

LETTERS TO THE EDITOR

Combined use of vitamin D and omega-3 fatty acid in breast cancer patients might be more beneficial for reducing aromatase inhibitors-associated arthralgia

Dear Editor,

Aromatase Inhibitor (AIs) are widely used in the adjuvant setting of hormone therapy to improve the survival of postmenopausal patients with hormone receptor positive breast cancer. Despite their beneficial effects on survival outcomes in breast cancer, AIs-induced arthralgia (AIA) is a common side effect which may lead to drug discontinuation and decreased AIs adherence among patients. Recently, a lot of studies concerning alternative treatment options in AIA have been performed to provide a good quality of life and to allow uneventful continuation of adjuvant hormone therapy [1]. Shen and colleagues in their article evaluated omega-3 (O3) fatty acid (FA) use for obese breast cancer patients with AIA [2] and they found that O3-FA use was associated with significantly lower worst pain scores at 24 weeks compared with placebo among obese patients. Several studies have demonstrated that patients who have insufficient or deficient levels of vitamin D are more likely to experience arthralgia during AIs therapy [3]. Taken all together, combined use of vitamin D and omega-3 fatty acid in breast cancer patients might be more beneficial for reducing AIA.

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Primary pulmonary follicular dendritic cell sarcoma: Successful treatment of an extremely rare case

Dear Editor,

A 52-year-old female was admitted with suspected diagnosis of echinococcus cyst in the upper lobe of the right lung. However, CT scan impression was highly suggestive of malignancy (Figure 1). Fibrobronchoscopy revealed no signs of compression or infiltration. CT-guided biopsy was not suggestive of malignancy. Following the initial evaluation, surgical intervention was indicated and right pneumonectomy was performed, as well as extensive mediastinal lymph node dissection. Macroscopically, the well-circumscribed pulmonary mass grossly measured 7.5 cm x 6.8 cm, having a firm consistency with focal calcifications, and a lobulated white to beige color. A panel of immunohistochemistry (IHC) stains demonstrated positive staining of the neoplastic cells for CD21, CD35, CD68, clusterin, CD23, HLA-DR and vimentin (Figure 2).

The patient was diagnosed with follicular dendritic cell sarcoma (FDCS) of the lung. Only one intralobar lymph



Figure 1. CT scan showing the presence of the tumor in close contact with major vessels on the right.

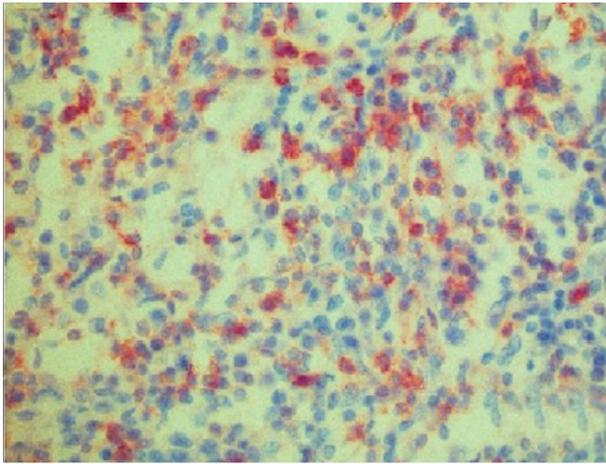


Figure 2. Immunohistochemistry (x20) with CD23 showing positivity in tumor cells organized in fascicles and whorls pattern.

node was involved by malignancy. She was treated with six cycles of chemotherapy (vincristine + doxorubicin + endoxan). Five years postoperatively, she is healthy, with no recurrences.

FDCS is an extremely rare tumor of lymph nodes and extranodal tissues, which usually presents as a painless mass without systemic symptoms [1]. It behaves like an intermediate-grade sarcoma with a substantial risk of local recurrence (28.1%) and distant metastasis (27.2%) [2]. Lung involvement is usually metastatic. Primary FDCS mainly affects lymph nodes, thus primary FDCS presenting in extranodal sites, such as lungs in our case, are worth the maximum attention due to their rarity [1,3]. The diagnosis of FDCS is established based on the findings of morphology and IHC that includes positive staining for CD21, CD23, CD35, vimentin, fascin, HLA-DR, epithelial membrane antigen, clusterin, and D2-40 [1]. Although various treatments including surgery, chemotherapy, radiation therapy,

and combinations of these modalities have been used, complete surgical resection is still the mainstay of treatment for primary FDCS. Only the tumor size and lymphoplasmacytic infiltration in tumor tissue are accepted as important prognostic parameters [2,3].

IHC plays a pivotal role in the diagnostic accuracy of this type of tumor due to the reliable tumor markers. Therefore, as soon as FDCS is suspected histologically, IHC stains for follicular dendritic cell differentiation should be performed to avoid the risk of misdiagnosis. Clusterin is a significantly useful marker in the differential diagnosis of FDCS to other dendritic cell tumors. We highlight the crucial importance of surgical treatment for this uncommon tumor, among the multidisciplinary modalities.

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BRAF mutations in oral malignancies

Dear Editor,

The BRAF gene is located on chromosome 7 (7q34), and the corresponding protein acts as transition agent for extracellular signals to the nucleus. It belongs to a significant signaling pathway: the RAS-(B) RAF-MEK-ERK/MAPK (Rat Sarcoma- Mitogen-Activated Protein Kinase) providing normal cell proliferation combined with differentiation and migration during epithelial tissue morphogenesis involved also in apoptosis. BRAF mutations lead to its oncogenic transformation as it happens in other similar growth factor receptors located also on the same chromosome: Epidermal Growth Factor Receptor (EGFR-gene locus: 7p12), MET proto-oncogene, receptor tyrosine kinase (c MET-gene locus: 7q31). Interestingly, specific point mutations such as BRAF V600E -detected by high sensitive polymerase chain reaction (PCR) technique - are correlated with increased response rates to targeted therapeutic strategies based on tyrosine-kinase inhibitors (TKIs) [1]. New generation anti-BRAF TKIs including dabrafenib, vemurafenib and

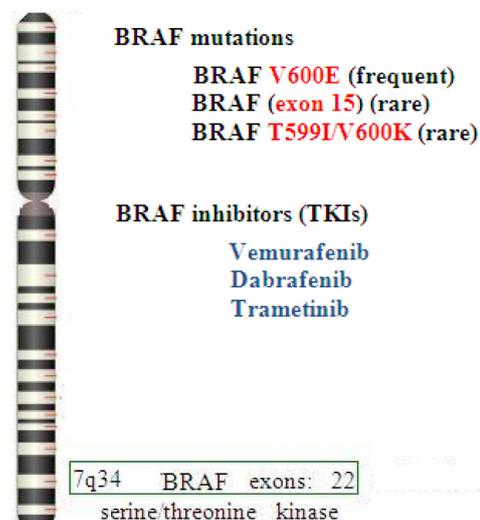


Figure 1. BRAF gene location; mutations and inhibitors.

trametinib have been proved effective in handling patients with BRAF(V600E)-mutant metastatic non-small cell lung carcinoma (NSCLC) and melanoma [2].

Although BRAF-mutant depended-NSCLC and also melanomas respond to those two agents in remarkable rates, there are limited data regarding BRAF mutations in oral cavity malignancies. Based on a multi-gene molecular analysis, Lyn et al. showed that driver mutations are rare in mutational hotspots of BRAF in oral mucosal melanoma. They also concluded that the majority of patients will not benefit from BRAF inhibitors [3]. In contrast to oral melanomas, patients with advanced oral squamous cell carcinoma (OSCC) demonstrate higher rates of BRAF mutations detectable by next-generation sequencing (NGS) implementation [4]. Furthermore, the role of BRAF mutations not only in advanced OSCCs but also in hyperkeratotic lesions is under investigation [5]. It seems that pre-neoplastic lesions harbor a spectrum of specific point mutations - not only the BRAF V600E - leading to a progressive malignant cell phenotype. In conclusion, primary mucosal melanoma of the oral cavity - which is a very rare malignancy - and OSCC demonstrate different BRAF mutational spectrum and rates. Concerning their response to new generation anti-BRAF TKIs, it seems that this depends on the type of point mutation.

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De-escalating systemic chemotherapy might be considered for pure triple negative apocrine breast cancer patients

Dear Editor,

Triple negative (TN) breast cancers have the highest relapse risk and the least favourable prognosis among all breast cancer subtypes, leading to a substantial escalation of chemotherapy (anthracyclines and taxanes) during recent years. Pure apocrine carcinoma (AC) is a rare TN breast cancer. Although TNAC are relatively rare and commonly treated as non-apocrine triple negative (NATN) tumors, few studies reported significantly different behavior and prognosis for TNAC when compared with most NATN tumors. A recent study analyzed the clinicopathologic features of a series of 46 TNAC tumors treated in a 15-year period. The patient mean age at diagnosis was 60 years. The authors reported that TNAC seems to represent a distinct group of TN breast cancer, characterized by a favorable long-term outcome. However, they did not describe that all TNAC cases were pure AC or not in this study [1]. I just analyzed my own breast cancer dataset. Among 6038 invasive breast cancers, 5 pure TNAC cases were identified. Their mean age was 62.2 (older age compared to all TN breast cancer cases). All cases were grade III except one with grade II. All tumors were androgen receptor positive as we reported in our

previous study [2]. All cases were diagnosed as stage I disease treated with adjuvant CMF. Median follow-up was 26 months. During follow-up, no recurrences were observed. Taken all together, de-escalating systemic chemotherapy might be considered for pure TNAC patients. This issue merits further investigation.

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Bcl-2 as a target in laryngeal squamous cell carcinoma

Dear Editor,

Apoptosis represents the programmed cell death mediated by a complex of proteins which influence positively or negatively intrinsic and extrinsic pathways. Two main pathways are involved in the previously described apoptotic procedure: intrinsic and extrinsic, respectively. In both of them several proteins are characterized as inducers or inhibitors of apoptosis [1]. The first uses mitochondrial proteins with prominent the cytochrome C from the inter-membrane space of the organelle. Its activity in the cytoplasm activates caspases (especially caspase-9) complex under the control of p53 and Bcl-2 (B-cell lymphoma-2) proteins. Apoptotic signals are triggered by intra-cell stress conditions including hypoxia, DNA damage, and altered protein accumulation. Concerning the extrinsic pathway, this is based on receptor-ligand complexes that are activated when the cell receives from its surface (membrane) the corresponding signals from the intercellular environment. Among the proteins that play a critical regulatory role in modifying apoptotic process, Bcl-2 acts as a main suppressor molecule, interacting also with other molecules such as p27 and p16 [2]. Bcl-2 protein production and localization are observed in the outer mitochondrial membrane and encoded by the corresponding gene on chromosome 18 (cytogenetic band location: 18q21.33). The protein demonstrates two isoforms, isoform 1 and isoform 2, which create specific biochemical structures for binding to BAD and BAK proteins. Deregulation of the gene based on the mechanism of chromosomal translocation involves chromosomes 14 and 18 in follicular lymphomas. Referring to the laryngeal squamous cell carcinoma (LSCC), Bcl2-aberrant expression leads cancer cells to escaping from their genetically programmed cell death and combined to telomerase overexpression immortalizes them. Many studies analyzing the molecule at DNA, mRNA and protein level have shown that Bcl-2 protein overexpression in LSCC patients is correlated with poor prognosis due to the increased resistance in radio-chemotherapeutic regimens. According to them, gene polymorphisms, such as BCL2-938C>A, could be considered as biomarkers for predicting the genetic profile of radiotherapy response [3]. In addition, combined BAX/Bcl-2 expression as a ratio at the mRNA level should be a potentially reliable molecular marker for following up LSCC patients with specific characteristics (low metastatic activity with negative lymph nodes) [4].

Quite recently, micro-RNAs (miRs) are considered as novel significant markers for discriminating patients based on their molecular characteristics. miRs are short, non-coding RNAs consisting of 20-25 nucleotides located at intra- or intergenic regions. Functional miRs mediate a

positive regulation of posttranscriptional gene silencing. Their deregulation in cancer cells due to genetic (mutations, translocations), epigenetic (DNA hypermethylation of tumour suppressor genes, extensive genomic DNA hypomethylation, aberrant histone modification patterns) and transcriptional alterations leads to a loss of miRs-mediated repression of target mRNA. A specific miR (miR-34c) seems to interact with Bcl-2 by targeting its protein expression and inhibiting its anti-apoptotic activity [5]. For this reason, there is an increasing research and development of anti-Bcl-2 agents in order to prevent its action inducing apoptotic rates in LSCC patients.

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Amazing result of Nivolumab in a patient with multiple carcinoma

Dear Editor,

Nivolumab, is a fully humanized IgG4 anti-PD-1 monoclonal antibody; its mechanism of action is mediated

through binding PD-1 (programmed death type 1) and preventing its linking with PDL-1 (programmed death ligand type 1). Nivolumab can help the immune system to recognize and fight cancer. PD-1 expression is increased in many

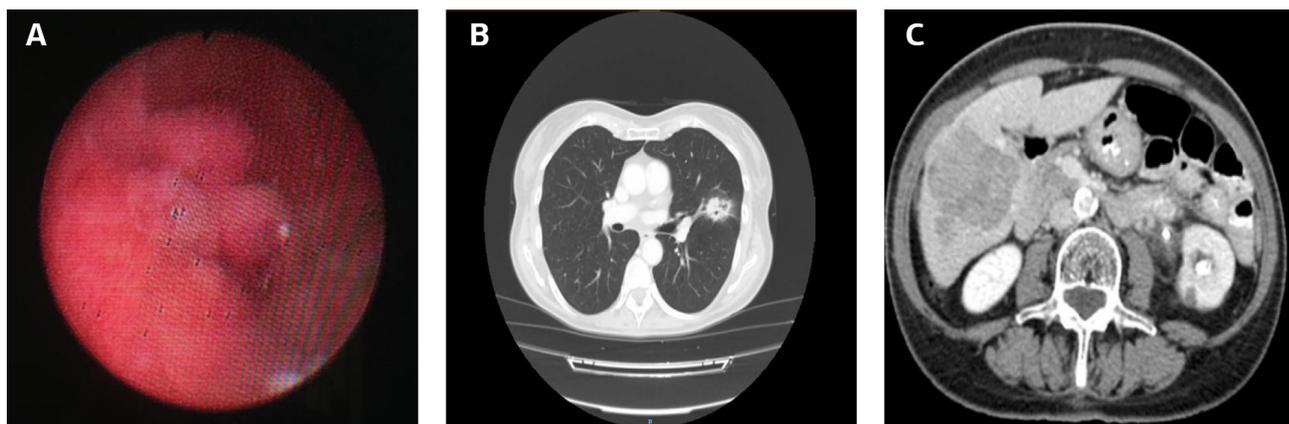


Figure 1. **A:** Urothelial carcinoma of the upper urinary tract. **B:** Lung nodule, **C:** Hepatic mass.

types of cancer and could be a possible resistance mechanism of the tumor against the host's immune response. FDA approved the use of Nivolumab as a first-line treatment for unresectable or metastatic melanoma, BRAF wild type (WT) or mutated, as a second-line treatment following a doublet platinum chemotherapy in squamous or non-squamous non-small cell lung carcinoma (NSCLC) and as second-line treatment after usage of tyrosine-kinase inhibitor for renal cell carcinoma [1,2], while recently it was approved as second-line treatment in hepatocellular carcinoma after first-line treatment with sorafenib [3].

FDA approved Nivolumab for primary or metastatic urothelial bladder cancer. It can be used for locally advanced or metastatic form in patients that experience disease progression during or following platinum-containing chemotherapy or have progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

A 67-year-old Caucasian Italian female with history of generalized anxiety, chronic obstructive pulmonary disease (COPD), osteoporosis and polyarthralgia is the case studied.

She was a heavy smoker, denied allergies to drugs and/or food and family history of pulmonary neoplastic disease.

In October 2015 she arrived to Magna Grecia University Urology Unit for abdominal renal colic type pain. Diagnostic left ureteroscopy showed a ureteral neoplastic lesion at the proximal third of the ureter (Figure 1A). Pathology showed low-grade urothelial carcinoma with infiltration of the subepithelial connective tissue, low-grade cytology and tumor size 1.5-2 cm. Staging total body CT scan revealed a 3.7 cm nodular opacity in the left lung (Figure 1B) and a 6 cm hepatic lesion, compatible with hepatocarcinoma (Figure 1C); the left renal pelvis appeared disfigured and with a hypodense area of unclear relevance, while paralumbar lymph nodes were negative. A following PET scan confirmed hepatic and pulmonary lesions.

In December 2015 she underwent left upper lobectomy with mediastinal lymphadenectomy. Histopathological study showed a poorly differentiated adenocarcinoma (G3), pT2a, pN0. In March 2016 she underwent segmentectomy of the V and VI liver segments that were consistent of poorly differentiated hepatocarcinoma (G3), p T1, G3.

The patient was put on clinico-laboratory follow-up while the urothelial cancer had not been treated due to her physical condition and for the previous surgical interventions.

In July 2016 a follow-up PET scan detected pathological uptake in mediastinal lymph nodes (SUV 11.5) and in C7-D1 vertebrae (SUV 8.5). The patient started radiotherapy (30 Gy for 15 days) and first-line platinum-doublet chemotherapy. (cisplatin 75 mg/m² q 21 days and gemcitabine 1000 mg/m², days 1 and 8 q 21 days for 3 months/August-November 2016). The choice of this regimen was due to the presence of two neoplasms (pulmonary and urothelial), both sensitive to these drugs.

Follow-up showed stable disease, but in April 2017 a whole body CT scan showed stable liver appearance but revealed a 3 cm nodular lesion in the left lung. The ureter appeared inhomogeneous and thickened and ureterocystoscopy showed evidence of urothelial progressive disease.

In May 2017 the patient started treatment with Nivolumab (3 mg/kg every 14 days). The successive CT scan and ureterocystoscopy (August 2017) demonstrated partial response in the urothelial cancer and stable disease in the lung. There was no local liver relapse.

In November 2017 she underwent urethrocytoscopy due to recurrent episodes of hematuria, that showed the presence of left bladder neof ormation.

The survival of these types of cancer is less than 1 year without some kind of treatment [4,5]. Our patient is still alive 41 months from the diagnosis of three cancers with good performance status (ECOG 0) and quality of life.

This incredible incidental diagnosis for a simple symptomatology, such as renal colic, that led to the discovery of three different neoplasias highlights the necessity that in many cases today, a multidisciplinary diagnostic and therapeutic team is fundamental and can lead to impressive results.

Although Nivolumab was indicated only one year ago mainly for advanced or metastatic squamous and non-squamous lung cancer, today there are many studies demonstrating efficacy and safety of Nivolumab in urothelial and hepatic malignancies [4,5].

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The importance of regorafenib and lenvatinib in the treatment of hepatocellular carcinoma

Dear Editor,

More than half of the liver cancers are diagnosed at advanced stage. Despite advances in cancer therapies, Sorafenib is used as the first treatment for advanced-stage liver cancer until recently. In the vast majority of patients, time-dependent resistance to Sorafenib will develop [1,2].

Regorafenib (Stivarga), which can be used if the disease does not respond to Sorafenib (Nexavar), is preferred. Regorafenib, which is also a multikinase inhibitor and derived by adding only 1 fluorine to the chemical structure of Sorafenib, is used in the treatment of different cancers, especially leukemia and melanoma. Its use in the treatment of hepatocellular carcinoma (HCC) was approved by the FDA in April 2017 for use only in patients resistant to Sorafenib. However, the mechanism of action and associated signaling pathways of this new drug are not yet fully known [3,4]. Regorafenib has been shown to inhibit tumor growth and metastasis by blocking VEGFR1-3, c-KIT, PDGFRB, FGFR-1 tyrosine kinases and RAS / RAF / MEK / ERK signaling pathways in *in vitro* studies on different cancer cell lines [4]. In the treatment-oriented phase III trials of Bruix et al. in the HCC patient groups that were resistant to Sorafenib, the risk of death compared to placebo was decreased by 38% in patients receiving Regorafenib after Sorafenib treatment, and the survival rate was 10.6 months in the Regorafenib treatment when the mean placebo rate was 7.8 months. In this sense, Regorafenib was the first second-line medication defined in the HCC that could be used in patients who failed to respond to Sorafenib [3].

One recent study presented at the 2017 ASCO meeting, predicted that Lenvatinib can be used with good results in the treatment of advanced-stage HCC. Thyroid cancer in 2015, with the FDA approval for the treatment of kidney cancer in 2016, Lenvatinib (market name Lenvima) acts by preventing the activation of tyrosine kinase receptor in the cell membrane [5]. Kudo et al. in their REFLECT phase 3 study, reported that half of advanced-stage HCC patients who had not received any treatment before and could not be operated were given Lenvatinib and the other half Sorafenib. At the end of the study, time to progression was approximately 4 months in the Sorafenib group and 9 months in the Lenvatinib group. However, only 9% of patients responded fully to Sorafenib, while this rate was 24% in patients undergoing Lenvatinib treatment. In addition, the median survival of patients using Lenvatinib was

approximately 13.6 months (95% CI 12.1-14.9), compared to 12 months in patients using Sorafenib (HR 0.92, 95% CI 0.79-1.06). Lenvatinib was more effective than Sorafenib in the treatment of advanced-stage HCC [5].

In conclusion, the results of the RESORCE [3] and REFLECT [5] studies should be verified by future studies in order for both Regorafenib and Lenvatinib to become standard treatment of advanced-stage HCC. The effects of RAS/RAF/MEK/ERK signaling pathways are not known yet. Clarifying these issues will help clinicians create new treatment strategies.

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