Journal of Community Hospital Internal Medicine Perspectives

Volume 13 | Issue 6 Article 27

2023

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Recommended Citation

Chennapragada, Suma Sri; Sharma, Shivani; Dadi, Neelakanta; Shi, Runhua; and Mansour, Richard P (2023) "Real-world data of leukopenia evaluation as seen in a community academic center," *Journal of Community Hospital Internal Medicine Perspectives*: Vol. 13: Iss. 6, Article 27.
DOI: 10.55729/2000-9666.1273
Available at: https://scholarlycommons.gbmc.org/jchimp/vol13/iss6/27

BRIEF REPORT

Real-world Data of Leukopenia Evaluation as Seen in a Community Academic Center

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Abstract

Leukopenia on routine laboratory testing creates a concerning situation for primary care providers due to its association with hematological malignancies. Although not all leukopenia is due to underlying cancer, it can trigger an expensive and exhausting work-up in the process of ruling it out. There is neither real-world data on the prevalent causes of leukopenia as seen in the community nor definitive guidelines on the utilization of flow-cytometry in this setting. We conducted this retrospective study at our community academic center to demonstrate the distribution of various causes of leukopenia as well as the utility of flow-cytometry. Our study demonstrates that benign reversible causes of leukopenia are most prevalent and flow-cytometry is useful only in some very specific settings. These results provide a real-world estimate for clinicians to make informed decisions while evaluating leukopenia.

Keywords: Leukopenia, Flow-cytometry, Hematological malignancies, Clinical utility

1. Introduction

Leukopenia and neutropenia are commonly seen in an internist's daily practice. Differentiating benign from malignant causes becomes essential. Flow cytometry, a non-invasive tool, has been widely used to preliminarily screen hematological malignancies. However, the overuse of flow cytometry can lead to unnecessary healthcare costs. We aimed to evaluate the utilization of flow cytometry testing in the work-up of leukopenia at our institution. We also bring to light the prevalent causes of leukopenia, as seen in our community.

2. Methods

We conducted a cross-sectional study of the leukopenia and neutropenia referrals made to the hematology clinic at our institution between 1993 and 2018. The inclusion criteria consisted of patients aged >18 years who had visited a hematologist at least once for the diagnosis of leukopenia or neutropenia. Exclusion criteria included prisoners, pregnant women, and those with leukopenia resulting from known cancer or chemotherapy side effects. Leukopenia was defined as a white blood cell count less than 3.9 K/uL, and neutropenia as an absolute neutrophil count less than 1500 K/uL. Our primary objective was to determine the number of flow cytometry tests ordered and their results. Our secondary objectives were to report the causes of leukopenia and the co-morbidities of the patients. Descriptive statistics and SAS were used for data analysis. The study was approved by the Institutional Review Board.

3. Results

152 patients met the inclusion and exclusion criteria. Flow cytometry was ordered in 36% of the cases but was positive for clonal hematological abnormalities only in 3.2% of the study population (5 patients). The identified conditions included Acute myeloid leukemia (AML), Natural killer cell large granular lymphocyte leukemia (NK-LGL), Myelodysplastic

Received 19 July 2023; revised 9 September 2023; accepted 14 September 2023.
Available online 4 November 2023

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https://doi.org/10.55729/2000-9666.1273

syndrome (MDS), clonal lymphoproliferative disorder, and monoclonal gammopathy of uncertain significance (MGUS).

The majority (54%) of leukopenia cases remained undiagnosed after a thorough workup and were idiopathic. The known causes were benign ethnic neutropenia (BEN) (17%), medication-related (12.5%), autoimmune (5.2%), viral infections (4.6%), malignancies (3.2%), and toxins like alcohol (2.6%) (Fig. 1). Among the causative medications, psychotropic medications were the most common culprits (24.32%) followed by anti-seizure medications (19.04%), immunosuppressive medications (19.04%), and antibiotics (14.28%).

Cardiovascular diseases were observed in 4.6% of the neutropenia referrals, liver diseases in 15%, and rheumatological conditions in 13% (Table 1). Underlying rheumatoid arthritis was found in one patient with monoclonal gammopathy of uncertain significance (MGUS) through flow cytometry analysis.

Table 1. Medical Co-morbidities of the patients with leukopenia.

Medical Co-morbidities	Percentage of the patients
Cardiovascular diseases	*4.6%*
Atrial fibrillation	42%
Congenital heart disease	28.5%
Coronary artery disease	28.5%
Congestive heart failure	14.2%
Supraventricular tachycardia	14.2%
Hepatic Diseases	*15%*
Chronic Hepatitis C Virus Infection	47.3%
Cirrhosis	36.8%
Liver metastases	5.26%
Rheumatological diseases	*13%*
Rheumatoid arthritis	47%
Systemic lupus erythematosus	30%
Myasthenia gravis	5.8%
Felty's syndrome	5.8%
Sarcoidosis	5.8%
Hepatomegaly	*3%*
Splenomegaly	*7.8%*

4. Discussion

Our study findings underscore the necessity for a comprehensive assessment of various factors, including chronicity, ethnic and family history, and concurrent medical conditions, prior to the decision to order flow cytometry in the evaluation of leukopenia. By presenting evidence of the prevalent benign causes of leukopenia in real-world scenarios, our study contributes significantly to this discourse.

Centering our analysis on the Centers for Disease Control statistical data, the documented nationwide incidence of hematological malignancies rests at a mere 13 cases per 100,000 individuals, equating to a minimal 0.013% of the population.[1] In direct contrast, within our study's participant pool, we found clonal hematological abnormalities in 3% of subjects. This observation emphasizes the increased utilization of flow cytometry, which led to excessive diagnosis of certain pre-malignant and indolent conditions that would otherwise remain clinically latent.

Another pertinent finding from our results is the notable fact that 90% of all ordered flow cytometry studies exhibited negative results for hematological abnormalities. This outcome significantly strengthens the argument for the judicious application of this diagnostic tool.

Considerable insights also emerged regarding the association of leukopenia with specific genetic variants, exemplified by the Duffy null phenotype prevalent in African Americans, attributed to its geographical advantage in safeguarding against malaria.[2] Noteworthy is our study's elevated percentage of African-American participants (51.3%), surpassing the national average (12%), which led to the identification of a higher prevalence of benign etiologies like BEN. Undertaking further investigations across diverse geographic regions catering to varied patient

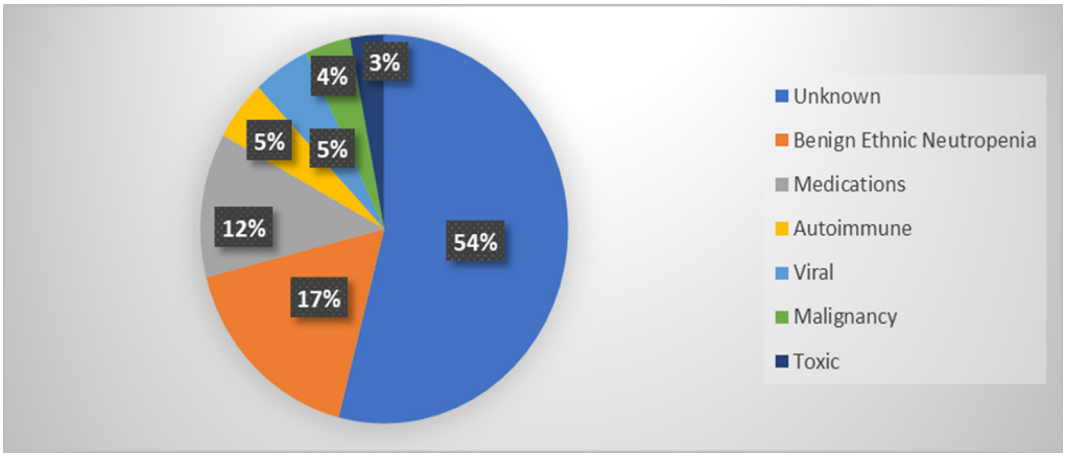

Fig. 1. Pie chart depicting the distribution of various causes of leukopenia.

demographics can furnish clinicians with a richer understanding of leukopenia's intricacies and its population-specific causative factors.

While our study refrains from definitively confirming the connection between leukopenia and concurrent medical conditions, we noticed an increased prevalence of congenital heart disease within our study cohort. This is consistent with previous research, which has demonstrated a potential correlation between Ventricular Septal Defect (VSD) and neutropenia.[3] Additionally, we unraveled the well-documented association of cirrhosis and HCV infection with leukopenia, attributed to the toxic effects of HCV and alterations in the bone marrow microenvironment influencing stem cell differentiation.[4] Furthermore, our study recognized the potential significance of identifying hematological malignancy in the context of autoimmune diseases, particularly rheumatoid arthritis (RA). Of note, although rare, Large Granular Lymphocytic (LGL) leukemia strongly associates with RA and could manifest as leukopenia.[5] This particularly underscores the necessity of flow cytometry evaluation for unexplained leukopenia in patients with autoimmune diseases managed with immunosuppression.

Guidelines endorsed by the American Society for Clinical Pathology recommend utilizing flow cytometry to investigate hematological malignancies when abnormal cells are evident in peripheral smears or when pre-test probability remains substantial.[6] Pre-existing evaluation protocols for leukopenia, such as the one outlined by Gibson et al., have highlighted the importance of ruling out ethnic, benign, medication-induced, infectious, and nutritional triggers before resorting to flow cytometry.[7] Our study bridges a critical gap by presenting real-world data that attests to the utility and efficacy of flow cytometry in addressing leukopenia—a void that had previously persisted.

In conclusion, while generic guidelines for leukopenia evaluation do exist within the literature, our study notably contributes by introducing concrete real-world data on the actual utilization of flow cytometry testing. Detailed evaluation of the chronicity of leukopenia, family history, social history including alcohol use, co-morbidities, and current medications is essential before obtaining flow cytometry for patients with leukopenia. Additionally, testing could be over-utilized in institutions where the African-American patient population is higher than the national average. This highlights the importance of institution-specific protocols for the utilization of flow cytometry testing and quality improvement studies to provide feedback to clinicians. Regular feedback is imperative to change practice, thus providing quality care to the patients.

Data availability

The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest

Suma Sri Chennapragada: None.
Shivani Sharma: None.
Runhua Shi: None.
Richard Mansour: None.

Disclaimer

The abstract has been presented as a poster at the American Society of hematology meeting at New Orleans, LA in December 2022 and the same has been published in a supplement to the journal Blood.

Sources of support

None.

Acknowledgements

None.

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