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Diagnostic approach to Haematologic Malignancies in Resource-Limited Settings- A Review

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Summary

Haematologic malignancies encompass a diverse group of cancers originating in the blood, bone marrow, and lymphatic system. Such diseases pose a significant health burden in Africa. This review provides a comprehensive overview of these malignancies, focusing on classification, diagnosis, treatment strategies, and prognosis determination in resource-constrained settings. We delve into the types leveraging on World Health Organization (WHO) classification system and other literatures. Diagnostic approaches encompassing morphology, immunophenotyping and cytogenetics are elaborated upon. Limited access to modern diagnostic techniques often hinders early and accurate diagnosis, leading to poorer patient outcomes. Therefore, strategies to improve skills of laboratorians and clinicians in making optimum use of affordable technologies for the diagnosis and management of haematologic malignancies should be embraced by all, while jettisoning inter and intra-professional rivalry which has potential to impede quality health services in Africa.

Keywords: Haematologic malignancies, diagnosis, management, resource-limited setting.

Introduction

Haematologic malignancies represent a significant global health burden. They are a heterogeneous group of diseases with significant variability in clinical presentation, prognosis, and response to therapy (Campo & Ferrero, 2022). Traditional risk stratification based on clinical features often provides a limited view of the underlying disease biology. Haematologic malignancies encompass a diverse group of cancers originating from blood cells or bone marrow. These include leukemias, lymphomas, myelomas, and myeloproliferative neoplasms. In Africa, the incidence and mortality rates of haematologic malignancies are rising, partly due to population growth and aging (Asoh *et al*., 2020). However, unlike developed countries, the disease burden in Africa often translates into poorer patient outcomes due to several factors including limited access to healthcare facilities, a shortage of trained haematologists, and, crucially, the lack of modern diagnostic techniques (Ikhuenbor *et al.,* 2023). All these factors contribute to delays in diagnosis and hinder the implementation of optimal treatment strategies (Shalev *et al*., 2021). Accurate diagnosis is the cornerstone of effective management in haematologic malignancies. Traditional methods like morphology and cytogenetics have limitations in differentiating specific types of malignancies and identifying clinically relevant genetic abnormalities. Fortunately, recent advancements in diagnostic tools offer increased accuracy, sensitivity, and specificity for haematological malignancies.

Prevalence of Haematologic Malignancies in Africa

Epidemiology and Prevalence Trends: Available studies on the prevalence of haematologic malignancies in Africa suggest a rising trend in their incidence (Adewole *et al.*, 2020). However, data on the prevalence is scarce and fragmented but the increase can be partially attributed to improved surveillance and diagnostic capabilities which also likely reflects a genuine rise in cases.

Common Types of haematologic Malignancies in Africa: The specific types of haematologic malignancies most prevalent in Africa differ from those commonly observed in high-income countries. While lymphomas, particularly non-Hodgkin lymphoma (NHL), and leukemias remain prevalent, studies suggest a higher proportion of aggressive subtypes compared to developed nations. Adult T-cell leukemia/lymphoma (ATL) caused by the Human T-cell lymphotropic virus type 1 (HTLV-1) shows a higher prevalence in certain regions of Africa with endemic HTLV-1 infection (Mbanefo *et al.*, 2023).

Risk Factors and Contributing Factors

Several factors that influence the prevalence and presentation of haematologic malignancies in Africa are discussed below.

Limited access to healthcare: The lack of well-equipped healthcare facilities and trained personnel hinders early diagnosis and optimal treatment (Adeloye *et al.*, 2022). This can lead to advanced disease stages at presentation, significantly impacting prognosis.

Environmental factors: Exposure to environmental toxins, pollutants, and certain infectious agents like Epstein-Barr virus (EBV) and Human Immunodeficiency Virus (HIV) are suspected to play a role in lymphomagenesis (Asosiasi *et al.*, 2020). Further research is needed to elucidate the specific mechanisms.

Genetic predisposition: While specific genetic mutations associated with haematologic malignancies are not as extensively studied in African populations compared to others, sickle cell trait and polymorphisms in certain genes might contribute to susceptibility (Makinde *et al.*, 2021).

Conventional diagnostic techniques for haematologic malignancies

1. Complete Blood Count (CBC) with Differential:

The CBC with differential is a fundamental initial investigation for suspected blood disorders. It provides vital information about the number, size, and maturity of various blood cell types, including red blood cells (RBCs), white blood cells (WBCs), and platelets. Abnormalities in these cell counts can point towards potential malignancies (Swerdlow *et al.*, 2020).

Elevated WBC Count: A persistently elevated WBC count, particularly involving specific cell types like neutrophils or lymphocytes, can signal leukemia or lymphoma (Greenberg *et al*., 2022). Anaemia: Anaemia, characterized by low RBC count, can be associated with various haematologic malignancies, including myelodysplastic syndromes (MDS) and leukemias (Steensma *et al.,* 2021). Thrombocytopenia: A low platelet count (thrombocytopenia) is another potential indicator of underlying malignancies, particularly MDS and acute leukemias (Malcovati *et al.*,).

The differential provides a breakdown of the various white blood cell types, with atypical percentages or abnormal morphologies further raising suspicion for a malignancy. While the CBC offers a rapid and cost-effective approach, its limitations include the inability to pinpoint specific malignancies and the need for further investigations for confirmation.

2. Peripheral Blood Smear

Peripheral blood smear examination involves microscopic evaluation of a blood sample spread on a glass slide. This allows detailed visualization of individual blood cells, including their size, shape, nucleus-to-cytoplasm ratio, and presence of abnormal inclusions (Bain *et al.*, 2020).

The smear can reveal characteristic features suggestive of specific malignancies as highlighted below. Leukemic blasts: Immature white blood cells observed in the smear can be indicative of leukemia (Walter *et al*., 2020). Dysplastic features: Abnormal cell shapes and sizes in red blood cells can be seen in MDS (Vannucchi *et al*., 2021).

Atypical lymphocytes: The presence of abnormal lymphocytes in the smear may raise suspicion for lymphoma (Campo *et al*., 2020). The blood smear, in conjunction with the CBC, provides valuable information for initial diagnosis and classification of haematologic malignancies. However, similar to the CBC, it requires expertise in interpretation and may not

be definitive in all cases (Bain *et al*., 2020).

3. Bone Marrow Aspiration and Biopsy

Bone marrow aspiration and biopsy are considered gold-standard procedures for definitive diagnosis of haematologic malignancies.

Bone marrow aspiration: A needle is inserted into the bone marrow cavity to extract a liquid sample. This sample is then analyzed for cell count, morphology, and presence of abnormal cells suggestive of malignancy (Estey & Döhner, 2020).

Bone marrow biopsy: A core of bone marrow tissue is extracted using a needle. This tissue is processed and examined microscopically by a Pathologist for cellularity, architecture, and the presence of malignant cells (Arber *et al.*, 2016). Bone marrow analysis allows for a more comprehensive evaluation compared to peripheral blood tests. It facilitates:

Differentiation between benign and malignant processes: The detailed cellular analysis helps differentiate reactive bone marrow changes from those caused by malignancies (Horwitz *et al*., 2021).

Classification of specific malignancies: Bone marrow examination can aid in subtyping different leukemias and lymphomas based on specific morphologic and immunophenotypic features (Swerdlow *et al.*, 2020). Assessment of disease burden: The analysis can reveal the extent of bone marrow involvement by the malignancy (Malcovati *et al*., 2020). While bone marrow procedures are considered the most definitive diagnostic modalities, they can be invasive and potentially uncomfortable for patients (Estey & Döhner, 2020).

4. Immunophenotyping

Immunophenotyping is a technique that utilizes specific antibodies to identify and characterize cell surface markers on blood cells (Muhibi *et al.,* 2019). Immunophenotyping is a technique that utilizes specific antibodies to identify and characterize cell surface markers on blood cells. This helps to distinguish between normal and malignant cells based on their unique antigen expression patterns (Porpaczy *et al*., 2020).

Flow cytometry is a widely used method for immunophenotyping. Blood cells are labeled with fluorescently tagged antibodies targeting specific cell surface markers. The flow cytometer analyzes the light scattering properties and fluorescence intensity of individual cells, allowing for identification and quantification of different cell populations based on their marker expression (Matsui *et al*., 2023).

Immunohistochemistry: This technique can be applied to bone marrow biopsy sections to visualize the expression of specific antigens within cells and the tissue microenvironment (Campo *et al*., 2020).

Immunophenotyping plays a crucial role in: Leukemia classification in identifying lineage-specific cell surface markers and helps in the classification of acute leukemias (myeloid vs. lymphoid) and define specific subtypes (Estey & Döhner, 2020).

Lymphoma diagnosis and subtyping: Immunophenotyping aids in differentiating between different types of lymphomas based on the expression of B-cell or T-cell markers and further subtyping based on specific antigen profiles (Swerdlow *et al.*, 2020).

Immunophenotyping can also be used to detect the presence of small numbers of residual malignant cells after treatment, which can predict relapse risk (Létocart *et al*., 2022). While immunophenotyping is a powerful tool, it requires specialized equipment and expertise for accurate interpretation (Porpaczy *et al*., 2020). Additionally, some malignancies may exhibit aberrant or heterogeneous marker expression, posing challenges for definitive diagnosis.

5. Cytogenetic Analysis

Cytogenetic analysis involves examining the chromosomes of blood or bone marrow cells for abnormalities. These abnormalities, such as translocations, deletions, or extra chromosomes, can be characteristic of specific haematologic malignancies (Begna *et al*., 2021a).

Karyotyping: This traditional cytogenetic technique involves visualizing the entire set of chromosomes under a microscope to identify numerical or structural abnormalities (Begna *et al*., b).

Fluorescence in situ hybridization (FISH): This technique utilizes fluorescent probes to target specific chromosomal regions, allowing for the detection of specific translocations or deletions associated with certain malignancies (Gaekwad *et al.*, 2023).

Cytogenetic analysis provides valuable information for diagnosis and subtyping of chromosomal abnormalities. Specific chromosomal abnormalities can be diagnostic of certain leukemias and lymphomas (Gaekwad *et al*., 2023). Also, the presence and type of chromosomal aberrations can influence the prognosis of patients with haematologic malignancies (Begna *et al.*, 2021a). However, cytogenetic analysis can be time-consuming and may not always detect all relevant genetic alterations (Begna *et al.*, 2021b).

The emergence of next-generation sequencing (NGS) offers a more comprehensive analysis of the genetic landscape of malignancies, opening doors for targeted therapies and personalized medicine approaches (Schleidgen *et al.*, 2021). However, traditional techniques will likely continue to play a vital role in conjunction with NGS, providing a robust diagnostic workup for haematologic malignancies.

Conclusion

Traditional diagnostic techniques, including CBC with differential, peripheral blood smear, bone marrow aspiration and biopsy, immunophenotyping, and cytogenetic analysis, remain the cornerstone for diagnosing and characterizing haematologic malignancies which requires special skills and expertise but is sub optimally available in most settings in the West Africa Sub-region. These methods provide valuable information for initial workup, classification, risk assessment, and guiding treatment decisions. While advancements like NGS offer a deeper understanding of the genetic basis of these malignancies, traditional techniques will likely continue to be employed for lack of access to more modern technology, forming a comprehensive diagnostic approach for optimal patient management.

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