SPECTRUM OF BONE MARROW CHANGES IN PATIENTS OF CHRONIC KIDNEY DISEASE (STAGE III, IV AND V)

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ABSTRACT

Objective: To see the various hematological changes in the bone marrow of patients with chronic kidney disease (CKD) stage III, IV and V.

Study Design: Cross sectional observational study.

Place and Duration of Study: Study was conducted in the department of haematology (Pathology), Army Medical College, Rawalpindi and duration was one year, from Mar 2015 to Feb 2016.

Material and Methods: Patients of both sexes and all age groups with CKD stage III, IV and V were included in this study. Patients' histories were recorded. Complete blood counts, bone marrow aspiration and trephine biopsy were done and evaluated microscopically. Mean blood counts of the patients in three groups of CKD were compared. Frequencies of various bone marrow (BM) findings in patients of CKD were calculated.

Results: Out of 57 patients, 41 (71.9%) were males while 16 (28%) were females. Mean age was 60 years. There was no statistically significant difference between the mean hemoglobin, mean white cell count and mean platelets count of the patients in three groups of CKD. Reactive changes due to underlying CKD and inflammation were the most frequent findings in the BM of the patients.

Conclusion: Anaemia of mild to moderate severity and reactive changes in the BM are the most frequent haematological findings encountered in patients suffering from advanced stage CKD. Since CKD is predominantly a disease of the elderly so it is not rare to find the co-morbidities including plasmacytosis, malignancies and their effects on the BM in patients of CKD.

Keywords: Advanced stage chronic kidney disease, Anaemia.

INTRODUCTION

Chronic kidney disease (CKD) is a health problem present worldwide and with the passage of time its incidence is increasing causing more and more burden on the health sector[1]. CKD is a collective term covering a number of primary disease processes that result in structural or functional kidney abnormalities, or both, persisting for at least 3 months[2]. It is related with premature mortality and decreased quality of life. Untreated cases can end up in end stage renal disease (ESRD) finally necessitating dialysis. In Pakistan more than 21 million people are affected by this disease[3].

CKD is known to effect hematological profile of the patients. The main causes are decreased production of erythropoietin from kidneys, shortened erythrocyte survival, blood loss, iron and other nutritional deficiencies, albumin toxicity, effects of uraemic inhibitors on the bone marrow (BM) and severe hyperparathyroidism[4].

The haematological effects are generally not seen in stage I and II[4]. They appear in advanced stage CKD i.e. in stage III and beyond. In our patient population CKD is quite common and almost every patient of advanced CKD suffers from some degree of hematological abnormalities, which affect the quality of life of such patients. Early diagnosis and timely interventions reduce the mortality and morbidity of such patients. This study was conducted to analyze various haematological manifestations of advanced stage CKD in peripheral blood and the

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Received: 21 Nov 2016; revised received: 21 Feb 2017; accepted: 28 Feb 2017

bone marrow (BM) of the patients, who were referred to us from the nephrology unit of our tertiary care medical set up, for the examination of BM.

MATERIAL AND METHODS

This cross-sectional study was conducted in haematology department, Army Medical College, National University of Medical Sciences (NUMS) in collaboration with department of nephrology, Military Hospital, Rawalpindi, from March 2015 to February 2016, after approval from hospital ethical committee.

Male and female patients of all age groups diagnosed with advanced CKD i.e. having kidney damage with reduction in glomerular filtration rate (GFR) below 59 mL/min/1.73 m^2 for more than 3 months were included in the study[5]. Estimated GFR had been calculated using Modification of Diet in Renal Disease (MDRD) study equation and CKD had been staged into various stages according to eGFR[5]. All the patients referred to us from Nephrology unit belonged to advanced stage CKD i.e. stage III, IV and V.

Patients were selected by non-probability convenient sampling. Detailed history with regard to erythropoietin therapy and co-morbidities was documented. Approximately 2 ml blood was sampled for complete blood count (CBC) and peripheral blood film, in ethylene diamine tetraacetic acid (EDTA) tube under aseptic conditions. CBC was done using automated haematology analyzer Sysmex KX-21. Patients were considered anaemic if the haemoglobin (Hb) was <13 g/dl in males and 11.5g/dl in females.

BM aspiration and trephine biopsy were done after written informed consent, following standard guidelines. Smears from BM aspirates were stained using Leishman's stain and Perl stain and examined under microscope[6]. Trephine biopsy specimens, were processed following the standard guidelines and stained with haematoxylin and eosin (H&E) and reticulin stains for examination under microscope[7].

Data was analyzed statistically by using SPSS version 22. Mean and standard deviation of quantitative variables were calculated. For qualitative variables frequency and percentages were calculated. Various groups were compared using one way ANOVA test for normal variables and non-parametric test for non-normal variables. A *p*-value of less than 0.05 was considered to indicate the statistical significance.

Table-I: Haematological parameters in patient of advanced CKD (n=57).

Stage of CKD	Haemoglobin (g/dl)	WBC (x10⁹/l)	Platelet count (x10⁹/l)	MCV (fl)
	Range (Mean ± SD)	Range (Mean ± SD)	Range (Mean ± SD)	Range (Mean ± SD)
III n=16 (28%)	7.7-18 (9.8 ± 2.3)	1.1-79.4 (20.7 ± 24.8)	92-863 (290.8 ± 190.3)	72.8-98.8 (89 ± 7.1)
IV n=21 (36.8%)	3.9-12.1 (8.74 ± 1.86)	0.8-77.9 (10.78 ± 15.8)	18-1341 (253.7 ± 337.6)	64.6-96.2 (84.1 ± 7.7)
V n=20 (35%)	8.1-15 (10.0 ± 1.61)	2.4-27.7 (10.3 ± 6.03)	11-423 (172.6 ± 125.4)	72-96.8 (82.6 ± 5.7)
p-value	0.07	0.12	0.13	(0.15)

RESULTS

During our study, we received 349 patients from different units of tertiary care hospital for BM examination. Out of these, 57 (16.3%) had advanced stage CKD. Age of patients sent for BM ranged from 22 years to 88 years with the mean age of 60 (± 14.0) years and median age was 62 years. There were 41 (71.9%) males and 16 (28.0%) females, showing male to female ratio

2.5:1. Haematological parameters did not show any significant statistical difference in patients of three groups as shown in table-I.

Most common indication for BM examination was anaemia which was seen in all the patients. Three (5.2%) patients also had thrombocytosis i.e. platelet count >450x10^9/l. There were two (3.5%) patients with monoclonal band on serum protein electrophoresis. One (1.7%) patient had BM examination because of pyrexia of unknown origin. All the anaemic patients had the history of having received erythropoeitin (EPO) therapy. BM was normocellular for age in 22 (38.6%) patients, hypercellular in 29 (50.8%) patients and hypocellular in 1 (1.7%) patient. Five patients (8.7%) showed patchy cellularity i.e. hypercellular areas as well as hypocellular patches. Erythropoiesis was normoblastic in 29 (50.8%) patients, depressed in 20 (35.0%) patients and normoblastic with mild megaloblastic changes in 4 (7.0%) patients. Whereas, erythropoiesis was hyperplastic with megaloblastic and dysplastic changes in 4 (7.0%) patients only. Myelopoiesis was active with normal maturation in 33 (57.8%) patients. Hyperactive myelopoiesis with normal maturation was present in 16 (28.0%) patients. Myelopoiesis was markedly depressed in 7 (12.2%) patients. There was only 1 (1.75%) patient who showed active myelopoiesis with decreased mature forms.

Megakaryopoiesis was normal in 48 (84.2%) patients, depressed in 8 (14.0%) patients and increased in only 1 (1.75%) patient. Iron was increased with decreased siderocytes and sideroblasts in 47 (82.4%) patients, absent in 6 (10.5%) and present in 4 (7.0%) patients. Bone marrow aspiration and trephine results in patients of advance stage CKD disease are shown in table-II.

Table-II: Bone Marrow examination results of advanced CKD patients (n=57).

Bone marrow examination diagnosis	III (n=16)	IV (n=21)	V (n=20)	Total (n=57)
Reactive changes to CKD and chronic disorder	03 (18.7%)	12 (57.1%)	10 (50%)	26 (43.85%)
Bone marrow plasmacytosis	03 (18.7%)	04 (19.0%)	03 (15%)	10 (17.54%)
Findings suggestive of infective process	02 (12.5%)	01 (4.76%)	04 (20%)	07 (12.5%)
Bone marrow showing metastasis	03 (18.7%)	0 (0%)	0 (0%)	03 (5.26%)
Lymphoproliferative disorders	02 (12.5%)	0 (0%)	01 (5%)	03 (5.26%)
Pure red cell aplasia	0 (0%)	01 (4.76%)	0 (0%)	01 (1.75%)
MAHA	0 (0%)	01 (4.76%)	0 (0%)	01 (1.75%)
Hypocellular marrow	0 (0%)	0 (0%)	01 (5%)	01 (1.75%)
Mixed deficiency	0 (0%)	01 (4.76%)	0 (0%)	01 (1.75%)
Acute myeloid leukemia	0 (0%)	01 (4.76%)	0 (0%)	01 (1.75%)
Megaloblastic anaemia	01 (6.25%)	0 (0%)	0 (0%)	01 (1.75%)
Peripheral destruction of platelets	01 (6.25%)	0 (0%)	0 (0%)	01 (1.75%)
CML	01 (6.25%)	0 (0%)	0 (0%)	01 (1.75%)
Normal marrow	0 (0%)	0(0%)	01 (5%)	01 (1.75%)

DISCUSSION

CKD is predominantly a disease of the elderly with incidence rising sharply after sixth decade of life. Most of our patients 39 (66.1%) were >60 years of age. In this study we found CKD to be 2.6 times more common in males than females in hospitalized patients. In two other studies male to female ratio was 2.86:1 and 3:1 respectively which is comparable to our study[3,8].

Anaemia is a very common problem in patients of CKD. There is generally a fall in Hb of 2 g/dl with every 10 mmol/l rise in the blood urea. However there are other factors which affect the equation such as deficiency of micronutrients, blood loss, dialysis, co-morbidities, EPO therapy and blood transfusions. Anaemia in our patients was generally mild to moderate in severity (haemoglobin >7 g/dl) except in a patient with co-existing acute leukaemia and another with pure red cell aplasia, in whom it was severe. Our study revealed gradual decrease in haemoglobin in patients as CKD advanced from stage III to stage IV but mean Hb in stage V was slightly higher which could be probably because of increased frequency of blood transfusion in advanced CKD. However the difference in mean Hb level in the three groups was not statistically different. Other studies conducted in Nepal and India showed a gradual decrease in Hb as the stage of CKD advances[9,10].

Anaemia in our patients was normocytic (71.9%) or microcytic (26.3%). While megaloblastic picture was present only in 1 (1.75%) patient. Mean corpuscular volume (MCV) in our study showed a gradual decline as CKD advanced from stage III to stage V (table-I). This could be because of decreased availability of iron to the erythroid cells either due to chronic inflammatory process or because of functional iron deficiency. Another study revealed a decrease in MCV from stage III to stage IV but showed a rise in stage V[9].

Anaemia parallels the degree of renal damage. Kidney's peritubular interstitial cells are the main site of production of EPO which is the major hormone regulating the production and viability of red cell. As kidney destruction and fibrosis advances there is a relative deficiency of EPO. Other factors include EPO resistance due to the presence of pro-inflammatory cytokines, nutritional deficiencies and reduced erythrocyte life due to uremia. As the blood urea nitrogen concentration increases the expression of phosphatidylserine on the outer red cell membrane increases leading to enhanced red cell recognition and destruction by macrophages, resulting in short life span of RBCs[11]. Co-morbidities including malignancies are also common especially in the elderly patients and contribute to pathogenesis of anaemia.

In our study mean platelet count showed slightly receding pattern as CKD advanced from stage III to stage V, which is statistically not significant. EPO also effects the megakaryocytic colony stimulating factors, acetylhydroase (PAF-AH) and paraoxonase (PON1). As EPO level decreases platelet count also declines. This can be logical as thrombopoietin closely resembles erythropoietin[11].

Our study showed reactive changes due to CKD and underlying inflammation as the most common findings on the BM examination. These changes include myeloid hyperplasia and increased iron stores with decreased siderocytes and sideroblasts. Another study reported almost same results with anaemia of chronic disorder being present in 44.8% cases[3].

BM plasmacytosis due to multiple myeloma (MM) was a common finding on the BM examination in our study. In another study MM has been reported in 6.9% cases[3]. MM and acute and chronic renal impairment are interrelated. Half of the newly diagnosed MM patients can have renal involvement, including 20% with severe kidney impairment and 10% requiring dialysis[12]. Main reason for kidney failure in MM is the increased production of nephrotoxic light chains which causes renal damage by causing obstruction, fibrosis and amyloidosis of the tubules[12].

Since CKD is predominantly a disease of the elderly so it is not surprising to find the co-morbidities and their effects on the BM in patients of CKD. Apart from MM other malignancies diagnosed on BM examination in our patients of CKD included lymphoproliferative disorder and metastatic carcinomas in 3 patients each; and acute myeloid

leukaemia and chronic myeloid leukaemia in one patient each.

In our study there were 6 patients (10.52%) who had findings suggestive of an underlying infective process on BM aspirate and trephine, reflected as myeloid hyperplasia and neutrophils showing toxic granulations. People with CKD are more prone to infections because of presence of related conditions such as diabetes, inadequate calorie and protein intake, and the access sites for dialysis, which make them vulnerable to infection. Infective process accelerates the process of CKD leading to end stage renal disease (ESRD)[11].

One of our patients had pure red cell aplasia. Although the patient had the history of EPO therapy, we could not establish the causative association due to non-availability of anti EPO antibody assay.

CONCLUSION

Anaemia of mild to moderate severity and reactive changes in the BM are the most frequent haematological findings encountered in patients suffering from advanced stage CKD. Since CKD is predominantly a disease of the elderly so it is not rare to find the co-morbidities including plasmacytosis, malignancies and their effects on the BM in patients of CKD.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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