

## HEMATOLOGIC PROFILE OF LEPROSY PATIENTS IN REACTIONAL EPISODE OF ERYTHEMA NODOSUM LEPROSUM

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**ABSTRACT-** *In this work, eighteen patients in reactional episode of erythema nodosum leprosum (ENL) had their hematologic parameters evaluated. Eight of these patients had intense and moderate ENL, and ten patients had mild ENL. The results showed that patients with intense and moderate ENL had significant alterations in the hematologic findings: iron deficiency, an increased euglobulin lysis time and hyperfibrinogenemia. Nevertheless, no alteration was observed in the other parameters studied (prothrombin time, Heinz body and fibrinogen degradation products), in all the cases of ENL.*

**Key Words:** *Erythema nodosum leprosum. Hematologic findings.*

### 1. INTRODUCTION

The greatest cause of morbidity in lepromatous patients are the reactional states. They represent an acute episode that interrupts the slow, insidious and chronic evolution of leprosy. Three types of reaction are described nowadays: the erythema nodosum leprosum (ENL); the reversal reaction and Lucio's phenomena.

The ENL happens mainly in lepromatous patients, but sometimes the BL patients<sup>(34)</sup> are affected as well.

The ENL is characterized by painful erithematous nodulations that grows in apparently normal skin. Other symptoms are fever, anorexia and indisposition.

The hematologic findings in ENL are scarce in the literature. Generally, they relate to the disorders of the coagulation process and fibrinolysis<sup>(27,31,32,40,47)</sup>

With this work, we aim to establish a valuation of the hematologic findings on leprosy patients with ENL, to understand its mechanisms

and suggest therapy for the ENL complications.

### 2. MATERIALS AND METHODS

Eighteen patients with ENL from the Instituto Lauro de Souza Lima, Bauru, Brazil, were valuated.

Clinically, we define three intensity grades of ENL:

- Mild: some skin nodulations without suppuration; the patients are well.
- Moderate: numerous skin nodulations, some with suppuration, and mild alteration of the health status.
- Intense: numerous skin nodulations with suppuration and/or necrosis. The health status of patients is bad.

(The neuritis and visceral symptoms weren't used in this work, because they happen in all grades, and sometimes are the only manifestations of ENL).

We studied two groups of patients:

- I. Eight lepromatous patients with moderate and intense ENL.

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II. Ten lepromatous patients with mild ENL.

All patients were subjected to: anamnesis, clinical evaluation, bacilloscopic and histopathologic examinations to establish the reactional state of leprosy.

### 3. STUDY OF HEMATOLOGIC FINDINGS

The tests were carried out with normal controls:

1. Red cell count. haemoglobin, hematocrit, white cell count.

2. Leukocyte differential counts and platelet count in blood smears staining by Wright-Giemsa.

3. Reticulocyte count. The reticulocyte count was established by manual counting, with staining by methylene blue.

4. Serum Iron and Total Iron Binding Capacity. We used the Labtest kit. The normal values to serum iron are 50-150 ug/dl to the total iron binding capacity (TIBC).

5. Heinz Body. We used the acetylphenylhydrazine assay.

6. Bone marrow study. The bone marrow aspiration was performed by the technic of sternal marrow aspiration. Bone marrow smears were stained with Wright-Giemsa, and the smears were screened for qualitative evaluation of red cells and leukocyte series, in the ENL reactions.

7. Prothrombin time. We used the QUICK<sup>(33)</sup> technic.

8. Activate partial thromboplastin time. We used the BELL-ALTON technic<sup>(7)</sup>.

9. Qualitative assay of fibrinogen degradation products (FDP). The FDP was detected by precipitation assay with protamine sulphate.

10. Fibrinogen assay. The measurement of fibrinogen consist of plasma precipitation by heat coagulation, centrifugation and observation of the final volume of sediment in a calibrated tub where 45 mg% of serum fibrinogen corespond to a division of 0,005 (normal values are between 150-400 mg%).

11. Euglobulin lysis time. This is a very effective test to plasma activators of plasminogen. We used the BUCKELL'S technic<sup>(11)</sup> In normal

situations the lysis happens between two and four hours.

### 4. RESULTS

The haemoglobin, white cell, platelet and reticulocyte counts results are in table 1. The serum iron, total iron binding capacity, prothrombin time, activate partial thromboplastin time and euglobulin lysis time are in table 2.

We didn't find Heinz Body in the patients we studied. The fibrin degradation products were negative too.

The compared statistical analysis of the two groups are in table 3.

Bone marrow study: The patients with moderate and intense ENL presented a cellular and hyperplastic marrow, with precursors predomination. We detected megaloblasts in all stages of erythrocyte development. The cytoplasm, in the very early stages, was deeply basophilic. The orthochromatic erythrocytes presented abundant cytoplasm, that looks mature, whereas the nucleus looks immature; these abnormalities characterise the megaloblastic transformation. The leukopoiesis and megakaryocytes were little affected, showing only hyperplasia (figure 1 and 2).

The patients with mild ENL presented normal bone marrow (figure 3 and 4).

### 5. DISCUSSION

With this work, we establish a profile of ENL patients. Some of the observed aspects leaded us to future observations, aiming to understand the alterations in ENL patients. Some of these observations are still in process.

The anemia, reticulocytosis and bone marrow hyperplasia, mainly to the erythroid hyperplasia, with megaloblastic features in the moderate and intense ENL suggest a hemolytic anemia. Among the hemolytic anemias, we selected the acquired hemolytic anemia, because all patients we studied were followed in the Instituto Lauro de Souza Lima. They had not any manifestations of inherited abnormalities before the ENL.

**Table 1** - Hematologic Parameters of ENL\*

PATIENT	ENL	Hb (g%)	Ht (%)	WC (/mm3)	RET.** (%)	PLAT.*** (/mm3)
1	INTENSE	5,60	19	12300	10,00	640000
2	INTENSE	6,00	20	14700	10,50	600000
3	INTENSE	5,50	19	19000	5,00	600000
4	INTENSE	7,90	27	16400	5,00	280000
5	INTENSE	8,00	27	21400	7,00	600000
6	MODERATE	8,50	27	20200	12,00	950000
7	MODERATE	8,40	28	13000	6,00	420000
8	MODERATE	9,00	30	17500	7,00	520000
	AVERAGE	7,36	24,63	16812,50	7,81	576250,00
	STD DESV	1,42	4,50	3323,27	2,67	193016,47
9	MILD	11,30	35	18700	2,00	320000
10	MILD	10,40	32	14200	2,50	220000
11	MILD	9,80	30	10000	1,80	581300
12	MILD	12,00	37	12600	0,50	300000
13	MILD	12,20	38	21600	2,00	300000
14	MILD	12,40	38	14300	0,80	280000
15	MILD	12,60	38	18600	0,80	320000
16	MILD	10,80	33	9300	7,00	270000
17	MILD	11,20	34	5400	0,70	280000
18	MILD	13,30	39	5300	2,20	420000
	AVERAGE	11,60	35,40	13000,00	2,03	329130,00
	STD DESV	1,09	3,06	5586,09	1,89	102167,68

\* Erythema nodosum leprosum. \*\* Reticulocyte. \*\*\* Platelet. STD DESV = Standard desviation

Considering the acknowledged pathogenesis of the ENL, the hemolysis may have immunologic or microangiopathic origins.

Thus, just like it happens in other illness with imuno pathologic basis<sup>(22)</sup>, the diminution of the number of suppressor T-cells could facilitate the self-aggression by dangerous clones, which would cause *the* hemolysis by auto-antibodies. SEN et al<sup>(39)</sup> describe a case of a patient with ENL and hemolysis, who had a positive result from the Coombs test.

In other hand, the extensive vascular lesion found in ENL may suggest a kind of microangiopathic hemolytic anemia which takes place during these occurrences.

The demonstration of immune complexes in ENL is inconsistent<sup>(35,46)</sup>. The alteration of the proportion T helper/T supressor cells, with reduction in T supressor cells, would be the first

point in the pathogenesis process, allowing the increase of quantity and/or affinity of precipitant antibodies by the *M. leprae* antigens<sup>(22)</sup>. This will lead to the formation of immune complexes, whose localization may be intra or extravascular; hence the stimulation, through various mechanisms, of acute or sub-acute inflammatory reactions, in specific inflammatory foci (skin, nerves, vessels), or in places where the immune complexes are retained (renal glomeruli). Each episode of ENL has variable extent and intensity, and, in the most serious occurrences, there is an intense vasodilatation; endothelials welling at the veno-capilar region; serous, fibrinous and neutrophilic exsudation on the interstitial tissue, sometimes with necrosis and formation of abscess. On the regions where the inflammation is most serious there is a great reduction of the veno-capilar flow, and also the formation of "roleaux" of erythrocytes,

**Table 2 - Others ENL\* Parameters**

PATIENT	ENL	EUGL. LYSIS** (minutes)	FIBRIN.*** (mg%)	IRON (ug/dl)	TIBC° (ug/dl)	PT°° (%)	APTT°°° (sec.)
1	INTENSE	440	405	42	458	100	37
2	INTENSE	400	585	44	430	100	23
3	INTENSE	450	585	29	499	100	40
4	INTENSE	490	720	36	446	100	44
5	INTENSE	354	675	58	440	100	25
6	MODERATE	270	650	42	429	100	26
7	MODERATE	280	630	46	428	86	36
8	MODERATE	310	460	51	441	100	41
AVERAGE		374,25	588,75	43,50	446,38	98,25	34,00
STD DESV		443,62	107,23	8,82	23,55	4,95	8,14
9	MILD	270	495	71	398	100	34
10	MILD	200	360	58	390	100	34
11	MILD	190	315	26	521	100	26
12	MILD	200	225	92	302	100	29
13	MILD	240	360	95	298	100	26
14	MILD	195	495	66	390	84	28
15	MILD	150	450	72	321	86	37
16	MILD	240	495	62	336	100	34
17	MILD	200	405	73	354	100	15
18	MILD	120	450	89	317	100	15
AVERAGE		200,50	405,00	70,40	362,70	97,00	27,80
TD DESV		443,62	90,00	20,12	66,90	6,34	7,71

\* Erythema nodosum leprosum. \*\* Euglobulin Lysis Time \*\*\* Fibrinogen.

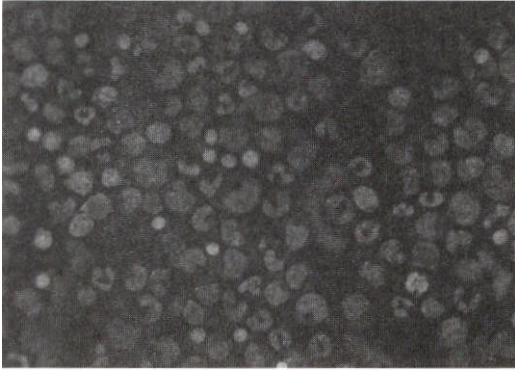
°Total Iron Binding Capacity. °°Prothrombin Time. °°°Activate Partial Phromboplastin Time.

STD DESV = Standard Desviation

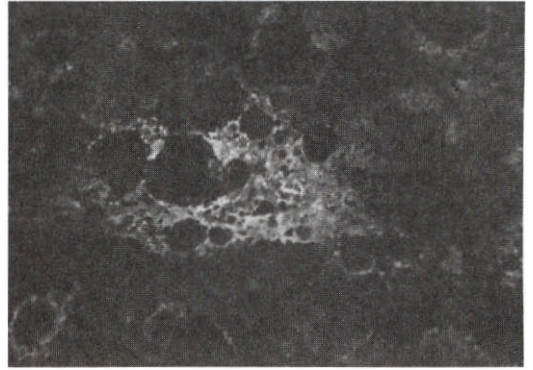
**Table 3 - Statistic Analysis**

PARAMETER	GROUP 1°		GROUP 2°		T	P
	AVERAGE	STD.DESV.	AVERAGE	STD.DESV.		
Hb	7,36	1,42	11,60	1,09	-7,17	S*
Ht	24,60	4,50	35,40	3,10	-6,04	S
RETICUL.	7,81	2,70	2,00	1,88	5,38	S
PLATELETS	576250	193016	329130	102167	3,50	S
WC	16812	3323	13000	5586	1,70	NS*
IRON	43,50	8,80	70,40	20,10	-3,50	S
TIBC	446,30	23,50	362,70	66,90	3,35	S
FIBRIN.	588,70	107,20	405,00	90,00	3,90	S
EUGL. LYSIS	374,30	83,10	200,50	43,60	5,72	S

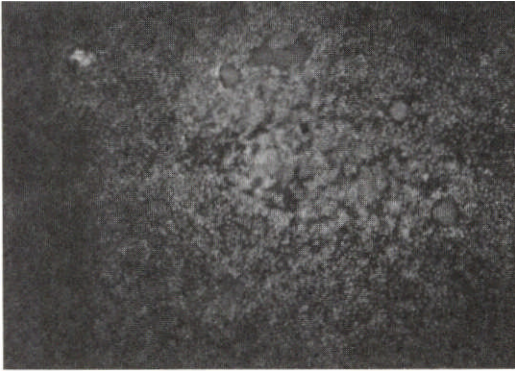
\* S = p<0,001; \*\* NS = no significant °ENH intense/moderate; °°ENH mild



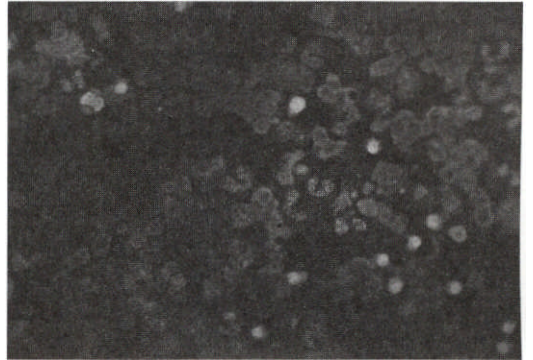
**Figure 1.** Bone Marrow smear of an intense/moderate ENL patient (40X).



**Figure 2.** Bone Marrow smear of an intense/moderate ENL patient (10X).



**Figure 3.** Bone Marrow smear of a mild ENL patient (40X).



**Figure 4.** Bone Marrow smear of a mild ENL patient (10X).

increase in blood viscosity. endothelial changes secondary to anoxia and thrombosis. The exudation may stretch to the walls of the dermis and sub-cutis larger blood vessels, causing dissociation of the muscular wall, endothelial lesion and thrombosis<sup>23,45</sup>

The microangiopathic hemolytic anemia may be found in some diseases, where the small vessels are damaged by immune mechanisms. Some connective tissue diseases, characterized by vasculitis, like lupus erythematosus<sup>(9,11)</sup>, Sjögren's syndrome and poliarteritis nodosa<sup>(22)</sup>, occasionally may lead to microangiopathic hemolytic anemia. The fragmentation of erythrocytes may be found in association with polymiositis<sup>(22)</sup>, scleroderma<sup>(37)</sup>, Wegener granulomatosis<sup>(13,29)</sup>

and giant cell arteritis. Some patients with the mentioned disease have shown fibrin deposits on the vascular lesions<sup>(20)</sup>. In these diseases, the circulating immune complexes initiate the coagulation process<sup>(43)</sup>, probably acting on the platelets. That results in the formation of fibrin deposits, which stimulates the proliferation of endothelial cells. The formation of fibrin deposits and the endothelial changes — including the damages on these cells, caused by the immune complexes—are responsible for the fragmentation of erythrocytes that occurs in diseases which are characterized by the presence of circulating immune complexes.

All the patients studied in this work showed a normalization of the hemoglobin levels

with the remission of ENL, without any specific treatment for anemia. We tested the patients for Heinz bodies, aiming to exclude the deficiency of G-6-P-D as a cause of their anemia — since they take sulphone, which causes strong oxidative stress.

The leprosy patients, who sometimes are also carriers of the deficiency of G-6-P-D, may, while using the sulphone — which is a oxidative stress — develop anemia, normally in the chronic form, with mild or moderate reduction of the hemoglobin levels. Thus, this sudden fall of hematocrits during the evolution of ENL cannot be explained only by the deficiency of G-6-P-D, associated with the use of dapsone — since most of the patients were already taking the sulphone before the occurrence of ENL.

The occurrence of leukocytosis is easily understandable, since there are various coexisting factors that lead to leukocytosis caused by neutrophilia: inflammatory process and formation of immune complexes deposits, as well as the great stimulation that occurs at the bone marrow, in hemolysis situations.

The same explanation (stimulation) may account for the increase in the number of platelets, in patients with anemia secondary to ENL.

We can observe an increase of euglobulin lysis time — which was very evident in the patients with intense or moderate ENL, thus reflecting a diminution in fibrinolysis. Under normal conditions, the fibrinolysis is a finely regulated process<sup>(03)</sup>. In some tissues— including platelets<sup>(15)</sup> and endothelium<sup>(42)</sup>, was found an inhibitor of the plasminogen tissue activator and urokinase, named PAI-1. The interleukine 1 (IL1) and the tumoral necrosis factor (TNF), diminish the secretion of plasminogen tissue activator and increases elaboration of PAI-1 in tissue cultures<sup>(38)</sup> SARNO et al<sup>(39)</sup> relate that 50% of the lepromatous patients with erythema nodosum leprosum showed high levels of TNF and IL1, concluding that TNF and IL1 may be involved in the leprosy reaction. The interleukines (TNF and IL1) are secreted by activated macrophages<sup>(48)</sup>, during acute inflammatory reactions. In our work, we met an increase of euglobulin lysis time, which confirms the results of previous works<sup>(04,26,27,31, 32,40,47)</sup> The

increase of TNF and IL1 may suggest that this is one of the responsible mechanisms for the diminution of the fibrinolytic activity in the ENL patients.

With regard to the prothombin time (PT) and activate partial thromboplastin time (APTT), the results found in this work were different from those mentioned by MUKHERJEE; GHOSH S<sup>(32)</sup> who met the APTT increased in 50% of the cases; and from those mentioned by WIRAVAN et al<sup>(08)</sup> who observed increase on the APTT values in 85% of the cases. The PT did not show changes in neither of the works. In our work, both the parameters (PT and APTT) had results within the normal patterns, which is compatible with the absence of bleeding or purpura in these patients. On the contrary, in previous observations, Pathology Service of the Instituto<sup>(16,17,18)</sup>, we noticed that the thromboembolic accidents were very frequent. The thrombosis would be caused by the association of the diminution of the fibrinolytic activity— related in this work — with the vascular lesion, which activate the coagulation through intrinsic and extrinsic pathways. The intrinsic pathway of coagulation would be activated by the exposition of collagen, acting as a contact factor, while the extrinsic pathway would be activated by the secretion of thromboplastin from the tissues damaged by the inflammatory process.

We could notice that our patients showed low levels of serum iron, and the total iron binding capacity was not high, as it happens usually in iron deficiency anemias<sup>(05,25)</sup>. In most of the cases, the total iron binding capacity was normal - or in the highest levels of normality. These findings are compatible with those met in patients who were carriers of cronic disease. In the latter, we found a diminution of the serum iron concentration, a reduction of the total iron binding capacity and a subnormal saturation of transferrin<sup>(05,12,21,44,45)</sup> In patients with infection, hypoferrremia develops early in the course of the illness, frequently within<sup>24</sup> hours<sup>(24)</sup>, and is observed even in acute, self- limited febrile diseases or after a single injection of typhoid vaccine<sup>(01,12)</sup>.The degree of hypoferrremia is related to the severity of the underlying illness<sup>(05,19,28)</sup>. Thus, when it comes to the ENL patients, we have two superimposed causes for the occurrence of hypoferrremia: the leprosy as primary illness,

and the ENL as an acute manifestation of inflammatory process. The results we obtained lead us to future investigations, aiming to analyse the type of hemolysis which happens in the ENL cases. They also suggest that the main treatment, in anemia's acute phase, is the supplement of folates, since they are the limiting factor under circumstances of great bone marrow stimulation. Another important conclusion relates to the

prophylaxis of thromboembolic accidents in the most serious cases of ENL, when all the fibrinolytic activity is deeply damaged. All the drugs that lead to the shortening of the ENL acute reactions must be taken in the early stages, especially those which diminish the acute inflammatory process, since the main events in ENL are directly related with the generalized acute inflammatory process in these patients.

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