RESEARCH COMMUNICATION

Liver Involvement in Multiple Myeloma: A Hospital Based Retrospective Study

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Abstract

Objective: This study was to assess liver involvement in multiple myeloma with the aid of liver function tests. Materials and Methods: A hospital based retrospective study was undertaken using data retrieved of multiple myeloma from the register maintained in the Department of Biochemistry of the Manipal Teaching Hospital, Pokhara, Nepal between 1st January, 2007 and 28th February, 2012. We collected biomarkers of liver profiles including bilirubin (Total, Direct and Indirect), total protein, albumin, AG ratio, SGOT, SGPT, ALP, γGT, LDH, ferritin, renal profile and hematological profile. Descriptive statistics and testing of hypothesis were used for the analysis using EPI INFO and SPSS 16 software. Results: Out of 37 cases of multiple myeloma, serum level of AST, ALT, ALP, γGT and LDH were increased above the cut-off point in 22 (59.5%), 24 (64.86%), 13 (35.13%), 9 (24.3%) and 11 (29.7%) respectively. The mean values of AST (65.5±28.18 U/L), ALT (68.37±29.74 U/L), ALP (328.0±148.4 U/L), γGT (44.5±29.6 U/L) and LDH (361.7±116.5 U/L), total protein (9.79±1.03 gm/dl) were significantly increased when compared with controls. In contrast, albumin (3.68±0.43 gm/dl) and the AG ratio (0.62±0.15) were significantly decreased. Similarly, anemia, hyperuricemia, azotemia, hypercalcaemia and Bence Jones proteinuria were found in 30 (78.9%), 27 (71.1%), 19 (51.5%), 15 (39.5%) and 16 (42.1%) respectively, in cases of multiple myeloma. Conclusions: While clinical manifestation of liver disease among the multiple myeloma was not common, abnormalities in liver function were characteristic.

Keywords: Multiple myeloma - liver disease - liver profile - renal profile - hematological profile - Nepal

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Introduction

Multiple myeloma (MM) is a malignant clonal proliferation of plasma cells predominantly located in the bone marrow. MM causes the neoplastic proliferation of plasma cells in the bone marrow which affects the hematopoiesis in bone marrow, active osteoclastic bone resorption and produces excessive monoclonal paraprotein (M-protein) (Ansari et al., 2007; Landgren & Korde, 2011). 1% of human cancers, almost 2% cancer death and 12-15% of all hematological cancers are due to multiple myeloma (Dores et al., 2009; Greenlee et al., 2000). The exact etiology of multiple myeloma is not known. However, some of the epidemiological studies reported that age, genetic factors, some of the occupational or environmental factors and chronic antigenic stimulation may have the role behind the pathogenesis of multiple myeloma (Sonoda et al., 2005; Khan et al., 2006). Worldwide prevalence of multiple myeloma is widely variation when compared with other hematological malignancies (Vineis et al., 1996). The age adjusted prevalence of multiple myeloma per 10000 population was found 0.5, 0.9-3.3 and 8.2 in Hawaiian Japanese men, most European Countries and San Francisco Bay Area black men respectively (Riedel & Pottern, 1992; Cartwright et al., 1999; Phekoo et al., 2004). Prevalence of multiple myeloma is lower in Asian country compared with western country. This dissimilar prevalence of multiple myeloma in different parts of the worlds has a considerable interests and reason behind it unclear. However, data regarding the prevalence of multiple myeloma in Nepal has not been reported so far. Myelomatous infiltration of extraosseous tissues is more frequently found in organs rich in reticuloendothelial tissues including liver, spleen and lymphnodes. Clinical signs of liver involvement are usually not seen. However, plasma cell infiltration in liver may occur. There are two pattern i.e. diffuse (sinusoidal) and modular for infiltration have been mentioned (Thomas et al., 1973). Invasive techniques for the liver involvement in multiple myeloma are rarely done in clinical practices and previously it was done exclusively in postmortem study. Involvement of liver in multiple myeloma has not been reported in Nepal. Thus, objective of our study was to find out the involvement of liver in multiple myeloma by examining

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liver function tests.

Materials and Methods

This hospital based retrospective study was carried out using data retrieved from the register maintained in the Department of Biochemistry of the Manipal Teaching Hospital, Pokhara, Nepal between 1st January, 2007 and 28th February, 2012. The variables collected were age, sex, liver function profile including bilirubin (total, direct and indirect), total protein, albumin, AG ratio, AST, ALT, ALP, γGT, LDH, ferritin, renal profile and hematological profile. Ethical approval for the study was taken from the institutional research ethical committee. All these biochemical parameters were analyzed using Human reagent kits on semi autoanalyser (Humalyser 3500, Germany). Laboratory standard operation procedures were maintained for all laboratory analysis. Internal quality control sera, both normal and pathological, were also run for each lot of the test, for the validation of the results. Inclusion criteria were confirmed cases of multiple myeloma. Controls were persons without clinical cancer who were seen at the same hospital for an annual physical examination. Exclusion criteria- Patients suffering from any other cancer was excluded from our study. Difference for continuous variables was assessed by using the t-test. The data was analyzed using Excel 2003, R 2.8.0 Statistical Package for the Social Sciences (SPSS) for Windows Version 16.0 (SPSS Inc; Chicago, IL, USA) and the EPI Info 3.5.1 Windows Version.

Table 1. Comparison of Laboratory Tests in Cases and Controls

Laboratory tests	Cases	Controls	P-value
Total Bilirubin (mg/dL)	00.95±00.37 (00.84-01.06)	0.66±0.16 (00.6-00.71)	<0.001
Direct Bilirubin (mg/dL)	00.43±00.22 (00.36-00.50)	00.24±00.08 (00.22-00.27)	<0.001
Indirect Bilirubin (mg/dL)	00.51±00.14 (00.46-00.56)	00.41±00.15 (00.36-00.5)	0.004
Total Protein (gm/dl)	09.79±01.03 (09.44-10.13)	06.94±00.57 (06.75-07.13)	<0.001
Albumin (gm/dl)	03.68±00.43 (03.50-03.80)	04.02±00.38 (03.90-04.13)	<0.001
AG Ratio	00.62±00.15 (00.57-00.67)	01.46±00.41 (01.32-01.60)	<0.001
AST (U/L)	65.45±34.16 (54.0-76.84)	29.56±06.15 (27.51-31.62)	<0.001
ALT (U/L)	68.37±31.30 (57.94-78.81)	30.94±08.00 (28.27-33.61)	<0.001
ALP (U/L)	328.1±155.6 (276.2-379.9)	220.7±66.02 (198.7-242.7)	<0.001
γGT (U/L)	44.45±23.93 (36.47-52.43)	028.1±08.72 (25.19-31.01)	<0.001
LDH (U/L)	366.9±158.2 (314.2-419.7)	287.4±76.35 (261.9-312.9)	0.007
Uric acid (μmol/L)	05.12±01.30 (04.68-5.55)	03.67±00.82 (03.39-03.94)	<0.001
Creatinine (μmol/L)	01.50±0.76 (01.24-01.75)	00.9±00.28 (00.8-00.99)	<0.001
Calcium (mmol/L)	10.80±03.05 (09.78-11.81)	07.81±03.37 (08.73-09.33)	0.001
Phosphorous (mg/dl)	04.24±00.74 (03.99-04.48)	03.83±00.64 (03.61-04.04)	0.014
Ferritin (ng/mL)	390±212.98 (319.4-461.4)	237.90±62.7 216.9-258.7)	<0.001
Hemoglobin (g/L)	010.25±2.13 (9.54-10.96)	14.55±01.25 (14.13-14.97)	<0.001
WBC ($\times 10^3/mm^3$)	07.10±02.10 (6385-7826)	06.58±01.92 (5339-7222)	0.273
Platelets ($\times 10^3/mm^3$)	305.4±655.6 (283.5-327.3)	257.9±895.9 (228-287.73)	0.011
ESR (mm/1st hr)	66.54±016.5 (61.03-72.04)	10.43±03.87 (06.50-09.00)	<0.001

* 'Mean±SD (95% CI)

Results

Among the 37 diagnosed cases of multiple myeloma, 22 were males and 15 were females. Not any case was found below the age group less than 30 years. One male and one female were belonged to the age group 30-40 years. Three males and two females were belonging to the age group 40-50years. Four males and three females were belonged to age group 50-60years. Eight males and six females were belonged to age group 60-70 years. Six males and three females were belonged to age group more than 70 years.

Table 1 shows the comparison of mean value of liver profile, renal profile and hematological profile in multiple myeloma cases and controls. The mean value of total bilirubin (P-value <0.001), direct bilirubin (P-value <0.001), indirect bilirubin (P-value 0.004), total protein (P-value <0.001), AST (P-value <0.001), ALT (P-value <0.001), ALP (P-value <0.001), γGT (P-value <0.001), LDH (P-value 0.007), uric acid (P-value <0.001), creatinine (P-value <0.001), calcium (P-value 0.001), phosphorous (P-value 0.014), ferritin (P-value <0.001), platelet (P-value 0.011) and ESR (P-value <0.001) were higher in multiple myeloma cases when compared with normal healthy controls. However, the mean value of WBC was not significantly higher in multiple myeloma cases when compared with normal healthy controls. The hemoglobin level (P-value <0.001), albumin (P-value <0.001) and AG ratio (P-value <0.001) in multiple myeloma was lower when compared with normal healthy

Table 2. Distribution of Patients with Laboratory Features

Laboratory features	No. of cases	Percentage
AST (<40 U/L)	22	59.45
ALT (<40 U/L)	24	64.86
ALP (<310 U/L)	13	35.13
γGT (<50 U/L)	9	24.32
LDH (<420U/L)	11	29.72
Anemia (Hemoglobin level <11.5mg/100ml)	30	78.94
Hyperuricemia (for male >416 μmol/L and for female >357 μmol/L)	27	71.05
Azotemia (BUN level >30 mg/100 ml)	19	50
Hypercalcemia (Calcium level >11 mg/100 ml)	15	39.47
Bence Jones proteinuria	16	42.1

*Mean±SD (95% CI)

controls.

Table 2 shows the distribution of multiple myeloma cases with different laboratory features above the cut-off points. Out of 37 multiple myeloma cases, the liver enzyme ALT (64.86%) was increased in highest number of multiple myeloma followed by AST (64.86%), ALP (35.13%), LDH (29.72%) and γGT (24.32%). Anemia, hyperuricemia, azotemia, hypercalcemia and Bence Jones proteinuria were found in 78.94%, 71.05%, 50%, 39.47% and 42.1% cases of multiple myeloma respectively.

Discussion

We observed maximum numbers of multiple myeloma cases (14, 37.83 %) between the age group 60 to 70 years. Only 2 (5.6%) cases of MM were found to be between 30- 40 years. However we could not get any cases below the age of 30 years. Our finding is similar to the study done by Blade et al. (1996).Though the obvious jaundice was not reported in our study, serum level of bilirubin (all total, direct and indirect) was found to be significantly higher compared with control groups. Observation of symptomatic liver disease is very rare in multiple myeloma and occasional jaundice may be seen (Thomas et al., 1985) which is almost associated with the amyloid deposition in hepatic tissues (Yamamoto et al., 1995). In this study, we found that 11 (29.72%) cases of MM had serum albumin level less than 3.5 gm/dl. Our result is similar to the study done by Thomas et al. (1973). A significant inverse relation between the serum level of albumin and globulin advocating that hypoalbuminemia was due to myeloma rather than associated hepatic or renal disorders. We found that serum level of AST and ALT was elevated in 59.45% and 64.86% respectively in multiple myeloma cases. Out of 37 cases of multiple myeloma, 13 (35.13%) cases were found to be serum ALP level higher than upper cut off point. Our finding is similar to studies done by Thomas FB et al and Kyle RA which showed mild rise of serum ALP in 25-40% of Multiple Myeloma cases (Thomas et al., 1973; Kyle et al., 1975). Increased level of serum ALP indicates plasmocytic infiltration of hepatic tissues. Clinical manifestations of liver disorders were rare. However, the liver function tests were found to be abnormal. Abnormalities of liver function are due to hepatic infiltration of plasma cells which is common in multiple myeloma. Different associated conditions including light chain deposition, amyloidosis, diffuse infiltrative process, extramedullary plasmacytomas etc are the prime factors to develop liver function abnormalities in multiple myeloma. Thomos et al describes two types of hepatic infiltration: tumor forming e.g. plasmacytomas and diffuse sinusoidal (Thomas et al., 1973). In this study we reported 11 (29.72%) of cases had high serum level of LDH. Barlogie et al. reported that high levels of serum LDH associated with high-grade lymphoma-like myeloma (Barlogie et al., 1989). Different studies reported high serum levels of LDH, CRP, IL-6, and the high fever in the course of multiple myeloma have been indicated poor prognostic rate with terminal stage (Barlogie et al., 1989; Murakami et al., 2000). Direct myeloma cell infiltration and amyloid deposit in lungs tissues associates with terminal stages of multiple myeloma (Suchman et al., 1981; Meijer et al., 1994).

In conclusion: Abnormalities in liver function were common among the cases of multiple myeloma. However, the clinical manifestation of liver disease among the cases was quite uncommon. Hepatic involvement in multiple myeloma due to plasma cell infiltration is frequently found.

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