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Short Communication

Cytoplasmic vacuolations in peripheral blood smear: A significant finding that is often ignored: An overview

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ABSTRACT

Cytoplasmic vacuolations are sometimes frequently seen in blood cells on peripheral smear but are often ignored. Presence of such vacuolations can be seen in red blood cells (RBCs) and WBCs (neutrophils, lymphocytes and monocytes). These vacuolations can be true or artefactual. Identifying this a quick, cheap and important way of guiding our diagnosis and treatment.

1. Introduction

Cytoplasmic vacuolations are sometimes frequently seen in blood cells on peripheral smear but are often ignored. Presence of such vacuolations can be seen in red blood cells (RBCs) and WBCs (neutrophils, lymphocytes and monocytes). These vacuolations can be true or artefactual. Identifying this a quick, cheap and important way of guiding our diagnosis and treatment.

1.1. Artefactual cytoplasmic vacuolations

In the peripheral blood smears, presence of degenerative vacuolation in neutrophils, monocytes, and lymphocytes can be seen blood samples have been allowed to stand for more than three hours after blood collection at room temperature. [1,2]

1.2. True cytoplasmic vacuolations

1.2.1. Cytoplasmic vacuolations in RBCs

The vacuolation are seen predominantly in red cell precursors affecting early precursors (pronormoblasts) more than late forms and these vacuolations are cytoplasmic rather than nuclear and are mostly reversible. Various causes like any direct cytotoxic effect of alcohol, metabolic acidosis and hypoglycaemia associated with acute alcoholic poisoning may be important factors in the pathogenesis of such vacuolations. [3,4] The vacuoles do not stain positively for fat, mucopolysaccharide, DNA, RNA, peroxidase, or acid and alkaline phosphatase. Cytoplasmic and nuclear vacuolation of only red cell precursors may be prominent in erythraemic myelosis. [5–8]

1.2.2. Cytoplasmic vacuolations in WBCs

1.2.2.1. Cytoplasmic vacuolations in neutrophils. Unstimulated neutrophils exhibit a smooth round cell shape with uniform cytoplasmic granularity, whereas irregular cell shape, toxic granulations, and cytoplasmic vacuolization can be observed in trauma-induced neutrophil activation. Tissue trauma induces migration and activation

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of neutrophils through specific mediators. This condition can also lead to local and systemic release of mediators capable of inducing a systemic inflammatory response syndrome (SIRS).[9] Cytoplasmic vacuolization is a known marker of cell degeneration and apoptosis. Moreover, nuclear fragmentation and vacuolization have also been demonstrated in that setting and represent irreversible apoptosis. Ischemia/ reperfusion and hypoxemia in septic shock patients provoke inflammatory response that leads to cytoplasmic vacuolization and lysis of cellular organelles in PMNs thorough a mechanism involving reactive oxygen species. Vacuolation of neutrophils and monocytes is most commonly associated with infections, like septic states and toxic conditions that includes metabolic disturbances such as diabetic ketoacidosis. Such vacuolar changes have also been reported in progressive muscular dystrophy.[10–12]

1.2.2.2. Cytoplasmic vacuolations in monocytes. Monocytes normally also have cytoplasmic vacuolations. That's why it is essential to differentiate unstimulated monocytes from stimulated monocytes showing cytoplasmic vacuolations.

1.2.2.3. Cytoplasmic vacuolations in lymphocytes. In peripheral blood smears, presence of vacuolated lymphocytes can be more clearly identified at the tail end of the thin blood film. Examination of blood film should be in a systematic manner with emphasis on detection of morphological characteristics of lymphocytes.

Monocytes may be confused with lymphocytes especially when they show cytoplasmic vacuolations but their glassy cytoplasm is characteristic. A total of 100 lymphocytes should be examined in the blood film, and if vacuolation is present, we should add comments on the characteristics and extent of the vacuolations present.[13–16]

Generally cytoplasmic vacuolations are uncommonly seen in lymphocytes. Presence of cytoplasmic vacuolation in peripheral blood lymphocytes suggests viral infections like infectious mononucleosis. Rare hereditary disorders like sphingomyelin lipidosis (Niemann-Pick disease), ganglioside lipidosis (Tay-Sach and Batten-Spielmeyer-Vogt diseases), type II glycogen storage disease (Pompe's disease), and genetic mucopolysaccharidosis (Hurler-Hunter syndrome) can also show presence of vacuolations. Accumulation of metabolic by-products due to metabolic disorder can present as vacuoles in lymphocytes. Therefore, identification of vacuolated lymphocytes in a pediatric patient with developmental delay should trigger more specific testings for metabolic disorders[11–15]

Accumulation of metabolic byproducts in metabolic disorderswhich can also manifest as cytoplasmic vacuoles in lymphocytes. Blood film review is always recommended in children suspicious for metabolic disorders. In addition, eosinophil granule abnormality seen in the image is commonly identified in GM1 gangliosidosis, a disease with lysosomal GM1 ganglioside accumulation due to β-galactosidase deficiency.[3,17]

In few cases presence of cytoplasmic vacuolations along with clinical features in conjunction is highly suggestive of a specific diagnosis, like juvenile subtype of Batten's disease (NCL3) in a child who presents with progressive blindness and developmental deterioration or acid maltase deficiency disease in a patient with periodic acid Schiff positive lymphocyte vacuolation and progressive cardiac or skeletal myopathy. If there are numerous large cytoplasmic vacuoles in lymphocytes with a clinical suspicion of infantile GM1 gangliosidosis, then β galactosidase deficiency may be demonstrated histochemically on the blood film. However, it is important to exclude other disorders, such as galactosialidosis, using enzymological methods. Likewise histochemical detection of acid esterase activity is also possible on blood films showing lymphocytes with small numbers of small and discrete vacuoles to confirm or exclude the diagnosis of Wolman's disease. Furthermore, in addition to histochemical methods, ultrastructural examination of the inclusions may help in further specific diagnosis and has particularly aided the identification of various subtypes of Batten's disease.[13,14]

Table 1: Metabolic storage disorders with vacuolated lymphocytes.

Storage disorders with few small vacuoles in many lymphocytes	**Storage disorders with many small vacuoles in many lymphocytes**
1. Pompe's disease (acid maltase deficiency)	1. G_{M1}-gangliosidosis type 1 (b-galactosidase deficiency)
2. Wolman's disease (acid esterase deficiency)	2. I-cell disease (mucolipidosis II)
3. Niemann-Pick disease type A (acid sphingomyelinase deficiency)	3. Infantile sialic acid storage disease
	4. Sialidosis (a-neuraminidase deficiency)
	5. Galactosialidosis
	6. Mannosidosis (a-mannosidase deficiency)
	7. Classic juvenile Batten's disease
	8. Morquio disease type B

Mere presence of cytoplasmic vacuolation in WBCs is not specific to a particular disease but in proper clinical context and with the help of other supporting tests, a definite diagnosis could be made. For this purpose, in most conditions in which definite specific diagnosis is possible, enzyme analysis of white blood cells or a fibroblast culture is considered the gold standard, along with specific gene defects study using molecular diagnostic techniques.

Lymphoid blasts also show presence of cytoplasmic vacuolations in Acute Lymphoblastic leukemia and in Burkitt's lymphoma that are PAS positive.[17]

2. Conclusion

There is a significant degree of clinical usefulness of meticulous examination of blood films for cytoplasmic vacuolation in patients with a history suggestive of metabolic disease. The test is cheap, rapid, and minimally invasive and provides a first line screening test with findings in some cases, providing strong clues as to the underlying diagnosis, particularly when appropriate and adequate clinical information is provided.

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4. Conflict of Interest

None.

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