ABSTRACT

Background: Albeit its rarity**,** melanoma is an aggressive skin malignancy with a high risk of metastasis and death rate. Recent researches suggested that melanoma growth is influenced by neuroblastoma rat sarcoma (NRAS) mutations. The prevalence of NRAS mutations in melanomas is 15-25%. NRAS mutations are associated with aggressive clinical manifestations and a poor prognosis. Some histopathological factors that influence the prognosis of melanoma are tumor thickness, ulceration, mitotic index, necrosis, lymphovascular invasion, and lymphocyte infiltration in tumors. Research on NRAS mutations in melanoma in the population in Indonesia has not been widely studied in Indonesia until now.

Objective: This study aims to determine the profile of NRAS mutations in primary skin nodular melanoma cases in Indonesia and its association with tumor thickness, ulceration, mitotic index, necrosis, lymphovascular invasion and lymphocyte infiltration in tumors.

Method: DNA samples were extracted from 51 formalin-fixed paraffin-embedded (FFPE) cases of primary skin nodular melanoma from the Anatomical Pathology Installation of the Central General Hospital (RSUP) Dr. Sardjito, Sleman, Yogyakarta and Central General Hospital (RSUP) dr. Soeradji Tirtonegoro, Klaten, Central Java in the period 2011 - 2019. NRAS mutations were assessed by quantitative real time-PCR (qRT-PCR). The assotiation between NRAS mutations and tumor thickness, ulceration, mitotic index, necrosis, lymphovascular invasion and lymphocyte infiltration in tumors were analyzed by Pearson Chi-Square statistical test and Fisher's exact test.

Result: Of the 51 samples, NRAS mutations were obtained in 10 samples (19.6%), where all (100%) with tumor thickness> 4 mm (pT4), 50% had ulceration, 60% had a mitotic index ≥20%, 90% with necrosis, 30% with lymphovascular invasion, 80% with positive TIL. There was no significant relationship between NRAS mutations with tumor thickness (p = 0.320), ulceration (p = 0.586), mitotic index (p = 0.499), necrosis (p = 0.069), lymphovascular invasion (p = 1,000) and lymphocyte infiltration in tumor (p = 1,000). Mutations occurred in exon 2 (G12) as many as 6 samples (60%) and mutations in exon 3 (Q61) in 4 samples (40%).

Conclusion: Positive NRAS mutations were found in primary skin nodular melanoma of 19.6%. The high proportionof NRAS mutations involving exon 2 (G12) is unique in this study and is likely related to nodular type melanoma. No significant association was found with tumor thickness, ulceration, mitotic index, necrosis, lymphovascular invasion and lymphocyte infiltration in tumors.

Keywords: Melanoma, NRAS mutations, tumor thickness, ulceration, mitotic index, necrosis, lymphovascular invasion and lymphocyte infiltration in tumors.

ABSTRAK

Latar belakang: Melanoma merupakan suatu keganasan kulit jarang dengan risiko tinggi metastasis dan angka kematian tinggi. Penelitian terkini menyebutkan bahwa pertumbuhan melanoma dipengaruhi oleh mutasi *neuroblastoma rat sarcoma* (NRAS). Prevalensi mutasi NRAS pada melanoma yaitu sebesar 15-25%. Mutasi NRAS berkaitan dengan manifestasi klinis yang agresif dan prognosis yang buruk. Beberapa faktor histopatologis yang mempengaruhi prognosis melanoma adalah ketebalan tumor, ulserasi, indeks mitosis, nekrosis, invasi limfovaskuler, dan infiltrasi limfosit pada tumor. Penelitian tentang mutasi NRAS pada melanoma pada populasi di Indonesia sampai saat ini masih terbatas.

Objektif: Penelitian ini bertujuan mengetahui profil mutasi NRAS pada kasus melanoma noduler kulit primer di Indonesia dan hubungannya dengan ketebalan tumor, ulserasi, indeks mitosis, nekrosis, invasi limfovaskuler dan infiltrasi limfosit pada tumor.

Metode: Sampel berupa 51 *formalin-fixed paraffin-embedded* (FFPE) kasus melanoma noduler kulit primer dari Instalasi Patologi Anatomi Rumah Sakit Umum Pusat (RSUP) Dr. Sardjito, Sleman, Yogyakarta dan dr. Soeradji Tirtonegoro, Klaten, Jawa Tengah pada periode tahun 2011 – 2019. Mutasi NRAS dinilai dengan *quantitative real time-PCR* (qRT-PCR). Hubungan antara mutasi NRAS dengan faktor-faktor histopatologi dianalisis dengan uji statistik *Fisher's exact test*.

Hasil: Dari 51 sampel, mutasi NRAS didapatkan pada 10 sampel (19,6%), semua (100%) dengan ketebalan tumor >4 mm (pT4), 50% dengan ulserasi, 60% memiliki indeks mitosis ≥20%, 90% dengan nekrosis, 30% dengan invasi limfovaskuler dan 80% dengan *TIL* positif. Mutasi NRAS tidak berhubungan signifikan dengan ketebalan tumor(p=0.320), ulserasi(p=0.586), indeks mitosis(p=0.499), nekrosis(p=0.069), invasi limfovaskuler(p=1.000) dan infiltrasi limfosit pada tumor(p=1.000). Mutasi terjadi pada exon 2 (G12) sebanyak 6 sampel (60%) dan mutasi pada exon 3 (Q61) sebanyak 4 sampel (40%).

Kesimpulan: Mutasi NRAS positif ditemukan pada melanoma nodular kulit primer sebesar 19,6%. Proporsi mutasi NRAS yang lebih tinggi pada exon 2 (G12) merupakan keunikan dalam penelitian ini dan kemungkinan terkait dengan melanoma tipe nodular. Mutasi NRAS tidak berhubungan signifikan dengan ketebalan tumor, ulserasi, indeks mitosis, nekrosis, invasi limfovaskular, dan infiltrasi limfosit pada tumor.

Kata kunci: Melanoma noduler, Mutasi NRAS, ketebalan tumor, ulserasi, indeks mitosis, nekrosis, invasi limfovaskuler dan infiltrasi limfosit.