Pseudo Chediak-Higashi Granules in Acute Lymphoblastic Leukemia: A Rare Entity

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Abstract Pseudo-Chediak-Higashi granules are giant cytoplasmic inclusions commonly encountered in myeloblasts or other myeloid precursors in acute myeloid leukemia and myelodysplastic syndromes. They derive their name from the inherited Chediak-Higashi syndrome that presents with oculocutaneous albinism, chronic infections and platelet dense granule deficiency. We report possibly the third case in world literature where these granules were seen in the blast cells of acute lymphoblastic leukemia in a 15-year-old male.

Keywords Pseudo Chediak-Higashi granules · Acute lymphoblastic leukemia · Morphology · Bone marrow · Flow cytometry

Introduction

Pseudo-Chediak-Higashi granules are giant cytoplasmic inclusions in myeloblasts or myeloid precursors, resembling those seen in the inherited Chediak-Higashi syndrome (CHS). They are commonly described in acute myeloid leukemia but have also been seen in chronic myeloid leukemia and myelodysplastic syndromes and a few other conditions [1–4]. These granules are only very

rarely present in acute lymphoblastic leukemia (ALL) with two cases reported in literature [5, 6]. We describe here a case of B-lineage ALL with similar granules in the lymphoblasts. The case is reported because of its distinctive and rare morphology in lymphoblasts.

Case Report

A 15-year-old male presented with fever and generalized body ache for one and half month. On examination he had pallor and bony tenderness; however no organomegaly or significant lymphadenopathy were noted. Investigations revealed hemoglobin 9 gm/dL, total leukocyte count $18.6 \times 10^9/L$ and platelet count $56 \times 10^9/L$. The peripheral smear showed 54 % blasts that were large with high nuclear/cytoplasmic ratio, coarse chromatin with 0–1 inconspicuous nucleoli and scant pale basophilic cytoplasm. A bone marrow aspirate was done and was hypercellular with 95 % blasts. Many blasts, both in the peripheral blood and the marrow aspirate showed peculiar large pink inclusions (pseudo-Chediak-Higashi granules or inclusions) in their cytoplasm. No Auer rods or other granules were present. These granules showed faint positivity on cytochemistry for periodic acid-schiff stain (PAS) and were negative for myeloperoxidase (MPO) stain (Fig. 1). A buffy coat preparation from peripheral blood was subjected to electron microscopic examination. Ultrastructurally, the granules revealed irregular membrane bound structure of variable sizes and contain multiple vesicles (Fig. 2). Flow cytometry done on the bone marrow aspirate showed blasts that were CD45dim and co-expressed CD19, CD10, CD22 and CD79a as well as CD34 and TdT (Fig. 3). The blasts were negative for all T-lymphoid and myeloid markers tested. Cytogenetic testing and

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reverse transcriptase PCR were unable to detect any specific abnormality. A final diagnosis of B-lineage ALL with pseudo-Chediak-Higashi granules was made. The patient was started on the standard chemotherapeutic induction regimen for ALL and remains on close follow-up.

Discussion

The CHS is an inherited disorder characterized by oculocutaneous albinism, chronic neutropenia and bacterial infections and platelet dense granule deficiency resulting in hemorrhage. Pseudo-Chediak-Higashi granules were first described by Didisheim et al. [7] in 1964 in a patient with acute promyelocytic leukemia as “large round reddish bodies, about a fourth the diameter of the cell, which had an affinity for the PAS stain”. In 1974, VanSlyck and Rebuck described similar granules in the leukemic cells of two patients with acute myelomonocytic leukemia and termed them the “Pseudo Chediak-Higashi anomaly” due to their resemblance to the inclusions of the inherited CHS [8]. Symes et al. proposed that these were formed by fusion of smaller granules and considered them abnormal peroxidase-positive variants of the primary granules lacking sulfated glycosaminoglycans. This differentiated them from the lysosomal origin granules of the inherited CHS that are characteristically MPO negative [9].

Pseudo-Chediak-Higashi granules are exceptionally rare in ALL, with only two previous cases reported in literature.

Maitra and Weinberg described the first case in a 15-year-old female [5] followed by Hayes who reported them in a 14-year-old male [6]. The blasts in both cases contained one or two intra-cytoplasmic glassy pink inclusions of varying sizes. Ultrastructurally, both cases showed collections of fairly uniform-sized vesicles that were lined by a unit membrane and irregularly shaped membrane-bound structures of varying electron densities [5, 6]. Our case too

Fig. 2 Ultrastructural examination shows presence of perinuclear membrane bound structure. These structures contain multiple uniform-sized vesicles lined by a unit membrane (EM $\times 10800$)

Fig. 1 Peripheral smear shows blasts with pseudo Chediak-Higashi granules (MGG-Giemsa stain, $\times 1000$, **a**). Bone marrow aspirate shows many blasts with similar large granules. (MGG-Giemsa stain, $\times 1000$ & Inset, **b**). PAS stain shows faint positivity for these blasts (PAS $\times 1000$, **c**) while these cells are negative for MPO (MPO $\times 1000$, **d**)

Fig. 3 Scatter plots depict multicolor immunophenotyping on bone marrow aspirate by flow cytometry. The events are seen on side scatter (SSC) versus forward scatter (FSC) plot. The cells in blastic region are gated as P1 and the same cells are analysed in subsequent plots (a). These cells show dual bright expression of CD19 and CD10 (b) along with dim expression of CD 20 (c). The same cell populations show expression CD22 (d). These cell show expression of CD79a, TdT, CD34 and HLA-DR (e, f)

was of similar age (15 years) and showed similar giant granules that were MPO negative and faint PAS positive with similar ultrastructural findings.

In conclusion we describe an extremely rare case of B-lineage ALL with pseudo-Chediak-Higashi granules. It highlights the fact that these entities are not pathognomonic of myeloid lineage blasts, and the necessity of flow cytometric immunophenotyping for accurate classification of these neoplasms. Until any prognostic/clinical relevance of these granules becomes established, they represent quaint morphological curiosities that may be encountered by the diagnostic hematopathologist in unexpected places.

Conflict of interest The authors declare that they have no conflict of interest.

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