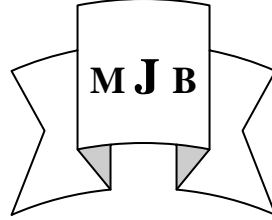


Studying Some Hematological Changes in Patients with Pulmonary Tuberculosis in Babylon Governorate

Muhammad Obaid Al-muhammadi
College of Medicine, University of Babylon, Hilla, Iraq.

Hayder Gali Al-Shammery



Abstract

The aim of this study is to investigate the changes of some hematological parameters in patients affected with pulmonary tuberculosis in Babylon province. 90 patients with pulmonary tuberculosis (45 males and 45 females) and 40 healthy controls (20 males and 20 females) have included in present study. Patients have been classified into 3 groups: group 1 includes newly diagnosed patients, group 2 includes patients after two months from starting treatment and group 3 includes patients after six months from starting treatment. The mean of ages was 44 ± 2 years for patients and 42 ± 2 years for the control. This study founded that values of Hb, PCV, platelets and ESR for both sexes were significantly changed in group 1 in comparison with group 2. Values of Hb, PCV, platelets and ESR for both sexes were significantly changed in group 1 in comparison with group 3. This study has show that values of Hb, PCV, platelets and ESR values for both sexes were significantly changed in group 1 in comparison with healthy controls. Values of platelets and ESR for both sexes and values of PCV for males were insignificantly changed while values of Hb for both sexes and values of PCV for females were significantly changed in group 2 in comparison with group 3. This study showed that values of PCV for males were insignificantly changed while values of Hb, platelets and ESR for both sexes and PCV for females were significantly changed in group 2 in comparison with healthy controls. The results has proved that the values of platelets and ESR for both sexes and Hb for females and PCV for males were insignificantly changed while values of Hb for males and PCV for females were significantly changed in group 3 in comparison with healthy controls.

الخلاصة

صممت هذه الدراسة لغرض تقييم بعض التغيرات الدموية في مرضى التدرن الرئوي في محافظة بابل. أجريت هذه الدراسة في الفترة من تشرين ثاني/٢٠١٠ ولغاية آذار/٢٠١١ في العيادة الاستشارية للأمراض الصدرية والتنفسية في الحلة، وحدة التدرن في قطاع الحلة للرعاية الصحية الأولية و وحدة التدرن في قطاع المسبب للرعاية الصحية الأولية وشملت (٩٠) مريض مصابين بالتدرن الرئوي (٤٥ من الذكور و ٤٥ من الاناث) كان متوسط أعمارهم $(٤٣,٥ \pm ١,٦$ عاماً) و(٤٠) عينة من الناس الاصحاء (٢٠ من الذكور و ٢٠ من الاناث) كان متوسط أعمارهم $(٤١,٧ \pm ١,٩$ عاماً). المرضى كانوا على ثلاثة مجاميع ، المجموعة الاولى شملت المرضى الجدد ، المجموعة الثانية شملت المرضى بعد شهرين من العلاج والمجموعة الثالثة شملت المرضى بعد ستة أشهر من العلاج.

النتائج: بينت الدراسة ان قيم خضاب الدم (Hb)، حجم الخلية المضغوطة (PCV)، عدد الصفيحات الدموية ومعدل ترسب خلايا الدم الحمراء (ESR) لكلا الجنسين أظهرت تغيرات معنوية في المجموعة الاولى مقارنة بالمجموعة الثانية من المرضى. قيم Hb، PCV، عدد الصفيحات الدموية و ESR لكلا الجنسين أظهرت تغيرات معنوية في المجموعة الاولى مقارنة بالمجموعة الثالثة. هذه الدراسة أشارت الى وجود تغيرات معنوية في المجموعة الاولى بالمقارنة مع مجموعة السيطرة في قيم Hb، PCV، عدد الصفيحات الدموية و ESR لكلا الجنسين. قيم عدد الصفيحات الدموية و ESR لكلا الجنسين و PCV للذكور أظهرت تغيرات غير معنوية، بينما قيم Hb لكلا الجنسين و

PCV للذكور أظهرت تغيرات معنوية في المجموعة الثانية مقارنة بالمجموعة الثالثة من المرضى. هذه الدراسة بينت ان قيم PCV للذكور أظهرت تغيرات غيرمعنوية، بينما قيم Hb، عدد الصفيحات الدموية و ESR لكلا الجنسين أظهرت تغيرات معنوية في المجموعة الثانية مقارنة بمجموعة السيطرة. النتائج اثبتت ان قيم عدد الصفيحات الدموية و ESR لكلا الجنسين و PCV للذكور أظهرت تغيرات غيرمعنوية، بينما قيم Hb و PCV للذكور أظهرت تغيرات معنوية في المجموعة الثالثة مقارنة بمجموعة السيطرة.

Introduction

Pulmonary tuberculosis is a highly infectious disease [1] in which single patient may have devastating effects on tuberculosis control program by infecting large number of people [2]. Tuberculosis (TB) caused by infection with *Mycobacterium tuberculosis*, which is part of a complex of organisms including *Mycobacterium bovis* (reservoir cattle) and *Mycobacterium africanum* (reservoir human) [3].

In 2009, there were an estimated 9.4 million incident cases of TB globally (equivalent to 137 cases per 100 000 population), most of the estimated number of cases in 2009 occurred in Asia (55%) and Africa (30%) [4]. Accurate and rapid diagnosis is the key to control the disease but, the current routine diagnostic tests for TB (chest x-ray, culture, tuberculin skin test and acid-fast staining) all have their limitations, in which chest x-ray alone is inconclusive, culture take too long to produce a result, the tuberculin skin test lacks specificity and reliability, serological tests using different TB antigens to detect *Mycobacterium tuberculosis* infection are fast but lack the desired sensitivity [5].

The primary method for diagnosing pulmonary tuberculosis in low-income and middle-income countries is direct sputum smear microscopy, which is fast, inexpensive, and specific for *Mycobacterium tuberculosis* but, it has low sensitivity because of variable quality of the test in program conditions [6]. New methods have been developed,

such as nucleic acid amplification technology which, although specific, can yield false-positive results, as well as immunologic tests which have their disadvantages and unanswered questions, so we still need accurate and rapid method of diagnosing both active and latent TB infection [5].

In pulmonary tuberculosis many hematological and biochemical abnormalities are common and they are valuable aids to diagnosis [7]. In pulmonary tuberculosis patients rise in hemoglobin and hematocrit levels are used as markers reflecting response to treatment [8].

The ESR is usually elevated in such conditions: infections, collagen diseases, metastatic malignant tumors and renal disease (said to be the leading causes of elevated values ≥ 100 mm/h.) [9]. Reduction in ESR were regarded as good indicator to observe drug response and disease progress or regress [10]. Anemia is a cardinal feature in patients with bacterial infections, particularly infections lasting longer than a month, including pulmonary tuberculosis [11] in which the precise mechanism of anemia in pulmonary tuberculosis is not clearly known [12]. The occurrence of anemia among patients diagnosed as active pulmonary tuberculosis was very high and it was contributed to anemia of chronic disease [13]. Reactive thrombocytosis is found in a number of clinical situations including infectious diseases such as pulmonary tuberculosis [14].

Aim of the study

This study has aimed to estimate some hematological changes in patients who are infected with pulmonary tuberculosis in Babylon province to help the medical staff in the early and precise detection and follow up of this disease. This study has designed to determine the following:

1. Measurement of hemoglobin concentration.
2. Packed cell volume.
3. Platelets count.
4. Erythrocyte sedimentation rate

Materials and Methods

The duration of the study since November / 2010 till March / 2011. There were 90 patients with pulmonary tuberculosis (45 males and 45 females) and 40 healthy controls (20 males and 20 females) assessed by specialist doctors on the basis of history, clinical examination, chest radiography and, direct smear sputum examination. The patients were classified into three groups and each group composes of 30 patients (15 male and 15 female). Group 1 included newly diagnosed patients before starting treatment, group 2 included patients after two months from starting treatment and group 3 included patients after six months from starting treatment (at the end of treatment). Those patients were the attendants to Al-Hilla Consultation Clinic for Chest and Pulmonary Diseases, Al-Hilla Primary Health Care District (TB Unit) and Al-Musayyib Primary Health Care District (TB Unit). Due to many conditions may interfere with the results of measured parameters and the outcome of the study, we exclude from the study subjects with the following conditions

1. Extra pulmonary tuberculosis.
2. Non-tuberculous pulmonary infections.

3. Chronic pulmonary disease.
4. Chronic liver disease
5. Chronic renal disease.
6. Diabetes mellitus.
7. Smoking.
8. Pregnancy.
9. Chronic cardiovascular diseases.

The collection of blood done in Al-Hilla Consultant Clinic for Chest And Pulmonary Diseases, Al-Hilla Primary Health Care District (TB Unit) and, Al-Musayyib Primary Health Care District (TB Unit) from 8.30 A.M. to 11.30 A.M. Five ml. of blood drawn for each hematological study in tubes contain EDTA as anti- coagulants to prevent clotting of blood. Each sample was labeled and given a serial number together with the patient name [15].

A cyanomethemoglobin method was used to estimate the hemoglobin contents of the blood. The method was based on Drabkin's cyanide- ferricyanide solution. Twenty micro liter (μL) of blood was added for 5 ml of Drabkin's solution mixing, and incubated for at least 5 minutes at 37°C and then the results were estimated by using Hb meter at 540 nanometer (nm) wave length [16].

Microhematocrit method was used to determine PCV. Heparinized capillary tubes used, and blood was filled to approximately three quarters of their lengths then the unmarked end is closed with modeling clay and put in the microhematocrit centrifuge. After centrifugation for 15 minutes, the red blood cells were separated from plasma and remain a band of buffy coat at the interface between them consisting of leukocytes and blood platelets [15].

This is done by taking 0.38 ml of diluting fluid (1% ammonium oxalate which hydrolyzes the RBCs,) and added to it 0.02 ml of blood taken by using hemoglobin pipette after having wiped

the tip of the pipette ,and then the counting chamber charged with the help of a Pasteur's pipette and placing the counting chamber in a Petri dish containing a moistened filter paper and let stand for 15 minutes to give time to platelets to settle ,then counted under high power (40 x objective) [15].

A Westergren tube: length- 300mm (open at both ends), diameter 2.5mm were used. One part of anticoagulant (3.8% trisodium citrate solution) was added to 4 parts of blood (0.5 ml of anticoagulant is added to 2 ml of blood). The mixture was drawn into a Westergren tube up to the zero mark and the tube was set upright in a stand with a spring clip on the top and rubber at the bottom. The level of the top of the red cell column was read at the end of 1 hour [15].

All values were expressed as mean ± SE. The data were analyzed by using of computer SPSS statistics 11 program. The differences were considered significant when the probability (P) was less than 0.05 (P < 0.05) and highly significant when the probability (P) was less than 0.01 (P < 0.01). ANOVA test was used to examine the differences between different groups [17].

Results

1. Hemoglobin (Hb)

Group 1 values for both males and females are highly significantly decreased (p < 0.01) in comparison with group 2, group 3 and healthy controls. Group 2 values of both males and females are highly significantly decreased (p < 0.01) in comparison with group 3 and healthy controls. Group 3 values of males are significantly decreased (p < 0.05) while for females they are insignificant (p > 0.05) in comparison with healthy controls.

2. Packed cells volume (PCV)

Group (1) values for both males and females are highly significantly decreased (p < 0.01) in comparison with group (2), group(3) and healthy controls. Group 2 values for both males and female show insignificant changes (p > 0.05) in comparison with group (3). While group (2) values for males are insignificant (p > 0.05) but for females they are significantly decreased (p < 0.05) in comparison with healthy controls. On the other hand group (3) values for both males and female show insignificant changes (p > 0.05) in comparison with healthy controls.

Table 1 The changes in Hb and PCV for pulmonary tuberculosis patients groups (Group 1 included newly diagnosed patients before starting treatment, group 2 included patients after two months from starting treatment and group 3 included patients after six months from starting treatment and controls.

	Sex	Group 1	Group 2	Group 3	Control
Hb (g/dl)		A	B	Ca	Cb
	Male	9.95 ± 0.269	11.900 ± 0.208	13.900 ± 0.220	14.800 ± 0.329
		A	B	C	C
	Female	8.870 ± 0.221	11.300 ± 0.197	13.200 ± 0.230	13.900 ± 0.350
PCV (L/L)		A	B	B	B
	Male	34.500 ± 1.300	45.100 ± 1.400	46.500 ± 1.117	47.200 ± 0.922
		A	B	B	B
	Female	31.600 ± 0.900	42.200 ± 1.00	43.600 ± 0.700	44.300 ± 0.622

- Values are mean ± SE.
- Different small letters indicates (p < 0.05).
- Different capital letters indicates (p < 0.001).
- Similar letters (capital & small) indicates no significant difference.

3. Platelets count

The values of platelets count for all the patient groups (1, 2 and 3) for male pulmonary tuberculosis patients are : 401.2 ± 9.294; 312.5 ± 4.609 and 226.7 ± 3.8 × 10³/mm³ respectively , and for females are: 325.0 ± 3.162; 280.2 ± 3.246 and 192.3 ± 5.144 × 10³/mm³ respectively. Group 1 values of both males and females are highly

significantly increased (p < 0.01) in comparison with group 2, group 3 and healthy controls. Group 2 values of both males and females are highly significantly increased (p < 0.01) in comparison with group 3 and healthy controls. Group 3 values of both males and females are insignificant (p > 0.05) in comparison with healthy controls.

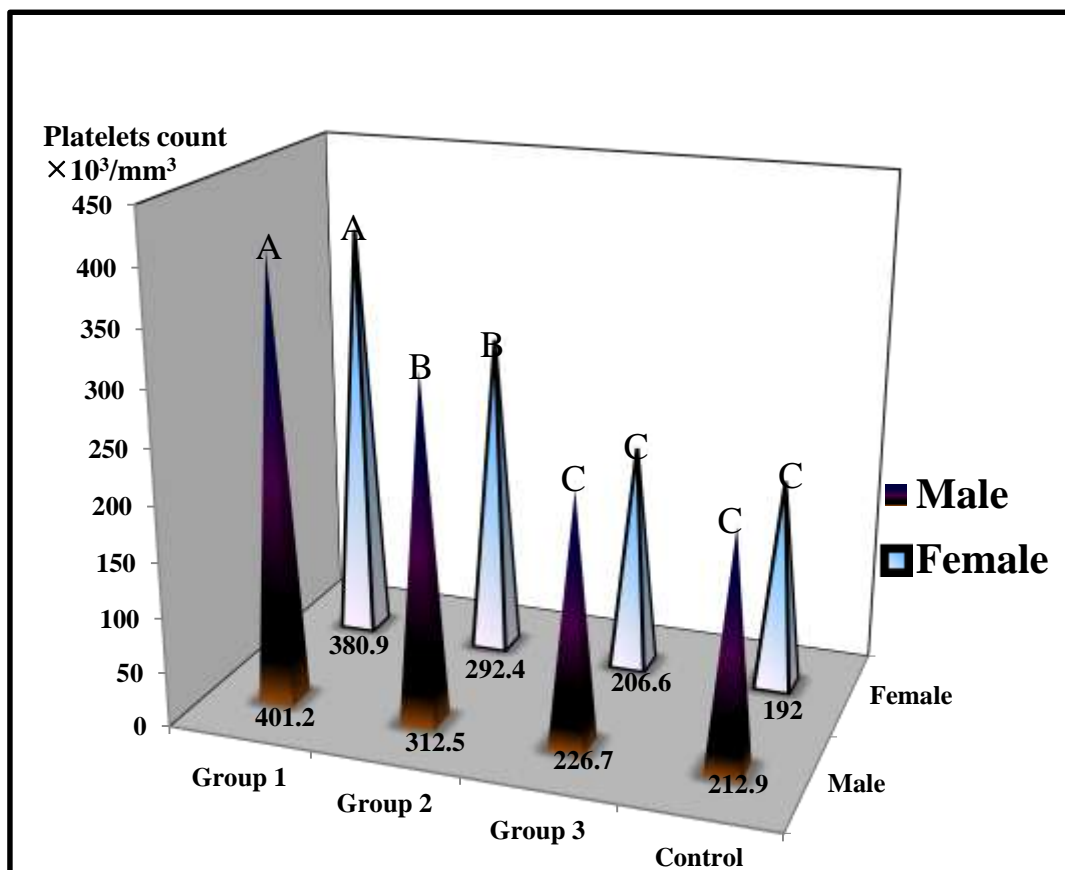


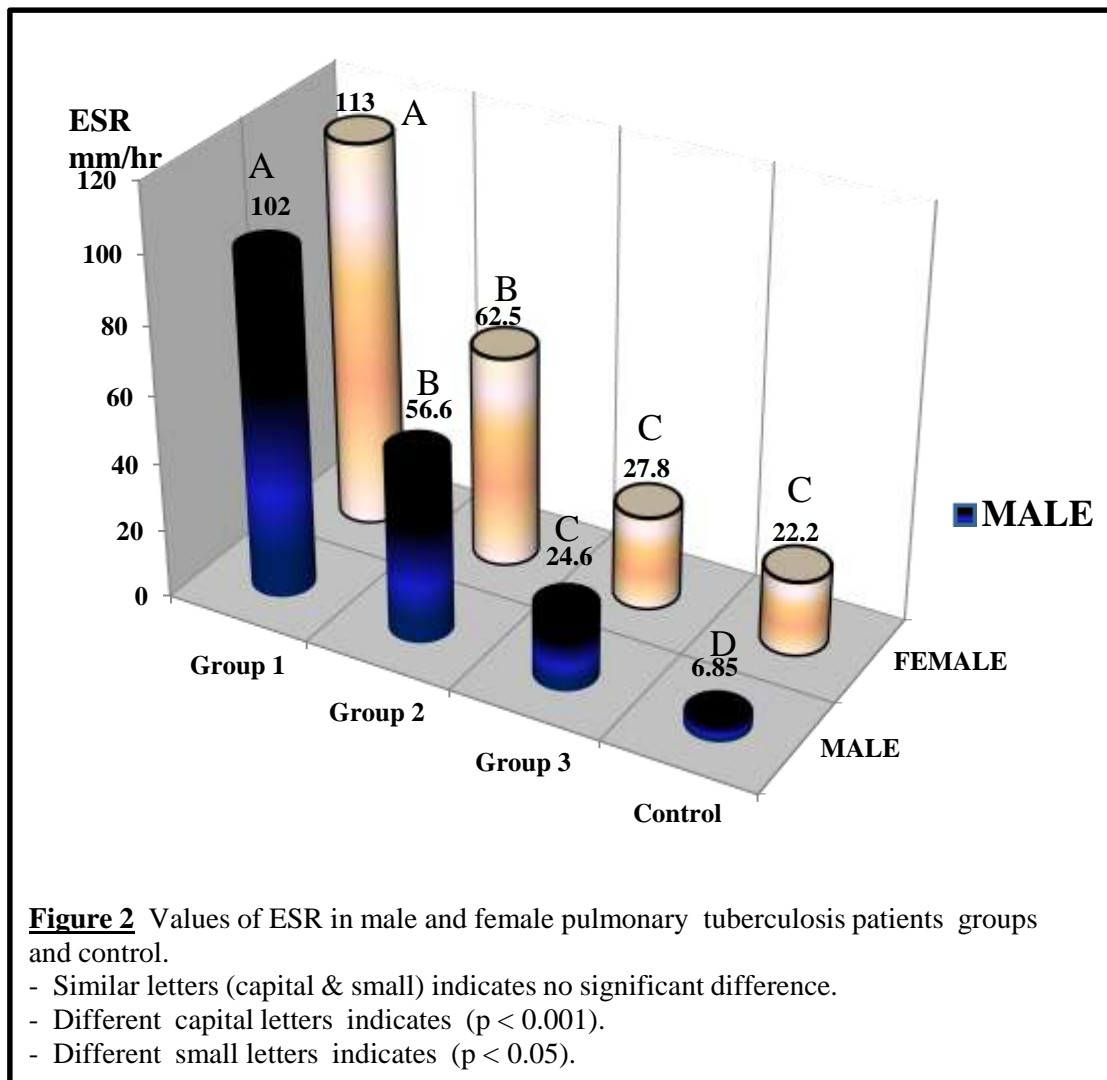
Figure 1 Values of plateletes count (mean) in male and female pulmonary tuberculosis patients groups and control.

- Similar letters (capital & small) indicates no significant difference.
- Different capital letters indicates (p < 0.001).
- Different small letters indicates (p < 0.05).

4. ESR

The values of ESR for all the patient groups (1, 2 and 3) for male pulmonary tuberculosis patients are : 102 ± 5.241 ; 56.6 ± 6.12 and 24.6 ± 3.982 mm/hr respectively , and for females are: 113 ± 3.91 ; 62.5 ± 6.7 and 27.8 ± 4.234 mm/hr respectively. Group 1 values for males and females are highly significantly increased ($p < 0.01$) in comparison with

group 2, group 3 and healthy controls. Group 2 values of both males and females are highly significantly increased ($p < 0.01$) in comparison with group 3 and healthy controls. Group 3 values of males are highly significantly increased ($p < 0.01$) while for the females they are insignificant ($p > 0.05$) in comparison with healthy controls.



Discussion

1. Hb and PCV

There was a high significant ($p < 0.01$) decrease in the values of Hb and PCV values of both males and females in newly diagnosed pulmonary tuberculosis patients in comparison with healthy controls as shown in table 1 and this is in agreement with Eyshi *et al.*[18] who states that occurrence of anemia among patients that were diagnosed as active pulmonary tuberculosis was very high and it was contributed to anemia of chronic disease.

As treatment with chemotherapy goes on there was a respectable gradual improvement in the levels of Hb and PCV towards control levels (table 1), this rise in hemoglobin and hematocrit levels can be used as a markers reflecting response to treatment as Al-Omar *et al.*[19] says, also Jemikalajab and Okogun [20] focused on this point saying that in pulmonary tuberculosis PCV is an essential hematological index and it is a regular feature in assessment of prognosis of the disease.

Weiss [21], Means[22] and Nemeth *et al.* [23] explain the mechanism behind the occurrence of anemia in pulmonary tuberculosis patients saying that the invasion of bacteria leads to activation of T-lymphocytes and macrophages, which induce the production of the cytokines like interferon gamma (INF-gamma), tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1) and interleukin-6 (IL-6) which with their products will cause diversion of iron into iron stores in the reticulo-endothelial system resulting in decreased iron concentration in the plasma thus limiting its availability to red cells for hemoglobin synthesis, inhibition of erythroid progenitor cell proliferation and in appropriate production and activity of erythropoietin,

the first leads to anemia and the latter two result in suboptimal response of the bone marrow to the anemia. Cytokines also impair red cell production in the marrow. IL-1 and TNF-alpha inhibit the production of erythropoietin, and together with INF-gamma impair responsiveness of progenitor cells to erythropoietin. An inhibitory effect of TNF-alpha on red cell production in the bone marrow has been demonstrated by both in vitro and in vivo studies. INF-gamma directly suppresses the proliferation of erythroid progenitor cells, in this way cytokines impair the physiological erythropoietin response to the anemia. In addition, TNF-alpha directly damages erythrocytes and decreases red cell life span. So the anemia of infection is therefore basically an underproduction anemia due to iron restriction, combined with inability of erythropoiesis to compensate adequately for the anemia.

Another study in Indonesia has been done by Karyadi *et al.*[24] also found an elevated levels of IL-6 and IL-1ra in the circulation and in unstimulated whole blood cultures from tuberculosis patients suffering from anemia.

2. The platelets count

From this study resulting data (figure 1) showed that values of both male and females of platelets count of group 1 tuberculosis patients were highly significantly increased ($p < 0.01$) in comparison with values of group 2, group 3 and healthy controls. These results may be attributed to the reactive thrombocytosis which is found in a number of clinical situations including infectious diseases such as pulmonary tuberculosis [25]. Also the increase in platelet count was noticed in Saudi pulmonary TB patients as compared with the normal Saudi persons [10].

The results have in contrast to Awodu *et al.* [26] who found that there was significantly lower platelet count in African pulmonary tuberculosis patients. In our study we notice that the values of platelets count of both males and females were changing from thrombocytosis to equalize the controls values and this was very clear because of the insignificance ($p > 0.05$) between the values of group 3 and the values of healthy controls (table 4.2) and this is compatible with Al-Omar *et al.* [10] who founded in their study that platelet count were elevated in pulmonary TB which is well influenced and corrected by using different combinations of antituberculosis drugs. Also Jemikalajab and Okogun [20] are on the same wave length in their study in which they states that: in pulmonary tuberculosis thrombocytosis is an essential hematological index and it is a regular feature in assessment of prognosis of the disease .

The explanation for these results returns to an elevated levels of IL-6 and IL-1ra in patients with pulmonary tuberculosis suffering from anemia as has been founded in a study in Indonesia doen by Karyadi *et al.*[24] .

IL-6-induced thrombocytosis is accompanied by enhanced hepatic thrombopoietin production and elevated thrombopoietin plasma levels [27] and although first proposed to be the primary regulator of platelet production 45 years ago, the gene for thrombopoietin was cloned only within the last decade. Since then, understanding of platelet production has increased considerably [28]. This regulatory pathway might be of relevance for the understanding of reactive thrombocytosis [27].

3. ESR

When an inflammatory process is present, the high proportion of fibrinogen

and other acute-phase proteins (haptoglobin, ceruloplasmin and CRP) and immunoglobulins in the blood causes red blood cells to stick to each other, these jammed red cells form what is called rouleaux which will settle and sediment faster [15].

In this work it has been found that the values of ESR for both males and females of pulmonary tuberculosis patients are highly significantly increased ($p < 0.01$) in comparison with group 2, group 3 and healthy controls and there were no significant difference ($p > 0.05$) between group 3 values and healthy control values (figure 2). These findings are fully supported by different reports and studies specifying high ESR levels in newly diagnosed and normal levels at the end of treatment of pulmonary tuberculosis patients like Al-Omar *et al.* [10] who stated that: erythrocyte sedimentation rate were elevated in pulmonary TB which is well influenced and corrected by using different combinations of antituberculosis drugs, other study says: erythrocyte sedimentation rate was significantly higher in pulmonary tuberculosis patients than controls, there was a significant reduction in the erythrocyte sedimentation rate from the 4th. week of therapy [26] and other one says: statistically significant hematologic abnormalities like high erythrocyte sedimentation rate founded in pulmonary tuberculosis patients in Ibadan, Nigeria [29].

Conclusions

Some hematological abnormalities are quite common in patients with pulmonary TB and physicians must maintain a high index of suspicion for diagnosis of pulmonary TB in patients with these abnormalities. As well as,

these parameters can be used as indicators in the assessment of response to chemotherapy. Furthermore during this study our understanding of anemia and it's mechanism of occurrence in pulmonary tuberculosis has increased considerably. Hopefully, this will perhaps yield an insights on the pathophysiology of this disease. However, many more questions remain about hematopoietic during course of TB waiting to be studied and the field remains ready and open for rich investigations and researches.

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