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Clonal histiocytosis associated with evolving acute myeloid leukemia: a case report and literature review

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ABSTRACT

Histiocytoses are rare disorders that may occur in association with hematologic malignancies, although reports preceding acute myeloid leukemia (AML), particularly in adults, remain scarce. We report the case of a 58-year-old female patient who presented with persistent fever, weight loss, and progressive lethargy. Initial laboratory evaluation demonstrated pancytopenia, and bone marrow studies revealed erythroid and megakaryocytic dysplasia, plasmacytosis, and hemophagocytic activity, along with extensive histiocytic infiltration containing Langerhans-like giant cells. Immunophenotyping at that time was negative for leukemia, and immunohistochemistry showed CD163 and S100 positivity, with no CD1a expression. The patient was initially managed with dexamethasone due to a suspected hemophagocytic lymphohistiocytosis (HLH)-like inflammatory syndrome, without adequate clinical response. Cytogenetic analysis revealed a clonal abnormality involving 11q23 in a subset of metaphases. After approximately 8 weeks, disease evolution was observed, and repeat bone marrow examination demonstrated 20% myeloblasts, with immunophenotypic findings consistent with AML. The patient, considered clinically pre-frail, received low-intensity chemotherapy with cytarabine in combination with venetoclax. Despite treatment, measurable residual disease persisted after two cycles, and she developed progressive clinical deterioration complicated by recurrent multidrug-resistant infections, ultimately evolving to death. This case highlights the diagnostic complexity of early clonal myeloid neoplasms presenting with histiocytic and hemophagocytic features and emphasizes the importance of recognizing HLH as a possible secondary and unconfirmed inflammatory syndrome in the setting of evolving hematologic malignancy. Further studies are needed to clarify the biological mechanisms linking histiocytic proliferations and progression to myeloid neoplasms.

Keywords: Histiocytic disorders; Histiocytosis; Hemophagocytic lymphohistiocytosis; Second malignancy; Acute myeloid leukemia.

INTRODUCTION

Histiocytic disorders are rare conditions characterized by the proliferation of macrophages and dendritic cells. According to the Histiocyte Society and World Health Organization (WHO) classification, these entities are grouped based on cellular origin and molecular features.[1]

Although most histiocytoses are benign or inflammatory, their association with hematologic malignancies, particularly myeloid neoplasms, has been increasingly recognized. However, cases in which histiocytic proliferation precedes acute myeloid leukemia (AML) remain exceptionally rare.[2-5]

Hemophagocytic lymphohistiocytosis (HLH) may occur in association with hematologic malignancies, especially AML, but is usually concomitant or secondary.[6] Preceding HLH-like presentations may represent early manifestations of occult or evolving neoplasia.[7]

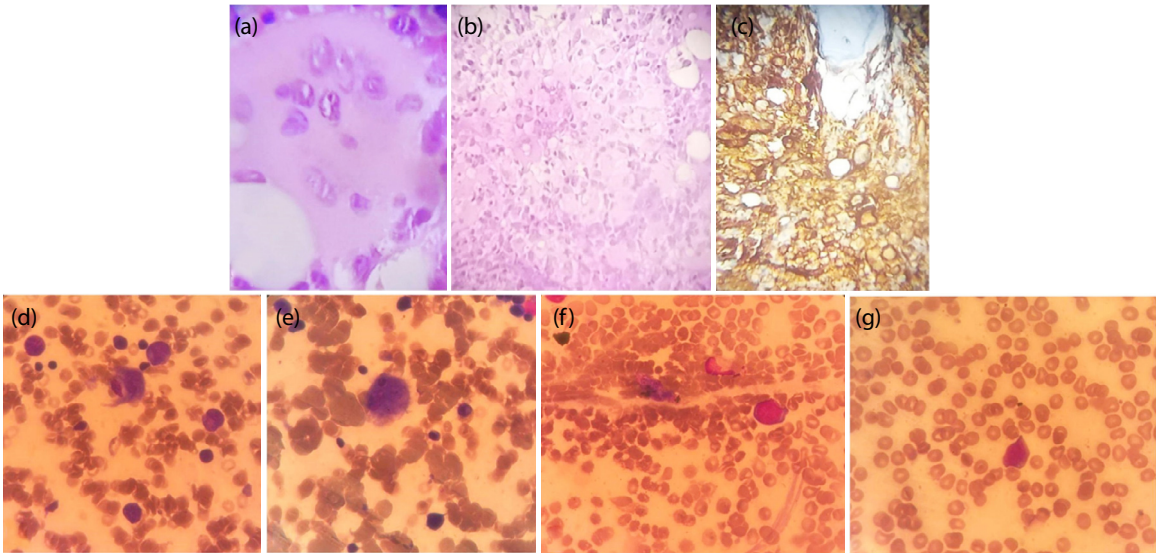
This report describes a case of histiocytic and hemophagocytic bone marrow involvement associated with clonal cytogenetic abnormality and subsequent progression to AML.

Case report

A 58-year-old woman was admitted to the Hospital Universitário Walter Cantídio (April 10, 2024), referred from an emergency care unit where she was seen due to syncopal episodes, preceded by a history of daily nocturnal fever (38–39 °C) and progressively worsening lethargy starting about 1 month prior, in addition to unintentional weight loss (5 kg over 6 months). She had pre-diabetes, type II diabetes mellitus, hypothyroidism, and vitamin B12 deficiency. There was no personal or family history of malignancies, nor of smoking or alcoholism. On physical examination, she had no hepatosplenomegaly, lymphadenopathy, or cutaneous lesions.

Laboratory tests revealed pancytopenia (red blood cells 2.48 million/mL; hemoglobin 6.96 g/dL; leukocytes 2,851 cells/µL, including 2% blasts, 16% neutrophils, 76% lymphocytes, 6% monocytes; platelets 37,420 cells/µL). Given the suspicion of acute leukemia, a bone marrow study was performed. The bone marrow aspirate revealed dysplasia in the erythroid and megakaryocytic series, hemophagocytic activity, and plasmacytosis. Immunophenotyping was negative for overt leukemia. G-banding karyotype showed a possible deletion involving 11q23 in 3/20 metaphases [46,XX,?del(11)(q23)], interpreted as a clonal abnormality requiring clinical and molecular correlation.

Histopathological examination of the bone marrow biopsy demonstrated extensive histiocytic infiltration (Fig. 1b) with Langerhans-like giant cells and hemophagocytic activity (Fig. 1d and e). These findings, together with laboratory results (ferritin 1,060 ng/mL; triglycerides 280 mg/dL; fibrinogen 467 mg/dL), supported a suspected diagnosis of secondary HLH rather than a confirmed diagnosis, given the absence of functional assays (natural killer [NK]-cell activity, soluble CD25) and H-score calculation. Immunohistochemistry showed strong diffuse CD163 expression, compatible with histiocytic proliferation, in addition to focal glycophorin and myeloperoxidase expression in granulocytic cells (Fig. 1c and Fig. 3). S100 positivity was observed in scattered dendritic-appearing cells, as well as CD117 in isolated cells, without a significant increase in hematopoietic precursors (CD34 negative in most cells; TdT negative). CD1a expression was absent, and mild-to-moderate plasmacytosis (CD138+) was identified in small aggregates.



Source: Elaborated by the authors.

Figure 1. Histological, immunohistochemical, and cytomorphological analysis. a) multinucleated giant cell (H&E, ×400); b) proliferation of histiocytes with clear cytoplasm (H&E, ×200); c) immunohistochemistry with strong and diffuse CD163+ staining; d and e) hemophagocytosis; f and g) hemophagocytosis and blasts.

The patient's condition persisted with daily fever. Frequent blood transfusions and pulse therapy with dexamethasone (40 mg for 4 days) were performed, without a sustained response. During hospitalization, she developed recurrent infections requiring broad-spectrum antimicrobial therapy, with subsequent identification of multidrug-resistant bacterial pathogens in blood cultures.

On day 56 of hospitalization, peripheral blood flow cytometry showed myeloblasts (9.1%). Following this finding, a new bone marrow study was performed. Smears revealed hematopoietic blasts (Fig. 1f and g). The bone marrow aspirate showed 20% blasts, consistent with AML. Immunophenotyping revealed an abnormal myeloid population representing 22% of blasts, with a phenotype characterized by strong CD34 and CD117 expression, strong HLA-DR and CD33 expression, moderate CD13 and CD45 expression, and partial CD56 expression, confirming AML. The G-banding karyotype was inconclusive due to a lack of cell growth, possibly secondary to hemodilution. Molecular testing for FLT3 mutations (ITD and TKD) was negative.

The patient was classified as pre-frail in a geriatric assessment, not meeting eligibility criteria for intensive chemotherapy or hematopoietic stem cell transplantation. On day 64 after admission, treatment for AML was initiated with low-dose cytarabine combined with venetoclax. After the first cycle, bone marrow evaluation showed 7.98% abnormal myeloid blasts. One month later, after the second cycle, histopathological examination demonstrated a hypocellular marrow for age, with grade III myelofibrosis and siderosis. Immunophenotyping revealed 6.6% CD34+ immature cells with an abnormal phenotype (CD13+, CD33+, CD34+, CD56+, CD117+, HLA-DR+), interpreted as measurable residual disease for AML.

Immunohistochemical analysis demonstrated extensive xanthogranulomatous infiltration associated with siderophages, with rare residual hematopoietic elements. CD1a, CD20, CD61, glycophorin A, myeloperoxidase, and TdT were negative, while CD34 was restricted to vascular endothelium and CD117 was positive in mast cells. Bone marrow aspirate was non-representative, precluding adequate morphological evaluation, and cytogenetic analysis showed insufficient cell growth. Throughout the clinical course, the patient experienced progressive clinical deterioration with recurrent severe infections, requiring multiple antibiotic regimens. Given the refractory disease and clinical decline, palliative care was instituted. The patient died five months after the initial diagnosis.

It is highlighted that the present study was approved by the research ethics committee of the Empresa Brasileira de Serviços Hospitalares and that the criteria established by the Declaration of Helsinki,[8] with its amendments, were followed.

DISCUSSION

Histiocytoses comprise a group of rare diseases characterized by infiltration of various tissues and organs by macrophages, dendritic cells, and monocytes.[1] These disorders were initially classified according to histological similarities with cells of the mononuclear phagocyte system, such as Langerhans cell histiocytosis (LCH) and non-Langerhans histiocytoses.[9-11] With advances in the understanding of pathogenesis and ontogeny, the classification has evolved and is currently based on cellular origin, tissue distribution, molecular alterations, and histological characteristics.[1,12]

Among histiocytoses, LCH is the most frequent entity,[13] with an estimated incidence of one to two cases per million adults per year.[14] However, histiocytic neoplasms remain rare and account for less than 1% of hematologic and lymphoid malignancies.[9,15] Within this spectrum, the association between histiocytosis and hematologic neoplasms has been increasingly recognized, particularly with myeloid malignancies.[6,7,16]

In the present case, the histopathological findings were compatible with a histiocytic proliferative process, with Langerhans-like giant cells and a mixed inflammatory infiltrate.[3] However, integration with immunohistochemistry and clinical features did not allow definitive classification within a specific subtype of histiocytosis according to current WHO categories.[12] The absence of CD1a expression and the presence of CD163 and S100 positivity in scattered cells suggest overlap between histiocytic and dendritic cell lineages, highlighting the diagnostic complexity of these entities.[17]

Importantly, the association between histiocytic disorders and hematologic malignancies has been documented in several series.[15,18,19] However, cases in which histiocytic and hemophagocytic features precede the diagnosis of AML, particularly in adults, remain extremely rare and are mostly limited to isolated case reports.[2-5]

In this context, cohort studies have demonstrated an increased risk of secondary malignancies in patients with histiocytoses, including LCH, Erdheim-Chester disease, and indeterminate cell histiocytosis (ICH).[6,17] Reported frequencies vary according to the ubtype, with higher rates observed in ICH, suggesting a stronger association with hematologic neoplasms.[13] Molecular studies have further demonstrated shared oncogenic mutations between histiocytic and hematologic neoplasms, supporting the hypothesis of a possible clonal relationship in selected cases.[2,4,5]

In the present case, a cytogenetic abnormality involving 11q23 was identified early in the disease course. Although this region is classically associated with KMT2A rearrangements in AML, the limited metaphase representation precluded definitive classification at that stage.[2,20-22] Therefore, this finding should be interpreted as a clonal cytogenetic abnormality requiring longitudinal correlation rather than an immediate diagnostic definition of AML.[1]

Regarding HLH, the patient fulfilled several HLH-2004 criteria, including fever, cytopenias, hyperferritinemia, and hypertriglyceridemia.[23] However, the diagnosis of HLH could not be confirmed due to the absence of functional assays such as NK-cell activity and soluble IL-2 receptor (sCD25),[23] as well as the lack of H-score calculation. Additionally, infectious complications during hospitalization may have contributed to systemic immune activation. Therefore, HLH is best interpreted in this case as a suspected secondary inflammatory syndrome rather than a definitive diagnosis.

The relationship between HLH and AML is complex.[22] HLH may occur concomitantly with hematologic malignancies or emerge during disease evolution and treatment.[15,19,23] However, cases in which HLH-like manifestations precede overt AML diagnosis are uncommon and may reflect early immune dysregulation associated with evolving clonal myeloid disease.[20,24,25]

Another relevant aspect of this case is the progressive emergence of myeloblasts over time, initially detected at low levels in peripheral blood and subsequently reaching diagnostic thresholds for AML in the bone marrow. This temporal evolution supports the hypothesis of an underlying clonal hematopoietic process that initially manifested with inflammatory and histiocytic features.[20,22]

Finally, this case highlights the diagnostic challenge of distinguishing reactive histiocytic and hemophagocytic processes from early manifestations of clonal hematologic neoplasms.[17,26] The overlap between histiocytosis, suspected HLH, and evolving AML underscores the importance of integrated morphological, immunophenotypic, cytogenetic, and clinical correlation. Early molecular characterization, when available, may be crucial for clarifying such complex presentations.[27]

CONCLUSION

The present case report contributes to the growing body of reports suggesting the existence of clonal relationships between histiocytic/dendritic cell neoplasms and other myeloid or lymphoid neoplasms. Furthermore, it reinforces the diagnostic challenge posed by histiocytoses, given the morphological and immunophenotypic overlap between their subtypes and the need for careful integration of clinical, histopathological, and molecular findings. Moreover, the initial manifestation of evolving AML can be non-specific, potentially mimicking conditions such as HLH. Similar cases are rare in the literature, which limits data discussion and makes standardizing conduct difficult. Documenting these cases is essential to expand clinical knowledge and provide subsidies that can guide medical practice in future presentations. Further studies are needed to determine which factors in patients with histiocytosis present a high risk of progression to hematological neoplasms.

CONFLICTS OF INTEREST

Nothing to declare.

DECLARATION OF USE OF ARTIFICIAL INTELLIGENCE TOOLS

There were none.

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DATA AVAILABILITY STATEMENT

Not applicable.

AUTHOR CONTRIBUTIONS

Conceptualization: Rocha ML. **Investigation:** Vasconcelos ETMFS. **Methodology:** Oliveira GM. **Formal Analysis:** Cunha FM. **Data Curation:** Vale KHAC. **Project Administration:** Duarte FB. **Funding Acquisition:** Duarte FB. **Writing:** Rocha ML. **Supervision:** Duarte FB, Rocha Filho FD. **Final Approval:** Duarte FB

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