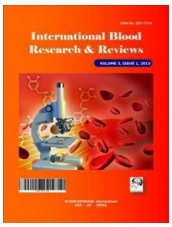

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Pseudo-Pelger-Huët Anomaly in Megaloblastic Anemia

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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Case Report

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ABSTRACT

The Pelger-Huët anomaly (PHA) is a morphologic abnormality of segmentation involving the neutrophils predominantly; however, all leucocytes may be variably affected; it is an autosomal dominant condition. It has a global prevalence; with certain Indian populations having a reported prevalence as high as 1 in 300. PHA should be considered when clinical labs suggest a profound left shift in the setting of normal leucocyte count. Clinically, PHA needs differentiation from the pseudo-Pelger-Huët anomaly (PPHA), which though morphologically similar is associated with multiple disease states such as; myelodysplasia, myeloproliferative disorders, leukemias, or drugs. PPHA with megaloblastic anemia is rarely seen. Reported herein, is a case of megaloblastic anemia with PPHA.

Keywords: Pelger-Huët anomaly; pseudo–Pelger-Huët anomaly; myelodysplasia; megaloblastic anemia; vitamin B12 deficiency.

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1. INTRODUCTION

Pelger, a Dutch physician [1] and tuberculosis specialist in 1928 observed in one of his tuberculosis patients, a peculiar nuclear abnormality in the neutrophils; most of which were stab forms, some had double or triple segmentations, none had more than three. Despite this apparent immaturity, the characteristic of the nucleus was otherwise mature with the presence of coarse chromatin and irregular clumps [1,2]. In 1931 Pelger observed similar changes in another patient suffering from tuberculosis. Consequently, it was initially believed to be an abnormality associated with the disease [2,3]. Later, Huët observed in one of the Pelger's patient the anomaly, who didn't have tuberculosis [4]. Additionally, his observation of the anomaly in many members of the same family, established its familial nature [3,4]. Huët was also instrumental in determining its benign nature, having observed three generations of such patients without any significant ailments [4]. Schilling is believed to have proposed the name Pelger-Huët anomaly (PHA) [5]. It was initially also known descriptively, with the term, "familial false shift to the left of leucocytes" [5]. PHA is reported globally, with prevalence ranging from 1 in 1000 to 1 in 6000 [3]. Some parts of India have the highest recorded global prevalence at 1 in 320. [6] Putting in perspective, PHA is approximately five times more common than Hereditary Spherocytosis—a relatively common entity in hematology practice [3]. Furthermore, lack of awareness of this entity may lead to misidentification of Pelger-Huët cells (PHCs) as myelocyte or metamyelocyte, leading to extensive clinical workup and pharmacological interventions [7]. Pseudo-Pelger-Huët anomaly (PPHA) is a similar morphological entity but seen in varied clinical conditions like myelodysplasia, myeloproliferative disorders, leukemias, megaloblastic anemia, drugs, or acute infections [3,5]. Telangana region in southern India, has sizeable tribal populations; yet, PHA and PPHA has not been reported in any frequency from this area, probably reflecting a lack of awareness of this entity. This case report describes PPHA from this region.

2. CASE REPORT

A 40-year-old female, presented with complaints of fatigue, nausea, and decreased appetite, during the last two weeks. The patient also complained of epigastric discomfort; she had a history of blood transfusion eight years back, comprehensive anemia workup was unfortunately not done then. On examination she was found to have pallor, hyperpigmentation of the palmar surface of hands including distal phalanges, nail folds and knuckles, along with the oral mucosa; vitals were found to be normal with BP 118/80 mm Hg, Pulse 88/min; her abdomen was soft, without hepatosplenomegaly.

The labs revealed: pancytopenia, raised mean corpuscular volume (MCV), mildly elevated bilirubin. Lactate dehydrogenase (LDH) was not available immediately. Considering her pancytopenia, macrocytosis, and hyper-pigmentation suggesting possible vitamin B12 deficiency, she was commenced on methylcobalamin 1000 microgram parenteral formulations, pending her vitamin B12, folic acid, iron indices and cortisol results; which later returned as B12 and folic acid deficiency along with normal iron indices (Table 1). Serum 8 am and 4 pm Cortisol returned as 18 µg/dl and 8 µg/dl respectively (normal 5-25 µg/dl). Upper gastrointestinal endoscopy (UGIE) including second part of duodenum (D2) biopsy to rule out atrophic gastritis, was normal. Stool antigen test for Helicobacter Pylori was negative. Anti-nuclear antibody (ANA) and anti-parietal cell antibody were both negative.

The folic acid replacement was initially delayed to avoid possible neurological deterioration. Parenteral methylcobalamin supplementation was continued on the home basis. The patient reported to the hospital on the sixth day; improvement in her general condition was seen, epigastric discomfort had decreased, and she felt overall well. Complete blood count (CBC) was repeated and is tabulated (Table 2). Her peripheral smear was taken for the study on the sixth day and revealed bi-lobed neutrophils/ PHA in around 40 percent of neutrophils (Table 3). Considering a possibility of PHA, her family members were also screened but found to lack such anomaly. After ten days of replacement, the peripheral smear was studied further and showed a decreasing trend in the number of bilobed cells (Table 3). Hence, the PHA in her case was considered secondary to B12 deficiency (PPHA). Folic acid supplementation was commenced from eleventh day onwards. She is under follow-up.

Table 1. Vitamin B12, folic acid, and iron indices

B12 (pg/ml)	Folic acid (ng/ml)	IRON (µg/dl)	FERRITIN (ng/ml)	TIBC (µg/dl)	TRANSFERRIN (mg/dl)
111	1.06	135	97	353	246

Reference range in parenthesis: folic acid (>5.5 ng/ml); iron (59-158 µg/dl); ferritin (22-322 ng/ml); total iron binding capacity (TIBC: 250-450 µg/dl); transferrin (176-280 mg/dl)

Table 2. Complete blood count (CBC)

	Hb (g/dl)	RBC ($\times 10^{12}$/l)	WBC ($\times 10^{6}$/l)	PLATELETS ($\times 10^{6}$/l)	MCV (fl)	RDW-CV (fl)	RDW-SD (%)
Day 1	5.3	1.47	3700	96000	121.5	20.3	79.9
Day 6	6.4	1.78	6700	136000	122.4	19.4	80.7

Hb: Hemoglobin; RBC: Red blood cells; WBC: White blood cells; MCV: Mean corpuscular volume; RDW-CV: Red cell distribution width-coefficient of variant; RDW-SD: Red cell distribution width-standard deviation

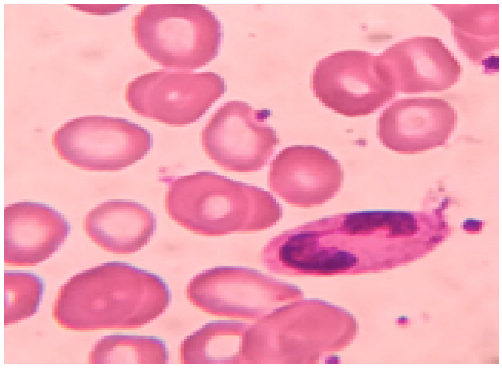

Image 1. Bilobed neutrophil with non-symmetrical lobes and irregular membrane outline of the chromatin, characteristic of the pseudo-Pelger-Huët anomaly. Also seen are macro-ovalocytes, increased central pallor (hypochromic), and poikilocytosis

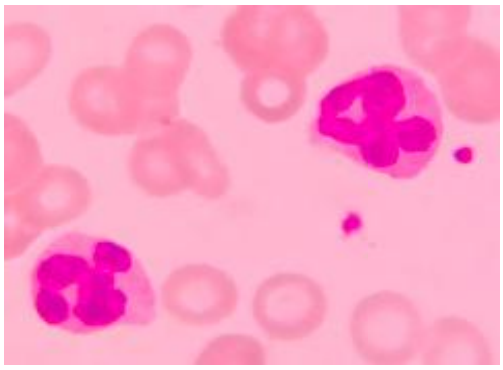

Image 2. Increased neutrophil segmentation with therapy

3. DISCUSSION

In healthy adults, peripheral blood smear shows neutrophils having a segmented nucleus; with the majority (70-75%) having three to four nuclear segments. Additional 15-20% of neutrophils have two lobes, 5% have more than four, and a further small percentage of neutrophils (3-5%) have no nuclear segmentation [7]. Such, percentage distribution of the polymorphonuclear leucocytes into five classes according to the number of segments or lobules in the nucleus, is called as the Arneth count [8].

PHA is an autosomal dominant benign condition, caused due to mutations in Lamin B-receptor gene [3]. Laminins in health is responsible for the structured link between the chromatin, resulting in the usually seen multilobular neutrophil nucleus; the physiologic advantage of such a 'chained chromatin' in neutrophil is the flexibility to squeeze through the endothelium during inflammation (diapedesis). Consequently, the mutation in Lamin B-receptor gene results in decreased laminin and hypo-lobulation of the chromatin. Notwithstanding the above-described physiological premise, the hypo-lobulated neutrophils in PHA are otherwise healthy and conduct themselves well in the innate defense [2,3].

Morphologically, neutrophils in PHA, possess hypo-lobulated nuclei, including bi-lobed forms, connected by a thin chromatin filament, the ensuing two lobes are symmetrical with regular chromatin outline (dumbbell or pince-nez appearance) [3]. Moreover, in PHA the nucleus retains coarse clumping and condensation, differentiating it from premature cells (myelocyte, metamyelocyte, and blast cells) [3,9]. In PHA, the majority of neutrophils (80-90%) are hypo lobulated. Additionally, hypo-lobulation in PHA is not confined to neutrophils alone and may involve other white blood cells like eosinophils. Conversely, PHA is not associated with any other hematological pathologies [3-5].

Table 3. Percentage of neutrophils with one through five or more lobes (Arneth count)

	PMN with I lobe	PMN with II lobe	PMN with III lobe	PMN with IV lobe	PMN with V or more lobe
Day 6	10%	40%	20%	20%	10%
Day 11	10%	20%	20%	35%	15%

PMN: Polymorphonuclear cells

Acquired or PPHA also possesses a bilobed nucleus, but the lobes are not symmetrical, and the chromatin has an irregular outline. Moreover, the cytoplasm in pseudo-PHCs is hypo granular, and the number of neutrophils involved in PPHA is usually in the minority. Additionally, the dysplasia in PPHA may also include platelets and red blood cells with the presence of occasional blast cells [3].

Myriad disease states result in PPHA like myelodysplasia, myeloproliferative disorders, leukemias, leukemoid reactions, infections, or drugs [3,9]. PPHA is only rarely reported with megaloblastic anemia [10]. Additionally, pseudo-PHCs are considered important markers of disease progression in many hematological conditions such as chronic myelocytic leukemia, acute myeloblastic leukemia, and myelofibrosis. Moreover, in many of these disease states, it is believed to precede the disease by many months, emphasizing the importance of its recognition in suspected clinical scenario [3].

Its clinical importance is underscored, in the workup of macrocytic anemia, as vitamin B12 deficiency and myelodysplasia can both present similarly. Additionally, both can have associated PHCs; distinguishing between these two entities although challenging, is essential as the treatment line differs significantly [3]. Care should be taken to not rush into more invasive procedures like bone marrow study when the B12 deficiency is suspected; as a myelodysplastic syndrome is a slowly progressive disorder, and B12 replacement when implicated can correct the abnormality, saving the patient from unnecessary procedures and anxiety. Conversely, when vitamin B12 is only marginally low and appears non-causative for the macrocytic anemia a thorough workup for myelodysplasia and other hematological pathologies should be initiated on the discovery of PHCs.

Vitamin B12 deficiency remains common in India [11]. In the present case, the PPHA was presumed secondary to vitamin B12 deficiency, on the following grounds: a documented vitamin B12 deficiency, lack of PHCs in immediate family members, and reduction of PHCs with the replacement of vitamin B12. The patient had associated folic acid deficiency, which may also cause PPHA [3,9]. However, her PHCs decreased with the replacement of vitamin B12 alone, as the folic acid replacement was delayed in her to avoid possible neurological deterioration, suggesting vitamin B12 deficiency as the sole cause of PPHA.

Hyperpigmentation of extremities with the prominence of such pigmentation over inter-phalangeal joints and nail fold, as in the present case, is commonly reported with vitamin B12 deficiency [12]. Oral hyperpigmentation is also common, [13] and represent a significant differential for Addisonian hyper-pigmentation, in regions with high prevalence of vitamin B12 deficiency such as India.

The causes of vitamin B12 deficiency are malabsorption secondary to intrinsic factor deficiency as in pernicious anemia; dietary deficiency; and a less recognized condition known as 'food-cobalamin malabsorption. The latter is a disorder of cobalamin release from food, resulting in cobalamin malabsorption despite an intact intrinsic factor [14]. It is secondary to *Helicobacter pylori* infection, which is extremely common in India [14,15]. The present case was presumed to be of dietary origin as her upper gastrointestinal endoscopy was normal, anti-intrinsic factor antibody and stool antigen test for *Helicobacter pylori* were both negative.

4. CONCLUSION

Vitamin B12 deficiency is common in India; it results in many hematological changes, including PPHA, premature cells and blast cells, lack of awareness of which can result in it being considered a more severe hematological disorder. As with most things in practice, the clinical guidance remains foremost, with PHCs being no exception. From benign to malignant disease course, PPHA have ramifications, making it necessary for clinicians to recognize

and understand its significance. Back to the clinician, bench remains the foundation for the bedside.

CONSENT AND ETHICAL APPROVAL

As per international standard or university standard, patient's written consent and written ethical approval have been collected and preserved by the author.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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