A prospective study of hospitalized patients with leukemoid reaction; causes, prognosis and value of manual peripheral smear review

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Introduction. Several diagnoses have been associated with leukemoid reaction (LR). In patients with LR the diagnostic and prognostic value of detailed manual blood smear counts (such as the percentage of band cells or grading of neutrophil toxic changes) has not been studied previously.

Methods. We prospectively recorded all hospitalized adult (> 18 years old) patients with LR ($\geq 30000/\mu\text{L}$) of neutrophilic predominance, excluding patients with pre-existing leukocytosis due to hematological malignancies. We examined the diagnoses and prognosis (in-hospital mortality and post-discharge mortality up to a year after the end of the study) of these patients as well as the value of manual peripheral smear review.

Results. We recorded a total of 93 patients with LR from January 2017 to December 2017. Infection was the most common diagnosis (70%), followed by malignancy (7.5%) and bleeding (6.5%). In-hospital mortality (45%) and post-discharge mortality (35% of those discharged) were very high. Among blood smear findings, only neutrophil vacuolation was significantly more common in patients with infections (34%), although it was also observed in many patients without any infection (13%). Blood smear findings were not associated with prognosis.

Conclusion. Detailed manual smear review is a labor-intensive procedure and it has limited diagnostic and prognostic value in unselected hospitalized patients with neutrophilic LR.

Key words: leukocytosis, causes, prognosis, blood smear, neutrophilia.

INTRODUCTION

A variety of non-hematologic conditions may result in very high white blood cell counts (WBCs), such as infections, advanced malignancies, drugs (mainly corticosteroids and recombinant hematopoietic growth factors), severe hemorrhage, splenectomy and tissue ischemia [1-6]. Several terms have been used to describe this finding, such as “leukemoid reaction” [2, 3], “extreme leukocytosis” [4, 5] or “extreme granulocytic leukocytosis” [1]. Variable cut-offs have been used, such as 25000/ μL [1, 4], 30000/ μL [3], 40000/ μL [5] or 50000/ μL [2, 6]. The above terms are typically used to describe leukocytosis of neutrophilic predominance [1, 3].

The majority of prior studies were retrospective. To our knowledge, only two prospective studies have been conducted, one focusing on oncological patients [5] and the other focusing on patients presenting to the emergency department [4]. Furthermore, none of the prior studies [1, 3-6] has systematically examined the blood smear findings in patients with leukemoid reaction (LR). Of note is that according to the International Consensus Group for Hematology Review, manual peripheral smear review is recommended for all patients with WBCs more than 30000/ μL [7]. Therefore, we

conducted a prospective study of hospitalized adult patients with neutrophilic LR with the aim to examine the diagnoses and outcomes of such patients, as well as the correlation of blood smear findings with prognosis and diagnostic categories.

MATERIAL AND METHODS

Study population

The study was conducted prospectively in a 412-bed community hospital located in Heraklion, Greece. We prospectively recorded all hospital admissions with a white blood cell (WBC) count $\geq 30000/\mu\text{L}$ with neutrophilic predominance ($> 50\%$), present either at admission or during hospitalization. The study was conducted from January 2017 to December 2017. Only hospitalized adult (age > 18 years old) patients without a previous diagnosis of hematological malignancy and without pre-existing leukocytosis were considered. In case of patients admitted more than once to the hospital only their first admission was recorded. Outpatients were excluded. The protocol was approved by the hospital’s scientific council. Considering the non-interventional design of our study, informed consent was not required.

Detection of patients with LR

When a white blood cell count $> 30000/\mu\text{L}$ is detected, blood smear examination represents routine practice in our hospital for patients with previously unknown LR. This is in agreement with international guidelines [7]. Based on this practice, the patients with LR were detected prospectively by the hematology laboratory.

Data collection

The following data were recorded for each patient: age, gender, department where the patient was admitted (namely: internal medicine, general surgery, neurosurgery, orthopedic surgery, urology, pneumonology, cardiology, intensive care unit – ICU, oncology, otorhinolaryngology, neurology), diagnoses, receipt of corticosteroids during the 24 hours before obtaining the complete blood count, prednisone-equivalent dose of corticosteroids, receipt of granulocyte-colony stimulating factor (G-CSF) during the prior 3 days, maximum WBC, outcome, and blood smear findings.

The following diagnostic categories were considered: infections (respiratory tract and urinary tract infection, bacteremia, intraabdominal infection, central nervous system infection, soft tissue infection, bone/joint infections and others), malignancy, ischemia (e.g. acute coronary syndrome, ischemic stroke, venous thromboembolism, mesenteric vein/artery thrombosis/embolism), acute pancreatitis, bleeding (e.g. intracranial hemorrhage and gastrointestinal bleeding), splenectomy. Patients included in the study were examined by at least one of the two first authors and were discussed with the treating physicians. The presence of infection was decided according to standard criteria based on the patients' history, physical examination, laboratory findings, culture data and imaging studies. The main cause of LR was decided by the investigators after reviewing these data and considering the timing of LR and the severity of each diagnosis. Patients were followed up to discharge or death. To evaluate post-discharge mortality (including in-hospital mortality in other hospitals and mortality in outpatients), we examined electronic records up to a year later (26 December 2018).

Hematologic laboratory evaluation

The Cell-Dyn 3700 hematology analyzer was used for blood counts. In agreement with international guidelines [7], a WBC > 30000 was followed by manual blood smear examination. In each smear 100-200 leukocytes were counted and the percentage of each cell type (myeloblasts, promyelocytes,

myelocytes, metamyelocytes, band neutrophil and segmented neutrophils) was calculated [8]. The presence of ≥ 2 + grade toxic changes (toxic granulation and neutrophil vacuolation) was also recorded [8].

Statistical analysis

Analysis of the data was conducted in Microsoft Excel and SPSS (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). To explore the statistical significance of observed differences we used: the Chi-square test for categorical variables and the Mann-Whitney-U test for continuous variables. Continuous variables were described with median and the interquartile range due to their non-normal distributions.

RESULTS

Characteristics of the study population

During the study period we recorded a total of 93 patients with leukocytosis $> 30000/\mu\text{L}$ of neutrophilic predominance. The characteristics of the study population are summarized in Table 1. Generally, most patients were elderly (median age 72, interquartile range 64-81, minimum age 35). Only two patients were younger than 40 and only 8 patients were aged 40 to 50. The following 3 departments contributed to the majority of the cases: internal medicine department (34.4%), general surgery department (12.9%) and intensive care unit (20.4%).

Diagnoses associated with LR

The diagnoses associated with LR in our study are summarized in Table 2. Infection was the most common diagnosis associated with LR (70% of the patients), followed by malignancy and bleeding. However, a combination of factors potentially contributing to LR were found in about half of the patients (Table 3). A combination of 2 or 3 diagnoses was found in 43% and 15% of our patients respectively (Table 3). Furthermore, about 40% of the patients were on corticosteroids (median dose 100 mg of prednisone equivalents during the prior 24 hours).

Only 2 patients were newly diagnosed with a hematological malignancy. A 41-years-old female with a WBC of 45900 at presentation was diagnosed with chronic myeloid leukemia (BCR/ABL1 positive, with associated splenomegaly 16 cm, and the characteristic "myelocyte bulge" on blood smear examination). The other patient was a female with acute myeloid leukemia and WBC > 300000 .

Complete blood count, blood smear and CRP

Laboratory findings (complete blood count, blood smear and CRP) are summarized in Table 4. The diagnostic (in terms of differentiating patients with *versus* without infection) and prognostic (in terms of predicting in-hospital mortality) value of these parameters was limited. Although some parameters were significantly different (p value < 0.05) in patients with infection compared to patients without infection (e.g. CRP, monocytes percentage and count, basophils percentage and count, neutrophil-to-lymphocyte count ratio, neutrophil

vacuolation) there was significant overlap between the 2 groups.

With regards to the presence of toxic changes in the blood smear, toxic granulation was present in about half of all patients and was not correlated with (in-hospital mortality or diagnostic category (presence *versus* absence of infection) (Figure 1). Neutrophil vacuolation was detected in about a third of the patients and was significantly more common in patients with infection (34%) compared to patients without infection (13%), but it was not significantly associated with in-hospital mortality.

Table 1
Characteristics of the study population

	Total	In-hospital death	Discharged alive	p value ^a
Number of patients	93	42 (45%)	51 (54.8%)	
Patients with infection	69	34 (49%)	35 (51%)	
Patients without infection	24	8 (33%)	16 (67%)	0.32
Age-median (IQR)	72 (64-81)	76 (64.75-82.5)	71 (63-81)	0.57
Males - n (%)	53 (57%)	23 (54.8%)	30 (58.8%)	0.69
Departments- n (%)				
Internal Medicine	32 (34.4%)	15 (35.7%)	17 (33.3%)	0.81
General Surgery	12 (12.9%)	4 (9.5%)	8 (15.7%)	0.38
ICU	19 (20.4%)	12 (28.6%)	7 (13.7%)	0.08
Oncology	9 (9.7%)	5 (11.9%)	4 (7.8%)	0.51
Hematology	2 (2.2%)	1 (2.4%)	1 (2.0%)	0.89
Gastroenterology	4 (4.3%)	1 (2.4%)	3 (5.9%)	0.41
Pneumonology	7 (7.5%)	1 (2.4%)	6 (11.8%)	0.09
ENT	1 (1.1%)	0 (0%)	1 (2%)	0.36
Urology	2 (2.2%)	0 (0%)	2 (3.9%)	0.19
Neurosurgery	2 (2.2%)	1 (2.4%)	1 (2.0%)	0.89
Neurology	2 (2.2%)	2 (4.8%)	0 (0.0%)	0.12
Orthopedics	1 (1.1%)	0 (0.0%)	1 (2.0%)	0.36

^a Comparison between those that died during the hospital stay and those that were discharged alive.

Table 2
Diagnoses associated with leukemoid reaction

	Primary diagnosis ^a n (%)	Total number of patients with each diagnosis ^b - n (%)
Infection	65 (69.9%)	69 (74.2%)
RTI	32 (34.4%)	34 (36.6%)
UTI	6 (6.5%)	6 (6.5%)
IAI	16 (17.2%)	17 (18.3%)
STI	4 (4.3%)	4 (4.3%)
BSI	4 (4.3%)	4 (4.3%)
BJI	1 (1.1%)	1 (1.1%)
Other	2 (2.2%)	3 (3.2%)
Malignancy	7 (7.5%)	25 (26.9%)
Bleeding	6 (6.5%)	10 (10.8%)
Ischemia	1 (1.1%)	5 (5.4%)
Leukemia	2 (2.2%)	2 (2.2%)
Growth factor	4 (4.3%)	4 (4.3%)
Corticosteroids	1 (1.1%)	36 (38.7%)
Stress in splenectomized patients	3 (3.2%)	4 (4.3%)
Pancreatitis	3 (3.2%)	3 (3.2%)
DKA/HHS	1 (1.1%)	1 (1.1%)

^a This diagnosis is considered as primarily responsible for the leukemoid reaction (based on the timing and severity of each diagnosis and the timing of severe leukocytosis).

^b In many patients more than one diagnoses potentially contributing to leukocytosis were present.

Abbreviations: RTI = respiratory tract infection, UTI = urinary tract infection, IAI = intraabdominal infection, STI = soft tissue infection, BSI = bloodstream infection, BJI = bone/joint infection

Table 3
Patients with more than one diagnoses potentially contributing to the leukemoid reaction

	n (% of all 93 study patients)
Patients with more than one concurrent cause of leukocytosis (examples below)	54 (58.1%)
Patients with 2 diagnoses	40 (43.0%)
Corticosteroids + Infection	16 (17.2%)
Corticosteroids + Bleeding	3 (3.2%)
Corticosteroids + Malignancy	4 (4.3%)
Infection + Ischemia	2 (2.2%)
Infection + Bleeding	1 (1.1%)
Infection + Malignancy	6 (6.5%)
Infection + Pancreatitis	1 (1.1%)
Infection + Splenectomy	1 (1.1%)
Pancreatitis + Tissue ischemia	1 (1.1%)
Malignancy + Splenectomy	1 (1.1%)
Malignancy + Bleeding	1 (1.1%)
Malignancy + Growth factor	2 (2.2%)
Bleeding + Growth factor	1 (1.1%)
Patients with 3 diagnoses	14 (15.1%)
Infection + Malignancy + Corticosteroids	6 (6.5%)
Growth factor + Infection + Malignancy	2 (2.2%)
Infection + Bleeding + Corticosteroids	3 (3.2%)
Infection + Splenectomy + Corticosteroids	1 (1.1%)
Infection + Ischemia + Corticosteroids	1 (1.1%)
Bleeding + Malignancy + Corticosteroids	1 (1.1%)

Table 4
Complete blood count, blood smear findings and CRP

	Total	In-hospital mortality	Discharged alive	p	Patients with infection	Patients without infection	p
Band cells % - median (IQR) ^a	22 (14-34)	21 (12-30)	26 (17-38)	0.181	26 (17-36)	17 (12-30)	0.057
Toxic changes ^a	65%	63%	66%	0.80	69%	52%	0.14
Toxic granulation ^a	57%	56%	58%	0.96	59%	52%	0.72
Neutrophil vacuolation ^a	31%	26.8%	34%	0.51	37%	13%	0.04
WBC - median (IQR)	35050 (31450-43800)	36900 (33000-48400)	33600 (31200-39700)	0.013	35000 (31400-44100)	35100 (32400-38600)	0.90
Lymphocyte % - median (IQR)	4 (2.8-5.5)	4 (2.8-5.7)	4 (2.7-5.5)	0.93	3.9 (2.6-5.2)	4.1 (3.1-7.5)	0.06
Lymphocyte count - median (IQR)	1398 (940-2081)	1501 (989-2472)	1368 (875-1908)	0.26	1368 (859-2050)	1502 (1190-3543)	0.07
Neutrophil % - median (IQR)	92 (88.9-97.0)	92.2 (88.5-94.7)	91.6 (88.9-94.0)	0.88	92.2 (90.1-94.7)	89.2 (82.5-93.4)	0.01
Neutrophil count - median (IQR)	31740 (941-38716)	33761 (29306-42255)	30373 (28236-37655)	0.10	31824 (28448-40080)	30899 (27820-40080)	0.20
NLCR - median (IQR)	22.8 (15.0-33.4)	23.4 (14.7-33.1)	22.1 (16.0-34.8)	0.93	23.5 (16.6-37.1)	22.0 (10.2-28.6)	0.048
Monocyte % - median (IQR)	3.8 (1.8-4.9)	3.7 (1.5-4.8)	3.8 (2.1-5)	0.4	3.7 (1.6-4.4)	4.7 (2.4-7.5)	0.01
Monocyte count - median (IQR)	1287 (700-1831)	1282 (606-2151)	1287 (768-1693)	0.91	1130 (646-1652)	1599 (1014-2473)	0.02
Eosinophil % - median (IQR)	0.04 (0.01-0.14)	0.02 (0.00-0.12)	0.05 (0.01-0.16)	0.3	0.02 (0.01-0.11)	0.08 (0.01-0.2)	0.09
Eosinophil count - median (IQR)	14 (3-52)	10 (0-50)	18 (4-53)	0.42	11 (3-43)	24 (4-73)	0.13
Eosinopenia (< 50/uL)	74%	75%	73%	0.79	78%	59%	0.08
Basophil % - median (IQR)	0.17 (0.08-0.36)	0.18 (0.09-0.40)	0.17 (0.08-0.29)	0.55	0.15 (0.07-0.29)	0.25 (0.12-0.56)	0.01
Basophil count - median (IQR)	55 (30-141)	101 (31-176)	52 (30-105)	0.18	49 (23-123)	99 (53-196)	0.008
Metamyelocytes % - median (IQR) ^a	0 (0-1)	0 (0-1)	0 (0-2)	0.51	0 (0-1.75)	1 (0-2)	0.15
Myelocytes % - median (IQR) ^a	0 (0-1)	1 (0-1.25)	0 (0-1)	0.15	0 (0-1)	0 (0-1)	0.74
Promyelocytes % - median (IQR) ^a	0 (0-0)	0 (0-0)	0 (0-0)	0.10	0 (0-0)	0 (0-0)	0.80
Blasts % - median (IQR) ^a	0 (0-0)	0 (0-0)	0 (0-0)	0.37	0 (0-0)	0 (0-0)	0.08
CRP (mg/dL) - median (IQR) ^b	16.0 (7.0-22.9)	17.6 (8.4-29.8)	13.5 (5.1-22.2)	0.44	18.0 (8.7-31.2)	8.9 (16.7-22.7)	0.03

Abbreviations: CRP = c-reactive protein, IQR = interquartile range, NLCR = neutrophil to lymphocyte count ratio, WBC = white blood cells

^a Evaluated by manual peripheral smear review.

^b At the day of detection of leukemoid reaction or the next day (if not available at the day of detection). A CRP measurement was available in n = 86 patients.

“Band cells” refers to the median percentage of band cells in the blood smear. Toxic changes, toxic granulation and neutrophil vacuolation refer to the percentage of patients with ≥ 2 + grade toxic changes in the blood smear. * p value < 0.05

Figure 1. Association between blood smear findings and in-hospital mortality and presence of infection.

Prognosis

In-hospital mortality was high ($n = 42$, 45.2%). Electronic records were also examined a year after the end of patient recruitment (December 2018). Among patients discharged alive, $n = 18$ (35.3%) had died during this follow-up time. Therefore, overall mortality up to December 2018 was 64.5%. In-hospital mortality did not differ significantly ($p = 0.18$) between patients with infection (49.3%) and patients without infection (37.5%). Among patients with malignancy ($n = 26$), in-hospital mortality was 50% and overall mortality was 80.8%. Among patients with severe bleeding ($n = 10$) in-hospital mortality was 60% and overall mortality was 60%. Among $n = 14$ patients with more favorable (prognostically) diagnoses, i.e. splenectomy ($n = 3$), granulocyte-colony stimulating factor ($n = 5$), hyperosmolar hyperglycemic state ($n = 1$), acute pancreatitis ($n = 4$), chronic myeloid leukemia ($n = 1$), in-hospital mortality was 14.3% ($n = 1$ patient with malignancy and leukocytosis due to granulocyte-colony stimulating factor and $n = 1$ due to acute pancreatitis).

DISCUSSION

Causes of LR in hospitalized patients

In agreement with prior studies [1, 3-6], a variety of conditions were associated with LR, including infections, malignancy, severe bleeding, and medications (granulocyte-colony stimulating

factors and corticosteroids). Infections were the most common cause of LR in our study, similar to other studies [1, 3, 4], although the percentage of cases of LR attributed to infection was higher in our study compared to some other studies [3, 5].

Paraneoplastic leukocytosis (LR in patients with high tumor burden and no alternative explanation) was found in a small percentage of our patients. The association between malignancy and LR is well known [1-3, 5]. In two prior studies among hospitalized patients, a solid malignancy was considered to represent the cause of leukocytosis in 6% [1] and 4.6% [3] of the patients. In the largest study so far [5] of 758 patients with LR associated with non-hematologic malignancies (including outpatients), most cases were associated with a secondary cause (69% hematopoietic growth factor, 15% infection, 5% high-dose corticosteroids). LR associated with granulocyte-colony stimulating factors was uncommon in our study, as this finding usually occurs in outpatient oncologic patients (who were excluded from our study). Of note is that in our study, many patients with an alternative cause of LR had an underlying malignancy (26.9%), suggesting that patients with solid malignancies may be more prone to LR (either due to association between malignancy and conditions associated with LR, or due to a paraneoplastic effect).

Finally, it is noteworthy that in more than half of our patients a combination of factors potentially contributing to the level of leukocytosis was co-existent. Therefore, LR may often be multifactorial. In contrast, prior studies by design only reported

a single cause for each case of LR and did not account for the possibility of multiple etiologies [1, 3-6].

Complete blood count, blood smear and CRP

In our study the diagnostic (in terms of differentiating infectious from non-infectious diagnoses) and prognostic (in terms of predicting in-hospital mortality) value of detailed blood smear findings (neutrophil differential count, neutrophil toxic changes) was limited. Nevertheless, although in the settings of our study hematologic malignancy was an uncommon diagnosis among hospitalized patients with new-onset neutrophilic leukocytosis, blood smear examination may still be useful to identify such patients. This is especially important for patients without an alternative obvious cause associated with the leukocytosis.

The above finding is in agreement with most prior studies evaluating the diagnostic value of band counts and neutrophil toxic changes in different patient populations. These parameters are neither specific nor sensitive enough to be used routinely for diagnostic or prognostic purposes and have limited additional value over automated WBC and neutrophil counts [9-11]. Furthermore, manual counts are labor intensive and inter-observer variability may be high [9].

Eosinopenia and neutrophil-to-lymphocyte count ratio (NLCR) are other markers that have been studied to differentiate patients with *versus* without infection and as prognostic markers, with conflicting results [12-14]. In this study (Table 4), among hospitalized patients with neutrophilic LR, none of these markers were significantly associated with prognosis (in-hospital mortality). NLCR was significantly higher and eosinopenia ($< 50/\mu\text{L}$) more common in patients with infection compared to patients without infection, but there was a significant overlap between the two groups of patients (Table 4).

Prognosis

In hospital-mortality was high (45.2%) and overall mortality up to one year later after the end of the study was even higher (64.5%), in agreement with prior studies [1, 3-6]. Mortality was slightly higher in patients with infections compared to patients without infections, but the difference was not statistically significant. Despite high mortality rate in the total study population, patients with more favorable diagnoses (e.g. splenectomy, chronic myeloid leukemia, hyperosmotic hyperglycemic state,

granulocyte-colony stimulating growth factor, acute pancreatitis) had a relatively lower mortality.

Strengths and limitations

A major strength of our study is that, in contrast to most prior studies, data were collected prospectively. Furthermore, blood smear findings were not studied in similar detail in prior studies of LR. Finally, we provide follow-up data for our patients regarding longer-term outcomes after discharge from the hospital.

A limitation of our study is that in many patients more than one conditions potentially contributing to leukocytosis were present (Table 3). Similar to prior studies, we decided by consensus (and based on the timing of LR and severity of each diagnosis) which was the major cause of LR. However, in contrast to prior studies, we also reported that in many patients the etiology of LR may be multifactorial. Another limitation is that investigators were not blinded to blood smear findings. However, potential bias and misclassification due to lack of blinding would most likely result in overestimation of the association between diagnoses and blood smear findings, which does not seem to be the case in our study.

CONCLUSIONS

A variety of non-hematologic diagnoses are associated with LR of neutrophilic predominance among hospitalized patients. Although many non-infectious conditions can cause LR (such as malignancy, severe bleeding, use of growth factors and corticosteroids), infections are the most common cause and should always be considered in the differential diagnosis. Labor intensive detailed manual counts (such as counting the percentage of band cells or quantifying the presence of neutrophil toxic changes) have limited diagnostic or prognostic value in most hospitalized patients with LR. Targeted blood smear review may be useful in selected patients when there is suspicion of underlying hematological malignancy. Finally, LR among hospitalized patients was associated with very high in-hospital and post-discharge : mortality.

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Introducere. Reacția leuceomidă (RL) se asociază mai multor diagnostice. Încă nu au fost studiate valorile prognostice și diagnostice ale frotiului de sânge periferic (numărul de neutrofile în bandă sau prezența granulațiilor toxice).

Materiale și metode. Au fost analizate toate spitalizările ale adulților cu RL (definite peste 30000 leucocite/ μ L) cu neutrofilie excluzând leucocitoza de cauză neoplazică. Au fost analizate diagnosticele și prognosticele acestor pacienți (mortalitatea spitalicească și post-internare).

Rezultate. Din ianuarie 2017 până în decembrie 2017 au fost incluși în studiu 93 de pacienți. Infecția a fost cel mai frecvent diagnostic (70%) urmat de malignitate (7.5%) și hemoragie (6.5%). Mortalitatea intraspitalicească (45%) și post internare (35%) a fost însemnată. Vacuolizarea neutrofilelor a fost asociată cu infecția (34%) deși a fost observată și la pacienți fără infecție (13%).

Concluzii. Evaluarea frotiului de sânge periferic este costisitoare și nu aduce beneficii la pacienții neselectați cu RL neutrofilică.

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REFERENCES

1. REDING M.T., HIBBS J.R., MORRISON V.A., SWAIM W.R., FILICE G.A. *Diagnosis and outcome of 100 consecutive patients with extreme granulocytic leukocytosis.* Am J Med. 1998;**104**(1):12-6.
2. SAKKA V., TSIODRAS S., GIAMARELLOS-BOURBOULIS E.J., GIAMARELLOU H. *An update on the etiology and diagnostic evaluation of a leukemoid reaction.* Eur J Intern Med. 2006;**17**(6):394-8.
3. POTASMAN I., GRUPPER M. *Leukemoid reaction: spectrum and prognosis of 173 adult patients.* Clin Infect Dis. 2013;**57**(11):e177-81.
4. LAWRENCE Y.R., RAVEH D., RUDENSKY B., MUNTER G. *Extreme leukocytosis in the emergency department.* QJM. 2007;**100**(4):217-23.
5. GRANGER J.M., KONTOYIANNIS D.P. *Etiology and outcome of extreme leukocytosis in 758 nonhematologic cancer patients: a retrospective, single-institution study.* Cancer. 2009;**115**(17):3919-23.
6. HALKES C.J., DIJSTELBLOEM H.M., EELKMAN ROODA S.J., KRAMER M.H. *Extreme leukocytosis: not always leukaemia.* Neth J Med. 2007;**65**(7):248-51.
7. BARNES P.W., MCFADDEN S.L., MACHIN S.J., SIMSON E. *The international consensus group for hematology review: suggested criteria for action following automated CBC and WBC differential analysis.* Lab Hematol. 2005;**11**(2):83-90.
8. PALMER L., BRIGGS C., MCFADDEN S., ZINI G., BURTHEM J., ROZENBERG G., et al. *ICSH recommendations for the standardization of nomenclature and grading of peripheral blood cell morphological features.* Int J Lab Hematol. 2015;**37**(3):287-303.
9. DUTCHER T.F. *Leukocyte differentials. Are they worth the effort?* Clin Lab Med. 1984;**4**(1):71-87.
10. WENZ B., GENNIS P., CANOVA C., BURNS E.R. *The Clinical Utility of the Leukocyte Differential in Emergency Medicine.* Am J Clin Pathol. 1986;**86**(3):298-303.
11. MALCOLM I.D., FLEGEL K.M., KATZ M. *Vacuolization of the neutrophil in bacteremia.* Arch Intern Med. 1979;**139**(6):675-6.
12. KARAKONSTANTIS S., KALEMAKI D., TZAGKARAKIS E., LYDAKIS C. *Pitfalls in studies of eosinopenia and neutrophil-to-lymphocyte count ratio.* Infect Dis. 2018;**50**(3):163-74.
13. KARAKONSTANTIS S., GRYLLOU N., PAPAZOGLOU G., LYDAKIS C. *Eosinophil count (EC) as a diagnostic and prognostic marker for infection in the internal medicine department setting.* Rom J Intern Med. 2018;10.2478/rjim-2018-0039
14. VELISSARIS D., PANTZARIS N.D., BOUNTOURIS P., GOGOS C. *Correlation between neutrophil-to-lymphocyte ratio and severity scores in septic patients upon hospital admission. A series of 50 patients.* Rom J Intern Med. 2018;**56**(3):153-57.

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