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The Afro-Egyptian Journal of Infectious and Endemic Diseases (AJIED) is a peer-reviewed journal that publishes clinical, parasitological, microbiological, physiological, biochemical, immunological and pathological studies in the field of infectious, endemic and tropical diseases. The scope of the journal includes also articles of endemic gastroenterology and hepatology. The journal is published quarterly by Endemic and Tropical Medicine Department, Faculty of Medicine, Zagazig University, Zagazig, 44519, Egypt.

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Different Treatment Modalities for Improving HCV Response

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Key words: Treatment,
HCV, response .

Background and study aim: Hepatitis C virus is a major health problem throughout the world .Interferon (INF) was the only therapeutic opinion until the mid 1990s.Ribavirin(RBV) when added improve the SVR rate (8 to 42%) in patients with genotype 4 infection. Nitazoxanide induces a naturally occurring antiviral intracellular protein and a key mediator of host cell defense against viral infection, it is also believed that it inhibits viral glycoproteins at the post translational level. We aimed to study the impact of NTZ in addition to PEG-INF α 2a and RBV on virological response in patients with chronic hepatitis C.

Patients and Methods: In this work, we studied 100 HCV patients who met the inclusion criteria of age, BMI, normal laboratory findings of liver and kidney functions, CBC, blood glucose level, thyroid functions and with absence of immunological disease. Quantitative PCR for HCV RNA and liver biopsy were done for each patient. Any patient showed more than F3 or A3 in this biopsy was excluded. All patients are followed clinically and by laboratory throughout the period of the study. All patients were

divided into three groups: Group (A) received the SOC: PEG-IFN α 2a 180 μ g and RBV (1000, 1200mg), group (B): received SOC and Nitazoxanide and group (C): received NTZ alone.

Results: EVR in group (A) patients was 83.3% compared to 86.6% in group B patients . 24 week PCR negativity was 76.6% for group A and 80% for group B . As regard NTZ as a monotherapy ; four patients (10%) showed pEVR (>2log drop in HCV RNA) but they failed to achieve – ve HCV RNA at the end of treatment, nineteen patients showed <2log drop in HCV RNA at week 12. Out of these nineteen patients, 15 patients showed further decrease in HCV viral load at weeks 24. Abdominal pain 7%, nausea 5% vomiting 2.5%, urine discoloration 2.5% were the most side effects of NTZ.

Conclusion: We can conclude that treatment modalities with PEG- INF, RBV and NTZ is associated with increase in virological response rates and monotherapy of CHC patients with NTZ decreases HCV RNA viral load in some patients, there was mild side effects attributable to NTZ.

INTRODUCTION

Hepatitis C virus is a major health problem throughout the world. The WHO estimates about 200 million people of those infected with HCV, 80% develops chronic hepatitis C infection [1].

More than 90% of HCV isolates from Egyptian patients are of the genotype 4 variant Egypt has the highest world wide prevalence of HCV (10-20%) [2].

Antiviral therapy for CHC has many goals, the primary goal is durable viral decrease as evidenced by the absence of HCV RNA in the serum

(virological response), the second goal is the reduction of liver damage as determined by either persistently normal ALT (biochemical response) or improved liver biopsy. (Histological response) . Antiviral therapy will delay or prevent cirrhosis, HCC, liver transplantation and death, as well as to prevent the viral spread to other persons and improving the patient's quality of life [3].

INF was the only therapeutic opinion until the mid-1990s. RBV added to INF resulted in improvement of SVR

rates (8 to 42%) in patients with genotype 4 infection [4].

Modification of the therapeutic molecules of INF through the attachment of polyethylene glycol (PEG) moieties (pegylation) is a common approach to optimize delivery of the drug and to avoid large fluctuating serum concentrations and the inconvenient dosing regimens associated with the standard INF- α . Two PEG-modified INFs have been approved for the treatment of CHC which are (PEG-INF α_{2a} and $2b$). the current treatment of CHC is the combination of PEG-INF and RBV [5].

Nitazoxanid is the first member of thiazolidines, anti-infective role which has an oral agent with no major side effects and licensed in the USA in treatment of cryptosporidium parvum and giardia lamblia [6].

A serendipitous observation during drug development revealed that some patients with cryptosporidium and AIDS who are coinfecting with HCV or HBV, had a reduction in serum ALT during therapy. NTZ induces double stranded RNA activated protein kinase (PKR) phosphorylation, which results in increased intracellular concentration of phosphorylated factor 2 [7].

Aim of the work :

The aim of this work is to study impact of NTZ in addition to PEG- α_{2a} and RBV on virological responses in patients with CHC.

PATIENTS AND METHODS

The present study was conducted in Tropical Medicine Department Zagazig University Hospital. This work comprised 100HCV patients attending the out patient clinics.

All patients were divided into the following groups:

Group (A): 30 patients received the SOC, PEG-INF α_{2a} 180/ μ g once weekly and RBV (1000-1200mg) based on body weight .

Group (B): 30 patients received NTZ 500mg tablet twice daily for 4 weeks lead-in phase followed by NTZ of the same dose plus PEG INF α_{2a} (180/ μ g once weekly) and RBV (1000-1200mg) for another 24 weeks. Patients in group A and B stopped treatment when EVR is not achieved as cost-effectiveness is crucial to maximize the health gain achieved in Egypt with

the highest prevalence of HCV which is considered a heavy economic burden.

Group (C): 40 patients received NTZ monotherapy 500mg tablet twice daily for 24 weeks.

All patients fulfilled the inclusion criteria which are age 18 years or older normal complete blood picture, normal kidney function tests, thyroid stimulating hormone is within normal level, positive HCV antibody and HCV-RNA with no contraindication to liver biopsy, if liver biopsy >F1 with elevated liver enzymes, if > F2 with normal liver enzymes, alpha fetoprotein <100 IU/ml, female patients participating adequate contraception. All patients who are pregnant female, lactating, decompensate liver cirrhosis, active epileptic fits, ischemic heart disease, chronic renal failure, autoimmune disease, retinal abnormality severe psychiatric condition or with BMI > 35 were excluded from the study. All patients underwent the following test:

- Full history taking and through clinical examination.
- BMI was calculated as weight / height (m²) <30
- Complete blood picture.
- Liver, kidney function tests, fasting, post prandial blood glucose level.
- Abdominal ultrasonography using aloka SSD-500.
- α Feto protein, pregnancy test, antinuclear antibody, thyroid stimulating hormone, ECG, funds examination, HCV antibody by Eliza method.
- Quantitative PCR for HCV at week, 0, 12, 24 was done by cobas amplicor HCV monitor test (HCV, V2.0 Roche Brungburg USA).
- Liver biopsy and fibrosis was evaluated using the metavir scoring system a scale f0-F4: f0 = no-fibrosis, F1= portal tract expansion, F2=less than 50% bridging fibrosis, F3=more than 50% bridging fibrosis without cirrhosis, F4= established cirrhosis .
- The grading of activity was classified as: A0, no histological activity, A1= mild activity, A2= moderate activity, A3= severe activity.

Statistical analysis:

The data were statistically analysed using microstate soft ware program (8) and the following statistical tests were applied :

- Studied "t" test for comparison of means two independent groups.

- ANOVA or f-test for comparison of means of more than two groups.
- Description of quantitative and qualitative variable.
- Chi-square test was to compare qualitative variables.
- Correlation co-efficient test (r-test) was used to rank different variables against each other directly or indirectly.
- P value >0.05 insignificant and P< 0.01 highly significant.

RESULTS

Table (1): Comparison of baseline demographic and laboratory characteristics of the three studied groups.

Variable	Group (A) (n=30)		Group B (n=30)		Group C (n=40)		F	P Value
Age (year)								
Mean ± SD	41.8 ± 9.5		40.3 ± 8		41 ± 7.5		0.246	0.78
Range	23-57		26-55		28-56			
Sex,	N	%	N	%	N	%		
male	20	66.7%	20	66.7%	30	75%		0.593
Female	10	33.3%	10	33.3%	10	25%		
BMI (Kg/m²)								
Mean ± SD	28 ± 2		27 ± 3		28 ± 1		2.448	0.09
Range	27-30		26-30		27-29			
Total bilirubin (mg/dl)								
Mean ± SD	0.7 ± 0.2		0.6 ± 0.2		0.6 ± 0.2		2.625	0.07
Range	0.4 – 1.5		0.3-1.4		0.3-1.4			
ALT (IU/L)								
Mean ± SD	73 ± 41		70.7 ± 36		61.4 ± 21.5		13.50	0.264
Range	15-153		30-140		15-109			
AST (IU/L)								
Mean ± SD	69.1 ± 45.9		58 ± 43		63.7 ± 36.3		0.540	0.585
Range	23-99		26-90		20-130			
PT (seconds)								
Mean ± SD	11.6 ± 0.9		11.5 ± 0.9		12.1 ± 0.8		4.996	0.09
Range	10-14.5		10-14		11-14			
S. creatinine (mg/dl)								
Mean ± SD	0.79 ± 0.19		0.7 ± 0.2		0.7 ± 0.2		0.000	1
Range	0.2 – 1.1		0.1 – 1		0.1 – 1.1			
WBC (x10³ cell/cmm)								
Mean ± SD	6 ± 1.4		5.8 ± 1.7		6.2 ± 1.3		0.648	0.525
Range	4.1 – 9.2		4-9		4.6 – 8.9			
HB (gm/dl)								
Mean ± SD	13.6 ± 1.1		13 ± 0.9		12.9 ± 1.6		2.829	0.06
Range	12-16		11.9-15		11-15			
Platelets (10³/cmm)								
Mean ± SD	191 + 46		196 ± 42		204 ± 33.4		0.939	0.3
Range	118-294		115-290		168-350			

Table (2): Baseline virological characteristics of three studied groups:

Variable	Group A (n=30)	Group B (n=30)	Group C (n=30)	F	P
HCV RNA (IU/ml x 10 ³) Mean ± SD	895 ± 230	836 ± 218	800 ± 356	0.958	0.387

Table (3): Frequency of virological response rates of the three studied groups.

Virological response	Group A (n=30)		Group B (n=30)		Group C (n=30)	
	N	%	N	%	N	%
EVR	25	83.3%	26	86.6%	6	15%
-ve HCV RNA after 24 week	23	76.6%	24	80%	0	0%

Table (4): Comparison of demographic, biochemical and histopathological characteristics of responders of group A and B.

Variable	Group A n=(23/30) 76.6%		Group B n=(24/30) 80%		t	P
Age (year)	44.6 ± 9.8 25-57		43.3 ± 8.4 26-51		0.4890	0.627
Sex,	No.	%	No.	%		
Male	15	50%	17	56.7%		0.760
Female	8	26.65	7	23.3%		
BMI (kg/m²)	27.8 ± 2.2 27-29		27.2 ± 1 26-29		1.2122	0.231
ALT (IU/ml)	48.5 ± 37.9 30-85		56.7 ± 36.9 30-102		0.7515	0.456
AST (IU/ml)	42 ± 37.4 25-99		51.2 ± 37.2 26-98		0.8453	0.402
Baseling viral load (IU/ml)x10³	850±240 410-1.200		782±238 344-1.820		0.9751	0.334
Histopathological fibrosis	No.	%	No.	%		
F1	14	46.6	14	46.6%		
F2	7	23.3	9	30%		
F3	2	6.7	1	3.3%		
Activity						
A1	13	43.3	14	46.6%		1
A2	7	23.3	9	30		
A3	3	10	1	3.3%		0.347

Table (5): Comparison of biochemical and hematological characteristics before and at the end of the study (24 weeks) for group C.

Variable	Before the start of the study	At the end of the study	t	P
ALT (IU/L) Mean ± SD Range	61.4 ± 21.5 15-109	29 ± 11.8 13-52	2.916	0.007*
AST (IU/L) Mean ± SD Range	63.7 ± 36.3 20-136	59 ± 40.7 19-160	1.021	0.316
Total bilirubin (mg/dl) Mean ± SD Range	0.6 ± 0.2 0.3-1.4	0.7 ± 0.3 0.4-1.7	-0.953 -1.467	0.349 1.53
S. creatinine (mg/dl) Mean ± SD Range	0.7 ± 0.2 0.1-1.1	0.8 ± 0.21 0.4-1.2	-2.015	0.053*
WBC (x10³ cell/cmm) Mean ± SD Range	6.2 ± 1.3 3.6-8.9	6.4 ± 1 4-8	-1.467	0.153
HB (gm/dl) Mean ± SD Range	12.9 ± 1.6 11-15.2	12.8 ± 0.8 11-14.3	0.930	0.360
Platelets (x10³/cmm) Mean ± SD Range	204 ± 33.4 168-350	213 ± 37 182-340	-1.845	0.076

Table (6): Quantitative serum HCV RNA over time for group C (n=40)

	Week 12		Week 24	
	N	%	N	%
Negative HCV RNA	2/40	5%	0	0%
>2 log drop of HCV RNA	4/40	10%	The four patients showed increase in HCV RNA viral load in comparison to week 12. however, it did not exceed baseline HCV RNA.	
< 2 log drop of HCV RNA	19/40	47.5%	* Fifteen patients (15/40) 37.5% showed further decrease in HCV RNA compared to week 12 and the mean reduction of HCV RNA is log. * Four patients (4/40) 10% showed increase in HCV RNA compared to week 12, however, it did not exceed baseline HCV RNA.	
Stationary viral load	5/40	12.5%	Stopped treatment	
Increased HCV RNA	10/40	25%	Stopped treatment	

Table (7): Comparison of biochemical and hematological characteristics at the end of the study (24 week) between the three studied groups.

Variable	Group A	Group B	Group C	t	P
ALT (IU/L)					
Mean ± SD	30.7 ± 9	31.9 ± 7.3	29 ± 11.8	0.849	0.431
AST (IU/L)					
Mean ± SD	28.6 ± 16.4	29.6 ± 15.8	59.407	13.363	0.001*
Total bilirubin (mg/dl)					
Mean ± SD	0.8 ± 0.2	0.8±0.23	0.8 ± 0.21	2.307	0.105
WBC (x10³cell/cmmm)					
Mean ± SD	4.2 ± 2	4.2 ± 1.9	6.4 ± 1	21.894	0.0001*
HB (gm/dl)					
Mean ± SD	11.4 ± 1.5	11.2 ± 1.8	12.8 ± 0.8	14.379	0.001*
Platelets (x10³/cmm)					
Mean ± SD	168 ± 76	167.4 ± 73.9	213 ± 37	6.299	0.003*

Table (8): Demographic and biochemical characteristics of 6 patients achieved negative and >2 log reduction of HCV RNA at week 12 and non responders of group C.

Variable	Negative and >2 log reduction of HCV RNA at week 12 (n=6)		Non responders (n=34)		t	P
Age (years)						
Mean ± SD	45 ± 4.2		43 ± 3		1.814	0.164
Range	32-56		28-52			
Sex	N	%	N	%		
Male	4	10%	26	65%		0.628
Female	2	5%	8	20%		
BMI (kg/m²)						
Mean ± SD	27.2 ± 1		28 ± 1		1.563	0.132
Range	27.2 ± 1		28 ± 1		1.536	0.132
ALT (IU/L)						
Mean ± SD	66.7 ± 32.1		62 ± 30		0.350	0.727
Range	20-114		26-156			
AST (IU/L)						
Mean ± SD	66.7 ± 32.1		62 ± 30		0.350	0.727
Range	20-114		26-156			

DISCUSSION

The WHO estimates that about 200 million people were infected with HCV of those infected with HCV 80% develops chronic infection [1].

INF was the only therapeutic opinion until the mid 1990s RBV was added to INF resulted in improvement of SVR rates (8.42%) in patients with genotype 4 infection [4].

Nitazoxanide induces double stranded RNA activated protein kinase (PKR) phosphorylation, which results in increased intracellular concentration of phosphorylated eukaryotic initiation factor 2 (eIF2 α), a naturally occurring antiviral intracellular protein and a key mediator of host cell defences against viral infection [7]. It is also believed that it inhibits viral glycoproteins

at the posttranslational level. This would prevent the final assembly of the virus before it can exit and affect another.

A serendipitous observation during nitazoxanide development revealed that some patients with cryptosporidiosis and are co-infected with HCV or HIV had a reduction in serum level of ALT during therapy. This observation led to studies of the antiviral activity of NTZ [7].

This work revealed that patients of group A showed an EVR of 83.3% and 24 week HCV RNA negativity of 76.6%. This is in accordance with the results of El-Makhzangy et al.,[10] who conducted a prospective trial to study the response to PEG-INF α -2a and RBV in 95 patients with CHC genotype 4 for 48 weeks with

results of an EVR of 82% and negative HCV RNA at week 24 achieved in 78% .

El-Zayadi et al. [11] studied the response of CHC patients with genotype 4 to 24 weeks of PEG INF α 2b and he reported as slightly lowered response rate than those reported in our study. This difference between these results may be attributed to the difference in the demographic characteristics of the patients and the difference between PEG-INF α -2a and 2b.

The mechanisms underlying in efficacy between the two PEG-INF- α foundation is not clear. However, the structure and the size of the polyether glycol moiety and the means of covalent attachment might affect the pharmacokinetics and pharmacodynamics of the two formulations, their antiviral activity and the therapy outcome [12].

Our results are contrary to those of Dimitroulopoulos [13] who studied the effect of ethnic origin on the treatment outcomes in patients chronically infected with HCV-4 (30 Europeans and 30 Egyptians) and with elevated baseline HCV RNA 7800.U/ml. They reported a RVR, EVR and HCV RNA at week 24 in Europeans and Egyptians were (RVR 26.7% vs, 30%) (23.3% vs 17.6%, 13.3% vs 16.7% respectively). This can be explained by the that patients selected in this study were with high baseline HCV RNA and advanced stage of liver histology.

As regard treatment modalities results in our study (group B), the EVR (86.6%, vs 83.3% for group A) and 24 week PCR negative was (80% vs 76.6% for group A). These results shows that NTZ increase EVR and PCR negativity at week 24.

Rossignol et al. [14] reported a cEVR for the SOC and treatment modalities with NTZ of 70% and 86% respectively while cEVR reported in our study was 80.3% vs 86.6% for the SOC and triple arm respectively while cEVR reported in our study was 80.3% vs 86.6% for the Soc and triple arm respectively.

A possible explanation to the difference between the two studies may be due to that Rossignol et al., conducted a 12 weeks lead in phase compared with a 4 weeks lead in phase with NTZ in our study.

Although, the required duration of NTZ lead-in phase is unknown and 12 weeks was selected as

an initial conservative estimate to optimize the potential benefit of NTZ pretreatment. A subsequent study has shown that a 4-week lead-in phase may be satisfactory [15,16].

Bacon et al. [17] reported a cEVR of 62% which is lower than the present study (86.6%) when studied a 4 weeks lead in phase of NTZ followed by NTZ, PEG-INF- α 2a and RBV for 48 weeks. This may be attributed to that genotype 1 is associated with poorer response to antiviral therapy. The most important clinical property of HCV genotype is different susceptibility to INF [18]. It is also possible that demographics, disease related characteristics of the populations that have been studied or pharmacokinetics might account for difference in responses to therapy.

The differences in INF response could be secondary to either differences in the viral virulence and/or replication rate among HCV types, or different in the host immune response to the different HCV genotype .

The poorer response of genotype 4 in Egypt possible because of various subtypes, to different forms of INFs or probably related to an intrinsic resistance to direct antiviral effect of INF [19].

Egyptian patients infected with HCV genotype 4 after IFN/RBN combination therapy have a high frequency (about double) and significant difference of BCL-2 genotype and allele for non-responders patients compared with responders as well as healthy controls. This suggests that polymorphism in BCL-2 gene can be augment the current array of predictors of therapeutic response to INF and RBV in HCV type 4 infected patients [20].

As regard NTZ monotherapy for treatment of CHC in this study two patients (5%) with very low viremia 3.000 and 70.000IU/ml showed cEVR and was instructed to continue on NTZ till the end of 24 week. However, these patients experienced viral breakthrough with positive HCV RNA at the end of the week 24. Four patients (10%) showed pEVR (>2log drop in HCV RNA) but they failed to achieve negative HCV RNA at the end of the treatment, nineteen patients showed <2log drop of HCV RNA at 12 week. Out these nineteen patients, fifteen patients showed further decrease in HCV viral load at week 24. So this study demonstrated that some patients experienced a partial virological response with NTZ.

Rossignol et al. [16] showed that treatment with NTZ monotherapy for patients with CHC genotype 4 at a dose of 500mg orally with food compared with placebo was associated with an ETR at week 24 of (7/23) 30.4% and SVR at week 48 of (4/23) 17.4% compared to 0% for placebo. Whereas, our study reported on EVR of (6/40) 15% and ETR (week 24) of 0%.

These results also confirmed by Mederake [21] who showed that during treatment with NTZ as lead-in phase for 12 week before PEG-INF and RBV, two of 53 patients had a decline of more than 1 Log₁₀ and just one patient achieved a cEVR.

We could find a significant correlation between high baseline viral load and treatment response these results, are in concordance with Kamel et al. [22] Zekri et al. [23].

Patients who responded to IFN treatment had statistically less number in both transitions and the genetic distances between the quasipseices. So, viral genetic complexity and variability may play a role in the response to IFN treatment. The fibrosis score negatively affected the response to IFN. Treatment and pretreatment viral load didn't affect the outcome of treatment [24].

Conclusion:

We can conclude that, treatment modalities with PEG-INF, RBV and NTZ is associated with increase in the virological response rates but with no statistically significant difference, monotherapy of CHC patients with NTZ decrease HCV RNA viral load in some patients. Mild side effects were present to NTZ as abdominal pain, nausea, vomiting and urine discoloration and we can recommend double dose of NTZ for improving the response or study the response of NTZ with STAT-S antiviral drugs as teleprevir & bociprevir when they are in our hand.

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Conflicts of interest: Non .

Ethical approval: Informed consents were routinely obtained from patients. The study was performed in accordance with the ethical standards on human experimentation and with the Helsinki Declaration of 1964.

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Serum Level of pro Brain Type Natriuretic Peptide in Diuretic Resistance and Diuretic Respondent Ascites in Cirrhotic Patients

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Background and Study aim: Diuretic resistance in patients with cirrhosis is clinically manifested by the failure to lose weight or ascetic volume despite high dosages of loop diuretics and sodium restriction. Natriuretic peptides (NP) promote natriuresis and diuresis. Atrial natriuretic peptide (ANP) is known to act as a rapid response hormone and Brain natriuretic peptide (BNP) more as a “back up hormone” activated only after prolonged ventricular overload. Pro BNP are more stable and have been suggested to have a longer biological half life than other natriuretic peptides.

The aim of this work is to study the effect of vascular volume on serum level of Pro BNP and to find out the difference of serum level of pro BNP in both diuretic resistant and diuretic responder ascites.

Patients and Methods: The study was conducted on 89 patients. Patients subdivided into 2 groups: group 1 (41 patients) described as diuretic resistance ascites and group 2 (48 patients) as diuretic respondent. In which both groups underwent laboratory and echocardiography study. NT-proBNP were measured by electrochemiluminescence immunoassay “ECLIA”, Doppler echocardiography by using a System FiVe digital ultrasound machine.

Results: There was no significant difference between the groups as regards age, serum potassium, liver enzymes, serum bilirubin, total proteins, international normalized ratio or partial thromboplastin time. The following parameters were significantly lower in the diuretic-resistant group: serum albumin and platelet count. However, the diuretic-resistant patients had higher blood urea nitrogen (BUN), serum creatinine and higher Child score. There were significant differences between both groups regarding serum level of pro BNP, serum and urinary NA, left atrial dimension (LAD) and left ventricular end diastolic dimension (LVEDD) in which all parameter were higher in diuretic responder versus resistant group. Also significant positive correlation was noted between Pro BNP and serum and Urinary NA, LAD and LVEDD.

Conclusion: Pro BNP is higher in diuretic responder than in diuretic resistance group, and although the latter group has a higher level of Pro BNP than the cut off point but it is not enough to induce diuresis. Also we found that decrease intravascular compartment may decrease cardiac chamber expansion with subsequent decrease in the level of natriuretic peptide leading to decrease the response of diuretic.

INTRODUCTION

Liver cirrhosis is a frequent consequence of the long clinical course of all chronic liver diseases (CLD) characterized by parenchymal damage [1, 2, 3].

Patients with cirrhosis and portal hypertension typically develop altered extracellular volume regulation with renal sodium and water retention. This eventually leads to the development of ascites, which is the most common of the major complications of cirrhosis [4, 5, 6].

Diuretic resistance in patients with cirrhosis has been variably defined but clinically is manifested by the failure to lose weight or ascetic volume despite high dosages of loop diuretics and sodium restriction, a functional definition of diuretic resistance is based upon the failure to increase 24-h urine sodium excretion to greater than 78 meq/day despite high-dose diuretics [6].

Diuretic resistance has several potential etiologies including high dietary sodium intake, poor intestinal

absorption of the diuretic, decreased glomerular filtration rate (GFR) and decreased renal blood flow with resulting decreased drug entry in the tubule lumen, proteinuria with decreased concentration of free diuretic in the tubule lumen [7,8]. The endocrine nature of the heart was first understood with the description of atrial natriuretic peptide (ANP) [9] and later detection of brain (B-type) natriuretic peptide (BNP), which is mainly released from the myocardium in humans [10,11,12]. B-type natriuretic peptide has similar biological effects to ANP. Both are produced primarily in the atria under normal conditions [13].

Natriuretic peptides promote natriuresis and diuresis, vasodilatation, and antagonize the effects of the renin-angiotensin-aldosterone and sympathetic nervous systems [14,15]. In the central nervous system, natriuretic peptides act as neurotransmitters and decrease sympathetic tone, reduce secretion of arginine-vasopressin and corticotrophin, and inhibit salt appetite and water drinking [16]. Natriuretic peptides modulate myocardial and vascular structure and function via antiproliferative and cytoprotective effects [14, 15, 17].

In response to cardiac pathologies with pressure or volume overload, ventricular myocytes re-express foetal genes including ANP and BNP. Then, most of the BNP is released from the ventricles [13]. NPs are increased in all oedematous disorders with salt and fluid overload and those with increased atrial or ventricular wall tension, e.g. in heart failure, renal failure and liver cirrhosis [14].

In cirrhosis, intestinal flora disorder, the transition of intestinal flora to mesenteric lymph nodes, bacterial translocation, and decreased hepatic clearance of endotoxins cause an endotoxemic medium. Consequently, various mediators (nitric oxide, von Willebrand factor (VWF), etc.) are released from endothelial cells and a hyperdynamic circulation occurs [18,19]. These changes result in functional and structural cardiac disorders in patients with liver cirrhosis [20].

Atrial natriuretic peptide (ANP) is known to act as a rapid response hormone and BNP more as a "back up hormone" activated only after prolonged ventricular overload [21]. The biological effects of ANP and BNP are

natriuresis, diuresis, and vascular relaxation, but patients with cirrhosis, especially with advanced disease, may be resistant to these effects [22].

The larger N terminal prohormone fragments of proBNP are more stable and have been suggested to have a longer biological half life. Finally, the requirements for blood sampling are less critical. Circulating proBNP concentration is less sensitive to rapid fluctuations caused by short term stimuli of secretion, such as change in body posture, exercise, or volume changes. ProBNP has therefore been suggested as an even better marker of heart failure or volume change than BNP [23].

Our present research tries to detect the effect of vascular volume on serum level of Pro BNP and to find out the difference of serum level of pro BNP in both diuretic resistant and diuretic responders ascites.

PATIENTS AND METHODS

From October 2011 to March 2012, the study was conducted on 89 patients (58 male and 31 female; mean age 50 ± 4.5 years) with liver cirrhosis and ascites, who were followed up in outpatient's clinics of Department of Internal Medicine in Zagazig University Hospitals. Liver cirrhosis was documented by clinical assessment, laboratory findings and evidence of liver cirrhosis upon abdominal ultrasound. Ascetic fluid analysis was done. Patients with evidence of portosystemic encephalopathy or intrinsic renal disease were excluded from the study, none of the patients had experienced recent gastrointestinal bleeding, none had signs of heart failure, diabetes, cancer, or any other major disease, and all patients had normal kidneys upon ultrasound and no proteinuria or active urinary sediment upon urine analysis. All patients kept under absolute salt restriction, additional cardiovascular medication, including beta blockers, was not prescribed for any of the patients. All patients had normal cardiac physical examination, and in those who had a chest x ray performed, signs of cardiomegaly were absent.

No evidence of heart failure by Echocardiography and ECG showed normal configurations apart from sporadic extrasystoles in some patients

Patients subdivided into 2 groups, (group 1 with 41 patients) described as diuretic resistance

ascites and (group 2 with 48 patients) as diuretic responders.

Criteria of diuretic resistance ascites were fulfilled according to Revised Diagnostic Criteria of Resistance Ascites (International Ascites Club)[24].

1. Treatment duration: patients must be on intensive diuretic therapy (spironolactone 400 mg by mouth daily and furosemide 160 mg by mouth daily) for at least 1 week and on sodium restricted diet of less than 90 mmol/L per day or 5.2 g of salt (NaCl) per day.
2. Lack of response: mean weight loss of <0.8 kg over 4 days and urinary sodium output less than the sodium intake.
3. Early ascites recurrence: reappearance of grade 2 or 3 ascites within 4 weeks of initial mobilization.
4. Diuretic-induced complications
 - a. Diuretic-induced hepatic encephalopathy: development of encephalopathy in the absence of any other precipitating factor.
 - b. Diuretic-induced renal impairment: increase of serum creatinine by >100% to a value >2 mg/dL in patients with ascites responding to diuretics.
 - c. Diuretic-induced hyponatremia: decrease of serum sodium by >10 mmol/L to a serum sodium of <125 mmol/L.
 - d. Diuretic-induced hypo- or hyperkalemia: change in serum potassium to <3 mmol/L or >6 mmol/L despite appropriate measures

On the other hand group 2 has proper weight reduction with dose less than maximum dose of diuretics.

Collection of 24-h urine sample for calculation of sodium was done in sterile plastic containers by recording the volume in 24 h, starting at 08:00. Verbal instructions were given to assure completeness of collection. Samples were centrifuged and sodium concentration was measured in mEq/L using a Beckman Synchron CX5 ISE (NJ, USA) chemistry analyzer. All

samples were processed on the day of collection. In order to obtain the whole 24-h urinary sodium, we multiplied sodium concentration by the volume in liters.

NT-proBNP were measured by electrochemiluminescence immunoassay "ECLIA" at Zagazig university hospitals on the Roche cobas e immunoassay analyzers (Roche Diagnostics, Inc., Indianapolis, IN).

Doppler echocardiography by using a System FiVe digital ultrasound machine (GE Vingmed Ultrasound) with a combined tissue imaging (2.5- to 3.5-MHz) and Doppler (2.75-MHz) transducer was done for all patients excluding any cardiac lesion or evidence of heart failure.

Statistical analysis:

Data were collected, revised, verified and edited on a PC. Data were then analyzed statistically using SPSS statistical package version 19 (SPSS, Chicago, IL, USA). Data were reported in the form of mean \pm SD. Student's t test was used to compare the interval variables. Correlation between 24-h urinary sodium and other variables was done using Pearson correlation.

RESULTS

As shown in Table1, there was no significant difference between the groups as regards age, serum potassium, liver enzymes, serum bilirubin, total proteins, international normalized ratio or partial thromboplastin time. The following parameters were significantly lower in the diuretic-resistant group: serum albumin and platelet count. However, the diuretic-resistant patients had higher blood urea nitrogen (BUN), serum creatinine and higher Child score. Table 2, showed significant difference between both groups regarding serum level of pro BNP, serum Na(121 \pm 8.2, 132 \pm 5) , urinary sodium(35.2 \pm 8.2, 125. \pm 8), LAD (36.2 \pm 4.3, 38.8 \pm 4.6) and LVEDD(46.3 \pm 1.8, 48.4 \pm 3.1). `Table 3, showed Significant positive correlation was noted between Pro BNP and serum NA ($r = 0.841$, $P = 0.001$), Urinary NA ($r = 0.741$, $P = 0.001$), LAD ($r = 0.630$, $P = 0.001$) and LVEDD($r = 0.561$, $P = 0.001$).

Table (1): Patients characteristics (mean \pm SD)

	Diuretic-resistant group (n = 41)	Diuretic-respondent group (n = 48)	P
Age (yr)	50 \pm 4	49 \pm 4	NS
Serum creatinine (mg/dL)	1.2 \pm 0.8	1.0 \pm 0.2	0.043
BUN (mg/dL)	45.5 \pm 9.3	19.5 \pm 9.2	0.013
Serum potassium (mEq/L)	4.1 \pm 0.7	4.2 \pm 0.6	NS
AST (U/L)	69 \pm 37	70 \pm 41	NS
ALT (U/L)	58 \pm 29	57 \pm 37	NS
Total bilirubin (mg/dL)	2.4 \pm 1.1	2.0 \pm 1.0	NS
Direct bilirubin (mg/dL)	1.7 \pm 1.1	1.5 \pm 0.9	NS
Total proteins (g/dL)	7.0 \pm 0.3	7.3 \pm 0.4	NS
Serum albumin (g/Dl)	2.3 \pm 0.3	2.7 \pm 0.3	0.012
Platelet count ($\times 10^9/L$)	83 \pm 23	109 \pm 59	0.014
INR	1.6 \pm 0.5	1.4 \pm 0.3	NS
Child classification (B/C)	11/30	30/18	0.011

Table (2): Mean difference \pm SD between both groups regarding serum and urinary Na, Pro BNP, LAD and LVEDD.

	Diuretic-resistant group (n = 41)	Diuretic-respondent group (n = 48)	P
Serum sodium (mEq/L)	121 \pm 8.2	132 \pm 5	0.001
Pro BNP(pg/ml)	256 \pm 82.5	612.3 \pm 249.7	0.001
LAD (mm)	36.2 \pm 4.3	38.8 \pm 4.6	0.019
LVEDD (mm)	46.3 \pm 1.8	48.4 \pm 3.1	0.016
24 hours urinary NA(mEq/L)	35.2 \pm 8.2	125. \pm 8	0.001

Table (3): Correlation between serum and urinary Na, LAD and LVEDD with serum Pro BNP in diuretic resistance group.

	Mean (n = 41)	Correlation	P
Serum Na(mEq/L)	121 \pm 8.2	.841	0.001
Urine Na (mEq/L)	35.2 \pm 8.8	.741	0.001
LAD (mm)	36.2 \pm 4.3	.630	0.001
LVEDD (mm)	46.3 \pm 1.8	.561	0.001

DISCUSSION

Approximately 10–20% of patients with ascites have adequate natriuresis and clinical response to dietary sodium restriction alone, and the majority of the remaining patients respond to diuretic therapy. However, 10% of patients do not respond to the above measures, or develop complications to diuretic therapy, and these patients are classified as having diuretic resistant ascites [24].

B-type natriuretic peptide (BNP) is a neurohormone synthesized along with atrial natriuretic peptide (ANP) in cardiac ventricles. BNP is released as preproBNP and then enzymatically cleaved to NT-proBNP and BNP

depending on ventricular myocytes stretching and volume overload [25].

NT-proBNP is influenced by age and the age related normal decline in glomerular filtration rate, therefore 2 cutoff points must be used; i.e., NT-proBNP > 125 pg/mL in patients younger than 75 years and > 250 pg/mL in patients older than 75 years[26].

Atrial natriuretic peptide (ANP) is known to act as a rapid response hormone and BNP more as a “back up hormone” activated only after prolonged ventricular overload (21). The biological effects of ANP and BNP are natriuresis, diuresis, and vascular relaxation, but patients with cirrhosis, especially with advanced disease, may be partially resistant to these

effects[22]. The larger N terminal prohormone fragments of proBNP are more stable and have been suggested to have a longer biological half life. Finally, the requirements for blood sampling are less critical. Circulating proBNP concentration is less sensitive to rapid fluctuations caused by short term stimuli of secretion, such as change in body posture, exercise, or volume changes. ProBNP has therefore been suggested as an even better marker of volume change than BNP [23].

Our present study showed significant difference between serum level of Pro BNP in diuretic resistant (256 ± 82.5) and diuretic respondent group (612.3 ± 249.7), in spite of plasma NT-proBNP levels were significantly higher in Child class C than in classes B, supported by Henriksen et al who documented that circulating proBNP concentrations are significantly increased in patients with advanced cirrhosis and that they are closely related to BNP concentrations, however, no signs of reduced hepatic degradation of proBNP or of BNP are present in patients with cirrhosis, suggesting that elevated levels of proBNP and BNP are related to markers of cirrhotic severity[23]. In our study most of patients of diuretic resistant group are of Child class C (30 patients) in contrast to patients of diuretic respondent group (only 18 of total 48 patients), in which this is not matched with Henriksen and Jeong Joo Woo, et al 2008 who documented that Pro BNP is increasing with advanced cirrhosis, but the event in this situation not related only to the severity of the disease but also to other factors[26].

Allan Jaffe, 2003 showed that pressure and volume overload of the cardiac chambers stimulate enhanced production and release of natriuretic peptides. Thus, these peptides reflect the common denominator present in patients with systolic or diastolic dysfunction, volume overload, and HF, regardless of the underlying cardiovascular disease [27], in which this agreed with our study suggested that there are other factors influencing the level of NP in cirrhotic patients.

Our study showed significant difference in serum and urinary NA, LAD and LVEDD in both group; diuretic resistance Vs respondent (121 ± 8 , 132 ± 5), (35 ± 5 , $125. \pm 8$), (36.2 ± 4.3 , 38.8 ± 4.6) and (46.3 ± 1.8 , 48.4 ± 3.1) respectively and also significant positive correlation between these parameter in diuretic resistant group and

Pro BNP, changes in these parameters showed that natriuretic peptides are importantly involved in water and sodium balance and cardiovascular homeostasis [28].

In response to an increase in filling pressures and stretch of the atrial and ventricular walls, atrial natriuretic peptide (ANP) and brain or B-type natriuretic peptide (BNP) are released into the bloodstream [29]. In addition, several neurohormones such as endothelin-1 (ET-1), arginine vasopressin (AVP), and catecholamines stimulate the secretion of natriuretic peptides; this leads primarily to a reduction in preload by increasing water and sodium excretion, but also by shifting plasma from the intravascular to the extravascular space [29]. So the serum and urinary NA reflect the state of intravascular volume, nearly all patient of diuretic resistant group used diuretic for a long period inducing reduction of intravascular volume and decreasing level of both serum and urinary NA and subsequent change of level of natriuretic peptide.

The relationship between LAD or LVEDD was studied by Woo, et al who reported increased serum level of Pro BNP in cirrhotic patients with increased both LAD and LVEDD [26] which agreed with our study. Also this issue reported with Brunner-La Rocca 2001[28]. Natriuretic peptides are importantly involved in water and sodium balance and cardiovascular homeostasis.

In response to an increase in filling pressures and stretch of the atrial and ventricular walls, atrial natriuretic peptide (ANP) and brain or Pro B-type natriuretic peptide (Pro BNP) are released into the bloodstream[29],this explaining the correlation between Pro BNP and both LAD and LVEDD. So decreased intravascular volume may be the key of all events from decreased LAD and LVEDD with subsequent decrease of Pro BNP. In spite of relatively higher level of Pr BNP in diuretic resistant group exceeding the cut-off point 125 pg/mL , but it is not enough to induce diuresis, and may be there is a new cut off point was created and needed to induce diuresis, this may explain that Patients with advanced cirrhosis and ascites have a reduced natriuretic response to natriuretic peptide despite elevated levels[24], in which it apparently clear in diuretic respondent group explaining the big difference in the level of Pro BNP in both group.

From the above we can conclude that Pro BNP is higher in diuretic respondent than in diuretic resistance group, and although the latter group

has a higher level of Pro BNP than the cut off point but it is not enough to induce diuresis.

Also we found that decrease intravascular compartment may decrease cardiac chamber expansion with subsequent decrease the level of NP leading to decrease the response of diuretic .

So we may expect two options can be used and may be useful to improve diuresis in diuretic resistance, first is intravascular expansion like albumin infusion improving diuresis with increasing plasma oncotic pressure and volume expansion with subsequent cardiac chamber expansion[30] and this may correlate with Wong et al, who showed that (volume expansion or greatly elevated levels of plasma atrial natriuretic factor associated with moderate volume expansion can improve blunted atrial natriuretic factor responsiveness in cirrhotic patients with refractory ascites. This appears to be achieved by way of a marked increase in distal delivery of filtrate in the kidney, with or without activation of distal natriuretic peptide factor receptors in the inner medullary collecting ducts [31]. Other issue concerning with BNP supplementation (Exogenous ANP administration, together with the splanchnic vasoconstrictor terlipressin to counter the hypotensive effect of ANP, increases renal blood flow, GFR and natriuresis in patients with refractory ascites [24].

In theory, the renal effects of natriuretic peptides, if preserved, may help to reduce the pressure in the portal vein. Furthermore, although natriuretic peptides do not seem to have direct effects on hepatic vascular conductance, the reduction in mesenteric blood flow may further contribute to a reduced portal venous pressure. This is in line with other experimental data, which show that natriuretic peptides may reduce portal venous pressure despite loss of renal effects in cirrhotic rats. It remains to be seen whether this is of therapeutic significance in humans with portal hypertension [29].

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Conflicts of interest: Non .

Ethical approval: The study was performed according to the ethical standards for human experimentation and was approved by the scientific committee of Zagazig University. Informed consent was obtained from the selected patients after explaining the aim of the study and the nature of the investigations required.

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Tuberculosis Effects in Urinary Tract by using Ultrasound in Sudan

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Background and study aim:

Tuberculosis (TB) is a huge public concern in Sudan. According to the world health organization (WHO), Sudan alone carries 15% of the TB burden in the Eastern Mediterranean Region. This study was designed with the aim to evaluate the clinical value of sonography in the diagnosis and determine the effects of TB in the urinary tract (kidneys, ureters and urinary bladder) of infected and untreated Sudanese subjects.

Patients and Methods: This prospective study was conducted at Al-Nihoud Teaching Hospital in West Kurdufan State- Sudan. It spanned a period of 4 years from January 2008 to January 2012, involving 200 untreated Sudanese patients (118; 59% males and 82; 41% females) and aged 1 to 85 years; mean age of 37 ± 2.9 years. Samples proved to have TB either by one urine culture positive for Mycobacterium TB, or a histopathological confirmation of caseating necrotic lesions in a biopsy or surgery specimen. Sonography was performed using Toshiba Just Vision 200

and Tokimec CS-2020 fitted with 3.5 MHz convex transducers.

Results: In TB patients, ultrasound findings in kidneys were varied and included wide spectrum of abnormalities like renal stones (24%), hydronephrosis (17%), renal cavitations (8%), renal cyst (16%), Pyelonephritis (12%), parenchymal renal disease (9%), renal abscess (3%), atrophied kidneys (5%), renal solid mass, end stage kidney disease and non visualized kidneys (2%). Findings in ureters include hydroureter (8%) and in urinary bladder (UB) ultrasound detected UB wall thickening (12.5%), vesicle stone (1%) and UB mass (0.5%).

Conclusion: Urinary tract sonography is a quick and non invasive method of evaluating the urinary tract in miliary TB conditions. Therefore, after proven TB infection either by urine culture or histological confirmation, ultrasound can be used widely to determine its effects in urinary tract and to monitor the therapeutic efficacy in a clinical situation.

INTRODUCTION

Tuberculosis (TB) remains a global health problem, with one-third of the world population infected and ~9.4 million new cases reported in 2008. 75% of the infected individuals are aged 15-54 years [1]. TB of the kidney and urinary tract is, like other forms of the disease, caused by members of the Mycobacterium TB complex [2]. The mechanisms of the spread to the kidney and urinary tract of miliary TB which involves the urinary system with a rather high incidence, and, if not detected, may result in a functionless kidney for the

often nonspecific symptomatology. These considerations account for the seriousness of the problem of urinary TB, whose great topical interest is unfortunately proven not only in the African continent where it is particularly common, but also in Europe [3].

Flank pain, back pain and hematuria are seen. However, fever, weight loss and night sweats are usually absent. The definitive diagnosis of urinary TB depends on a positive urine culture, acid fast staining and histological diagnosis [2,4]. Early diagnosis of renal TB is important and can prevent

occurrence of renal failure as TB is still common with rising incidence in certain countries, especially Middle East and Africa [5].

Ardalan et al. determined the radiological findings in renal TB where the most common findings were ureteral stricture and dilation (13/25, 52%), bladder involvement 13/25 (52%), autonephrectomy 12/25 (48%) and renal parenchymal calcification 10/25 (40%). The most common combined pattern was ureteral stricture-dilation with contralateral autonephrectomy and bladder irregularities. Also they reported that: "Kidney TB remains undiagnosed until the advanced stages and awareness about the intravenous urography (IVU) imaging pattern could help in early diagnosis of this entity" [6].

Profile of renal TB was studied by Najjar et al. where they conclude that: Renal TB should not be a difficult diagnosis to make in patients with urinary symptoms plus abnormal urine analysis that should be screened for TB after routine urine cultures have been found to be negative [7].

In renal TB hydrocele, hydronephrosis with or without debris, loss of corticomedullary differentiation, cortical thinning, and calcification are seen on sonography, echogenic rim are reported as the most common findings [8, 9].

PATIENTS AND METHODS

This was a prospective study that spanned a 4 years period from January 2008 to January 2012, involving 200 untreated Sudanese patients proved to have TB (aged 1 to 85 years; mean age of 37 ± 2.9 years) were selected from the outflow of the patients at Al-Nihood Teaching Hospital, Radiology and Medical Imaging Department, West Kurdufan State, Sudan.

At inclusion, we included samples had urinary tract TB proven either by at least one urine culture positive for Mycobacterium TB, or a histopathological confirmation of caseating necrotic lesions in a biopsy or surgery specimen. The medical records of such 200 qualified patients were analyzed with regard to age, sex, medical history and symptoms. The remaining patients had been treated on strong clinical suspicion alone and were, therefore, excluded from the study. An informed consent was obtained from all the subjects before scanning but, in addition, a review and authorization of the study protocols was done by the Ethical

Committee available at Al-Nihood Teaching Hospital.

Urinary tract sonography was performed using Toshiba Just Vision 200 and Tokimec CS-2020 fitted with 3.5 MHz convex array transducers. Ultrasound machines used were connected with digital graphic printer, 100 V; 1.5 A; and 50/60 Hz, with serial number of 3-619-GBI-01 and made by Sony Corporation- Japan.

The examination begins with the patient in the supine position. The highest frequency transducer permitting adequate penetration is used. A phased array sector probe with its small footprint permits subcostal and intercostal scanning. Scans were performed in the sagittal and transverse planes from the anterior approach using the liver and spleen as acoustic windows. Various maneuvers may enhance demonstration of the kidneys: left lateral decubitus or lateral oblique positions for the right kidney and right lateral decubitus or lateral oblique positions for the left kidney. Coronal longitudinal and transverse scans may also be obtained and are recommended for evaluating the renal pelvis and proximal ureter on hydronephrotic patients [10].

The bladder should be full enough. It is important to have the correct degree of bladder fullness since too little fluid may not provide the window necessary for adequate pelvic scanning. A bladder that is too full can compress or displace structures so they are not visualized. An overfull bladder can also create the disappearance of pathology. After the scans are performed, if there is any doubt about the influence of the full urinary bladder on adjacent structures, have the patient partially void and rescan the bladder [11]. Specific ultrasound features used to diagnose TB complications in urinary tract such as masses, cysts; abscess and stricture were according to the international bases of sonographic features that used to diagnose such clinical situations. So to determine positive TB result, first line of diagnosis is clinical and lab tests then to see the complication in the urinary tract, ultrasound should take place immediately.

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1964.

Results statistical analysis, overviewed in a form of tables and graphs by using Microsoft Office Excel package depend on the frequencies and the percentages of variables among the scanned samples.

RESULTS

A total of 200 Sudanese patients (118; 59% males and 82; 41% females) aged from 1 to 85 years; mean age of 37 ± 2.9 years, proved to have TB either by at least one urine culture positive for *Mycobacterium TB*, or a histopathological confirmation of caseating necrotic lesions in a biopsy or surgery specimen.

The duration of TB symptoms was 4 months to 3 years; mean of 20 months in the scanned subjects. The common clinical features detected in TB patients were loin pain, hematuria, dysuria and frequency, fever, ureteric colic, hypertension and renal failure. Out of 200 untreated TB subjects 72 (36%) presented with loin pain, 20 (10%) presented with hematuria, 24 (12%) presented with dysuria and frequency, 27 (13.5%) presented with fever, 36 (18%) presented with ureteric colic, 18 (10.5%) presented with hypertension (HTN) and 3 (1.5%) had renal failure. There are no co-morbidities detected in whole patient of this study, as diabetes mellitus (DM), and glomerulonephritis and systemic lupus. (Table 1 and Figure 1).

Table 1: Clinical features of urinary tract TB in the scanned samples

Clinical features	Frequency in patients	Percentage
Loin pain	72	(36%)
Hematuria	20	(10%)
Dysuria and frequency	24	(12%)
Fever	27	(13.5%)
Ureteric colic	36	(18%)
Hypertension	18	(9%)
Renal failure	3	(1.5%)
Total	200	(100%)

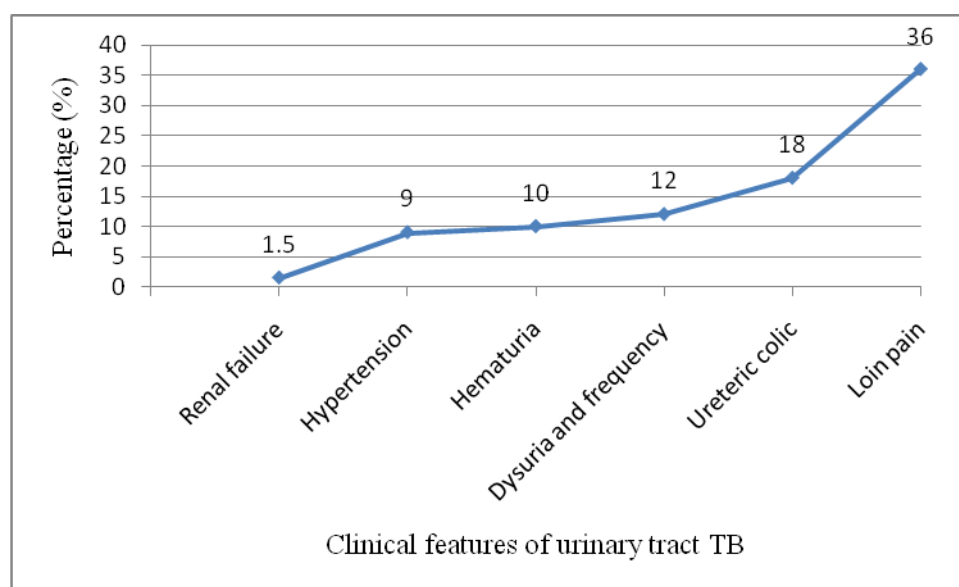


Figure 1: Clinical features of urinary tract TB in the scanned samples

All the patients in this study did have any investigation for natural resistance. The majority of our patients live in the same rooms with other people where 18 (9%) subjects had family members with tuberculosis.

Ultrasound findings in kidneys of untreated TB subjects were varied and included a wide spectrum of abnormalities. In which renal stones in 48 (24%), hydronephrosis in 34 (17%), renal cavitations in 16 (8%), renal cyst in 32 (16%),

pyelonephritis in 24 (12%), parenchymal renal disease in 18 (9%), renal abscess in 6 (3%), atrophied kidney in 10 (5%), renal solid mass, end stage kidney disease and non visualized kidneys in 4 (2%) (Table 2 and Figure 2).

Table 2: Ultrasound findings in kidneys of 200 untreated TB patients in the scanned samples

Kidneys ultrasound findings	Frequency in patients	Percentage
Renal stone	48	(24%)
Hydronephrosis	34	(17%)
Renal cavitations	16	(8%)
Renal cyst	32	(16%)
Pyelonephritis	24	(12%)
Parenchymal renal disease	18	(9%)
Renal abscess	6	(3%)
Atrophied kidney	10	(5%)
Renal solid mass	4	(2%)
End stage kidney	4	(2%)
Non visualized Kidney	4	(2%)
Total	200	100%

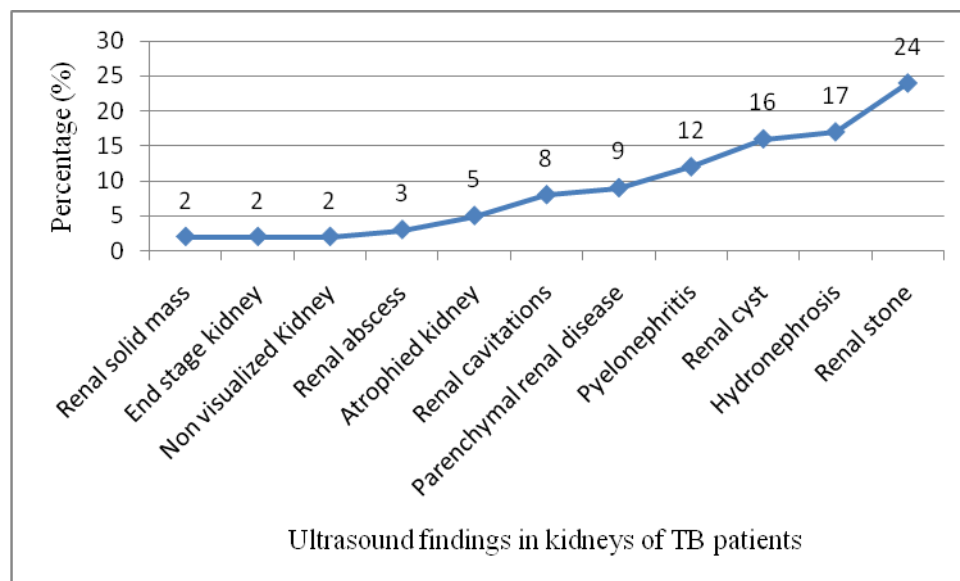


Figure 2: Ultrasound findings in kidneys of untreated TB patients

In addition, ultrasound findings in the ureters of untreated TB subjects include hydroureter in 16 (8%) cases (Table 3 and figure 3).

Table 3: Ultrasound findings in ureters of 200 untreated TB patients in the scanned samples

Ureters ultrasound findings	Frequency in patients	Percentage
Hydroureter	16	(8%)
Normal Ureter	184	(92%)
Total	200	100%

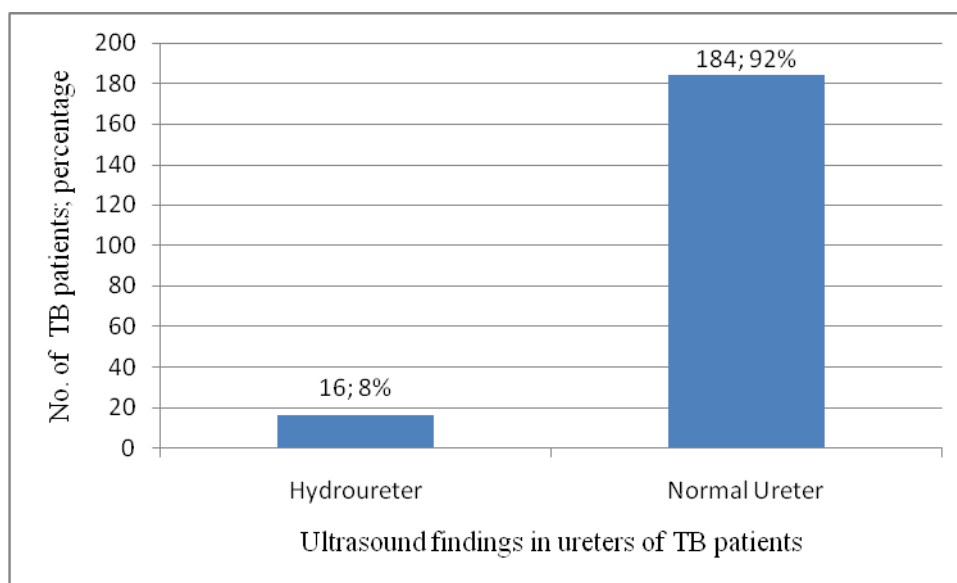


Figure 3: Ultrasound findings in ureters of untreated TB patients

In the urinary bladder (UB) of untreated TB subjects, ultrasound detected features such as UB wall thickening in 25 (12.5%), vesicle stone in 2 (1%) and UB mass in 1 (0.5%) (Table 4 and Figure 4).

Table 4: Ultrasound findings in UB of 200 untreated TB patients in the scanned samples

UB ultrasound findings	Frequency in patients	Percentage
UB wall thickening	25	(12.5%)
Vesicle stone	2	(1%)
UB mass	1	(0.5%)
Normal UB	172	(86%)
Total	200	100%

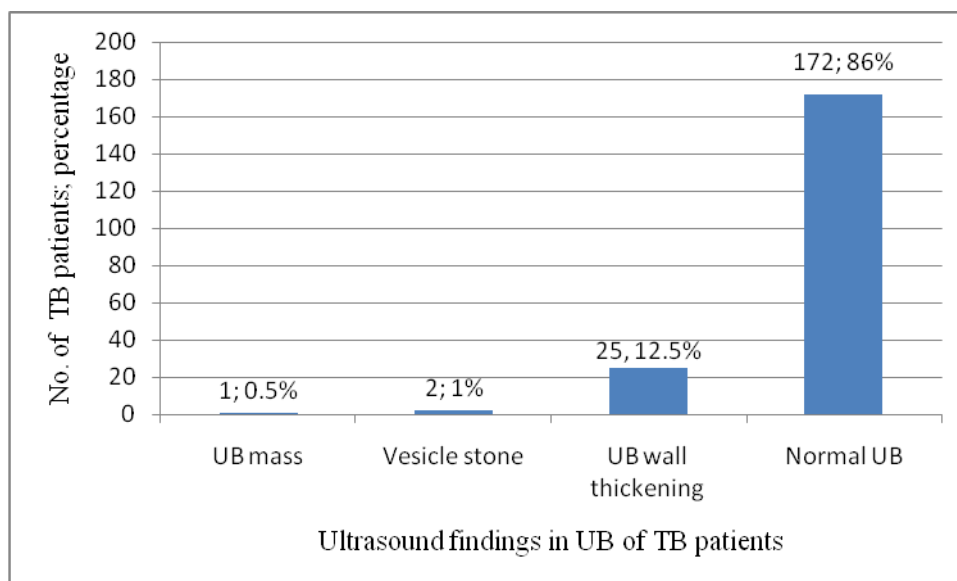


Figure 4: Ultrasound findings in UB of untreated TB patients

In this study the researchers follow up the treatment in all cases proved to have TB by ultrasound and the result of this follow up shows that there is a complete resolution in the

majority- unless renal solid masses, end stage kidney disease and atrophied kidneys- of conditions which confirm the response to treatment.

DISCUSSION

Out of 200 untreated TB cases, 118; 59% were males and 82; 41% females. Dominant of males has been reported in various other studies such as Najar et al. and O' Flgnn [7,12]. Results showed that urinary tract TB generally presents in adults (mean age is 37 ± 2.9 years) because of the time elapsed between primary infection and manifestation of the renal spread [6,7,13].

TB infection in the urinary tract could be assess clinically and microscopically but ultrasound is the cheapest, accurate and noninvasive method that give us further details about the wide spectrum of complication caused by military TB in the urinary tract, such as renal cavitations, renal abscess, atrophied kidneys, vesicle stones and others. Theses spectrum of complication cannot be answered or seen by clinical or microscopic methods alone. Microscopic exam just used to confirm the presence of TB but the study of complication was done using ultrasound.

The most frequent presenting symptoms for active urinary tuberculosis reported by Simon et al. where dysuria in 34%, hematuria in 27%, flank pain in 10% and pyuria in 5% also Najar et al. reported that 36% had dysuria and frequency, 24% hematuria, 20% loin pain, 8% ureteric colic, 11% hypertension and renal insufficiency each

and 3% presented as acute febrile illness [14,7]. While in this study, the common clinical features detected in TB patients were loin pain, hematuria, dysuria and frequency, fever, ureteric colic, hypertension and renal failure. 72 (36%) presented with loin pain because of ureteral obstruction due to stricture or the passage of blood clots or necrotic debris, 20 (10%) presented with hematuria, 24 (12%) presented with dysuria and frequency from urinary inflammation, 27 (13.5%) presented with fever, 36 (18%) presented with ureteric colic, 18 (10.5%) presented with hypertension and 3 (1.5%) had renal failure as confirmed by Narayana [15].

The role of imaging studies in urinary tuberculosis has been to assess the extent of involvement, to monitor the effect of treatment, and to discover complications. Early findings are best detected on IVU or retrograde pyelography. Late or chronic changes are optimally evaluated with computed tomography and sonography. Recently, however, sonography has been performed more often because it is more easily available and is economical [9,17,18,19]. In this study ultrasound detected a wide spectrum of abnormalities in kidneys (**Figures 5 A, B, C and D**), ureters and UB (**Figure 6 A and B**) of TB infected subjects.

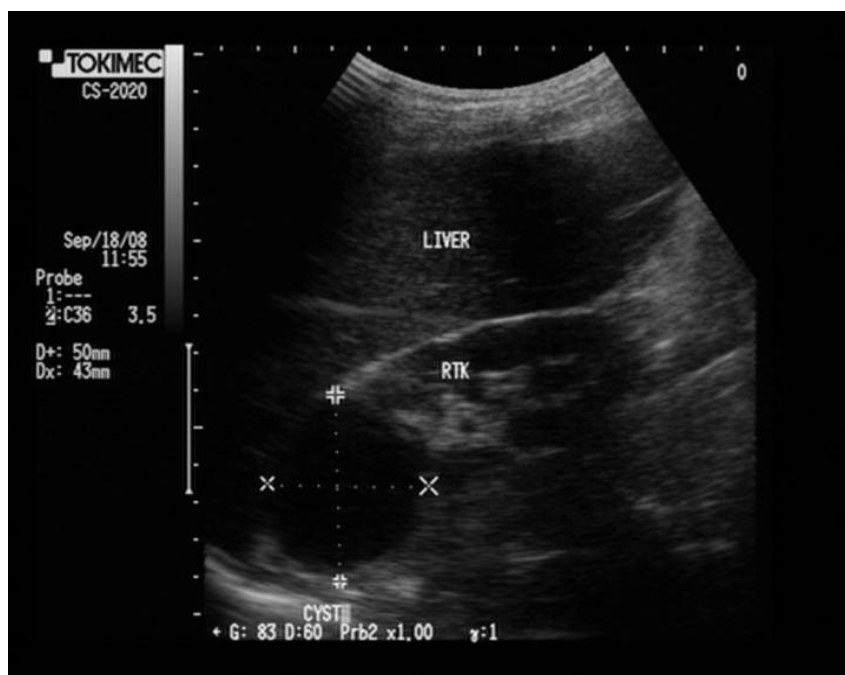


Figure 5A: Longitudinal renal sonogram in TB patients; upper polar simple renal cyst

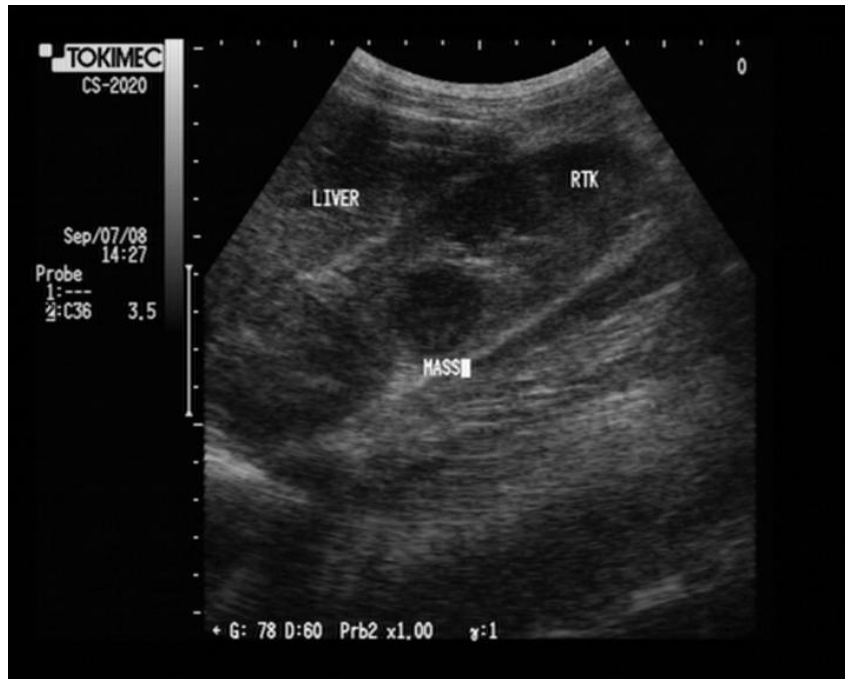


Figure 5B: Longitudinal renal sonogram in TB patients; mid polar solid renal mass

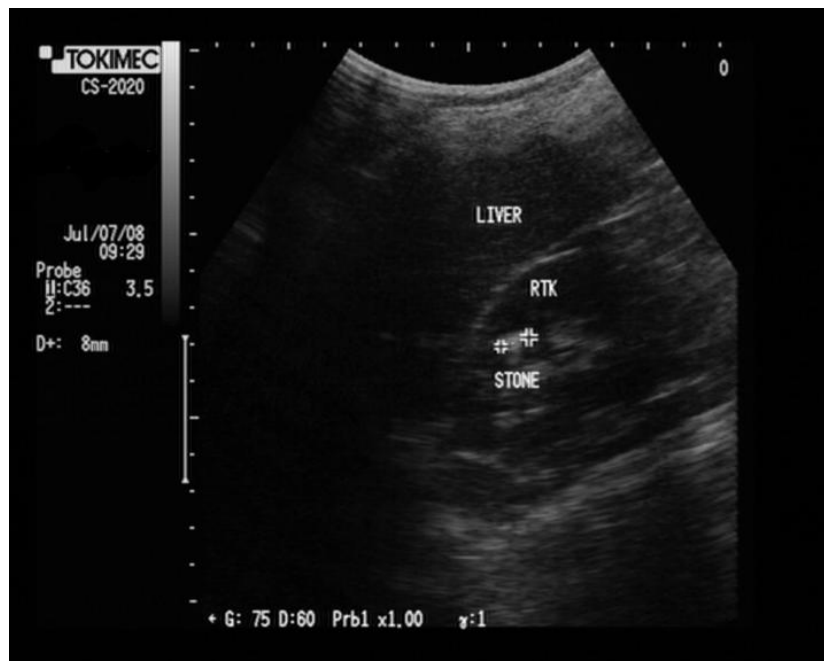


Figure 5C: Longitudinal renal sonogram in TB patients; pelvicalyceal calculi

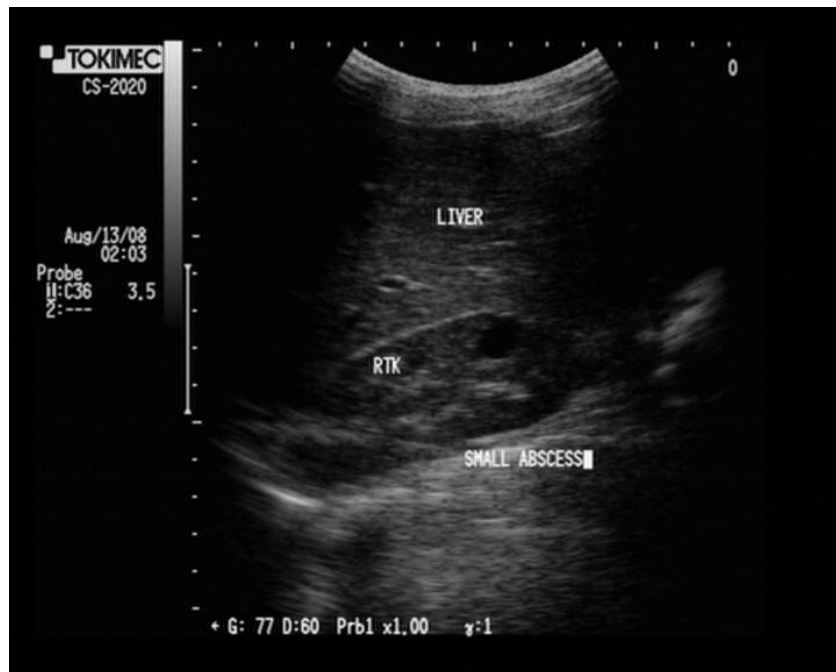


Figure 5D: Longitudinal renal sonogram in TB patients; renal abscess



Figure 6A: Short axis renal sonogram in TB patients; hydronephrosis with hydroureter

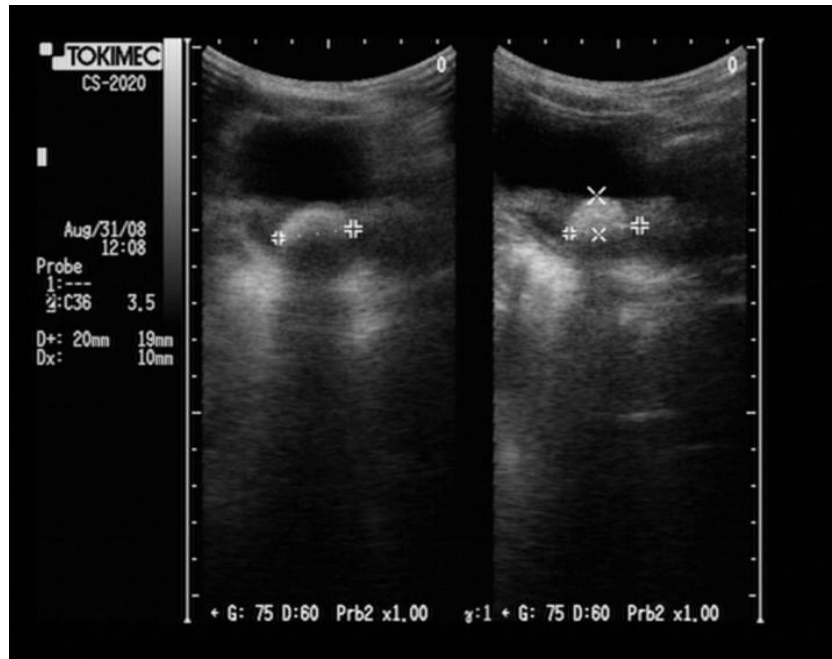


Figure 6B: Short axis UB sonogram in TB patients; Vesicle stone with UB cystitis

In kidneys, tuberculosis effects were renal stones in 48 (24 %), hydronephrosis in 34 (17%), renal cavitations in 16 (8%), renal cyst in 32 (16%) Pyelonephritis in 24 (12%), parenchymal renal disease in 18 (9%), renal abscess in 6 (3%), atrophied kidney in 10 (5%), renal solid mass, end stage kidney disease and non visualized kidneys in 4 (2%). In ureters, ultrasound was able to detect hydroureter in 16 (8%). UB wall thickening in 25 (12.5%), vesicle stone in 2 (1%) and UB mass in 1 (0.5%) were found in UB as complication of TB infection. Conditions of *Schistosoma haematobium* or *Schistosoma mansoni* especially in the ureter and urinary bladder were not detected among cases, because this study was done in west of Sudan which is an area geographically away from the classical causes of *Schistosoma*.

Such findings were supported in a study that evaluate high resolution sonographic features of urinary tuberculosis, where Vijayaraghavan et al. found that sonographic features included parenchymal masses, cavities, mucosal thickening of the collecting system and urinary bladder, stenosis of the collecting system, a contracted urinary bladder, vesicoureteric reflux, and calcifications. Their proof of tuberculosis was by urinalysis, culture, and biopsy. Which confirm that high resolution sonography in appropriate clinical situations is useful in diagnosis of urinary tuberculosis. The various high-resolution sonographic findings in urinary

tuberculosis are illustrated. The distinguishing features are visualization of involvement of multiple sites and multiple stages of disease in the same patient [16].

CONCLUSION

It could be concluded that ultrasonography is a quick and non invasive method of evaluating the urinary tract in miliary TB conditions. Therefore, after proven TB infection either by urine culture or histological confirmation, ultrasound can used widely to determine its effects in urinary tract and to monitor the therapeutic efficacy in a clinical situation.

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Acute Diarrheal Illness – The Most Common Medical Problem Worldwide

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Diarrhea can result in significant morbidity and mortality, depending on the degree of severity. The history and clinical presentation should dictate initial treatment and management.

INTRODUCTION

Acute diarrheal illness is one of the most common medical problem worldwide. It can be caused by bacteria, protozoa, or viruses and can demonstrate a wide spectrum of clinical severity. The medical history and physical examination are the keys to an effective diagnosis. Laboratory investigations and antibiotic therapies are useful in select situations, but they often do not augment effective management. Acute diarrhea is defined as the abrupt onset of abnormally high fluid content in the stool, more than the normal value of approximately 10mL/Kg/d in the infant and young child, and more than 200g/d in the teenager and adult. This situation typically implies an increased frequency of bowel movements, which can range from 4-5 to more than 20 times per day. Diarrheal episodes are classically distinguished into acute and chronic based on their duration. Acute diarrhea is thus defined as an episode that has an acute onset and lasts no longer than 14 days; chronic diarrhea is defined as an episode that lasts longer than 14 days.

EPIDEMIOLOGY

Children living in developing countries have more frequent episodes of diarrhea than other children and

develop intestinal immunity to the majority of enteric pathogens[1]. As a result of improved sanitation and food processing, travelers from the Western World lack this immunity and often develop diarrhea when abroad. Travelers diarrhea is usually caused by the organisms responsible for pediatric diarrhea in those areas.

The most common cause of infectious diarrhea worldwide is rotavirus[2]. Mortality from acute diarrhea is overall declining but remains high. Most estimates have diarrhea as the second cause of childhood mortality, with 18% of the 10,6 million yearly deaths in children younger than age 5 years. In countries where the toll of diarrhea is highest, poverty also adds an enormous additional burden, and long-term consequences of the vicious cycle of enteric infections, diarrhea, and malnutrition are devastating. Most cases of infectious diarrhea are not sex specific. Females have a higher incidence of campylobacter species infections and hemolytic uremic syndrome. Viral diarrhea is most common in young children. *Rotavirus* and *Adenovirus* are particularly prevalent in children younger than 2 years[3]. *Astrovirus* and *Norovirus* usually infect children younger than 5 years. *Yersinia enterocolitis* typically infects children

younger than 1 year, and the *Aeromonas* organism is a significant cause of diarrhea in young children. Very young children are particularly susceptible to secondary dehydration [4] and secondary nutrient malabsorption. Age and nutritional status appear to be the most important host factors in determining the severity and the duration of diarrhea. The younger the child, the higher is the risk for severe, life-threatening dehydration as a result of the high body-water turnover and limited renal compensatory capacity of very young children.

PATHOLOGY

The pathogens or toxins that produce acute infectious diarrhea are usually ingested unknowingly. Inadequate sanitation and poor hygiene figure prominently in many patients with diarrhea. Defence mechanisms, such as the acidic pH of the stomach, rapid transit time of the small bowel, and antibodies produced in the in the jejunum and proximal ileum reduce number of microorganisms. The ileocecal valve normally prevents the movement of colonic bacteria into the small bowel; individuals with a deficiency in any of these processes are at increased risk of developing diarrhea. Pathogenic organisms can pass through the acidic milieu of the stomach if they are acid-resistant, such as *Shigella*. Massive ingestion of contaminated food or water can also yield an adequate number of viable organisms. Food can neutralize acid locally and provide a haven for microorganisms. The organisms that survive and reach the small bowel, such as *E.coli* or *Vibrio cholerae*, can colonize the area and cause diarrhea. Mucosal invasion is another pathogenic mechanism and occurs with *Salmonella* sp, *Shigella*, and *Campylobacter jejuni*. Passage into the colon allows organisms, such as *Salmonellae*, to invade the local mucosa. Enteric pathogens or their toxins can cause diarrhea either by increasing small intestinal secretions beyond the colon's absorptive capacity or by impairing the colon's absorptive capacity directly.

DIAGNOSIS

Diarrhea is most commonly due to viral gastroenteritis with *Rotavirus*, which accounts for 40% of cases in children under five [5]. In travelers however bacterial infectious predominate [6]. Various toxins such as mushroom poisoning and drugs can also cause acute diarrhea. Chronic diarrhea can be the part of the presentations of a number of chronic

medical conditions affecting the intestine. Common causes include ulcerative colitis, Crohn's disease, microscopic colitis, celiac disease, irritable bowel syndrome, and bile acid malabsorption. *Norovirus* is the most common cause of viral diarrhea in adults [7] but *Rotavirus* is the most common cause in children under five years old [8]. *Adenovirus* types 40 and 41 [9] and *Astroviruses* cause a significant number of infections [10]. The bacterium *Campylobacter* is a common cause of bacterial diarrhea, but infections by *Salmonellae*, *Shigellae* and some strains of *Escherichia coli* are frequent [11]. In the elderly, particularly those who have been treated with antibiotics for unrelated infections, a toxin produced by *Clostridium difficile*, often causes severe diarrhea [12]. Parasites do not often cause diarrhea except for the protozoan *Giardia*, which can cause chronic infections if these are not diagnosed and treated with drugs such as metronidazole [13] and *Entamoeba histolytica* [14,15]. Other infectious agents such as parasites and bacterial toxins also occur [6]. In sanitary living conditions where there is ample food and a supply of clean water, an otherwise healthy person usually recovers from viral infections in a few days. However, for ill or malnourished individuals, diarrhea can lead to severe dehydration, and can become life-threatening [16].

LABORATORY STUDIES

The following may be noted in patients with diarrhea.

In patients with diarrhea, a stool pH level of 5.5 or less or presence of reducing substances indicates carbohydrate intolerance, which is usually secondary to viral illness and transient in nature.

Enteroinvasive infections of the large bowel produce leukocytes, predominantly neutrophils, to be shed into stool. Absence of fecal leukocytes does not eliminate the possibility of enteroinvasive organisms. However, presence of fecal leukocytes eliminates consideration of enterotoxigenic *E.coli*, *Vibrio* species, and viruses.

Examine any exudates found in stool for leukocytes. Such exudates highly suggest colitis. 80% positive predictive value colitis can be infectious, allergic, or part of inflammatory

bowel disease (Crohn's disease, ulcerative colitis).

Many different culture mediums are used to isolate bacteria.

With stool not cultured within 2 hours of collection, refrigerate at 40 C or place in a transport medium. Although stool cultures are useful when positive, yield is low.

Always culture stool for *Salmonella*, *Shigella*, and *Campylobacter* organisms and *Yesterocolitica* in the presence of clinical signs of colitis or if fecal leucocytes are found.

Look for *C.difficile* in persons with episodes of diarrhea characterized by colitis and or blood in the stools. Remember that acute-onset diarrheal episodes associated with *C. difficile* may also occur without a history of antibiotic use.

Bloody diarrhea with a history of ground beef ingestion must raise suspicion for enterhemorrhagic *E.coli*. If *E.coli* is found in the stool, determine if the type of *E.coli* is 0157 H7. This type of *E. coli* is the most common, but not only, cause of hemolytic uremic syndrome (HUS).

History of raw seafood ingestion or foreign travel should prompt additional screening for *Vibrio* and plesiomonas species.

DIARRHEA SYNDROMES

Gastroenteritis, as a result of food contamination is a common cause of acute infectious diarrhea. Only severe clinical presentation or the threat of botulism requires hospitalization.

Traveler's Diarrhea, The spectrum of traveler's diarrhea is primarily the result of enteric pathogens contracted orally while visiting a foreign country. This syndrome is primarily caused by enterotoxigenic *E.coli*. The illness is usually benign and self-limited, but it may have severe presentations with dehydration or bloody diarrhea.

Diarrhea in patients with AIDS, Although diarrhea in patients with AIDS is a broad topic, the same principles of treating acute diarrhea apply. *C.difficile* is commonly found in patients with AIDS because of increased hospital exposure and frequent antibiotic use .

INITIAL TREATMENT OR PROGNOSIS

In general, most causes of acute diarrhea will last only one week to ten days, especially when the patient receives specific therapy. When the diarrheal illness persists for more than two weeks, the differential diagnosis may include lactose deficiency, which can be produced by small bowel pathogens, including viral agents, enterotoxigenic *E coli* or *G.lambli*a. In many cases of diarrhea, replacing lost fluid therapy, or, in severe cases, intravenously. Diet restrictions such as the BRAT diet are no longer recommended [1]. Research does not support the limiting of milk to children as doing so has no effect on duration of diarrhea.

ANTIBIOTICS

While antibiotics are beneficial in certain types of acute diarrhea, they are usually not used except in specific situations [17]. There are concerns that antibiotics may increase the risk of hemolytic uremic syndrome in people infected with *Escherichia coli* 0157. H7 [18].

BISMUTH COMPOUNDS

While bismuth compounds (pepto- Bismol) decreased the number of bowel movements in those with traveler's diarrhea, they do not decrease the length of illness [19]. These agents should only be used if bloody diarrhea is not present [20].

BILE ACID SEQUESTRANTS

Bile acid sequestrates such as cholestyramine, colestipol and colesevelam can be effective in chronic diarrhea due to bile acid malabsorption. Therapeutic trials of these drugs are indicated in chronic diarrhea if bile acid malabsorption cannot be diagnosed with a specific test, such as SeHCAT retention.

CONCLUSION

Acute diarrheal illness is one of the most common medical problems worldwide. The viral, bacterial, and protozoal causes of diarrhea can result in significant morbidity and mortality, depending on the degree of severity. The history and clinical presentation should dictate the initial treatment and management. The majority of patients will require only volume repletion until the diarrheal process resolves. Extensive diagnostic evaluation should be

reserved for patients with moderate-to-severe acute or chronic illness. This approach will result in a higher diagnostic yield and more specific and cost-effective treatment.

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Gastrointestinal Stromal Tumors with Unusual Presentations: Case Series

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Key words:

Gastrointestinal stromal tumors, hematemesis, melena, abdominal mass, immunohistochemistry.

Background: Gastrointestinal stromal tumors are rare mesenchymal tumors; and it may be presented by a variety of manifestations..

Case Presentation: A 56-year-old Egyptian male patient presented with a massive gastrointestinal bleeding with hemodynamic instability, with history of previous two mild attacks. After initial resuscitation, endoscopic, pathological and immunohistochemical examination; diagnosis of gastrointestinal stromal tumor was confirmed. The patient's tumor is of low risk and complete surgical excision with safety margins was performed. Another 60-year-old Egyptian

female diabetic patient presented for preoperative assessment for cataract operation. On examination large abdominal mass was discovered. After initial diagnostic work up surgical resection was done. Pathological and immunohistochemical examination confirmed the diagnosis of gastrointestinal stromal tumor.

Conclusion: Gastrointestinal stromal tumors, should not be overlooked while investigating cases of massive upper gastrointestinal bleeding and cases of large abdominal masses especially in elderly patients.

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors specific for the gastrointestinal tract (GIT) and are rare, representing 0.1–3% of all GIT cancers with an estimated incidence of 15 per million. Gastrointestinal tract bleeding (50%) is the most common presentation, followed by abdominal pain (20–50%), obstruction (20%) and approximately one third are detected incidentally [1]. GISTs initially presenting as an abdominal mass are exceedingly rare [2]. From 10 to 30% of them are malignant and show liver metastases or intra-abdominal spread at the time of diagnosis [3].

GISTs can be a cause of obscure GIT hemorrhage and should be kept in mind when conventional investigations such as esophagogastroduodenoscopy (EGDS) and colonoscopy fail to

detect bleeding lesions, especially when located in the small bowel [3].

The digestive hemorrhage occurs if they erode or ulcerate through the bowel mucosa they can cause bleeding that is usually intermittent, but massive bleeding is uncommon [4,5].

Diagnosing these lesions is difficult because they tend to be inaccessible to routine diagnostic methods. Variable sensitivities and specificities for diagnosing GISTs are found and includes EGDS, barium studies, selective visceral angiography, wireless capsule endoscopy, radioactive isotope bleeding scans, CT scans, MRI and exploratory laparotomy is often the last option [5,6].

We recorded a case with recurrent attacks of hematemesis and melena admitted due to a massive upper GIT

bleeding and a case with accidentally discovered large abdominal mass originating from the transverse colon proved to be GIST to raise the awareness among clinicians about the uncommon presentation of these tumours.

Case 1

History

A 56-year old rural male patient presented by a massive attack of hematemesis and melena with no history of chronic medical disease. On detailed history taking he gave history of 2 previous mild attacks of hematemesis and melena.

Examination

At admission the patient was extremely pale, blood pressure 80/40, pulse 126 with regular rhythm, otherwise free.

Investigations and management

Initial resuscitation measures were done (2 wide bore canulae were inserted, fresh blood transfusion, colloids and crystalloids infusion). Full laboratory investigations were done including complete blood counts, liver function tests, kidney function tests, coagulation profile and all were free apart from severe normocytic anemia of 6.5 gm%. Decision to examine the patient by EGDS was taken.

Endoscopic findings

- a- Pale mucosa, small hiatus hernia and fungating corpus cauliflower mass easily bleed on touch with luminal encroachment, multiple punch biopsies were taken for histopathology (Figure 1).
- b- Pathological examination of endoscopic biopsies revealed pieces of tumor tissue formed of oval and spindle cells with vesicular nuclei and high mitotic index, picture highly suggestive of GIST for immunohistochemistry (Figure 2).

Immunohistochemistry

Sections were prepared from paraffin block, processed in Benchmark XT (Ventana) and stained by monoclonal antibodies, using DAB as chromogen and hematoxylin as counter-stain. The sections were treated against C. kit (CD117) and CD 34 and tumor cells were strongly positive for it (Figure 3).

Surgical Resection

Surgical resection of a large wedge of the stomach 10x14 cm including the tumor with safety margins was done.

Pathological examination

Pathological examination of the resected part of the stomach revealed: non capsulated tumor mass of 3.5x2.5x1 cm. Sections prepared showed tumor tissue formed of spindle cells. Mitotic activity was 2-3/ 50 high power field (HPF), with congested vessels and ulcerated mucosal covering. Sections prepared from the surrounding gastric wall showed free surgical margins.

Case 2

History

A 60-year old female patient with type 2 diabetes presented for preoperative assessment for cataract operation with no other manifestations.

Examination

On examination the patient was generally good, blood pressure 130/70, pulse 80 with regular rhythm, large firm mildly tender, limited mobility mass felt in left lumbar region with normal overlying skin. She denies nausea, vomiting, weight loss or bowel habits disturbance.

Investigations and management

- 1- Abdominal ultrasound showed ill defined mass related to the colon
- 2- Abdominal CT scans showed large heterogeneous mass 9x6 cm inseparable from the colon and extending to the abdominal wall (Figure 4).
- 3- Laboratory investigations: liver functions, kidney functions, complete blood counts showed anemia with hemoglobin level of 10.2 gm%.
- 4- Surgical Resection: On laparotomy the mass was originated from the transverse colon and attached to the lateral abdominal wall. Surgical resection of the mass and related colon with safety margin and re-anastomosis was done.

Pathological examination:

Pathological examination of the resected part revealed: non capsulated tumor mass 8x7x4 cm. Sections prepared showed tumor tissue formed of spindle cells intermingled with mixed inflammatory cell infiltrate. The growth involved colonic wall. Cut colonic margins were free. Two dissected lymph nodes were free from the tumor and showed reactive hyperplasia. Mitotic activity was 2-3/ 50 HPF.

Immunohistochemistry

Sections were prepared from paraffin block, processed in Benchmark XT (Ventana) and stained by monoclonal antibodies, using DAB as chromogen and hematoxylin as counter-stain. The sections were treated against C. kit (CD117) and CD34 and tumor cells were strongly positive for both.

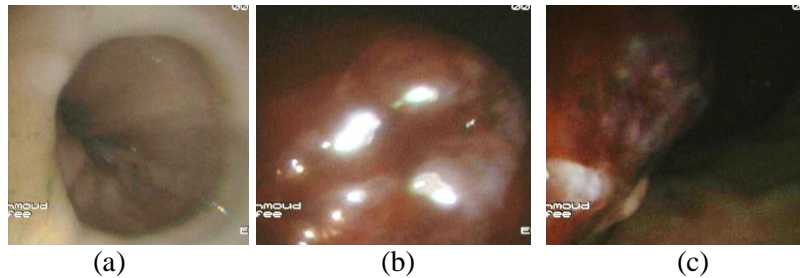


Figure (1): Endoscopic findings; (a) sliding hiatus hernia with pale esophageal mucosa, (b) large fundal mass, (c) ulcerated surface of the mass

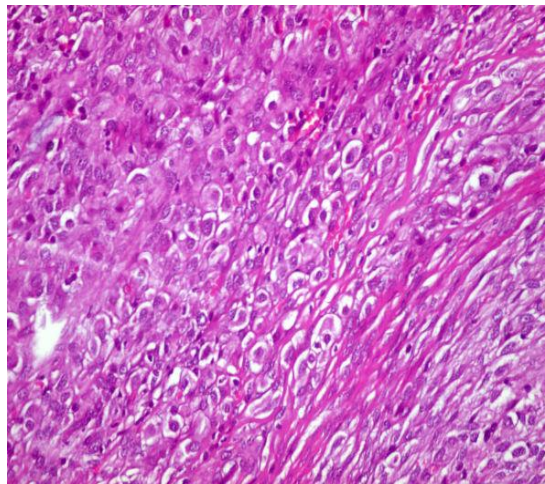
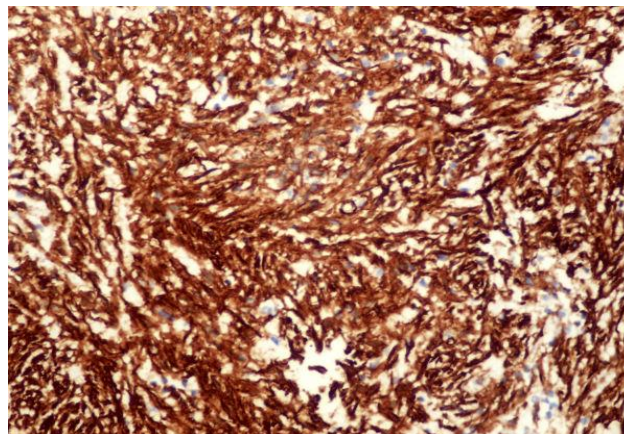


Figure (2): Pathological sections from the tumor showing spindle shaped cells with high mitosis



Figure(3): Immunohistochemistry showing the tumor positivity for CD 117

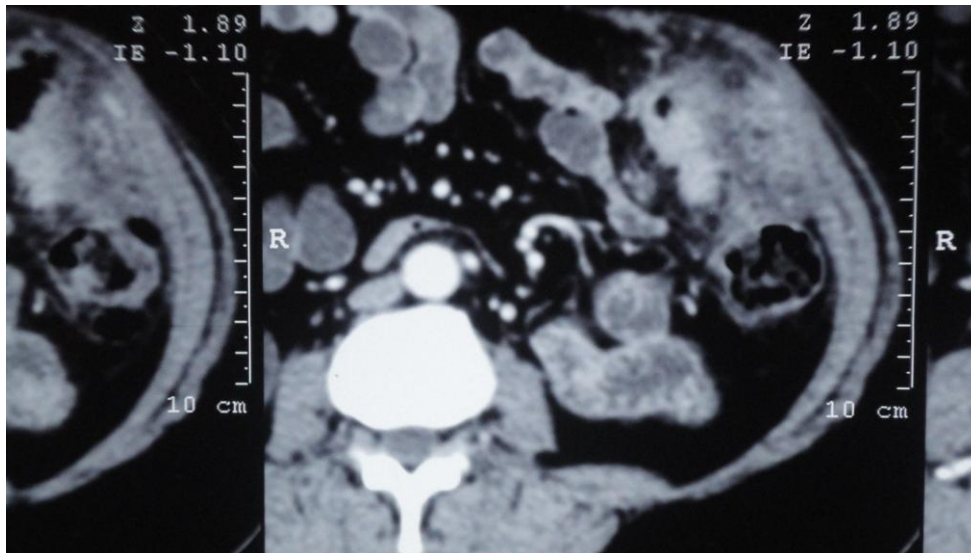


Figure (4): CT scan shows the mass related to colon and abdominal wall.

DISCUSSION

It is now believed that GIST tumors arise either from stem cells that differentiate towards interstitial cells of Cajal (these cells form part of the myenteric plexus in the GIT and regulate peristalsis i.e. link the autonomic innervations of the gut with smooth muscle cells and regulate GIT motility) or directly from interstitial cells of Cajal and not from smooth muscle cells [7]. GIST usually seen in adults in the sixth decade of life [8] and this coincide with the findings of our cases.

These tumors grow intraluminally or extraluminally. When the growth pattern is extraluminal, patients may be symptom free for a long time and present with very large exoluminal masses [8], this is obvious in our second case where the patient presented by huge intra-abdominal mass that was accidentally discovered while examined for preoperative assessment. When it grew intraluminally manifestations develop, and hence our first case experienced recurrent attacks of bleeding inspite of the small size of the resected tumor due to erosions into the covering mucosa and the surrounding vessels.

In Egypt variceal bleeding is the most common cause of upper GIT bleeding [9], and GIST represent a very uncommon cause in comparison to variceal bleeding and that is why it is not usually thought when investigating cases of upper GIT bleeding in our community.

GIST is an unusual cause of upper GIT bleeding, and has a high likelihood to rebleed and this

explains the recurrent attacks of bleeding reported in the first case. These bleeding tumors need to be investigated urgently as an inpatient rather than as an outpatient [10]. This is obvious in our case, the patient was admitted due to a massive GIT bleeding, and that is why urgent resuscitation was performed hand in hand with the battery of investigations performed. Early surgical intervention, either open or laparoscopic resection, is the treatment of choice to prevent re-bleeding [10], in the 12 months follow up period after successful surgical resection our case had no attacks of bleeding and no additional morphological changes on endoscopic examination.

The second case presented here mimicked other abdominal conditions like colon cancer, mesenteric mass, stomach cancer, ovarian cancer and retroperitoneal tumor both clinically and radiologically. Although there is no specific CT findings for GIST tumors, we performed a contrast-enhanced CT scan because it is the imaging modality of choice for patients with suspected abdominal mass, as it helps in both pre-operative staging and to evaluate for metastatic disease [11]. Preoperative biopsy carries a risk of hemorrhage due to the friable nature of these tumors [2], and hence we avoided it because we planned for a definitive surgery.

Kit protein is a tyrosine kinase growth factor receptor present in 90% of GIST cells. The incidence of GISTs has increased in the last few years due to better detection as all mesenchymal tumours are now being tested for CD117. CD117

(Kit protein) is the product of c-kit proto-oncogene, located on chromosome 4q11-21 [12]. Our cases tested positive for CD117 by immunohistochemistry and this leaves no doubt that it is a case of GIST.

Complete surgical resection is accomplished in 40-60% of all GIST patients, and in >70% of those with primary non-metastatic GIST [10]. In our cases we had completely excised the tumor, and this was confirmed by the safety margin on pathological examination.

GISTs exhibit a highly variable behavior after resection of the primary tumor. These patients need to be followed up on a long term basis as local recurrence and metastases can occur many years after surgery. These tumors spread by the haematogenous route predominantly to the liver. Lymph node involvement is very rare and therefore lymphadenectomy is not routinely indicated [13]. In the first case no extragastric spread was reported at the time of diagnosis nor in the 12 months follow up period. While in the second case no intraluminal nor extraluminal recurrence was reported in the 12 months of follow up.

Local recurrence or metastases develop in approximately 50% of patients who had potentially curative operation [14]. The two most important tumor factors for local recurrence and metastasis are tumor size and mitotic rate (size >5 cm and mitosis >5 per 50 HPF increases the risk). Other prognostic factors are completeness of resection, age, and tumor location. Gastric GISTs have a lower risk of tumor recurrence than esophageal, small bowel or large bowel GISTs [15].

The first case seemed to be a low risk case and this is directly related to the small size of the tumor <5cm, low mitotic index (2-3/50 HPF) and complete excision of the tumor with free safety margins; this explains the good general condition and absence of rebleeding after surgical resection through the follow up period.

The second case seemed to be an intermediate risk; large size of the tumor (>5cm) is a high risk parameter contrary to the low mitotic index (2-3/50 HPF) and complete excision of the tumor with free safety margins. Similar controversy in the correlation between tumor size and mitotic index was also reported by Patil et al. [2].

The median disease survival for patients with primary GIST is approximately 5 years [16].

This is not elucidated in these cases because we followed the patients for 12 months only.

Imatinib (a tyrosine kinase inhibitor) is approved for the treatment of advanced disease. The recommended starting dose is 400-600 mg, this drug is safe and effective [17]. Because the tumors were completely resected, low risk of resected tumors; this drug was not given and these cases were candidates for regular follow up.

CONCLUSION

Gastrointestinal stromal tumors, should be kept in mind while investigating cases of massive upper gastrointestinal bleeding and cases of large abdominal masses especially in elderly patients.

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Video case: Diagnosis of Achalsia by Abdominal Ultrasonography

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Comment

A-55-year old female presented by progressive dysphagia over a long period, she refused endoscope examination for a long period. On abdominal ultrasonic examination the

esophagus appeared dilated and tapers in a funnel shaped manner. Upper endoscopic examination and barium swallow confirmed the diagnosis.

Image Case: Extraction of an Impacted Coin in Upper Esophagus in 3 Years Old Female

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A 3-year-old female swallowed a large metallic coin (one Egyptian pound; the largest coin in Egypt). Laryngeal examination failed to demonstrate the coin and serial X ray films showed the

coin impacted in the upper esophagus. Extraction under general anesthesia was done 5 days after swallowing. Areas of pressure necrosis at the site of impaction, as well as changes in the coin were noticed.

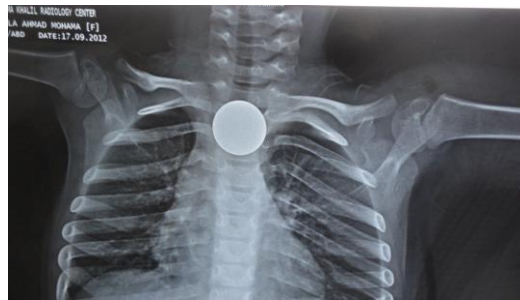


Figure (1): X ray showing the coin impacted in upper esophagus.



Figure (2): The extracted coin.