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International Journal of Medical Science and Dental Health (ISSN: 2454-4191)
Volume 11, Issue 12, December 2025
Doi: https://doi.org/10.55640/ijmsdh-11-12-10

Morphological Variations of Neutrophils Nuclear Appendages: Sex-Based Differences and Contextual Insights from Sudan

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Received: 03 December 2025, **accepted:** 15 December 2025, **Published Date:** 24 December 2025

Abstract

Background: Neutrophil nuclear morphology, with its typical multilobation and other nuclear appendages, is a complex and intriguing area of study. The sex-chromatin drumstick, a well-acknowledged physical characteristic in females, is indicative of the dormant X chromosome. However, its identification is often complicated by non-specific nuclear projections, including sessile nodules, tags, clubs, and hooks, which can manifest in both sexes. The accurate distinction between authentic sex-chromatin appendages and non-specific variations underscores the importance of morphological precision and diagnostic expertise.

Objective: To examine and elucidate the morphological spectrum of neutrophil nuclear appendages, highlight sex-based disparities, and address diagnostic factors pertinent to the Sudanese setting.

Materials and Methods: A narrative mini-review style was used to synthesize insights from traditional hematology literature and contemporary studies (2018–2024) on neutrophil nuclear morphology, sex-chromatin characteristics, and morphological aberrations, including drumstick and sessile nodule alterations. Local environmental, dietary, and viral aspects relevant to Sudan were integrated to offer contextual interpretation. A functional text-based diagnostic flowchart was created for laboratory use.

Results: True drumstick appendages are present in roughly 1–5% of neutrophils in females and are characterized morphologically by a tiny, compact spherical head linked by a slender filament. Non-specific appendages, such as sessile nodules, tags, and hooks, are devoid of this distinguishing filament and are present in both sexes. The Pelger-Huët anomaly (PHA) and acquired pseudo-Pelger-Huët anomaly (PPHA) have distinctive bilobed ("pince-nez") nuclei that are not associated with sex chromatin. In Sudan, folate insufficiency, tuberculosis, HIV infection, and drug exposure may induce morphological heterogeneity and complicate interpretation.

Conclusion: Accurate identification of authentic drumstick morphology necessitates stringent criteria to prevent misdiagnosis. Drumsticks indicate sex chromatin; however, other nuclear appendages are non-specific and should not be utilized for sex determination. Nutritional and pathogenic variables may alter neutrophil morphology in the Sudanese population; therefore, local reference data are necessary. The included diagnostic flowchart facilitates uniform classification and reporting in resource-constrained laboratory settings.

Keywords: Neutrophil morphology; Drumstick appendage; Sex chromatin; Pelger-Huët anomaly; Sudan; Peripheral smear; Hypersegmentation.

Introduction

Peripheral blood smear interpretation is a practical and essential tool in hematologic diagnostics. It allows direct observation of cellular morphology, enabling you to quickly and confidently identify both benign and malignant events [1]. The valuable clues provided by nuclear segmentation and appendage patterns in neutrophils extend beyond basic blood tests; they can also be used to make cytogenetic inferences and advance medical knowledge [2].

The nuclear morphology of neutrophils exhibits a variety of structural polymorphisms that possess diagnostic, cytogenetic, and significant instructional importance. The sex-chromatin drumstick, a compact chromatin structure connected by a slender filament to a nuclear lobe, is a recognized indicator of X-chromosome inactivation and is usually seen in a small proportion of female neutrophils in peripheral blood smears [3, 4]. This appendage, first described in the mid-20th century, indicates the presence of two X chromosomes, one of which undergoes lyonization to form the inactive sex chromatin. Historically, its identification has served as a cytological surrogate for sex determination; however, contemporary practice underscores its restricted diagnostic value outside particular situations [4].

Beyond drumsticks, neutrophils may display several non-sex-specific nuclear projections such as sessile nodules, tags, clubs, and hooks, which are often erroneously identified as drumsticks, particularly in male smears [4,5]. These appendages, although morphologically distinct under oil-immersion microscopy, require meticulous examination to prevent diagnostic inaccuracies. Misinterpretation may lead to unfounded conjecture about chromosomal abnormalities such as Klinefelter syndrome (47, XXY) or chimerism, both of which can infrequently yield drumstick-positive neutrophils in males [6,7].

Nuclear segmentation patterns, alongside appendages, provide crucial insights into underlying hematologic or systemic disorders. The congenital Pelger-Huët abnormality (PHA), an autosomal dominant laminopathy, is characterized by bilobed 'pince-nez' nuclei with coarse chromatin and is considered benign. However, the pseudo-Pelger-Huët anomaly (PPHA) is a different story [8, 9]. It is associated with acquired conditions such as myelodysplastic syndromes (MDS), TB, or exposure to certain medications (e.g., tacrolimus, mycophenolate), and may indicate significant underlying pathology. This underlines the clinical significance of understanding these patterns [10]. Similarly, hypersegmented neutrophils, characterized by ≥6 lobes or >3% with ≥5 lobes, are traditionally linked to megaloblastic anemia resulting from vitamin B12 or folate insufficiency, but may also occur in chronic renal illness, iron deficiency, or myelodysplastic syndromes (MDS) [11].

Ethnic variance significantly affects baseline neutrophil segmentation. Research indicates that persons of Black descent, especially Sudanese communities, may demonstrate elevated average lobe counts, necessitating consideration when utilizing established thresholds for hypersegmentation [12]. This is particularly important in Sudan, where dietary inadequacies, persistent infections (e.g., tuberculosis), and exposure to pharmaceuticals are not just common but also prevalent and may obscure morphological evaluation [13]. Even though these nuclear traits are essential for diagnosis, there isn't much specific evidence from Sudan. There is an urgent requirement for localized investigations to determine normative ranges and authenticate morphological criteria within the framework of regional epidemiology. This minireview elaborates on morphological criteria, sex-based expectations, and Sudan-specific considerations, synthesizes global research, and presents a feasible diagnostic flowchart to help people understand neutrophil nuclear variations for routine laboratory use.

Morphological spectrum for Neutrophil Appendages

1. Sex-Chromatin Drumstick

The sex chromatin drumstick is a well-defined nuclear structure primarily found in female neutrophils. It manifests as a diminutive, spherical, dense chromatin aggregate measuring around 1–1.5 µm in diameter, linked to a nuclear lobe by a slender filament or stalk [**Figure 1**]. Cytogenetically, it denotes the inactivated X chromosome (Barr body), condensed into heterochromatin and visible with Romanowsky stains such as Wright–Giemsa or Leishman [14].

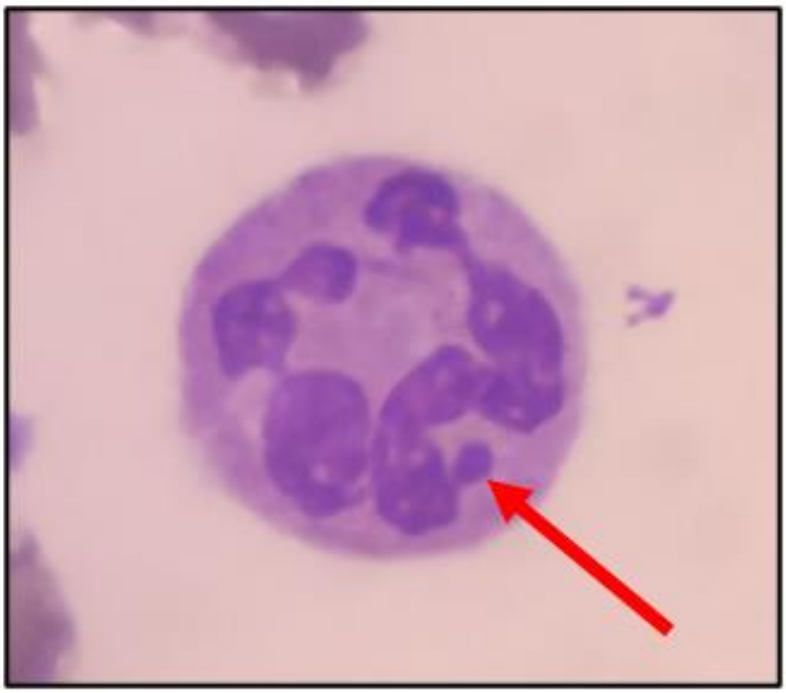

Figure 1: Drumstick-positive neutrophil (red arrow) (x1000, MGG stain) in a 38-year-old female exhibiting hyperlobulated nuclear morphology. *The cell displays a compact, spherical sex-chromatin appendage ("drumstick") connected by a slender filament, consistent with X-chromosome inactivation.*

Drumsticks are generally observed in 1–5% of segmented neutrophils in females, with prevalence increasing in cells with greater nuclear segmentation. Their occurrence in male smears is exceptionally uncommon and, with morphological confirmation, should raise suspicion of sex-chromosome abnormalities such as Klinefelter syndrome (47, XXY), mosaicism, or chimerism [6]. Nonetheless, misclassification is prevalent, and rigorous morphological criteria, including the existence of a slender stalk and a spherical head, must be employed to prevent diagnostic inaccuracies.

2. Non-Specific Appendages

Neutrophils may have several non-sex-specific nuclear projections resembling drumsticks; however, these projections are not cytogenetically relevant. These comprise: **Sessile nodules**: Broad-based projections lacking a connecting filament [**Figure 2**]. **Tags/clubs**: Small pedunculated projections exhibiting diverse forms. **Hooks/rackets**: curved appendages featuring robust bases and tapered extremities.

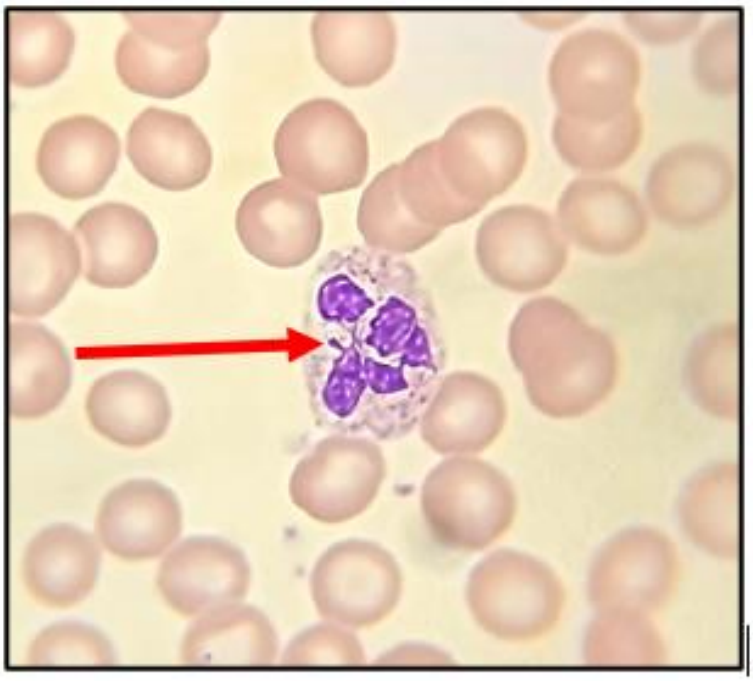

Figure 2: Neutrophil with sessile nodule (red arrow) (x1000, MGG stain) in a 43-year-old male with normal nuclear segmentation. *The broad-based projection lacks a connecting filament and is morphologically distinct from sex-chromatin drumsticks. Sessile nodules are non-specific and may appear in both sexes.*

These variants are present in both genders and are regarded as normal morphological variations. Misidentification of non-specific appendages as drumsticks is a common source of error in peripheral smear analysis, especially in male patients [4]. Accurate distinction requires oil-immersion microscopy and an understanding of morphological subtleties [3].

3. Pelger-Huët Anomaly (PHA) and Pseudo-Pelger-Huët (PPHA)

The PHA is a genetic laminopathy resulting from mutations in the LBR gene. It presents as bilobed "pince-nez" nuclei characterized by coarse chromatin and is often benign. Conversely, PPHA is an acquired condition that may indicate underlying pathologies such as MDS, severe infections, and drug exposures (e.g., mycophenolate mofetil, tacrolimus). PPHA emulates the congenital variant but occurs within a clinical context and may remit with therapy for the underlying etiology. The identification necessitates linkage with clinical signs and, if persistent, may prompt bone marrow evaluation [4, 14].

4. Hypersegmentation

Hypersegmented neutrophils [**Figure 3**], characterized by six or more nuclear lobes or by comprising more than 3% of neutrophils with five or more lobes, carry significant clinical implications that warrant attention [15]. This pattern, traditionally associated with megaloblastic anemia resulting from deficiencies of vitamin B12 or folate, is a complex condition that can also manifest as MDS, chronic infections, renal illness, and, occasionally, iron deficiency [16]. It's crucial to analyze hypersegmentation alongside red cell morphology (e.g., macro-ovalocytes) and biochemical indicators (e.g., serum B_{12}, folate) [14, 17]. This comprehensive approach will equip you with a deeper understanding and enhance your diagnostic skills.

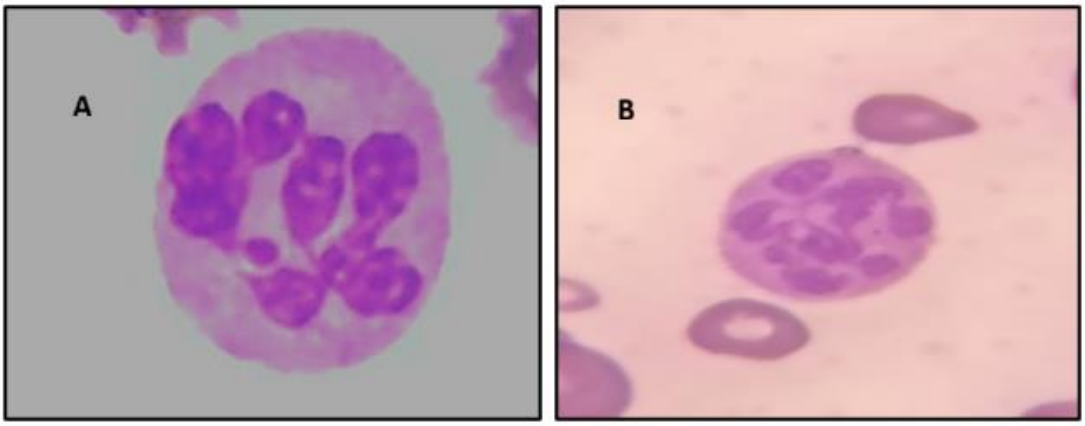

Figure 3: Hypersegmented neutrophil in a female with vitamin B12 deficiency (x1000, MGG stain). *The nucleus in panel A or B exhibits six or more distinct lobes, consistent with defective DNA synthesis. Hypersegmentation is a hallmark of megaloblastic anemia and should be interpreted in conjunction with red cell morphology and biochemical indicators.*

Sudanese Context and Diagnostic Considerations

Neutrophil nuclear morphology is influenced not only by intrinsic genetic variables but also by environmental, nutritional, and pharmacologic exposures [2]. In Sudan, many context-specific factors may modify neutrophil segmentation and appendage patterns, confounding smear interpretation and heightening the likelihood of misdiagnosis. Tuberculosis (TB), prevalent in many areas of Sudan, is another factor contributing to altered neutrophil morphology. Severe infections, such as tuberculosis, have been linked to acquired hypolobation that resembles the PHA, referred to as PPHA [18, 19]. This pattern may be ephemeral or enduring based on the underlying cause.

Ethnic diversity also plays a significant role in neutrophil morphology. Research suggests that individuals of Black heritage, particularly Sudanese ethnicities, may exhibit higher baseline neutrophil segmentation compared to other demographics [20, 21]. This finding underscores the need for caution when applying conventional hypersegmentation standards, which were primarily established for Western populations. It's crucial to consider these ethnic differences to ensure accurate diagnosis and treatment.

Despite the significant impact of genetic, environmental, and Sudan-specific factors on neutrophil morphology, there is a crucial gap in our understanding. We urgently need reference data on neutrophil nuclear morphology unique to Sudan. This data will not only determine normative ranges and authenticate morphological criteria but also inform laboratory reporting protocols. The resulting data will significantly enhance diagnostic precision, reduce false positives, and strengthen training initiatives in hematology and laboratory medicine, all within Sudan's unique context (**Figure 4**). Future Sudanese investigations should include controlled morphometric evaluations of neutrophil appendage frequency and nuclear segmentation indices across different sexes and age groups to provide population-specific reference intervals. This data will improve the precision of morphological interpretation, reduce diagnostic bias, and facilitate the establishment of localized hematologic standards.

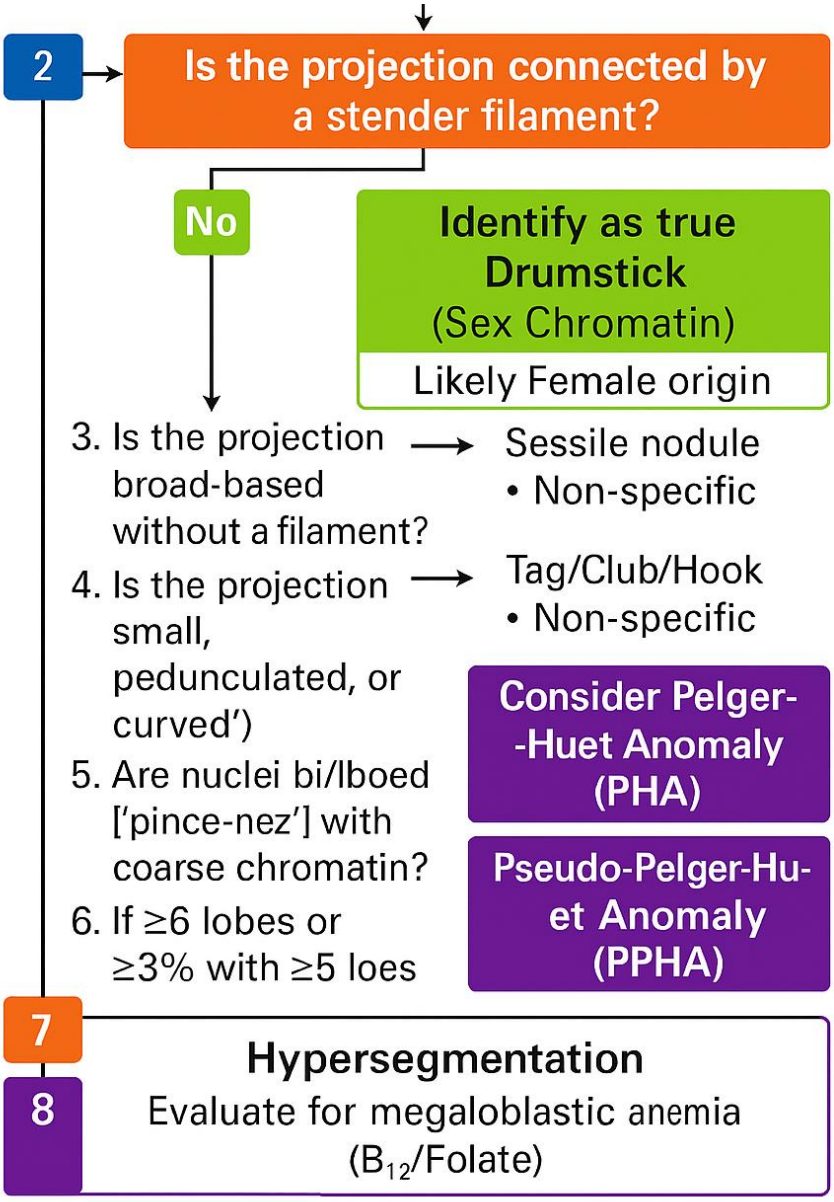

Figure 4: Diagnostic Flowchart for Neutrophil Nuclear Appendage Interpretation

Conclusion

Neutrophil nuclear appendages provide significant diagnostic insights but necessitate meticulous interpretation. Drumsticks are sex-linked and physically unique, whereas other projections are prevalent and non-specific. Nutritional and infectious factors in Sudan must guide smear interpretation. This review establishes a framework for precise classification and advocates for local research to enhance diagnostic standards.

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