea [1].

Preclinical findings of vemurafenib have shown that the drug had no association with hypertension. However, there were no sufficient data concerning monitoring of the subjects in relation to hypertension. Herein we share our experience of hypertension in our 11 metastatic melanoma patients treated with vemurafenib. At the pre-treatment stage we measured, monitored and recorded all patients' blood pressure (BP) levels. After initiation of vemurafenib, all subjects were followed with monthly visits. During the follow-up period all adverse event reports and BP were recorded by the attending physician. Of the 11 patients, 5 had hypertension history which was regulated with anti-hypertensive drugs. Besides, 6 patients' BP results were within normal range. Following vemurafenib therapy, 3 patients were diagnosed with grade I hypertension according to the JNC 7 diagnostic criteria, who had normal BP before treatment. Furthermore, 4 patients having hypertension history before vemurafenib therapy showed hypertension and their anti-hypertension treatment was rearranged to control their hypertension.

Hypertension is a common toxicity of tyrosine-kinase inhibitors that target VEGFR, such as sunitinib, sorafenib, and axitinib or monoclonal antibodies against vascular endothelial growth factor such as bevacizumab [3,4]. While the etiology concerning how target-based specific therapeutic agents lead to hypertension is unknown, bevacizumab-induced hypertension might be related to

a decrease in VEGF-induced NO (nitric oxide) synthesis and/or to the rarefaction of the capillary bed, as shown by capillaroscopy [4]. Despite the fact that the development of hypertension has been regarded as the efficiency and success of therapy, recurrence of target organ damage need to be monitored. The mechanism of vemurafenib-induced hypertension is unknown. However, recent data showed that BRAF inhibitors can activate the MAP kinase pathway in cells that lack BRAF mutation. This activation may pertain to hypertensive effects seen with vemurafenib by unknown mechanism. In conclusion, vemurafenib may induce hypertension in melanoma patients, which may occur at any time after therapy initiation. Clinicians must be aware of this issue and add periodic blood pressure monitoring to standard medical care.

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A case of thoracic ancient schwannoma with a challenging approach

Dear Editor,

An otherwise healthy 65-year-old man presented with a persistent lower respiratory tract infection, shortness of breath and feeling of heaviness in the left side of his chest. X-ray revealed a large, well-defined opacity in the left lower lobe, which was further characterised on computerized tomography (CT) as a large, well-defined, paravertebral

soft tissue mass, most likely extrapulmonary with no mediastinal lymphadenopathy. Bronchoscopy demonstrated only extrinsic compression and was unsuccessful in obtaining tissue samples, but CT-guided biopsies revealed nonspecific hyalinised tissue (no evidence of malignancy).

After a multidisciplinary meeting with the neurosurgeons a decision was made for removal of the tumour under the care of thoracic surgeons.

The patient underwent a left-posterolateral thoracotomy with entry through the sixth intercostal space. The first thoracotomy was performed through the 6th intercostal space (instead of the "classic" 4th/5th intercostal-space) for better and safer approach of the tumour. However, the base of the tumour was adhered to the surrounding tissues and the surgeon felt quite uncomfortable to dissect "blindly" into and around the tissues. For this reason, a safe approach via an additional posterolateral thoracotomy was decided. In order to fully visualise and safely gain access to the inferior and superior aspects of the tumour, additional access through the 9th intercostal space was attained.

The mass appeared to arise from the sympathetic chain. The inferior margin was on the diaphragm and it was intimately associated with the thoracic aorta and vertebral column. There were short thick feeding and draining vessels running from the tumour into the chest wall, which were ligated and the mass was excised safely.

The patient made an uneventful postoperative recovery (apart from a superficial wound infection). Histology confirmed the diagnosis of a benign thoracic ancient schwannoma (TAS).

He is still symptom-free at 26 month-follow-up.

There are few cases of TAS reported in the literature. Schwannomas arise from Schwann cells in the myelin sheath of peripheral nerves and most commonly originate in the head and neck, but ancient schwannomas have been reported in the retroperitoneum, pelvis and thorax [1].

They are generally benign, encapsulated tumours, representing 0.8% of soft tissue tumours [2], with 4-20% of cases related to neurofibromatosis type-I [3].

Sixty-three percent occurred in females, with a peak incidence in the 4th decade of life [3].

Symptoms are related to pressure/erosion by the gradually enlarging mass, although there are some reported incidents of conversion to malignant tumour, with Bhatia et al. citing less than 10 cases found in the literature [4].

Definitive diagnosis of ancient schwannoma is only possible after histopathological examination [3], and the degenerative findings are indeed responsible for the term "ancient" [5].

Changes, such as hyalinisation, cyst formation, calcification, haemosiderin deposition, interstitial fibrosis, vascular hyaline degeneration and nuclear atypia can sometimes result in misdiagnosis as a malignant tumour [3].

Due to this degeneration, TAS appear as homogeneous masses on CT scan and become heterogeneous on intravenous contrast administration.

This case highlights the importance of full preoperative assessment before attempting to remove tumours of this size in the thorax (in order to exclude involvement of the spinal tract and vascular structure in the vicinity, and confirm resectability), and also of intraoperative flexibility to gain the optimal, safe, surgical approach.

Upon suspicion of intraspinal extension MRI is the best investigational tool.

In conclusion, this quite unusual method (opening two intercostal spaces via one skin incision) enables better access and visualisation of the thorax, facilitating safe removal of large or complicated structures.

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Adult Langerhans' cell histiocytosis: a rare cause of parotid gland enlargement

Dear Editor,

Langerhans' cell histiocytosis (LCH) is a dendritic cell disorder, the etiology and pathogenesis of which are still unclear. Manifestations may include bone lesions, lung infiltrates, dermatologic eruptions, hematopoietic and endocrine dysfunction [1]. Involvement of the parotid gland by LCH is extremely rare. We herein describe a case of LCH confined to the parotid gland.

A 46-year-old male presented with a 2-year history of gradual painless enlargement of the left parotid gland. He was admitted to the oncology outpatient clinic. Physical examination showed non-tender, painless swelling on the left side of his face obliterating the angles of the jaw. Examination of the different systems revealed no abnormality: hemoglobin 14.4 g/dL, white blood cells: 8600 mm³, platelets: 235000 mm³, erythrocyte sedimentation rate 12 mm/h. Renal and liver functions were normal and the PPD

test was negative. Chest X ray was normal. A computed tomography (CT) scan of the neck revealed diffuse enlargement of the left parotid gland without calcification or necrosis. Fine needle aspiration of the parotid gland showed infiltrating cells mainly consisting of eosinophils, lymphocytes and histiocytes with occasional cells displaying large nuclei and distinct nucleoli. Immunohistochemical studies identified CD1a and S-100 positivity on the tumor cells. Electron microscopy was not performed. Based on the above findings, the patient was diagnosed as LCH. Internal organ involvement was not detected by whole body CT scan, and bone scintigraphy was normal. At this stage, a definitive diagnosis of isolated LCH of the parotid was made. Total surgical resection of the left parotid gland was performed. Regular follow-up examinations did not reveal tumor recurrence in 7 years.

LCH is a rare disease that primarily affects the mononuclear phagocyte system and the dendritic cell system. Despite advances in understanding the clinical course, the pathogenesis of LCH is still unknown. The criteria for definitive diagnosis of LCH is demonstration of Birbeck granules in the cytoplasm of Langerhans cells by electron microscopy or CD1a and S-100 antigenic determinants on the surface of the cells by immunocytology or immunohistology [1].

This condition typically presents with involvement of bone, lung, skin, lymph nodes and multiple sites. To the best of our knowledge, only few cases of LCH of the parotid gland have been reported in the medical literature. Darvishian et al. documented a case of a 34-year-old Korean male with LCH involving the parotid gland and an adjacent lymph node. The patient underwent parotidectomy followed by adjuvant chemotherapy consisting of weekly vinblastine plus daily prednisone. There has been no evidence of local recurrence or disease progression during 20 months after diagnosis [2]. Kojima et al. and Iqbal et al. described cases of LCH involving both parotid glands; the first one in an 18-month-old boy and the second in an 81-year-old woman [3,4]. Takahama et al. [5] reported a 3-year-old boy with LCH with a painful swelling in the left parotid region for almost 6 months. Treatment of unifocal disease consists of bone curettage, surgical excision and/or radiotherapy (RT). RT is especially recommended for the treatment of lesions where weight bearing bones or organ function is threatened. Also chemotherapy is an

essential treatment method for patients with multifocal disease. Various chemotherapeutic agents including vinblastine, vincristine, corticosteroids, mercaptopurine and etoposide are recommended for the treatment of multifocal LCH [1]. In adults unilateral parotid gland enlargement usually appears from benign causes. The differential diagnosis includes sialadenitis, Mikulicz's syndrome, benign lymphoepithelial lesion, Kimura's disease, and extranodal marginal zone B-cell lymphoma of MALT, inflammatory pseudotumor, fibrohistiocytic tumors, sclerosing lymphoma, sarcoidosis and neoplasm of the salivary glands. Although very rare, parotid gland involvement by LCH should be kept in mind in the differential diagnosis of parotid gland enlargement.

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Etoposide hypersensitivity

Dear Editor,

Over the past 30 years advances in the treatment protocols improved the prognosis of testicular cancer. Approximately 80% of the patients with metastatic disease are cured with combination chemotherapy. Etoposide is an active drug that is part of the BEP protocol, which is regarded as the standard treatment in advanced testicular

cancer. Hypersensitivity reactions to etoposide rarely occur and manifested by hypotension, hypertension, flushing, diaphoresis, dyspnea, chest discomfort and bronchospasm [1]. Considering the importance of etoposide in the management of testicular cancer, the occurrence of hypersensitivity reactions is an important clinical problem. Herein we report on a patient who, despite experiencing a hypersensitivity reaction to intravenous etoposide, tolerated

the subsequent administration after both using etoposide phosphate and lower infusion rate with premedication .

A 20-year-old male patient with stage IV testicular embryonal cell carcinoma was admitted to the hospital for his first cycle of BEP chemotherapy. During the first cycle, and within minutes after the start of the etoposide infusion, the patient developed shortness of breath, pruritus, diaphoresis and rash on the face and chest. On examination, he was hypotensive and tachycardic. The infusion was stopped after only 5 mL of etoposide had been administered. He was given oxygen and antihistaminics and steroids intravenously, which resolved his symptoms rapidly. Etoposide phosphate preparation which does not contain polysorbate-80 is not available in our country. He obtained the preparation from another country and the treatment was readministered without any allergic reaction. For the second cycle of chemotherapy, etoposide phosphate could not be provided. The patient was premedicated with hydrocortisone and phenyramine and etoposide was given at a slower rate. The patient tolerated the infusion well and did not exhibit any hypersensitivity symptoms. He completed the prescribed 4 cycles of BEP using the same regimen of premedication and infusion rate.

The exact underlying mechanism of etoposide hypersensitivity is unclear. It may be due to etoposide itself or to the polysorbate 80 diluent which is used to dissolve etoposide [2]. Etoposide phosphate doesn't contain polysorbate 80. It can be considered an alternative approach for patients experiencing etoposide hypersensitivity

[3]. There have been cases of etoposide hypersensitivity re-treated by administering premedication, reducing the infusion rate, or concentration, or using oral etoposide [4]. In our case, we have completed the treatment without any complication after both using etoposide phosphate or etoposide with lower infusion rate and premedication . Patients who develop hypersensitivity reactions to etoposide can be rechallenged successfully in different ways .

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Fertility sparing surgery for early cervical cancer

Dear Editor,

Vemurafenib is an inhibitor of the BRAF V600E muIn this communication we present 11 women with early cervical cancer who liked to preserve their fertility and underwent radical trachelectomy. The selection criteria were absence of capsule invasion, well differentiated grade, favorable histologic type, no evidence of intra-operatively suspicious lesions such as enlarged lymph nodes and no distant metastasis on MRI or CT. Informed consent was taken from all patients. A frozen section from the upper margin of the cervix was used to confirm that the tumor had been completely excised. A cerclage suture was used around the isthmus to provide competence at the level of the internal orifice. All cases were subjected to lymph node dissection. Three squamous cell carcinomas and 8 adenocarcinomas were found. Two cases had stage IA2 and 9 stage IB1. Seven patients had grade 2 and 4 grade 3 tumors. The median duration of follow-up was 47.1 months (range 15-60). One patient underwent radical hysterectomy with preservation of both ovaries because of no clear margins in the frozen section, while one patient underwent ovarian transposition and radiotherapy for the same reason. One patient recurred at 45 months

after primary surgery and underwent chemoradiation. All of our patients were alive during follow-up. Two patients attempted pregnancy with in vitro fertilization (IVF). One term pregnancy was achieved and it was uneventful.

MRI can accurately estimate the tumor dimension, as well as its proximal extension to ensure clear surgical margins. According to Cibulla et al. the key limitation for the decision of trachelectomy is the cranial extent of the tumor towards the internal cervical os [1]. In a tumor <2 cm, the overall recurrence rate after vaginal radical trachelectomy is 3-6% and mortality 2-5% [2]. In our centre, none of our patients was downstaged because we used the strict criterion of tumor diameter <2 cm to proceed. Frozen section should be performed to evaluate the surgical margins, because, if the tumor is found within 5 mm of the endocervical margin, then extended surgery is necessary [3]. According to previous studies, no statistically significant differences were found in the oncological outcomes (histology, median number of lymph nodes excised, node positive rate, lymphovascular space involvement or deep stromal invasion) regarding the surgical method [vaginal or abdominal (laparotomic, laparoscopic or robotic) trachelectomy] [4]. The only difference was the median parametrial length which was measured in a study as

1.45 and 3.97 cm in the vaginal and the abdominal radical trachelectomy, respectively [4]. To further minimize the extent of the operation sentinel lymph node biopsy is also suggested. Close follow-up is proposed in such women. The emotional rollercoaster following diagnosis and treatment of cervical cancer is high and for this reason waiting for 6-12 months until proceeding to pregnancy is proposed to couples. Regarding postoperative conceptions and births, the results of the different studies vary from 33-66% [5]. However, in our series 2/11 women underwent IVF and one of them had an uneventful pregnancy. Common complications of radical trachelectomy could be irregular menstrual bleeding or amenorrhea, cerclage erosion, cervical stenosis and preterm labor (2-3-fold higher risk) [2]. Finally, central pelvic recurrence, particularly in patients with adenocarcinoma, is another complication. For this reason, hysterectomy is proposed to avoid such a serious complication as soon as childbearing is achieved.

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Granulocyte colony stimulating factor-induced tumor lysis-like syndrome: leucolysis

Dear Editor,

Tumor lysis syndrome (TLS) is common in patients with hematologic malignancies but it is rarely observed in patients with solid tumors [1]. Initiation of anticancer treatment, such as chemotherapy, radiotherapy, surgery, glucocorticoid therapy or sometimes spontaneously from tumor necrosis prior to the onset of anticancer therapy, may result in TLS [2]. Granulocyte colony stimulating factor (G-CSF) is a recombinant protein produced by recombinant DNA technology [3]. Leucocytosis is an important and well recognized side effect of granulocyte colony-stimulating factor (G-CSF).

A 61-year-old man diagnosed with stage II diffuse large B cell non-Hodgkin's lymphoma was admitted to our clinic 10 days after the administration of the third course of R-CHOP chemotherapy due to febrile neutropenia and weakness. He was administered meropenem 3 g / day, ampicillin 1000 mg/day, and neupogen (G-CSF) 48 MU/ day. In the 3rd day of antibiotic therapy, the patient became afebrile and in the 7th day his neutrophils reached 5400/mm³. Considering the existing improvement all antibiotics and G-CSF were stopped and the patient was discharged. Eight days later after persistent nausea and vomiting with lethargy, weakness and anorexia, the patient was admitted to the emergency service of the hospital. On arrival he was alert and in poor general condition, pale, with low blood pressure and tachycardia. Lab investigations revealed BUN 127 mg/dL with serum creatinine 8.5 mg/dL, calci-

um 5.5 mg/dL, potassium 7.6 mEq/dL, phosphorus 9.8 mg/dL, uric acid 19.5 mg/dL, and lactate dehydrogenase 1145 IU/L. His white blood cell count was 235000/ mm³ with absolute neutrophil predominance without blast cells. Obstructive uropathy was excluded by retroperitoneal ultrasound. The patient went into oliguric acute renal failure and was treated with intravenous fluids. However, renal function did not improve over the next 2 days, and hemodialysis started along with rasburicase. Lab abnormalities were consistent with TLS. After increased body temperature, the patient was diagnosed with pneumonia, and wide spectrum antibiotic therapy was initiated again. In the 3rd week of therapy the patient died of septic shock. On reexamining the patient's anamnesis we found that, ignoring the clinical prescription and recommendations, the patient continued to get subcutaneous G-CSF for 7 days. Since there was no other additional medication, this situation regarded as G-CSF-induced spontaneous tumor lysis-like syndrome (TLLS), leucolysis.

G-CSF stimulates the production of mature, functional neutrophils in bone marrow and reduces the incidence of febrile neutropenic episodes in cancer patients [5]. Leucocytosis is an important and well recognized side effect of G-CSF [4]. It is considered that such an increase in leukocyte count is not associated with any clinically significant harmful effects. However, in the presented case, overdose of G-CSF led to spontaneous leucolysis and death. Especially the development of TLLS following the 3rd chemotherapy cycle with limited tumor volume, and

excess use of G-CSF convinced us to consider the existing event as G-CSF-induced spontaneous TLLS. The etiology of G-CSF-associated spontaneous TLLS is unknown; however, it may emerge as a result of sudden death of myeloid cells that spread to the blood circulation. To the best of our knowledge, this is the first report that shows G-CSF may induce spontaneous TLLS. The use of G-CSF is vitally important to decrease the morbidity and mortality in patients with cancer. However, there is a need for leucocyte count monitoring to avoid any potential complications.

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