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LETTERS TO THE EDITOR

Metastatic occult breast carcinoma to gallbladder initially presenting as acute cholecystitis

Dear Editor,

Breast cancer usually metastasizes to bone, lung, lymph nodes, liver and brain. The gallbladder is an infrequent site of metastatic malignant disease. Breast cancer has rarely been reported to metastasize in the gallbladder [1]. Occult breast cancer (OBC) is defined as a clinically recognizable metastatic carcinoma from an undetectable primary breast tumor. It accounts for 0.3-1% of all breast cancers, often presenting with lymph node, bone, and skin metastases [2,3]. Herewith I present a very rare case of an acute cholecystitis with metastatic occult breast carcinoma to gallbladder. A female patient, 50-years old, presented to the emergency department with symptoms of biliary colic and acute abdomen. After cholecystectomy, the resected gallbladder was histologically considered to be a metastatic lesion arising from breast cancer. All the gallbladder wall was infiltrated with metastatic malignant cells which showed diffuse GATA III positivity. Tumor cells were hormone receptor-positive and HER-2-negative with low Ki-67 positive. Mammography and breast MRI did not show any sign of primary site. PET-CT scan showed peritoneal carcinomatosis with ascites. Physical examination showed subcutoneous nodules located in the abdomen and chest. One of the subcutaneous nodules was excised and pathology showed metastatic breast cancer with luminal A pathology. The patient started receiving letrozole and ribociclib. This case report is the first occult breast cancer presenting with metastatic gallbladder.

References

1. Missori G, Serra F, Prestigiacomo G et al. Case Report: Metastatic breast cancer to the gallbladder. F1000Res 2020;9:343.
2. Barbieri E, Anghelone CAP, Gentile D et al. Metastases from Occult Breast Cancer: A Case Report of Carcinoma of Unknown Primary Syndrome. Case Rep Oncol 2020;13:1158-63.
3. Altan E, Altundag K. Clinical and pathological characteristics of occult breast cancer and review of the literature. J BUON 2011;16:434-6.

Kadri Altundag

MKA Breast Cancer Clinic, Ankara, Turkey.

Corresponding author: Kadri Altundag, MD.
Email: altundag66@yahoo.com

EGFR mutational landscape in nasopharyngeal carcinoma

Dear Editor,

Nasopharyngeal carcinoma (NPC) is a unique, aggressive pathological entity included in the Head and Neck Carcinoma (HNC) family of malignancies. Concerning its histological origin, the malignancy is derived from the nasopharyngeal epithelia demonstrating a high invasive and metastatic potential mainly correlated with poor prognosis. Keratinizing, non-keratinizing and basaloid carcinoma represent its pathological variants that reflect the corresponding cytogenetic features [1]. Epstein-Barr virus (EBV) latent but persistent infection is predominantly implicated in its development and progression. Among oncogenes that are involved in its development and progression by two main deregulated mechanisms (gene amplification and mutations), epidermal growth factor receptor (EGFR) remains one of the most significant. The EGFR (other names include: ERBB ERBB1 HER1) gene is located on the short (p) arm of chromosome 7 at 12 position (cytogenetic chr band 7p12.1). The protein encoded by the corresponding gene acts as a transmembrane glycoprotein. It is a member of the v-erb-b2 erythroblastic leukemia viral oncogene (ErbB)/human epidermal receptor (HER) family of receptor tyrosine kinases, that includes also other three cell membrane receptor tyrosine kinases: HER2/c-neu (ERBB2), HER3 (ERBB3) and HER4 (ERBB4). All of those members share mainly a common domain structure consisting of a large extra cellular ligand-binding region, a single hydrophobic transmembrane bridge adjusting to an intracellular juxtamembrane (JM) region, a tyrosine kinase domain and finally a C terminal tail with multiple tyrosine residues acting as a regulatory region (with the exception of HER3 that lacks direct kinase activity). Three main EGFR depended pathways have been already identified including the PI3K-AKT-PTEN-mTOR, the RAS-(B) RAF-MEK-ERK/MAPK and also the IL6-JAK1/2-STAT3 [2].

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Concerning EGFR gene deregulation in NPCs, molecular studies have revealed a panel of mutations - most of them different compared to lung carcinoma- including predominantly exons 18 and 20. In fact, there is a spectrum of rare mutations in low frequencies detected in NPC analyzing series. A study group identified the E709A substitution - encoded in exon 20 reported also in non-small cell carcinoma (NSCLC) [3]. Additionally, another study detected 2 mutations affected exons 18 and 20 in the same patient enrolled in a clinical trial (phase II) treated by icotinib, a novel highly selective oral EGFR tyrosine kinase inhibitor [4]. Interestingly, in a series of NPCs analyzed by whole exome DNA sequencing, a significant sub-group of patients was found to harbor mutations in different oncogenes (EGFR/PI3K/Akt/mTOR). Among them, two novel EGFR mutations (p.L49F, p.K253R) were detected [5]. Anti-EGFR therapies combined or not with radiotherapy seem to be a very promising tool in handling the corresponding patients with NPC that demonstrate specific genetic signatures, especially EGFR point mutations.

References

1. Zhao L, Fong AHW, Liu N, Cho WCS. Molecular subtyping of nasopharyngeal carcinoma (NPC) and a micro-RNA-based prognostic model for distant metastasis. J Biomed Sci 2018;25:16-28.
2. Harari PM. Epidermal growth factor receptor inhibition strategies in oncology. Endocr Relat Cancer 2004;11:689-708.
3. Zhang ZC, Fu S, Wang F, Wang HY, Zeng YX, Shao JY. Oncogene mutational profile in nasopharyngeal carcinoma. Onco Targets Ther 2014;7:457-67.
4. Hu W, Wang W, Yang P et al. Phase I study of icotinib, an EGFR tyrosine kinase inhibitor combined with IMRT in nasopharyngeal carcinoma. Int J Clin Exp Med 2015;8:15675-83.
5. Chow YP, Tan LP, Chai SJ et al. Exome Sequencing Identifies Potentially Druggable Mutations in Nasopharyngeal Carcinoma. Sci Rep 2017;7:42980-86.

Arezina Manoli[1], Spyros Katsinis[1], Dimitrios Roukas[2], Evangelos Tsiambas[3]

[1]*Department of Otorhinolaryngology, Thoracic Diseases General Hospital "Sotiria", Athens, Greece.* [2]*Department of Psychiatry, 417 VA Hospital (NIMTS), Athens, Greece.* [3]*Department of Cytology, 417 Hospital (NIMTS), Athens, Greece.*

Corresponding author: Evangelos Tsiambas, MD, MSc, PhD.
Email: tsiambasecyto@yahoo.gr

Management of multifocal HER-2 positive and hormone receptor negative microinvasive (T1mic) breast carcinoma; To treat or not to treat?

Dear Editor,

As the use of screening mammography grows, the proportion of invasive breast cancer with tumor size 1 cm is increasing. Microinvasive breast carcinoma is defined as invasive carcinoma of the breast with no invasive focus measuring more than 1 mm (T1mic) [1]. It is almost always encountered in the setting of ductal carcinoma in situ (DCIS); thus, it is commonly referred to as ductal carcinoma in situ with microinvasion. It is less commonly seen in association with lobular carcinoma in situ (LCIS) or in the absence of carcinoma in situ. There is a rare data about biologic markers such as hormone receptor status and human epidermal growth factor receptor 2 (HER2) overexpression in microinvasive breast carcinoma [2]. There have been no clinical trials specifically addressing the role of adjuvant endocrine therapy, chemotherapy, and/or trastuzumab in the treatment of microinvasive breast carcinoma. Herewith I present a 41 years-old female patient who was diagnosed with right DCIS grade III and one foci of microinvasive breast carcinoma. She initially wanted to get bilateral mastectomy. She underwent right simple mastectomy and SLND and left prophylactic simple mastectomy and breast reconstruction with silicon implant. Left mastectomy showed precursor lesions for DCIS. Pathology of the right mastectomy and SLND showed no evidence of lymph node involvement and DCIS grade III with comedo-necrosis, focal hormone receptor positivity and 2 microinvasive foci. Two microinvasive lesion were hormone receptor negative and HER-2 positive. Then patient did not receive any further endocrine or trastuzumab treatment. NCCN guidelines donot recommend T1mic HER2 positive tumors [3]. However, management of HER-2 positive and hormone receptor negative T1mic tumor with multıple foci (two or more) are still debatable issue and warrants further investigation.

References

1. Missori G, Serra F, Prestigiacomo G et al. Case Report: Metastatic breast cancer to the gallbladder. F1000Res. 2020;9:343.
2. Barbieri E, Anghelone CAP, Gentile D et al. Metastases from Occult Breast Cancer: A Case Report of Carcinoma of Unknown Primary Syndrome. Case Rep Oncol. 2020 Sep 28;13(3):1158-1163.
3. Altan E, Altundag K. Clinical and pathological characteristics of occult breast cancer and review of the literature. J BUON. 2011;16(3):434-6.

Kadri Altundag

MKA Breast Cancer Clinic, Ankara, Turkey.

Corresponding author: Kadri Altundag, MD.
Email: altundag66@yahoo.com

Impact of BRAF mutations in nasopharyngeal carcinoma

Dear Editor,

Nasopharyngeal carcinoma (NPC) is a unique, aggressive pathological entity included in the Head and Neck Carcinoma (HNC) family of malignancies. Epstein-Barr virus (EBV) latent but persistent infection is predominantly implicated in its development and progression. Interestingly, EBV micro-biomarkers – including mRNAs – are involved in the development and progression in NPC. Concerning its histological origin, the malignancy is derived from the nasopharyngeal epithelia demonstrating a high invasive and metastatic potential mainly correlated with poor prognosis [1]. Keratinizing, non-keratinizing and basaloid carcinoma represent its pathological variants that reflect the corresponding cytogenetic features. Chromosome instability (CI) and specific gene deregulations are frequent and crucial genetic events in solid malignancies, including NPC. Aberrations in significant genes located on chromosome 7 lead to specific molecular signatures in a variety of carcinomas. 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 (cMET-gene locus: 7q31). New generation anti-BRAF tyrosine kinase inhibitors (TKIs) including dabrafenib, vemurafenib and trametinib have been proved effective in handling patients with BRAF(V600E)-mutant metastatic non-small cell lung carcinoma (NSCLC) and melanoma. Interestingly, specific point mutations such as BRAF V600E - detected by an extremely sensitive polymerase chain reaction (PCR) technique - are correlated with increased response rates to targeted therapeutic strategies based on TKIs, as it is already applied in thyroid papillary carcinoma, in non small cell lung carcinoma and also in oral cavity carcinoma [2,3].

Concerning the impact of BRAF aberrant expression in NPC biological behavior and its clinical significance, many molecular studies have reported different levels of mutations combined or not with other oncogenes' deregulation. A study group co-analyzing PD-L1, BRAF and EGFR protein expression levels by immunohistochemistry concluded that PD-L1 expression and BRAF mutational status - focused on BRAF V600E- are correlated to poor prognosis in patients with NPC [4]. In contrast, another extensive genetic analysis based on a set of oncogenes (ie AKT1, AKT2, CDK, ERBB2, FGFR1, FGFR3, FLT3, JAK2, KRAS, MET, RET, NRAS, KIT, PIK3CA, PDGFRA, ABL, KIT, PDGFRA, EGFR, BRAF, and PIK3CA) reported low levels of BRAF mutations in NPC [5]. Interestingly, the only detected mutation was the G464E substitution instead of the classic BRAF V600E.

References

1. Zhao L, Fong AHW, Liu N, Cho WCS. Molecular subtyping of nasopharyngeal carcinoma (NPC) and a microRNA-based prognostic model for distant metastasis. J Biomed Sci 2018;25:16-28.
2. Cardarella S, Ogino A, Nishino M et al. Clinical, pathologic, and biologic features associated with BRAF mutations in non small cell lung cancer. Clin Cancer Res 2013;19:4532 40.
3. Papanikolaou V, Kyrodimos E, Tsiambas E, Chrysovergis A. BRAF mutations in oral malignancies. JBUON 2019;24:863-4.
4. Cao Y, Chan KI, Xiao G, Chen Y, Qiu X, Hao H, Mak SC, Lin T. Expression and clinical significance of PD-L1 and BRAF expression in nasopharyngeal carcinoma. BMC Cancer 2019;19:1022-26.
5. Zhang ZC, Fu S, Wang F, Wang HY, Zeng YX, Shao JY. Oncogene mutational profile in nasopharyngeal carcinoma. Onco Targets Ther 2014;7:457-67.

Spyros Katsinis[1], Arezina Manoli[2], Sotirios Papouliakos[3], Evangelos Tsiambas[3]

[1]*Department of Otorhinolaryngology, Thoracic Diseases General Hospital "Sotiria", Athens, Greece.* [2]*Department of Otolaryngology GNA Hospital "Gennimatas", Athens, Greece.* [3]*Department of Cytology, 417 Hospital (NIMTS), Athens, Greece.*

Corresponding author: Evangelos Tsiambas, MD, MSc, PhD. Email: tsiambasecyto@yahoo.gr

Isolated left pleural metastasis after 31 years of disease-free interval in early-stage breast cancer patient: the latest recurrence in the literature

Dear Editor,

Late breast cancer recurrence is described 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 20 years are not very frequent, and their recurrent pattern and prognosis have not been thoroughly analyzed [2]. Herein I report on a case of early breast cancer with the latest systemic recurrence after 31 years of disease-free interval. To the best of our knowledge this is the latest recurrence case of breast cancer in the literature.

A 77-year-old woman underwent left modified radical mastectomy for infiltrating ductal carcinoma of the breast

in 1989. The disease was staged as T1N1M0 and she refused to receive chemotherapy and only adjuvant radiotherapy was given. Hormone receptors and HER-2 status were not known at that time. She was under follow-up without any medication. Thirty-one years after surgery the patient complained of shortness of breath in November 2020. Thoracic CT showed left pleural effusion. PET-CT scan revealed left pleural effusion without pathological FDG uptake. Pleural catheter was inserted for pleural fluid drainage. Pleurodesis with talc was applied after satisfied drainage was accomplished and at the same time pleural biopsy was taken. Immunohistochemical analysis showed diffuse GATA III and ER and PR expression and HER-2 was negative compatible with metastatic breast cancer. Letrozole and ribociclib were initiated.

Late recurrences (>10 years) of breast cancer are generally observed in hormone positive tumors. The yearly relapse rate is 0.5 % after 10 years [3]. In a recent study [4], Bosco et al found that nodal involvement, poor tumor grade 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. I report on this patient for she had the latest recurrence after 31 years of disease-free interval reported in the literature.

References

1. Montgomery DA, Krupa K, Cooke TG. Locoregional relapse after breast cancer: most relapses occur late and are not clinically detected. Breast J 2009;15:163-7.
2. Durdu Keskin O, Kertmen N, Karakas Y et al. A systemic late recurrence after the first operation in a patient diagnosed with early-stage breast cancer: the latest recurrence in the literature. J BUON 2015;20:348.
3. Hess KR, Puszati L, Buzdar AU et al. Estrogen receptors and distinct patterns of breast cancer relapse. Breast Cancer Res Treat 2003;78:105-18.
4. Bosco JLF, Lash TL, Prout MN et al. Breast cancer recur¬rence in older women five to ten years after diagnosis. Cancer Epidemiol Biomarkers Prev 2009;18:2979-83.
5. Natarajan L, Pu M, Parker BA et al. Time-varying effects of prognostic factors associated with disease-free survival in breast cancer. Am J Epidemiol 2009;169:1463-70.

Kadri Altundag

MKA Breast Cancer Clinic, Ankara, Turkey.

Corresponding author: Kadri Altundag, MD.
Email: altundag66@yahoo.com

Atezolizumab plus bevacizumab for advanced, unresectable hepatocellular carcinoma

Dear Editor,

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and one of the most frequent causes of cancer-related mortality in western societies [1]. Despite the fact that treatment of early HCC seems to achieve cure in the vast majority of patients, unfortunately, many patients with HCC are usually diagnosed in advanced stages. This fact minimizes the possibilities for curative strategies, while palliative procedures are focusing in downstaging or to alleviating a locally advanced disease [2].

The therapeutic options in advanced HCC are limited due to chemoresistance. Systemic therapy with doxorubicin or cisplatin yields low response rates while drug-combinations may offer a better disease control without succeeding in improving the survival rate. In addition, in cases of background liver disease and compromised liver function, HCC patients have limited tolerance to full doses of poly-chemotherapy. Sorafenib is an oral multikinase inhibitor that was the first agent to achieve a statistically significant improvement of overall survival in Child-Pugh class A patients with advanced HCC. In addition, administration of sorafenib in patients with Child-Pugh class B has also given promising results [2].

Finn et al in a landmark study reported that the combination of atezolizumab-bevacizumab was superior to sorafenib as first line therapy for cirrhotic patients with "locally advanced, unresectable HCC or both [3]. "While these patients may have had tumors that were unresectable, it is unclear why these patients were not eligible for standard locoregional therapies (transplant, ablation for BCLC-A and chemoembolization for BCLC-B) according to the most recent AASLD/EASL guidelines [4,5]. In addition, it would be important to know if any unresectable patients with early HCC became eligible for locoregional therapy after atezolizumab-bevacizumab treatment. The authors concluded that the combination of atezolizumab-bevacizumab resulted in better overall survival (OS) and progression free survival (PFS) among patients with unresectable HCC. Although this conclusion was valid for BCLC-C HCC, BCLC-B patients did not seem to benefit from atezolizumab-bevacizumab versus sorafenib (OS, HR: 1.09, 95%CI:0.33-3.53; PFS, HR: 0.65, 95%CI:0.33-1.30); a subgroup analysis among BCLC-A patients was not feasible due to the limited number of patients. As such, atezolizumab-bevacizumab may be superior to sorafenib among patients with advanced BCLC-C HCC, yet the data did not necessarily support this conclusion for earlier stage unresectable HCC.

References

1. Beal EW, Tumin D, Kabir A et al. Trends in the Mortality of Hepatocellular Carcinoma in the United States. J Gastrointest Surg 2017;21:2033-8.
2. Dimitroulis D, Damaskos C, Valsami S et al. From diagnosis to treatment of hepatocellular carcinoma: An

epidemic problem for both developed and developing world. World J Gastroenterol 2017;23:5282-94.

3. Finn RS, Qin S, Ikeda M et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020;382:1894-905.
4. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182-236.
5. Marrero JA, Kulik LM, Sirlin CB et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2018;68:723-50.

Diamantis I. Tsilimigras[1], Dimitrios Moris[2]

[1]*Department of Surgery, Division of Surgical Oncology, The Ohio State University Wexner Medical Center and James Comprehensive Cancer Center, Columbus, Ohio, USA.* [2]*Department of Surgery, Duke University Medical Center, Durham, North Carolina, USA.*

Corresponding author: Dimitrios Moris, MD, MSc, PhD.
Email: dimmoris@yahoo.com

Breast cancer diagnosis at earlier age in left-handed patients: Still debatable issue?

Dear Editor,

Intrauterine estrogens or testosterone exposure is blamed to be a risk factor for breast cancer. Left-handedness is known to be linked with high fetal estrogens exposure [1]. The earlier breast cancer diagnosis in left-handed patients may support this hypothesis. We investigated the relationship between breast cancer and hand preference. A total of 898 patients with breast cancer were analyzed for handedness, basic characteristics and survival. There was no statistically significant difference between the groups related to ER or PR status, TNM classification, tumor localization, menopausal status, HER2 or histological subtype. However the median age of diagnosis in right-handers was higher (48-46 years, p=0.02). We concluded that the onset of breast cancer was 2 years earlier in left-handed patients with similar disease characteristics compared to right handed [2]. Furhermore, Sosa and his colleagues evaluated a group of patients with breast cancer to study the prevalence of left-handedness and to compare it to a control group of women without breast cancer [3]. They studied the clinical characteristics of the patients and classified them into three groups: left-handed, right-handed, and ambidextrous. There were no differences between the three groups. They concluded that their study clearly shows that in postmenopausal women being left-handed are not linked to breast cancer diagnosis. When we look at the median age at diagnosis of breast cancer, lef-handed cases were diagnosed at earlier age compared to right-handed cases (48 vs. 52, p: 0.269). However, numbers of cases in both groups are small which might not give right conclusion. We therefore suggest this difference to be meaningful. As a consequence, it may be advocated that the screening of left-handed patients might start earlier. This issue warrants further investigation in a larger patient population.

References

1. Titus-Ernstoff L, Newcomb PA, Egan KM et al. Left-handedness in relation to breast cancer risk in postmenopausal women. Epidemiology 2000;11: 181-4.
2. Altundag K, Isik M, Sever AR. Handedness and breast cancer characteristics. J BUON 2016;21:576-9.
3. Sosa M, Saavedra P, Alonso B, Vega V, Vicente E, Vilchez M. Left-handedness is not associated with breast cancer. Breast J 2020 Oct 4. doi: 10.1111/tbj.14061.

Kadri Altundag

MKA Breast Cancer Clinic, Ankara, Turkey.

Corresponding author: Kadri Altundag, MD.
Email: altundag66@yahoo.com