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(CASE REPORT)

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Pure erythroid leukemia *De Novo* in 16-years-old girl: A case report and literature review

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Abstract

Pure erythroid leukemia (PEL) is an extremely rare type of acute myeloid leukemia (AML), accounting for fewer than 1% of all AML cases. A 16-year-old girl, without any medical history, presented fever, severe fatigue and mucocutaneous bleeding. Her peripheral blood smears showed myeloid blasts with deep basophilic cytoplasm and circulating erythroblasts. Her bone marrow aspiration showed a very rich marrow with 93% erythroblastic hyperplasia with 30% excess of proerythroblasts, and 4% of myeloblasts. PEL appeared to be the definitive diagnosis after evaluating the immunophenotypic findings. Her general condition deteriorated during medical diagnosis, and she died soon after starting chemotherapy.

Keywords: Pure erythroid leukemia; PEL; Acute myeloid leukemia; AML; *De novo*

1. Introduction

Pure erythroid leukemia (PEL) is a rare and aggressive form of acute myeloid leukemia (AML) [1]. It accounts for <1% of all AML cases and has a very poor prognosis [1]. According to the 2016 World Health Organization (WHO) classification, PEL is the only type of acute erythroid leukemia that consists of ≥ 80% of immature erythroid precursors with ≥ 30% proerythroblasts among all nucleated bone marrow cells [2]. Since PEL is extremely rare and its diagnosis can sometimes be challenging, further information on its clinical course, diagnosis, and pathophysiology is crucial to develop novel treatment options and appropriate palliative care. Therefore, our aim is to contribute towards its diagnosis and, moreover, shed light on the importance of a differential diagnosis for PEL from various other AML. Here, we report a case of de novo PEL that was challenging to diagnose.

2. Case report

A 16-year-old woman, without any medical history, was referred to our hospital with complaints of fever, severe fatigue and mucocutaneous bleeding. On physical examination, conjunctival pallor was observed, with splenomegaly and no enlarged lymphnode detectable from the body surface. A complete blood count (CBC) showed pancytopenia with normochromic normocytic non-regenerative anemia (Hb 7.8 g/dL; MCV 94 fL; MCH 35 pg; reticulocytes 35.5 G/L), thrombocytopenia (Platelets 67 G/L) and neutropenia (Neutrophilic polynuclear 0.468 G/L). Other laboratory tests showed a severely increased lactate dehydrogenase level (220 U/L), ferritin (18 ng/mL), and C-reactive protein (30 mg/dL). A peripheral blood smear showed the presence of 5% large circulating blasts with a nucleocytoplasmic ratio of 8:10, regular nuclei with finely nucleated chromatin, a rarely granular basophilic cytoplasm, an anisopoikilocytosis with

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a high number of circulating erythroblasts (12 erythroblasts per 100 white blood cells) and no platelet aggregates. (Figure 1)

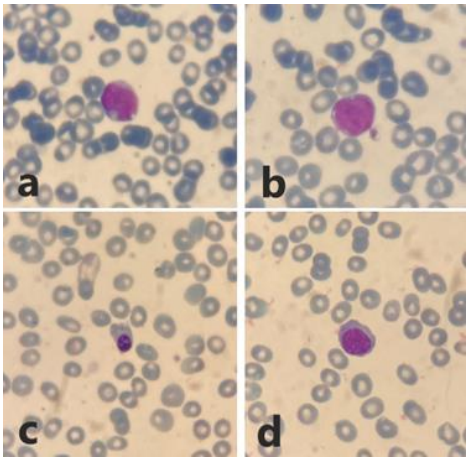

Figure 1 Peripheral blood smears (May-Giemsa staining, 100× oil immersion objective) showing (a,b) large myeloid blasts with deep basophilic cytoplasm and (c,d) circulating erythroblasts

A smear of the bone marrow fluid showed very rich marrow with rare megakaryocytes. It has been noted the presence of 93% erythroblastic lineage hyperplasia with 30% excess of proerythroblasts without associated megaloblastosis, the presence of 4% of myeloblasts with a nucleocytoplasmic ratio of 8:10, regular nuclei with finely nucleated chromatin, a rarely granular basophilic cytoplasm and a total repression of other lineages (Figure 2). At this point, the diagnosis of PEL has been established.

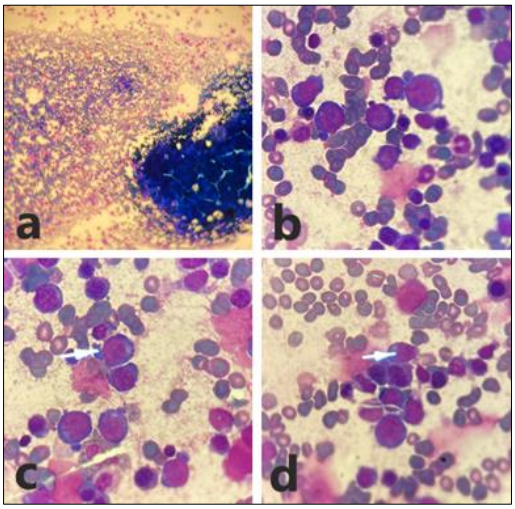

Figure 2 Bone marrow smears (May-Giemsa staining). (a) 10× dry objective showing a very rich marrow with rare megacaryocytes. (b,c,d) 100× oil immersion objective showing (b) erythroblastic hyperplasia, (c) proerythroblasts (d) myeloblasts

The results of the flow cytometry analysis of the bone marrow aspirates were available on day 12. Analyses with CD45/side scatter gating demonstrated that abnormal cells were partially positive for CD4 (33%), CD13 (46.2%), CD33 (63.3%), CD71 (42%), glycophorin A (27%), and HLA-DR (56.4%), whereas other myeloid and lymphoid markers were negative. Induction chemotherapy was performed, which comprised daunorubicin and cytarabine. However, the treatment was ineffective, and the patient died of multiple organ failure three days after initiating the treatment.

3. Discussion

Pure erythroid leukemia (PEL) is a form of acute myeloid leukemia (AML) [1]. The definition has been reviewed several times (table 1) [3].

Table 1 Definition of acute erythroid leukemia (AEL) and primary erythroid leukemia (PEL) using different classification systems [3]

	AEL (Blasts)	**AEL (Background)**	**PEL**
FAB (1976)	> 30% myeloid blasts among all nucleated cells	> 50% erythroid cells among total cells	
FAB (1985)	> 30% myeloid blasts among non-erythroid cells	> 50% erythroid cells among total cells	
WHO (2001)	> 20% myeloid blasts among non-erythroid cells	> 50% erythroid cells among total cells	> 80% erythroid cells with no expansion of myeloid blasts
WHO (2008)	> 20% myeloid blasts among non-erythroid cells	> 50% erythroid cells among total cells	> 80% erythroid cells with no expansion of myeloid blasts requires
WHO (2016)	> 20% myeloid blasts of total cells and classified as AML-NOS and AML MRC; < 20 myeloid blasts of total cells classified as MDS	N/A	> 80% erythroid cells and > 30% proerythroblasts

According to 2016 WHO definition of PEL, the only type of acute leukemia with bona fide erythroid differentiation, at least 80% marrow erythroid precursors are required and at least 30% should be proerythroblasts. In cases with a history of prior therapy, a diagnosis of therapy-related myeloid neoplasm should be made, although a modifier of pure erythroid leukemia is recommended. AML MRC is distinguished from pure erythroid leukemia by the presence of 20% or more myeloblasts [2].

AEL is a rare disease and most clinical reports on its concern, include both PEL and the historic types of AEL that are no longer included in the WHO classification. In these reports, AEL accounts for 3–5% of all AML cases and appears to be more common in males [4]. Most patients are elderly and some studies suggest a bimodal age distribution, with a smaller peak below 40 years of age and a more definitive and broader peak in the seventh decade of life [5]. Acute erythroleukemia is also very rare in children. In one report from the Children's Oncology Group, patients with FAB-classified AEL comprised 2.3% of all patients with AML [6]. Congenital erythroleukemia is exceedingly rare, with only six cases reported in the literature [4].In this article, we reported a rare case of PEL in a 16-years-old girl.

A limited number of reports suggests that PEL may evolve from pre-existing myelodysplastic syndrome (MDS), and prior chemoradiotherapy exposure could also affect its incidence [7]. As Wong E et al. reported [7] that PEL usually evolves from pre-existing MDS or is due to a medical history of chemoradiotherapy. Out of the 13 patients with PEL, excluding 2 cases for which medical history were not available, 7 (64%) received either chemotherapy or radiotherapy before the diagnosis of PEL, and only 2 cases (18%) had no medical history. In our case, the patient did not receive chemotherapy or radiotherapy before admission and her medical history is without any particularities.

Most commonly, patients with AEL present symptoms due to pancytopenia such as fatigue, mucocutaneous bleeding, and infections. Organomegaly is common and varies between 20 and 40% depending on other studies [8]. Extramedullary disease and CNS involvement are rare [9].

Anemia is present in most patients and is often severe (mean, 7.5 g/dl) [10]. Thrombocytopenia and neutropenia are also common and most patients have leukopenia [10].

Peripheral blood finding may also include a high level of schistocytes and nucleated red cells and pseudo Pelger–Huet neutrophils. The most frequently observed abnormalities include spiculated red cells (echinocytes, acanthocytes), schistocytes, dacryocytes, and basophilic stippling in more than 40% of cases [11]. Additional findings in peripheral blood include dysplastic neutrophils, as well as giant and hypogranular platelets and circulating micromegakaryocytes [11]. Almost half of the patients have no significant blasts in peripheral blood.

The bone marrow in patients with erythroleukemia (specifically PEL) are typically hypercellular and are composed of sheets of leukemic cells that replace sheets of marrow. Blasts are large with round nuclei and often one or multiple prominent irregular nucleoli and deeply basophilic cytoplasm. The cytoplasm often contains vacuolization and lack granules. Erythroid cells often show dysplasia. Megakaryocytes, when present, are often dysplastic and characterized

by small monolobated forms, micromegakaryocytes, and/or hyperchromatic forms [12]. Erythrophagocytosis by pathological erythroblasts has been described [13]. Interestingly, Park et al. described 7 cases of PEL with extensive necrosis [14]. Potential diagnostic pitfalls for PEL include megaloblastic leukemia, hemolytic leukemia, acute undifferentiated leukemia, other types of AML myeloid neoplasms with abundant erythroid precursors, and nonhematopoietic malignancies such as carcinoma and sarcoma.

Immunophenotypic studies are necessary but can be challenging in the evaluation of PEL. Blasts are typically negative for CD34 and HLA-DR, while CD117 is partially or weakly positive and some may show CD33 expression [14]. Further evaluation with erythroid markers is often necessary. Antiglycophorin A is the most widely used antibody for diagnosing PEL by flow cytometry. In one series, glycophorin A was positive in 78% of PEL cases and in only 3% of non-PEL cases, but it can be negative as well [15]. CD71 (transferrin receptor) is also found in AEL, but it is nonspecific and can be positive in other subtypes of AMLs [16]. Erythroblasts may also express CD36, a thrombospondin receptor, but this marker is also expressed in megakaryocytes and monocytes [17]. E-cadherin is another marker that is frequently helpful in clinical diagnosis of PEL. GATA1, a critical transcription factor for erythroid and megakaryocytic development, is a sensitive and specific nuclear marker for erythroid and megakaryocytic precursors. Lee et al. found that using a rabbit monoclonal antibody against GATA1, GATA1 consistently marked the blast populations of pure erythroid leukemia [18]. Of note, GATA1 staining alone cannot distinguish between the blast forms of erythroid and megakaryocytic lineages and needs to be combined with morphologic assessment as well as additional studies that are already routinely used. Both acute pure erythroid leukemia and acute megakaryoblastic leukemia exhibit strong nuclear GATA1 reactivity and will require additional markers, such as CD61 and CD71, for subclassification [18]. Some cases of pure erythroid markers may show expression of P53 [19].

There are no recurrent cytogenetic or other molecular aberrations that appear to be specific for AEL. Karyotypically, de novo pure erythroid leukemia appears to uniformly demonstrate an abnormal karyotype. The karyotype is generally complex (≥ 3 abnormalities), with most cases showing highly complex genetic alterations (> 10 abnormalities). Many, though not all, pure erythroid leukemia cases contain recurring myeloid-associated cytogenetic abnormalities, such as del(5q), −7/del(7q), and 17/17p deletions [20, 21]. Table 2 lists frequencies of complex karyotype in AEL and PEL.

Earlier investigational studies had associated AEL with a high frequency of mutations with mutational profiles significantly different from other AML subtypes. AEL is characterized by far lower NPM1 and FLT3 ITD mutation rates and higher mutational rates in TP53 when compared with other AML subtypes [22, 23] (Table 2).

Table 2 Studies of AEL and PEL in literature and reported rates of complex karyotype and frequent mutations

	PEL	**AEL**	**Complex karyotype**	**Frequent mutations (%)**
Park et al. [14]	2	5	50%	TP53 (50%)
Montalban-Bravo G [24]	27	167	96%	TP53 (92%)
Iacobucci I et al. [25]	15	22	47%	TP53 (40%), NPM1 (26%), RUNX1 (20%), ETV6 (20%)
Ko PS et al. [26]	8	N/A	57%	N/A
Reinig EF et al. [12]	15	15	100%	N/A
Wong E et al. [19]	7	N/A	83%	N/A
Wang et al. [20]	N/A	77	37%	TP53 (33%), CEBPA (9%), DNMT3A (8%), NRAS/KRAS (8%)
Cervera N et al. [23]	N/A	40	34%	TP53 (35%), DNMT3A (20%, NPM1 (17.5%), NRAS (17.5%)
Grossmann V et al. [22]	N/A	92	40%	TP53 (43%), NPM1 (16%) DNMT3A (13%)
Hasserjian RP et al. [10]	N/A	124	43%	N/A

Iacobucci et al. have identified recurrent mutations in multiple genes involved in cell cycle/tumor suppression, cohesin complex formation, RNA splicing, transcription, signaling, DNA methylation, and chromatin modification [26]. Rose et al. reported on molecular mutation data in a cohort of 166 AEL patients and showed that TP53 was the only gene occurring at a higher frequency within AEL as compared with the remaining overall AML cohort [27]. Recent data reveal an especially high prevalence of at least two TP53 abnormalities (both mutations and aberrant or deleted chromosome 17p) in > 90% of PEL [24]. Allelic frequencies of TP53 mutations suggested that a founder TP53 mutation was always

present, suggesting a crucial role of TP53 in leukemic transformation [24]. In their study of 159 childhood and adult AEL, Iacobucci et al. found that the mutational spectrum of adult AEL was intermediate between those of MDS and AML [25]. Specifically, they found a lower frequency of canonical genes mutated in AML, such as FLT3 and NPM1 in AEL, compared with non-erythroid AML, but they were more common than in MDS. Conversely, MDS-associated mutations such as in SF3B1 and ASXL1 were less frequent in AEL compared with MDS but more common than in nonerythroid AML. Compared with childhood MDS, childhood AEL was characterized by a higher frequency of mutations in FLT3 and WT1 and a lower frequency of mutations in GATA2 and ASXL1. Mutation profile patterns varied in pediatric and adult AEL with NUP98-fusions, PTPN11, GATA1, and UBTF mutations more frequent in pediatric AEL and TP53 and KMT2A mutations predominant in adult AEL [3].

Due to the rarity of the disease (2–5% of all leukemias), there are no prospective clinical trials available in patients with AEL and most do not discriminate between PEL and older types of AEL. Patients with AEL are usually treated similarly to patients with other types of AML [4]. There is no established therapy for PEL, and induction chemotherapy and hypomethylating agents are the current treatment options [28]. When treated with intensive chemotherapy, the median overall survival (OS) of AEL patients range between 7.6 and 9 months [29]. Santos et al. reported on clinical outcomes of AML M6 in 91 patients and found no significant difference in survival between M6 and other AML types [30]. Studies that have looked at PEL specifically note a median overall survival ranging from 1.4 to 6.6 months [12]. Recent focus has been on evaluating efficacy of hypomethylating agents (HMAs) in treating TP53 mutated leukemia. In a study of 36 AEL patients, decitabine showed comparable overall survival when compared with cytarabine-based agents [31]. Montalban-Bravo found in their cohort that survival of both AEL and PEL patients is unfavorable and HMAs did not improve outcome, in contrast to the recent data reporting high response rates to decitabine in patients with TP53-mutant AML [32]. Almeida et al. found that in their largest series to date of 217 AEL patients treated with hypomethylating agents (HMA) showed an overall response rate of 46% in the front-line setting, with a complete response (CR) rate of 30%[33]. Standard induction led to a higher OS rate when compared with first-line HMA but similar progression-free survival. Initial responses were seen after a median of 79 days, but the best responses were documented after a median of 120 days, confirming that responses improve with continued treatment and reinforcing the importance of not interrupting treatment too early due to a lack of response. Although HMAs may be a good treatment option for patients not eligible for transplant, allogeneic transplant improves outcome of patients with AEL and should be used when possible. New therapies based on a more detailed molecular pathway in AEL may improve outcome.

4. Conclusion

Erythroleukemia is a distinct form of AML characterized by poor risk karyotype and bad prognosis, as defined in the updated WHO 2016 diagnostic criteria. Studies have provided valuable insights into the genetic landscape of AEL and may pave the way for the transformation from a morphologic/phenotypically based classification to an enhanced molecular classification of prognostic and therapeutic relevance. Further refinements in future definitional criteria are expected, incorporating emerging mutation and chromosomal data garnered from studies inspired by a growing interest and recognition of PEL.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest

Statement of ethical approval

The present research work does not contain any studies performed on animals/humans subjects by any of the authors.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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