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Editorial

Muhammad Akram Randhawa

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It is a matter of great honour and pleasure for me to introduce the journal of Rawalpindi Medical College and write the editorial for its first issue.

I think this introduction would remain incomplete unless a brief relevant history of relatively younger college of ours is not narrated. This college came into being in 1974, and was placed in the Kisan Hall of Agriculture University, Faisalabad along with the Punjab Medical College. To start with one hundred students were admitted in first year and only two Professors were recruited for Anatomy and Physiology Departments. The same year in November, the college was shifted to Rawalpindi and accommodated in the science block of Gordon College because there was no suitable building for that near any of the big Government Hospitals in the city. Central government Hospital (new named Rawalpindi General Hospital), District Head Quarter Hospital and Holy Family Hospital were attached for clinical teaching and training. The consultants of various specialties were appointed as Professors and Assistant Professors of their respective subjects. Most of the efforts and time of senior teachers used to be spent in the development of buildings and departments, recruitment of the ancillary staff and solving the administrative and students problems. One could hardly think and spare time for research and academic writing. Over engagement of the teaching staff in the patient care remains another important factor.

Gradually, over the years, the conditions have improved. Number of students has increased up to about 250 in each class, so the doctors qualifying each year and there is sufficient teaching staff in every department. Many young doctors, after obtaining the highest degrees in various specialities from within the country and abroad have joined the college who are quit experienced in research and medical writing and are interested to continue research activities and improve professional skills.

Besides medical conferences, seminars and workshops the medical writing is an important source of communication of knowledge, experience and exchange of views. Since ancient times the man was aware of this need and we can find excellent examples in old Greek, Egyptian, Indian and Chinese literature. Some of their explanations of diseases and remedies remain true till today. Diabetes has been explained by Aristotle. Ibne Ali Sina gave the concept of a controlled clinical trial on the diagnosis and treatment of diabetes i.e. ants will come to the urine of diabetes and not to that of normal individuals and the treated group.

The standard of Medical Education and research of an institution can be judged from the amount and quality of publications coming out from there. As we did not have any journal of our own, our professionals and post-graduate students used to send their articles for publication in the journals of other institutions. Some times they had to wait for months and years before their papers could be published.

Thanks to the Pakistan Medical and Dental Council (PMDC) for its recommendations for the appointment and promotion of the professional staff in the medical colleges and post-graduate institutes which require original publications in the international journals included in the Medline or local journals approved by the council. That has increased trends in medical writing and the need to have more journals. I believe there is no dearth of publishable material, and with a team effort, JRMC can achieve a standard, sufficient enough not only for its recognition by PMDC, but also for its indexation with index medicus.

I hope JRMC will remain a source of encouragement and inspiration for our colleagues to further improve their research activities and medical writing.

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Spontaneous Bacterial Peritonitis in Hospitalized Chronic Liver Disease Patients

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Hospitalized patients with chronic liver disease were prospectively evaluated for the presence of spontaneous bacterial peritonitis (SBP). Out of total 73 patients with chronic liver disease and ascites, SBP was diagnosed in 24 (32.9%) patients; 8 patients had classical SBP while neutrocytic ascites was seen in 16 patients. Hepatic encephalopathy (87.5%), abdominal pain (80%), jaundice (79.2%), fever (67.5%), upper gastrointestinal bleeding (58.5%) and abdominal tenderness (51.5%) were common clinical presentations in SBP group. Patients with SBP and without SBP were comparable for age and sex. Patients with SBP were more likely to have abdominal tenderness (100% vs 0%), splenomegaly (100% vs 69.4%), hepatic encephalopathy (87.5% vs 59.2%), jaundice (79.2% vs 28.6%), leucocytosis (54.2% vs 28.6%) and diabetes mellitus (33.3% vs 8.1%). Mean ascitic fluid protein concentration was low in SBP group (9.7 g/l vs 12.5 g/l) but the difference was not statistically significant (p > 0.05).

Introduction

Spontaneous bacterial peritonitis (SBP) is infection of the ascitic fluid in the absence of a recognizable cause of peritonitis(1). First case of SBP occurring in a patient with cirrhosis was reported by Caroli in 1958(2). Initially it was considered to be a complication of alcoholic cirrhosis, the most common cause of cirrhosis in the western world, but later on it was also documented in patients with cirrhosis due to other causes. SBP is a serious complication resulting in high morbidity and mortality; 50% of patients with SBP are likely to die during their hospital admission(3). The route by which organisms reach the peritoneum is not definitely known; however, it is thought to be by haematological spread. SBP is more likely to occur in patients with decompensated cirrhosis(4) and in hospitalized patients with upper gastrointestinal haemorrhage. As the opsonic activity of ascitic fluid is proportional to its protein content, therefore SBP is more likely to occur if ascitic fluid protein is low(5,6). There are no classical features of SBP and hence a high index of suspicion is needed to diagnose this condition at an early stage.

Aims and objectives of this study were to find out the prevalence of SBP in hospitalized chronic liver disease patients, to document the clinical presentations and to compare the presentation of patients with SBP with those of without SBP.

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Patients and methods

All patients with clinically suspected chronic liver disease and with ascites admitted to the medical unit II of Rawalpindi General Hospital between 1st December 1994 and 30th November 1995 were evaluated for inclusion in the study.

Patients with anyone of the following were excluded from the study:

1. an evidence of intra-abdominal focus of infection.
2. abdominal paracentesis in the preceding two weeks
3. a history of antibiotic use within 7 days prior to the admission
4. an evidence of intra-abdominal malignant lesion
5. haemorrhagic ascites
6. neutropaenia in peripheral blood

Diagnosis of chronic liver disease for the purpose of this study was clinical with suggestive findings on ultrasonography (a coarse liver echo pattern and dilated portal vein). Histological confirmation for the presence of chronic liver disease by liver biopsy was done where indicated but was not considered essential for inclusion in the study.

In patients who fulfilled the inclusion and exclusion criteria a detailed history, with special emphasis on presence or absence of fever, jaundice,

upper gastrointestinal bleed and features of hepatic encephalopathy, was taken and thorough physical examination was carried out and the findings were recorded in the performa. Under strict aseptic conditions and using a disposable 20 cc syringe 20 cc of ascitic fluid was collected from the left flank. 5 cc of this fluid was shifted to a clean bottle and was sent to the laboratory for estimation of protein content and for total and differential white blood cell count. Remaining 15 cc of ascitic fluid was immediately transferred to commercially prepared blood culture bottle and was sent to the laboratory for culture and sensitivity testing.

In all patients tests for haemoglobin, total and differential white cell count in the peripheral blood, prothrombin time, serum albumin, total serum bilirubin, serum alanine aminotransferase, serum alkaline phosphatase, serum creatinine and fasting blood glucose estimation was done.

On the basis of microscopic examination and culture report of the ascitic fluid, patients included into the study were divided into the following two groups:

1. SBP group

i. ascitic fluid polymorphonuclear cell (PMN) count more than 250 cells/cmm and positive culture-Classical SBP

ii. ascitic fluid PMN count more than 250 cells/cmm but culture negative-Culture Negative Neutrocytic Ascites (CNNA)

iii. ascitic fluid PMN count less than 250 cells/cmm but positive culture-Monomicrobial Non-neutrocytic Bacterial ascites (MNB)

2. Non SBP group

Ascitic fluid PMN count less than 250 cells/cmm and culture negative-Sterile ascites.

Results

The study was conducted from December 1994 to November 1995. A total of 73 patients fulfilled the requirements for inclusion in the study; 34 (46.6%) were males while 39 (53.4%) were females. According to the laid down criteria 24 (32.9%) patients had SBP. Main features of presentation of SBP and non-SBP groups are given in table I. Both the groups were comparable for age and sex. In SBP group jaundice (79.2%), fever (75%), abdominal pain (66.7%) and upper gastrointestinal bleeding (58.3%) were common clinical manifestations. All patients in SBP group had a palpable spleen. Hepatic encephalopathy at presentation was seen in 87.5% patients with SBP and 59.2% patients without SBP ($p < 0.02$). Fever was also documented in 44.9% of patients without SBP. In patients without SBP abdominal tenderness could not be elicited.

Table II presents the biochemical findings in both the groups. Anaemia, raised serum alanine aminotransferase and a prolonged prothrombin time were present in most of the patients in both the groups and the differences between the two groups were not significant. Patients with SBP had a low mean serum albumin and mean ascitic fluid protein concentration but the difference was not statistically significant ($p > 0.5$).

Table III presents subtypes of SBP group. Classical SBP was seen in 8 (33.3%) patients while 16 (66.7%) patients had culture negative neutrocytic ascites (CNNA). No patient of monomicrobial non-neutrocytic bacterial ascites (MNB) was seen in this study.

Table I. Comparative analysis of clinical presentation in patients with and without SBP

	SBP Group (%)	Non-SBP Group (%)
Total patients	24 (32.9)	49 (67.1)
Males	11 (45.8)	23 (46.9)
Females	13 (54.2)	26 (53.1)
Age (in years) -range (mean +/-SD)	14-80 (49.9 +/- 16.4)	13-80 (55.2+/- 13.2)
Fever	18 (75)	22 (44.9)
Jaundice	19 (79.2)	14 (28.6)
Abdominal pain	16 (66.7)	12 (24.5)
Abdominal tenderness	10 (41.7)	0 (0)
Splenomegaly	24 (100)	34 (69.4)
Upper GI bleed	14 (58.3)	24 (49)
Hepatic Encephalopathy	21 (87.5)	29 (59.2)
Diabetes Mellitus	8 (33.3)	4 (8.1)

Table II. Comparative analysis of biochemical findings in patients with and without SBP

Lab. Findings	SBP Group	Non-SBP Group
Haemoglobin g/dl (mean +/- SD)	9.67 +/- 2.3	9.85 +/- 4.7
Leucocytosis (TLC>11x10³/cmm)	13 (54.2%)	14 (28.6%)
Raised ALT (>35u/l)	22 (91.7%)	46 (93.9%)
Raised Serum Creatinine (>1mg/dl)	2 (8.3%)	3 (6.1%)
Prolonged Prothrombin Time	16 (66.7%)	31 (63.3%)
Serum albumin g/l (mean +/- SD)	16.2 +/- 8.4	20.3 +/- 9.7
Mean Ascitic fluid protein concentration g/l (mean +/- SD)	9.7 +/- 4.4	12.5 +/- 6.1

Table III. Subtypes of SBP Group
Total patients : 24 (32.9%)

Classic SBP	8 (33.3%)
CNNA	16(66.7%)
MNB	None

Discussion

Out of the 73 patients with chronic liver disease and ascites who were eligible for inclusion to this study, 24 (32.9%) were found to have spontaneous bacterial peritonitis. Our figure correlates with the reported prevalence of 33% as previously reported from Agha Khan University Hospita(7). This figure reflects a very high prevalence of SBP in patients with chronic liver disease; however our study was hospital based and thus this figure is likely to be an over estimate, as patients with chronic liver disease and complications, including SBP, are more likely to attend the hospitals, and actual prevalence in the community is likely to be much lower.

In our study out of 24 patients with SBP 8 patients (33.3%) had a positive ascitic fluid culture. This low yield was observed inspite of the fact that we inoculated the ascitic fluid in the blood culture bottles at the bedside, a method that is reported to give high yields and upto 90% culture positivity has been reported by using this technique(8). However our figure compares well with 27% culture positive reported by Chowdhry et al(9) and 30% reported by Puri et al(10). Probably the explanation holds true that patients with cirrhosis in our population may have a very low bacterial concentration in ascitic fluid(7).

Sixteen patients had CNNA and if the diagnosis of SBP was made on the basis of a positive culture only, then these cases would have been missed. Cell criteria for the diagnosis of SBP appears to be a better method because it can provide an early diagnosis and thus early anti microbial therapy can be initiated preventing serious complications(11). However importance of ascitic fluid culture cannot be ignored because, apart from giving a definite aetiological diagnosis, it also provides the drug sensitivity pattern of the causative organisms. Recently Ortiz et al, using an automated calorimetric microbial detection system, BacT/ALERT, reported an earlier microbiological diagnosis of SBP than by using conventional blood culture bottles(12).

75% of patients with SBP were febrile as compared to 44.9% of patients from non SBP group. Bruce et al(13) reported fever in 67.5% of their patients with SBP and their figure is comparable to that of ours. Presence of fever in both the groups renders it a non-specific feature. Other than due to infection, patients with cirrhosis may be febrile due to hepatocellular failure(14). A significant number of patients with SBP in our study (25%) were not febrile and this indicates that absence of fever in patients with chronic liver disease does not rule out SBP. Abdominal pain has been reported to be present in 80% of patients with SBP(15) while abdominal tenderness occurs in 51.5%(13). Our figures are 66.7% and 41.7% respectively. Person to person variation on the part of the patients in the perception and tolerance of pain and eliciting the tenderness on the part of the examiners does exist and therefore diversity of results is expected. Although abdominal tenderness was present in less than half the patients with SBP it was a highly specific finding; all patients with tenderness on abdominal palpation had SBP.

Infection anywhere, including SBP, can precipitate hepatic encephalopathy(16) and it is therefore expected that features of hepatic encephalopathy will be more frequent in patients with SBP. In our study 87.5% of patients with SBP were in hepatic encephalopathy compared to 50.2% of patients without SBP; a difference that is statistically significant ($p < 0.02$). Bruce et al reported hepatic encephalopathy in 82% of their patients with SBP(13). Jaundice was observed in 79.2% patients in SBP group and in 28.6% of patients in non-SBP group. Patients with advanced liver cell dysfunction and resultant jaundice are probably more prone to various infections including SBP and SBP itself can cause further deterioration of liver function and deepening of jaundice. Patients with recent upper gastrointestinal haemorrhage are also more prone to develop SBP(17). This is because gastrointestinal bleeding increases translocation of flora to mesenteric lymph nodes and hypovolumaeia due to blood loss impairs the phagocytic activity of the reticuloendothelial system(18). In our study there was no statistically significant difference in both the groups in this regard (58.3% vs 49%).

Opsonic activity of ascitic fluid is proportionate to its protein concentration and that is why patients with low ascitic fluid protein concentration are more prone to develop SBP(5,6). In our study mean ascitic fluid protein concentration was lower in SBP group as compared to that in non-SBP group (0.97+/-0.44 g/dl vs 1.25 +/- 0.61 g/dl) but when analysed statistically, this difference was not significant. Leucocytosis was present in higher proportion of patients with SBP(54.2% vs 28.6%, $p < 0.05$). Diabetes was more often seen in patients

with SBP; increased susceptibility of diabetics to various infections, probably including SBP, may be the likely explanation. Inference on the basis of a single observation cannot be justified but we believe this observation may serve as a good hypothesis for future work.

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Inadequacy of Henderson-Hasselbalch Equation in the Calculation of the Influence of pH on the Renal Excretion of Drugs

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It is commonly described that the influence of pH on weakly acidic and basic drugs can be determined from their degree of ionization or ratio unionized/ionized forms (Ratio U/I) as calculated from the Henderson-Hasselbalch Equation (HHEq). pKa is the limiting factor for the calculation of Ratio U/I from the HHEq when pH remains constant. pKa values and 24 hour urine excretion of many basic drugs in acidic and alkaline urine have been reported in the literature. We calculated ratios acidic/alkaline urine excretion (Ratios Ac/Al) of 10 basic drugs with similar pKa values (8.99 to 9.57). Considering that interpretations according to HHEq are true there should be a good correlation between their pKa values and Ratios Ac/Al. Ratios Ac/Al of these drugs were extremly different from each other (1 to 99) and not related to their pKa values (r = 0.039 and P = 0.915). Therefore it is proposed that HHEq is inadequate in the calculation of the influence of pH on the renal excretion of drugs.

Introduction

It is generally described that most drugs are weak acids or bases that are present in solution as both the nonionized or ionized species. The nonionized molecules are usually lipid soluble and can diffuse across the cell membrane. In contrast, the ionized molecules are usually unable to penetrate the lipid membrane because of low lipid solubility.

The ratio of unionized to ionized drug (Ratio U/I) at each pH can be calculated from the Henderson-Hasselbalch Equation (HHEq) :

$$pH = pKa + \log\frac{B(unionized)}{BH(ionized)} \quad \text{.....(for a weak base) .. (1)}$$

$$pH = pKa - \log\frac{HA(unionized)}{A(ionized)} \quad \text{.....(for a weak acid) .. (2)}$$

An important application of this phenomenon is in the anticipation of the influence of pH on renal excretion of drugs. The basic drugs are ionized in acid urine, become less soluble in lipids, less reabsorbed and readily excreted. They are nonionized in alkaline urine, become more soluble in lipids, better reabsorbed and slowly excreted. Their degree of ionization can be calculated from the HHEq when their pKa is known (1-3).

Equations 1 and 2 indicate that pKa is the limiting factor in the calculation of the degree of ionization when pH remains constant; and that drugs with similar pKa values should be equally influenced by constant changes in the urine pH.

pKa values and the renal excretion of many basic drugs in the acidic and alkaline urine has been studied by many investigators in normal human volunteers and their data is available in the literature.

We selected 10 basic drugs with similar pKa values (8.99 - 9.57) whose 24 hours excretion in acidic and alkaline urine was known (references mentioned in table 1). We calculated their ratios acidic/alkaline urine excretion (Ratio Ac/Al), giving a measure of the influence of pH on their renal excretion. These ratios varied wide apart (from 1 to 99) and were not corresponding to their pKa values.

We then correlated Ratios Ac/Al of these drugs with their pKa values. We did not find any significant relationship.

Methods

1. Ratios Ac/Al of 10 basic drugs were calculated from the amount of drug excreted within 24 hours in acidic (pH range 4.5 - 5.0) and alkaline (pH range 7.5 - 8.0) urine in normal human volunteers from the data available in the literature (references mentioned in table 1).

2. pKa values of these basic drugs were mostly obtained from Katzung(3) or other published sources refered in table 1.
3. Correlation coefficient (r) was determined between their Ratios Ac/Al and pKa values.

Results

24 hours urine excretion and Ratio Ac/Al of 10 basic drugs along with their pKa values are presented in table 1.

The relationship (r) between Ratio Ac/Al and pKa values did not reach statistical significance (r = 0.039 and P = 0.915) (Figure 1).

Table 1. 24 hour acid and alkaline urine excretion, Ratios Ac/Al and pKa values of 10 basic drugs.

S No	Drugs	pKa	Urine Excretion (µgm)		Ratios	Reference No.
			Ac	Al	Ac/Al	
1	Procainamide	9.3	160	146	1.1	6
2	Acebutolol	9.4	91000	91000	1.0	7
3	Practolol	9.5	150	148	1.0	4
4	Flecainide	9.3	123600	19000	6.5	12
5	dl-Fenfluramine	9.57	3407	477	7.1	10, 11
6	Amphetamine	9.7	6841	701	9.8	10, 11
7	Norfenfluramine	9.22	1731	56	30.9	10, 11
8	Methadone	8.99	1786	46	38.8	13
9	Propranolol	9.45	869	12	72.4	4
10	d-fenfluramine	9.57	2377	24	99.0	10, 11

Discussion

Kaye et al(4) studied the renal excretion of practolol and propranolol which have similar pKa values (9.5 & 9.45) and found that urinary excretion of propranolol markedly decreased as pH of urine rose and that of practolol was not affected.

Hicks and Turner(5) studied the buccal absorption (BA) of propranolol, practolol, pindolol and Ro 3-3528 (pKa values 9.45, 9.5, 9.3 and 9.25, respectively) at pH 5.5 - 9.5 and reported that despite similar pKa values their buccal absorption was quite different. BA of propranolol and pindolol was greatly increased (60-80%) as pH increased to 8 and 9; while that of practolol and Ro 3-3528 increased to only 20-30% at these pH levels.

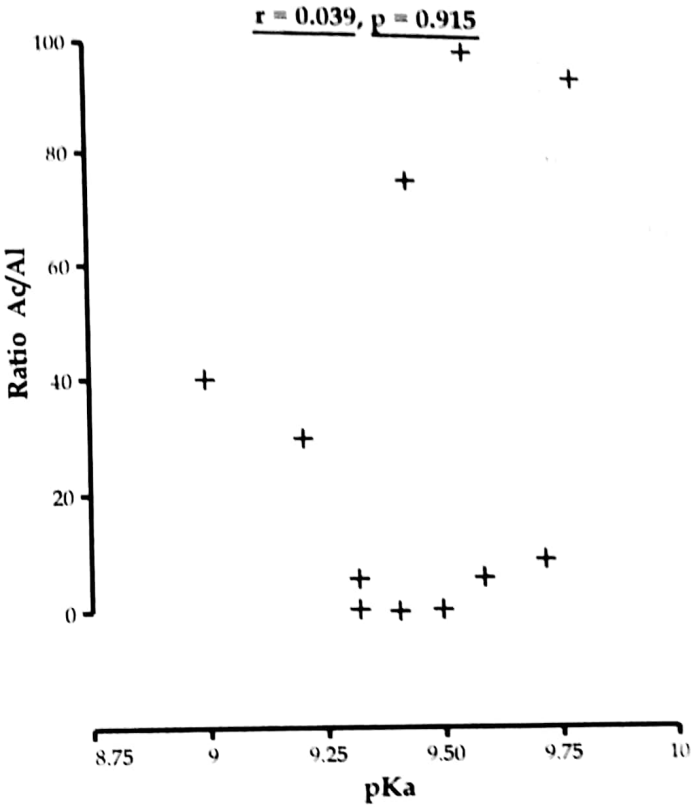

Fig. 1: Correlation Between Ratio Ac/Al Urine Excretion and pKa of 10 Basic Drugs

Meyer et al(6) and Kaye and Long(7) studied the influence of pH on buccal absorption and renal excretion of procainamide (pKa 9.3) and acebutolol (pKa 9.4) and reported that pH did not affect much their buccal absorption and renal excretion.

A careful review of these studies reveals that BA and renal excretion of drugs with similar pKa values are not equally influenced by constant changes in pH; contrary to what is expected from calculations of HHEq. However, pH dependent changes in BA do correspond to those of renal excretion.

Randhawa and Turner(8) have reported an excellent correlation (r - 0.969 and P < 0.001) between pH dependent buccal absorption and the influence of pH on the renal excretion of 18 basic drugs.

Considering non dependence of the influence of pH on the buccal absorption of many basic and acidic drugs on their pKa values Randhawa et al(9) have proposed that Henderson-Hasselbalch Equation is inadequate for the measurement of transmembrane diffusion of drugs.

Table 1 and figure 1 show that drugs with similar pKa values have wide difference in their pH dependent changes in the renal excretion as their

Ratios Ac/Al vary from 1 to 99 and the relationship (r) between their Ratios Ac/Al and pKa values do not reach to a significant value.

Non-dependence of the effect of pH on the renal excretion of drugs on their pKa values indicates that HHEq is inadequate for the calculation of the influence of pH on renal drug excretion.

Conclusion

The Henderson-Hasselbalch Equation is inadequate in the calculations of the influence of pH on the renal excretion of drugs.

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Incidence of Different Streptococcal Serotypes in Clinical Infections and Their Antibiograms

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During a 22 month period 87 isolates of Beta-haemolytic Streptococci were obtained from the clinical material, in which 31 isolates of group A, 25 of group B, 2 each of groups F and G and, 1 of group D were identified; 26 isolates were non-typable. Most of the group A Streptococci were isolated from pus, group B from urine and the non-typable Streptococci were also mostly isolated from urine. Data on serotyping of the isolates is also presented, along with details of the in vitro antibiotic susceptibility of the strains.

Introduction

Streptococci are a heterogenous group of organisms constituting a genus that includes some 20 species of bacteria. Although members of the genus share a significant number of morphologic and physiologic characteristics, they differ widely among themselves in certain biologic properties, especially in their capacity to produce disease in man and other animals.

The clinical manifestations of streptococcal infections are well known. Indeed such infections are among the commonest encountered in clinical medicine world wide.

It has proved difficult to make a logical subdivision of streptococci as a whole, which is essential for the study of epidemiology of the diseases produced. Initially the need was for characters and tests for them, that could be used to predict the behaviour of streptococci of medical or commercial importance, such as those that caused important diseases in man or domestic animals, or those present in scatter cultures in the dairy industry. The first character to prove useful for such classification was revealed when Schottmuller, in 1903, observed that streptococci causing the common pyogenic infections of man induced beta-haemolysis of red blood cells in culture media(1). Instead of classifying streptococci by their cultural and biochemical activities, other workers made use of differences in cellular structure. Lancefield (1933) detected a series of group antigens that made possible the classification of pyogenic streptococci based on antigens, which are cell wall polysaccharides(1).

It is possible that different serotypes and the diseases produced by them vary from place to place and so do their sensitivities to various antibacterial drugs.

Therefore this study was undertaken to determine the frequency and distribution of different Lancefield's groups of streptococci isolated from the clinical material and the types of infections caused by them and their antibiograms.

Materials and Methods

(a) Identification of beta-haemolytic Streptococci

All the specimens submitted to the Bacteriology Laboratory of the Khyber Medical College, Peshawar, were routinely cultured on Blood agar, MacConkey's agar and Chocolate tellurite agar plates. The cultures were examined after 18 hours of incubation at 37°C , all beta-haemolytic streptococcal colonies were picked up identified by standard methods(2), and serologically typed by Strepslide (Cambridge Biomedical Ltd, United Kingdom) by the method recommended by the manufacturers as under:

(b) Serological Typing

With a sterile bacteriological loop at least three colonies of streptococci, to be typed, were picked up from blood agar plate and emulsified in 0.4 ml of extraction enzyme in a tube. The mixture was incubated in a water bath at 37°C for 10 minutes. The tube was shaken vigorously after 5 minutes.

One drop of latex reagent of each type of streptococcus (A, B, C, D, F & G) was dispensed into each appropriatly labelled circle on the test slide. Over each circle one drop of the extract was added with a pasteur pipette. These two drops (latex reagent and extract) were mixed together in each circle with a separate wooden stick. The slide was rocked for one minute and observed for agglutination. Positive controls were used with the tests.

Strong agglutination with any latex reagent was considered to indicate a positive identification of that type.

(c) Antibiotic Sensitivity

Antibiotic sensitivity tests of the different types of streptococci isolated were carried out by paper disc diffusion method on the day of isolation, using Wellcome nutrient agar plates containing 5 percent sheep blood.

The potency of the antibiotic discs used and the break up points used for reading the results were those recommended by National Committee for Clinical Laboratory Standards(3,4). The standards used for some of the newer antibiotics were those described previously(5,6,7,8).

Results

During the period from January 1992 to October 1993, 87 isolates of beta-haemolytic streptococci were obtained and studied for their serological typing and sensitivity to antibiotics.

There were 31 isolates of streptococcus group A (S pyogenes), 25 of group B, 1 of group D and 2 each of groups F and G. There were 26 isolates which were non-typeable. There was no isolate of group C streptococcus (Table 1).

Group A strains were mostly isolated from post-burn infections, wound pus and other types of pus, only two strains were isolated from throat. Group B streptococci were mostly isolated from urine, causing urinary tract infections and these were mostly from females. The two group F streptococcal isolates were from throat. The non-typeable streptococci were mostly isolated from urine and throat (Table 1).

Antibiograms of different streptococci types are given in Tables 2, 3 & 4.

Cefoperaone and Ceftazidime were the drugs most effective against group A streptococci, Clindamycin and Amoxicillin were also very effective.

Cefoperazone and Cefaclor were the drugs most effective against group B streptococci, Clindamycin and Amoxicillin were also very effective.

Against non-typeable streptococcal isolates Erythromycin was the most effective drug, Amoxicillin and Cefoperazone were also very effective.

Table 1. Incidence of different streptococcal types in different specimens.

Specimen	Numbers of each group isolated						
	A	B	C	D	F	G	* N.T.
Pus, post burn	9	0	0	0	0	0	0
Pus, wound	7	3	0	0	0	0	0
Pus, boil, pyoderma, osteomyelitis	7	0	0	0	0	0	1
Throat	2	0	0	0	2	1	7
Sputum	1	1	0	0	0	0	4
Urine	4	21	0	0	0	1	10
Stool	0	0	0	0	0	0	3
Semen	0	0	0	1	0	0	0
Blood	0	0	0	0	0	0	1
H.V.S.	1	0	0	0	0	0	0
Total	31	25	0	1	2	2	26

* Non-typeable

Discussion

Streptococci cause a wider variety of clinical infections than any other genus of the bacteria, which may vary at different places; We observed that urine yielded the greatest numbers of streptococcal isolates. Pus from wound swabs including post-burn infections, boils and osteomyelitis ranked second as a source of these organisms. Throat also yielded a significant proportion of strains, others were isolated from sputum, stool, semen, blood and H.V.S.

Group A (S. pyogenes) was the major streptococcus isolated, and the majority of these were isolated from post-burn infections, there were very few isolates from throat infectio ns, this was a significant finding, as generally pharyngitis and pyoderma both are the commonest manifestations of infections due to group A streptococci(9). This finding was also significant as the late non-suppurative sequelae of group A streptococcal pharyngitis include rheumatic fever and glomerulonephritis, although glomerulonephritis but not rheumatic fever can also result from streptococcal pyoderma(9).

Most of the group B isolates were obtained from urine samples mostly in females, which is highly significant in view of serious nature of streptococcal infections of neonates.

Table 2 : Antibiogram of different streptococcal types to penicillins and cephalosporins.

Streptococcal groups	No. of isolates	Ampicillin	Amoxy-cillin	Cloxacillin	Carbeni-cillin	Cepha-lexin	Cefaclor	cefopera-zone	Cefuro-xime	Ceftazidime
A	31	67.7	83.4	77.4	63.3	61.2	83.8	90.3	80.6	90.3
B	25	80	84	76	72	44	88	88	64	68
D	1	100	100	100	0	0	100	100	0	0
F	2	100	0	0	50	50	100	100	100	50
G	2	100	0	100	100	100	100	100	50	50
Non-typeable	26	61.5	23	50	65.3	50	65.3	84.6	73	57.6

Table 3 : Antibiogram of different streptococcal types to tetracyclines and various other antibiotics.

Strepto-coccal groups	No. of isolates	Tetra-cycline	Oxytetra-cycline	Doxy-cycline	Mino-cycline	Erythro-mycin	Clinda-mycin	Strepto-mycin	Linco-mycin	Kana-mycin	Cotrimo-xazole	Chloram-phenicol
A	31	12.9	25.8	19.3	19.3	74.1	87	6.4	80.6	25.8	6.4	58
B	25	4	24	8	12	64	84	0	32	50	0	60
D	1	0	0	0	100	100	100	0	0	0	0	0
F	2	0	0	0	0	50	50	0	100	50	0	50
G	2	0	0	0	0	0	50	15.3	100	100	0	50
Non-typeable	26	26.9	34.6	38.4	42.3	46.1	69.2	1	53.8	50	19.2	57.6

Table 4 : Antibiogram of different streptococcal types to aminoglycosides and quinolones.

Streptococcal groups	No. of isolates	Gentamicin	Tobramicin	Amikacin	Nalidixic Acid	Norfloxacin	Ofloxacin	Ciprof-loxacin	Enoxacin
A	31	80.6	76.6	28	9.6	45.1	61.2	35.4	22.5
B	25	20	24	11	8	20	28	24	8
D	1	0	0	0	100	0	100	0	0
F	2	50	50	50	0	0	0	50	50
G	2	50	100	0	0	50	50	50	0
Non-typeable	26	92.3	50	34.6	23	26.9	62.5	34.6	34.6

Non-typeable streptococci ranked second in frequency although they probably comprised of heterogenous group of streptococci and the majority of these were isolated from urine and throat. The significance of their isolation from throat is not clear, but these organisms (especially group H and other non-groupable streptococci) are the most frequent etiologic agents of bacterial endocarditis(9).

As was their frequency of isolation from different sites significant, so were their cultural characters and antibiograms.

Group A streptococci though inhibited by 1/4000 potassium tellurite(2), there were two isolates which were able to grow on chocolate tellurite agar which contains 0.03% potassium tellurite.

The streptococci are usually highly sensitive to a wide range of antibacterial drugs including penicillins and cephalosporins and resistance to tetracyclines and quinolones is usually high. Benzyl-penicillin (Penicillin G) is highly effective against group A streptococci. Penicillin G resistant strains of S pyogenes are at present unknown(10), but flucloxacillin ampicillin and cephalosporins are less effective(10), Tetracycline resistance was for several years confined mainly to burn wards, from about 1960, it became prevalent in the general population of the United States, Britain and some other countries, but not every where(11).

In the present study organisms were not tested against Penicillin G, therefore development of

resistance to it amongst group A streptococci is not known, but as in other studies resistant strains to all the other antibiotics were found including the Penicillin group (cloxacillin, ampicillin, carbenicillin and amoxicillin) so much so that about 30% of the isolates were resistant to them.

The best drugs were the newer cephalosporins; cefoperazone, ceftazidime, and cefaclor.

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Antibiotic Susceptibility Pattern of Salmonella Typhi Isolated from Blood Cultures in Rawalpindi

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During routine investigation of blood cultures at Microbiology laboratory, Department of Pathology, Rawalpindi Medical College, Rawalpindi forty strains of *Salmonella typhi* were isolated. The isolates showed sensitivity to ampicillin (41.6%), ampicillin-clavulinic acid (52.8%), doxycycline (29.2%), trimethoprim-sulphamethoxazole (15.5%), gentamicin (80.4%), ceftazidime (80.9%). All of the isolates (100%) were sensitive to ciprofloxacin, ofloxacin & enoxacin. Keeping in view the sensitivity pattern of *S. typhi*, conventional and inexpensive antibiotics like ampicillin, ampicillin-clavulinic acid and trimethoprim-sulphamethoxazole can not be recommended as drugs of choice for treatment of typhoid fever. Therefore one of the quinolones may be used as empirical therapy in men, non-pregnant women and children over 14 years of age; while one of the 3rd generation cephalosporins like ceftazidime may be used in pregnant women and children under 14 years of age.

Introduction

Typhoid fever caused by *Salmonella typhi* is endemic in Pakistan(1). It is very important to diagnose the disease promptly because it is a life threatening illness due to bacteremia(2) alongwith complications like intestinal perforation. Diagnosis of the disease requires isolation of *S. typhi* from blood, bone marrow, faeces and urine of the patients(3). Isolation of the organism from blood is the most reliable of all of these.

The patient responds to treatment by antibiotics but treatment failures do occur due to development of antibiotic resistance. Several reports of resistance acquired by Salmonella species to the commonly used antibiotics have appeared in the literature(4,5). Plasmid-mediated resistance to ampicillin, trimethoprim-suphamethoxazole & chloramphenicol has been reported in an outbreak in Mexico in 1972 involving more than 10,000 cases(6). This type of resistance is more serious as it is transferred more rapidly to other bacteria. Due to injudicious and indiscriminate use of antibiotics even in the hands of medical experts in Pakistan, bacterial resistance is very high; same may be the case with *S. typhi*. In present study, antimicrobial susceptibility of *S. typhi* to various antibiotics was tested to have awareness about empirical therapy of typhoid fever.

Materials and Methods

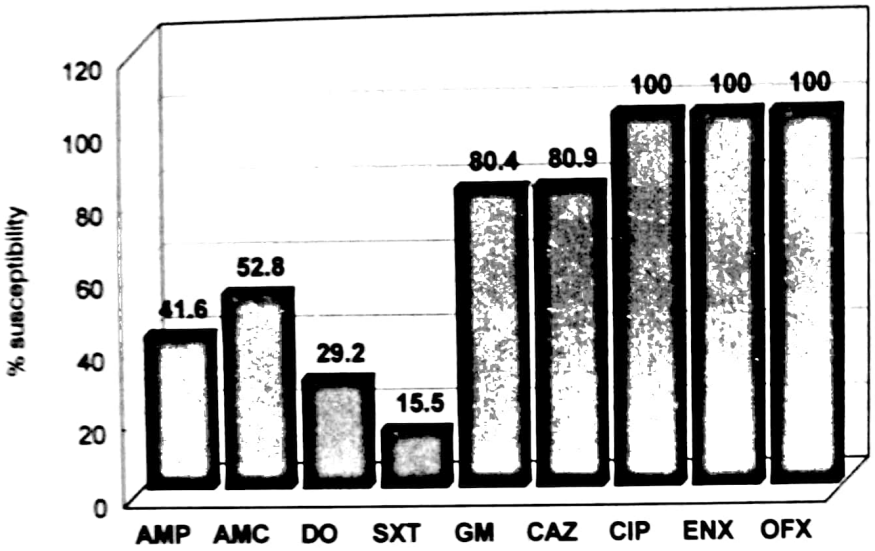
During the years 1995-96, 5-10 ml of patients blood suspected of having bacteraemia was added to 60 ml of Brain Heart Infusion broth and was incubated aerobically at 37°C for 18-24 hours. The broth was subcultured daily onto blood agar and MacConkey agar plates for 7 days before being discarded. Any non-lactose fermenting colonies on MacConkey agar were further identified by gram staining, oxidase test, citrate utilization and reaction on triple sugar iron medium as described by Cheesbrough(7).

Antibiotic susceptibility was determined by Kirby-Bauer disc diffusion method(8) using nutrient agar and discs of standard strength. Sizes of zones of inhibited growth were measured and sensitivity/resistance was interpretted using standard method.

Results

Out of the total 238 blood samples cultured, *Salmonella typhi* could be isolated from 40 samples. Percentage susceptibility patterns of these isolates to various antibiotics is shown in figure 1. All of the isolates were sensitive to all the quinolones tested. The isolates gave sensitivity of 80.4% and 80.9% to gentamicin and ceftazidime; while 41.6% of the isolates were sensitive to ampicillin, 52.8% to ampicillin-clavulinic acid, 29.2% to doxycycline, 15.5% to trimethoprim-sulphamethoxazole.

Fig. 1: Percentage susceptibility of *Salmonella typhi* isolated from blood cultures.



Key : AMP, Ampicillin; AMC, Ampicillin-clavulinic acid; DO, Doxycycline; SXT, Trimethoprim-sulphamethoxazole; GM, Gentamycin; CAZ, Ceftazidime; CIP, Ciprofloxacin; ENX, Enoxacin; OFX, Ofloxacin.

Discussion

Typhoid fever is one of the very important diseases of great concern in Pakistan particularly due to its endemicity and associated complications. Therefore there is need that it should be promptly diagnosed and treated. One very important problem of great concern is increasing resistance of the causative agent to commonly used antibiotics like ampicillin, trimethoprim-sulphamethoxazole and chloramphenical(6,9,10). This observation is being confirmed by present study. However, this study does not correspond with another study conducted at Rawalpindi(11) where majority of the *S. typhi* isolates were sensitive to these antibiotics. This could be due to firstly, that only seven isolates were included in that study and secondly, generally increasing resistance of the microbes to antibiotics(12) as may be the case with *S. typhi*. Corresponding with other studies(9,11), the isolates in our study showed good sensitivity (>80%) to ceftazidime (a 3rd generation cephalosporin) & gentamicin and all the isolates were sensitive to the quinolones tested. Keeping in view the sensitivity pattern of *S. typhi*, conventional and inexpensive antibiotics like ampicillin, trimethoprim-sulphamethoxazole and chloramphenicol can not be recommended as drugs of choice for treatment of typhoid fever. Therefore one of the quinolones may be used as empirical therapy in men, non-pregnant women and children over 14 years of age; while one of the 3rd generation cephalosporins like ceftazidime, ceftriaxone, cefixime may be used in pregnant women and children under 14 years of age where quinolones are not recommended. The same has been suggested in other reports(9,10).

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Study of Renal Function Profile and Insulin Immuno-Assay in Insulin Dependent (IDDM) and Non Insulin Dependent Diabetic (NIDDM) Patients

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In the present study 120 subjects referred to NIH, Islamabad, were grouped into IDDM, NIDDM and normal healthy controls. The parameters studied were blood sugar, urea, creatinine, uric acid, Insulin (by immunoassay) and urine for proteins. NIDDM patients showed significant increase in the levels of urea and creatinine as compared to IDDM and normal control. Uric acid levels were high in our NIDDM females as compared to other two groups. Blood sugar and Insulin levels were high in both types of diabetics but the percentage was high in NIDDM patients. All the parameters tested were high in diabetics as compared to controls. Both the diabetic groups are at risk for developing diabetic nephropathy but our NIDDM patients showed more abnormal results which may be due to the presence of other factors i.e. obesity, hypertension, long duration of disease and poor glycemic control, etc.

Key words : Renal function, Insulin Immunoassay, Insulin Dependant Diabetes Mellitus (IDDM), Non Insulin Dependant Diabetes (NIDDM).

Introduction

Insulin Dependant Diabetes Mellitus (IDDM) is not a benign disease and despite prolonged survival of patients due to insulin therapy, it is associated with a high prevalence of complications that affect the microcirculation of eye, kidneys, nerves and large vessels. Increase in blood pressure accelerates nephropathy in patients with micro as well as macro albuminuria(1). Incidence of nephropathy increases at puberty(2), because at puberty a diabetic patient has a poor metabolic control(3). Once clinical proteinuria is established, it is progressive and is refractory to treatment, It leads, after few years, to renal failure(4) Cardiovascular mortality is much higher in patients with persistent proteinuria than in patients without proteinuria and indicates a possible link between micro and macro-vasculopathy(5). Like IDDM. nephropathy also develops in NIDDM. Microalbuminuria in type I is predictive of clinical proteinuria and increased mortality(6).

Hyperglycemia in the obese NIDDM patients tends to worsen unless there is mitigation of obesity. In NIDDM there is hyperglycemia with hyperinsulinemia which promotes atherosclerosis(7).

Our present study was based on the assessment of renal function profile and insulin immunoassay in the two types of diabetics. The results were interpreted with respect to age, sex, weight, duration of disease and hypertension in the patients studied.

Materials and Methods

One hundred and twenty cases referred from various hospitals of Rawalpindi and Islamabad were included in the study. The subjects were divided as follows:

1. Apparently healthy volunteer controls : This group comprised a total of 38 apparently healthy subject (20 males, 18 females).
2. IDDM patients : In this group 41 cases (21 males & 20 females) with age less than 40 years were included. All these cases were on insulin injections only.
3. NIDDM patients : This group included 41 cases (15 males & 26 females). All of them had developed diabetes after the age of 40 years. They were mostly obese and were on dietry control and/or oral hypoglycemic agents. A brief history regarding age, sex, duration of disease, hypertension, past history, family history, addiction and treatment etc. was noted.

In all the cases, a 10 ml blood sample was drawn from the cubital vein, between 8.30 and 10.00 a.m. The samples were collected at random for detection of blood sugar, urea, creatinine, uric acid and insulin levels. Urine was tested for proteins by

dipstick method. The results of these group were statistically compared by using students 't' test.

Results

As shown in table 1 and 2, both IDDM and NIDDM patients showed significant increase of blood sugar levels as compared to control (p value <0.05). Urea and creatinine were raised in our NIDDM patients as compared to IDDM patients and controls, but our IDDM females also showed levels of creatinine to be on higher side compared to IDDM male patients and controls.

Uric acid levels were on a higher side in our NIDDM females as compared to all other groups. Clinically significant proteinuria was detected in 20% NIDDM patients and 17% IDDM patients. The duration of disease was longer in our NIDDM patients (average: 10 years) as compared to IDDM patients (average: 6 years). The sex ratio of females was high in NIDDM patients. It was equal in IDDM patients. The incidence of hypertension was more in NIDDM patients (n-22) compared to IDDM patients (n-9). The Insulin levels were raised in both groups, but more so in IDDM patients (Table 3).

Table 1: Results of Kidney Function Tests in IDDM and NIDDM Females

Parameters (mg/dl)	Control n=18 Mean	SD	ID n=20 Mean	SD	NID n=26 Mean	SD
Blood sugar	82.39 ±	1.67	280 ±	25.61 *	278 ±	25.9 *
Urea	23.61 ±	1.10	29.9 ±	2.88	37.69 ±	4.57
Creatinine	0.57 ±	0.02	1.05 ±	0.21	1.06 ±	0.12 *
Uric acid	4.98 ±	0.20	5.38 ±	0.32	5.92 ±	0.26

* Students "t" : $p < 0.05$

Table 2: Results of Kidney Function Tests in IDDM and NIDDM Males

Parameters (mg/dl)	Control n=18 Mean	SD	IDDM n=20 Mean	SD	NIDDM n=26 Mean	SD
Blood sugar	84.15 ±	3.1	235.4 ±	27.47 *	208.20 ±	2.82 *
Urea	23.25 ±	1.21	25.43 ±	1.59	32.07 ±	2.82 *
Creatinine	0.87 ±	0.07	0.83 ±	0.04	1.21 ±	0.127
Uric acid	5.77 ±	0.34	5.41 ±	0.37	5.51 ±	0.35

* Students "t" : $p < 0.05$

Table 3: Insulin Levels in IDDM and NIDDM Patients, as Compared to Controls

Group	Insulin Levels (μIU/ml)	
	Males	Females
IDDM	34 - 406	30 - 349
NIDDM	18 - 168	18 - 201
Control	10 - 39	12 - 27

Fasting normal range 0 -30 μIU/ml

Discussion

In the clinical course of IDDM, 40% of patients develop nephropathy which is the main cause of morbidity and mortality(8). Other important factors are poor glycemic control, hypertension, long duration of disease and smoking etc(1). In our case nephropathy was present in 17% of IDDM patients as judged by clinical proteinuria. Blood urea and creatinine levels were not significantly elevated in males when compared to normal control. In females the creatinine levels were slightly elevated compared to IDDM males and controls but other parameters of kidney functions were not significantly different from IDDM males and controls. The reason for a relatively normal kidney function profile in our IDDM patients was probably short clinical course of disease i.e. an average of 6 years.

Like IDDM patients, NIDDM cases also have a tendency to develop renal complications(6). In our cases, nephropathy was present in 20% of NIDDM patients as detected by clinical proteinuria. Comparing with IDDM patients and controls, significant increase in urea level was observed in our NIDDM patients ($p < 0.05$). Our NIDDM males again showed significant increase in creatinine levels ($p < 0.05$) compared to IDDM male patients and controls. Creatinine levels were also on higher side in our NIDDM patients, and a significantly elevated level was observed in our NIDDM male patients ($p < 0.05$) as compared to IDDM males and control. Uric acid was raised in our NIDDM female patients compared to control and IDDM female patients. Blood sugar was significantly raised in both the diabetic groups indicating poor glycemic control.

Thus, in the present study a greater impairment of renal functions was observed in NIDDM patients; this observation may be correlated to the presence of certain additional factors in our NIDDM patients, i.e., a long duration of disease (10

years), hypertension, obesity, etc., Beard et al have shown that raised levels of uric acid can accompany obesity(9). Similarly, Herman et al showed that impaired glucose tolerance can accompany elevated uric acid levels(10). This finding is in accordance with our study, because our female NIDDM cases were also obese, hyperglycemic and hypertensive.

Insulin levels were raised in both the diabetic groups. In IDDM patients, exogenous insulin injections might have lead to the formation of antibodies preventing early clearance of insulin from blood. The finding of hyperinsulinemia in our NIDDM patients may be correlated to endogenous insulin secretion caused by oral hypoglycemics and also to obesity causing insulin resistance/ hyperinsulinemia(11&12). It has been proposed that insulin may play a role in atherogenesis and thus also in hypertension, which can hasten the renal impairment especially in the presence of poor glycemic control(7,12-15).

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Prevalence of β - Thalassemia Trait in and Around Islamabad

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β-Thalassemia is prevalent in Pakistan as reported in some studies carried out at Rawalpindi, Lahore and Karachi. We have carried out a study for the detection of prevalence rate of β-thalassemia trait in and around Islamabad. For that, we randomly selected 1,000 individuals who presented for complete blood counts at clinical pathology laboratory of Federal Government Services Hospital, Islamabad. The Discrimination Factor (DF = MCV - RBC - 5Hb - 3.4) was below zero in 37, and between zero and +5 in 8 cases. HbF estimation, Hb electrophoresis and HbA2 estimation were performed in all the 45 cases who had DF below +5. Our diagnostic criteria for β-thalassemia was HbA2 level above 4.0%. The prevalence rate of β-thalassemia trait thus estimated was 3.9% amongst the population studied.

Introduction

β-Thalassemia is an autosomal recessive disorder of haemoglobin synthesis, manifested clinically as microcytic hypochromic haemolytic anaemia(1). It is characterized by absence or depression of synthesis of β globin chains of haemoglobin molecule. The homozygous β-thalassemia (Thalassemia Major) is characterized by a severe haemolytic disease, whereas in heterozygous state (Thalassemia Trait) the affected individuals are almost normal, and manifest only mild microcytosis and hypochromia(2). It has been estimated that about 3% of world population or 150 million people carry a β-thalassemia gene(3).

The diagnosis of β-thalassemia trait is achieved after performing HbA2 estimation by haemoglobin electrophoresis(4) or by column chromatography(5). The cut-off value of HbA2 for establishing β-thalassemia trait in an individual is taken as 4%. One of the persistent haematological features in β-thalassemia carriers is reduction of Mean Corpuscular Volume (MCV) to below the lower limit of normal. This parameter, along with red cell count and haemoglobin level, is now commonly measured directly on automated electronic haematology counters.

England et al proposed a formula for calculation of Discrimination Factor (DF) which distinguishes between β-thalassemia trait and iron deficiency(6):

$$DF = MCV - RBC - (5 \times Hb) - K,$$

where K = 3.4, if haematocrit is corrected for plasma trapping.

In β-thalassemia trait DF is a negative value, i.e. below zero, whereas in iron deficiency it is a positive value. It has been suggested that DF has a useful purpose in screening populations, even if they are likely to have mild iron deficiency(7).

A ratio between microcytosis and hypochromia (M/H ratio), as evaluated by laser based optical assembly of haematology autoanalyzers, can also be used to differentiate between β-thalassemia trait and iron deficiency(8). Similarly, a ratio between MCV and RBC count (MCV/RBC) can also help in such a differentiation(9).

In the present study we have estimated the prevalence of β-thalassemia trait in subjects who were referred to the clinical laboratory of Federal Government Services Hospital, Islamabad, from outpatient departments for complete blood counts. For this purpose, we used the Discrimination Factor as proposed by England et al(6) and then confirmed the presence of β-thalassemia by performing HbA2 estimation using elution technique after performing Hb electrophoresis on cellulose acetate paper.

Materials and Methods

a. SELECTION OF CASES: This study was undertaken in 1,000 cases who were referred from outpatient departments to clinical laboratory of

Federal Government Services Hospital, Islamabad, for complete blood counts. On three days in a week (i.e., Saturdays, Mondays and Wednesdays) all such cases who presented between 9:00 am and 1:00 pm were included.

b. SAMPLE COLLECTION: About 5.0 ml of blood sample was obtained by a clean venepuncture, and was transferred to an EDTA containing vial. The sample was mixed gently and thoroughly.

c. LABORATORY INVESTIGATIONS:

1. All the selected individuals were subjected to following investigations on a fully automated haematology analyzer (Sysmex 1,000) : haemoglobin estimation, packed cell volume-PCV, red cell count, mean corpuscular volume-MCV, mean corpuscular haemoglobin-MCH, mean corpuscular haemoglobin concentration-MCHC, total leucocyte count-TLC and platelet count. The analyzer was calibrated on daily basis, and normal and abnormal controls were run with each batch of tests. The laboratory data thus obtained in every case was subjected to the following equation(6):

   Discrimination Factor (DF) =

   = MCV - RBC - (5 x Hb) - 3.4

2. Blood samples from cases who had values of below +5 were subjected to confirmatory tests of β-thalassemia trait. For this purpose, haemolysate was prepared after washing the cells in physiological saline, treating them with distilled water and carbon tetrachloride, and then centrifuging for about 15 minutes. This haemolysate was used for the following tests:

   i. Haemoglobin estimation by Betke's method(10).

   ii. Hb electrophoresis on cellulose acetate paper, at pH 8.6, using Tris-EDTA-Borate buffer. For every electrophoresis batch, a control of HbA, F, D, and A2 was run. The electrophoretic pattern thus obtained was visually interpreted.

   iii. HbA2 estimation was carried out by elution method(5)

d. DIAGNOSTIC CRITERIA: The cases who were found to have an HbA2 level above 4.0%, were labelled as having β-thalassemia trait.

Results

In the present study, 1,000 randomly selected individuals who presented at clinical laboratory of Federal Government Services Hospital (FGSH), Islamabad for complete blood counts were included. Amongst these individuals, the DF less than +5 was observed in 45, and below zero in 37 cases, respectively. Therefore, according to the protocol of this study, all the 45 cases showing a DF < +5 were subjected to the confirmatory test for β-thalassemia trait. Haemoglobin A2 level above 4.0% was observed in 39 cases; 37 of them had DF below zero, and two between zero and +2. (None of the five cases who showed DF between +2 and +5 had an HbA2 level more than +4.0%). Therefore, the prevalence of β-thalassemia trait amongst the investigated individuals was 3.9%.

The ranges and mean ± SD values of haemoglobin levels, red cell counts, packed cell volumes, mean corpuscular volumes, mean corpuscular haemoglobin concentrations, white cell counts and platelet counts are elaborated in table 1. Figure 1 show the distribution of DF values in all the cases who had a DF below +5, including 39 cases of confirmed β-thalassemia trait. Table 2 shows levels of HbF and HbA2 in these cases.

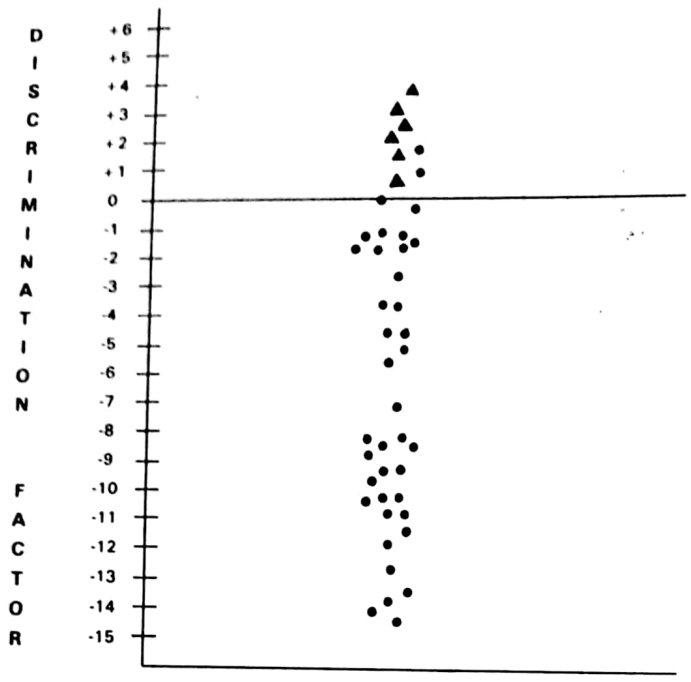
Table 1. Ranges and Mean ± SD Values of Various Haematological Parameters in 39 Established Cases of β-Thalassemia.

Parameters	Range	Mean ± SD
Haemoglobin (G/dl)	9.7-14.4	12.2 ± 1.47
RBC Count ($x10^{12}$/l)	5.05-7.19	5.74 ± 0.47
PCV (l/l)	30.5-52.3	39.1 ± 4.48
MCV (fl)	60.4-74.9	66.2 ± 5.53
MCH (pG)	17.7-24.6	22.0 ± 1.95
MCHC (G/DL)	22.8-32.3	30.5 ± 1.93
White Cell Count ($x10^9$/l)	4.6-13.4	9.5 ± 3.1
Platelet Count ($x10^9$/l)	221-435	294 ± 37.5

Table 2. Values of HbF and HbA2 in Cases of β-Thalassemia Trait

Parameters	Range	Mean ± SD
HbF (%)	2.2 - 6.3	4.15 ± 1.01
HbA2 (%)	4.5 - 7.1	5.6 ± 1.61

Fig. 1: Cases showing Discrimination Factor (DF) less than +5



- DF in established cases of β-Thalassemia trait (HbA2 > 4.0%)
- ▲ DF in cases not established as β-Thalassemia trait (HbA2 < 4.0%)

Discussion

A number of epidemiological studies regarding β-thalassemia trait have been carried out previously in different areas of Pakistan, on various types of population groups. Stern et al in 1968 detected five cases of β-thalassemia trait (4%) amongst 129 Pathan subjects(11). Farzana et al performed HbF and HbA2 estimation in blood samples of 400 professional blood donors and 210 hospital staff members in Karachi(12). The criteria for diagnosis of β-thalassemia trait in this study was an HbA2 level above 3.4%, thereby leading to an incidence of β-thalassemia trait as 3.5% amongst blood donors and 0.96% amongst hospital staff members. In two more reports published in 1976, the incidence of β-thalassemia trait in Karachi population was 1.5%, as compared to 4.0% in Pathans residing there(13&14). Latif(15) reported a series of 437 anaemic patients from Lahore; 9.61 of his cases had β-thalassemia trait. Saleem et al studied 1,187 anaemic patients from northern areas of Pakistan; they diagnosed 5.8% of them as having β-thalassemia trait(16). Hameed et al reported an incidence of β-Thalassemia trait as 1.6% among 300 apparently healthy subjects studied in Lahore(17). Khattak et al(18) reported a series, in which they screened 500 apparently healthy adults from northern areas of Punjab and NWFP, for the prevalence of heterozygous β-thalassemia. They detected trait in all ethnic groups, with an overall prevalence rate of 5.4%. They also observed that Pathans had signifantly higher ($p < 0.02$) prevalence rate (7.96%) as compared to Punjabis (3.26%). Sheikh et al conducted a study on 12,250 consecutive subjects who presented for complete blood counts at Agha Khan University Hospital, Karachi(19). They calculated the discrimination factor (DF) as proposed by England and Fraser(6). According to this report, the prevalence of β-thalassemia trait in the studied population at Karachi was 3.4%.

England et al have suggested that DF has a useful purpose in screening populations, even if they are likely to have mild iron deficiency, as this formula can identify correctly 99% of thalassemia minor cases(6). However, Saleem et al (20) observed that if cut-off value of DF is taken as zero, then the specificity and sensitivity of diagnosis of β-thalassemia trait were 84.1% and 86.5%, respectively. Therefore, while planning the present study, we presumed that if DF alone is applied for the study of prevalence of β-thalassemia in a population, there would be at least a possibility of missing some cases, in which the DF values would fall as positive values near zero.

The present study was conducted on 1,000 randomly selected cases who presented for complete blood counts. We calculated DF in all these cases, and screened out all of them who showed the DF as a negative value or a value between zero and +5. Then we performed Hb electrophoresis and HbA2 estimation in these screened cases. The diagnosis of β-thalassemia trait was thus established by an electrophoretic evidence (i.e., HbA2 level above 4.0%).

In a total of 1,000 cases studied in this series, DF was below +5 in 45 cases, and below zero in 37 cases. β-thalassemia was established electrophoretically in a total of 39 cases (i.e., all the 37 cases who had a DF value below zero and two more subjects in whom the DF was between zero and +2). Therefore, the prevalence of β-thalassemia trait amongst 1,000 subjects who presented at FGSH, was 3.9%. This value is close to some of the previous comparable studies (12, 18, and 19). We feel that DF is a suitable approach in screening populations for the prevalence of β-thalassemia trait and the borderline cases (with DF between zero and +5) can be confirmed by performing HbA2 estimation. It is proposed that

similar studies should be undertaken in different parts of the country in order to exactly evaluate the magnitude of this problem at national level.

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Bone Marrow Fibrosis in Acute Leukemias

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Bone Marrow Fibrosis (BMF) is a frequent finding in leukemias. In this study we have presented the frequency and pattern of BMF in 32 cases of acute leukemias including 18 acute lymphoblastic (ALL) and 14 acute myeloid leukemia (AML) cases. A variable degree of fibrosis was observed in 78.2% of patients. It was more common in ALL (83.3%) as compared to AML (71.4%). Grading of BMF in ALL showed grade 1 in 27.8%, grade 2 in 16.6%, grade 3 in 33.3% and grade 4 in 5.6% of cases. In cases of AML, grade 1 was observed in 21.4%, grade 2 in 35.7%, grade 3 in 14.3% and grade 4 in none of the patients. The grading was done according to the system adopted at Armed Forces Institute of Pathology, Rawalpindi.

Introduction

Leukemias are a heterogeneous group of malignant neoplasia arising from the bone marrow. They are characterized by malignant proliferation of marrow cells, presence of immature cells in the peripheral blood and features of bone marrow failure. Along with these features, a variable degree of bone marrow fibrosis can be detected on trephine biopsy. Whereas the degree of fibrosis is variable in various types of leukemias, it is the most profound in chronic myeloid leukemia and AML-M7(1,2,3). MacCarthy has enlisted a number of conditions responsible for secondary BMF, and included ALL as well as AML in the list of malignant conditions associated with myelofibrosis(4).

BMF is a generic term used to describe fibrotic changes, which may lead to bone marrow failure. For evaluation of a patient with BMF, in addition to trephine biopsy, a careful history, a detailed clinical examination, routine haematological profile, biochemical tests and radiological investigations play an important role(5). Over the years, a semi-quantitative evaluation of fibrous tissue content (FTC) in marrow fibrosis has attracted a great deal of attention from a large number of workers(2,6,7-9).

Kundel et al studied reticulin fibrosis in patients of ALL using H & E stain, modified Hortiga-Foot stain and Mason connective tissue stain for routine, reticulin and collagen evaluation(10). They graded the amount of reticulin in the bone marrow as follows: Trace or Normal (occasional reticulin fibers); 1+ (slight increase in reticulin); 2+ (moderate increase in reticulin); 3+ (marked increase in reticulin), and 4+ (as in 3+, along with presence of collagen).

Manorahen et al(9) studied marrow reticulin content by trephine biopsy in adult acute leukemia patients, at presentation and subsequently during the course of their illness. They observed reduction in FTC with effective treatment and also noticed an increase in reticulin content upon relapse. Manorahen and other workers have used variable grading systems for semi-quantitative assessment of FTC in various disorders(3,8,9,11).

In the present study, we have determined the frequency and pattern of BMF in patients of ALL and AML. For the semi-quantitative assessment of FTC, we have used a slightly different criteria than the previous studies, as mentioned in the end of materials and methods.

Materials and Methods

A total of 160 cases of various haematological disorders were studied for BMF at Armed Forces Institute of Pathology (AFIP), Rawalpindi over a period on one year extending from November, 1988 to October, 1989. Findings of 32 of these patients who had acute leukemias (18 ALL and 14 AML cases) are being presented in this paper.

History and Clinical Examination: All the patients were interviewed, and information was recorded in a proforma, with emphasis on age, sex, fever, general weakness, loss of weight and appetite, haemorrhagic manifestations and symptoms due to infection. A thorough systemic examination was carried out with particular attention to visceromegaly and lymphadenopathy.

Laboratory Investigations were carried out as follows:

a. Peripheral Blood examination: About 03 ml of venous blood was obtained in EDTA container. Following tests were performed:

a: Haemoglobin estimation, total leucocyte count, total red cell count, haematocrit and absolute values on a coulter counter, model S-7.
b: Differential leucocyte count, after staining blood smears with Leishman's stain(12).
c: Platelet count by visual method(12).
d: Reticulocyte count(12)

b. Bone marrow aspiration was performed, after injecting 2% lignocaine with adrenalin, from posterior superior iliac spine with the help of Saleh aspiration needle. The smears were stained by Leishman's stain. Cytochemical stains, i.e., PAS, Sudan Black, acid phosphatase and esterase stains(12), were performed according to requirements.

c. Bone marrow trephine biopsy was also performed, using Islam biopsy needle. Impression imprints were prepared on slides and the biopsy was fixed in 10% buffered formal-saline. After decalcification in 3% HNO_3, the specimens were dehydrated through ascending grades of alcohol, cleared in xylene, and embedded in paraffin wax. Blocks were prepared and thin (3-5 micron) sections were cut. The trephine sections were stained with H & E stain, Gomori's reticulin stain and Van Giesen's stain for reticulin fibers.

Measurement of Fibrous Tissue Content: Bone marrow trephine sections were evaluated semi-quantitatively for fibrosis, according to the following grading system, adopted at AFIP:

No Fibrosis (Normal): Small amount of fine argyrophilic fibers seen around blood vessels and alongside bony trabeculae.

Grade 1: Focal network of fine argyrophilic fibers away from normal sites (Total involved area upto 25%).

Grade 2: Diffuse network of argyrophilic fibres involving >25%, but upto 50% of marrow space. Occasional coarse fibers were also present.

Grade 3: Diffuse network of both fine and coarse argyrophilic fibers involving >50%, but upto 75% of marrow space.

Grade 4: Diffuse network of mostly thick argyrophilic fibers involving more than 75% of marrow space. Collagen was also demonstrable.

Results

As shown in table 1, age of patients of ALL ranged from 5-44 years, with a mean age of 18 years. In cases of AML, age ranged from 18 to 70 years, with a mean of 40 years. The relatively younger patients, especially in ALL group, could not be included, as in these cases trephine biopsy was inconvenient. Majority of patients were males, with a male: female ratio of 8:1 in ALL and 6:1 in AML group.

Common clinical & laboratory manifestation in both ALL and AML patients were pallor, hepatomegaly, splenomegaly, Hb level <10.0 G/dl, neutropenia, and thrombocytopenia. Lymphadenopathy was very frequent in ALL, but relatively uncommon in AML cases.

The pattern on FTC and BMF in all 32 cases of ALL and AML is presented in table II.

Table 1. Common Clinical and Laboratory Manifestations In Cases Of ALL And AML.

Parameters		ALL	AML
Age (Yrs)	Range	5-44	18-70
	Mean	18	40
Sex	Male: Female Ratio	8:1	6:1
Pallor		93%	80%
Hepatomegaly		60%	70%
Splenomegaly		86%	30%
Lymphadenopathy		73%	10%
Haemoglobin <10.0 G/dl		80%	10%
Neutropenia		73%	50%
Thrombocytopenia		86%	90%

Table 2. The Pattern Of Fibrous Tissue Content (FTC) And Bone Marrow Fibrosis (BMF) In ALL and AML Cases.

Pattern	ALL (18 Cases)		AML (14 Cases)	
	Number	%	Number	%
Normal FTC	03	16.6	04	28.6
Grade 1 BMF	05	27.8	03	21.4
Grade 2 BMF	03	16.6	05	35.7
Grade 3 BMF	06	33.3	02	14.3
Grade 4 BMF	01	5.6	-	-

Discussion

Bone marrow fibrosis is characterized by proliferation of fibroblastic cells, thereby leading to an increase in marrow fibrous tissue content. It accompanies many haematological conditions, including bone marrow malignancies. In the present

study, the FTC in biopsied marrows of acute leukemia patients was observed. Reticulin was the connective tissue fibre selected for semi-quantitative evaluation. The grading of BMF thus performed showed variable results in ALL and AML patients.

Amongst 18 cases of acute lymphoblastic leukemia, the distribution of FTC was: Normal=3, Grade 1=5, Grade 2=3, Grade 3=6, Grade 4=1. Amaki et al (7) studied 17 such biopsies, which yielded the results as: Type-1 (Normal)=Nil, Type-2=9, Type-3=7, Type-4=1. Manoharan et al studied 12 patients of ALL and described the results of FTC as: Normal=3, 1+=2, 2+=1, 3+=2, and 4+=4. The results of the present series are close to the other two studies, except for higher incidence of grade 4 fibrosis (Collagen +ve) in the study by Manoharan et al(9).

In 14 cases of acute myeloid leukemia, the pattern of FTC was observed as follows: Normal=4, Grade 1=3, Grade 2=5, Grade 3=2, Grade 4=Nil. Amaki et al studied 43 biopsies from 18 patients of AML and presented the results as: Type-1 (Normal)=6, Type-2=23, Type 3=14, Type 4=Nil. Manoharan et al reported their results on 32 biopsies from patients of AML as: Normal=9, 1+=9, 2+=10, 3+=1, 4+=3.

In the present study, we observed that extentsive fibrosis was more frequent in ALL (grade 3&4=39.9%) in comparison to AML (grade 3&4 only 14.3%).

It was, however, interesting to observe that clinically assessed bone marrow function (on the basis of number of granulocytes, haemoglobin level, platelet count, and reticulocyte count in the blood) was more affected in ALL (Hb<10 G/dl - 80%, Neutropenia in 73% cases) as compared to AML (Hb<10 G/dl in only 10% and Neutropenia in 50%). Platelet counts were almost equally affected in ALL and AML.

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Prevalence and Intensity of Haemophagocytosis in Haematological and Non-Haematological Conditions

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Histiocytic hyperplasia with haemophagocytosis is seen in a wide variety of haematological and non-haematological conditions. In the present study, a total of 1,710 consecutive bone marrow aspirates were examined, and a variable degree of haemophagocytosis was observed in 130 cases (7.6%). The number of cases showing haemophagocytosis in different conditions was as follows: neoplastic haematological disorders - 45 cases (34.6%); non-neoplastic haematological conditions - 43 cases (33.3%); non haematological malignancies - 4 cases (03%); infections - 20 cases (15.3%); autoimmune disorders - 2 cases (1.5%); storage disorders - 3 cases (2.0%) and miscellaneous disorders - 13 cases (10%). Most of the cases (53.07%) showed mild (grade I) degree of haemophagocytosis. Only 8.46% had severe degree (grade III) of haemophagocytosis. Cases showing severe degree of intensity were mostly associated with infection (viral, bacterial as well as parasitic). The severity of haemophagocytosis had a profound effect on clinical features and haematological parameters, particularly on haemoglobin levels and platelet counts.

Introduction

Phagocytosis of all blood cells, mature and developing, by activated histiocytes of reticuloendothelial system is known as haemophagocytosis. It has been reported in the literature under various diagnostic terms, including familial haemophagocytic reticulosis, familial erythrophagocytic lymphohistiocytosis, histiocytic medullary reticulosis, malignant histiocytosis and infection associated haemophagocytic syndrome(1). It may result from an immunologic activation of the mononuclear phagocyte system or may be due to a neoplastic proliferation of histiocytes(2). A syndrome of exaggerated histiocytic proliferation and activation characterized by fever, pancytopania, organomegaly, haemolysis, jaundice and coagulopathy, has been defined(3). It is usually associated with systemic viral infection, and uncommonly with bacterial, fungal and protozoal infections. In the past, the vast majority of cases of histiocytic hyperplasia with haemophagocytosis were grouped under the designation of histiocytic medullary reticulosis or malignant histiocytosis and were invariably thought to represent a malignant disorder. Recent studies have demonstrated that a similar phenomenon may develop in association with a variety of non-neoplastic conditions(4). Haemophagocytosis in such instances represents a reactive, secondary phenomenon that will regress with appropriate therapy directed against the underlying process. It thus may be broadly divided into two groups; reactive (secondary) and malignant histiocytosis(4).

The exact pathogenesis underlying various histiocytic disorders resulting in prominent haemophagocytosis is not full understood. In infection associated hamophagocytosis it is possible that macrophages may be reacting to a foreign antigen adsorbed onto the formed elements, including erythrocyte(5).

An alternative explanation is, that exaggerated hamophagocytosis might be secondary to excessive lymphokine production by normal or neoplastic T-lymphocytes. Such a lymphokine has been isolated from CD4 positive T-lymphocytes(6). This lymphokine can stimulate the differentiation and phagocytosis of IgG-coated red blood cells. It is hypothesized that in certain clinical situations, particularly in association with defective T-cell function, there exists a state of abnormal immune regulations. A precipitating event, such as an infection, results in marked stimulation of the immune system. T-cells become activated and elaborate a lymphokine termed as phagocytosis inducing factor (PIF). The excessive lymphokine production continues unchecked with marked stimulation of mononuclear phagocytes and the development of haemophagocytic syndrome(6).

Material and Method

In this study 1710 consecutive bone marrow aspirates, performed at the department of

Haematology of AFIP, Rawalpindi were looked into for the presence of haemophagocytosis. In all cases where it was observed, the patients were called back for further investigations. The patients were interviewed and thorough physical examination was performed. In addition to bone marrow aspiration, complete blood counts, reticulocyte count, RBC morphology and trephine biopsy were performed in all the cases.

In the light of history, physical findings and findings in blood and bone marrow one or more of the following investigations were carried out to determine the aetiology: Viral screening, widal test, liver function tests, coagulation profile, test for LE cells, anti nuclear factor, and bone marrow culture for microbes.

Bone marrow aspiration slides (Leishman stained) were systematically examined, under low power as well as under oil immessian lens, for following parameters : Cellularity of bone marrow, Cellularity and maturation of erythropoiesis, Cellularity and maturation of myelopoiesis, Megakaryocytes: number and maturity, Lymphocytes, Plasma cells, Abnormal cells, Histiocytes/ marcophages and haemophagocytosis and parasites.

Grading of intensity of haemophagocytosis was done on bone marrow aspiration smears. The slides were mounted and scanned under low power (x10) in at least 10 random fields for presence or absence of haemophagocytosis. Slides were then scanned and examined under high power (high dry x 40) to confirm the presence of haemophagocytosis.

If haemophagocytosis was seen, it was graded in the following manner. The number of haemphegocytic cells were counted in 10 random fields and average of such cells per high power field was calculated. Following criteria was used to grade the intensity.

Grading	No. of Haemophagocytic cell / HPF
Grade I (Mild)	1-3
Grade II (Moderate)	4-6
Grade III (Severe)	7-10
Grade IV (Very Severe)	>10

Results

A total of 1,710 patients were subjected to bone marrow examination. A variable degree of haemophagocytosis was observed in 130 (7.6%) of cases.

Age and Sex Distribution: The age of patients ranged from 08 months to 72 years (mean age 27 years). Male to female ratio was 2.1:1

Symptoms: Fever (38.5%) was the most common symptom at the time of presentation. It was followed by bleeding manifestations (19.2%), generalized weakness (15.4%), diarrhoea (10.8) and night sweats (7.7%), respectively.

Physical Signs: Most of the patients (66%) had pallor at the time of presentation. Liver was palpable in (30.8%) of patients. Splenomagaly lymphadenopathy, jaundice, bruises and purpuric spots were other important physical findings observed in our patients.

Haematological parameters have been shown in table 1. 12.3% of patients were thus anaemic Hb<12.0 G/dl. 15.4% cases had a white cell count less than $4x10^9/l$. 36.9% of patients had platelet count below $150x10^9/l$, while 15.4% had platelet count above $400x10^9/l$.

Intensity of Haemophagocytosis (table 2). Out of 130 cases, 69 (53.1%) patients showed mild or grade 1 haemophagocytosis. Moderate or grade 2 haemophagocytosis was observed in 50 (38.5%) patients, while in 11 (8.4%) patients the haemophagocytosis was severe or of grade 3.

Aetiological Factors : As shown in table 3, neoplastic haematological conditions constituted the largest group (34.6%). The next largest group was of cases with non-neoplastic haematological conditions (33.3%). Infection associated conditions showing reactive haemophagocytic histiocytosis were recorded in 15.4% of cases. Most of our patients belonged to reactive (benign) haemophagocytosis group (99.2%). Only one case was that of malignant histiocytosis (0.8%).

Table 1 : Haematological Parameters In 130 Cases Showing Haemophagocytosis

Parameters	Range	Mean	<Normal	>Normal
Haemoglobin (G/dl)	1.9-17	9.8	125 (96.1%)	0
Total leukocyte counts (x10⁹/l)	0.78-196.2	12.5	20 (15.4%)	45 (34.6%)
Platelet counts (x10⁹/l)	9.865	225	48 (36.9%)	20 (15.4%)

Table 2 : Intensity of Haemophagocytosis in 130 Cases

Intensity	Grade	Numbers	Percent
Mild	I	69	53.1
Moderate	II	50	38.5
Severe	III	11	8.4
Very Severe	IV	0	0

Discussion

The histiocytic haemophagocytic disorders have been classified into malignant and benign reactive types(7,8). The clinical manifestations of these disorders show a considerable overlap with distinctive features (9).

The malignant syndromes related to Rappaport's malignant histiocytosis are characterized by atypical cells with pleomorphic nuclei, large irregular nucleoli, numerous mitotic figures, isolated phagocytosis, tumor mass formation and loss of immunohistochemically detectable lysozyme in poorly differentiated neoplastic histiocytes(10). The benign histiocytic hamophagocytic syndrome was identified by Risdall et al in 1979 as a virus associated reactive histiocytic proliferation in immunosuppressed patients, as a different entity from malignant histiocytsis. The macrophages found in these cases showed a mature, cytologically benign appearance with a striking phagocytic activity. The architecture of the involved organ was usually preserved(3). The benign reactive character of the histiocytic proliferation in all these cases was suggested by the bland appearance of the cells and their transitory coarse in several cases(11).

The main etiologic agents involved in the reactive hamophagocytic syndrome are several viruses, including herpes, simplex, varicella-zoster, Epstein-Barr's, cytomegalo-virus, adenovirus, parainfluenza, and rubella virus(12). There are also several reports on hamophagocytic histiocytosis, associated with non-viral infections including tuberculosis(13), leishmaniasis(14), fungi, and gram positive and gram negative bacteria(1). Some other conditions associated with a generalized histiocytic proliferation are familial hamophagocytic lymphohistiocytosis, breast carcinoma(15) gastric carcinoma(16), Hodgkin's disease, and acute as well as chronic leukaemias(2).

Although there are many case reports on existence of hamophagocytosis in various benign and malignant disorders, the literature is scanty on its correlation with bone marrow function. Haemophagocytosis is not an infrequent finding in bone marrow smears. In our study we found a variable degree of this feature in 130 (7.6%) cases out of 1,710 bone marrow biopsies. Most of our cases belonged to benign (reactive) haemophagocytic histiocytosis group (99.2%); malignant histiocytosis was a rare entity and was encountered only in one case.

In our study three most important clinical conditions showing haemophagocytosis, in order of frequency were neoplastic haematological conditions (34.6%), non-neoplastic haematological conditions (33.3%) and infections, autoimmune disorders, certain chronic disorder and non-haematological malignancies.

Among neoplastic haematological conditions Hodgkin's disease constituted the largest group (40%). Other important disorders in this group included Non-Hodgkin's Lymphoma (26.6%) and acute leukaemias (11%). In case of Hodgkin's disease, all the patients showed either grade 1 (mild) or grade 2 (moderate) degree haemophagocytosis. None of these cases showed severe degree of haemophagocytosis. There was apparently no effect of either bone marrow infiltration or chemotherapy on the degree of haemophagocytosis.

Amongst 4 case of non-haematological malignancies subjected to bone marrow examination, patient with bronchogenic carcinoma showed moderate haemophagocytosis; rest of the cases had mild phagocytosis. All of these cases had fever at the time of bone marrow examination. Although reactive haemophagocytosis and histiocytic hyperplasia have been observed in gastric carcinoma(17) and carcinoma breast(15), but its evidence in the literature is lacking in other non haematological malignancies. Nevertheless its occurrence in pre-existing malignancies is expected to be the result of underlying immunosuppression(2).

Patients presenting with different underlying infections comprised the third largest group (15.3%). Eleven cases presumably had viral infection. They presented with fever and variable degree of haemophagocytosis. Three cases presented as reactive haemophagocytic syndrome with pancytopaenia or bycytopaenia, hepatosplenomegaly & lymphadenopathy. One case had jaundice and evidence of hemolysis. None of these cases had coagulation defect. Most of these cases with presumed viral infection had either moderate (36.5%) or severe

Table 3 : Etiology of The Cases With Different Grades of Haemophagocytosis (130 Cases)

Etiology	Grade I	Grade II	Grade III
Malignant			
Malignant Histiocytosis	1(.76%)	-	
Malignant Haematilogical Disorders			
Hodgkins Disease	13(10%)	5(3.84%)	-
Non-Hodgkins Lymphoma	7(5.38%)	5(3.84%)	
Burkitt's Lymphoma	01(0.76%)	-	-
Multiple myeloma	2(1.53%)	1(0.76%)	-
Plasma cell leukaemia	1(0.76%)	-	-
Acute Myeloid Leukaemias	2(1.53%)	1(0.76%)	-
ALL	2(1.52%)	-	
ALL in remission	2(1.53%)	-	-
Myelodysplastic Syndrome	1(0.76%)	-	-
Chronic Myeloid Leukaemia	-	1(0.76%)	-
Non Malignant Haematological Disorders			
Megaloblastic anaemia	6(4.61%)	5(3.84%)	2(1.53%)
Iron deficiency anaemia	5(3.8%)	3(2.3%)	-
Aplastic anaemia	3(2.3%)	3(1.53%)	-
Megakaryocytic aplasia	-	2(1.53%)	-
Immune Thrombocytopaenic purpura	4(3.07%)	3(2.3%)	-
Haemolytic anaemias	2(1.53%)	1(0.76%)	-
Congenital dyserythropoietic anaemia	-	1(0.76%)	1(0.76%)
Sideroblastic anaemia	-	1(0.76%)	-
Pure red cell aplasia	-	1(0.76%)	-
Infections			
Viral Infection	1(0.76%)	5(3.8%)	5(3.84%)
Tuberculosis	-	3(2.3%)	-
Enteric Fever	1(0.76%)	2(1.53%)	1(0.76%)
Parasites			
Malaria	-	-	1(0.76%)
Visceral Leishmaniasis	1(0.76%)	-	-
Non Haematological Malignancies			
Hepatocellular carcinoma	1(0.76%)	-	-
Bronchogenic carcinoma	-	1(0.76%)	-
Ewing's Sarcoma	1(0.76%)	-	-
Metastatic Disease	-	-	1(0.76%)
Storage Disorders			
Niemann Pick Disease	2(1.53%)	-	-
Gaucher's Disease	1(0.76%)	-	-
Autoimmune Disorders			
Dermatomyositis	1(0.76%)	-	-
Scleroderma	1(0.76%)	-	-
Miscellaneous			
Chronic Disorders	3(2.3%)	5(3.84%)	-
Hypersplenism	3(2.3%)	-	-
Amyloidosis Liver	1(0.76%)	-	-
Insect Bite	1(0.76%)	-	-
Total	69(53.1%)	50(38.5%	11(8.4%)

degree of haemophagosytosis (45.5%); only 2 cases had mild (grade 1) haemophagocytosis. The haemophagocytosis in viral infection may be due either to a primary alteration in the phagocytic cells or in the ingested elements. Risdell et al suggested that the histiocytic reaction may represent and exaggeration of the normal function of the histiocytic system(3). An alteration of the ingested element by interaction with virus is possible.

Three cases with an established diagnosis of enteric fever showed a variable degree of haemphocytosis (grade I, II, III). A case with severe degree (grade III) actually presented as reactive hemophagocytic syndrome with fever pancytopaenia, hepatosplenomegaly, and evidence of haemolysis.

Three of our cases had pulmonary tuberculosis although, bone marrow AFB cultures were negative. Nevertheless these cases had positive family history and chest radiographic evidence of pulmonary tuberculosis. One patient was already on antituberculous therapy. Campo et al have reported 3 autopsy cases of hemophagocytic syndrome associated with acute tuberculous sepsis. Benign histiocytic proliferation with striking hamophagocytosis was present in a disseminated, multisystem pattern in all three cases. They postulated that haemphagocytic histiocytosis in these cases may be related to some underlying immunologic derangement(7).

One case of visceral leishmaniasis presented with mild degree of haemophagocytosis and bicytopaenia which could be attributed to hypersplenism. The association of visceral leishmaniasis and haemophagocytosis has been reported previously(14). A patient with falciparum

Table 4 : Etiological Distribution and Grades of Haemophagocytosis

Etiology	I	II	III
Malignant (n = 1)	0	2.0%	0
Malignant Haematological Disorders (n = 44)	44.9%	26.0	0
Non Malignant Haematological Disorders (n = 43)	29.4%	40.0%	27.3%
Infections (n = 18)	2.8%	2.0%	54.5%
Parasites (n = 4)	1.4%	0	9.1%
Non Haematological Malignancies (n = 3)	28%	2.0%	9.1%
Storage Disorders (n = 3)	4.3%	0	0
Autommune Disorders (n = 2)	2.8%	0	0
Miscellaneous (n = 13)	11.6%	10.0%	0

Table 5 : Comparison of Physical Findings and Haematological Parameters in Patients with Different Grades of Haemophagocytosis.

	Grade I	Grade II	Grade III
Physical Findings			
Mean Age	28 years	30 years	21 years
M : F ratio	1.5 : 1	2.5 :1	10.1 :
Fever	49.2%	42%	63.3%
Splenomegaly	17.3%	20%	45%
Mild	41%	67%	80%
Moderate	56%	33%	Nil
Marked	03%	Nil	20%
Hepatomegaly	27.5%	32%	63.6
Lymphadenopathy	21.7%	16%	9.0%

Table 6 : Comparison of Haematological Parameters in Different Grades of Haemophagocytosis

	Grade I	Grade II	Grade III
Haematological parameters			
Mean Hb (gm/dl)	10.5	9.46	7.2
Mean TLC ($x10^9$ / l)	14.8	10.5	5.4
Mean Platlet Count ($x10^9$ / l)	246	215	140

malaria presented as reactive haemophagocytic syndrome with pancytopaenia, organomegaly, jaundice and fever. Probably no case of malaria has been reported before as a case of haemophagocytic syndrome.

Among the non neoplastic haematological condition, 33% showed reactive haemophayocytosis. Magaloblastic anaemia ranked at the top in this category (30%), and was followed by aplastic anaemia (16.2%). In most of these cases moderate to marked haemophagocytosis was observed particularly in megaloblastic anaemia, haemolytic anaemias, and dyserythorpoietic anaemias and a few cases of iron deficiency anaemia.

In our study only one case was that of malignant (non-reactive) haemophagocytosis. This patient was 70 years old, and presented with high grade fever, hepatosplenomegaly, lymphodenopathy, anaemia, pancytopaenia, jaundice and rapidly fatal course. The bone marrow examination revealed proliferation of abnormal (malignant) histiocytes with high N/C ratio, reticular chromatin, prominent nucleoli and scanty cytoplasm. Erythrophagocytosis was moderately present and the cells were ingested mostly by benign looking histiocytes. The malignant histiocytes were positive for acid phosphatase. The non-specific esterase was unremarkable. The pancytopaenia in this case was attributed to the proliferation of abnormal histiocytes. Esseline et al(18), described malignant histiocytosis in 10 cases and stressed upon the value of bone marrow aspiration for the diagnosis of this condition. Warnke et al(10) studied clinicopathologic features of 29 cases of malignant histiocytosis and the results were very much comparable to the study of Esseltine et al. The cytological features observed in our patient of malignant histiocytosis were similar to the results of Esseltine et al and Warnke et al.

Most of our cases belonged to grade 1 (53%), followed by grade 2 (38.4%), and grade 3 (8.4%), respectively. As shown in table 4, most of the cases in grade 3 group with severe haemophagocytosis had infections (63.6%), whereas in grade 1 and 2 group, most of the cases belonged to neoplastic haematological conditions and non-neoplastic haematological conditions.

Constitutional symptoms were more marked in grade 3 group. Fever (63.6%). splenomegaly (45% cases) and hepatomegaly (63.3%), were frequently observed in patients of grade 3 (table 5).

As a result of increased intensity of haemophagocytosis in grade 3 group mean Hb, TLC and platelet counts were low as compared to other two groups. Most of the patients in grade 3 group were thombocytopaenic (table 6).

Although in Grade III group mean values of Hb, TLC and platelet counts were low as compared to other groups but statistically significant difference among three groups was only found in haemoglobin level and platelet counts. The difference of haemoglobin was significant between grade I & II ($p<0.05$) and grade II & III ($p<0.05$), while it was highly significant between grade I & III ($p<0.005$). There was statistically significant difference between platelet counts of grade I & III ($p<0.05$) while it was not significant between grade I & II and grade II & III. The difference of TLC among all three groups was not significant.

The increased severity of haemophagocytic phenomenon in our study was mainly attributed to underlying infections (viral, bacterial and parasitic) as observed in grade III group. We presume that these underlying infection were largely responsible for low haemoglobin, platelets and TLC counts in grade III groups as compared to other groups, although statistically significant difference was only depicted in haemoglobin estimation and platelet counts. Increased

severity of haemophagocytosis phenomenon was responsible for bone marrow dysfunction (mainly erythroid component) thus resulting in abnormal haematological parameters. There was likewise profound effect on physical findings with increased severity of haemophagocytosis as observed in patients of grade III groups.

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Management of Bleeding Oesophageal Varices - A Review

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Portal hypertension resulting in bleeding oesophageal varices is a commonly seen condition in medical practise in Pakistan. There is enough evidence available in the local literature to show this as one of the most common causes of upper GI bleeding(1).

Natural history of patients bleeding from oesophageal varices varies, depending upon the cause of portal hypertension, with worst prognosis for patients with ongoing liver damage and poor liver reserve(2,3). Amongst numerous causes of portal hypertension, the most commonly is seen in Pakistan is cirrhosis of liver secondary to viral hepatitis, followed by non-cirrhotic portal hypertension (Idiopathic Portal Hypertension) and extra- hepatic portal vein obstruction.

Patients bleed due to portal hypertension which results because of increased portal blood flow or increased resistance. The latter can develop at pre-hepatic, intra-hepatic or post-hepatic level, depending upon the underlying pathology. Portal blood flow is increased because of hyperdynamic circulation due to shunting of blood(4), and is characterised by high cardiac output and decreased systemic peripheral resistance, resulting in increased portal inflow as a consequence of splanchnic hyperaemia. Peripheral arterial vasodilatation initiates pathogenic events resulting in water and sodium retention. Current concept of hyperdynamic circulation implicates enhanced circulating levels of endogenous vasodilators and reduced vascular sensitivity to vasoconstrictors (Despite increased catecholamine activity in cirrhotics)(5,6).

About 30% of cirrhotic patients with demonstrable varices manifest bleed (2,7). The time elapsed from the diagnosis of varices to the first haemorrhage varies between 1-187 weeks. Almost all haemorrhages occur within 2 years of initial observation. Although it is not possible to predict the candidates for bleed, but once bleeding occurs 40-50% cirrhotic patients die within first six weeks following their initial episode of variceal bleed (2,3), therefore different modalities have been used to prevent this first bleed. It is conceivable that reduction in bleeding and mortality in 1/3 of all patients i.e., patients who eventually bleed, maybe offset by the morbidity and mortality caused by prophylactic treatment in the majority who are not at risk. Patients with extra-hepatic portal obstruction rarely die during their first episode.

Bleeding can be predicted by the size of varix as seen on endoscopy and also by the presence of "cherry red spots" on the varix, which signifies increased wall tension (8,9). Deterioration of liver function and development of ascites also have shown to increase the incidence of bleeding in patients with varices (10).

A patient of varices who presents with upper gastro-intestinal bleeding has a 70% chance of bleeding from varices and 30% chance of bleeding from gastritis (11). Correlation of the lesion with severity of bleeding reveals that in majority of patients bleeding from varices is severe, whereas bleeding from gastritis is mild. Since the management of bleeding varices differs significantly from that of bleeding from other causes, therefore it is important to establish the diagnosis on emergency basis. Physical examination may reveal stigma of portal hypertension, especially in form of splenomegaly. Upper GI endoscopy represents the single most reliable technique to diagnose the presence of bleeding from varices.

About 50% of all the patients with acute bleeding from varices will die during the same hospitalization (12). Mortality is related not only to severity of bleeding but also to the degree of hepatic dysfunction i.e., about 10% in Child's A, 25% in B and over 50% in C patients. Statistics tell us that once a patient bleeds from varices there is an 80% incidence of rebleeding. Mortality seen with every rebleeding is about 60% (2,3). Every rebleeding is associated with worstening of functional status of liver. Every rebleeding even if treated successfully utilizes a lot of hospital resourses, especially blood, which is always in a short supply.

The risk of continued variceal bleeding or rebleeding as well as survival are related to the

severity of liver disease. However, there are no specific measures that can improve liver cell function.

Today we have very effective and simple ways of controlloing the acute bleeding but we have not been successful in achieving the goal of prevention of re-bleeding in patients with oesophageal varices. Ideal procedure would be one that prevents re-bleeding without worstening the liver function

Different modalites used in the management of oesophageal varices are based on two principles :

1. Oblitration of varices
2. Decreasing the pressure in the varices

These principles are aimed at achieving the following three goals :

A. Prevention of Bleeding in Asymptomatic Patient with Oesophageal Varices.

As mentioned early only 30% patients with varices will eventually bleed from varices. To prevent bleeding in these 30% patients means subjecting the remaining 70% to an unnecessary treatment.

Different modalities available are:-

a. Drugs that reduce Portal Pressure.

i. Vasoactive Drugs.

1. Beta Blockers have been widely studied for the prevention of bleeding in cirrhotic patients with varices and most of the studies show a beneficial effect in prevention of bleeding(13), decreasing the incidence from 27% to 17% as shown by Pascal (14) and from 22% to 4% shown by Bosch (15). Meta-analysis of different studies show B-Blockers to be effective in reducing the risk of first bleed and could have a slight beneficial effect on survival in cirrhotics with oesophageal varices. This effect was lost in non-compliant patients (i.e. not taking treatment for at least 2 consecutive days), and in patients with ascites.
2. Alpha2-adrenergic agonist clonidine has shown to decrease elevated sympathetic activity in cirrhotic and to decrease portal hypertension (16). Long term beneficial effects need to be confirmed.
3. Nitrovasodilators have shown to decrease the hepatic venous pressure, but a clinical study comparing isosorbide-5-mononitrate and propranolol on prevention of first bleeding showed no difference between the two as far as risk of bleeding and survival rate is concerned (17).
4. 5-hydroxytryptamine receptor antagonist. Ritanesin and ketanesrin both decrease hepatic venous pressure gradient. Addition of Ketanesrin in cirrhotic on propranolol caused further reduction in hepatic wedge pressure gradient, and this effect was also seen in non-responders to propranolol (18).

ii. Diuretics: Patients with portal hypertension have an elevated blood volume. Chronic administration of diuretics is associated with decrease in portal pressures(19). This effect is independent of presence of ascites. Cirrhotic patients on propranolol when given spironolactone show further decrease in the hepatic wedge pressure gradient.

b. Sclerotherapy: Injection sclerotherapy of varices which have not bled has been advised and practised because of technical ease. Properly conducted studies have failed to substantiate any benefit to prophylactic sclerotherapy to prevent occurrence of first bleed (20-23), rather some studies have shown a higher bleeding rate and mortality than control even when used in association with propranolol.

c. Standard Porto-Caval Shunt: Porto-caval shunts had been used to prevent bleeding in patients. Randomised trials mainly in alcoholic cirrhosis have shown no benefit with this approach (24,25), rather there was a significant increased incidence of encepalopathy in shunted patients and in one of the studies their was actually shortened survival.

d. Selective Distal Splenorenal Shunt: This has become the shunt of choice in therapeutic settings. Due to poor results of total shunts in prophylactic settings , SDSRS has not been studied in prophylactic settings in West. Selective distal splenorenal shunt has been studied in non-alcoholic cirrhotics in China, where 39% patients had this done for prophylaxis. In prophylactic situations the incidence of bleeding and encepalopathy were lower with better long term survival (26).

e. Devascularization Operations: Operative devascularization has also been practised to prevent occurrence of bleeding in cirrhotic patients. Japanese studies have shown prevention of bleeding with no increase in morbidity or mortality and improved long-term survival with this approach when used in Child's A & B patients, but with poor results in Child's C patients (27,28)

B. Control of Acute Bleeding from Varices.

This is an emergency situation, which is associated with a 50-60% mortality.

Management includes correction of hypovolaemia and shock, and specific measures to stop the bleeding. Over the years different specific measures have been used, some discarded, some re-discovered and some still being used. We will individually discuss them.

1. **Balloon Tamponade:** Direct compression of the varies by means of an oesophageal balloon has been available for over 4 decades and has saved a lot of lives over the years. When used during acute bleeding it stops bleeding in over 60% of the patients with varices (11). It has to be deflated within 24-36 hours in order to avoid pressure necrosis. Unfortunately majority of the patients i-e about 60% rebleed within a short period (29). Moreover it is associated with a very high complication rate in form of aspiration pneumonia. In hospital mortality has not shown to decrease when this technique was used to control the bleeding. Today it is mainly used in an occassional patient who has failed to respond to more effective non-operative means and is awaiting a surgical procedure.

2. Drugs are of help as they reduce portal pressure, increase tone of oesophagogastric junction or reduce gastric secretion.

Drugs That Reduce Portal Pressure. Vasoactive Drugs: Drug therapy is the optimal first treatment for variceal bleeding because it is the only one that can be administered immediately and does not require sophisticated equipmeent or specialized training. The optimal drugs should be safe, effective, easy to administer and any side effects should not require discontinuation of the drug. Currently available drugs do not fulfil all these requirements but their limitations must be considered in the context in which they are used. These drugs reduce portal blood flow thus reducing portal pressure and allowing hemostasis at the bleeding point. B Blockers e.g., Propranolol, because of their hypotensive effects, are NOT used during acute bleeding.

Vaso-active Drugs: Vasopressin (ADH) is a naturally occuring nonapeptide produced by the posterior pituitary. This hormone regulates the permeability of collecting tubules of kidneys to water. At higher plasma concentrations it acts as a powerful direct arteriolar vasoconstrictor. It causes splanchnic vasoconstriction, thus reducing the portal pressure(30). It has been in use for last 40 years. It has to be used as continous intra-venous infusion after a bolus dose. It has been used in continous intra arterial infusion in the mesenteric artery, but this approach has not shown any benefit over intravenous infusion (31). Its significant drawback is vasoconstriction of systemic arterioles particularly cardiac and skin arterioles. Myocardial infarction, skin and mesenteric gangrene have all been reported with the use of vasopressin (32). In 20% of the patients drug had to be discontinued because of serious cardiac complications. In actual practise for the control of acute bleeding the trials have shown no benefit of vasopressin when compared with a placebo (33) All major European centres have abandoned the drug in bleeding varices.

Vasopressin and Nitroglycerin: The addition of nitro vasodilators significantly reduces the systemic side-effects of vasopressin maintaining the hypotensive effect in the portal circulation. Three studies have shown that side-effects of vasopressin are significantly reduced with nitroglycerine used either sublingually or intravenously or transdermally. All these studies were not able to confirm the therapeutic benefit as far as effectiveness in controlling the bleeding is concerned (34).

Glypressin with or without nitroglycerin: This is a triglycyl-lysine synthetic analogue of vasopressin. Its advantage is that it can be given by bolus injection, as it has a longer half-life than vasopressin. It can be used with nitroglycerin to prevent systemic complication. Randomised trials comparing it with vasopressin show no difference in efficacy (35).There is only one trial which shows a reduction in mortality in bleeding varices (36).

Somatostatin and Octreotide: Somatostatin is a naturally occurring peptide, which acts as a growth hormone release-inhibiting factor. It displays a wide range of inhibitory biological actions. The motility and secretion functions of gastro-intestinal tract are inhibited by somatostatin. Like vasopressin, somatostatin causes splanchnic vasoconstriction. This is a selective action on mesenteric circulation and unlike vasopressin has no effect on systemic blood pressure(37). This peptide not only decreases portal pressure in portal hypertension but also shows a more marked fall than vasopressin in Azygous blood flow for similar reduction in portal pressure, meaning it selectively decreases the blood flow in collateral vessels i-e oesophageal varices (38). In spite of its attractive biological profile the natural peptide is far from ideal drug and this is because of its short half life, making intravenous infusion mandatory.

Octreotide is asynthetic analogue of somatostatin with a longer half life. Studies have shown that it decrease portal pressure in patients with bleeding oesophageal varices and actually decreases the blood transfusion requirement by 50% (39).They achieve all this with no major complication and on top of it octrotide offers ease of adminiustration (40).

Octreotide followed by sclerotherapy has been compared with sclerotherapy, showing a marked decrease in blood requirement and decrease in 5 days rebleeding rate with combination therapy (41). Rather

their are studies which show octreotide to be as effective as sclerotherapy in control of acute bleed (42,43).

Drugs Increasing Lower Oesophageal Sphincter Tone Pharmacological increase of LOSP may reduce the inflow of blood into the submucous venous plexus of the oesophagus and hence into the oeophageal varices. Metacloprmide, domperidone and cisapride have been used. Mastai et al demonstrated that the administration of metaclopramide and domperidone causes significant reduction in azygous blood flow as compared to placebo (44). The actual results in controlled setting in their effectiveness to control the acute bleeding are contradictory and more results are awaited to draw a final conclusion

3. **Endoscopic Sclerotherapy:** In 1939, Crafoord and Frenckner described the technique of direct injection of sclerosing solution into the oesophageal varices by rigid oesophagoscope (45). It was tried but never gain exeptence because of technical difficulties. Availability of fibro-optic endoscope brought with it the technical ease with which sclerotherapy could be done. The decade of 70,s and 80,s saw sclerotherapy as the procedure of choice for management of acute bleeding from the varices, with reports reaching a 90% success rate in control of acute bleeding (46). It became a gold standard because of such high initial success rate and ease of performance right at the time of confirmation of diagnosis by endoscopy. Early re-bleeding was seen to be in the range of 20-30% , a rate far superior than ballon tamponade and vasopressin (47,46). This early rebleeding rate has been decreased with addition of octreotide along with sclerotherapy (41).Long term re-bleeding rates were still very high, 50-60% (48). There is a 23% non-bleeding complications associated with sclerotherapy. For this procedure to be effective it requires a 24 hours availability of a trained endoscopy set-up for the whole population at risk of upper GI bleeding.

4. **Endoscopic Variceal Band Ligation (EVL):** EVL was introduced by Stiegmann in 1986 (49). Procedure in which varix is aspirated and pulled up to form a pedicle, an elastic band is released to ensnare the varix. The strangulated varix thrombosis and the tissue sloughs in 3-5 days, leaving a shallow ulcer which heals in 2-3 weeks. This is almost the same procedure as descibed by Barron for haemorrhoids. Results show this to be a more effective procedure with less complications as compared to sclerotherapy (50,51). EVL requires less treatment sessions than Endoscopic sclerotherapy for eradication of varices.

Radiological Oblitration of Varices: Injection of sclerosing agents in the varices under radiological control was developed and practised in 70's. This was an effective way of controlling the bleeding from the varices (52), but required highly sophasticated laboratory and a skilled radiologist. Introduction of endoscopic sclerotherapy has made this procedure a historical event.

5. **Transjugular Intrahepatic Portosystemic Shunt, Tips:** A radiological controlled procedure where a stent is placed between the hepatic vein and portal vein, inside the liver substance. Procedure is done under floroscopy and in expert hands is a quick and safe procedure. This procedure lowers the portal pressure. Physiologically it is a narrow lumen side to side Porto caval shunt. A 90% success is achieved in controlling the bleed(53,54). Initial impression that it will not be associated with encephalopathy has proved not to be true and encephalopathy incidence of upto 30% is being seen after this procedure. More over their is a 30-50% occlusion rate necessitating replacement of stent(55). This procedure requires a skilled radiologist with a well equipped radiology department. As the anatomy around the liver is not disturbed when TIPS is introduced, thus liver transplant operation is not made difficult after this procedure. In Western countries it is becoming the procedure of choice to control acute bleeding in patients who are waiting for liver transplants(56).

6. **Operative Ablation Of Varices / Devascularization:** These were one of the first procedures used to control bleeding. A whole host of operations have been described over the last 60 years. Starting from Tanner's procedure to Sugiwara's procedure. A latest simple but high-tech addition being the stapling of the lower oesophagus with an end-to-end Stapling gun. Studies show that primary stapling of oesophagus is as effective as injection sclerotherapy in acute control of bleeding(57). All these procedures have a common goal i-e to directly oblitrate the varices. They are again an effective means to control the acute bleeding but require an operation in a sick patient. These procedures are associated with an operative mortality though not as high as seen with emergency shunt operations. Moreover as the underlying Portal hypertension persists, these operations are associated with recurrence of varices and bleeding. Sugiwara's operation as practised in Far East has been reported with very good long term results (58). Haseeb's Procedure developed in Egypt for portal hypertension due to schistosomiasis, has proved the superiority of ablative procedures over

shunt operations in this specific type of portal hypertension (59).

Today ablative procedures like direct ligation and stapling are still being practised as emergency salvage operations when non operative measures like sclerotherapy fail to control the acute bleed from varices, and procedures like TIPS are not available.

7. **Emergency Shunt Operations.**

Total Shunts: First done by Eck on dogs in the last centuary, Portocaval shunt was introduced by Whipple for the control of bleeding from varices(60). For next 3 decades this was the procedure of choice. This operation not only effectively stops the acute bleeding but also prevents recurrent bleeding in the survivors. It is associated with an unexpectedly high mortality and morbidity in form of encephalopathy (61). Though in long term follow-up there is no difference in mortality when compared with sclerotherapy(62).This procedure has been universally abandoned exept for one centre in the World which is still doing it and have shown an improved long term survival in cirrhotics(63).

Numerous other shunts have been used like Proximal spleno-renal shunt, Mesocaval shunt, Clatsworthy shunt, but essentially all of them stop the bleeding by diverting blood away from the portal system thus not only decreasing the portal pressure but stealing blood from an already deceased liver. This results in encephalopathy , incidence varying from 30 to 60 %. And to do the operation in a patient who is already sick from blood loss is associated with very high mortality.

Selective Shunt: Warren's selective spleno renal shunt is a time consuming difficult operation, therefore has not been used or advocated in control of acute bleeding from the varices.

Partial Shunt: I. J. Sarfeh has recently described a shunt, in which a narrow lumen Polytrtrafluroethylene (PTFE) graft is interposed between potal vein and inferior vena cava. This operation is a variation of old fashioned meso-caval shunt and side-to-side porto-caval shunt, the difference being a narrow communication between the two systems. Sarfeh has advocated that this narrow lumen will prevent total diversion of portal blood, thus preventing encepalopathy, incidence of encephalopathy being about 15% as compared to 40% seen with 20mm meso-caval shunts (64). Moreover hemodynamics associated with a narrow shunt i-e increased velocity will prevent shunt occlusion. This is technically a quick and relatively an easy operation. This procedure has not been fully investigated in acute bleeding, but if performed early on in the course of acute bleeding, it should give results comparable with TIPS, because physiologically they result in same hemodynamics. Advantage being a close to 100% shunt patency when compared with a 60% patency of TIPS.

C. Prevention of Recurrent Bleeding

Very effective means as discussed, are available to stop an acute bleed from varices. Exept for the shunt operations all are associated with a very high re-bleeding rates.

Modalities available to prevent this high rebleeding are:-

1. Drugs that reduce Portal Pressure.
2. Sclerotherapy
3. Prophylactic Porto-Caval shunts.
4. Surgical oblitration /Devascularization procedures.

Drugs That Lower Portal Pressure: Beta-Blocker propraolol is the drug most widely used to prevent re-bleeding of oesophageal varices. Though some of the trials have shown decreased incidence of rebleeding, majority of the long term studies have not shown a statistical difference with bete-blockers. But if the subset of patients with well-compensated cirrhosis and with no ascites are studied, bete-blockers definately did show a decreased incidence of rebleeding i-e 20% as compared to 40% seen in controls and also improved survival (65).

Addition of nitrates enhances the effect of beta-blockers and there are are studies which show this combination to be as effective if not more than sclerotherapy in decreasing the incidence of rebleeding(66).

Repeated Sclerotherapy: After successful control of acute bleeding with sclerotherapy, repeated sclerotherapy to abolish the varices has been used to prevent rebleeding. Sclerotherapy performed over intervals does oblitrate the varices, which again reappear and bleed in responce to the raised portal pressure. More-over repeated sclerotherapy has given rise to a new entity, congestive gastropathy which then becomes a source of bleeding.

Numerous trials have been carried out to study the effectiveness of sclerotherapy as compared to medical therapy. Repeated sclerotherapy carried out at 7-10 days interval will eradicate varices in 85% patients.Varices will recur in 60% of these eradicated patients within 6 months and this incidence of recurrence is not related to the severity of the liver disease and they can again be oblitrated (67). Rebleeding rates were decreased in some studies, but still a 25-55% rebleeding rates is seen and this

incidence is related to the severity of liver disease, with non-bleeding complications seen in upto 23% patients with sclerotherapy and no improvement in the survival rates (68). Similarily studies have been carried out comparing repeated sclerotherapy with shunt surgery. Incidence of rebleeding was seen to be significantly decreased with shunt surgery but there was no difference in survival (68). The only study which showed improved survival with sclerotherapy, also showed that 1/3 patients required salvage shunting for uncontrolled rebleeding. In fact it was the combination of sclerotherapy and salvage surgery which actually reduced the mortality and improved the long term survival (69).

Transjugular Intrahepatic Portosystemic Shunt: This procedure as described earlier is very effective in acute control of variceal bleeding. TIPS will prevent rebleeding as long as it stays open. 30% patients within 1 year require replacement or redilatation of the shunt (55), making it an expensive intervention requiring highly sophasticated radiological facility. TIPS is associated with encephalopathy rate which reaches the rates seen with side to side porto-caval shunts. At present it is the procedure of choice for patients awaiting liver transplant (56). There are on-going studies comparing TIPS with distal shunts.

Total Porto-Caval Shunts: Porto-caval shunts or variations have been around for a long period. Total shunts were the standard treatment for this disease. All shunts have been able to decrease the rebleeding rates significantly, with rates as low as 5% seen with standard end to side port-caval shunts (70). Moreover with better support services operative mortality has been brought to acceptable levels, when shunt operation is carried in elective settings as compared to emergency shunt operations for control of an acute bleed (71). But unfortunately all total shunts are associated with encephalopathy, which is related to their success in lowering the portal pressure by diverting the blood away from the liver. Exept for Orloff, no one has shown an improvement in survival rates in patients undergoing shunt operation (63). The main reason Orloff has been able to show an improved long-term survival after standard portacaval shunts is because this is the primary treatment used in all patients presenting with variceal bleed and is done within 24 hrs of admission and not as a last resort in a dying patient when every other modality has been tried unsuccessfully. There has been a renewed interest in shunt surgery, studies have shown no difference in long-term survival between shunted patients and patients subjected to repeated sclerotherapy (62). Similarily better survival was seen when early shunts were performed in patients labelled as sclerotherapy failure (72). Total shunts are being re-discovered as a part of planned management protocols in patients with varices.

Partial Shunt: The newer Sarfah shunt as described earlier, makes sence in preventing rebeed just like total shunts with a lower incidence of encephalopathy and maybe improved survival (64). One of the major advantage of this shunt is the technical simplicity as compared to other shunts, the disadvantage being use of a prosthetic material. Functionally it is the same as TIPS, but with better patency rates.This is a shunt that should be preferred to total shunt in patients with prograde flow (73). A randomised study is required to see its efficacy as compared to DSRS.

Selective Distal Spleno-Renal Shunt (DSRS): Warren introduced the concept of dividing portal system into two systems. Splenic system which drains blood from the stomach, spleen and oeophagus. And mesenteric system which drains blood from the intestines. He proposed an operation in which the two systems were disconnected. Shunt was created between the splenic system and systemic venous system (Distal spleno-renal shunt). Thus decompressing the Oesophageal varices and allowing prograde mesenteric blood flow into the liver. This shunt over the years has proved to be associated with very low incidence of encephalopathy, because it maintains prograde hepatic flow (75).

There are studies in the literature which show loss of this selectivity over the years as new collaterals develop between splenic and mesenteric system (76). This phenomena can lead to loss of selectivity, therefore result in delayed development of post-shunt encephalopathy. This loss of selectivity was seen mainly in alcoholic cirrhosis (77). At the same time there are enough studies in the literature which show improved long term survival in bled patients with oesophageal varices due to non-alcoholic cirrhosis (77). Rather it is the only therapy available (besides liver transplant) which has shown improved survival rates in cirrhotics with history of bleeding varices.

Devascularization Procedures: Simple ligation of varices or stapling of lower end of oesophagus are very effective in acute control of bleeding, but they are associated with a very high rate of recuurent bleeding. Sugiwara procedure which consists of distal oesophagectomy, proximal gastrectomy and splenectomy have proved to be very successful procedures with less than 10% rate of rebleeding (58). These results could not be duplicated in the West.

Haseeb as shown a devascularization procedure which is effective in patients with portal hypertension due to schistosomiasis. With devascularization their survival is increased (79). These patients do very badly when subjected to standard shunt operations.

Liver Transplant: Liver transplant over the years has become a standard treatment for chronic end stage liver disease and acute liver failure. When done in patients with end stage liver disease and bleeding oesophageal varices, it has effectively prevented rebleeding without the complications of encephalopathy. No doubt this should be the treatment of choice for patients with bleeding oesophageal varices.

This is a technically demanding operation. It requires a donor, which unlike liver can only be a cadaver. Patients will require life long immuno-suppression. Partial liver transplants from live donor are used in children with congenital liver diseases, but not in adults.

Hepatitis viral reinfection of donor liver and subsequent development of disease in transplanted liver is seen. Though survival of patients with hepatitis C is better after transplant, even when the donor liver is re infected.

When 5 year survival of Child's A patient with DSRS was compared with patients undergoing liver transplant for end stage liver disease, survival was better in the former (78). Liver transplant is the treatment of choice for patients with oesophageal varices with advanced liver disease (Child's C)

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Percutaneous Nephrolithotomy in Later Period of Pregnancy

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Case Report

Renal colic secondary to stone disease is the most common nonobstetric cause of acute abdominal pain in gravid patients, seen in approximately 1 of every 1500 pregnancies(1). We dealt with 4 such cases during the last four years. Two cases were treated conservatively while in one case non invasive intervention of DJ stent insertion was applied till the term was over. We performed percutaneous nephrolithotomy in one pregnant lady for her impacted stone(2). There is only one such example in the international literature(3).

Our case was a 30 years old lady with 25 weeks pregnancy having an obstructing stone of 11 mm diameter below her right pelviureteric junction. She presented with severe spasmodic pain with temperature. TLC was high and laboratory urine examination showed plenty of red and white blood cells. Ultrasonic examination showed marked dilation of her right kidney (Fig. 1). Plain X-ray film showed a stone of about 11 mm size just below the right pelviureteric junction. Retrograde ureter catheter and DJ stent was tried but even the guide wire could not pass by the impacted stone. Percutaneous nephrolithotomy was performed in that case.

Prior to operation an 8F ureter catheter was inserted retrograde into right ureter, till the obstruction was felt, to hold the stone so that small fragments do not pass down the ureter as the ultrasonic stone disintegration was planned.

Patient was lain prone in semioblique position (Fig. 2). A hard pillow was placed under her rib cage and pelvic bone on the side of stone to distribute the weight of body and spare the foetus from stress. A lead apron was placed under the foetus to save it from scattered X-ray beams/load.

The procedure was performed under complementary local anaesthesia. Kidney was punctured at an appropriate site, through the middle calyx, under ultrasonic guidance. It was less steep than usual puncture for percutaneous surgery (Fig. 3). Channel was dilated under fluoroscopic control. Nephroscope was inserted in and impacted stone was broken ultrasonically (Fig. 4). Fragments were removed and a nephrostomy drain was inserted which was removed after 3 days of operation. The patient was discharged on the 5th postoperative day completely symptom free and she gave birth to a healthy baby after full term of pregnancy. Total hospital stay was 7 days.

Discussion

Ratio of stones is 0.06% among the data of 34,000 pregnant patients collected by Jones from different sources(4). The prevalence of stone in primipara or multipara, and right or left ureter in gravid or non gravid patients is debatable. Ninety percent of the cases present in IInd or IIIrd trimester of pregnancy(5-7). According to our statistics in Pakistan the incidence of stone function, among 1500 pregnant patients managed at the department of gynaecology of our hospital during the last four years, came out to be 0.3%. The number of primipara and multipara was equal while all the 4 cases had the stones on their right side. One patient appeared with the symptoms of stone disease during Ist trimester of pregnancy while 3 patients in their IInd or IIIrd trimester.

Approximately 80% of the symptomatic renal and ureteric stones pass spontaneously in gravid patients(4,8,9). Among the remaining 20%, most of the cases can be postponed till post partum period. It is very seldom that the stone is removed during pregnancy. Coe and associates found 210 gravid cases with stone in literature and among them ureterolithotomy or nephrectomy was performed in 11 (5%) cases(10).

During pregnancy a ureteral claculus, associated with persistent pain, urosepsis or complete obstruction secondary to its impaction, should be considered as urological emergency(11). Indication of operation is

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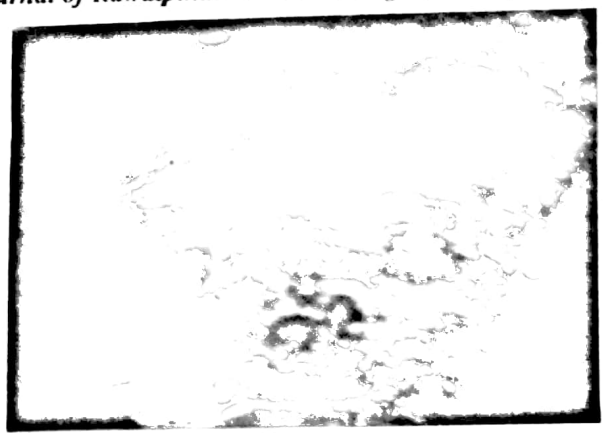

Fig. 1: Ultrasonography of dilated kidney - cause of dilatation is stone impaction

Fig. 2: Position of the patient during operation.

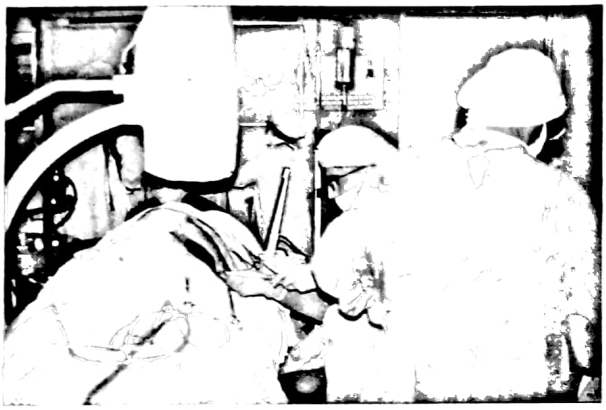

Fig. 3: Puncture is less steep as compared to routine PCNL.

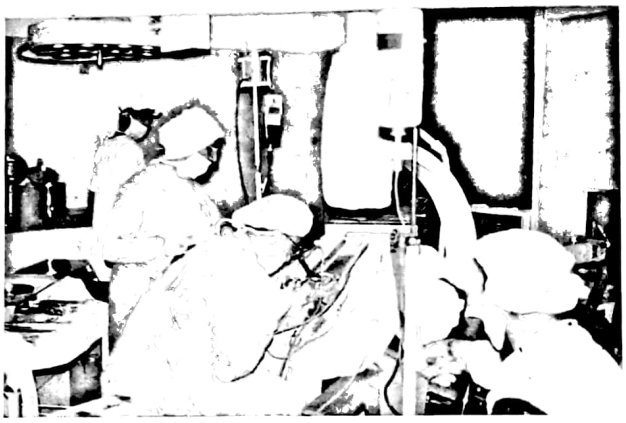

Fig. 4: Nephroscope in position and removal of stone fragments.

the intolerable pain or fever due to infection which do not subside with medicinal therapy. Previously, in case of conservative therapy failure, open surgery was performed among pregnant patients with stone. With the development of endoscopic techniques the operation could be postponed till postpartum period by inserting retrograde ureter catheter or DJ stent. In case of unsuccessful retrograde trial, nephrostomy drain is inserted for urinary passage diversion(12,13). We agree with Holman et al(3). That once nephrosotomy drain is inserted, it is worthwhile to remove the stone as well. It is advantageous not only for foetus but also for the mother who does not suffer from the physical as well as psychological torture by holding a drain for her later period of pregnancy. Here it is worth mentioning that extracorporeal shockwave lithotripsy (ESWL) is contraindicated during pregnancy. The energy generated by ESWL has a potential to endanger the foetus(14).

As far as the exposure to radiations is concerned, according to the literature, during the Ist trimester of pregnancy which is the most precarious period, abortion is advised above the direct exposure of 10 rads(15) because that much radiation load is believed to cause congenital malformation in 1% to 3% cases(16). Generally, single abdominal exposure delivers a load of 0.2 rads in direct beams while one intravenous urogram entails an X-ray load of 0.4-1.2 rads, depending upon the number of exposures. The calibration data of an average fluoroscope is, in direct X-ray beams with 90 kV and 30 mA is 10 mGy/hr or one rad[3]. While, in our case, the mother was not in the Ist trimester of pregnancy, the foetus was saved from the exposure to direct beams and he was protected from scattered beams with the help of Lead apron. As the exposure time was 15 seconds in our case, by keeping in mind the above mentioned facts, it is justifiable to say that the exposure was negligible for the foetus.

Emphasis to radiation exposure is important because not only among the laymen but also to some of the physicians, there is mystic apprehension towards exposure during pregnancy. Certainly a pregnant lady should not be exposed to radiation if it

is not absolutely necessary. But necessary diagnostic procedures are performed, if required, provided those are within safety limits for the foetus.

Positioning of the patient is a difficult job during the procedure. During routine percutaneous operation patient lies prone on the table and a hard cushion is placed under the upper abdomen. In case of a pregnant patient, foetus should be saved from stress. A comfortable semi oblique prone position is adapted in such case (Fig. 2) and a hard cushion is placed under the ribs and hip bone so that the weight of body is distributed on those two points to spare abdomen of the mother.

It is a debatable question that why not only a nephrostomy drain or pigtail catheter is inserted under ultrasonic guidance if retrograde ureter catheter or DJ stent is unsuccessful. In our opinion there is no significance difference between nephrostomy drain insertion and nephrolithotomy if the procedure is done with skillful hands. The patient is more prone to infection if a persistent fistula is present for a long time. Furthermore it is not easy for the patient that she takes care of the drain for her remaining period of pregnancy and yet another painful intervention is waiting for her after delivering the baby.

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Fanconi's Anaemia

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A number of inherited disorders are associated with aplastic anaemia. These diseases are labelled as constitutional aplasatic anaemias(1). Pancytopenia with bone marrow aplasia, congenital malformations, chromosomal abnormalities and increased occurrence of leukaemias and other malignancies characterize these constitutional anaemias(2,3). The disorders included in this group are; Fanconi's anaemia, Dyskeratosis congenita, Xeroderma pigmentosa, Pancytopenia at birth and Schwachmann's syndrome. In 1927, Fanconi, in Switzerland, described a family in which three brothers developed aplastic anaemia alongwith multiple congenital malformations(5). Fanconi's anaemia is an autosomal recessive disorder and has a strong familial predilection(6). In this paper we have presented a case of this rare entity.

Case Report

A male child, seven years of age, resident of Mianwali, presented with a history of weakness since birth and progressive pallor for the previous three months. For the last two months, the child had repeated episodes of bleeding per rectum. He showed reduced mental capabilities. On examination he revealed pallor without lymphadenopathy and any visceromegaly. He appeared short statured and small for his age. His thumbs were hypoplastic (Fig 1). Reduced number of carpel bones was seen on his X - rays of hands. His chest radiograph revealed moderate cardiomegaly (Fig 2).

On investigations, his haematological parameters were as follows: Haemoglobin 4.4 G/dl; white cell count 1.2 X 10^9/1; Platelet count 30 x 10^9/1; Reticulocyte count 0.1% and a normocytic normochromic red blood cells morphology. The differential leucocyte count showed Neutrophils 12%, Lymphocytes 85%, Monocytes 02% and Eosinophils 01%. The fetal haemoglobin estimation by Betke's method revealed an elevated HbF level of 45%.

The bone marrow aspiration was performed at the posterior superior iliac spine. The smears stained with May - Grunwald Giemsa stain showed hypocellularity of erythroid, myeloid and megakaryocytic series with a relative prominence of lymphocytes. Bone marrow trephine revealed aplastic anaemia.

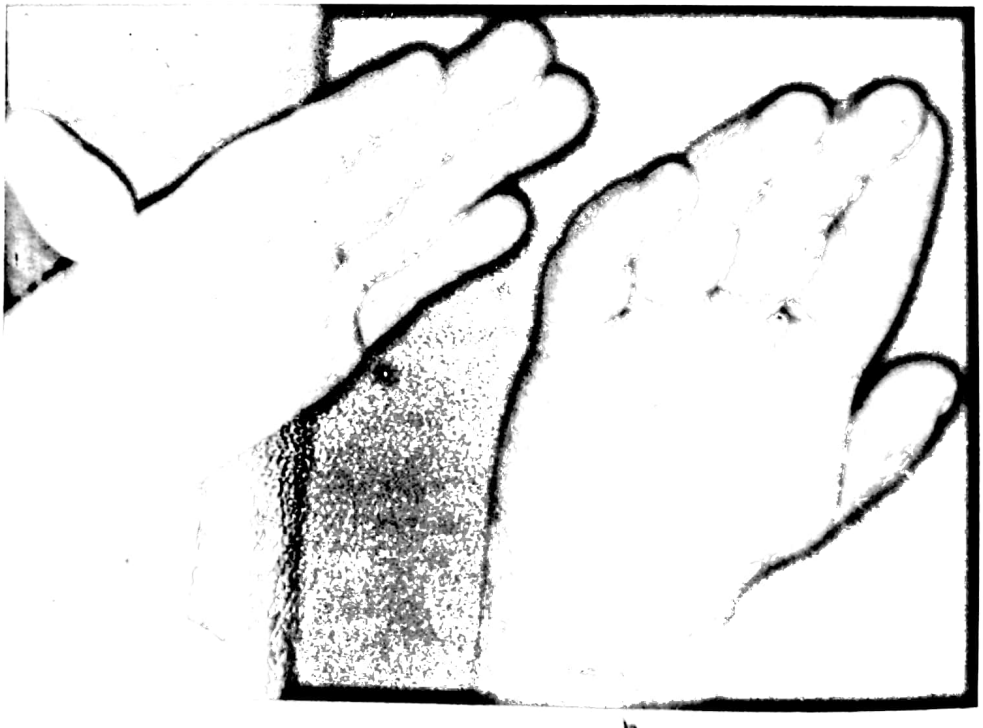

Fig. 1: Hypoplastic Thumbs in a case of Fanconi's Anaemia.

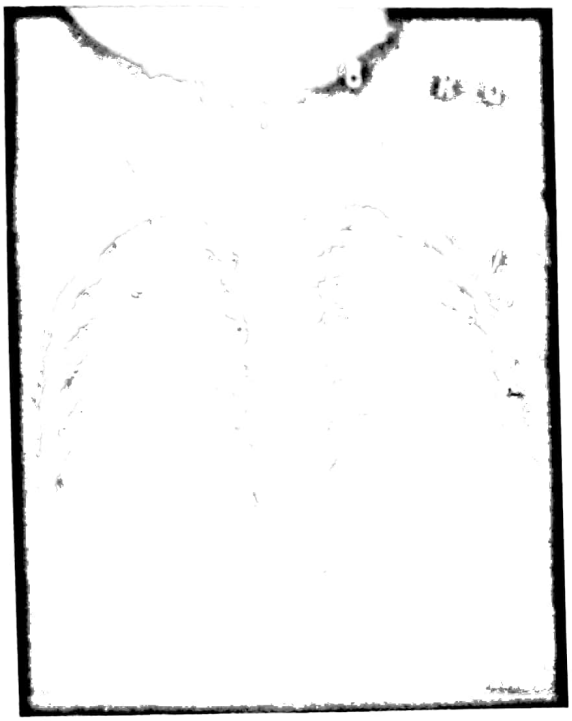

Fig. 2: Moderate degree of cardiomegaly.

On the basis of short stature, mental retardation, microopthalmia, hypoplastic thumbs, reduced number of carpel bones, elevated level of fetal haemoglobin, pancytopenia and severe aplastic anaemia, a diagnosis of Fanconi's anaemia was made.

Discussion

Fanconi's anaemia is an autosomal recessive disorder and is one of the best characterized entity of constitutional aplastic anaemia(7,8). Haematologic abnormalities present since infancy, a familial occurrence and associated congenital defects characterize this anaemia(9,10).

The mechanisms leading to aplasia in this disease are poorly understood. Bone marrow cellular studies have revealed impaired in-vitro haematopoiesis(11). Biological abnormalties, found by cytogenetic studies, have shown a diminished capacity for DNA repair and increased random chromosome breakage during mitosis. These aberrations, involving DNA, may serve as an initiating event in the development of aplastic anaemia, or of leukaemia which occur more frequently in individuals with decreased DNA repair capability (12-14).

The usual age of onset of Fanconi's anaemia is 5-10 years. The common clinical features are: low birth weight, short stature, mental retardation, small mouth and jaw, growth hormone deficiency, microcephaly, microopthalmia,, microstomia, skeletal abnormalities (particularly of thumbs and radii), hypoplastic hypothenar eminences, generalized increased pigmentation of skin, patches of hyperpigmentation, patches of depigmetation, cryptorchidism, abnormalities of renal anatomy (horse - shoe kidney, pelvic kidney), stabismus, hyperreflexia and vascular abnormalities(13, 15-19).

Blood counts are usually normal at the time of birth. Features associated with bone marrow failure do not usually present until the child is 5-10 years old. A low platelet count is the most common presenting haematological abnormality. A modest fall in platelet count may antedate the development of full marrow failure by several years; anaemia then gradually becomes apparent and granulocytes are the last effected. Macrophage activity is a prominent feature and is associated with erythrophagocytosis and iron deposition (20-21).

Different follow up studies reveal that in the natural course of the disease the patients remain transfusion dependent. If left untreated, the majority of patients die of haemorrhage, but in an appreciable percentage there is a terminal transformation into acute leukaemias, usually acute myeloid leukaemia(22-25). Apart from this, malignancies of gastrointestinal tract, skin and other regions are common in these patients(26-27).

The first line of treatment is blood transfusion. Other treatment protocols consist of anabolic steroids, GM-CSF administration, haematopoitic stem cell transplantation and bone marrow transplantation (28-31).

Our patient of Fanconi anaemia was a male child who presented with short stature, mental retardation, hypoplastic thumbs, cardiomegaly, elevated levels of fetal haemoglobin, pancytopenia and severe aplastic anaemia. Cytogenetic studies could not be performed as this facility is not available in our institution. In general, Fanconi anaemia has a varied presentation at diagnosis. The findings may even vary at different times in the natural history of a patient. This variability in manifestations can be, hypothetically, ascribed to the nature and extent of genetic lesions in a particular patient at a specific time.

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Massive Chondrosarcoma of the Bone - Presenting as a Soft-Tissue Mass

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Introduction

The thigh is a common site for the development of various types of soft-tissue sarcomas in adults. Fibrosarcoma, liposarcoma and malignant fibrous histiocytoma tend to from huge masses in the thigh and remain at the top in the differential diagnosis of rapidly developing lesions at this site. Wide surgical resection with sparing of the limb is presently the treatment of choice in these cases(1).

We are reporting a case of primary chondrosarcoma of the pubic bone who presented as a huge soft-tissue mass in the thigh hanging down to the knee.

Case Report

A 60 years old male presented with a large mass in the, left thigh for the last six months. It was extending from the thigh to the knee, was firm in consistency and not fixed to the femur bone. The radiograph of the region did not show its attachment with the femur and appeared as a soft shadow. Therefore the presumptive diagnosis of a soft tissue sarcoma was made.

Fine needle aspiration cytology of the mass revealed a few chondroblasts with irregular nuclei and abundant, intensely purple, fibrillary chondroid ground substance in the background. Possibility of a low grade chondrosarcoma was considered. Different X-Ray films of the region and pelvis were taken, which disclosed an osteolytic lesion in the left lower pubic ramus with splotchy calcification. The diagnosis of chondrosarcoma was established and the option of hemipelvectomy was planned, so as to have a sufficiently wide resection of the tumour, because chondrosarcomas do not respond to other types of therapy(2).

The patient refused to opt for this procedure and agreed for a conservative surgery with preservation of the limb. A modified, conservative surgery was performed. Left pubic ramus along with a huge, well demarcated extension of the neoplasm in the thigh was removed en mass with conservation of quadriceps muscle, hip joint, femoral vessels and nerve (fig 1). The tumour was 4.8 Kg in weight and measured 24 X 21 X 19 cm (fig 2). Its sections showed myxoid appearance and histological examination of the multiple sections confirmed a well differentiated (law grade) chondrosarcoma.

Discussion

Chondrosarcoma is very frequently located in the pelvis ~~is a common site for the development of chondrosarcoma~~. In the pelvis and flat bones, these tumours tend to expand into the soft tissue earlier than when they arise in the long bones where they are contained for a long period(3). Chondrosarcomas have a wide spectrum of biological aggressiveness. Their behavior can be determined by the histological appearance of the lesions into low, intermediate and high grades. Low grade (Grade I) chondrosarcomas have small nuclei and show high chromatin density. Intermediate grade chondro-sarcomas (grade II) have medium sized, regular nuclei with loose chromatin structure. The chondrosarcomas of high grade (grade III) show polymorphic nuclei(4). Radiological features of chondrosarcoma are classical and show destructive lesions with intralesional mottled calcification. Grade II and grade III tumours in addition show atypical radiological features(5).

The natural history of low grade chondrosarcomas is persistent but slow growth over months to years, and they grow to massive sizes. The danger to these patients is the local damage and recurrence. The high grade chondrosarcomas tend to metastasize earlier and progress rapidly to death(3). Low and intermediate grade lesions therefore require wide margins while the high grade tumours should have radical margins usually in the form of radical amputation(6).

Careful evaluation of the clinical presentation and correlation with radiological findings are the basic parameters which can be utilized for the preoperative diagnosis of bone tumours. However it is generally agreed that even when the clinical and radiological findings strongly indicate the diagnosis, biopsy should be taken for its establishment before a definite treatment is undertaken. In contrast to other malignant tumours of the bone, histological assessment for grading is of great value in predicting the behavior, surgical intervention and final outcome in chondrosarcomas. Soft tissue implantation following biopsy is a well known complication in chrondrosarcomas and is a limiting factor in the

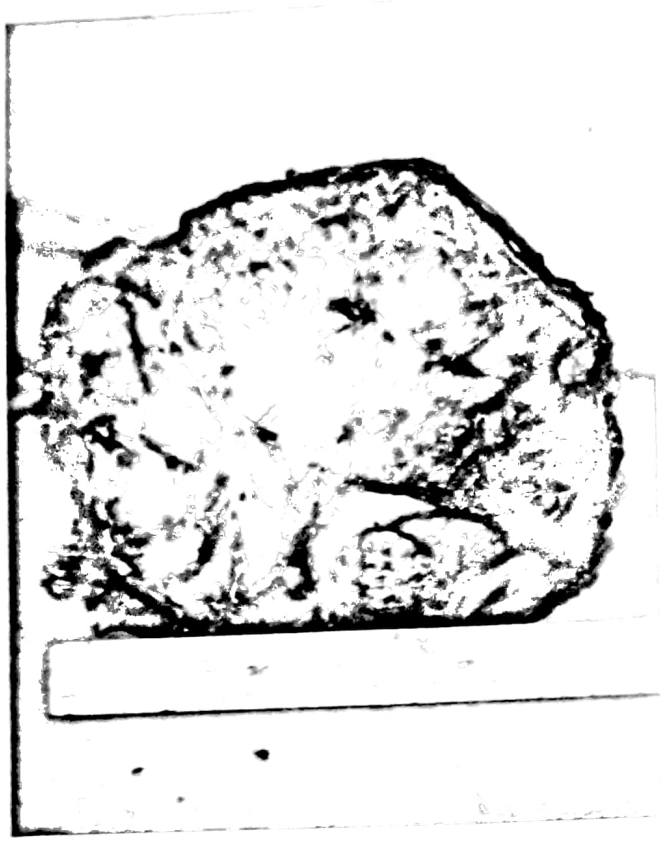

Fig. 1: Gross Appearance of the Mass (Lateral View).

Fig. 2: Operation Site ~~after Research~~ of the Mass

proper assessment in these lesions(7). Fine needle aspiration cytology is utilized for the diagnosis and grading of chondrosarcomas and has been found to provide sufficient information for the definite diagnosis and planning of treatment(8).

In our case, fine needle aspiration cytology enabled us to diagnose the cartilaginous origin of this massive swelling in the thigh which looked like a soft-tissue sarcoma. In conjunction with radiological findings, origin and grading of the chondrosarcoma could be established. Magnetic resonance imaging should also have been utilized for the demarcation of lesion and staging. This could not be done due to economic reasons. Prognosis in this case might not be very good because of huge size of the tumour and its extension in the soft-tissue. Due to the low grade of the neoplasm on histological examination of the multiple sections, almost complete enucleation from the soft tissue extension and clear resected margins at its origin in the pubic bone however favour a positive response to the conservative surgical option which had to be carried out due to patient's desire.

We therefore feel that chondrosarcomas can present as a massive soft-tissue swelling. For the proper evaluation of such cases fine needle aspiration may be supplemented with other investigations e.g. X-Ray, bone scan and MRI. A conservative surgical option with adequate wide margins may be given a due consideration in low grade chondrosarcomas.

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