ORIGINAL ARTICLE

Incidence of Decline in Vitamin B12 Level into Diagnosed Patients of Multiple Myeloma

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ABSTRACT

Background: It is well-known and augmented frequency of pernicious anemia in already diagnosed subjects of multiple myeloma (MM). The most frequent reason of vitamin B12 insufficiency is pernicious anemia. Diagnosis of vita: B12 insufficiency is made with presenting complaints of subject, physical sign and symptoms, and laboratory investigation explain decrease in serum vita: B12 level which is most probably present in subjects of MM. Pernicious anemia along with peripheral neuropathy are repeatedly correlates with MM and vita: B12 insufficiency.

Methods: An existing study was cross sectional study in which we select 250 subjects of MM on OPD basis from multiple cancer hospitals in Pakistan. The selected patients are already diagnosed as MM with their lab findings of pteroylglutamic acid (folate) in serum and in red blood cells (RBC). Serum Folate levels were assessed on commercially available Folate ELISA (Cortez Diagnostic USA). Red cell folate levels were evaluated on commercially available Folate RBC electro cheiluminescence immunoassay (quantitative) ECLIA (Roche Diagnostics International Switzerland), serum Vita: B12 levels were estimated on commercially presented Vita: B 12 ELISA Kit (Abnova USA) Methylmalonic Acid in Serum / Plasma / Urine ELISA Kit (RECIPE Chemicals, Munich / Germany) and Homocysteine HPLC Assay (Eagle Biosciences, Inc. Germany).

Results: Total 250 patients were finalizing on the basis of clinical criterion and laboratory evaluation as MM out of which 73 (29.2%) having laboratory values showed cyanocobalamin deficiency and the residual 177 subjects (70.8%) are clear.

Keywords: Pernicious anemia, multiple myeloma (MM), cyanocobalamin, Homocysteine, neuropathy,

INTRODUCTION

MM is the frequently occurring B-cell malignancy of myeloma (plasma cells) in bone marrow section and in extra osseous tissue in multiple focal styles which produce non standard (abnormal) quantity of immunoglobulin (Ig)[1]. The exclusive triad of MM is bone lytic lesions, unusual marrow plasmacytosis and monoclonal gammopathy is distinctive. The length of disease (MM) may be localized and converted into dispersed and distinctive form. The incidence of vita: B12 insufficiency along with subjects with MM is largely unidentified. Previous studies shows that lower level of serum Vita: B12 may be due to the interference of myeloma cells paraproteins[2]. The subjects of MM experience neuropathy due to anemia caused by vit: B12 insufficiency and it has strong association with plasma cell dyscrasias. To recognize insufficiency of vit: B12 in diagnosed patients of MM might assist to recover from anemia and amplify their acceptance in the near future effects of lethal and toxic substances which may affects central nervous system[3].

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MATERIALS AND METHODS

We carry out cross-sectional study on 250 repeated patients with MM and register at the different sanatorium of entire Pakistan between 2007 and 2014. Patients with a diagnosis of MM had levels of serum folate, red blood folate, serum cyanocobalamin, serum methylmalonic acid (MMA), and homocysteine levels in plasma all these laboratory investigations are calculated as a component of early evaluation and as selected in afterward stages. Laboratory investigations were carried out in the hematology and chemical pathology laboratory at Sheikh Zayed Hospital Lahore. Serum folate, red cell folate, cyanocobalamin serum methylmalonic acid (MMA), and plasma homocysteine assays were performed by Folate ELISA Kit (Cortez Diagnostic USA), Folate RBC electrochemi luminescence immunoassay (quantitative) ECLIA (Roche Diagnostics International Ltd Switzerland), Vitamin B 12 ELISA Kit (Abnova USA), Methylmalonic Acid in Serum / Plasma / Urine ELISA Kit (RECIPE Chemicals, Munich / Germany) and Homocysteine HPLC Assay (Eagle Biosciences, Inc. Germany) respectively. Samples were processed and analyzed following the manufacturers' recommendations for each assay.

Standard for analysis of MM had a monoclonal protein, immunophenotyping, cytogenetics, complete skeletal survey, neoplastic plasma cell (> 1.2 X 10^{12} /m^2) in biopsy sample taken from bone marrow included other features such as anemia , lytic bone lesions renal failure and associated increased in serum calcium level (hypercalcemia). Amyloid deposit is also seen in biopsy samples in subjects with Amyloidosis. subject with blazing MM their bone marrow biopsy shows monoclonal proteins along with less than 10% of myeloma cells does not having kidney insufficiency, decreased in hemoglobin concentration (anemia) increase in serum calcium level (hypercalcemia). Subjects having retiring plasmacytoma having histological verification of a myeloma cell can affect the bone in the deficiency of other bone lesions, anemia, renal insufficiency, hypercalcemia, the trephine marrow biopsy shows monoclonal chains of proteins associated with 10% myeloma cells. Vita: B12 insufficiency is diagnosed thru lab estimations in which serum B12 level is less than 15.6pmol/l along with increase in MMA level in the absence of renal injury which is designated as creatinine level is 1.3mg/dl. Vita: B12 insufficiency is uncertain or suspicious when MMA is not increased or Vita: B12 is greater than 15.6pmol/l. The Vita: B12 levels were hypothetical unknown if all necessary biochemical tests do not subsist for the assessment support to the above standard. Here aforesaid lab standard to measures and characterize vita: B12 insufficiency in three different stages. First less than 6% of subjects diagnosed with greater than 300pg/ml of vita: B12 characterize as increased levels of serum MMA and homocysteine which is receptive to B12 treatment[4]. Second cyanocobalamin level less than 200pg/ml have a highly specific for vita: B12 insufficiency. Third if subjects with uncertain lab test results of vita: B12 between less than 300pg/ml and greater than 200pg/ml than these patients are diagnosed and their analysis of cyanocobalamin deficit established by an amplified intensity of MMA and serum homocysteine when accessible.

The test requires 5ml of blood. All sera were stored at –20°C before measurement. The Sample size was calculated by using the software “Power and sample size” at 5 % level of significance and 80 % power of test. Constant variables were evaluating by using Student t-test when appropriate and are stated as signify SD. Unconditional variables were estimate with the chi-square test when appropriate and are stated as fraction. No crossing point was distinguished. P value less than 0.05 was consider statistically significant. The data entered and analyzed by using SPSS Version 15.0

RESULTS

Among 250 total patients in which 73 (29.09%) patients are of MM, having biochemically identify as cyanocobalamine insufficiency and the left behind 173 (70.91%) did not have cyanocobalamin deficiency. The parameter in Table: 1 had shown intensity of mean serum level of mecobalamine, MMA, and homocysteine of the 73 patients with Vita: B12 insufficiency. Table: 2 sum up all subjects demographics values, MM staging, and cyanocobalamin status by MM staging type for the entire 250 study member. During this study comparison with monoclonal gammopathy of undetermined significance (MGUS) and Amyloidosis, subjects having MM had diagnosed with higher incidence of mecobalamine insufficiency (8%, 8%, vs. 18% respectively) this discrepancy is insignificant statistically (p=0.18). The (MCV) mean corpuscular volume was of careful consideration. Laboratory investigation shows 14 subjects out of 73(19.1%) having MCV 88 fl and remaining 58 subjects (80.8%) having MCV >94 fl. An increase statistical marker of MCV was distinguished among the patients of MM with and without cyanocobalamin insufficiency (94.5 fl vs. 88 fl, respectively; P 0.008). Still, only 20 of the 58 patients had increase number of macrocytes diagnosed cyanocobalamin insufficiency while no patient with MCV <88 fl had cyanocobalamin deficiency. Statistical analysis also revealed greater incidence of vita:B12 deficiency among the diagnosed patients who have IgA, MM appraise by way of persons who have IgG or IgM MM (22.0% vs. 11.6%, correspondingly; P 0.012). According to statistical analysis IgA had preserved its significance.

Table 1: Biochemical measurements of 73 Patients with MM and B12 insufficiency

Parameters	**B12<199 (pg/ml) (*n* =49)**	**199 < serum B12 < 299 pg/ml and MMA> 374 nmol/l (*n*=19)**	**Patients receiving B12 injections (n=5)**
Mean serum B12 (pg/ml)	159.6	248.4	424
Mean MMA (nmol/L)	346.5	562.7	367.8
Mean homocysteine (µmol/l)	12.1	11.81	9.85

Table 2: Laboratory Demographic Data by Type of Myeloma Cell Dyscrasis

Parameters	MM	MGUS	Amyloidosis	SMM	Plasmacytoma	All PCD
Age (yrs)	65.2	69.5	63.3	61.6	60.9	64.5
IgG	70	60	68	86	53	67
IgM	2	16	12			11
IgA	26	22	17	17	47	29
Hb (gm/dl)	10.2	10.3	11.0	11.2	10.1	10.7
MCV (fL)	95	91	93	89	88	92
B12 (pmol/L)	10	11	11	13	14	10.2
MMA (nmol/L)	319	258	396	295	234	311
Homocystine (µmol/L)	14	14	13	12	15	14
B12 Def (%)	71	12	4	0	1	88

DISCUSSION

The objective for this study goal is to initiate the incidence of cyanocobalamin insufficiency between the diagnosed subjects of MM. These effects demonstrate so as 29.09% of our patients with MM had cyanocobalamin insufficiency. Cyanocobalamin insufficiency diagnosed according to biochemical markers, patients presenting complains, including with signs and symptoms to identify the causative factor which leads to progression of B12 insufficiency. The effect of present study is to predict cyanocobalamin insufficiency on the basis of lab investigations. During this research period one cannot appreciate the apparent cause which shows this enhanced frequency of Vita: B12 insufficiency along with subjects of MM. Previous research shows that paraproteins of MM may produce hindrance during cyanocobalamin test[5]. This after effects may leads to decrease in number of outcomes in otherwise large number of subjects having decrease cyanocobalamin results in the absence of vita: B12 insufficiency. The amplification of biochemical levels of MMA in serum and assessment of homocystine while accessible, defeat this feasible constraint while kidney damage is excluded.[7] The chance of Cyanocobalamin insufficiency and MM is increased with age after 40 years. In this research outcome age is not related with the increased in incidence of vita: B12 deficit. Autoimmunity is the most often cause of vita: B12 deficit that includes pernicious anemia along with MM that engages unusual genetic copy of Ig fabrication. Monoclonal antibody (mAb or moAb) proteins contain the ability to opposed streptolysin O, human IgG, and (alpha) lipoprotein. It is consequently potential that (mAb) protein working against and provide impedance in absorption mechanism of vita: B12 which is going normal otherwise. [8] Ig secretory structures are IgA so this hypothesis is maintained because of the relationship between MM, IgA and cyanocobalamin deficit. Due to this association IgA had vital role in pathogenesis of vita: B12 insufficiency. In plasma cell malignancies the B12 stocks of body are speedily utilizes and therefore enhance the chance of vita: B12 insufficiency. MM cells are taken from biopsy of bone marrow which gives picture of amplified loading of vita: B12 during process of hematological culture. It would be expected that vita: B12 insufficiency incidence is increased in subjects who have diagnosed case of MM and in subjects with increased number of plasma cells both are increased in comparison of (MGUS)[9]. Subject with clinically significant signs of increased number of macrocytes anemia, and peripheral neuropathy will necessitate and go for a workup that might help in the finding of Vita: B12 insufficiency. In adding together, when subjects of MM during their treatment course received chemotherapy build up neuropathy, which are adverse effects of this therapy chemotherapeutic[10]. B12 insufficency is not the primary feature of peripheral neuropathy. On the other hand, if subject develops neuropathy than chemotherapeutic agents are used with caution or take some restrictions in subjects having repeated or intractable MM. Hyper-homocystinemia is known to be self-regulating is life threatening feature connected with venous thrombosis.[11] Diagnosed subjects with MM, having increased threat for mounting deep venous thrombosis (DVT). Regardless of the conservative treatment schedule, especially subjects getting managed with a grouping of immune-modulators, increased steroids doses, and chemotherapy agents like anthracyclines.[11] 23 out of 73 patients (31.5%) received anticoagulation therapy in tablet warfarin form, increased homocysteine in serum only about 28% devoid of analyzing B12 insufficiency. B12 deficit is frequent, but changeable, and threatening feature for hyper-homocysteinemia in subjects of MM[12]. MM subjects verify their cyanocobalamin levels may assist to put off thromboembolic phenomenon and augment efficacy of anticoagulants.

CONCLUSION

Cyanocobalamin deficiency significantly associates MM. B12 insufficiency is diagnosed according to lab-biochemical parameters, sign and symptom, and

evaluate primary factor of Vita: B12 insufficiency. In conclusion the factor causing B12 insufficiency is not evidenced during present and previous studies, according to discover of present studies point out B12 insufficiency is extensive in subjects of MM predominantly as IgA (monoclonal proteins). Mean corpuscular volume, anemia is not the predictors of Vita: B12 insufficiency. Vita: B12 levels are used for early assessment of subjects of MM may not be limited into subjects having anemia, increased number of macrocytes and of neuropathy. Recognizing cyanocobalamin insufficiency is particularly essential in subjects getting chemotherapy for PCD which has impending (CNS) neurotoxic adverse consequences.

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