A high neutrophil-to-lymphocyte ratio as a potential marker of mortality in patients with Merkel cell carcinoma: A retrospective study

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Background: The prognostic relevance of a high blood neutrophil-to-lymphocyte ratio (NLR) has been reported in many cancers, although, to our knowledge, not investigated in patients with Merkel cell carcinoma (MCC) to date.

Objective: We assessed whether the NLR at baseline was associated with specific survival and recurrence-free survival in MCC.

Methods: We retrospectively included MCC cases between 1999 and 2015 and collected clinical data, blood cell count at baseline, and outcome. A Cox model was used to identify factors associated with recurrence and death from MCC.

Results: Among the 75 patients included in the study, a high NLR at baseline (NLR ≥4) was associated with death from MCC in univariate (hazard ratio 2.76, 95% confidence interval 1.15-6.62, $P = .023$) and multivariate (hazard ratio 3.30, 95% confidence interval 1.21-9.01, $P = .020$) analysis, but not with recurrence.

Limitations: Because of the retrospective design, we excluded patients with missing data and not all confounding factors that may influence the NLR were available.

Conclusion: A high NLR at baseline was independently associated with specific mortality in patients with MCC. The NLR seems to constitute an easily available and inexpensive prognostic biomarker at baseline. (J Am Acad Dermatol 2016;75:712-21.)

Key words: absolute lymphocyte count; absolute neutrophil count; blood neutrophil-to-lymphocyte ratio; Merkel cell carcinoma; prognostic factor; specific survival.

Merkel cell carcinoma (MCC) is a rare primary neuroendocrine skin cancer, with high rates of recurrence and mortality.[1,2] Surgery, radiotherapy, and chemotherapy can be used, depending on the stage of the disease, the patient's general condition, and

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performance status (PS).[3] Despite these therapeutic options, the prognosis remains poor, with a 5-year survival of 50% to 60% for all stages.[4] In 2008, the discovery of the association between MCC and the Merkel cell polyomavirus[5-8] contributed to new insights into the pathogenesis of this skin tumor. Immunosuppression plays a crucial role in MCC development and prognosis.[9,10] This is suggested by the 10-fold increase in the incidence of MCC,[11-13] together with an increased risk of progression[14] and mortality,[9,15] in immunocompromised patients. It has also been shown that patients with MCC and lymphopenia[16] and those with absent or sparse intratumoral infiltration by CD8 T cells[17-19] have poorer outcome.

CAPSULE SUMMARY

- A high blood neutrophil-to-lymphocyte ratio is associated with shorter survival in patients with cancer.
- A high neutrophil-to-lymphocyte ratio at baseline is independently associated with specific mortality in patients with Merkel cell carcinoma.
- The neutrophil-to-lymphocyte ratio constitutes an easily available and inexpensive prognostic biomarker at baseline in this rare cancer.

Interactions between the tumor and the immune system are essential for tumor progression. A high blood neutrophil-to-lymphocyte ratio (NLR) during the initial evaluation or during metastatic progression constitutes an indirect but simple marker of these complex interactions. An elevated NLR has been consistently associated with increased mortality in a wide range of cancers, including solid malignancies (eg, lung cancer,[20] breast cancer,[21] colorectal cancer,[22] gastric cancer,[23] hepatocellular carcinoma,[24] and urologic cancers[25]) and in hematologic diseases (eg, B-cell lymphoma[26] and multiple myeloma[27]). The prognostic value of baseline blood NLR has also been evidenced in patients with stage IV melanoma undergoing surgery[28] and those receiving systemic treatment.[29-32] Neutrophilia can be a manifestation of tumor-induced inflammation. Moreover, tumors stimulate neutrophils to promote angiogenesis[33] and immunosuppression, thus becoming promoters of tumor growth.[34] The relevance of monitoring neutrophils in blood and tumor tissues was reported for many human cancers during the last decade, with consistently reported prognostic impact of elevated blood neutrophils and tumor-infiltrating neutrophils at baseline.[35] On the other hand, lymphocytes play a crucial role in the anticancer immune response, whose strength and type have a strong impact on disease progression. Lymphocytes also have functions in regulation of cell proliferation and angiogenesis via the secretion of antitumoral cytokines.[36] The NLR may combine the level of inflammatory and proangiogenic reaction, and the inhibited antitumor immune response.[37-39]

A recent meta-analysis of 100 studies including 40,559 patients[40] reported that a NLR greater than 4 was associated with increased mortality, with a hazard ratio (HR) of 1.81 (95% confidence interval [CI] 1.67-1.97; $P < .001$). The aims of our study were to evaluate whether NLR at baseline was associated with specific survival and recurrence-free survival (RFS) in patients with MCC.

METHODS

Study design, participants, and settings

We retrospectively collected cases of MCC diagnosed between 1999 and 2015 in the dermatology departments of 6 French hospitals. The diagnosis of MCC was based on the morphology of the tumor and positive immunostaining for cytokeratin 20 and/or the neuroendocrine markers synaptophysin and chromogranin A. Follow-up had been per-formed as recommended in the National French Guide-lines[3] by clinical examination every 3 to 6 months and imaging (lymph node ultrasonography and/or computed tomography) every 6 to 12 months. Computed tomography or positron emission tomography-computed tomography scans were performed for patients with suspected relapse or metastases. The study was approved by the Ethics Committee of Tours, France (no. ID RCB 2009-A01056-51).

Clinical data

The following characteristics were collected at baseline (defined by date of histologic diagnosis): age, sex, ethnicity, tumor stage according to the American Joint Committee on Cancer (AJCC) classification[41] and PS (graded from 0-4) according to the World Health Organization definition, history of smoking and/or alcohol use, the presence of immunosuppression (defined by history of solid organ transplantation, current hematologic or solid malignancies, HIV, and chronic immunosuppressive drugs, as previously described in patients with MCC[15]), type of treatment (surgery, radiation therapy, chemotherapy), and intake of systemic steroids. MCC-specific survival was defined as the occurrence of death related to MCC from the date of initial confirmed histologic diagnosis of MCC. RFS was defined by the occurrence of a clinical event