Letter to the Editor

Acquired Pelger–Huët anomaly associated with ibuprofen therapy

Dear Editor,

Pelger–Huët anomaly (PHA) is a benign inherited condition characterized by hyposegmentation of the neutrophils nucleus and excessive chromatin clumping [1]. An acquired neutrophils dysplasia similar to PHA has been already described in hematological diseases [2,3] and in some clinical conditions, especially under certain drugs effect [4–9]. It has been known as acquired or pseudo Pelger–Huët anomaly. A previous report of our group showed that the incidence of acquired PHA in kidney transplanted patients under immunosuppressive therapy in a local Brazilian Hospital was 5.3% (9 out of 170 patients) [10].

In March 2008, a healthy 7-year old child was punctioned in a small laboratory in Mateus Leme/MG for a routine hemogram analysis. Her blood cells showed to be normal under quantitative and qualitative points of view. Two months later, this child had fever, without other symptoms and 17 drops of ibuprofen was given to her, from 4 to 4 h during 1 day and night. Next day, as the girl's condition became worse, she was conducted to the same laboratory for another routine blood analysis. This dose (510 mg/24 h) was >12 times higher than that recommended (40 mg/24 h). The leukocytes count was 12,500/μL with 22% band form neutrophils, 50% segmented neutrophils, 20% lymphocytes and 8% monocytes, erythrocyte sedimentation rate (60 min.) was 6 mm and Reactive C Protein was negative. However, blood film revealed that segmented neutrophils nucleus had a poor segmentation, with only bilobular nuclear form or peanut shaped and the chromatin was excessively clumped (Fig. 1 a, b, c and d). Later on a more experienced observer has diagnosed the child as a carrier of PHA. Since there was a normal blood analysis reported 2 months ago, the hypothesis of benign inherited PHA was discharged. The apparent neutrophils' shift left (22% band forms) was not coherent with the child's symptoms, she only had fever once, with no infection symptoms. Five days later, a new blood analysis was done and the total leukocytes were 5300/μL persisting 21% of band neutrophils. Six months later, the child had fever again and other blood analysis was required. The leukocytes count was 17,700/μL and 5% band neutrophils (without alterations), 54% segmented neutrophils, 32% lymphocytes, 2% monocytes and 7% eosinophils (Fig. 1e) was found, which confirm the transitory character of neutrophil abnormalities observed when the child was under ibuprofen use. All data are shown in Table 1. It was not suspected that this case of transitory neutrophil abnormalities was caused by ibuprofen, since it was the only drug that the child had received. Only one report on ibuprofen use and pseudo PHA has previously been described [11].

Although some hypotheses were raised to explain this phenomen, the mechanism of nuclear change is still unclear. The first hyphothesis is related to abnormalities in the sequence of lamin B receptor (LBR) gene resulting in a lack of LBR protein. This protein is essential for chromatin binding to nuclear membrane. In the absence of LBR, neutrophils and also erythroblasts, monocytes, lymphocytes, plasma cells, eosinophils and basophils carry chromatin hypercondensation [12,13]. The second suggests that pseudo PHA is not actually an abnormality in neutrophil maturation but represents an apoptotic cell, since ultrastructurally pseudo PHA neutrophils looked like mature cells undergoing apoptosis (compact chromatine moved toward the periphery of the nucleus and condensation of the cytoplasm with abnormally shaped organelles) [2]. The third hypothesis suggests that pseudo PHA is related to 17p deletions [14,15].

A careful review of the pertinent literature revealed that almost all reports of pseudo PHA associated to either drugs use or to several diseases were described until middle of 1980. To date, almost all reported cases are associated to either myelodysplastic syndrome or other hematological diseases as well as to use of immunosuppressive drugs by grafted patients.

Curiously, automated hematological procedures including differential leukocytes counting were widely diffused from end of the 1980s. This fact raises an important question "Can automatic cell blood counters reveal neutrophils' morphological changes consistent to PHA such as abnormal bilobular or monolobular nuclear forms and excessive chromatin clumping?" PHA whichever its cause, if it is not registered by automated counters may constitute a serious problem considering that clinical laboratories do not examine most of stained blood films on the microscope.

The contribution of this report is to alert laboratory professionals and clinicians for pseudo PHA diagnosis. Considering previous reports and our own experience, in addition to the frequent use of drugs with no clinical prescription (automedication), one can admit that other cases similar to that one reported here due to administration of ibuprofen (or other drugs) in high doses may be occurring frequently. Whether this phenomenon has clinical implication remains to be elucidated. At least, however, when pseudo PHA is described, its possible cause must be investigated.

Finally, considering that acquired PHA is a common finding in myelodysplastic syndrome [2,3], a doubt may be about a predisposition for developing bone marrow diseases in individuals who showed these neutrophils under certain conditions. However, no report regarding this issue was found in the literature and a follow up of these individuals is essential to elucidate this important question.

References

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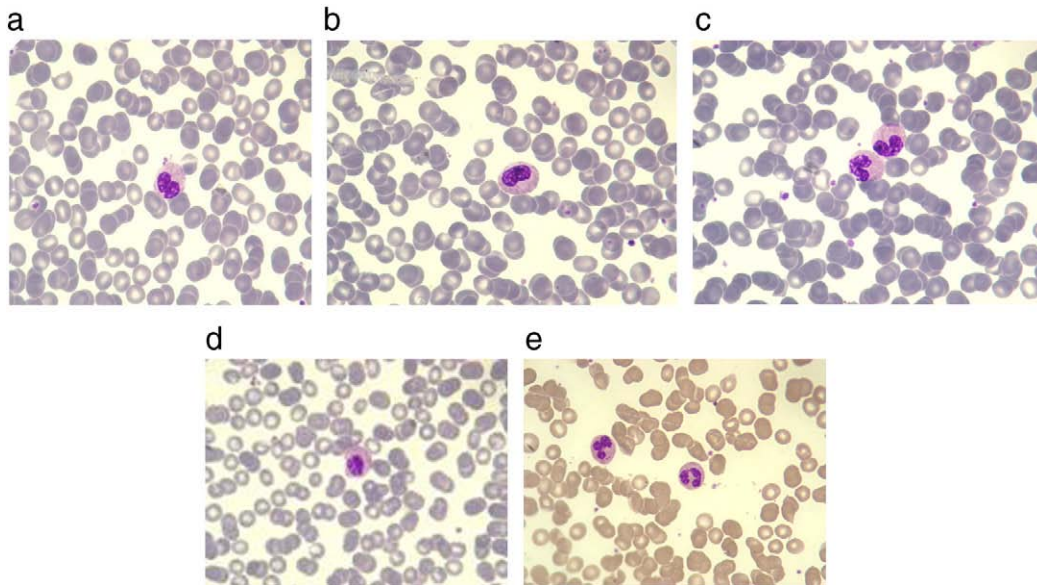
Fig. 1. Neutrophils with chromatin excessively clumped. a) Segmented neutrophil b, c) band forms neutrophils d) neutrophil with rodlike nucleus. e) Segmented neutrophils with no abnormalities.

Table 1
Laboratorial results at different occasions.

Parameters	March 2008	May 2008	May 4 days after	November 2008
Leukocytes count	9100/μL	12,500/μL	5300/μL	17,700/μL
Band form neutrophils	1%	22%	21%	5%
Segmented neutrophils	62%	50%	23%	54%
Lymphocytes	25%	20%	50%	32%
Monocytes	7%	8%	5%	2%
Eosinophils	5%	0%	1%	7%
Erythrocyte sedimentation rate (60 min)	–	6 mm	–	–
Reactive C Protein	–	Negative	–	–

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