Indicators of Cellular and Developmental Disorders in Multiple Primary Cancers

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ABSTRACT

In human organism development is a very complex and highly regulated system that enables the functional balance of each organ in a whole body. Disorders and tumor micro-environment weaken host immune system that is not able to recognize the tumor as an unknown body and fight against its uncontrollable forces. Tumor avoids the immune system in a way that promotes immunosuppression and orientation cytokine production towards Th2 immune responses which are responsible for infection appearances. Some of infectious agents (viruses) can cause oncogene activation and inhibition of tumor suppressor genes. It is also known that oncology treatment can be detrimental to the host immune system. The drugs or radiation can activate different signaling pathways which lead to a vicious circle from which there is no return. Experimental models of tumor biology and molecular events in vivo are patients who have multiple primary cancers (MPC) diagnosed during life. Such patients confirm the complexity of disorders that occur in the cell and explain all the influences and contributions to developmental tumor cascade.

Key words: multiple primary cancers, breast cancer, cellular disorders, immune system, chemotherapy

Introduction

In the tumor cell, the major cellular processes are disturbed at the level of genes, chromosomes, signaling pathways, immune system. Disorders present at the level of the genes are point mutations, translocations, deletions and amplification. These changes mostly lead to the appearance of gain or loss of chromosome, microsatellite instability (MSI), DNA (Deoxiribonucleic Acid), mutation in DNA repair mechanisms and telomere maintenance. Patients who have multiple tumors diagnosed during life can be in vivo models and they can show us complexity of tumor biology and molecular events like investigations in vitro on experimental models. Multiple primary cancers were first described by Billroth in 1889. In 1932, Warren and Gates published the first study of 1,259 patients with multiple neoplasms. Ever since, there have been numerous reports addressing the occurrence of second primary neoplasms. Synchronous cancers occur at the same time or within an interval of two months, while metachronous cancers follow in sequence and more than two months apart. There is the most used classification of multiple tumors (Table 1).

Epidemiology and Etiology of MPC

In the literature the prevalence of MPC is estimated between 0.73% and 11.7% and the incidence is increasing with age. Breast cancer was found to be one of the most frequent malignant tumors associated with other primary cancers. The most frequent malignant associations are breast-breast, breast-endometrium and breast-ovary. It was showed that twenty-one patients developed the first breast cancer at an early age under 50 years, before menopause. So it is suggested that Oncotype Dx testing is useful in MPC. Oncotype Dx testing on multiple primary breast cancers altered management in regards to chemotherapy recommendations and should be considered for multiple primary breast cancers. The median period of time between the two primary cancers was 10.69 years. The most frequent synchronous malignant tumors are breast cancers, mostly because of the use of mammography as a screening method. Usually the metachronous breast malignant lesions were discovered because of the follow-up of the first malignant tumor. Qualitatively, there seems to be a greater difference in genetic profile in tumors appearing simultaneously on different breasts.

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when compared to multiple tumors on the same breast. There was no association between distance between tu-
more than 30 genes are known to be related to the occurrence of malignant tumors, and those closely related to
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increased risk for MP Care tumor suppressor genes and DNA repairing genes. Latest studies found that genomic
increased risk for MP Care tumor suppressor genes and DNA repairing genes. Latest studies found that genomic
instability and changes in gene expression profile (such as tumor suppressor genes and DNA epairing genes) and
even mutation and deletion of chromosomes were closely related to the occurrence of multiple primary cancers15–6.

Breast cancer in MPC

The epidermal growth factor receptor (EGFR) is implicated in breast cancer progression and is associated with an
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aggressive phenotype. The presence of EGFR mutations in exons 18–21 in breast cancer, as in non-small-cell
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lung cancer. 50% of TP53 (mutations within the TP53-coding region), associated lung cancers were squamous
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cell carcinoma and 20% of TP53 mutations associated with ‘high differentiation’ cancers and 25.9% of TP53 mu-
cell carcinoma and 20% of TP53 mutations associated with ‘high differentiation’ cancers and 25.9% of TP53 mu-
tations were ‘mid differentiation’ cancers14. Data suggested that EGFR mutations in concert with P53 mutations
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accelerate cancer development and lead to evolution of therapeutic resistance15. In the second patient in case re-
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port 2 all four tumors are associated with mutation of p5314,15. In CLL, p53 mutation is much more frequent in
patients who have received chemotherapy prior to sample extraction16,17. The excessive skin melanoma in breast can-
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cancer survivors was attributed to the relationship with Breast Cancer genes 2 (2 BRCA2) and cyclin-dependent
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kinase inhibitor 2A (CDKN2A) mutation-positive pa-
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tients. CDKN2 has a critical target or targets in the reti-
tients. CDKN2 has a critical target or targets in the reti-
noblastoma (RB) pathway which mutations are associated with breast cancer, melanoma and lung cancer15. While
nnoblastoma (RB) pathway which mutations are associated with breast cancer, melanoma and lung cancer15. While
most human solid tumors neutralize this tumor-suppres-
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sive pathway at the level of p53 itself (TP53) melanoma
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provides a notable exception to this rule. It became clear
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that functional inactivation of p53 could be achieved by
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the melanoma cell through other signaling pathways. In
the melanoma cell through other signaling pathways. In
fact, concomitant deletion of the CDKN2A locus does occur
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in the face of activating Cyclin-dependent kinase 4
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(CDKN4) mutations suggesting that abrogation of the RB
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pathway through cyclin dependent kinases mediated
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mechanisms is still insufficiently explored18.
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MSI was noticed to occur more frequently in cases of
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MPC than in sporadic cancers19. Cancer does not occur
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Cellular and Molecular Disorders in MPC

The pathogenic mechanisms of multiple primary lung cancer are rather complicated, but currently available
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clinical and fundamental study data are rare. Analyses on the main reasons for increased incidence of multiple
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primary lung cancer can help improve the understanding
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on the pathogenic mechanisms of the disease. Besides en-
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vironmental factors, genetic factors also have important
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role in the occurrence of malignant tumors. At present,
from a single gene mutation in a single gene. Instead, the development of cancer involves multiple mutations within several key genes, including mutations in proto-oncogenes, tumor suppressor genes, and DNA repair genes. So we can assume that when one mutation happened it can lead to novel different tumors associated with that mutation. The drugs or radiation can activate different signaling pathways which lead to a vicious circle from which there is no return. It is also known that tumor evade host immune system and that our treatments can cause deeper impairment of the cellular immunity had been identified. Merkel cell carcinoma frequently appers in immunocompromised especially in recipient of great number of chemotherapy protocols and radiotherapy and in patients with polyoma virus infection. Anaplastic lymphoma kinase (ALK-1) mutation associated with non-Hodgkin lymphoma. ALK protein was detected with high frequency in Merkel cell carcinomas and was useful in distinguishing Merkel cell carcinoma from small cell lung carcinoma. It was shown that one reason may be our chemotherapy or radiotherapy used for the first malignancy. That treatment could result some damage of specific regions of DNA with chromosome rearrangement or loss responsible for tumorigenesis.

Conclusion
Most patients with MPC are geriatric. The majority of the patients with quadruple cancers present with breast and upper aero-digestive tumors. The reports on patients with multiple primaries include patients at an earlier stage 0 (carcinoma in situ), while others limit the study to patients with quadruple cancers present with breast carcinomas and was useful in distinguishing Merkel cell carcinomas from small cell lung carcinoma. It was shown that one reason may be our chemotherapy or radiotherapy used for the first malignancy. That treatment could result some damage of specific regions of DNA with chromosome rearrangement or loss responsible for tumorigenesis.

REFERENCES
POKAZATELJI MOLEKULARNIH POREMEĆAJA U RAZVOJU MULTIPLIH TUMORA

SAŽETAK

Razvoj organizma u čovjeka vrlo je složen i visoko reguliran sustav koji omogućava funkcionalnu ravnotežu svakog organa u cjelini. Glavni stanični procesi u tumorskoj stanici poremećeni su na razini gena, kromosoma, signalnih putova, imunoškog sustava itd. Na razini gena prisutni su poremećaji u smislu točkastih mutacija, translokacija, amplifikacija i delecija. Navedeno vodi ka nastanku viška ili manjaka kromosoma, mikrosatelitnih nestabilnosti, poremećaja mehanizama popravka DNK (deoksiribonukleinske kiseline), dugovječno održavanje telomeraza i slično. Poremećaj stanica vodi ka slabljenju imunoškog sustava domaćina koji bi trebao prepoznati tumor kao nepoznato tijelo i boriti se protiv njegove nekontrolirane snage. Tumor izbjegava imunoški sustav na način da potiče imunosupresiju tj. orijentira imunoški odgovor ka stvaranju Th2 citokina. Tumorski mikrookoliš omogućava nastanak i rasplamsavanje infekcija (npr. virusa) koji potiču onkogene a koče tumor supresor gene. Također je poznato da i onkološka terapija dodatno može smanjivati imunitet domaćina i aktivirati signalne putove koji naše bolesnike vode u začarani krug iz kojeg nema povratka. Eksperimentalni modeli tumorske biologije i molekularnih zbivanja in vivo jesu bolesnici koji imaju multiple tumore dijagnosticirane tijekom života. Takvi bolesnici nam potvrđuju svu složenost poremećaja koji nastanu u stanici i što sve može utjecati i doprinositi nezaustavljivoj tumorskoj kaskadi.