ultrastrutal investigation on Pseudo Chediak–Higashi abnormality in acute lymphoblastic leukemia: A case report

Jing Liu¹, Shu-xu Dong¹, Ying Li², Yi-dan Xu¹, and Yong-xin Ru³

¹State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Institute of Hematology Blood Diseases Hospital, Chinese Academy of Medical Sciences Peking Union Medical College

²Tianjin Neurological Institute, Tianjin Medical University General Hospital

³Chinese Academy of Medical Sciences and Peking Union Medical College State Key Laboratory of Experimental Hematology

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Abstract

Pseudo Chediak-Higashi (PCH) granules are mainly common in acute myeloid leukemia. Here we found a patient diagnosed with common-B acute lymphoblastic leukemia(ALL) with PCH cytoplasmic granules, which was rarely seen in daily diagnosis. The morphology of the granules is different in transmission electron microscope (TEM) from cases reported before. There is a vesicle with various-sized particles surrounding the nucleus, in addition to the particles, a multiple-layer membrane structure was also detected in the vesicle.

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Pseudo Chediak-Higashi (PCH) granules are mainly common in acute myeloid leukemia. Here we found a patient diagnosed with common-B acute lymphoblastic leukemia(ALL) with PCH cytoplasmic granules, which was rarely seen in daily diagnosis. The morphology of the granules is different in transmission electron microscope (TEM) from cases reported before. There is a vesicle with various-sized particles surrounding the nucleus, in addition to the particles, a multiple-layer membrane structure was also detected in the vesicle.

1.Introduction

Pseudo–Chediak–Higashi (PCH) anomaly is seen in various types of leukemia,including acute monoblastic leukemia(AML-M₅)¹,mixed phenotype acute leukemia²,acute myeloid leukemia^{3, 4},chronic myeloid leukemia(CML)⁵, and myelodysplastic syndrome(MDS)⁶.PCH is characterized by the appearance of eosinophilic granules of different sizes in cytoplasm of abnormal leukocytes when examined by light microscope. The disease shares similarities in appearance with the granules noted in Chediak–Higashi syndrome(CHS).In some rare cases, intracytoplasmic vacuoles are positive for myeloperoxidase(MPO) and periodic acid–Schiff (PAS) around the myeloblasts, which probably result from the accumulation of metabolic waste or damaged organelles³.Although there are some reports on the abnormality of cells in acute lymphoblastic leukemia(ALL)⁷⁻⁹,the abnormal granules have been rarely interpreted. Herein, we report a rare case of ALL in a young patient because of rare morphology.

2. Case description

A 9-year-old girl was admitted to our hospital for moderate anemia and mild splenomegaly and was diagnosed with common B-acute lymphatic leukemia (B-ALL) based on laboratory examinations. Peripheral blood examination indicated a white blood cell (WBC) count of $2.45 \times 10^9/L$, red blood cell (RBC) count of $2.27 \times 10^{12}/L$, hemoglobin (HGB) of 64g/L, and platelet count of $68 \times 10^9/L$. Flow-cytometry analysis revealed that the leukemic cell was strongly positive for CD10; moderately positive for CD34, HLA-DR, CD13, CD33, CD19, TDT, and cCD79a; weakly positive for CD38 and CD22; and negative for CD20, cIgM, sIgM, and MPO. Cytogenetic and molecular testing demonstrated that the leukemic cells were positive for TEL/AML1 fusion gene.

Wright–Giemsa staining of the bone marrow aspiration smear suggested that a few giant pink inclusions were present in the cytoplasm. These inclusions, which were located next to the nucleus, exhibited differences in size and appearance upon light microscopic observation (Figs. 1A, 1B, 1C, and 1D). There was marked heterogeneity among the granules. Some of them were translucent, while others were dark. Moreover, the inclusions exhibited slight reactivity in PAS staining (Figs. 1E and 1F). Cytochemical examination indicated negative expression for MPO.

Transmission electron microscopy (TEM) showed that most of the giant inclusions were located in the perinuclear region, which contained a well-defined membrane. Glycogenosomes of various sizes were present inside giant inclusions, and several multiple-membrane vacuuous structures were observed (Figs. 2A, 2B, 2C, 2D, 2E, and 2F). The glycogenosomes were not distributed homogeneously.

3. Discussion

The PCH granules are found in many types of cells, including immature myeloid cells, lymphocytes, and monocytes. Gavillet⁹ et al. reported an elderly patient with the presence of PCH granules after relapse of diagnosed with B-ALL. The expression of CD20 was lost upon comparison with the primary diagnosis. The existence of a connection between the recurrent disease and the missing expression of CD20 is yet to be established. In our study, we first found a novel morphological entity of lymphoblastic cells through TEM. There were <30% (27.7%) aberrant cells among the total nucleated cells. These anomalous lymphoblasts positively expressed CD10 but not CD20, which is consistent with the case report of Agrawalet al⁷. Nevertheless, the complete blood count (CBC) results signified that the main blood components were present at below-normal levels, which differed from the findings in common leukemia. Interestingly, the phenomenon of leucopenia could be found in leukemia, accompanied by anemia or thrombocytopenia^{10, 11}.

The PCH granules resemble the inclusions noted in CHS, which is a heritable disease linked to the lysosome. The patients with CHS frequently face severe hematologic abnormalities, including hemorrhagic tendency and bacterial infections. The disease is also accompanied by nervous system disorder. Some individuals are initially found to have symptoms of albinism. The Chediak–Higashi syndrome (CHS1)/lysosomal trafficking regulator (LYST) gene was found to be mutated in the disease¹². Subsequently, the functioning of the lysosomal trafficking protein was compromised by the defective gene, and non-functional enlarged lysosomes were formed in eosinophils, neutrophils, and other granulocytes in the body¹³. Abnormal intracytoplasmic granules, which are generated by a complex process of granular fusion, cytoplasmic injury, and phagocytosis at the moment of secretory granule maturity, were detected in the leukocytes of both peripheral blood and bone marrow^{14, 15}. The PCH granules were taken the eosinophilic feature in the cytoplasm⁸. Ultrastructural research on PCH has demonstrated the characteristics of PCH in acute myeloid leukemia. Similar to the case reported by Pallavi et al.⁷, these eosinophilic inclusions were positive for PAS but negative for MPO in our study. At the same time, a well-defined irregular membranous structure, which contained a variable number and volume of particles, was positioned next to the nucleus. These particles exhibited a high electron density. Some reports have suggested that PCH is a fusion of abnormal peroxidase-positive small particles⁷. On the contrary, Tulliez¹⁶ et al. demonstrated that the abnormal granules result from the integration of azurophilic granules in acute myeloid leukemia. However, the PCH particles observed under TEM were composed of membrane-encapsulated scattered glycogen particles. Some of them contained abnormal structures that were

surrounded by membranes but without any contents, which is different from the CHS granules. The exact mechanism of formation of this abnormal structure is unclear.

In case of B-ALL, the process of B-cell differentiation is arrested. Consequently, the normal hematopoietic process is inhibited due to the increasing number of blast cells. The fusion of TEL-AML1 is common in case of ALL in children and serves as a common leukemogenic marker with favorable outcomes¹⁷. The TEL-AML1 fusion occurs *in utero* during the embryonic development stage. In other words, it could be detected before the clinical symptoms become visible¹⁸. The pathogenic gene acting on hematopoietic stem cells (HSC) progresses in the presence of other risk factors. The fusion protein alters the activation of the IFN α / β pathway and affects the differentiation and self-renewal abilities of the hematopoietic progenitor cells (HPC)¹⁹. Ultimately, multiple signaling pathways are activated, thereby promoting the progression of B-ALL²⁰. Hatem et al.²⁰ demonstrated that the fusion of TEL-AML1 could give rise to the blocked differentiation of B cell. TEL/AML1 fusion is correlated with a good response to chemotherapy, leading to a high survival rate. In the present case, the TEL/AML1 fusion gene was detected in ALL blasts. There is a possibility that the abnormal blasts failed to differentiate into the next stage but proliferated rapidly. The immune function might have been disrupted owing to the existence of these non-effective lymphocytes. Consequently, the abnormal lymphoblasts containing PCH granules may be a manifestation of TEL/AML1 gene fusion.

Herein, we have reported a special ultrastructural manifestation of PCH in the case of B-ALL. The findings testify that the entity of PCH is a glycogenosome although the exact mechanism of its formation remains to be clarified.

Conflict of Interest

The authors declare that there is no conflict of interest.

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Figure legend

Figure 1. The morphology and PAS staining of giant inclusions in lymphoblastic cells.

A, B, C, D. Giemsa–Wright’s staining of patient’s bone marrow smear

The inclusions are located next to the nucleus, showing heterogeneous coloring.

E, F. PAS staining of lymphoblast in the bone marrow. The inclusions are mildly positive in lymphoblastic cells (as indicated by the arrow).

Figure 2. PCH granules by TEM

A. The lymphoblast with PCH granules located near the nucleus. PCH consists of a membrane-enclosing structure within glycogen granules.

B. The enlarged view of a rectangular area of Figure A. The PCH granules are composed of compact glycogen granules.

C. The different morphology of PCH granules indicated in the rectangular area.

D. The enlarged view of the rectangular area of Figure C. In addition to the sparsely distributed glycogen granules, three multiple-membrane vacuous structures can be seen.

E, F. Different PCH inclusions in patient's lymphoblastic cells (as indicated by the arrow).

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