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The Pelger-Huët Anomaly. From morphology to clinical suspicion

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Abstract
The careful observation of blood cells morphology in many cases reveals distinctive aspects of specific pathologies, such as hematologic or oncohematologic disorders, or can suggest a diagnostic hypothesis. The particular conformation of the nucleus in polymorphonuclear neutrophils characterize the Pelger-Huët anomaly. The anomaly can be inherited or acquired. In the first case it does not show abnormal functions of polymorphonuclear neutrophils, in the second, excluding the severe sepsis, the hypothesis to consider oncohematological diseases (myelodysplastic syndromes, acute myeloid leukemia, myeloproliferative neoplasms) should be mandatory.

1. Introduction

An important abnormal morphological characteristic of polymorphonuclear neutrophils (PMNs) is linked to the nucleus, so that in vitamin B12 and/or folate deficiency the hypersegmentation in several cells is a distinguishable trait. In myelodysplastic syndrome (MDS), leukemia and sepsis, the PMNs morphology can be characterized by hyposegmentation of the nucleus. However, in Pelger-Huët anomaly (PHA), an autosomal dominant inherited condition, the hyposegmentation of the nucleus in PMNs has a peculiar morphology (1) (2).

In humans the PHA prevalence is between 0.01% and 0.1%; the anomaly affects the white people, black and Asian in all ages and in equal ratio between males and females. The PHA is also present in other mammals such as mice, dogs and cats.

2. Case Report

A 61 year old man, several months after surgery for gastric cancer, was admitted for sepsis and massive embolism arteriovenous biliary fistula. Laboratory tests showed microcytic and hypochromic anemia (Hb = 103 g/L, MCV = 77 fL), mild leukopenia (WBC = 3.9 x 10^9/L) without neutropenia, and thrombocytopenia (PLT = 74 x 10^9/L). Peripheral blood smear evaluation showed characteristic nuclear alterations of PMNs. Over 50% of PMNs had unsegmented nucleus whose chromatin was coarsely aggregated (Figure 1A); in some cases the nucleus was bilobed with internuclear bridge (Figure 1B).

3. Discussion

In PHA a defective gene located on chromosome 1 (1q41-43) that encodes for the Lamin-B receptor (LBR) is responsible for the abnormal morphology. The LBR is a protein responsible for the "trafficking" of heterochromatin, as well as the nuclear lamin proteins that control both the shape and scaffold of the nuclear membrane (3) (4).

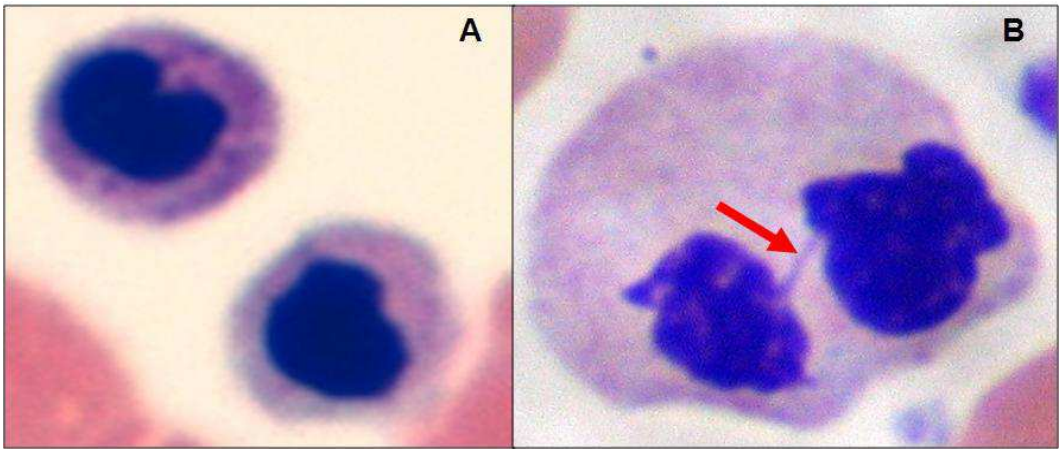

Figure 1. *A) Polymorphonuclear neutrophils with "unique" nucleus and aggregate chromatin. B) Polymorphonuclea rneutrophils with bilobed nucleous and internuclear bridge (arrow).*

In homozygous carriers for LBR gene mutation, the hyposegmentation of the nucleus in PMNs is present when the amount of LBR is half the normal amount (5). The nucleus is unique or slightly indented and its segmentation is outline or absent. The bone marrow shows normal morphology of granulocytic precursors, myelocyte stage (6). Moreover, due to a nonsense mutation on the LBR gene, cognitive impairment, heart defects and skeletal abnormalities (Hydrops-ectopic calcification-"moth-eaten" (HEM)/Greenberg dysplasia), are reported (7) (8). Several studies in animals report similarity between homozygous PHA and HEM/Greenberg dysplasia, unlike in humans in which the HEM is a severe clinical condition, universally lethal (7). Although the PHA is always associated with a clinically benign isolated defect, a genetic and phenotypic marked heterogeneity with wide clinical spectrum may occur.

In heterozygous phenotype the Pelger-Huët cell shows high nucleus/cytoplasm ratio, halting nuclear segmentation with bilobed nuclei, "dumbbell"-shaped, often connected by a thin filament.

The basic morphological and clinical characteristics between congenital and acquired pseudo-PHA are reported in table I.

Table I. *Morphological and clinical characteristics between congenital and acquired pseudo-PHA*

PHA	Cytoplasm	Chromatin clumping	% PMN's with PHA morphology	Cytopenias	Chromosomal Abnormalities
Congenital	Normal	In multiple cell lines	≈ 63–93%	Absent	Absent
Acquired	± Vacuoles	Neutrophils only	Range 0-38%	Often present	Often present

In PHA, biochemical, metabolic, and phagocytic functions, as well as bactericidal activity of PMNs, are not affected, and they are comparable with normal neutrophils. The abnormal morphology of the nucleus makes the PH cells not always fully able to migrate through small spaces (9) (10). A functional impairment of PMNs by defective diapedesis can be current and join with soft tissue infection.

The pseudo-PHA cells prevalently are detected in patients with MDS, acute myeloid leukemia and chronic myeloid leukemia (11). The PH cells can be an important diagnostic warning in suspected MDS and may resemble an early myeloid cell undergoing apoptosis, as well as an apoptotic condition of the band cells prior to take the multilobulated form (12).

The pseudo-PHA due to drugs is known in the literature, mainly in transplanted patients (13), and different are the drugs responsible for pseudo-PH cells (Table 2).

Table 2*. Medications associated with PHA*

Drug	Pharmacologic Action
Mycophenolate mofetil	Immunosuppression
Tacrolimus	Immunosuppression
Valproate	Inhibition of GABA transaminase
Sulfisoxazole	Antibiotic
Ganciclovir	Antiviral DNA polymerase
Fluconazole	Antifungal cytochrome P450
Ibuprofen	Inhibition of cyclooxygenase
Paclitaxel	Antimitosis
Docetaxel	Antimitosis
G-CSF (filgrastim)	Growth factor
GM-CSF (molgramostim)	Growth factor
Colchicine	Antimitosis
D-penicillamine	Immunosuppression

The morphological alteration of neutrophils is reversible, indeed, suspending or adjusting the amount of the drug the normal morphology of neutrophils is restored. The

morphological data can often be confused with a SMD. In this regard, a diagnostic algorithm for pseudo-PHA identification in peripheral blood and/or bone marrow has been proposed (14).

In PHA, interference in automatic differential leukocyte count is possible because the hyposegmentated PH cells may be reported as immature cells.

4. Conclusion

The PHA is a distinctive morphological appearance between a benign hereditary condition and acquired or transient alteration, e.g. MDS, acute or chronic leukemia, myeloproliferative neoplasm rather than sepsis. Its detection must always be reported.

A good practice is that, any hematological feature that differs from the normal morphology must always be reported because can already provide a diagnostic suspicion.

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