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SERUM LEVELS OF NO, IL-18 AND MDA IN PATIENTS WITH BREAST CARCINOMA

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SERUMSKI NIVOI NO, IL-18 I MDA KOD PACIJENATA SA KARCINOMOM DOJKE

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SAŽETAK

U borbi protiv tumora, postoje tri glavna zadatka koja je potrebno obaviti: senzitivan skrining, rana diagnoza i kontrola malignog tumora. Smatramo da ispitivanje nespecifičnih biomarkera može pružiti dosta korisnih informacija o „antitumorskom stanju" imunskog sistema i odnosu tumora i organizma, naročito ako se prati kombinacija ovih biomarkera koja povećava senzitivnost testova. U tom smislu smo ispitivali serumske nivoe nespecifičnih markera, kao što su: azot-monoksid (NO), IL-18 i malonil-dialdehid (MDA) kod pacijenata sa karcinomom dojke. U serumu 60 pacijenata sa karcinomom dojke (podeljenih u grupu sa lokalizovanim i grupu sa metastatskim tumorom) i 10 kontrola smo određivali NO (spektrofotometrijskom metodom zasnovanoj na Griess reakciji), IL-18 (ELISA-om) i MDA (korišćenjem tiobarbiturne kiseline, TBA).Nivoi ovih biomarkera, u poređenju sa kontrolom, su bili značajno viši kod pacijenata sa karcinomom dojke (posebno kod pacijenata sa lokalizovanim tumorom). Zapazili smo da su svi pacijenti imali povećanje bar jednog biomarkera. Zapaženo povećanje serumskog nivoa ispitivanih biomarkera kod pacijenata sa lokalizovanim tumorom se može objasniti izraženim imunskim odgovorom organizma na tumor. Zapravo, niže vrednosti od pomenutih (a opet, više od kontrolnih) u odmaklom stadijumu bolesti mogu biti rezultat sloma kapaciteta imunskog odgovora. Kombinacijom biomarkera možemo povećati senzitivnost testova u ispitivanju karcinoma dojke.

Ključne reči: azot-monoksid, IL-18, MDA, karcinom dojke.

ABSTRACT

Three major tasks in antitumor health care are sensitive and competent screening, early diagnosis and satisfactory control of malignant tumors. We believe that investiganting of nonspecific biomarkers provides more information about the antitumor state of immune system and relations between tumor and host organism, especially if we use a combination of biomarkers to enlarge sensitivity of tests. In this regard we investigated serum levels of nonspecific biomarkers, such as nitric oxide (NO), IL-18 and malonyl-dialdehyde (MDA), in patients with breast carcinoma.

In sera of 60 patients with breast cancer (devided into group with localized and group with metastatic tumor) and 10 control subjects, we detected NO by spectrophotometric method based on the Griess reaction, IL-18 with ELISA and MDA was performed with the use of TBA (thiobarbituric acid).

The levels of these biomarkers were significantly higher in patients with breast cancer (especially in patients with localized tumor), when compared to the control group. When used together, we observed that all patients had at least one biomarker increase.

Evident increase in serum levels of all tested biomarkers was observed in patients with localized breast cancer and this rise may indicate active host defense against tumor. However, lower values were observed in the terminal stage of the disease wich is possible to explain through breakdown of defense capacity of the organism in that stage. Also, we observed that combination of those biomarkers had increased sensitivity of tests in breast carcinoma investigation.

Key words: nitric oxide, IL-18, MDA, breast cancer

INTRODUCTION

Progression of tumor growth and disemination of metastases are one of most frequent cause of death in women, today (1). Both arises as result of predominance of malignat cells influence over immune system control mechanisms. Nitric-oxide, IL-18 and malonyl-dialdehyd can be a palette of host/tumor relation nonspecific parametars.

Nitric-oxide (NO) is bioactive molecul which by paracrine or autocrine influence regulates vascular tonus, neurotransmission, antimicrobial defence and cancerogenesis (2–4). Depending of concentration NO showed dual roll in tumor growth. Actually, when present in low concentration, it stimulates tumor growth, while in high concentrations inhibits tumor progression (5). Considering that NO is a product of neutrophils and activated macrophages and that posseses tumorotoxic and microbicide effect, we can say that NO is the main effector molecule of these cells (6–8). Mechanism of its citotoxity is probably related with nitric and oxide radicals, where NO reacts very fast with superoxide which is product of NADPH oxidase activity (9). The target of free oxigen mediators are poly-unsaturated fatty acids of cell membrane in process of lipid peroxidation. Lipid peroxidation represents chain reaction which continuously provides suply with free radicals, initiators of lipid peroxidation process. Secondary product of this process is malonyl-dialdehyde (MDA) which is useful indicator of this reaction (10). Lipid peroxidation has important role in regulation of membrane lipids metabolism and calcium ions transport between citosol and inner membrane structures of the cell (11). Today it is well established fact, that presence of both benign and malignant tumor within the organism elevates the rate of lipid peroxidation (12-14).

Biosynthesis of NO from semi-essential aminoacid L-arginine is mediated by NO-synthase (NOS) activity. In immune system of particular importance is inducibile NOS (iNOS) which expression in macrophages can be inducted and amplified by cytokines or endotoxine (15). Biological consequence, on such way synthesized citotoxic NO, is death of malignant cells or microorganisms (6,

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