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LETTERS TO THE EDITOR

Metastasis-acquired changes in clinically actionable genes in triple negative breast cancer patients with central nervous system metastases: Focus on HER2 targeted therapies

Dear Editor,

Breast cancer is the second most common cause of metastatic disease in the central nervous system (CNS). The treatments for patients with CNS metastasis have not advanced at the same rate as for patients without CNS involvement. Those patients remain an disproportionately low represented population in early phase clinical trials as a function of their poor performance status and expected lack of efficacy in the treatment of CNS metastases with therapies primarily directed towards extracranial disease. Patients with HER2 positive (HER2+) or triple negative breast cancer (TNBC) [1] are at highest risk of developing CNS metastasis. Among the breast cancer subtypes, TNBC patients with CNS metastases have a worse prognosis emphasizing the need for urgent targeted therapies. One of the difficulties to find developmental therapeutics for TNBC CNS metastasis is the lack of knowledge on metastasisacquired features and important expression changes in clinically actionable genes [2,3]. Accordingly, a recent study investigated whether there are intrinsic subtype differences between primary tumors and matched CNS metastases and to uncover CNS metastases-acquired alterations that are clinically actionable [4]. Twenty cases of primary breast cancer tissue and resected CNS metastases were studied. The authors found that approximately 20% of TNBC patients with CNS metastases showed copy number alteration and/or single-nucleotide variation. These results implicate that some of TNBC patients with CNS metastases may be treated with anti- HER2 targeted therapies.

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Novel techniques for morphometric and geometrical analysis in squamous intraepithelial lesions on cervical smears

Dear Editor,

Accurate detection and categorization (Bethesda 2001-revised 2014 criteria) of squamous intraepithelial lesions (SILs) based on Papanicolaou test (Pap test) is a crucial step in handling the corresponding patients by applying colposcopy, biopsy and ancillary examinations (HPV DNA test, E6/E7 mRNA test, protein markers: p16/ ki 67). Low to high grade SILs demonstrate a broad spectrum of abnormal cytological characteristics. Increased Nuclear/Cytoplasm

(N/C) ratio combines usually with specific atypical features. Nuclear enlargement, hyperchromasia, irregular nuclear membrane contours, perinuclear cytoplasmic cavities (HPV-depended koilocytic morphology) and keratinizing cytoplasmic formations are the main of them. Introduction of Atypical Squamous Cells of Undetermined Significance (ASC-US) and Atypical Squamous Cells not excluding HSIL (ASC-H) terminology shows the subjectivity regarding the interpretation on diagnostically borderline cases.

A major issue in semi- or fully-automated/robotic digital image analysis systems is the level of successful segmentation of the overlapping cells, especially in cluster formations. A study group designed an experimental data cluster analysis-based classification of overlapping nuclei in Pap smears. They showed that an updated detection of overlapping was achieved by performing a fuzzy clustering algorithm. Based on this, two local minima-based and three shape-dependent features are extracted for determination of the presence or absence of overlapping [1]. Similarly, other investigators showed that an improved level of cytoplasm and nuclei segmentation was assessed by applying an automatic color cervical smear image using an efficient superpixel-based Markov random field (MRF) gap-search framework. According to this technique, the whole image changes to an undirected probabilistic graphical model. An automatic label-map mechanism determines nuclear, cytoplasmic and background regions [2].

The authors of another study focused on the management of high-density digital image databases regarding Pap test slide analysis. They developed a framework for creating realistic synthetic bright-field microscopy images that can be used for algorithm development and benchmarking [3]. Furthermore, an experimental digitized analysis of the spatial distribution and thickness of liquid-based specimens was performed by another study team. They concluded that by considering the thickness of the specimen, an improved focal map can be produced providing an exhaustive high-resolution scan of the examined slides [4]. Concerning the level of accuracy in detecting abnormal cells on Pap test slides, a quite recently published study explored the role of a reference and calibration grid on conventional coverslips by employing a novel, efficient technique of laser-based micromachining. The study group showed that grid-based microscopy led to a more reliable diagnosis compared to the conventional one by identifying an increased number of abnormal cells. They suggested that the described grid acts as a calibration and orientation visual aid during the on-site screening process providing significant advantages compared to expensive digital imaging techniques [5].

In conclusion, a variety of novel, sophisticated techniques have been designed and applied in Pap test slide diagnostic process. Implementation of morphometric/ densitometric algorithms (measurement of areas, max/min diameters, aspect ratios, staining intensity levels, number of deep-stained nuclei) and also complete geometrical screening-mapping of the entire slides seem to improve the accuracy in cytological examination. These should be closely related to cytologist's critical experience and deep knowledge in cytomorphology (Figure 1).

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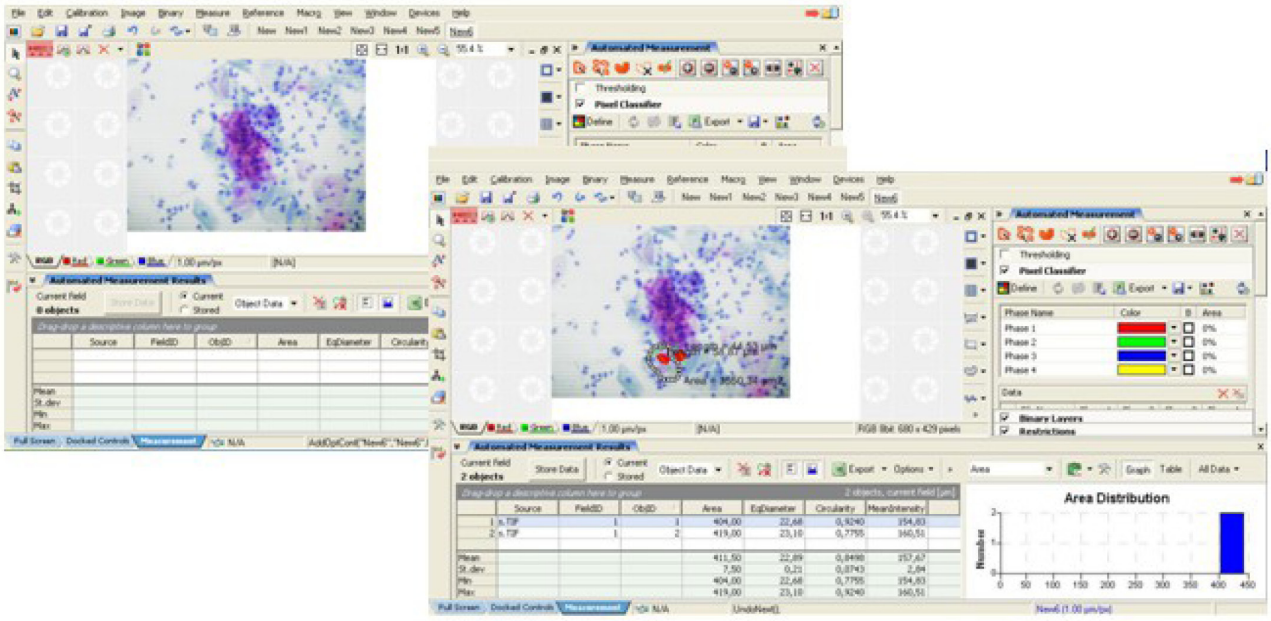

Figure 1. Implementation of a digital image analysis algorithm for measuring morphometric/geometrical features regarding abnormal cervical smears demonstrating koilocytic morphology (LSIL based on Bethesda 2014 taxonomy system, Pap test slide). Red spots cover the entire nucleus space estimating staining intensity levels, aspect ratio, N/C ratio in conjunction to membrane periphery drawing, max diameter and total area (units:μm,μm^2, respectively). Original magnification: 40x, Papanicolaou stain, software: NIS-Elements, Nikon Corp, Jp.

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T1 invasive breast lobular tumor and ductal carcinoma with HER-2 positive characteristics: Is it rationale to use adjuvant trastuzumab?

Dear Editor,

One of the challenging areas in the management of HER2 positive breast tumors are T1a HER2 positive tumors. Furthermore, some rare tumors consist of infiltrative ductal and lobular components and HER2 positivity is more often presented in the ductal component of the tumor. The size of the ductal component is therefore an important indication to start adjuvant trastuzumab treatment. Generally, if the tumor size of HER2 positive portion of all tumor is more than 5 mm, adjuvant trastuzumab treatment is recommended. If the tumor size with HER2 positivity is smaller than 5 mm with multifocal component, again some medical oncologists advise to use adjuvant trastuzumab. Trastuzumab duration of administration for these tumors is still debatable. Most authors advise to use one year of trastuzumab and others may recommend just 9 weeks [1].

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Synchronous double primary gastric tumors: sarcoma and adenocarcinoma

Dear Editor,

Gastric cancer is the third most common cause of death among all types of malignancies. Of all types of malignant gastric neoplasms 95% are adenocarcinomas [1]. Synchronous occurrence of two separate tumors with different microscopic features in the stomach is an uncommon entity with poor prognosis [2-5].

We report the case of a 74-year-old white male patient with a six-month history of postprandial discomfort, poor appetite and 8.5 kg body weight loss. Upper gastrointestinal tract endoscopy revealed a large ulcerated mass arising from the stomach. Pathology identified gastric adenocarcinoma. Computerized tomography (CT) disclosed extensive thickening of the lesser and greater curvature extending to the tail of the pancreas and the transverse colon with enlarged lymph nodes in the hepatogastric ligament and across the splenic vessels.

The patient underwent an exploratory laparotomy. Total gastrectomy with Roux-en-Y esophagojejunostomy, D2 lymph node dissection, spleenectomy, distal pancreatectomy and partial resection of the transverse colon were performed. Due to immediate deterioration of the patient's postoperative condition, no systemic chemotherapy was scheduled. The patient died two months after surgery.

Macroscopically 14.2x8.9 cm mass showed full

thickness infiltration of the gastric wall. The margins of the specimen were free. Two out of 6 lymph nodes on the greater curvature were infiltrated. The pancreas and the mesentery were infiltrated by the adenocarcinoma. Moreover, microscopic study showed adenocarcinoma of intestinal type with both tubular and papillary features. Apart from the first cancerous lesion, a second one was confirmed as an undifferentiated grade III sarcoma.

The case presented is a combination of two different types of gastric cancer, one originating from epithelia and another one from the interstitial tissue. Only few publications presented simultaneous detection of a mesenchymal tumor and an adenocarcinoma of the stomach. Several decades ago, Fonkalsrud et al. and Ejeckam et al. reported two cases of two simultaneous but separate cancerous lesions of the stomach, a leiomyosarcoma and an adenocarcinoma [2,3]. More recent studies, such as those of Namikawa et al. and Telugu et al. published cases of adenocarcinoma with the synchronous occurrence of a gastric gastrointestinal stromal tumor (GIST) [4,5].

The origin of synchronous malignant stromal gastric tumors and gastric adenocarcinomas is not clarified yet. The hypothesis of gene mutations or the effect of one carcinogenic agent to more than one gastric region cannot be safely supported. Either incidental or not, the rare coexistence of an adenocarcinoma and a sarcoma in the stomach is a condition that demands further consideration in regards of the optimal therapeutic approach. In the case of metastatic lymph node disease of such cases the selection of the first line treatment between neoadjuvant chemo/radiotherapy and surgical resection definitely remains controversial as the biological origin of the simultaneous existence of two different tumors is unknown.

Due to the rarity of this type of malignancy, the reasons still remain unelucidated. Therefore, studies based on biological agents of adenocarcinoma, sarcoma and their possibly not incidental association in terms of their precursor features may enlighten the mechanisms and further behavior of combined separate gastric tumors.

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Anatomical variations in the human body

Dear Editor,

We read with great interest the article by Raikos and Smith [1] entitled "Anatomical variations; How do surgical and radiology training programs teach and assess them in their curricula?", while for their valuable information we would like to congratulate them.

As it is known, any deviation in structure and position of anatomical features from the typical range of normality is accounted for anatomical variation. Especially in radiation oncology, back in 90s, anatomical variations in the location of target volumes based on bone structures have shown the necessity of computerized tomography (CT) based target delineation [2]. In a work by Kantzou et al. we have already confirmed the errors in target delineation when a conventional simulation is used instead of an individualized CT-based one, by means of accurate data information delivered from CT images and not from bone structures only [3].

Anatomical variations have caused many headaches and troubles not only to medical doctors but also to the law people and the National Health Services amounted to billions of dollars whenever they have to deal with a case of malpractice or medical negligence. Trainers must insist and explain to trainees doctors, especially to surgeons and orthopedics, that before they get in hands the surgical knife they must have in mind the probable existence of a variation in the region of interest [4].

However, variations vary not only between individuals but even in the same person; just an example, look at the rear surface of your right and left hand and you will face the fact of the different course of the veins in the one and the other. We have the impression that the only thing we can do to help medical people under training, in general, is to state in the start of the preface in anatomical textbooks, that, what is written in them refers to normal/classical anatomy only and not to variations.

As a conclusion we quote the thoughtful of Morgani: "those who have dissected or inspected many bodies have at least learnt to doubt; while others who are ignorant of Anatomy and do not take the trouble to attend it are in no doubt at all [5].

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Should patients with HER2 loss after neoadjuvant treatment still be treated with adjuvant trastuzumab treatment?

Dear Editor,

The impact of neoadjuvant chemotherapy on immunohistochemical markers in breast cancer specimens remains debatable [1]. Wang and his colleaguesl [2] investigated the prevalence and prognostic impact of HER2 loss in breast cancer patients with HER2-positive disease treated with neoadjuvant weekly paclitaxel plus carboplatin with or without trastuzumab (PCT vs PC alone). Of all 549 consecutive HER2-positive patients, 50.9 and 25.9% were having pCR in PCT and PC cohorts, respectively ($p<0.001$). HER2 loss was more frequent in the PCT cohort with 19.8%, compared to 9.4% in PC alone cohort ($p=0.009$). Interestingly, in the PCT cohort, patients with loss of HER2 expression tended to have a higher risk of relapse compared to patients with maintained HER2 expression ($p=0.029$). As the authors discussed this issue, they claimed that this biological discordance may be related to intra-tumoral heterogeneity. However, it is common question whether patients with HER2 loss should be still treated with adjuvant trastuzumab treatment or not. Relying on the fact that these tumors showed HER2 positivity at the time of initial diagnosis, such patients should still be treated with HER2-targeted therapy at adjuvant treatment [3]. Moreover, research is needed for patients who were initially positive but subsequently had negative HER2 status due to neoadjuvant treatment.

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The role of nutrition in the prevention of prostatic adenocarcinoma

Dear Editor,

Prostate cancer (PCa) has become a major global health problem as it is the most frequently diagnosed malignancy in elder males in both Europe and USA with the only well-established risk factors being increasing age, ethnic origin and heredity. Moreover, there are indications that environmental factors such as dietary habits, pattern of sexual behavior, alcohol consumption, exposure to ultraviolet radiation and chronic inflammation may also be

associated with PCa development or its progression into clinical significant status. Identification of environmental risk factors would be of great interest as PCa is an ideal malignancy for exogenous preventive measures, such as dietary habits, due to the high prevalence of the disease, the long latent period characterizing most patients, the already established endocrine dependency and also the availability of prostate specific antigen (PSA) as tumor marker [1].

On the basis of previous epidemiological and clinical data suggesting that selenium and vitamin E could reduce the risk of developing PCa, a double-blinded randomized study was performed in order to further investigate whether selenium or vitamin E could prevent PCa in relatively healthy men (Selenium and Vitamin E Cancer Prevention Trial - SELECT). The trial included 32,400 men randomized in four groups receiving selenium, vitamin E, combination of selenium and vitamin E or placebo. Study results convincingly demonstrated no benefit from either study agent ($p < 0.0001$) and no possibility of a benefit to the planned degree with additional follow-up as there were no significant differences in any prespecified cancer endpoints [2].

Another dietary agent with potential preventive benefits in PCa development is lycopene. Lycopene is a member of the carotenoid family, whose strong anti-oxidant properties have been originally hypothesised to assist in the prevention of PCa. In a meta-analysis of eight randomized controlled studies by IIic et al, the effectiveness of lycopene versus placebo in the prevention of PCa was investigated. The authors concluded that lycopene use was not associated with a significant decrease in the incidence of PCa. A meta-analysis of two studies only indicated a decrease in PSA levels in men diagnosed with prostate cancer, who received lycopene [3].

The metabolic syndrome (MS), consisting of a cluster of five components: atherogenic dyslipidemia, arterial hypertension, dysglycemia and a pro-thrombotic and pro-inflammatory state is documented as a traditional risk factor for atherosclerotic cardiovascular disease and type 2 diabetes. In addition, there is strong evidence that MS is also associated with some common forms of cancer, including PCa, and it can affect cancer mortality. Regardless this hypothesis, existing evidence about the association of PCa with MS remains conflicting. A series of meta-analyses failed to demonstrate any statistically significant link between the two diseases. A recent study by Xiang et al. also failed to detect any association between the two entities, a result probably originating both from the heterogeneity of the included studies and the fact that the individual components of the MS might exert antagonistic actions on one another. However, it was demonstrated that the MS is related to PCa of higher Gleason score or advanced clinical stage or even increased prostate cancer-specific mortality [4]. On the other hand, if we analyze each component of the definition of MS (insulin resistance, abnormal adipose fat deposition, hypertension, increased levels of triglycerides and low levels of HDL) only hypertension and waist circumference > 102 cm were associated with a significantly increased risk of PCa [5].

In conclusion, up until now no specific dietary interventions proved to be effective in the prevention of PCa. Although MS is weakly and non-significantly associated with the risk of PCa development, further investigation is needed in order to overcome the heterogeneity of existing studies.

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Prognosis of women with invasive pleomorphic lobular carcinoma compared with classical invasive lobular carcinoma: Still debatable issue?

Dear Editor,

Invasive pleomorphic lobular carcinoma (IPLC) is an uncommon and different subtype of classical invasive lobular carcinoma (ILC). This special variant is characterized by significant cytological atypia and pleomorphism which differs from the cytological uniformity of ILC. IPLC has been shown to have some poor prognostic factors such as axillary node metastasis and higher histological grade which may lead to poor clinical course including a short time to relapse, increased risk of recurrence and decreased survival [1]. Liu and colleagues compared the prognosis of

women with IPLC with classical invasive lobular carcinoma (cILC) and reported that IPLC was initially associated with worse progression-free survival (PFS), but this was attenuated after adjustment for cancer stage, and there were no differences in overall survival (OS) [2]. We recently published a similar study that compared IPLC with cILC [1]. The aim of our study was to investigate the clinicopathological characteristics and prognosis of IPLC in comparison with cILC and also to evaluate if IPLC is a different clinical entity compared to ILC. Among 4418 breast cancer patients, 210 were diagnosed with cILC and 23 (9.8%) were diagnosed with pure IPLC. The mean follow-up time for ILC and IPLC was 39.4 months and 20.9 months, respectively. Patients with IPLC had an increased rate of higher histologic grade, extracapsular extension, lymphovascular invasion and lower percentage of hormone positivity than those with cILC. Patients with IPLC had a worse DFS and OS duration than patients with cILC (p=0.02 for OS, p=0.04 for DFS). A bias for our study was that we did not adjust cases for cancer stage. However, poorer pathological characteristics were connected with IPLC cases. On contrary to the study by Liu et al. [2], we suggest that IPLC is a unique and aggressive variant of classical type of ILC and differs from ILC in several clinicopathological characteristics. However, more trials including large number of patients are required to confirm previous studies.

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