

# ACUTE PROMYELOCYTIC LEUKEMIA WITH PSEUDO-CHEDIAK-HIGASHI ANOMALY: A CASE REPORT AND REVIEW OF THE LITERATURE

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The hypergranular type of acute promyelocytic leukemia (APL) is characterized by heavy granulation and the presence of Auer rods. These granules are usually small, azurophilic, and have the appearance of the primary granules of normal promyelocytes. There have been several reports of myeloid leukemias,<sup>1-11</sup> including APL, with the unusual finding of large granules (inclusions) simulating the inclusions of Chediak-Higashi, which were given the term "pseudo-Chediak-Higashi anomaly" (PSCA).<sup>1</sup>

In this report, a case of hypergranular type APL with numerous Auer rods and PSCA is described with a literature review of this unusual morphologic anomaly.

## Case Report

A 40-year-old woman was admitted in 1995 with headache and blurred vision. Physical examination was remarkable for ecchymoses and bilateral eye fundal hemorrhage. No organomegaly or adenopathy was present. Laboratory studies showed hemoglobin (Hb) of 98 g/L, WBC of  $1.74 \times 10^9/L$ , and a platelet count of  $53.0 \times 10^9/L$ . Differential count showed 12% neutrophils, 30% lymphocytes, 10% monocytes, 3% myelocytes, 22% promyelocytes and 13% blasts. Coagulation studies demonstrated a prothrombin time (PT) of >120 sec. (normal range: 9.5-14.4 sec.), partial thromboplastin time (PTT) of 38.6 sec. (normal range: 26-39 sec.), fibrinogen level of 0.6 g/L (normal range: 2-4 g/L), and a positive D-dimer test of 1000-2000 ng/mL. Bone marrow aspirate and trephine biopsy were performed. The aspirate was used for morphologic and immunophenotypic studies (see below). Acute promyelocytic leukemia (APL), hypergranular type with disseminated intravascular coagulation was diagnosed.

Bone marrow aspirate, peripheral blood smears and bone marrow trephine biopsy imprints were stained with

May-Grünwald-Giemsa (MGG) stain. Cytochemical stains were performed on the smear from the bone marrow aspirate, using the following stains: Sudan black B (SBB), periodic acid-Schiff (PAS), combined  $\alpha$ -naphthol AS-D chloroacetate (CAE) and  $\alpha$ -naphthyl acetate esterase (ANAE) stain, and acid phosphatase (AP). The marrow trephine biopsy was stained with the hematoxylin-eosin and PAS stains.

Cell-suspension immunophenotypic studies were performed using the following antibodies: CD3, CD5, CD7, CD10, CD13, CD19, CD20, CD22, CD33 and HLA-DR.

The marrow aspirate was markedly hypercellular, with predominance of hypergranular promyelocytes (71%). Many contained Auer rods, with some of them in bundles. Approximately 5% of these promyelocytes contained large inclusions of 1-2  $\mu$  in size. The granules were generally round and pink, and appeared to represent fusion of granules (Figure 1). The peripheral blood also showed heavily granulated promyelocytes. By cytochemical stains, both the granules and the Auer rods were positive for SBB and CAE. The cytoplasm had tinge positivity with PAS, while the large granules and Auer rods were strongly positive, and the large granules were shown more clearly by this stain. The ANAE stain was positive with fluoride inhibition.



FIGURE 1. Bone marrow aspirate smear showing promyelocytes with large inclusions (May-Grünwald-Giemsa, 1125x).

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The biopsy was hypercellular with marked infiltration by immature cells with abundant eosinophilic cytoplasm. The granules were not evident on the hematoxylin-eosin stain. However, occasional cells on the PAS stain contained large inclusions.

By immunophenotypic studies, the leukemic cells were positive for CD13, CD33 and negative for CD3, CD5, CD7, CD10, CD19, CD20, CD22 and HLA-DR.

### Discussion

Granules and inclusions are seen in cases of acute myeloid leukemia (AML). These are usually Auer rods and azurophilic granules. Rarely large inclusions have been described.<sup>1-11</sup> In 1974, Van Slyck and Rebeck<sup>1</sup> described the pseudo-Chediak-Higashi anomaly (PSCA), in which granules similar to those seen in Chediak-Higashi syndrome were identified in the leukemic cells from two patients with acute myelomonocytic leukemia (AML<sub>M4</sub>). The granules were described as pink and azurophilic. Since then, 15 cases of adult leukemia with the PSCA have been described.<sup>2-11</sup> There were four APL, one AML highly suggestive of APL, three AML<sub>M4</sub>, one chronic myelocytic leukemia (CML), and six cases of AML which were not further subtyped. In addition, the majority of cases in a series of APL<sup>12</sup> displayed oval or elliptical inclusions occupying one-third to one-half of the cytoplasm.

The inclusions were described as large but variable in size, from 1  $\mu$  to giant inclusions of 7  $\mu$ m, which simulated phagocytosed red blood cells.<sup>4,5,11</sup> The inclusions in all these cases with one exception were present only in the leukemic cells.<sup>4</sup> These giant granules were described in a variable but usually small proportion up to 10% of cells.<sup>11</sup> Some reports describe the granules as pink, while the majority describe azurophilic and purple inclusions. Occasionally, both azurophilic and pink granules have been seen in the same case.<sup>1,4</sup> In the majority of cases, the inclusions were described as round and homogenous. However, irregular granules have been described, and some were reported to be present in vacuoles.<sup>4,9,11</sup> Auer rods were also present in many cases, in addition to the large granules,<sup>3-7</sup> while in others, only the granules were present.<sup>9-11</sup>

By cytochemistry, these inclusions were positive for peroxidase, with only one exception. They were also positive for PAS except for two cases.<sup>7</sup> The esterases have been reported in a few cases. The CAE has been reported positive in two cases,<sup>7,11</sup> and negative in two others.<sup>4</sup> The ANAE has been reported negative in three cases, while the BE has been positive in two.<sup>7,11</sup> The acid phosphatase was positive in two cases.<sup>4</sup>

The case reported here showed the typical positivity for SBB and the CAE. The positivity for the nonspecific esterases in this case and the previously reported cases is unusual. Tomonaga et al.<sup>13</sup> described seven of 25 cases of

APL positive for the  $\alpha$ -naphthyl butyrate esterase, which were suggestive of a myelomonocytic differentiation. Similar findings were reported by Das-Gupta et al.<sup>14</sup> of five out of 37 cases of APL showing ANAE positivity.

In children, the presence of these inclusions seems not to be associated with specific clinical features, and the prognosis is similar to those cases without the anomaly.<sup>15</sup> However, there have not been studies of its significance in adults.

Disseminated intravascular coagulation (DIC) was a prominent feature in the case reported here, and in five of the reported cases.<sup>2,6,8,10,11</sup> All of these cases were APL, suggesting that this is more related to the type of leukemia than the presence of large inclusions. The origin of these large inclusions is believed to be a result of fusion of azurophilic granules,<sup>10</sup> since by electron microscopy they were found to contain numerous microcrystalline structures like those of Auer rods. Tsai et al.<sup>9</sup> speculated that the abnormality may be a manifestation of an underlying abnormal granulogenesis, and that it may be associated with an increased susceptibility to infections due to defective leukocyte function.

In summary, large inclusions simulating the Chediak-Higashi inclusions can be seen in leukemias, and in particular APL. They can vary in size and in staining, but usually have the staining pattern of the granules of APL. They can be shown more clearly with the PAS stain. They are believed to represent fusion of azurophilic granules. In the small series studies performed in children, they seem to have no clinical significance. However, no large series are available, especially in adults, to evaluate their clinical significance, in particular any association with a higher incidence of DIC.

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