

LETTERS TO THE EDITOR

A systemic late recurrence after the first operation in a patient diagnosed with early-stage breast cancer: the latest recurrence in the literature

Dear Editor,

Late breast cancer recurrence is defined as a tumor that was pathologically or clinically diagnosed 5-10 years after diagnosis in the same breast as the original tumor or in any regional or distant site. Most recurrences – approximately in 25% of the patients – occur in the first 5 years after surgery [1]. Recurrences more than 15 years are not very frequent, and their recurrent pattern and prognosis have not been thoroughly analyzed. Herein we report on a case of early breast cancer with the latest systemic recurrence after 27 years of disease-free interval. To the best of our knowledge this is the latest recurrence case of breast cancer in the literature.

A 45-year-old woman underwent right modified radical mastectomy for infiltrating ductal carcinoma of the breast in 1985. The disease was staged as T1N0M0 and she did not receive chemotherapy or radiotherapy. Hormone receptor status was not known at that time; that's why the patient was under follow-up without any medication. Twenty-seven years after surgery the patient developed bone ache, headache and weakness, and investigations revealed diffuse lung, liver, brain and bone metastases. Liver biopsy of metastatic lesions showed infiltrative ductal carcinoma. Immunohistochemical analysis showed positive estrogen (80%) and progesterone receptors (10%), and HER2 positivity (3+). Examination of the left breast was normal. Mammography and left breast MRI showed normal findings. Following initiation of palliative radiotherapy to the metastatic brain and bone lesions, the patient started a weekly regimen including paclitaxel 80 mg/m², carboplatin AUC 2, trastuzumab 2-4 mg/kg and zoledronic acid 4 mg/q3w. Despite a partial response in the brain and liver lesions after 4 chemotherapy cycles, new lytic bone lesions were detected in the left femoral shaft. After consultation with the radiation oncology department, palliative radiotherapy started to this area. For systemic therapy, the patient started second-line therapy with anastrozole 1 mg/d, trastuzumab 6-8 mg/kg and zoledronic acid 4 mg/q3w. After the fourth cycle the patient developed jaundice (total and direct bilirubin 8 and 5 mg/dl, respectively). CT scan and hepatobiliary ultrasonography revealed diffused tumor infiltration of the liver with significant progression. Due to bile ducts' dilatation interventional radiologists placed a biliary stent percutaneously to decrease bilirubin levels, after which the patient gradually recovered from jaundice. Then, the patient received vinorelbine 25 mg/m²/week, trastuzumab 2-4 mg/kg/week and zoledronic acid 4 mg/q3w as third-line therapy. After 2 cycles stable liver disease was observed. We plan to continue with the same regimen while the patient is under close follow-up.

Late recurrences (>10 years) of breast cancer are generally observed in hormone positive tumors. The yearly relapse rate is 0.5 % after 10 years [2]. These relapses occur even if adjuvant chemotherapy was given. Studies have shown that estrogen-negative tumors mostly recur within the first 5 years after diagnosis, while estrogen-positive tumors recur later [3]. More aggressive tumor characteristics and inadequate primary tumor therapy increase the risk of recurrence after 5 years [2]. In a recent study [4], Bosco et al. found that nodal involvement, poor grade tumor and breast-conserving surgery without radiation therapy increase the recurrence rates. Not receiving adjuvant tamoxifen vs receiving adjuvant tamoxifen, was also positively associated with late recurrence among women with estrogen receptor positive/unknown tumors [5]. Most late recurrences present as advanced disease, which is difficult to treat in older women. We report on this patient for she had the latest recurrence after 27 years of disease-free interval reported in the literature. Although we didn't have the opportunity to evaluate the hormone receptor status of the primary cancer, most probably the patient's hormone status was positive. If the patient's hormone status positivity was detected early and she had adjuvant tamoxifen, disease recurrence would be further delayed.

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Acquired C1 esterase inhibitor deficiency in a marginal zone lymphoma patient treated with rituximab

Dear Editor,

Angioedema is a local, non pruritic and pitting edema involving deeper layers of skin or mucosal tissues. It may be recurrent or transient, with facial, tongue, laryngeal or abdominal localisations [1]. Although most angioedema cases are idiopathic, others may be immunologic such as IgE, bradykinin and complement-mediated or non-immunologic. Bradykinin-mediated angioedema, which is non urticarial, occurs with C1-esterase inhibitor deficiency (C1-INH) and may be hereditary or acquired. Hereditary angioedema occurs after mutation in the gene encoding C1-INH, resulting in deficiency of its synthesis. Acquired angioedema is characterized by low levels of C1-INH due to its increased catabolism [2].

A 74-year-old woman was admitted in the Emergency Department with sudden-onset swelling of the lips, tongue and treated with adrenaline and corticosteroids. She was referred to the Allergy and Medical Oncology Department due to recurrent episodes of angioedema, anemia and thrombocytopenia. The Allergy Department advised clemastin fumarate and trexamamic acid, which didn't help. The patient complained also for fatigue, night sweat, weight loss and abdominal swelling. Physical examination revealed enlargement of spleen (10 cm below the left subcostal margin) and ascites, without peripheral lymphadenopathy. On respiratory examination sparse crepitations were audible at both bases. She didn't report urticarial lesions, vasculitis, rashes, atopic or similar illnesses in the family. She had been operated with 3-coronary artery bypass 3 years ago. Lab tests were as follows: hemoglobin 10.6 g/dl, platelet count 135000/mm³, leukocyte count 6800/mm³, vitamin B12: 380 (126-590) pg/ml, folic acid 4.2 (3.1-19.9) ng/ml, ferritin 134 (110-307) ng/ml, erythrocyte sedimentation rate 30 mm/h, LDH 159 (<247), and B-type natriuretic peptide 242 (0-100) pg/ml. Abdominal ultrasonography revealed splenomegaly and massive ascites. Portal Doppler was normal. PET/CT showed anterior mediastinal nodal and splenic involvement. Serum complement levels were: C3: 95 (79-152) mg/dl, C4: <1.67 (16-38) mg/dl, C1-INH level: 0.03 (0.15-0.35) g/l. Serology for antinuclear antibodies, retroviral studies, hepatitis B surface antigen, hepatitis C antibodies, Epstein-Barr virus and cytomegalovirus antibodies were negative. Ascitic cytology was normal. Echocardiogram showed global hypokinesia with ejection fraction 31% and pulmonary hypertension. Peripheral blood film showed atypical lymphocytes. Bone marrow aspiration revealed aggregation of atypical lymphocytes which were strongly positive for CD20 but negative for CD5, CD10, CD23, CD23 and TRAP, consistent with marginal zone lymphoma. The patient was thought to

have acquired angioedema due to C1-INH deficiency with marginal zone lymphoma. She started treatment with rituximab without antracycline because of cardiac failure. After two cycles of treatment the patient's attacks resolved completely and her C4 level increased to 16 (16-38) mg/dl, and C1-INH level increased to 0.15 (0.15-0.35) g/l.

Angioedema related to acquired C1-INH deficiency was first described by Caldwell in 1972 [2]. The pathogenesis of acquired C1-INH deficiency is not completely understood but it can be explained by activation of the classical complement pathway with immune complexes or monoclonal antibodies produced by the tumor tissue or autoimmune diseases. As a result, uncontrolled activation of the complement system leads to decreasing levels C4, C1q and C1-INH [2-5]. The patient herein had low level of C4, C1-INH and normal levels of C3, consistent with the diagnosis of acquired C1-INH deficiency associated with marginal zone lymphoma. This is supported also by the fact that she had not atopy history or family history. The most common lymphoproliferative diseases, especially B cell lymphoma, have been reported in C1-INH deficiency [3-5]. Treatment of underlying disease has been shown to result in remission of symptoms of angioedema and increase in C1-INH levels.

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Targeted immunotherapies overtaking emerging oncology market value based growth

Dear Editor,

European spending on pharmaceuticals within the rapidly evolving oncology indication field tops policy maker's agendas. This is the case mostly due to massive industry R&D investment followed by successful innovation and blossoming of "prosperity diseases" led by cancer among the aging European nations [1]. Emerging Eastern European pharmaceutical markets have experienced particularly sudden and profound changes during the past 25 years. Serbia could be observed as the proper example of these events as the largest Western Balkan market [2].

Unfortunately, both morbidity and mortality from cancer in Serbia grew steadily from 25,755 newly diagnosed cases (out of which 13,708 deceased) in 2004 up to 26,949 (14,924 deceased) in central Serbia in 2011 according to last update by the National Institute of Public Health "Batut". Annual reports released by the Medicines and Medical Devices Agency of Serbia allowed us an insight into oncology-related public expenditure during nine-year time span. Antineoplastic medicines value based turnover evolved alongside increased domestic demand and global supply with innovative medicines from € 19,166,161 in 2004 to € 75,968,429 in 2012. Oncology share in the national pharmaceutical market in the same time doubled, from 5.65 to 10.24%.

Regardless of undisputed growth, features of inner market transformation were far more interesting. Conventional cytotoxic agents and traditional hormonal treatments accounted for approximately 64 % market share in 2004, while only 44 % nine years after. At the same time targeted immunotherapies share grew from 37% to an impressive 56 %. Among the latter, absolute challenge was posed by protein kinase inhibitors whose total expenditure grew even 87.4 fold at a 12.5 annual rate. Highest single budget impact was attributed to monoclonal antibodies (mAbs) whose value based turnover increased from € 1,033,313 to € 19,687,454. Few others, such as interferons or TNF α inhibitors, accounted for spending exceeding € 5,000,000 in 2012.

Improved availability of novel medicines to the patients was actually rather limited in clinical practice because there are narrow indication related criteria limiting reimbursement of these medicines only to a low portion of patients. Affordability of such treatments to the ordinary citizens when financed as out-of-pocket expense is actually as poor as elsewhere across Commonwealth of Independent States (CIS), Balkan and eastern EU economies [3]. Survival rates in several key malignancies have not improved significantly based on issues of affordability and few others such as diagnostic time lag until the initiation of the first treatment protocol.

Additional burden is imposed by current, recession-caused, crisis of pharmaceutical financing sustainability across the Balkans [4]. Disputed cost-effectiveness of some mAbs in few indications has sparked additional debate among regional policy makers [5]. Targeted immunotherapies remain the promising field of industrial innovation improving both patients' survival and life quality. Nevertheless, their overall budget impact has become almost unbearable, particularly to the small national economies bordering EU economic area. Legal framework on market access and reimbursement of these pharmaceuticals has to be developed further in line with their increased availability in a variety of clinical indications. More efficient funding of these products might actually reach the patients most likely to benefit from them, thus both improving clinical outcomes and keeping the costs to a reasonable level.

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Table 1. Total and annual increase in public expenditure on pharmaceuticals indicated in oncology across key ATC code groups; Serbia 2004/2012 *(official exchange rates of National Bank of Serbia in respective years 2004 / 2012 were applied)

	2004 or closest year available	2012 or closest year available	Total public expenditure increase 2004 - 2012	Annual public expenditure increase*
L01XE Protein kinase inhibitors**	€ 96,131	€ 8,405,932	87.4	12.49
L01AB Alkyl sulfonates**	€ 145	€ 9,662	66.7	8.34
L01XC Monoclonal antibodies	€ 1,033,313	€ 19,687,454	19.1	2.12
L03AX Other immunostimulants	€ 10,837	€ 179,496	16.6	1.84
L01AD Nitrosoureas**	€ 9,758	€ 116,878	12.0	1.50
L04AC Interleukin inhibitors**	€ 25,856	€ 264,902	10.2	2.56
L01AX Other alkylating agents	€ 65,373	€ 626,057	9.6	1.06
L02BB Anti-androgens	€ 94,450	€ 823,698	8.7	0.97
L02AB Progestogens	€ 104,250	€ 749,478	7.2	0.80
L02AE Gonadotropin-releasing hormone analogues	€ 299,824	€ 2,046,541	6.8	0.76
L02BG Aromatase inhibitors	€ 598,066	€ 3,056,435	5.1	0.57
L01BC Pyrimidine analogues	€ 1,113,679	€ 3,833,980	3.4	0.38
L01CD Taxanes	€ 2,394,477	€ 7,937,944	3.3	0.37
L01BA Folic acid analogues	€ 179,897	€ 530,706	3.0	0.33
L01XA Platinum compounds	€ 1,762,908	€ 4,392,501	2.5	0.28
L03AA Colony stimulating factors	€ 734,219	€ 1,723,632	2.3	0.26
L01XX Other antineoplastic agents	€ 1,100,523	€ 2,502,959	2.3	0.25
L03AB Interferons	€ 3,022,492	€ 5,154,633	1.7	0.19
L04AD Calcineurin inhibitors**	€ 1,319,384	€ 2,135,309	1.6	0.32
L01CB Podophyllotoxin derivatives	€ 441,171	€ 681,169	1.5	0.17
L04AB Tumor necrosis factor alpha (TNF- α) inhibitors**	€ 3,779,070	€ 5,765,002	1.5	0.38
L01DB Anthracyclines and related substances	€ 1,350,572	€ 1,853,392	1.4	0.15
L04AX Other immunosuppressants	€ 373,019	€ 502,395	1.3	0.15
L01AA Nitrogen mustard analogues	€ 289,056	€ 359,153	1.2	0.14
L02BA Anti-estrogens	€ 816,893	€ 879,884	1.1	0.12
L01CA Vinca alkaloids and analogues	€ 113,151	€ 85,295	0.8	0.08
L01DC Other cytotoxic antibiotics**	€ 147,319	€ 86,624	0.6	0.08
L01BB Purine analogues	€ 443,594	€ 240,307	0.5	0.06
L04AA Selective immunosuppressants	€ 2,814,495	€ 1,463,550	0.5	0.06

*Source of data - Medicines and Medicinal Device Agency of the Republic of Serbia; ALIMIS: Annual Report on Turnover and Consumption of Pharmaceuticals 2004-2012. **Annual rate calculation differed among ATC codes groups due to missing reported values; in few marked ATC therapeutic classes, the observation period range was 5-8 years instead of 9 (the majority of cases).

Extracranial recurrence in the bone marrow of adult medulloblastoma patient – a therapeutic trap

Dear Editor,

The systemic recurrences of medulloblastoma in bone marrow are rare but diagnostically and therapeutically challenging. Only two such cases in adult medulloblastoma patients have been published thus far [1,2]. We present the third one in which bone marrow was the only site of recurrence.

In 2006, a 24-year-old female patient developed recurrent loss of balance. A tumor of the left cerebellar hemisphere (50x30x40 mm) was detected by means of magnetic resonance imaging (MRI). The patient was subjected to radical left suboccipital craniotomy and histopathologic examination of the tumor confirmed the presence of medulloblastoma infiltrating the vermis; metastases to other organs were excluded. The patient was subjected to conformal whole-brain radiotherapy including the posterior cranial fossa and spinal cord, along with 6 cycles of adjuvant PE chemotherapy (cisplatin 80mg/m², day 1; and etoposide 100mg/m², days 1-3, q3w).

In February 2008, the patient was subjected to bone marrow biopsy and flow cytometry due to severe anemia and thrombocytopenia. Cytological examination confirmed the presence of abnormal blast cells, and the diagnosis of massive bone marrow involvement by medulloblastoma was established. Neither local recurrence nor other distant metastases were observed.

In March 2008, chemotherapy with PCV (lomustine 110mg/m² P.O., day 1; vincristine 1.4 mg/m² i.v., days 8 and 29; and procarbazine 60 mg/m² P.O., days 8-17, q45 days) started. Bone marrow biopsy documented complete remission of bone marrow metastases following 4 courses of chemotherapy. However, thrombocytopenia was again observed at the end of November 2008, and bone marrow biopsy confirmed progression of the disease. Consequently, PCV chemotherapy was re-implemented and was discontinued after the third course due to unfavorable tolerance profile (hematological toxicity, opportunistic infections). Nevertheless, partial remission of bone marrow lesions was observed (about 30% of medulloblastoma cells in the bone marrow). Due to another progression (signs of thrombocytopenia, about 50% of medulloblastoma cells in the bone marrow), the patient was qualified to third-line ICE chemotherapy (ifosfamide 3g/m² i.v., day 2; carboplatin 500mg/m² i.v., day 2; etoposide 150 mg/m² i.v., days 1-3, q3w) in July 2009 with mesna and granulocyte colony stimulating factor (G-CSF) prophylaxis. After 2 courses

and 90% remission of bone marrow lesions, the patient was qualified to mobilization chemotherapy with cyclophosphamide and hematopoietic stem cell separation. However, the insufficient mobilization of hematopoietic stem cells precluded high-dose chemotherapy and autologous bone marrow transplantation.

Beginning December 2009, the patient was hospitalized many times due to massive pancytopenia. Despite blood transfusions, stimulation with G-CSF, and corticosteroid therapy, she died in May 2010 due to hematological complications resulting from bone marrow involvement.

The recurrence of our patient was diagnosed based on biopsy performed due to severe hematological disorders. This suggests that anemia and thrombocytopenia do not necessarily result solely from the toxicity of the applied therapeutic protocol. The therapy of bone marrow recurrence is particularly challenging. We have attempted all available methods of medulloblastoma recurrence treatment, and considered high-dose chemotherapy with autologous transplantation of hematopoietic stem cells. However, the specific location of recurrence in our patient induced a kind of vicious circle: the more aggressive were the applied therapeutic modalities, the greater was the injury of the bone marrow; this in turn impaired the mobilization of hematopoietic stem cells. The abovementioned evidence suggests that we are still not prepared for the treatment of rare extracranial recurrences of medulloblastoma.

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Intra-carotid chemotherapy of mandible osteosarcoma

Dear Editor,

Osteosarcoma is the most common malignant neoplasm of the skeletal system. Localization to flat bones such as the jaw is extremely rare. From May 2009 to October 2011 we treated 3 patients with osteosarcoma of the maxilla and 1 patient with osteosarcoma of the mandible (2 males and 2 females, 47 years old on average). The chemotherapy pump was embedded in the carotid artery in all cases. The proximal end of the tube should reach the bifurcation of internal and external carotid artery, and the catheter was connected to the chemotherapy pump which was embedded in the supraclavicular fossa near the incision. A total dose of epirubicin 50 mg/m² and cisplatin 120 mg/m² were continually administered through the chemotherapy pump for 3 days at low speed and the minimum transfusion time was 7 hrs each day. The next cycle of chemotherapy was repeated after 2-3 weeks. The curative effect was evaluated after 3 cycles of chemotherapy.

The average follow-up duration was 28 months. After 3 cycles of intra-arterial chemotherapy, the pain was clearly alleviated, with 2 cases showing complete remission and 2 cases partial remission. Three cases showed good imaging response consisting of shrinkage of soft tissue, reduction in tumor size and enhanced calcification on CT scan. There was no obvious imaging change in 1 case with a large tumor, but the pain was significantly relieved. The 3 cases with obvious imaging progression were administered intraarterial chemotherapy after the operation to avoid recurrence, with the interval between chemotherapy cycles gradually extended. One patient could not be operated due to the large size of the tumor, and chemotherapy was continued to relieve the symptoms. None of the 4 patients had lung metastasis during follow-up.

Like many other tumors, the pathogenesis of osteosarcoma of the jaw is not clear. Distant metastasis of osteosarcoma of the jaw is rare (6-7%) according to Huh et al. [1], while lung metastasis was the most frequently reported. A consensus has been reached that radical oper-

ation with sufficient clear margins is the most important factor for good prognosis [2]. Since the incidence of osteosarcoma of the jaw or the head and neck is generally low, then the treatment strategy for osteosarcoma of the long bone was used as a reference, which was consistent with a previous study [3]. For local control, we believe that intra-arterial chemotherapy is more effective than intravenous chemotherapy [4].

In conclusion, osteosarcoma of the jaw is characterized by local invasion and very low metastatic potential. In order to achieve local control, intra-arterial chemotherapy can be used to reduce the size of the tumor and to establish a surgical boundary between the tumor and normal tissue before radical resection.

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