Original Article

Hematological Findings in Nephropathic Cystinosis: Single Center Experience.

Hanan Abdelaziz Ahmed[1], Neveen A. Soliman[1], Asmaa A Abdelgawad[1], Shahira K.A. Botros[2], Asmaa A. Abdelaal[2], Iman A. Shaheen[2], Rasha Helmy[1]
1- Department of Pediatrics, Kasr Al Ainy School of Medicine, Cairo University, Cairo, Egypt.
2- Department of Clinical Pathology, Kasr Al Ainy School of Medicine, Cairo University, Cairo, Egypt.

ABSTRACT

Introduction: Cystinosis is a rare autosomal recessive lysosomal storage disorder characterized by cystine crystals accumulation in almost all cells and tissues. Patients often develop end organ dysfunction and kidney failure. We aimed to characterize the hematological manifestations and bone marrow involvement in patients with cytopenia affecting more than one hematologic cell line and to correlate it with patients' growth, thyroid and kidney functions.

Methods: Twenty patients with nephropathic Cystinosis were included. All patients subjected to thorough clinical examination including weight, height standard deviation scores and slit lamp examination for localization and scoring of corneal cystine crystals. Laboratory investigations included renal functions, complete blood count, bone marrow examination for patients with bicytopenia or pancytopenia.

Results: Sixteen cases (80%) had anemia. A significantly higher CCC score, creatinine level, ferritin level and a lower thyroid function level were found in the anemic group of patients (p= 0.044, 0.016, 0.022 and 0.016 respectively) compared to the non anemic group. Three patients (15%) experienced cytopenia in more than lineage, bone marrow examination showed cystine crystal deposition, normal bone marrow cellularity with trilineage hematopoiesis.

Conclusion: Cystinosis patients experienced hematological complications, anemia was present in most of the patients, patients with hypothyroidism and higher corneal crystals depositions had lower hemoglobin level, so these patients need monitoring of their blood count. Although cystine crystals were seen in the bone marrow of our cases, cytopenia and hematological symptoms were not attributed to bone marrow suppression by cystine crystals deposition. Various other etiologies should be thoroughly investigated.

Key words: Cystinosis- Anemia- Bone marrow biopsy – cystine crystals

Corresponding Author: Rasha Helmy, MD
Assistant professor of Pediatrics, Kasr Al Ainy School of Medicine, Cairo University, Cairo, Egypt.
Email : rhelmy_1985@hotmail.com

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INTRODUCTION

Cystinosis is a rare autosomal recessive lysosomal storage disorder in which the amino acid cystine accumulates in the lysosomes of cells [1] throughout the whole-body systems, including eyes, thyroid gland, muscles & CNS [2, 3] and bone marrow [4].

Patients frequently experience anemia due diminished renal erythropoietin production, uremia, or cystine crystals in the bone marrow [5]. In patients with cystinosis, hypocoagulability and platelet dysfunction have also been reported [6]. Rarely, patients will also experience pancytopenia related to bone marrow suppression by cystine crystal deposition [7].

The aim of this study was to characterize the hematological manifestations and bone marrow involvement in patients with cytopenia affecting more than one hematologic cell line and to correlate it with patients' growth, thyroid and kidney functions.

METHODS

This study included 20 patients (from 18 families) with confirmed nephropathic cystinosis being cared for at the Cystinosis outpatient clinic, Cairo University Children's Hospital, Cairo University.

Clinical as well as demographic data were obtained from medical records and interviews with the patients including the following: age at diagnosis, consanguinity of parents, history of affected sibling(s) with the same disease, age at onset of symptoms in months

Clinical examination included anthropometric assessment including weight and height standard deviation scores for age and gender, slit lamp ophthalmological examination for localization of corneal cystine crystals as well as Corneal Cystine Crystal Scoring (CCCS) as described by Ghal and colleagues [8]. All the patients were subjected to abdominal ultrasound examination.

Laboratory investigations included: blood urea nitrogen (BUN), serum creatinine concentration by beckman coulter analyzer AU480, USA, thyroid functions i.e. serum TSH and free T4 using Immulite 1000 H2075 analyzer , Japan; Iron profile (Serum iron, total iron binding capacity using the ADVIA 1800 analyzer, Japan; and serum ferritin using the ADVIA Centaur XPT analyzer, Japan.

Hematological assessment: CBC was performed using the x5-800i-sysmex analyzer, Japan. Reticulocytes preparation and staining were done by the standard technique described by Briggs and Bain [9].

Procedure of Bone marrow examination:

Sample collection: Bone marrow aspiration and trephine biopsy samples were performed from the posterior superior iliac spine. All included BM cores were adequate, consisting of at least 1.5 cm or more than 5 inter trabecular spaces. Bone marrow samples were processed and sections were prepared according to Bain et al (2001) [10].

Data analysis: Data were coded and entered using Microsoft office excel 2010. Statistical analysis was done using

IBM SPSS version 24. Frequencies (number) and relative frequencies (percent) were used to summarize qualitative variables while mean and standard deviations were used for quantitative variables. Comparison between groups were done using Fisher's Exact Test and Mann-Whitney Test. Spearman's rho non- parametric correlation was used to test for possible correlations between quantitative variables. P value less than or equal to 0.05 was considered significant.

Ethical issues: the study protocol and all procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. The local Medical Ethics Committee of each of the Clinical Pathology Department and the Pediatrics Department, Cairo University approved the study.

RESULTS

This study was conducted on 20 patients (from 18 families) with confirmed nephropathic cystinosis, 9 were males (45%) and 11females (55%), being cared for at the Cystinosis outpatient clinic, Cairo University Children's Hospital.The age of the patients, anthropometric measurements of the studied patients, and their start of symptoms and ESRD are shown in **[Table 1]**. Corneal cystine crystals was detected by slit lamp in 18 patients (90%) with CCCS 3, 2.5, 2, 1.5 in 35% (n=7), 30% (n=6), 15% (n=3) & 10% (n=2) of the patients respectively **[Figure 1&2]**. Six patients (30%) have hypothyroidism on L-thyroxin. Laboratory data of the patients are shown in **[Table 2]**.

Hematological manifestation among the studied patients: Anemia was present in 16 cases (80%), the anemia was normocytic in 11cases (68.8%) and microcytic in 5 cases (31.2%).

The association between the different clinical, hematological and biochemical profile among the anemic and non-anemic patients was studied and revealed a significantly higher CCC score, creatinine level, ferritin level and a lower thyroid function level in the anemic group of patients (p= 0.044, 0.016, 0.022 and 0.016 respectively) **[Table 3]**.

BM examination in patients with cystinosis: Three Out of twenty patients, 3/20 (15%) experienced cytopenia affecting more than one hematologic cell line. Pancytopenia was encountered in case 1, anemia and thrombocytopenia in case 2, anemia and leukopenia in case 3, **[Table 4]**.

Table 1: Demographic and clinical data of the studied patients.

	Minimum	Maximum	Mean	Std. Deviation
Age in years	1	**20**	**7.52**	4.09
Age of onset of symptoms in months	**4**	**24**	**7.35**	4.6
Age of diagnosis in months	**5**	**84**	**26.9**	25.1
Age of ESRD in year	**5.5**	**8.5**	**7**	1.29
Weight (kg)	**5.5**	**26**	**16**	4.77
Weight SDS	**- 4.2**	**-0.4**	**-2.49**	0.96
Height (cm)	**66**	**120**	**95.4**	14.7
Height SDS*	**-7.4**	**-1.6**	**-4.7**	1.6

*Standard deviation score (SDS) according to the Egyptian Growth Curves for age and gender

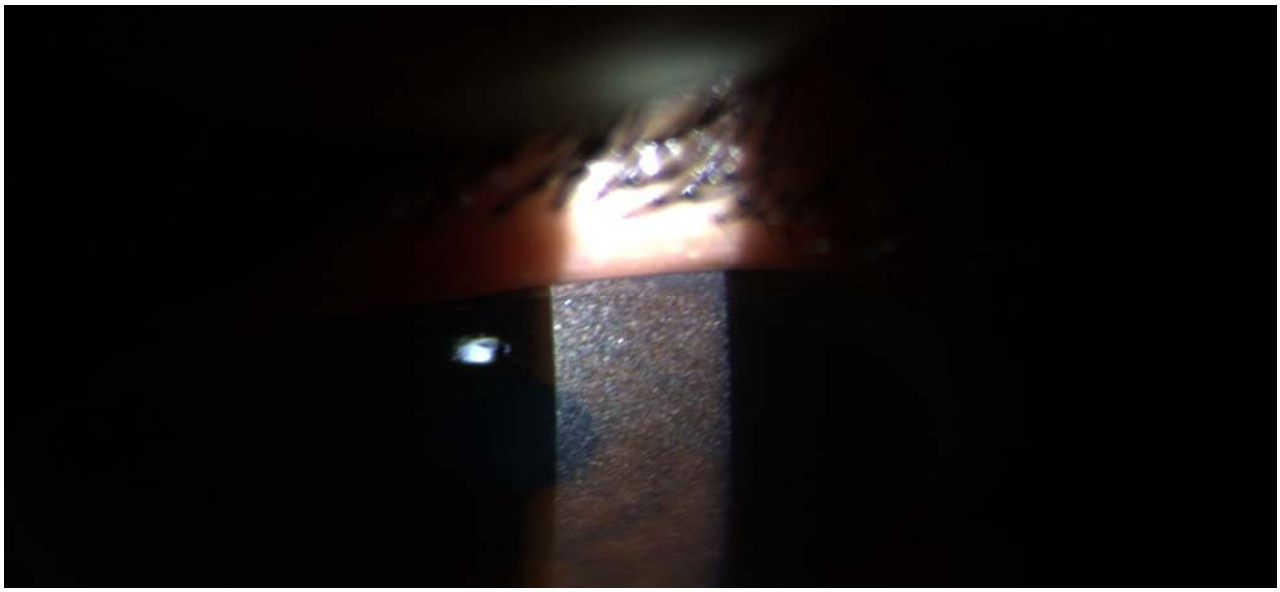

Figure 1: Slit lamp examination of a case showing corneal cystine crystal deposition

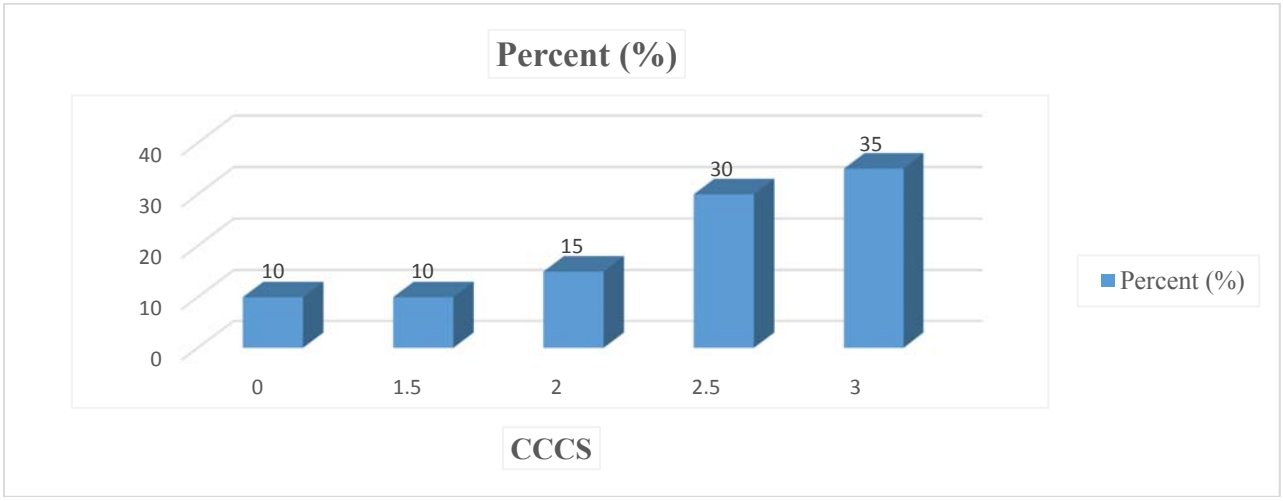

Figure 2: Corneal cystine crystal scoring (CCCS) of cases

Table 2: Laboratory data of the studied patients (n = 20).

	Ref. ranges	Minimum	Maximum	Mean	Std. Deviation
HB (g/dl)	11-13	6.00	13.80	**9.5200**	2.02474
MCV (fl)	78-100	66.70	90.90	82.1050	6.78865
MCHC	32.25	32.25	32.25	32.25	0
Platelet (×10^3/µl)	150-500	109.00	506.00	303.9000	105.51872
WBC (×10^3/µl)	4-11	3.20	15.40	8.0400	3.04638
Retics (%)	0.5-2	.50	5.00	1.6400	1.00964
Serum Iron (µg/dl)	50-120	29.00	153.00	61.5500	29.09418
Serum Ferritin (µg/dl)	15-300	34.00	4337.00	**641.6000**	1098.5532
TIBC (ng/ml)	250-450	195.00	810.00	343.850	133.9651
Creatinine	0.2-0.8	0.20	7.10	**2.7050**	2.26122
BUN (mg/dl)	5-23	4.00	115.00	29.9700	27.26897
TSH(mIU/l)	0.7-6.4	1.31	75.00	**8.5495**	17.02377
Free T4(ng/l)	0.8-2	.40	11.60	2.3415	2.93087

TIBC: total iron binding capacity, TSH: thyroid stimulating hormone.

Table 3: Clinical, hematological & biochemical profile in anemic & non-anemic studied Cystinosis patients.

	Anemic (n=16)			Non anemic (n=4)			P value
	Mean	Standard Deviation	Median	Mean	Standard Deviation	Median	
Age	8.09	4.31	8.25	5.25	2.18	4.25	.117
Age of onset of symptoms in months	6.19	2.40	6.00	12.00	8.49	9.00	.085
Age of diagnosis in months	28.06	25.76	12.00	22.25	25.22	10.50	.600
Weight SDS	-2.68	.70	-2.50	-1.79	1.60	-1.70	.276
Height SDS	-4.88	1.53	-4.70	-4.10	2.07	-4.00	.395
CCCS	2.44	.79	2.50	1.50	1.08	1.75	**0.044**
HB	8.2	2	8	12.4	1.4	12.5	**0.001**
HCT	24.5	6	27.7	38.44	3.5	38.6	**0.001**
MCV	82.13	7.35	84.40	82.00	4.67	80.20	.887
Platelet	283.00	101.66	282.00	387.50	84.80	368.00	.073
WBC	7.48	2.42	7.90	10.28	4.60	9.85	.321
Retics	1.74	1.11	1.55	1.25	.21	1.25	.507
Creatinine	3.20	2.27	2.65	.73	.38	.70	**0.016**
BUN	34.38	28.85	27.00	12.35	5.55	13.20	.119
TSH	10.13	18.81	4.11	2.23	.63	2.45	**0.016**
Free T4	1.84	2.16	1.45	4.35	4.93	2.35	.368
Serum Iron	65.31	31.00	62.00	46.50	13.33	46.50	.170
Serum Ferritin	783.875	1191.85	249.5	72.50	28.90	79.00	**0.022**
TIBC	352.625	146.87	332.5	308.75	61.17	285.50	.617
Age of start of Cysteamine in months	37.13	31.54	18.00	21.75	25.85	12.00	.249
Duration of Cysteamine therapy in months	58.38	51.74	54.00	40.50	5.74	39.00	.705
Dose of Cysteamine (mg/kg/d)	31.00	8.14	31.75	21.88	13.73	21.50	.343

TIBC: total iron binding capacity, P≤0.05 is considered significant

Table 4: Detailed data of the three cystinosis patients with bi/pancytopenia*

	Case NO 1	Case NO 2	Case NO 3
Sex	**female**	**male**	**female**
Age in year	20.5	10	10.5
consanguinity	yes	yes	yes
Weight	26	20	20
Weight SDS	-4.2	-2.5	-2
Height	120	102	113.5
Height SDS	-7	-5.6	-4.4
No of similar condition	1	0	1
Age of onset of symptoms in months	6	6	6
Age of onset of diagnosis in months	60	11	8
Interval between first reported presentation and diagnosis	54	5	3
Age of ESRD in year	5.5	6	6
CCCS	3	3	2.5
HB (g/dl)	7.8	9	7.4
HCT%	26.2	29.8	22
MCV (fl)	91.3	86.6	94.8
MCH (pg)	27.2	26.2	31.9
Platelet ($\times 10^3/\mu l$)	124	109	246
WBC ($\times 10^3/\mu l$)	3.2	10.8	3.3
Retics (%)	5	0.5	2.5
Serum Iron (µg/dl)	153	71	37
Serum Ferritin (µg/dl)	2850	4337	258
TIBC (ng/ml)	220	195	222

Table 4: Detailed data of the three cystinosis patients with bi/pancytopenia* **(continued)**

	Case NO 1	Case NO 2	Case NO 3
Creatinine*	4.2	1.5	10
BUN(mg/dl)*	39	8	10
pH	7.34	7.66	7.32
TSH(mIU/l)	75	2.7	2.9
Free T4(ng/l)	0.4	1.3	1.6
Age of start of cysteamine in months	60	12	12
Duration of cysteamine in therapy months	180	108	108
Dose of cysteamine (mg/kg/d)	34.5	25	22.5
Age of start cysteamine eye drops	60	12	12
Frequency of cysteamine eye drops	6	0	2

CCCS: cystine corneal crystal scoring P≤0.05 is considered significant

Case 1: A female 20.5 year old with hereditary cystinosis on chronic hemodialysis (>10 years), developed pancytopenia.

During this time, she had moderate hepatosplenomegaly and routine work up revealed positive hepatitis C virus.

Bone marrow biopsy examination revealed normal bone trabeculae separating a normocellular BM for age with erythroid and megakaryocytic hyperplasia. Macrophages were increased (5-10%) with excessive intracytoplasmic as well as free refractile crystal deposition occupying 10% of marrow cellularity, **[Figure 3]**.

Case 2: Male patient 10-year-old with hereditary cystinosis on chronic hemodialysis (>4 years). During this time, he had mild hepatomegaly.

He developed chronic anemia and required several blood transfusions and had to be placed on erythropoietin injections; later on, he developed mild thrombocytopenia. Bone marrow examination revealed a normocellular BM for age with megakaryocytic hyperplasia. Macrophages were increased (10-15%) with intracytoplasmic as well as free refractile crystal deposition occupying 10 to 15% of total marrow cellularity, **[Figure 4]**.

Case 3: Female patient, 10-years-old girl with hereditary cystinosis. Eventually, she developed chronic anemia and leukopenia. Careful history taking revealed history of recurrent chest infection. Bone marrow examination of BM aspirate smears revealed a normocellular BM for age with erythroid hyperplasia with megaloblastic changes, bone marrow macrophages were increased by (5-10%) with intracytoplasmic refractile crystal deposition, **[Figure 5]**.

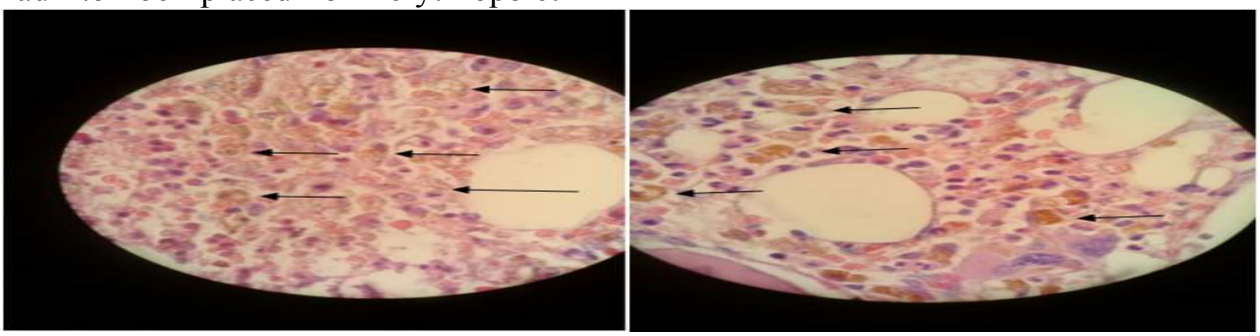

Figure 3: Bone marrow core smear of case 1 showing: Numerous rhomboid and rectangular shaped, birefringent cystine crystals are visualized.

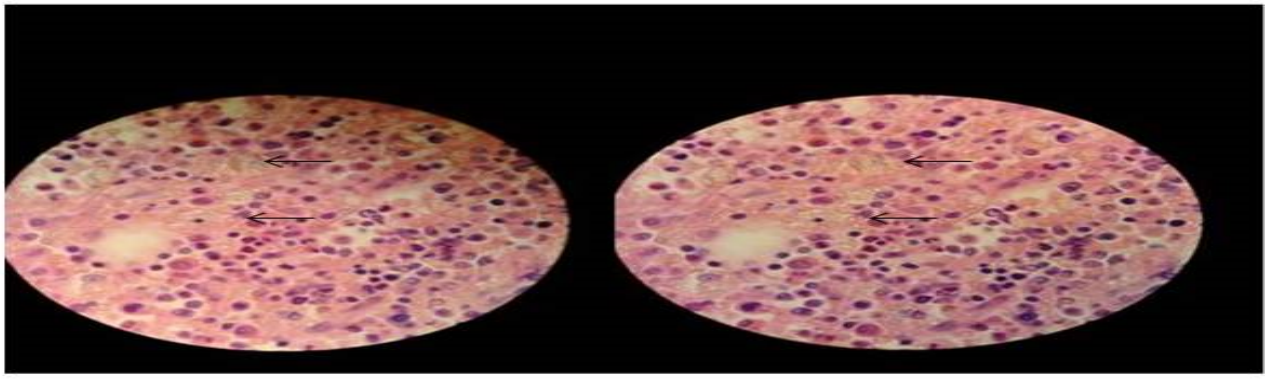

Figure 4: Bone marrow biopsy of case 2 showing: macrophages laden with colorless cystine crystals of varying shapes and size.

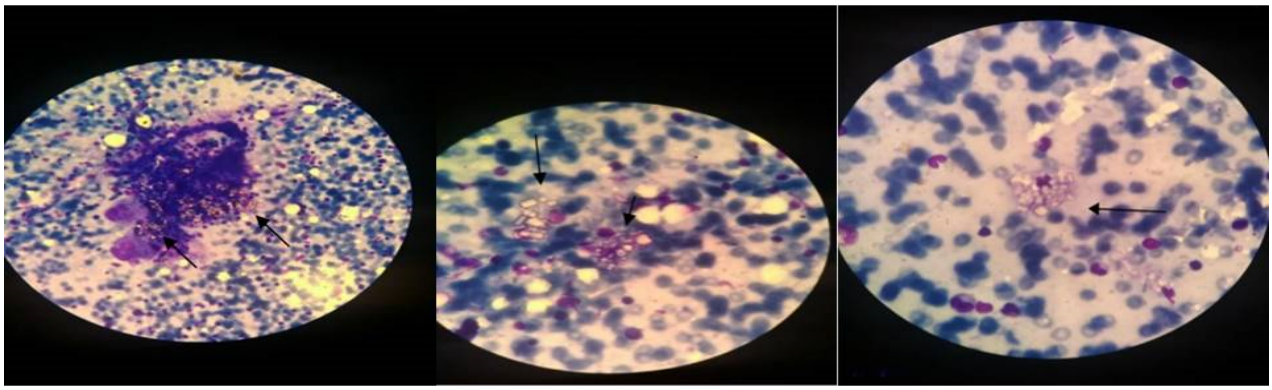

Figure 5: Bone marrow aspirate smear of case 3 showing: macrophages laden with Colorless cystine crystals of varying shapes and size.

DISCUSSION

Infantile nephropathic cystinosis is the most severe and most common form (~95% of cases) [11]. Kidney involvement, started with Fanconi's syndrome and ends in end-stage renal disease (ESRD) before the age of ten years in untreated patients.

Hematological manifestations is one of its complication and few previous studies was investigating this complication, so our objective to focus on this complication.

Cystinosis is a chronic kidney disease (CKD), the anemia of CKD is generally normocytic and normochromic. In our study, 80% of the patients were anemic, 68.8% had normocytic normochromic anemia while 31.2% had microcytic hypochromic anemia due to iron deficiency.

Microcytic hypochromic anemia can be explained by simple anorexia reduced iron intake caused by renal failure, also reduced intestinal absorption that occurs in ESRD patients on dialysis or predialysis due to the intestinal mucosal changes seen in uremia [12].

As kidney disease progresses, anemia increases in severity, also corneal cystine crystals deposits progressively increase with age in patients with cystinosis [13] and so there is a direct relation between corneal cystine crystals and anemia.

Our study showed a statistically significant difference between the anemic and non-anemic patients as regard CCCS

which was more pronounced in anemic patients (2.44±0.79), compared to non-anemic patients (1.5±1.08) (p value = 0.044).

There was a statistically non-significant difference between the anemic patients and the non-anemic patients regarding mean weight and height SDS, (-2.68 +.7 vs-1.79 + 1.6 respectively) (p value = 0.276). (-4.88 + 1.53 vs-4.1+2.07 respectively) (p value = 0.395), this is presumably attributed to the small numbers of the studied patients.

Progressive accumulation of cystine and crystal formation in thyroid follicular cells causes fibrosis and atrophy leading to primary hypothyroidism [2].

Hypothyroidism was diagnosed in 30% of our cystinosis patients. Thyroxine is needed for potentiation of erythropoietin action on erythroid colony formation [14], documented that hypothyroidism leads to decreased blood counts and clonogenic potential of erythroid Burst Forming Units (BFU-E) ultimately leading to decreased erythropoiesis.

In our study, there was a statistically significant difference between the anemic and non-anemic as regard TSH which was higher in anemic patients (10.13±18.81 mIU/l), compared to non-anemic patients (2.23±.63 mIU/l) (p value =0.016).

Early initiation of treatment when indicated to optimize thyroxine effect on erythroid series as an integral adjuvant therapy for anemia, thereby avoiding un necessary blood transfusion.

As kidney function declines the likelihood of anemia associated increases because of insufficient quantities of erythropoietin & uremic anorexia could result in reduced iron intake.

The present study, revealed a statistically significant difference between the anemic patient and non-anemic as regard serum creatinine which was more impaired in anemic patient (3.2±2.27), compared to non-anemic patient (0.73±0.38), (p value =0.016).

Symptomatic bone marrow disease is uncommon in cystinosis and only reported in case reports [5, 15 & 16].

Although cystine crystals were widely seen in bone marrow aspirates, cytopenia and hematological symptoms were rarely reported in cystinosis cases.

In the current work three out of 20 patients (15%) experienced cytopenia affecting more than one hematologic cell line, so bone marrow examination ordered.

The first case had pancytopenia, bone marrow examination revealed a normocellular BM for age, free refractile crystal deposition but has HCV and splenomegaly that progressed to hypersplenism and pancytopenia.

The second case had normocytic anemia and thrombocytopenia, with a normocellular BM for age, free refractile crystal deposition; erythroid series were normal. Thrombocytopenia was not attributed to depressed megakaryopoiesis, but due to ineffective thrombopoiesis that is commonly seen in ESRD patients (low platelet count despite normal megakaryocyte number) previously described in CKD patients [17].

The third case had normocytic normochromic anemia and leucopenia. BM examination revealed a normocellular BM for age, with intracytoplasmic refractile crystal deposition. Erythroid series showed hyperplasia with mild megaloblastoid changes. Explanation of leucopenia was that this patient had recurrent chest infection. Follow up CBC

of the patient revealed a normalized white cell count.

Interestingly BM examination was performed in several studies of nephropathic cystinosis cases presenting with pancytopenia.

Our findings agree with the study of [18] who reported a 6-year-old boy with bicytopenia (anemia and thrombocytopenia), bone marrow biopsy revealed 90% cellularity and numerous clear cystine crystals apparently free and within macrophages and increased reticulin fibers.

However [16] reported a case with cystinosis and other comorbidities who developed pancytopenia, investigations were done and common causes of pancytopenia were ruled out, on bone marrow biopsy showed extensive deposits of cystine crystals, cellularity was 5% which was thought to be the cause of her myelosuppression leading to her pancytopenia.

Also, [19] reported another case of cystinosis that developed anemia and leucopenia at a follow-up examination. A bone marrow biopsy was performed, revealing a hypocellular bone marrow with mild megaloblastoid erythropoiesis and numerous cystine crystals which was thought to be the cause of her myelosuppression leading to her pancytopenia.

CONCLUSION

Inspite of cystine crystals deposition in the bone marrow of our cases, cytopenia and hematological symptoms were not attributed to it as bone marrow cellularity was normal.

There is a relation between anemia & degree of cystine deposition in the cornea by CCCS, hypothyroidism & kidney functions. Anemia in cystinosis could have various etiologies other than bone marrow failure and should be thoroughly investigated.

Limitations of the study: The small number of patients examined, is a limitation in the present study. This is attributed to the low prevalence rate of this disorder. Future study on a larger sample size is recommended to confirm the results in addition to extended follow up to monitor the hematological effect of cystine crystals deposition in the bone marrow.

ABBREVIATIONS

BM	Bone Marrow	HB	Hemoglobin
CBC	Complete Blood Count	HCT	Hematocrit
CCCS	Corneal Cystine Crystal Scoring	MCHC	Mean Corpuscular Hemoglobin Concentration,
CKD	Chronic Kidney Disease	MCV	Mean Corpuscular Volume
CNS	Central Nervous System	TIBC	Total Iron Binding Capacity
ESRD	End Stage Renal Disease	TSH	Thyroid Stimulating Hormone

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AUTHORS' CONTRIBUTIONS

The submitted manuscript is the work of the author & co-author. All authors have contributed to authorship, have read and approved the manuscript.

Conception and design of study: 1st, 2nd & 4th authors

Acquisition of data: all authors

Analysis and/or interpretation of data: 1st and last author

Drafting the manuscript: all authors

Revising the manuscript critically for important intellectual content: 1st, 2nd and last author

Approval of the version of the manuscript to be published: all authors

STATEMENTS

Ethics approval and consent to participate

The study was ethically conducted in compliance with the World Medical Association's Helsinki Declaration.

The Institutional Review Board of Cairo University approved the study protocol.

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