Case Report

# Faggot cells in acute myeloid leukemia with *NUP98*::*HOXA9*

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**ABSTRACT**

Faggot cells are abnormal cells containing multiple Auer rods in the cytoplasm. They are usually found in acute promyelocytic leukemia (APL), typically characterized by *PML*::*RARA* fusion. We describe a rare case in which faggot cells were observed, but the patient was ultimately diagnosed with acute myeloid leukemia (AML) with *NUP98*::*HOXA9*. A man in his 40s presented with fever, pneumonia, and coagulopathy. Peripheral blood examination revealed an increased number of blast cells with Auer rods. Bone marrow (BM) aspirate smears showed the proliferation of abnormal promyelocyte-like cells showing strong myeloperoxidase positivity; some contained multiple Auer rods, consistent with faggot cells. Flow cytometric analysis of the BM revealed an APL-like immunophenotype, characterized by the expression of myeloid markers and the absence of CD34 and HLA-DR. Based on these morphological and immunophenotypic findings, the patient was initially suspected to have APL and was treated with all-trans retinoic acid (ATRA) in combination with cytotoxic induction chemotherapy. However, subsequent molecular analyses revealed the presence of *NUP98*::*HOXA9* mRNA and absence of *PML*::*RARA* mRNA. Therefore, APL was excluded, and the patient was diagnosed with AML with *NUP98* rearrangement. Consequently, ATRA was discontinued. Chromosomal analysis revealed the presence of t(7;11)(p15;p15), supporting the revised diagnosis. Despite exhibiting APL-like morphological and immunophenotypic features, the disease was ultimately diagnosed as non-APL AML based on genetic and chromosomal testing. This case highlights the fact that faggot cells are not entirely specific for APL and emphasizes the importance of integrating morphological, immunophenotypic, and genetic/cytogenetic findings for accurate diagnosis and appropriate treatment.

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**Key Words**
faggot cells, Auer rods, acute myeloid leukemia, *NUP98*::*HOXA9*

## I. Introduction

In hematological malignancies such as acute myeloid leukemia (AML), it is necessary to combine morphological examination, flow cytometry, chromosomal analysis, and genetic testing to make an accurate diagnosis and enable appropriate treatment planning. Although a traditional method, morphological examination contributes to clinical practice as a method with the advantage of rapid performance, often aiding clinical decision-making in specific contexts.

Faggot cells are abnormal myeloid cells that contain multiple Auer rods within their cytoplasm. These cells are considered characteristic findings of acute promyelocytic leukemia (APL), which is typically caused by the *PML*::*RARA* fusion gene. Here, we report a case in

which faggot cells were morphologically observed; however, chromosomal and genetic findings ultimately led to the diagnosis of non-APL AML, specifically AML with *NUP98*::*HOXA9* fusion.

## II. Case report

A man in his 40s visited his previous physician because of a fever. Radiological examination revealed an infiltrative shadow in the upper left lobe of the lung. Blood tests revealed severe inflammation, thrombocytopenia, and elevated levels of fibrin/fibrinogen degradation products (FDP). Consequently, the patient was admitted with diagnoses of pneumonia and coagulopathy. A subsequent peripheral blood (PB) smear revealed an increased number of blast cells with Auer rods, leading to a referral and transfer to our hospital with suspected AML.

Blood tests conducted at our hospital yielded the following results: white blood cell count, 13.58 × $10^9$/L (blast cells: 84.5%, neutrophils: 8.0%, and lymphocytes: 7.5%); red blood cell count, 2.63 × $10^{12}$/L; hemoglobin, 9.3 g/dL; platelet count, 54 × $10^9$/L; lactate dehydrogenase, 619 U/L; prothrombin time, 13.2 s; activated partial thromboplastin time, 22.1 s; fibrinogen, 455 mg/dL; FDP, 33.3 μg/mL; thrombin-antithrombin complex, 4.9 ng/mL; and plasmin-alpha2-plasmin inhibitor-complex, 6.8 μg/mL. In the PB smear, the cells counted as blast cells were large with a fine chromatin network, clear nucleoli, and cytoplasm containing fine granules. Some contained a single Auer rod (**Figure 1A**). A bone marrow (BM) aspirate smear showed hypercellular marrow with proliferation of abnormal promyelocyte-like cells. These cells were medium-to-large, with a basophilic cytoplasm, often containing fine granules. They exhibited a nuclear-to-cytoplasmic ratio of ≥ 50%, a fine chromatin network, and distinct nucleoli. Some cells contained one or more Auer rods, resembling the faggot cells observed in patients with APL (**Figure 1B–D**). Based on these morphological features, these cells were counted as promyelocytes, resulting in 57.6% promyelocytes. In addition, 13.8% of the cells were blast cells, similar to those observed in the PB smears. Promyelocytes were strongly positive for myeloperoxidase (MPO) staining. Pseudo–Pelger–Huët neutrophils were also observed, although only as a subtle and minor finding. BM flow cytometry analysis showed that the CD45-dim cell population was positive for CD13 (65.6%) and CD33 (98.4%) and negative for CD3, CD19,

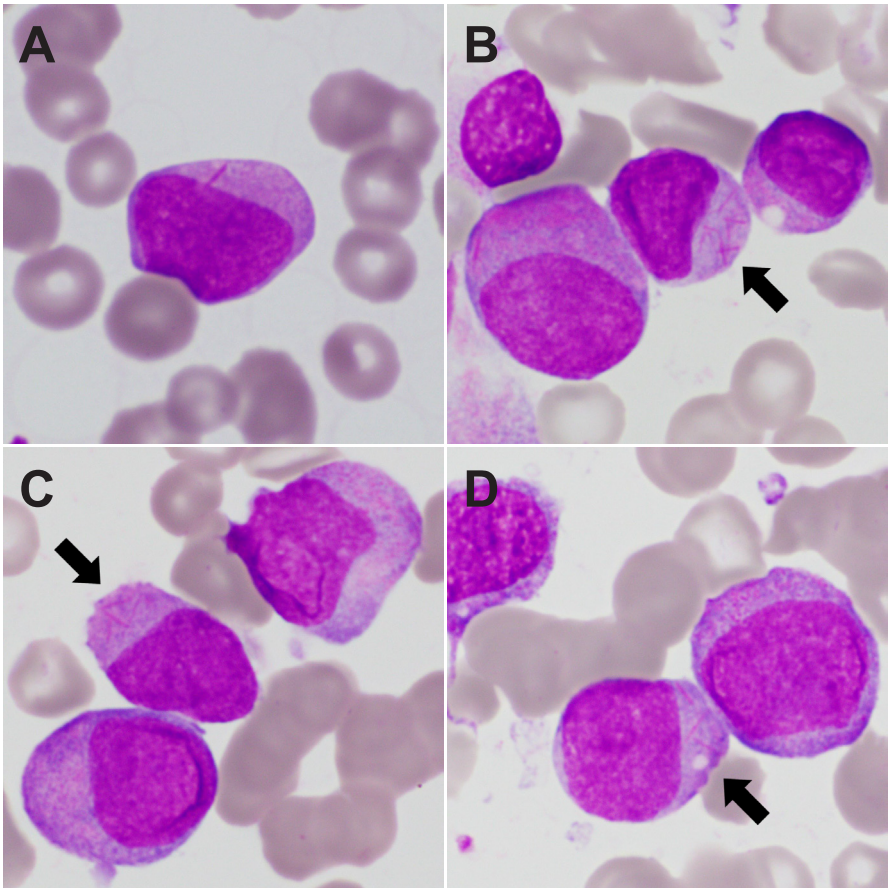


**Figure 1** May-Grünwald-Giemsa stain; magnification, 1000 ×. (**A**) Peripheral blood smear showing the blast cell with a single Auer rod. (**B-D**) Bone marrow aspirate smear showing faggot cells (arrows).

CD34, CD41, and HLA-DR (**Figure 2**). Based on the morphological features and flow cytometry findings, the patient was initially suspected to have APL and was treated with all-trans retinoic acid (ATRA) in combination with cytotoxic induction chemotherapy.

On day 4 after initiating the induction therapy, results of the real-time polymerase chain reaction screening for leukemia chimeric genes in the BM became available. The screening revealed the presence of *NUP98*::*HOXA9* mRNA ($2.7 \times 10^4$ copies/μg RNA) and absence of *PML*::*RARA* mRNA. Based on these findings, APL was ruled out, and the patient was diagnosed with AML with *NUP98* rearrangement. Accordingly, ATRA was discontinued. Subsequent chromosomal analysis using G-banding confirmed a karyotype of 46,XY,t(7;11)(p15;p15)[15]/46,XY[5], corresponding to the exclusion of APL and presence of *NUP98*::*HOXA9* fusion (**Figure 3**). Other genetic testing was negative for *FLT3*-internal tandem duplication. Cytotoxic induction therapy was continued, and a complete hematological remission was confirmed on day 29 by BM examination. After completing three courses of consolidation chemotherapy, the patient underwent allogeneic BM transplantation during the first complete remission. However, approximately 9 months later, the AML relapsed. In the PB and BM aspirate smears, blast cells increased, but no faggot cells were observed. The reinduction chemotherapy led to a reduction in blast cells, and umbilical cord blood transplantation was planned. However, the patient died due to the exacerbation of organizing pneumonia.

## III. Discussion

Faggot cells are mostly observed in APL. Although their presence has also been reported in non-APL settings such as AML with inv(16) or myelodysplastic neoplasms, they are extremely rare[1)-3)]. In this non-APL AML case, we discuss the possible mechanisms underlying the appearance of faggot cells and describe the associated morphological characteristics.

Azurophilic granules are cytoplasmic particles that are stained purple-brown to purple-red with azure dyes. In granulocytes, these granules correspond to primary granules and contain antimicrobial substances such as MPO. During granulocyte differentiation, primary gran-

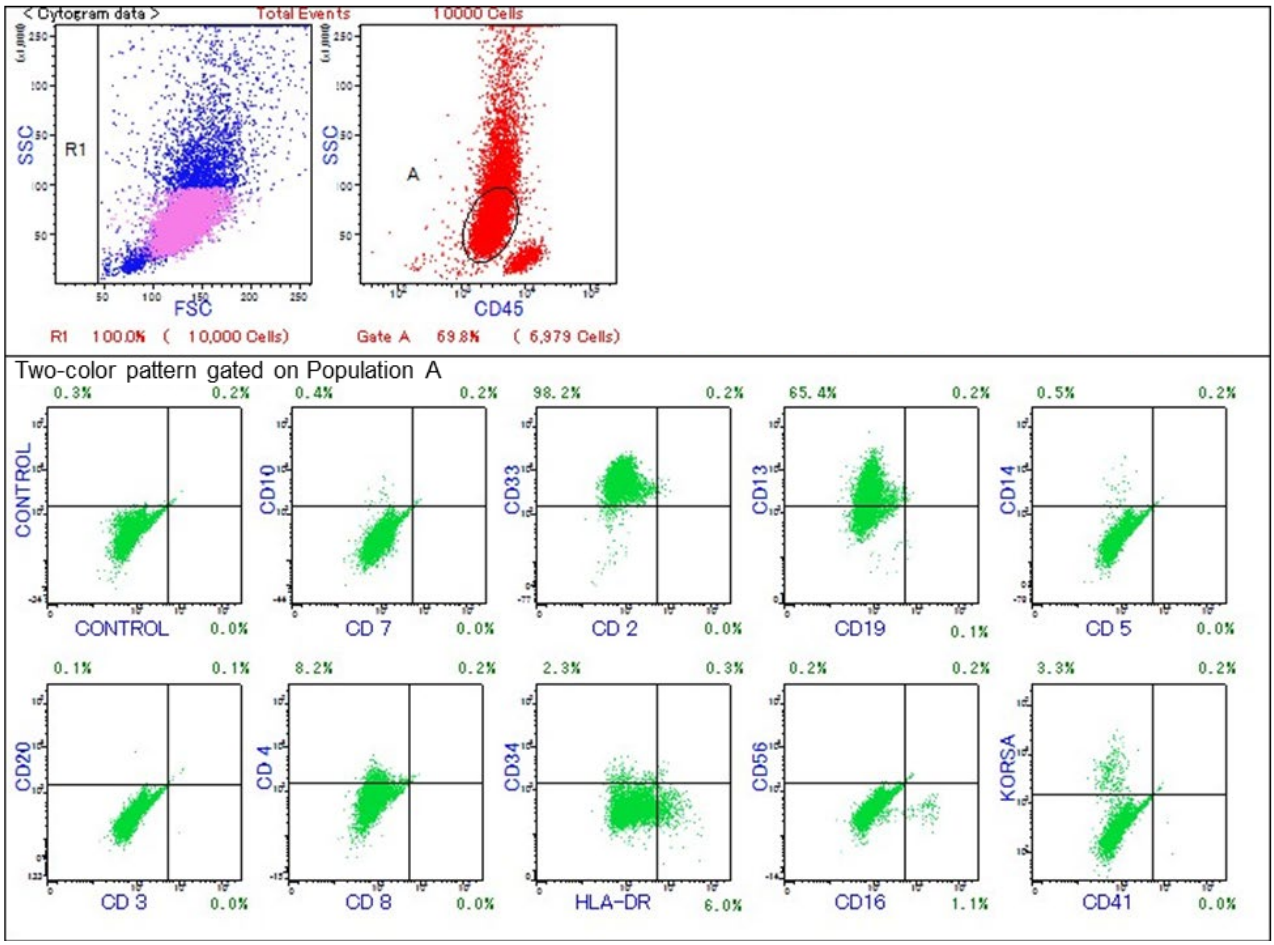


**Figure 2** Flow cytometric analysis of cell surface markers in bone marrow aspirate: Two-color pattern gated on Population A.

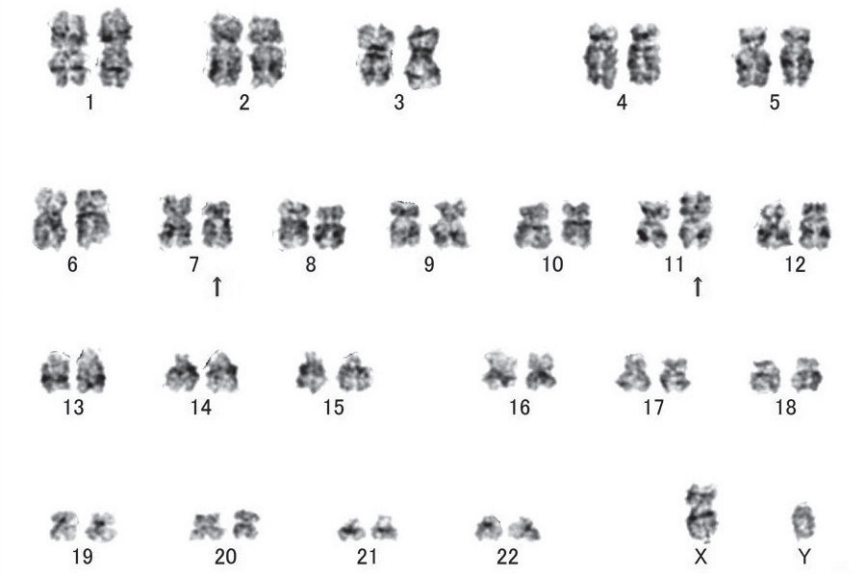


**Figure 3** Chromosomal analysis using G-banding, showing translocation t(7;11)(p15;p15) in 15 of the 20 analyzed cells.

ule production ceases at the myelocyte stage, after which specific granules, called secondary granules, begin to form. Auer rods are reddish-purple, needle- or rod-shaped cytoplasmic inclusions thought to be azurophilic granules that fail to mature normally and fused together[4]. They are found in leukemic cells, but not in normal cells, and their presence in acute leukemia strongly suggests AML. Auer rods are typically observed in myeloblasts and promyelocytes and may appear singly or in multiples within the cytoplasm. Cells containing bundles of Auer rods are termed faggot cells and are characteristically found in the abnormal promyelocytes of APL[5].

AML with *NUP98*::*HOXA9* fusion is rare, has a poor prognosis, and is caused by a translocation t(7;11)(p15;p15). NUP98 is one of the proteins that constitute the nuclear pore complex and is involved in the transport of mRNA and proteins between the nucleus and cytoplasm[6]. *HOXA* is one of the clusters of *HOX* genes that encode transcription factors with a DNA-binding domain[6]. The expression level of *HOXA9* is normally downregulated during hematopoietic differentiation. However, in this disease, continuous activation of *HOXA9* by the NUP98 promoter due to the *NUP98*::*HOXA9* fusion is thought to inhibit normal hematopoietic differentiation[6)-9)].

The *PML*::*RARA* fusion, typically responsible for APL, represses RARα-dependent transcription, thereby blocking myeloid differentiation at the promyelocyte stage[10]. Accordingly, typical APL exhibits an immunophenotype of $CD13^+$, $CD33^+$, $CD34^-$, and $HLA\text{-}DR^-$. This pattern, characterized by positivity for myeloid lineage markers (CD13 and CD33), coupled with the loss of early precursor markers (CD34 and HLA-DR), indicates that the cells have progressed to the promyelocyte-like stage. Notably, the immunophenotype at the initial onset in the present case was similar, suggesting arrest at a similar promyelocyte-like stage. Therefore, we hypothesized that the arrest of leukemic cell differentiation at this promyelocyte-like stage may have contributed to the accumulation of Auer rods, resulting in the formation of faggot cells. Conversely, the immunophenotypes of the CD45-dim population at the time of recurrence were $CD13^+$, $CD33^+$, $CD34^+$, and $HLA\text{-}DR^{weakly+}$, indicating the proliferation of more immature cells relative to the initial onset; no faggot cells were observed. Most AML cases with *NUP98*::*HOXA9* fusion are classified as AML M2 according to the French-American-British (FAB) classification[11),12)]. Nevertheless, unlike typical cases, leukemic cells at the initial onset in the present case appeared to show differentiation arrest, particularly at the promyelocyte-like stage; the precise mechanism underlying this remains unclear.

Morphologically, the Auer rod bundles in this case appeared thinner and longer than those typically observed in APL. Additionally, pseudo–Pelger–Huët anomaly, which is usually absent in APL, was identified in some neutrophils. These findings resemble the characteristic features of AML with *RUNX1*::*RUNX1T1* fusion[4),13)]. To our knowledge, only two cases of faggot cells being found in AML with *NUP98*::*HOXA9* fusion have been reported globally[14)-16)], and further accumulation of cases is essential to clarify these morphological features from those of APL.

The need for an integrated diagnostic approach was

evident in this case. Accurate diagnosis is of paramount importance because hematopoietic tumors encompass various subtypes, each requiring distinct treatment approaches and presenting with different prognoses. As evidenced by the continued use of the FAB classification proposed in 1976, the careful observation of blood cells is essential[11]. APL is a prime example of a condition in which rapid diagnosis is critical, and morphology contributes significantly. APL frequently presents with a high complication rate of disseminated intravascular coagulation accompanied by life-threatening hyperfibrinolysis, making early diagnosis and immediate treatment crucial. Therefore, when faggot cells are observed, it is prudent to suspect APL and initiate ATRA therapy[2]. However, if the disease is not APL, the treatment approach may be ineffective and unnecessary. Thus, methods other than morphological testing, specifically genetic and chromosomal testing, are essential for a definitive diagnosis of APL. In the present case, although the disease displayed APL-like morphological characteristics and immunophenotypes, genetic and chromosomal testing ultimately ruled out APL. Collectively, an integrated diagnostic approach utilizing complementary techniques is essential for an accurate diagnosis and appropriate treatment; findings from the present case reinforce this necessity.

## Authorship contributions

MU drafted the manuscript. MU, SO, NA, and DO performed morphological examinations. MU and NA captured microscopic images. MY, AN, IK, and KK were physicians involved in patient care. SO, FK, and KS-I revised the manuscript. All the authors have read and approved the final version of the manuscript.

## Disclosure of conflicts of interest

The authors declare no conflicts of interest associated with this manuscript.

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## Previous abstract presentation

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