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Role of Absolute Eosinopenia as Marker of Enteric Fever: Experience from a Tertiary Care Hospital in the United Arab Emirates

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Abstract

Background: Involvement of bone marrow is common in salmonella infections. Enteric fever is a cause of morbidity and mortality world wide. **Materials and Methods:** We conducted a retrospective study of 51 blood cultures or widal positive salmonella patients who were admitted to a tertiary care hospital. Medical records and laboratory information system were used to collect the data. **Results:** The result established that significant eosinopenia was present in all enteric fever patients and eosinophil count of zero was almost diagnostic of enteric fever in the right clinical setting. **Conclusion:** Absolute eosinopenia is an important finding that should help timely diagnosis and early treatment initiation of enteric fever.

Key words: Eneteric fever, Eosinopenia, Salmonella

Introduction

Enteric fever is caused by gram negative bacteria *Salmonella* Typhi (*S typhi*), *S paratyphi* A and, less commonly, by *S paratyphi* B and *S paratyphi* C. Over 21 million people worldwide get infected annually with estimated mortality of 200,000 people per year. Incidence of typhoid fever is high in south-central Asia, Southeast Asia and, possibly, Southern Africa (1). *S. typhi* is a human pathogen that spreads by ingestion of contaminated food or water mostly by feco-oral route (2). Once ingested, typhoidal salmonella is taken up by the ileal lymphatic system and presented to macrophages. Then it spreads through reticuloendothelial system reaching liver, spleen, lymph nodes, and bone marrow. It ultimately destroys the macrophages in the blood stream, and presents as a multiorgan disease (3). Enteric fever is a disease of progressive severity within its first month of onset. Most patients will recover and clear the pathogen, but some will be asymptomatic carrier responsible for spread of disease. Atypical presentations do exist (5).

The definite diagnosis of enteric fever is the isolation of

salmonella from the culture of blood, urine, stool or bone marrow, but the delay of days or weeks in isolating the organism, previous use of antibiotic, and the availability of resources in developing endemic countries decrease its significance in early treatment of the diseases (6). Blood cultures are 100 percent specific with sensitivity from 73 to 97 percent in first week, but can be as low as 40 to 70 percent depending on bacterial load, volume of blood taken for the culture, prior use of antibiotics, timing of blood culture collection and the intracellular nature of salmonella. Bone marrow aspirates are 90 percent sensitive but can not be the test of first choice (7). The sensitivity of intestinal and stool cultures varies from 27 to 80 percent, depending on the duration of illness (8). PCR and monoclonal antibodies tests are not widely available and they are not cost effective in endemic areas (9). Serological widal tests have moderate sensitivity and low specificity, but still are widely used in resources-deficient countries (10). Despite concerns regarding the specificity of Widal test, In health care settings where the more specific method of diagnosis enteric fever are not available this test is still the most common tool available and used. (11).The presence of detectable antibodies in normal population reduces its diagnostic precision but the levels are 0usually low .Studies supports that high titers (>1/160 for Salmonella typhi "O" and >1/320 for Salmonella typhi "H" antigens) in the Widal test performed on single acute-phase sera significantly improve the diagnostic yield (12).

Hematological tests are easily done and interpreted. Anemia, elevated erythrocyte sedimentation rate (ESR), thrombocytopenia, relative lymphopenia, elevated prothrombin time (PT), thromboplastin time (aPTT), and decreased fibrinogen levels are all observed, but lack specificity. Leucopenia is considered a key feature of enteric fever, but studies have shown it to be present in only 20-25 percent of cases (13). Conflicting reports exist with some cases showing normal or high eosinophil count and others suggesting that absolute eosinopenia may be present in up to 80 percent cases of confirmed enteric fever (14). We have therefore studied the eosinophil count in confirmed cases of enteric fever and determine whether presence or absence of absolute eosinopenia help in making accurate early diagnosis.

Patients and Methods

This study was a retrospective chart review of all cases with a diagnosis of enteric fever admitted to medical wards at Sheikh Khalifa Medical City (SKMC), a tertiary care hospital in Abu Dhabi during the period of July 2002 to April 2010. Enteric fever was defined as confirmed clinical diagnosis with positive blood culture or significantly positive widal test with titer of 1/320 in patients clinically suspected of it. Following institutional review board approval from our institution, the records were retrieved from the Electronic Medical Records section of the hospital after going through the computer records using 'enteric fever, typhoid fever or paratyphoid fever' as discharge diagnosis in the search criteria.

Absolute eosinopenia was considered as blood eosionphil count of zero reported by hematology using Sysmex Automated machine (Sysmex Corporation, Kobe, Japan). Blood cultures were done using BACTEC automated blood culture system (Becton Dickinson, New Jersey, USA) and Salmonella identified by vitek identification system and Vi antigen confirmation (Bio Merieux sa, Marcy l'Etoile, France.) before first antibiotic dose was given. Widal tests were performed using standardized kits (Murex Biotech Ltd, Kent, UK.). Serum samples of patients were screened with a slide agglutination test which measures agglutinating antibodies against the lipopolysaccharide 'O' and protein flagellar 'H' antigens of *S. typhi* and Para typhi A and B. Serial dilution of sera starting at a dilution of 1:40 were made with 0.9% saline and examined for visible agglutination. H antigen value above 160 and o antigen of more than 320 in single paired sera was taken as positive (12)

As control group, an equal number of charts was randomly selected and retrieved from patients who were admitted in our hospital during the same above period with diagnosis of fever and subsequent on discharge proved not to have enteric fever (both widal and blood cultures were negative for salmonella).Control group had patients with diagnosis of pneumonia, urinary tract infections, cellulitis and admission diagnosis of fever of uncertain etiology. Patients were sick enough to warrant admission to hospitals Patients with blood disorder, liver diseases, renal diseases, or were immunocompromised, had active alcohol consumption, were on steroids and taking drugs affecting hematological profile were excluded. Groups were compared using unpaired student's *t* test. An alpha of 0.05 was used to determine significance. Normal distribution of the samples was assumed.

Results

A total of 51 patients with confirmed diagnosis of enteric fever were included in the study (Table 1). Out of these, 29 had positive blood culture while the remaining 22 patients had a significant positive Widal test. Thirty-six patients out

Table 1. Laboratory values comparing enteric fever group and control group. Comparisons (using Student *t* test) with *p* values less than 0.05 were considered as significant. Age is shown as age ± standard error.

	Enteric Fever Group	Control Group
Number of Cases	51	51
M:F ratio	37:14	32:19
Mean Age	**28.6 ± 2.2***	**40.8 ± 2.5***
Hb Below 100 g / L	15 % (n=8)	15 % (n=8)
WBC Below 4000 / mm^3	**19 % (n=10)***	**6 % (n=3)***
WBC Above 11000 / mm^3	7 % (n=4)	15 % (n=8)
Platelet Below 150000 / mm^3	35 % (n=18)	23.5 % (n=12)
Absolute Eosinopenia	**73 %* (n=37)**	**25.4 % (n=13)**

** t-test significant with an alpha = 0.05*

of 51(71%) were *S. typhi* while 15 (29%) were positive for Paratyphi. Thirty-seven patients out of 51 had an absolute eosinophil count of zero (73%). This is a significant contrast from the control group, where the majority of patients (38 out of 51 (74.5%) did not have absolute eosinopenia.

Twenty-four out of 29 patients (83%) with positive blood culture enteric fever had an absolute eosinophil count of zero while only 13 out of 22 patients (59%) with only positive widal test enteric fever had an absolute eosinophil count of zero.

In the control group, 15% of patients had leukocytosis (8 patients), and only 6% had leucopenia (3 patients), which was significantly different from the enteric group where, leukocytosis was seen only in 7% cases (4 patients) and 19% had leucopenia (10 patients). All other differences in measures between the two groups did not reach significance.

Discussion

Enteric fever caused by salmonella has high incidence of mortality and morbidity in developing countries. Diagnosis of enteric fever is derived from clinical suspicion and substantiated by laboratory tests. With prompt and appropriate antibiotic therapy, enteric fever is typically a short-term febrile illness with few complications and a 0.2% risk of mortality (15). If left untreated, enteric fever is a life-threatening illness with high long-term morbidity. The case fatality rate in the United States in the pre-antibiotic era was 9 to13% (16).

Cultures of urine, stool, bone marrow and blood have a sensitivity from 30 to 80% with variable specificity in endemic area. Widal test, thyphoid M, Typhidot test and Tubex test have collective sensitivity and specificity of 44 to 95% depending on duration of illness and prevalence of diseases in the community. Polymerase chain reaction (PCR) and nested polymerase chain reaction have a sensitivity and specificity close to 100% but are not commonly available. Due to the universal nature of availability hematological tests and ease of their performance, investigators have tried to find some specific hematological parameters in enteric fever, but most of hematological changes are non specific .These include anemia, leucopoenia, thrombocytopenia and low eosinophil count.

Eosinophils normally account for only 1 to 3% of peripheral blood leucocytes with an upper limit of the normal range of 350 cells/mm^3 (17). The level of eosinophils is regulated by adrenal glucocorticosteroids and epinephrine. Rapid peripheral sequestration of circulating eosinophils occurs in response to chemotactic factors such as C5a and fibrin, which play a part in early response to infection. Eosinopenia, as a response to acute infection, is well known

and has been well characterized (18). It was first described by Zappert in 1893 (19) and in the early 1900s, was considered a useful diagnostic tool (20). Gil and colleagues observed that sepsis associated with an eosinophil count <40 cells/mm^3 is related to bacterial infections (21). In acute bacterial infection of infants, absolute eosinophil count of zero was reported (22,23). Peripheral blood eosinopenia is described in adult and pediatric patients with typhoid fever (13) and has been observed in association with other agents of sepsis (24). The potential utility of eosinophil count as a predictor of bacteremia was investigated by Lipkin (25). In their study of 75 blood culture positive patients, they found a positive correlation between positive blood culture and eosinopenia. They observed that no patient with 2 positive blood cultures had a peripheral blood smear of more than 1% eosinophil, suggesting a possible relationship between bacteremia and low eosinophil. Though eosionpenia has been studied in variety of infective diseases, sepsis, infective exacerbation of chronic obstructive lung diseases and Intensive care admission with sepsis (26), the optimal cut off value is still uncertain. In our study, we sought to understand the relationship between absolute eosinophil count of zero and salmonella infection in adults. We found absolute eosinopenia in 73% cases of enteric fever similar to previous reports (18,19,22,23). Of interest, that patients with positive blood culture had tended to have absolute eosinopenia (83%) compared to those diagnosed on Widal test alone (59%), although this did not reach significance. This supports the earlier reports that presence of bacteremia could increase the probability of having absolute eosinopenia (8,10,13,25).

Furthermore, 73% of our patients with enteric fever had a white cell count within the normal range, which is consistent with earlier reports of 85% WBC count within the same range (27,28). Leucopenia is said to be a common hematological finding in typhoid fever. In our study, leucopenia was observed only in 10 cases. However, it is comparable to prior observations (28,29). Anemia is supposed to be common due to suppression of bone marrow and hemophagocytosis (13), but there is wide variation in the reporting of anemia among different studies (28-31). In our series, only 15% of patient had a hemoglobin level below 100 g/L, a figure lower than most reported above. Thrombocytopenia was present in 35% of our patients, a figure higher than reported by most other studies (28,29). Leucopenia, eosinopenia, thrombocytopenia and anemia in enteric can be attributed to the myeloid maturation arrest, decrease in the number of erythroblasts and megakaryocytes and increased phagocytic activity of histiocytes in the bone marrow (13).

In conclusion, eosinopenia is common in bacterial infection correlating well with CRP and procalcitinin but the eosinophil cut off values have not yet been established. This may vary with the clinical setting and the site and the etiology of infection (26). Absolute eosinopenia in the proper clinical settings can give a strong clue to the diagnosis of enteric fever. It could be used as marker in strongly suspected cases of enteric fever to promptly initiate therapy particularly in setting of limited diagnostic resources. Other hematological changes such as anemia, leucopenia, leucocytosis and thrombocytopenia are not very common nor specific in enteric fever compared to other bacterial infections and may not be employed for diagnostic purposes.

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