LETTERS TO THE EDITOR __

Triple-negative breast cancer patients with isolated lung metastases and concomitant COVID-19 infection; does cytokine storm result in better efficacy?

Dear Editor,

The COVID-19 pandemic presents health-care professionals a unique set of challenges in managing breast cancer patients. Expert consortium presented recommendations for prioritization, treatment, and triage of breast cancer patients during the COVID-19 pandemic [1]. Authors also mentioned management of triple-negative breast cancer (TNBC). However, they did not discuss the use of immunotherapy in metastatic TNBC during COVID-19 pandemic. Immunotherapy has emerged as a promising treatment modality for TNBC. Initial trials have established a role for anti-PD-L1 in the first-line metastatic setting in combination with chemotherapy. IMpassion130 was a phase III trial that demonstrated progression-free survival benefit, and potentially overall survival benefit, of first-line chemotherapy (nab-paclitaxel) plus anti-programmed death ligand 1 (PD-L1) atezolizumab, among PD-L1-positive metastatic triple-negative breast cancers [2]. Severe pneumonia caused by COVID-19 is often associated with induced hypercytokinemia, also termed cytokine storm, and uncontrolled overproduction of inflammatory cytokines contributes to acute lung injury and acute respiratory distress syndrome [3]. Taken all together, if TNBC patients with isolated lung metastases receiving immunothrapy plus chemotherapy get infected

with COVID-19 pulmonary infiltration, one would expect that their metastatic lung nodules might be treated better in this increased cytokine storm atmosphere. This issue merits further investigation.

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Enhancing PTEN suppressor gene expression in pancreatic carcinoma

Dear Editor,

Pancreatic cancer is one of the most lethal gastrointestinal malignancies and the fourth leading cause of cancer associated cases of mortality worldwide. The main cause is late detection -called "silent killer" - and lack of methods for the proper evaluation of response to the therapeutic regimens. Combined k-ras oncogene overactivation and suppressor genes downregulation frequently are observed in pancreatic carcinogenesis [1]. The PI3K/AKT/ PTEN/mTOR signaling transduction pathway regulates many critical cell functions including cell proliferation, protein synthesis and survival. Concerning carcinogenesis, gene imbalances lead to tumor growth and angiogenesis by deregulating VEGF and hypoxia-inducible factor-1 expression [2]. *PTEN* (gene locus: 10q23.3-phosphatase and tensin homolog deleted in chromo¬some 10) is a tumor

suppressor gene that is deleted, mutated or epigenetically hyper-methylated in a variety of human malignancies. PTEN acts as a negative regulator of this specific pathway. Normal expression of PTEN induces growth suppression by promoting cell cycle arrest. It is also correlated with decreased levels and nuclear local-ization of cyclin D1 regulated by AKT that positively induces cell cycle [3].

PTEN downregulation in pancreatic carcinoma seems to be a significant genetic event inducing the aggressiveness of the malignancy, such as proliferation and invasion. Novel therapeutic molecular approaches are based on specific agents that target critical proteins including PTEN. Enhancement of molecules' expression stabilizes the corresponding signaling transduction pathways. Two recent studies analyzed the effects of epigallocatechin 3 gallate and nimesulide on the inhibition of proliferation and induction of apoptosis of pancreatic cancer cells [4,5]. Both molecules where shown to have promising positive effects on pancreatic cancer by enhancing the expression of PTEN and by suppressing the expression of AKt/mTOR and therefore limiting the proliferation of cancer cells. Interestingly, nimesulide acts as a proliferation inhibitor and apoptosis inducer by cleaved caspase-3/Bax overexpression and bcl-2 downregulation. Concerning its exact role at gene expression balance, the molecule acts as a selective COX-2 inhibitor and also as a PTEN enhancer. Similarly, epigallocatechin 3 gallate suppresses the expression of p Akt and p mTOR proteins in the corresponding pathway.

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Poor histological subtype and response to neoadjuvant treatment in triple-negative breast cancer

Dear Editor,

Previous studies showed encouraging antitumor activity and good safety profile associated with pembrolizumab, an anti-programmed death 1 monoclonal antibody, in patients with early triple-negative breast cancer. Schmid et al [1] randomized patients with previously untreated stage II or stage III triple-negative breast cancer to receive neoadjuvant therapy with four cycles of pembrolizumab every 3 weeks plus paclitaxel and carboplatin (784 patients; the pembrolizumab-chemotherapy group), or placebo every 3 weeks plus paclitaxel and carboplatin (390 patients; the placebo-chemotherapy group); the two groups then received an additional four cycles of pembrolizumab or placebo, and both groups received doxorubicincyclophosphamide or epirubicin-cyclophosphamide. They reported that the percentage with a pathological complete response was significantly higher among those who received pembrolizumab plus neoadjuvant chemotherapy than among those who received placebo plus neoadjuvant chemotherapy among patients with early triple-negative breast cancer. However, the distribution of histologic subtype in the two arms was not defined. Histologic heterogeneity (metaplastic breast cancer vs. medullary breast cancer vs. others) in triple-negative breast cancer significantly affected the survival outcome [2]. Therefore, pathological complete response rates might be affected by the percentage of triple-negative breast cancer with poor histological subtypes such as metaplastic breast cancer in each arm. This issue merits further investigation.

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Sentinel lymph node biopsy in papillary breast cancer; to do or not to do?

Dear Editor,

Papillary carcinoma (PC) of the breast is a rare breast tumor that accounts for 0.5-1% of breast cancers. Cur-

rently, there is no consensus on the management of PC. Common management is usually local surgical excision followed by radiotherapy or systemic therapy. The role of sentinel lymph node biopsy (SLNB) is still a debatable issue [1]. Layon et al presented a cohort of 44 breast papillary carcinoma (PC) patients and examined the clinicopathological features and outcome of loco-regional staging. They showed only one histologically confirmed PC case had evidence of nodal metastasis [2]. They proposed that SLNB should not be routinely indicated for patients with PC treated with breast conservation. In my own breast cancer dataset with 6318 patients, 13 breast cancer patients with PC were found. Among these, 2 (15%) patients were having nodal metastases. Therefore, PC cases are very rare breast cancers, and SLND procedure indication is not clear in PC. Our cases seem to support potential utility of SLND in PC. This proposal should be studied in larger cohorts with PC.

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Diabetes mellitus as a risk factor in oral squamous cell carcinoma development

Dear Editor,

Diabetes mellitus (DM) is a serious metabolic disease and seems to be involved in the onset of a variety of carcinomas. A recently published study showed that the risk of developing Head and Neck Squamous Cell Carcinomas (HNSCCs) was decreased among diabetic patients compared to non-diabetic ones [1]. Interestingly, this risk was further decreased among diabetic metformin users even if they were current smokers or exposed to chronic alcohol consumption. It is known that metformin is an oral anti-hyperglycemic agent used to treat type 2 DM. In conjunction with the previous results, another study group concluded that metformin prevents the progression of dysplastic mucosa even in non-diabetic patients [2]. They analyzed the results of adjuvant metformin therapy for treating recurrent and multifocal dysplastic lesions in previously treated nondiabetic HNSCC patients. Interestingly, all examined cases showed complete or partial regression of the remaining mucosal lesions and did not require any additional operations. Understanding the mechanisms of DM involvement in onset and progression of oral squamous cell carcinoma (OSCC) is a promising field in molecular categorization and handling of these patients. A study group explored the role of persistent hyperglycemia in the malignant transformation of oral pre-malignant epithelial lesion (leukoplakia). They detected a statistically significant difference between the two clinicopathological entities in a series of patients that developed OSCC [3]. Similarly, other studies analyzing the etiopathogenetic relation between DM and HNSCC including OSCC - showed that this metabolic deregulation leads to carcinoma development and progression (increased metastatic potential) due to hyperglycemia, hyperinsulinemia and insulin resistance, or chronic inflammation [4]. In order to identify specific molecules that are implicated in OSCC development, as study analyzed saliva samples from DM patients using also the corresponding healthy people samples as a control group [5]. They observed that Annexin A8, Peroxiredoxin-2 and Tyrosine kinase were overexpressed in the metabolic syndrome patient group. Because these proteins have been recognized also in OSCC saliva samples, they proposed them as reliable biomarkers for an early detection of the malignancy. Furthermore, the

preventing role of specific anti-diabetic agents, such as metformin in the development and progression of the current malignancy seem to be crucial even in non-type 2 DM patients. The last earn benefits of resistance in the carcinogenetic process even demonstrating dysplastic squamous cell mucosa, evidence that this drug acts as a suppressor agent in cell proliferation. In conjunction to this, identification of altered genes in the pre-malignant stages (oral leukoplakia) correlated with DM should be a significant approach in detecting subgroups of them demonstrating specific genetic signatures and high or low risk for developing OSCC.

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Is there a role of anthracycline use in the management of *de novo* HER-2 positive metastatic breast cancer?

Dear Editor,

Differences in disease characteristics and clinical outcomes have also been reported for patients with HER2 positive metastatic breast cancer (MBC) presented at first breast cancer diagnosis (i.e., *de novo* MBC) versus patients diagnosed with metastatic disease after an early breast cancer (EBC) diagnosis (i.e., recurrent MBC). Treatments targeting HER2 have become important agents in the management of metastatic HER2-positive breast cancer and have altered significantly the natural course of this disease [1]. Anthracyclines are commonly used in the management of HER2-positive EBC. However, anthracycline use is commonly limited in the management of patients diagnosed with HER2-positive metastatic disease after an EBC diagnosis who use anthracyclines as adjuvant or neoadjuvant treatment because of the cardiotoxicity risk and expectable resistance of metastatic tumor cells to anthracyclines. However, the situation is different in *de novo* HER2-positive MBC. In this patient population, first-line (taxanes and trastuzumab and pertuzumab) and second-line (trastuzumab-emtansine) anti-HER2 regimens are commonly preferred. However, treat-

ment of choice as a third-line is still controversial. At this step, anthracyclines might be alternative efficacious agents in the management of *de novo* HER2-positive MBC [2]. This proposal should be explored in randomized studies.

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Specific histological subgroups in invasive lobular carcinoma might affect outcome in both chemotherapy and non-chemotherapy groups

Dear Editor,

Invasive lobular carcinoma (ILC) is the second most common histologic form of breast cancer, representing 5-15% of all invasive breast cancers. Several variants of ILC have been described like classical type, mixed type, pleomorphic lobular type with different survival oucomes [1]. Watanuki et al retrospectively investigated the impact of neoadjuvant and adjuvant chemotherapy on ILC [2]. They just reported that neoadjuvant and adjuvant chemotherapy significantly improved 10-year survival rates for ILC, particularly in patients with large tumor size and lymph node metastases. The authors did not mention pathological characteristics of ILC. We could estimate that most cases seem to be classical ILC. However, subgroups suc as ILC + invasive ductal carcinoma (mixed type) or pleomorphic lobular carcinoma cases might exist in both chemotherapy and non-chemotherapy groups. These specific subgroups might give better response to chemotherapy and affect the outcome in both chemotherapy and non-chemotherapy groups. This issue merits further investigation.

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Comment on Raze's views on cancer and the introduction of chemotherapy

Dear Editor,

We read and enjoyed the fascinating article published in the $24^{\rm th}$ volume of this journal, entitled "Rhazes' (864-

925) views on cancer and the introduction of chemotherapy" by Gregory Tsoucalas et al. We were filled with interest to find valuable information about a Persian physician and philosopher, Abu Bakr Muhammad ibn Zakariya al-Razi,

which can show the keen manner of the authors in the history of medicine.

The bright spot of this paper lies with its introduction of Razi among the first ones who adhered to chemotherapy and one who described some pediatric disorders and the differentiation between smallpox and measles.

Nevertheless, there are some arguable points in this article. It writes that Razi was an Arab physician in the Arabo-Islamic medicine school and that he authorized the Al-Havi book. Moreover, it discusses that Razi was a pupil of Hunayn Ibn Ishaq (809-873), who dominated several medical doctrines such as Hindi medicine. Additionally, it argues that Razi learned medicine from Abu al-Hasan Ali ibn Sahl Rabban al-Tabari (a Persian physician), who lived in the 9th century AD [1].

According to our researches about the nationality of Razi, he was a Persian physician who lived during the Persian-Islamic era. In fact, the Islamic culture entered and grew in the context of Persian culture, building on ancient Persian achievements, which contained Unani/Greek medicine too [2].

Although Ishaq-ibn-Honayn was contemporary with Razi and resided and translated several non-Arabic texts to Arabic for physicians in Baghdad, there is no evidence to demonstrate the authority of Honayn in Indian medicine, whether compilation or translation. Nor can we find a document that shows Razi as a pupil of Ishaq-ibn-Honayn [3].

There is also some doubt as to whether Razi was a pupil of Tabari. According to Persian-Islamic historical texts, Abu al-Hasan Ali ibn Sahl Rabban al-Tabari was a Persian physician born in 916 (death in 986 AD) [4], whereas Razi is considered to have lived through 864-925 AD. Therefore, Tabari was prior to Razi and it is inconceivable for Razi to be a pupil of Tabari. Also, it is hypothesized that Al-Havi fi Al-Tib was not a book authorized by Razi; it seems to be a collection of Razi's or his pupil's pieces of handwriting, entitled in Persian as Konash Al-Havi [5].

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Immunohistochemical characteristic of each foci in multifocal or multicenter breast cancers should be deciphered to determine the best adjuvant treatment of choice

Dear Editor,

Studies have looked at immunohistochemical heterogeneity of foci in mulifocal (MF) and multicenter (MC) breast cancers. Different histologies in the same breast might lead to change in adjuvant treatment [1,2]. A 45-yearold lady came to my clinic with a diagnosis of right breast cancer. Right mastectomy with sentinel lymh node dissection was performed due to MC and MF disease pattern of breast cancer. Two sentinel lymph nodes were negative with tumor infiltration. Four foci of primary breast cancer were determined with 0.5 cm, 0.9 cm, 0.8 cm, and 0.4 cm in size. The first focus was having invasive ductal carcinoma with luminal A subtype characteristics and the second and fourth foci were diagnosed as micropapillary carcinoma having hormone receptor negative with HER2 positivity. The third focus was pure invasive lobular carcinoma with luminal A subtype characteristics. She then started receiving four cycles of adjuvant doxorubicin and cyclophosphamide followed by taxane and 1 year of trastuzumab and adjuvant endocrine treatment. Taken all together, decipherig the histological and phenotypic differences among foci could determine the best adjuvant treatment choice in MC or MF breast cancers.

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Clinical and pathological characteristics of breast cancer patients with sarcoidosis

Dear Editor,

Sarcoidosis is a chronic inflammatory condition that may increase the risk of cancer, but limited information is available on the occurrence of cancer in these patients [1,2]. In my own dataset including 6496 invasive,breast cancer patients, three female patients were diagnosed with chronic sarcoidosis with pulmonary involvement before or after the diagnosis of breast cancer. The first patient was 49 years old post-menaopausal woman diagnosed with left breast cancer. She had a diagnosis of sarcoidosis 1 year before breast cancer diagnosis and had breast conserving surgery (BCS) and sentinel lymph node dissection (SLND). Her stage was T1N0M0 with luminal A subtype and she received adjuvant radiotherapy and 5 years of anastrozole and she was in remission with 80 months of follow-up. The second patient was 49 years old pre-menopausal woman diagnosed with left breast cancer. She had a diagnosis of sarcoidosis 4 years after breast cancer diagnosis and had left modified radical mastectomy. Her stage was T1N1M0 with luminal B and HER-2 positive subtype and she received six adjuvant cycles of FAC and radiotherapy, followed by 3 years of tamoxifen and 2 years of exemestane and she was in remission with 131 months of follow-up. The third patient was 40 yearsold pre-menaopausal woman diagnosed with right breast cancer. She had a diagnosis of sarcoidosis 7 years before

breast cancer diagnosis and had BCS and SLND. Her stage was T1N1M0 with luminal A subtype with oncotype Dx score of 20 and then she received six adjuvant cycles of CMF and adjuvant radiotherapy and is still receiving adjuvant tamoxifen and she is in remission with 30 months of followup. Taken all together, clinical-pathological characterics of breast cancer patients seem to be heterogeneous. Although the number of cases is so small, their survival outcome appears to be fairly good.

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