Predictive Value of Glycated Hemoglobin and Body Mass Index for Pretreatment Neuropathy in Patients With Multiple Myeloma

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Abstract

We assessed 29 patients with newly diagnosed multiple myeloma (MM) for peripheral neuropathy using the Total Neuropathy Score, reduced (TNSr) and Total Neuropathy Score, clinical (TNSc). Neuropathy was found in 51.7% and 17.2% of patients by TNSr and TNSc, respectively. Glycated hemoglobin (HbA1c) ≥ 5.6% and body mass index (BMI) ≥ 23.7 kg/m^2 predicted baseline neuropathy. This may indicate the contribution of abnormal glucose metabolism and metabolic syndrome to pretreatment neuropathy in patients with MM.

Background: Peripheral neuropathy (PN) is detected in up to 62% patients with multiple myeloma (MM) at diagnosis. No specific risk factor for pretreatment neuropathy has been identified. **Patients and Methods:** We evaluated 29 sequential patients with MM attending our tertiary care center for peripheral neuropathy at diagnosis using symptoms, clinical examination, and nerve conduction studies (NCSs). Total Neuropathy Score, reduced (TNSr) and Total Neuropathy Score, clinical (TNSc) were calculated, and a score of ≥ 2 in each scale was considered diagnostic of PN. The study was approved by our institutional review board. **Results:** We found that 51.7% (n = 15) and 17.2% (n = 5) of patients had pretreatment neuropathy by TNSr and TNSc scales, respectively. Higher glycated hemoglobin (HbA1C) ($P = .022$), higher body mass index (BMI) ($P = .008$), higher serum creatinine levels ($P = .023$), and higher blood urea levels ($P = .006$) were associated with neuropathy by TNSr in univariate analysis. Higher blood urea levels ($P = .023$), higher serum creatinine levels ($P = .003$), and higher serum β_2-microglobulin levels ($P = .013$) were associated with neuropathy by TNSc in univariate analysis. Higher HbA1c levels ($P = .036$; odds ratio [OR], 9.46) and BMI ($P = .028$; OR, 1.78) were associated with neuropathy by TNSr on binomial logistic regression analysis. Cutoffs of 5.6% (sensitivity, 60%; specificity, 71.4%) and 23.7 kg/m^2 (sensitivity, 80%; specificity, 71.4%) were obtained for HbA1c (area under the curve [AUC], 0.75) and BMI (AUC, 0.79), respectively, on receiver operating characteristic (ROC) curve analysis to predict neuropathy. The combination of HbA1c $\geq$ 5.6% and BMI $\geq$ 23.7 kg/m^2 had higher odds of neuropathy by TNSr (OR, 27.0; 95% confidence interval [CI], 2.0-368.4) when compared with either factor alone. **Conclusion:** Use of TNSr, which incorporates electrophysiological abnormalities in addition to clinical manifestations, improves the detection rate of neuropathy. We found that high HbA1c and high BMI together are risk factors for neuropathy at diagnosis in patients with MM.

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Introduction

Multiple myeloma (MM) constitutes 1% of all cancers and 10% to 15% of hematologic malignancies and its incidence is gradually increasing.[1] As a multisystem disorder, MM affects hematopoiesis, the skeletal system, and renal function. Another frequent problem in patients with MM is the occurrence of peripheral neuropathy (PN). The reported prevalence of PN in MM varies between 0% and 62%.[2-5] This broad range is the result of heterogeneity in techniques used in the assessment for PN. In a study conducted in North India by Malhotra et al, the prevalence of PN among 29 newly diagnosed patients with MM was 62%, 38% of whom had subclinical PN evident on electrophysiological assessment only.[5] However, most clinical trials in MM used only clinical assessment for evaluation of PN at baseline and reported significant PN in only 0% to 15% of previously untreated patients.[2,3,6]

The proposed causes of PN in MM are amyloid deposition, cryoglobulins, autoimmune mechanisms (IgM antibodies against myelin glycoprotein, which impairs interactions between Schwann cells and the axon) and cytokine-mediated injury.[4,7] Other causes of PN such as diabetes mellitus, alcohol-related polyneuropathy, nutritional deficiency (thiamine, pyridoxine, pantothenic acid, and methylcobalamin), and primary peripheral nerve diseases may also contribute to PN detected at diagnosis in patients with MM.

The PN of MM is typically a distal symmetrical sensory-motor polyneuropathy, and autonomic involvement is rare.[7] To the best of our knowledge, no single predictive factor for the presence of PN has been established in patients with MM in previous studies.[5,8] In individuals who do not have MM, a higher body mass index (BMI) has been associated with sensory PN in a few previous studies.[9,10] Apart from long-standing diabetes mellitus, prediabetes is also known to be associated with otherwise unexplained PN.[11] In patients with diabetes mellitus, the incidence of PN is related to metabolic control reflected by glycated hemoglobin (HbA1c) level.[12]

In our study, we aimed to evaluate the association of BMI, HbA1c, diabetic status, and other baseline patient characteristics, such as renal dysfunction, with the presence of PN at diagnosis in patients with MM.

Patients and Methods

Patients

Newly diagnosed consecutive patients with symptomatic MM who attended the Adult Hematology Clinic at our institution from January 1 to December 31, 2014 were included in the study. Diagnosis of MM was made according to the International Myeloma Working Group criteria.[13] Patients who had received previous neurotoxic chemotherapy were excluded from the study. Local radiotherapy, brief exposure to steroids for hypercalcemia, and bisphosphonate therapy were not considered contraindications for enrollment in the study. Written informed consent was obtained from all patients before enrollment. The study was approved by our institutional review board.

Patient Assessment

At enrollment, data were collected from all patients regarding demographics, comorbid medical conditions and addictions, paraprotein isotype, presence of plasmacytomas and lytic bone lesions, basic hematologic and biochemical parameters, and serum β_2-microglobulin. Estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft-Gault equation. BMI was calculated from body weight (measured to closest 1 kg) and erect height (measured to closest 1 cm). HbA1c was estimated using high-performance liquid chromatography (Bio-Rad Laboratories, Chennai, India) calibrated according to Diabetes Complications and Control Trial standards. The lower and upper detection limits for the assay were 3.8% and 18%, respectively, and the intraassay and interassay coefficient of variation was less than 2%. A clinical diagnosis of diabetes mellitus was made if the patient had a previous diagnosis of diabetes mellitus and was receiving pharmacologic or nonpharmacologic therapy or had an HbA1c value of 6.5% or more. Fasting and postprandial plasma glucose measurement was not used to define diabetes mellitus.[14] All patients underwent abdominal fat pad fine-needle aspiration with Congo red staining and polarized microscopy as part of the routine workup for amyloidosis. MM was staged according to the International Staging System.

All patients were assessed for PN by history, clinical examination, and a nerve conduction study (NCS). The NCS was performed and interpreted by a qualified neurologist using a Viking Select electrodiagnostic system, version 10.0 (VIASYS Healthcare Inc, Conshohocken, PA) available in the neurophysiology laboratory of the department of neurology in our institution. NCS was restricted to right upper and lower limb nerves to conserve time and resources. Motor NCS for median, ulnar, tibial, and common peroneal nerves; sensory NCS for median, ulnar, and sural nerves; and F-wave latencies for median and tibial nerves were recorded. The patient was categorized as having sensory, motor, or sensorimotor PN with axonal or demyelinating physiological characteristics according to standard criteria.[15]

Based on the clinical and NCS data, Total Neuropathy Score—reduced (TNSr) and Total Neuropathy Score—clinical (TNSc) were calculated. A baseline score of ≥ 2 in TNSr or TNSc was taken to indicate pretreatment PN as described in a previous study.[16]

Statistical Methods

All quantitative continuous variables were summarized as medians. Categorical variables were summarized as frequencies. The Fisher exact test was used for testing associations between qualitative variables. Independent-sample t tests and Mann-Whitney U tests were used for comparing continuous observations with random distribution and nonrandom continuous and ordinal observations, respectively. Binomial logistic regression analysis was used to test for associations between risk factors that were significant on univariate analysis and the presence of PN. For all statistical tests used, a 2-tailed P value $< .05$ was considered significant. All calculations were done using IBM SPSS Statistics, version 22.0 (SPSS Inc, Chicago, IL).

Results

Pretreatment Patient Characteristics

During the study period, 29 sequential patients with MM were enrolled. Table 1 presents the clinical and laboratory characteristics and comorbid conditions in the study population at recruitment.