Leukemoid Reaction: Spectrum and Prognosis of 173 Adult Patients

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Background. The prognosis of patients with leukemoid reaction (LR) depends mainly on their underlying illness. Our aim was to investigate the etiologies and prognosis of a mixed group of patients with LR.

Methods. We identified 173 patients who had \( \geq 30.0 \times 10^9 \) leukocytes/μL without hematologic malignancies. Causes of LR and factors contributing to death were analyzed.

Results. Patients with LR constituted 0.59% of all admitted adults. The median age was 75 years, but 20 patients were aged <40 years. There was no difference in LR prevalence by gender (female/male = 88/85). Average white blood cell (WBC) count was \( 37.7 \times 10^9/\mu L \). Fourteen patients (8.0%) had a WBC count of >50.0 \( \times 10^9/\mu L \). The median duration of LR was 1 day, but 39 patients had prolonged LR (>1 day).

Infection was the most common cause of LR (n = 83, 47.9%; 95% confidence interval, 40.7–55.4), followed by ischemia/stress (27.7%), inflammation (6.9%), and obstetric diagnoses (6.9%). Higher WBC counts were significantly associated with positive blood cultures \( (P = .017) \) or a positive \( Clostridium difficile \) toxin \( (P = .001) \). Antibiotics were prescribed for 140 patients (80.9%).

Sixty-six patients (38.1%) died during hospitalization. Those with prolonged LR had an in-hospital mortality rate of 61.5%. Factors found to be highly correlated with death were age (odds ratio [OR] = 1.051, \( P < .001 \)), any infectious diagnosis (OR = 2.574, \( P = .014 \)), and sepsis (OR = 3.752, \( P = .001 \)).

Conclusions. LR carries a grave prognosis, especially among the elderly and those with sepsis. LR was found to have multiple etiologies including infections, stress, inflammation, and obstetric diagnoses.

Keywords. leukemoid reaction; extreme leukocytosis; sepsis; elderly; etiology.

Most patients hospitalized in general teaching hospitals, particularly those admitted for elective surgery, have normal leukocyte counts. Those admitted with an acute disease, be it infectious or not, may have leukocytosis. A minority of these patients present with (or may develop later) neutrophilic leukemoid reaction (LR). For the internist, a patient presenting with LR is always a diagnostic challenge. Since LR may have many etiologies, differentiating this reactive process from myeloid malignancies and pinpointing its exact etiology are of prime significance.

The term “leukemoid reaction” was initially coined by Krumbhaar in 1926 [1]. Since then, it has become clear that this term should be reserved for cases with nonhematologic malignancies [2–4], yet the exact definition of LR remains to be settled. While some authorities have used a cutoff of \( 25.0 \times 10^9 \) leukocytes/μL [2], others have applied a cutoff of \( 30.0 \times 10^9/\mu L \), \( 40.0 \times 10^9/\mu L \), or even \( 50.0 \times 10^9/\mu L \) [3–6]. A further refinement of the term is based on the absolute neutrophil count and not leukocytes. In general, elevated neutrophil count of LR is accompanied by a left shift, signs of neutrophil activation, and absence of basophilia and dysplastic changes [4].

The range of conditions that cause LR is dependent primarily on the spectrum of patients studied. Thus, the large study by Reding et al, carried out at a Veterans Administration (VA) hospital 15 years ago, was skewed toward the male gender (98%) [7]. In contrast, the recent large study by Granger and Kontoyiannis [4]...
focused on nonhematologic cancer patients. However, infectious diseases consultants at general teaching hospitals who are often called to see patients with LR need to recognize the full range of underlying causes so that decision making (eg, withholding antibiotics) is facilitated. Review of the available literature on LR reveals that there is a paucity of data derived from large, heterogeneous groups of patients. Our study reports the etiologies and prognostic factors of LR in 173 patients without hematologic malignancies.

METHODS

The Bnai Zion Medical Centre (BZMC) is a 411-bed university hospital located in Haifa, Israel. It contains all basic departments except for neurosurgery, cardiovascular surgery, and solid-tumor oncology. The respiratory intensive care unit holds 6 patients, but additional respirators are in use in the 3 departments of medicine. During an average year, there are 29,508 hospitalizations of adults (aged >18 years) with 150,000 hospitalization-days and an average occupancy of 92%.

The study period spanned from March 2011 through February 2012. Initially, the hospital’s hematology laboratory computer was searched for all blood counts, with an arbitrary cutoff of ≥30.0 × 10^9 leukocytes/μL and a granulocyte count of >50%. Children aged ≤18 years were excluded. The search yielded 218 records. The authors reviewed the charts of these patients and excluded 45 patients (for hematologic malignancies). Thus, this study depicts the details of 173 (79.3%) patients. Patients were eligible throughout their hospital stay and whenever they were admitted.

The following data were extracted from the patients’ charts: age, sex, principal discharge diagnosis, date of hospitalization, date of maximum white blood cell (WBC), and admission from home/nursing home. In addition, we recorded any of the following conditions, which may instigate LR: ketoacidosis, acute bleeding, acute renal failure, labor/delivery, eclampsia, splenectomy, hemolysis, poisoning, solid tumor, chronic lung/heart disease, and diabetes mellitus. Admission diagnoses were grouped into the following 9 major categories: sepsis (defined by previously established criteria [8]), pneumonia, urinary tract infections, other infections (diarrhea, cellulitis, and gangrene), obstetrics/gynecology (mostly labor), tissue ischemia or stress (postsurgical pain or extreme dyspnea), inflammation (eg, pancreatitis, splenectomy), malignant solid tumors, and “other.” Specifically, patients with symptoms/signs of sepsis but without a definite site of infection were classified as having sepsis. The authors validated the diagnosis of sepsis by reviewing the patients’ charts. A search was also carried out for specific drugs that these patients received and that could have caused excessive leukocytosis including corticosteroids (special note for those >20 mg prednisone), lithium, adrenalin, minocycline, and carbamazepine. When/if the patient underwent an operation, the date was recorded along with the time interval from operation to the maximum WBC count. In every patient, the maximum WBC count, its duration, its interval from the hospitalization day, and the differential were also recorded. Other critical parameters such as sepsis, positive blood cultures, receipt of antibiotics, diarrhea, a positive Clostridium difficile toxin assay (enzyme-linked immunosorbent assay), and death were also recorded. Fever was defined as an oral temperature >38°C. Pneumonia was defined as the presence of fever, cough with/without purulent sputum, dyspnea, and a new infiltrate on chest x-ray. Urinary tract infection was defined as the presence of significant pyuria and a positive urine culture. In patients with a solid malignant tumor, the LR was attributed to the malignancy when there was no other obvious cause (eg, infection, splenectomy). Other groups included patients with ischemia (eg, acute myocardial infarction, gangrene, and bowel obstruction), surgery, and inflammation (eg, pancreatitis). The authors reviewed the charts of the 173 patients and reached a consensus about the instigating factors causing LR.

Statistical Analyses

Simple statistical analyses were performed using features of Microsoft Excel. Two parameters, maximum WBC count and death during hospitalization, were examined as dependent variables. Correlation of these 2 parameters with other clinical variables was identified using correlation analysis: linear or logistic regression. Difference of distributions in patients’ subgroups was examined by nonparametric tests (Mann–Whitney, Kolmogorov–Smirnov). A P value < .05 was assumed to denote statistical significance for all tests (2-tailed). Statistical analysis has been executed using SPSS software (release 17.0.2, SPSS Inc., 2009).

The Helsinki Committee of the BZMC approved the study.

RESULTS

During 1 year at a general teaching hospital we identified 173 patients with LR, constituting 0.59% of all adult patients who were admitted. This cohort was relatively old, with a median age of 75 years (Table 1); however, 20 patients were aged <40 years. LR was found evenly in both genders (female/male = 88/85). While most patients were admitted from home, almost a third (n = 53, 30.6%) were admitted from a nursing home, reflecting the catchment area of the BZMC. Nearly half of these patients had a history of cardiovascular disease (Table 2), and 26.5% had diabetes mellitus.

The average WBC count was 37.7 × 10^9/μL (Table 1), with a maximum count of 88.0 × 10^9/μL. Fourteen patients (8.0%) had an extreme WBC count of >50.0 × 10^9/μL (of these, 5 had infections while others suffered from inflammatory, ischemic, and extreme physiological stress conditions). The differential
In most patients (n = 134), LR was a single-day event. However, in 39 (22.5%), LR continued for up to 17 days (median = 2 days, mean = 3.9 days, interquartile range = 2). Twenty-four patients (61.5%) in this group of 39 died during hospitalization, as opposed to 31.3% among those with a 1-day duration LR (Pearson’s χ² test, P = .001). The higher death rate was linked to the higher mean age of the “long LR” group (79.2 ± 11.5 years).

Infection, with or without positive blood cultures, was seemingly the most common cause of LR, occurring in 83 patients (47.9%). Other common causes of LR were ischemia/stress (n = 48, 27.7%) followed by inflammation (n = 12, 6.9%, mostly pancreatitis and splenectomy). Obstetric/gynecologic diagnoses were also common (n = 12), mostly vaginal delivery (n = 6) followed by cesarean section (n = 3), ectopic pregnancy, uterine contractions, and vaginal bleeding. Interestingly, although only 83 patients had an infection, 140 patients (80.9%) received antibiotics; apparently not only for obvious infectious diseases.

The following 3 factors were found to affect the degree of leukocytosis by univariate analysis: finding of a positive blood culture, a positive *Clostridium difficile* toxin assay, and prolonged LR. The finding of a positive blood culture was associated with higher WBC counts (exceeding median value for 68.2% of these patients vs 46.0% of patients without positive blood culture; P = .017 by Mann–Whitney test). The highest WBC counts were found in patients with either a positive blood count of the entire cohort showed a shift to the left with a median of 91% neutrophils, which is in concordance with the definition of LR.
Table 3. Abbreviated Logistic Regression of Predictors of Death

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenalin</td>
<td>9.37</td>
<td>1.04–84.18</td>
<td>.046</td>
</tr>
<tr>
<td>Age</td>
<td>1.05</td>
<td>1.02–1.08</td>
<td>.000</td>
</tr>
<tr>
<td>Any diagnosis related to infection</td>
<td>2.57</td>
<td>1.21–5.47</td>
<td>.014</td>
</tr>
<tr>
<td>Sepsis</td>
<td>3.75</td>
<td>1.78–7.98</td>
<td>.001</td>
</tr>
<tr>
<td>Constant</td>
<td>.005</td>
<td>1.12</td>
<td>.000</td>
</tr>
</tbody>
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culture or a positive C. difficile toxin (66.7% and 44.2%, respectively; P = .001). Notably, we found no statistical correlations between the degree of leukocytosis and survival. Eight patients received adrenalin; 7 of them died. Six of the 8 had sepsis. The clinical conditions leading to receipt of adrenalin were sepsis/septic shock (n = 3), gastrointestinal bleeding (n = 2), cardiac arrest/congestive heart failure (n = 2), and bowel obstruction (n = 1).

Sixty-six patients of this cohort (38.1%) died during hospitalization, in contrast with a hospital-wide mortality rate of 5.71% (557/9750) among those aged ≥70 years (P < .0001). The in-hospital mortality rate was influenced by several factors, notably advanced age. The mean age of those who died was 79.4 ± 11.2 years (vs 63.3 ± 21.2 of those who survived, P = .0001). The age-specific mortality rates were as follows: 1/48 (2.1%) for those aged <60 years, 29/58 (50%) for those 60–79, and 36/67 (53.7%) for those >80. The basic model appears to provide a reasonably good fit (P = .001, Nagelkerke R² = 0.408, H-L statistic = 0.925). The following 4 factors were found to have a significant association (Table 3) in relation to death: receipt of adrenalin (odds ratio [OR] = 9.370, P = .046), age (OR = 1.051, P < .001), any infectious diagnosis (OR = 2.574, P = .014), and sepsis (OR = 3.752, P = .001).

DISCUSSION

Current knowledge about the incidence, spectrum, course, and prognosis of patients with LR is scarce. It is based on individual case reports and only a few series of specific groups of patients [2, 4, 5, 7]. Internists who are confronted with LR are often asked to propose a differential diagnosis. The present survey, which is the largest comprised of noncancer patients, is based on 1 year of experience at a general teaching hospital; it expands the information as to the incidence of LR, its diverse etiologies, underlying predisposing medical conditions, prognostic indicators, and mortality. In spite of the low annual incidence of LR reported here (0.59%), the accompanying high in-hospital mortality rate (38.1%) emphasizes its tremendous clinical significance. Comparable mortality figures were reported from an emergency room in Israel (32%) and a VA medical center in Minneapolis (31%) [2, 7]. The grave prognosis found by all 3 groups thus represents a medical emergency that necessitates hospitalization, quick diagnostic evaluation, and prompt therapeutic intervention.

The present cohort was older than the group Reding et al evaluated [7] (75 years vs 68 years) and the group Granger and Kontoyiannis evaluated [4]. This may represent the aging of the population or merely a different patient mix (Reding et al studied a VA hospital population). Possible explanations for the high rate of LR in the elderly may include age-associated "atypical" clinical presentation yielding a diagnostic delay and postponed hospitalization, presence of comorbidities, and polypharmacy. Interestingly, despite their advanced age, these patients were able to increase their neutrophil count to the range of LR, indicating adequate bone marrow reserve. Alternatively, LR might represent a functional compensatory response to several age-related defects in neutrophil functions, including compromised chemotaxis and phagocytosis [9]. Advanced age has already been observed in other series of patients with LR. However, in contrast to our findings, it has not yet been reported to be a statistically significant variable of in-hospital mortality [2, 5, 7].

LR was found to carry a high in-hospital mortality rate; this high rate was found to be significantly related to advanced age as well as to etiology of infection, particularly sepsis. The latter stands in contrast with Reding et al [7] who reported a particularly high mortality rate in those with noninfectious diagnoses. Our data indicate that those patients who died during hospitalization were 16.1 years older than those who survived. Lawrence et al reported similar findings (85 years deceased vs 75 years survived) [2].

For the internist who is confronted with LR, knowledge of the diagnostic priorities is important. Infections were found to top the list of etiologies in our survey (47.9%), as in the 2 other series [2, 7]. The most common entities in this category were sepsis, pneumonia, and urinary tract infections; however, cellulitis, gangrene, and diarrhea (mostly C. difficile–associated [10, 11]) were also noted; all involve a "straight-forward" diagnoses. However, slightly more than half of the cases were caused by conditions that are infrequently associated with LR, such as stress, inflammation, obstetrical diagnoses, and paraneoplastic phenomena. Dior et al recently studied the association between delivery and leukocytosis [12]. In this large series, extreme leukocytosis was found in <1% of febrile parturients. The authors found no correlation in parturients between positive bacterial cultures and higher leukocyte counts; however, they did find higher rates of positive cultures among those with extremely elevated neutrophils (>90th percentile). Notably, none of our 12 obstetric cases had signs of infection or diarrhea, and only 1 received high-dose steroids, which may account for LR. Only 2 reports addressed the issue of LR associated with fulminant postpartum
Clostridium sordellii infection [13, 14], but other clostridia are likely to cause LR as well. The importance of recognizing conditions such as puerperal leukocytosis lies mainly in withholding unnecessary prescription of antibiotics when obvious infection is absent.

This study shows an immense overuse of antibiotics. While only 83 patients had an infection based on the author’s judgment, 140 received antibiotics; 40.7% received antibiotics unjustifiably. This anomaly has several possible explanations. First, at the level of the emergency department, extreme leukocytosis is often equated with significant bacterial infection even if fever is absent. Second, the hospital-wide policy allows antibiotic prescription for 24 hours until an infectious disease consultant sees the patient.

Prolonged LR (>1 day) was found in 22.5% of this cohort and carried a grave prognosis. Our literature search failed to find previous studies addressing this issue. What is the cause of “prolonged LR”? First, one may speculate that the inciting cause of LR was not eliminated promptly. Second, considering that these patients were older, we hypothesize that their neutrophils probably suffered from some degree of senescence [9].

This study has certain limitations. First, the retrospective and clinical nature prohibited “purification” of the cases. Namely, in some patients it was difficult to assign a single cause for the LR. When a clear-cut infection was apparent, it was given priority over other etiologies, which may have caused some bias. Second, the reliance on electronic charts prevented the collection of data from fever curves and finding additional correlations. Third, the cohort studied was relatively old, as compared to those in other studies [4, 6]; however, this mirrors the aging of the population in general. Still, 20 patients were aged <40 years.

In conclusion, we tried to describe a 1-year experience with LR at a general teaching hospital. Although infections with a grave prognosis stand out in this series, other causes must be recognized and included in the differential diagnosis and obviate the “reflex” to prescribe antibiotics.

Notes

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Potential conflicts of interest. Both authors: No reported conflicts.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References