

Marked Leucocytosis Masquerading Chronic Leukemia: case series

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ABSTRACT: The term leukemoid reaction (LR) was initially coined by Krumbhaar in 1926. Since then, a lot of studies have been conducted to understand the pathophysiology and its role in various diseases. The cut off value for LR has not yet been defined; however a clear cut distinction has to be made between LR and chronic leukemia as both are treated differently. Present study is a case series of ten patients presenting with high total leucocyte count ranging from 55,300 cells/mm³ to 1,49,000 cells/mm³; mean 73,500 cells/mm³. A total leucocyte count of about 1,49,000/mm³ as seen in this case series can masquerade chronic leukemia. A simple laboratory test like Leucocyte alkaline phosphatase can help to distinguish between them. LR is a rare condition, which can be challenging as it is associated with increased mortality among patients so it requires a careful diagnostic work-up including a combination of complete blood count with peripheral blood smear which shows marked neutrophilia with left shift and a high LAP score.

Keywords: Chronic leukemia, Leucocyte alkaline phosphatase score, Marked leucocytosis.

I. Introduction

The term leukemoid reaction (LR) was initially coined by Krumbhaar in 1926 [1]. Since then, a lot of studies have been conducted to understand the pathophysiology and its role in various diseases [2,3]. A markedly elevated total leucocyte count (TLC) has been associated with various haematological malignancies, but the cut off value for LR has not yet been defined as some authorities have used a cut off 25,000 cells/mm³, 40,000 cells/mm³ and 50,000 cells/mm³ respectively [2,3,4]. However a clear cut distinction has to be made between LR and chronic leukemia as both are treated differently. Leucocyte alkaline phosphatase (LAP) is an enzyme present in the cytoplasmic microsomes of neutrophils, band forms, metamyelocytes and myelocytes but not in lymphocytes or monocytes. Immature neutrophils such as those observed in chronic myeloid leukemia (CML) have decreased LAP score while the stimulated neutrophils of LR have increased LAP score [5]. Leucocyte alkaline phosphatase score has been used since long to distinguish between LR and chronic leukemia [6,7]. The absence of basophilia, eosinophilia and monocytosis along with increased leucocyte alkaline phosphatase (LAP) distinguishes LR from CML [3].

II. Material And Methods

Here we studied 10 cases whose total leucocyte count low level cutoff was 55,000 cells/mm³. Review of patient record was done. All patient details like chief complaints, past and family history, general and systemic examination findings, diagnosis, investigations were noted. Patients having haematological malignancies were excluded. 2ml of peripheral venous blood sample was collected in K₂-EDTA vacutainer for haemogram and peripheral blood smear examination. Haemogram was done on Beckman coulter LH-750 fully automated hematology analyser. Blood smears were made on clean glass slides and stained by Leishman stain.

Two blood smears were made on clean glass slide using finger prick blood for LAP score staining. Similarly a single slide from finger prick blood of pregnant women in their third trimester were obtained and stained for LAP score which were used as control.

Leishman stained smears were thoroughly examined with special emphasis on differential cell count, LAP score staining and interpretation (Table.1,2 and Fig.1) which was done as per the procedure in Dacie and Lewis Practical haematology [7].

III. Results

Ten cases with leukemoid reaction with a cut off lower limit of 55,000/mm³ were included in the study. The age of patients ranged from 14 years to 75 years, with mean age of 44.8 years. More male were having LR as compared to females; the male to female ratio was 2.3:1. Infection was the most common underlying cause seen in 80% cases while inflammation was seen in 20% cases. Renal abscess 3/8 (37.5%), sepsis 3/8 (37.5%), pneumonia 2/8 (25%) respectively were the infective causes. Acute pancreatitis 2/2 (100%) constituted the

inflammatory cause. Most of the patients were referred from other hospitals in critical condition who had a very short duration of hospital stay with fatal outcome. The duration of hospital stay ranged from 1 to 26 days; while the mean was 7.8 days. Mortality was seen in 6/10(60%) cases while improvement was seen in 4/10(40%) cases. The highest total leucocyte count which was documented ranged from 55,300 cells/mm³ to 1,49,000 cells/mm³; mean of 73,500 cells/mm³ (Fig.2) Differential count revealed left shift upto myelocyte stage with predominance of neutrophils. Neutrophils showed hypersegmentation with toxic granules (Fig. 3). Last documented TLC ranged from 4,600 cells/mm³ to 1,49,000 cells/mm³; mean of 44,530 cells/mm³. Cases whose last documented TLC count was high had a fatal outcome; thus the relationship between total leucocyte count and outcome was statistically significant (p-value 0.01 by Mann-Whitney test.) Leucocyte alkaline phosphatase score was elevated in all the cases (Fig.4 and 5) score ranged from 280 to 400, mean 344.8; control score mean was 208.3. Case details with reference to the outcome is shown below in Table 3.

IV. Discussion

Present cases showed left shift with predominance of neutrophils. Neutrophilia may be associated with the presence of left shift including band forms, metamyelocytes and blasts[8] The absence of basophilia, eosinophilia, monocytosis, increased leucocyte alkaline phosphatase score (LAP) distinguishes LR from CML.[3]

In our case series also the major causes of LR were severe infections, inflammation like pancreatitis intoxications, malignancies, severe haemorrhage, acute hemolysis[2,3]. Our study revealed fatal outcome in cases of infections, while Reding et al reported a high mortality rate with non-infectious diagnosis[9]. Mortality was seen more in female patients in a study by Lawrence et al while our study showed similar prediction for gender[4].

Reding et al and Waheed et al found that patients with TLC more than 25,000/mm³ at admission had higher mortality rate[9,10] whereas in our study it was not so, however cases who were having high last documented total leucocyte count had fatal outcome (p value < 0.05).

Present study showed age independent mortality, whereas possible explanation for high mortality in elderly may include age associated atypical clinical presentation yielding a diagnostic delay, postponed hospitalisation and presence of comorbidities[2]. Alternatively, LR might represent a functional compensatory response to several age related defects in neutrophil functions, including compromised chemotaxis and phagocytosis[11].

V. Conclusion

Leukemoid reaction is a rare condition that can be challenging as it is associated with increased mortality among patients. With a very high TLC bone marrow aspiration and biopsy is a necessary investigation but may not be done in critically ill patients who die within a day or two of hospitalisation. So careful diagnostic work-up, including complete blood count with peripheral blood smear revealing marked neutrophilia with left shift and high LAP score would definitely lead to the proper diagnosis and prior initiation of treatment, so we should always have a high index of suspicion.

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Figure 1: Steps involved in preparing and staining for LAP score.

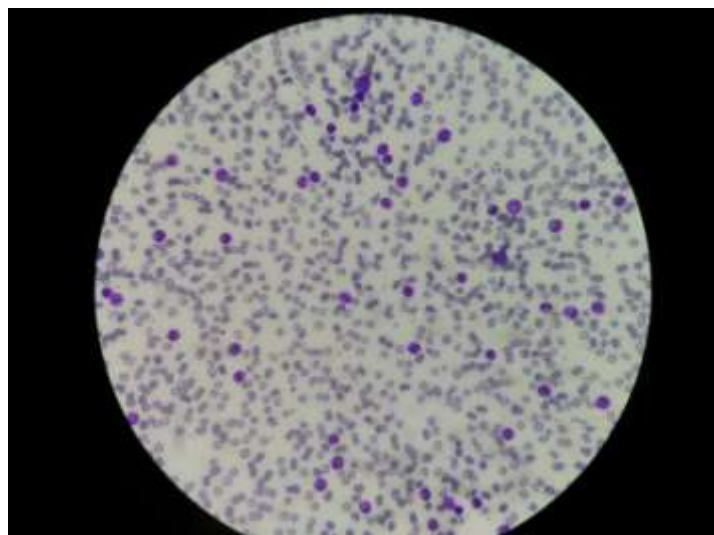


Figure 2: Peripheral blood smear showing marked leucocytosis (Leishman stain 400X)

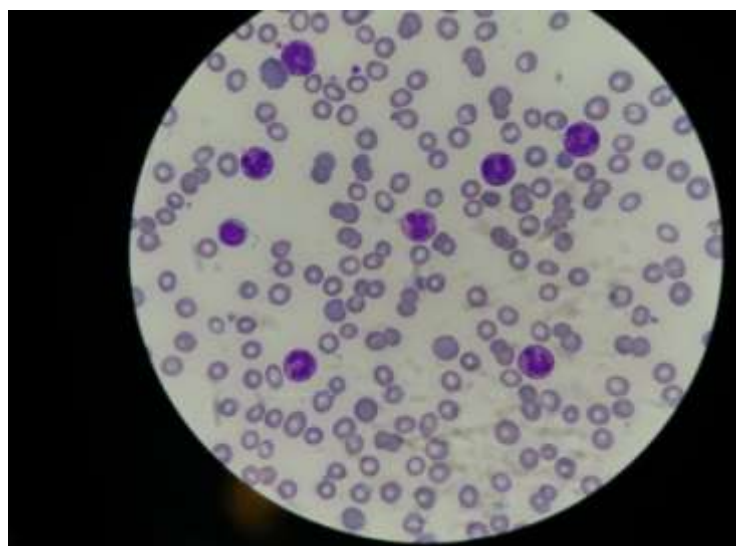


Figure 3: Peripheral blood smear showing Neutrophilia with toxic changes. (Leishman stain 1000X)

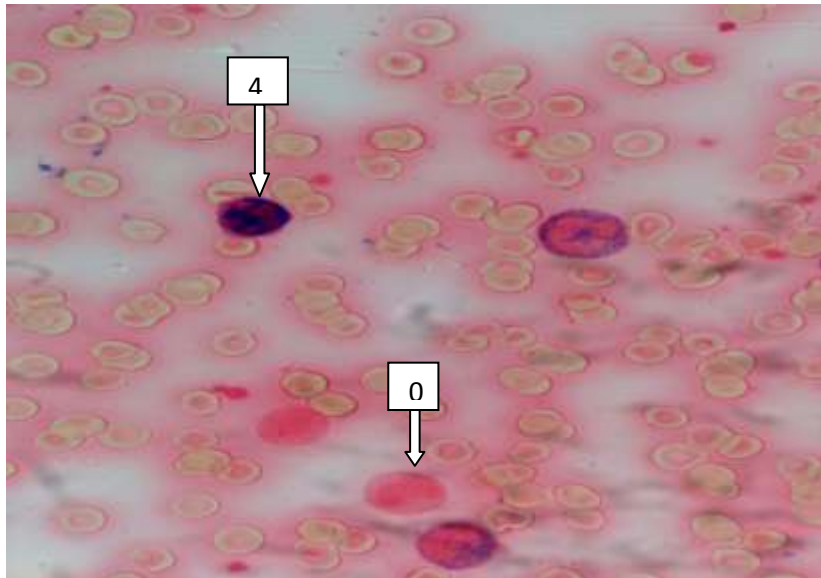


Figure 4: Peripheral blood smear showing Leucocyte alkaline phosphatase staining score 4 and 0 respectively(Leucocyte alkaline phosphatase stain 1000X)

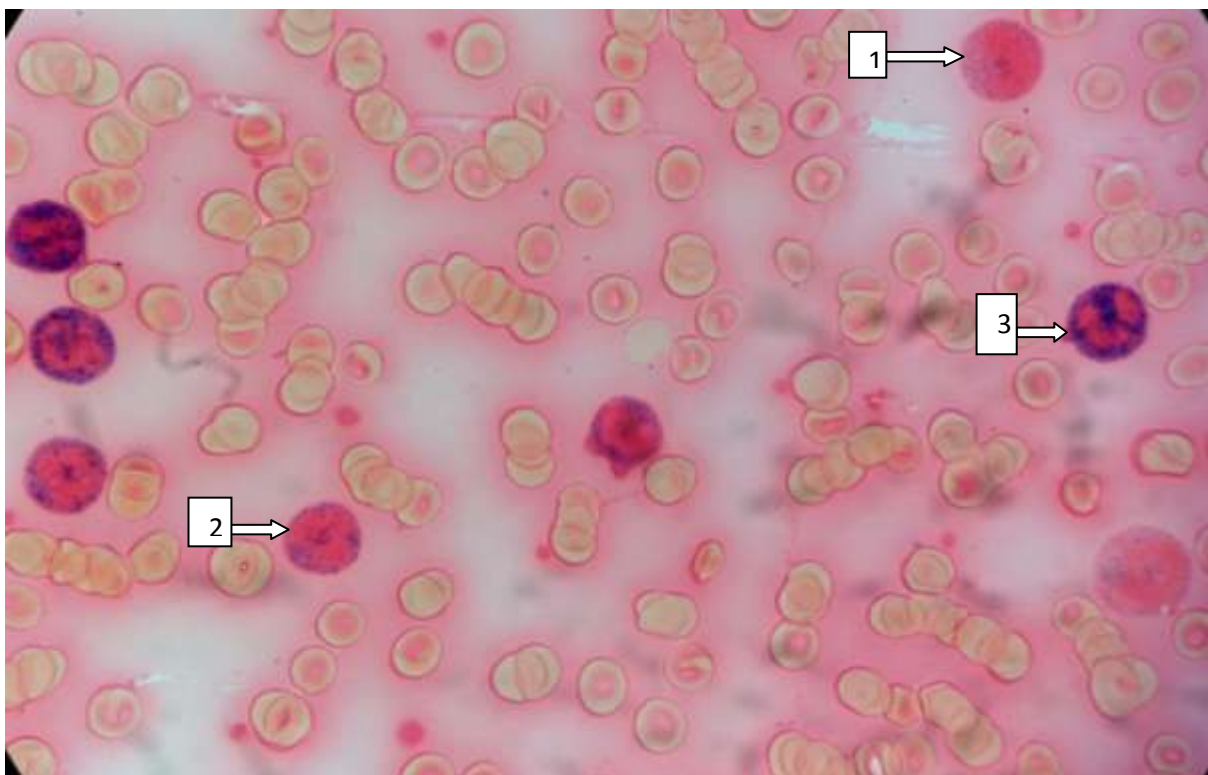


Figure 5: Peripheral blood smear showing Leucocyte alkaline phosphatase staining ; score 3,2 and 1 respectively(Leucocyte alkaline phosphatase stain 1000X)

Table 1: Reagents used for making stain for LAP.

Fixative	4% formalin methanol
Substrate	Naphthol AS phosphate (Sigma N-5625)
Stock substrate solution	30mg naphthol AS phosphate disodium salt + 0.5ml N,N-dimethylformamide (Sigma D-4551) + 100ml 0.2mol/l Tris buffer pH 9.0. Mix thoroughly
Coupling azo dye	Fast blue BB salt (Sigma F-0250)
Working solution	40 ml stock substrate solution + 24mg Fast Blue BB. Mix thoroughly. Filter and use
Counterstain	0.1% Neutral red or 0.1% Safranin

Table 2: Interpretation for LAP stain

Step 1. The differential cell count (DLC) of all cases and controls was done on Leishman's stained peripheral blood smears.	
Step 2. The overall LAP score was obtained by assessing the intensity of the stain in 100 consecutive neutrophils	0- Negative, no granules 1- Occasional granules scattered in the cytoplasm 2- Moderate number of granules 3- Numerous granules 4- Heavy positivity with numerous coarse granules crowding the cytoplasm, frequently overlying the nucleus

Table 3: Case details in relation to patient outcome is as shown in table below

Outcome	Number of patients	Highest TLC cells/mm ³ (Mean)	Last TLC cells/mm ³ (Mean)	LAP score (Mean)	Hospital stay in days(Mean)
Expired	6	76,600	67,150	348	6
Improved/Cured	4	68,850	5,780	339	10