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Increased Circulating Myeloid-Derived Suppressor Cells and S100A8 Correlate with Clinical Stage in Nasopharyngeal Carcinoma

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Abstract

Nasopharyngeal carcinoma (NPC) is a squamous epithelial cancer arising from the lateral wall surface of nasopharynx, shows a clear regional and racial prevalence. Developments of tumors are influenced by many factors, generally an interaction between genetic, environmental, and immune system. There is a role of myeloid derived suppressor cells in the process of immune suppression. The presence of MDSC has been described in the peripheral blood and tumors of patients with various forms of cancers. MDSC are able to strongly promote tumor progression by inhibiting anti-tumor immune responses by multiple mechanisms. S100A8 proteins are elevated in inflammation and cancer and are chemotactic; they may contribute to the recruitment and retention of MDSC. MDSC not only have receptors for S100A8/A9, but also synthesize and secrete these proteins, providing an autocrine pathway for MDSC accumulation. The aim of this study is to analyze the expression of MDSC (through CD14 and CD15 genes) and S100A8 gene in relation to clinical stage in nasopharyngeal carcinoma. Peripheral blood specimen and biopsy from primary tumor were collected from 16 nasopharyngeal carcinoma patients. The samples collected undergone RNA isolation and qRT-PCR examination. The Data were analyzed by $2^{-\Delta\Delta Ct}$ method and statistical analysis. MDSC and S100A8 genes were expressed in blood higher than in tumor tissue. MDSC and S100A8 expression in nasopharyngeal carcinoma blood were significantly high correlated to clinical stage (r=-0.879, p=0.000 for MDSC; r=-0.791, p=0.0000 for S100A8). The MDSC expression also correlated with age (p=0.002), T classification (p=0.003), N classification (p=0.006), and clinical stage (p=0.001). The S100A8 expression correlated with age (p=0.041) and T classification (p=0.022). The result indicated that the high expression of MDSC was correlated with clinical stage of nasopharyngeal carcinoma especially in blood.

Introduction

Nasopharyngeal carcinoma (NPC) is a squamous epithelial cancer arising from the lateral wall surface of nasopharynx, shows a clear regional and racial prevalence [1]. The differences in geographic and ethnic distribution reflect the multifactorial etiology of NPC, including the Epstein Barr virus (EBV) infection, ethnics, genetic susceptibility, environmental factors, and food consumption [1].

NPC is a frequent cancer in Indonesia, rating as the fourth most common tumor after cervical cancer, breast cancer, and skin cancer, and is the most common malignancy in the head and neck [1,2]. In Indonesia, which has an ethnically diverse population of 225 million people, NPC is prevalent among different native people and presents a major socioeconomic problem, with an overall incidence estimated at 6.2/1,00,000 or about 12,000 new cases per year [2].

Developments of tumors are influenced by many factors, generally an interaction between genetic, environmental, and immune system. There is a role of myeloid derived suppressor cells in the process of immune suppression.

Myeloid-derived suppressor cells (MDSC) are heterogeneous population of cells comprising immature myeloid progenitors for neutrophils, monocytes, and DC [3-11]. MDSC are potently immunosuppressive, markers that typical for PMN-MDSC is CD15 in blood circulation, while for MO-MDSC is CD14 [4-6]. The presence of MDSC has been described in the peripheral blood and tumors of patients with various forms of cancers [4,6,7,11-16]. MDSC are able to strongly promote tumor progression by inhibiting anti-tumor immune responses by multiple mechanisms [9].

S100A8 is the member of S100 family of calcium binding proteins that are inflammatory mediators released by cells of myeloid origin. These intracellular molecules are released to extracellular compartments in response to cell damage, infection, or inflammation, and function as proinflammatory danger signals [8,17]. Increased of S100A8 expressions are seen in tumor-infiltrating cells in many epithelial tumors like nasopharyngeal carcinoma. The proteins function predominantly as S100A8 heterodimers and are chemotactic for leukocytes, thereby amplifying the local proinflammatory microenvironment, mediate their effects by binding to plasma membrane receptors on their target cells. These receptors include heparan sulfate, TLR4, and carboxylated N-glycans. Carboxylated N-glycans is constitutively expressed on endothelial cells, macrophages, and dendritic cells and is recognized by the mAbGB3 [17]. S100A8 proteins are elevated in inflammation and cancer and are chemotactic; contribute to the recruitment and retention of MDSC [8,17]. MDSC not only have receptors for S100A8, but also synthesize and secrete these proteins, providing an autocrine pathway for MDSC accumulation [17]. S100A8 inflammatory proteins have