CASE OF THE QUARTER

Jitakshi De, M.D.[1] and Megan S. Lim, M.D., Ph.D.[2]

1. Deepath Medical; Human Immune Monitoring Center, Palo Alto, CA
2. Department of Pathology,University of Michigan Hospital System, Ann Arbor, MI

Diagnosis: ACUTE MYELOID LEUKEMIA, NOS

INTRODUCTION

Here we describe the clinical, morphologic and immunophenotypic features of a novel acute myeloid leukemia (AML)-associated translocation, t(8;19)(q24;q13.1), found in an elderly female patient with no prior history of a hematologic disorder and primary presentation of septic arthritis. An unusual t(8;19) translocation was identified as the sole karyotypic abnormality at diagnosis and relapse, while the karyotype was normal during remission. The clinical course was that of incomplete response to standard chemotherapy and relapsed leukemia.

CLINICAL HISTORY

This 77-year-old female patient presented to the orthopedic clinic with a chief complaint of left knee pain. Cultures obtained from the septic knee joint grew *Granulicatella adiacens*, requiring a knee implant. CBC analysis revealed leukocytosis (WBC 27.9 K/μl) with 77% blasts, macrocytic anemia (Hgb 7.3 g/dL, MCV 103.2 fL), and thrombocytopenia (PLT 71 K/μl). The

patient was treated with 7 days of infusion with cytarabine followed by 3 days of duanorubicin (7 + 3). Due to residual leukemia at day 14, she underwent re-induction chemotherapy with cytarabine and duanorubicin (5 + 2) to which a complete immunophenotypic and cytogenetic response was achieved. A follow-up bone marrow evaluation performed 14 months later due to persistent thrombocytopenia demonstrated evidence of relapse (Fig 1). Consequently, the patient underwent re-induction chemotherapy regimen consisting of idarubucin, fludarabine, cytarabine, and granulocyte colony-stimulating factor. She was referred to University of Michigan Comprehensive Care Center for a second opinion.

PATHOLOGIC DATA

Morphology:

Morphologic review was performed on the diagnostic and all follow-up peripheral blood smears and bone marrow biopsies. The original peripheral blood revealed macrocytic anemia, thrombocytopenia, neutropenia, and 77% blasts (Fig 2). Bone marrow aspirate showed 66% blasts that were intermediate to large with moderate amounts of pale blue cytoplasm, round to delicately folded nuclear contours, 2-6 distinct nucleoli, and readily identifiable 1-2 long slender Auer rods (Fig 3a-c). There was dysplasia in the erythroid and myeloid (hypogranularity) lineages (Fig 3b-d). Additionally, unusual morphologic features of the blasts were salmon-colored and azurophilic Chediak-Higashi (CH)-like cytoplasmic granules, the latter being prominent after initial round of chemotherapy (Fig 3e). There was morphologic evidence of what appeared to be erythrohemophagocytosis (Fig 3f). The bone marrow was extensively occupied by blasts containing pink granular cytoplasm (Fig 3g). The final bone marrow biopsy prior to referral to our institution showed left-shift of the granulocyte precursors consistent with recent granulocyte colony-stimulating factor therapy, and no evidence of residual leukemia.

Immunophenotype:

Multiparametric flow cytometry analysis performed at Spectrum Health laboratory revealed myeloid blasts which were positive for CD13, CD33, CD34, CD117, HLA-DR, CD7, and CD9 expression; and negative for CD11b, CD18, CD19, CD56, CD61, CD64, and glycophorin. The blast immunophenotype at relapse was similar including aberrant CD7 expression.

Cytogenetic analysis:

By conventional karyotype analysis, 24 and 48 hour unstimulated bone marrow cultures revealed a female karyotype with t(8;19)(q24;q13.1) as the sole cytogenetic abnormality in all 20 metaphases (Fig 4). In Day 14 marrow, 14/20 metaphases had this abnormality. Post re-induction chemotherapy and in subsequent follow-up marrows at 6 months intervals, cytogenetics showed normal female karyotype. At relapse, 14 months after the original diagnosis, t(8;19)(q24;q13.1) re-emerged as the only karyotypic abnormality in all 10 analyzable metaphases. FISH analysis for *MYC* rearrangement was negative.

Mutation Analysis:

Mutation analysis was performed from DNA extracted from the diagnostic formalin-fixed biopsy material and showed no evidence for *FLT3* (internal tandem duplication or D835), *KIT* D816V, or *NPM* exon 12 insertion mutations.

DISCUSSION

By the WHO classification, AML categorization relies on the presence of recurrent genetic abnormalities and prior histories such as myelodysplasia (MDS), myeloproliferative neoplasm and chemotherapy exposures. Such classification schema allow for risk stratification, therapy guidance, and prognostication. However, when a disease-defining genetic abnormality or history leading to a certain subclassification is not found, the leukemia is considered as not otherwise specified (NOS), and further described based on the previous FAB classification which heavily relied on morphologic features such as evidence of maturation.

This report highlights an important diagnostic dilemma of risk stratifying AML patients with unusual/non-recurrent chromosomal translocations and no other cytogenetic abnormalities. In the setting of no prior history of MDS or evidence of MDS-associated cytogenetic abnormalities, we theorized that the novel t(8;19)(q24;q13.1) karyotypic abnormality represents a true *de novo* translocation. The SH/EAHP 2010 consensus categorization of this entity was AML, not otherwise specified. Nevertheless, MDS-related pathobiology based on morphologic features in this case could not be definitively excluded. Aberrant CD7 expression on myeloid blasts at diagnosis and relapse is an unfavorable feature and consistent with suboptimal response to standard chemotherapy and a relapsing disease course in this patient.

This is the first description of the novel t(8;19)(q24;q13.1) associated with AML. Unusual morphologic features include blasts with readily identifiable long slender Auer rods and prominent salmon-colored and CH-like granules. Giant azurophilic and myeloperoxidase-positive CH-like granules have been reported in AML, including ones with myelomonocytic features [1] and in association with *MYC* amplification[2]; and as anomalous in acute promyelocytic leukemia where some cells with Auer rod-like inclusions, and others containing immature azurophilic granules with surrounding cytoplasmic clearing and prominent golgi apparatus have been described [3,4]. By electron microscopy, such inclusions have been identified as large peroxidase-positive granules [5]. These previously described cases and the current case have a unifying theme

of an underlying maturation defect in granule formation during myelopoiesis. FISH analysis did not detect *MYC* abnormalities in our case.

Two cases of AML with t(8;19)(q22;q13.1) have been previous described, one in a 17-year-old female and the other in a 45-year-old male, both manifesting as AML with maturation. These were considered simple variants of t(8;21)(q22;q22)/AML1-ETO[6], a typically *de novo* AML distinctly associated with salmon-colored granules in leukemic blasts. Contrary to these two cases, the fusion transcript in the current case involved unknown partner genes on 8q24 and 19q13.1. To our knowledge, this chromosomal rearrangement has not been previously reported in association with AML. Indeed, we are aware of only one report of t(8;19)(q24;q13) which was alluded to in a German doctoral thesis where the translocation was detected by spectral karyotyping in a Jeko-1 mantle cell lymphoma cell line.

The pattern of cytogenetic findings wherein t(8;19)(q24;13.1) was the sole cytogenetic abnormality at diagnosis and relapse, and was absent during remission, suggests that t(8;19)(q24;13.1) represents a key event in leukemogenesis. Genes involved in a balanced translocation often contribute to a novel fusion protein with transforming properties of unabated growth and defects in maturation. Identification of partnering oncogenes in 8q24 and 19q13.1 chromosomal hotspots containing other oncogenes such as *MYC* and *CEPBA*, respectively, and studying the mechanism of leukemic transformation is an important area of further research.

FIGURES

Figure 1: Percentages of circulating and marrow blasts at diagnosis, day 14 induction, and at relapse are depicted in this graph. The t(8;19)(q24;q13) coincided with the presence of blasts.

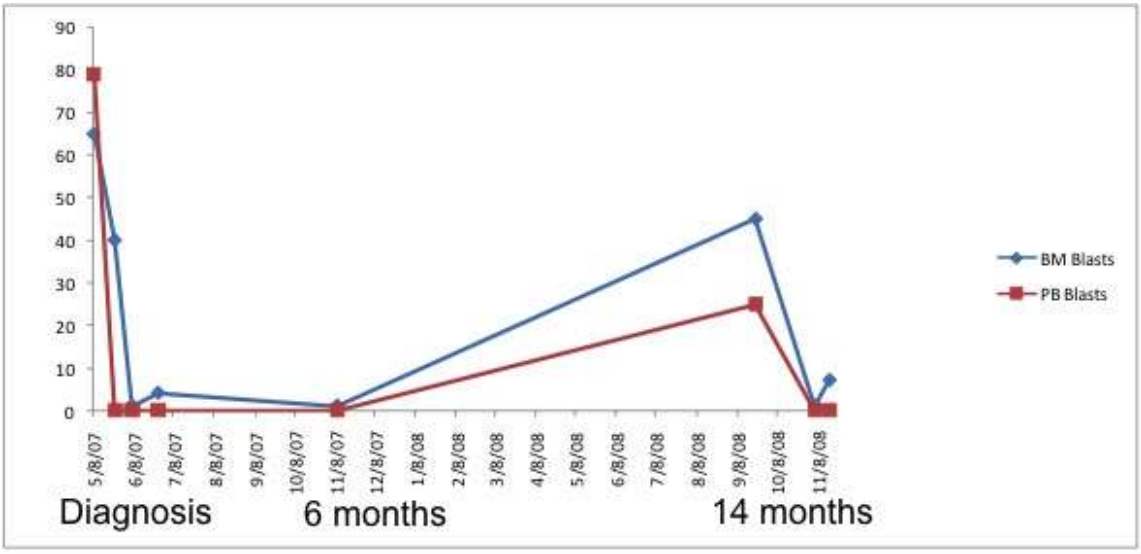


Figure 2: Peripheral blood blasts with 1-2 slender Auer rods and salmon-colored granules are shown.

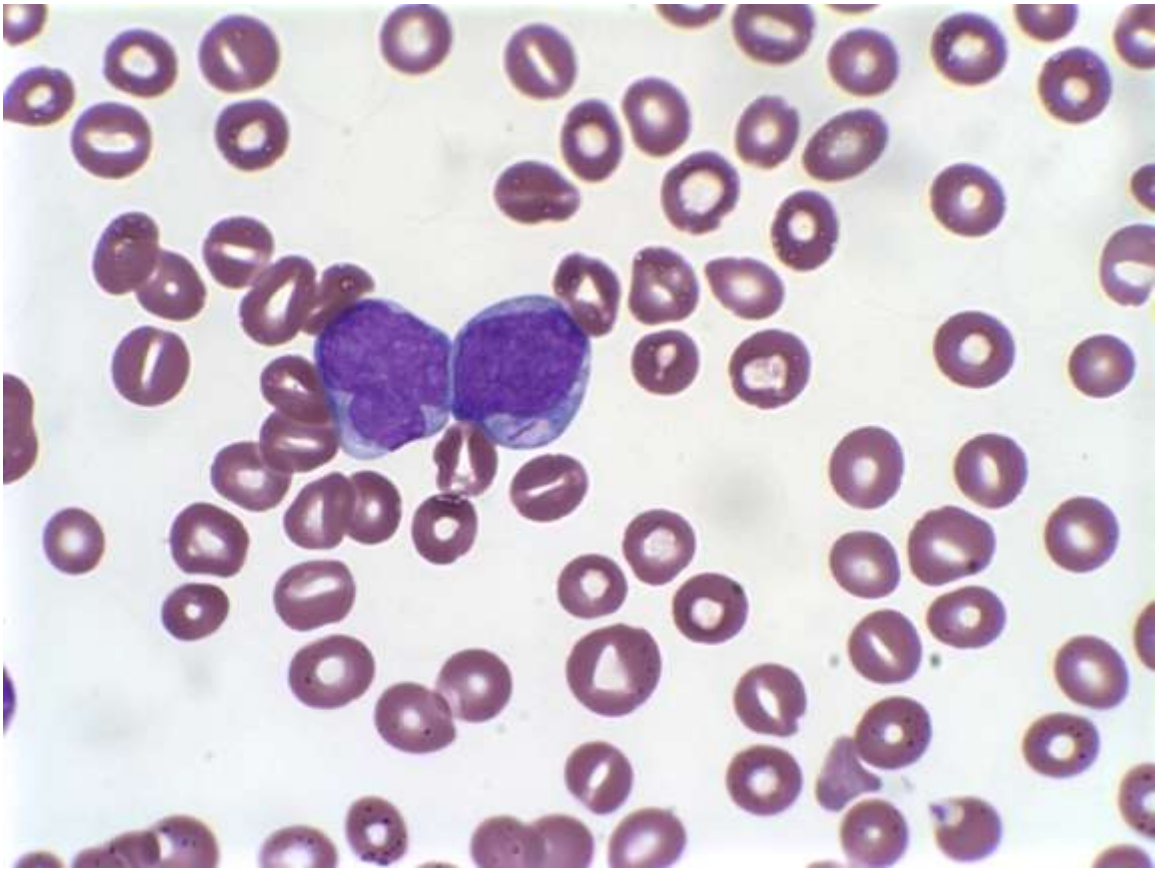


Figure 3: Bone marrow aspirate with blasts containing salmon colored granules; mild dyserythropoiesis and dysgranulopoiesis at diagnosis (a-d), prominent Chediak-Higashi-like granules post-induction chemotherapy (e), neutrophils with possible erythrohemophagocytosis (f), core biopsy extensively involved by sheets of blasts with pink granular cytoplasm (g).

Figure 3a:

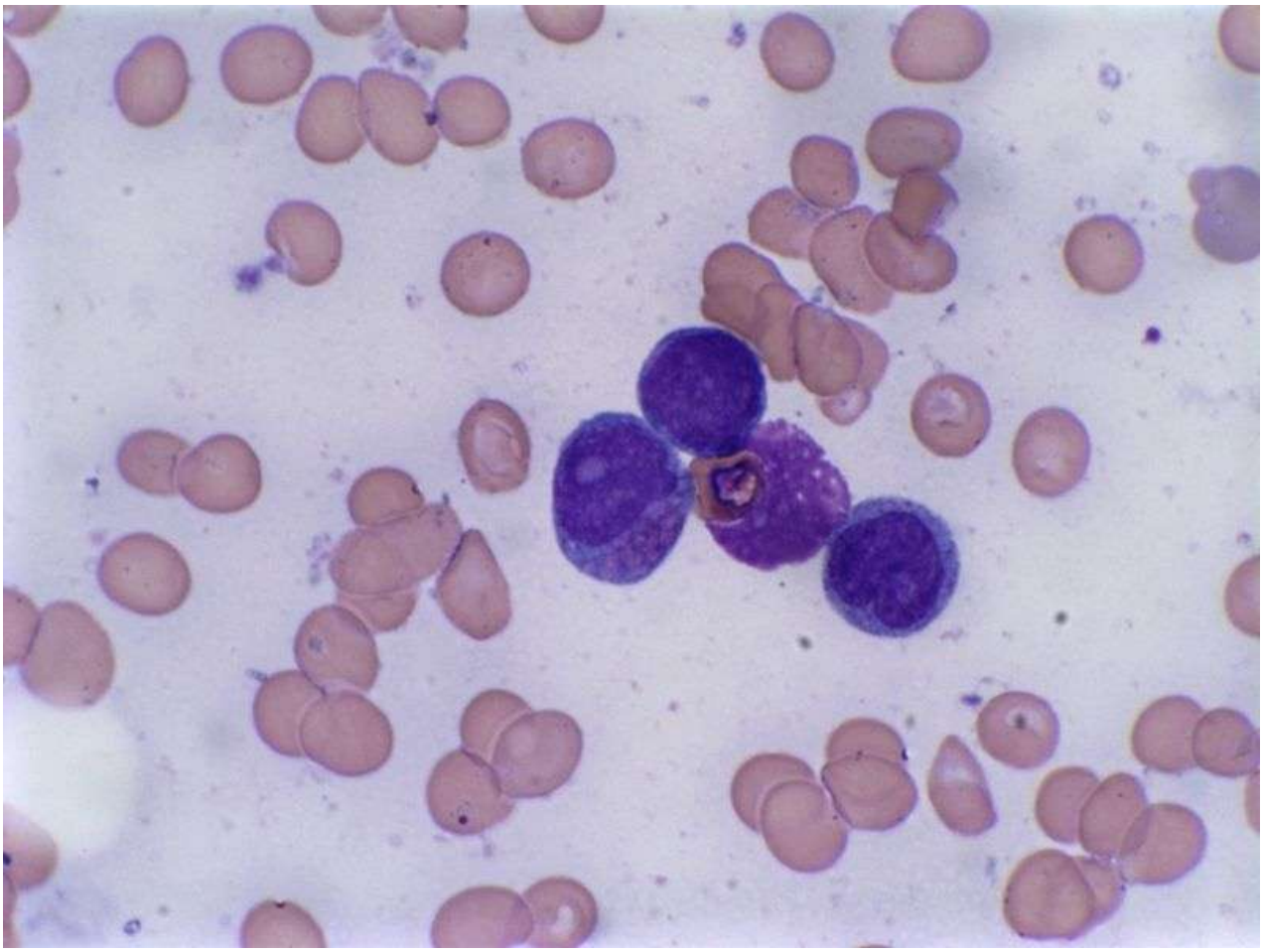


Figure 3b:

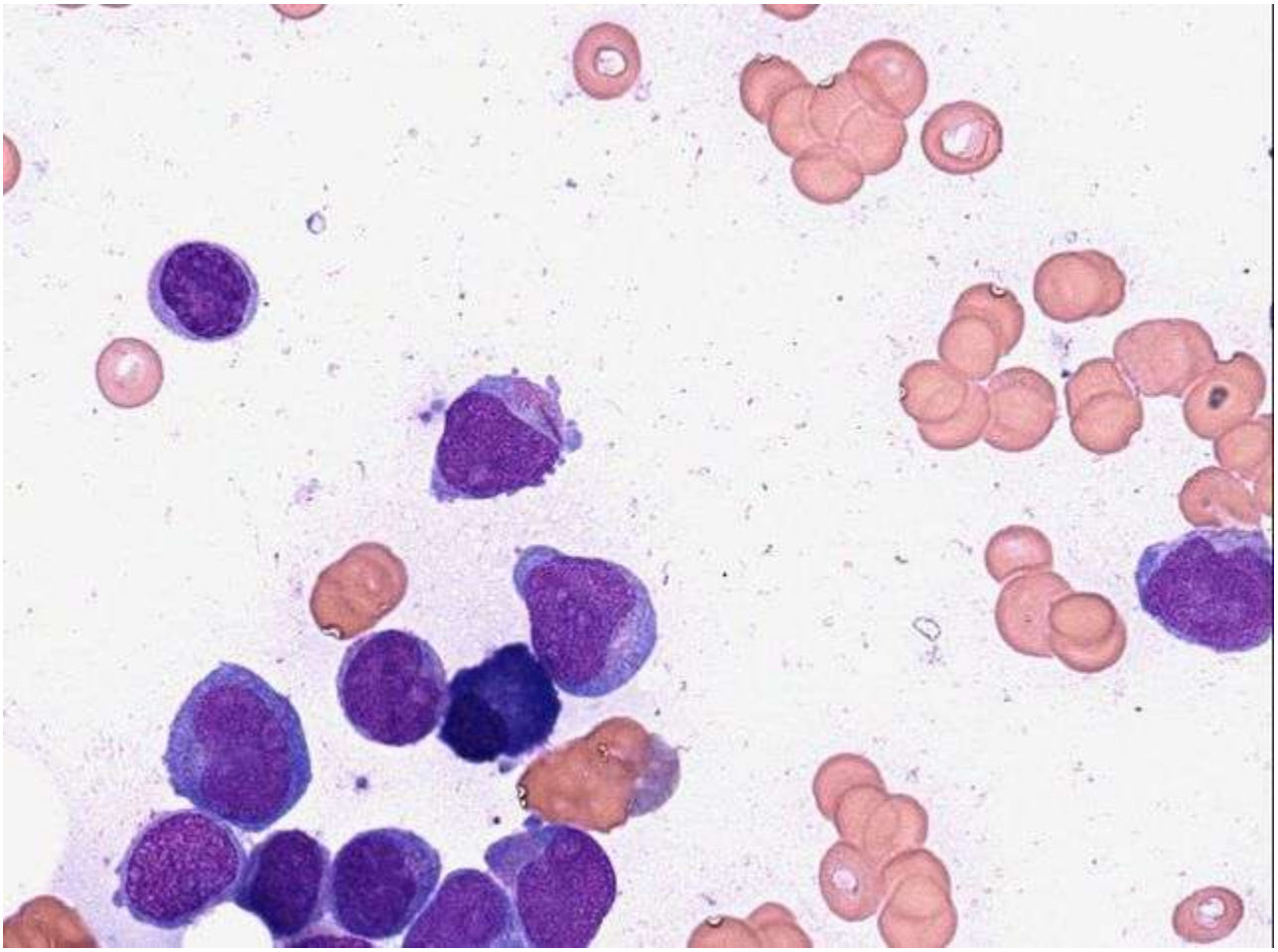


Figure 3c:

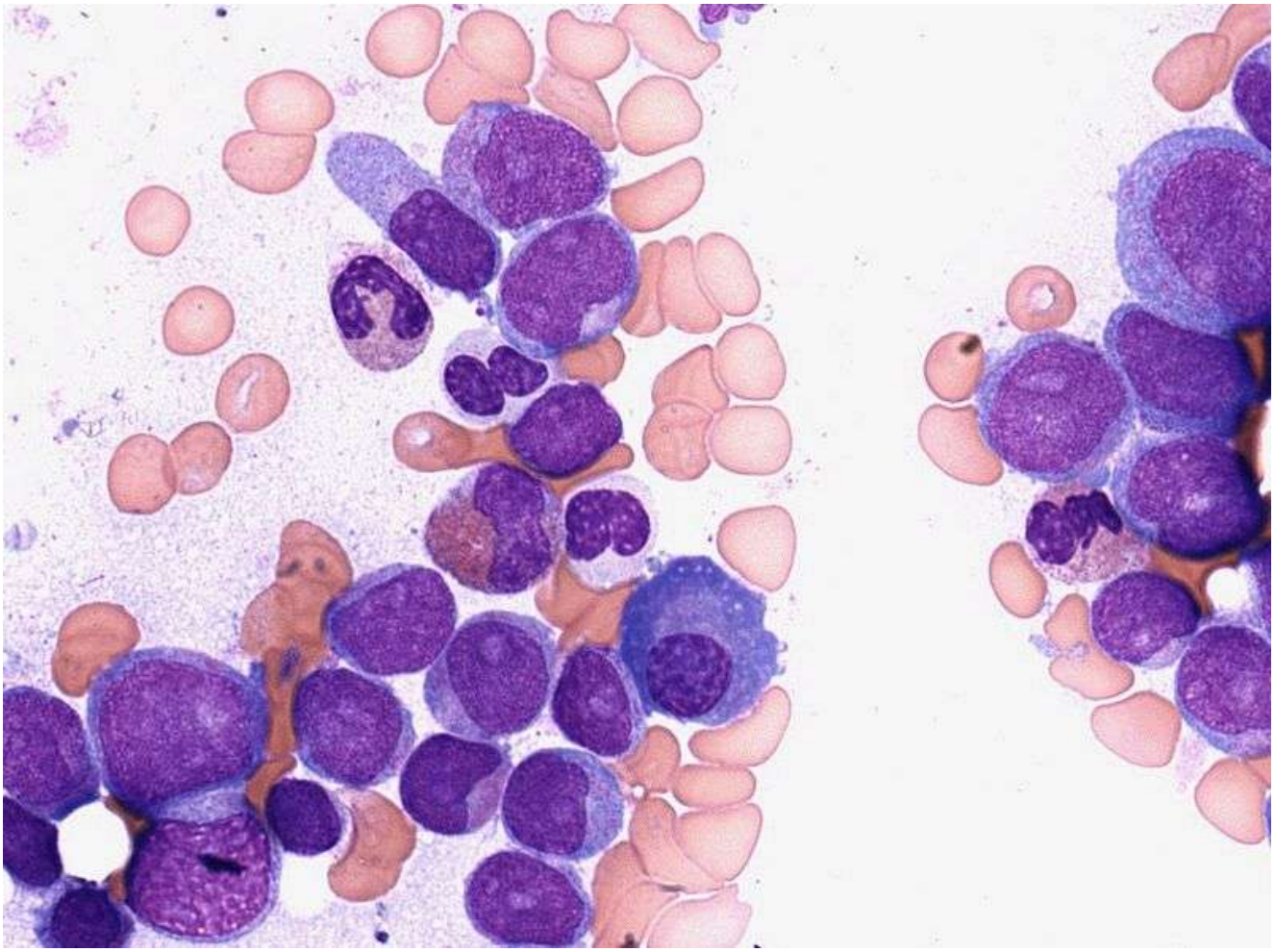


Figure 3d:

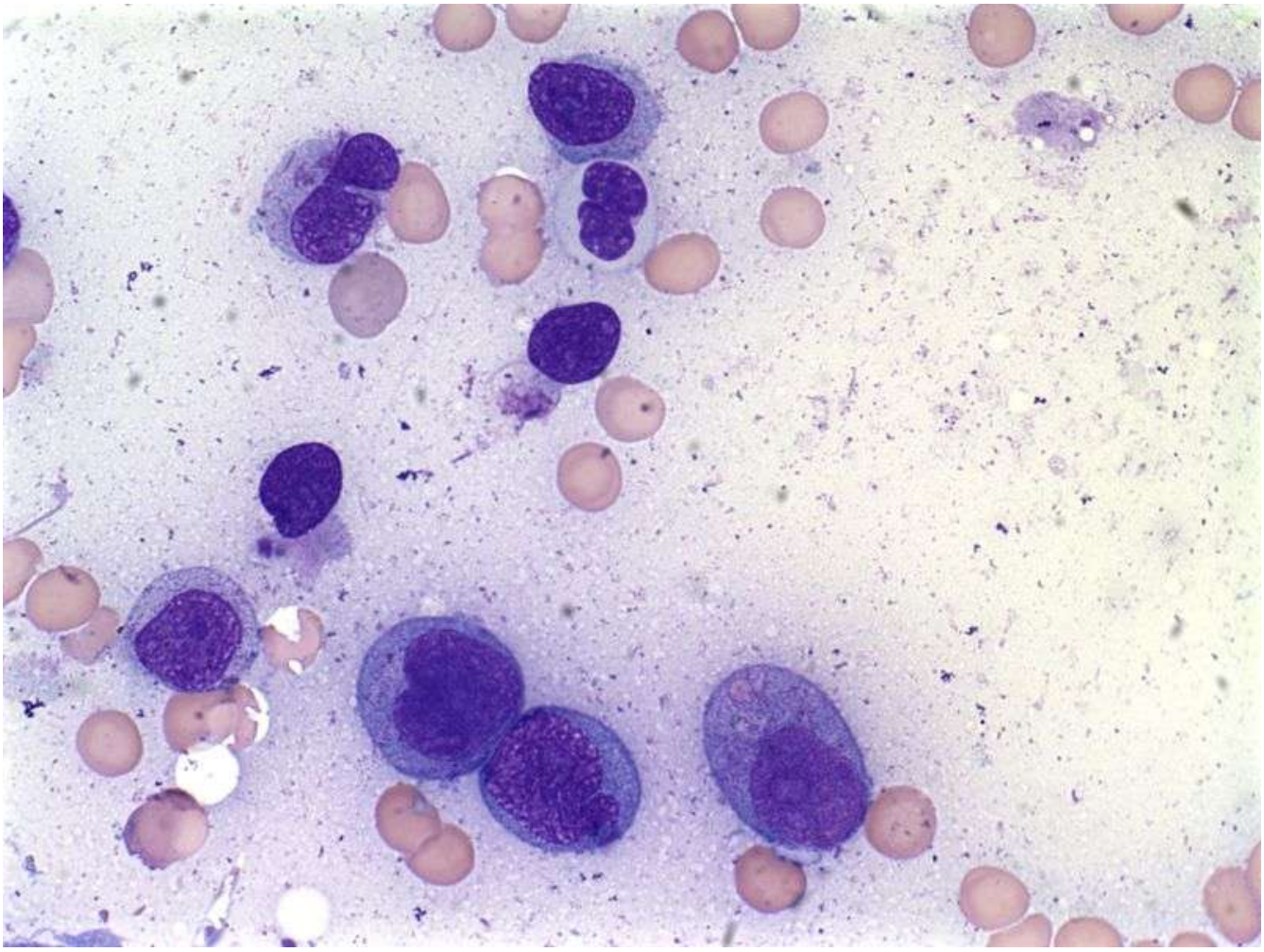


Figure 3e:

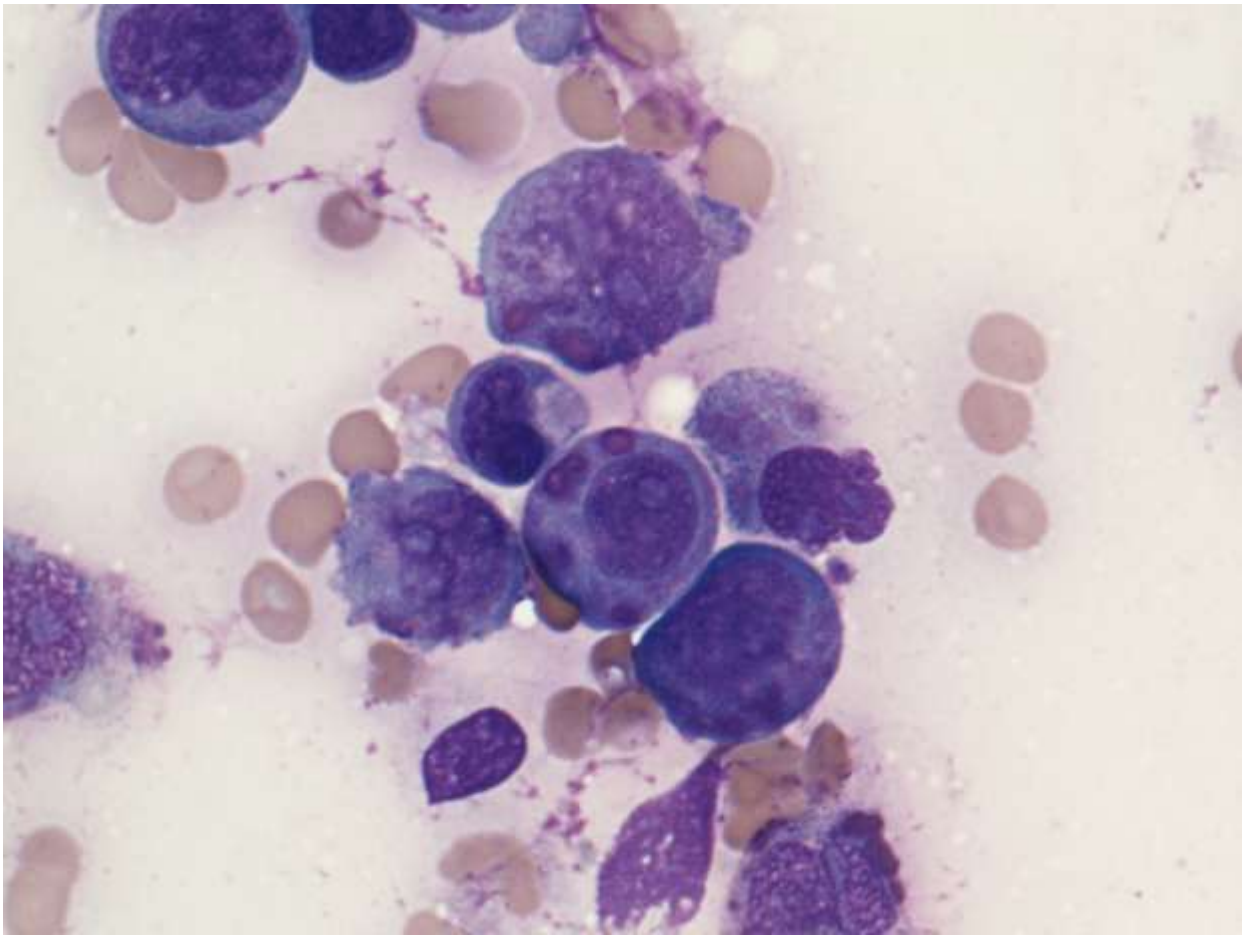


Figure 3f:

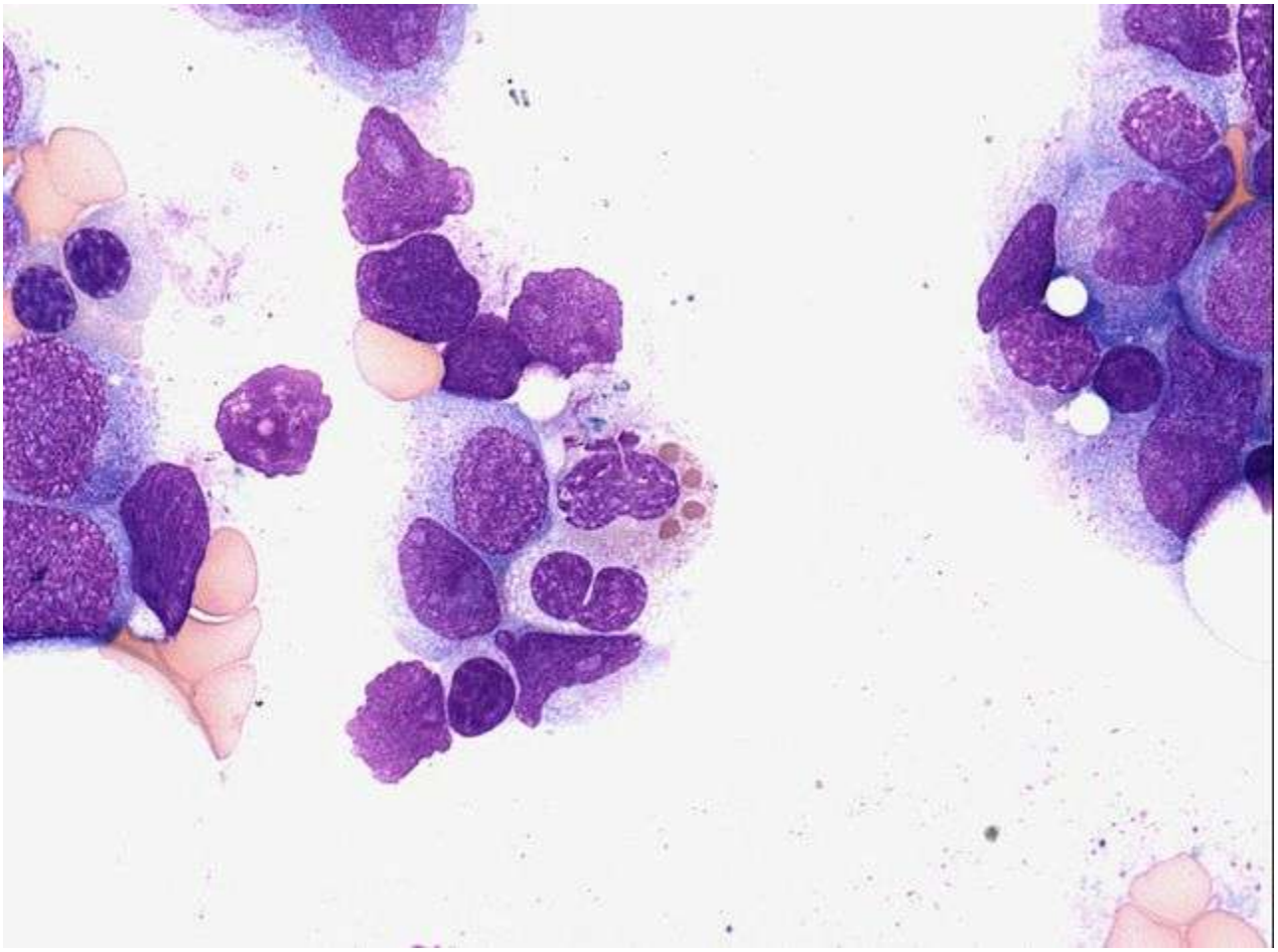


Figure 3g:

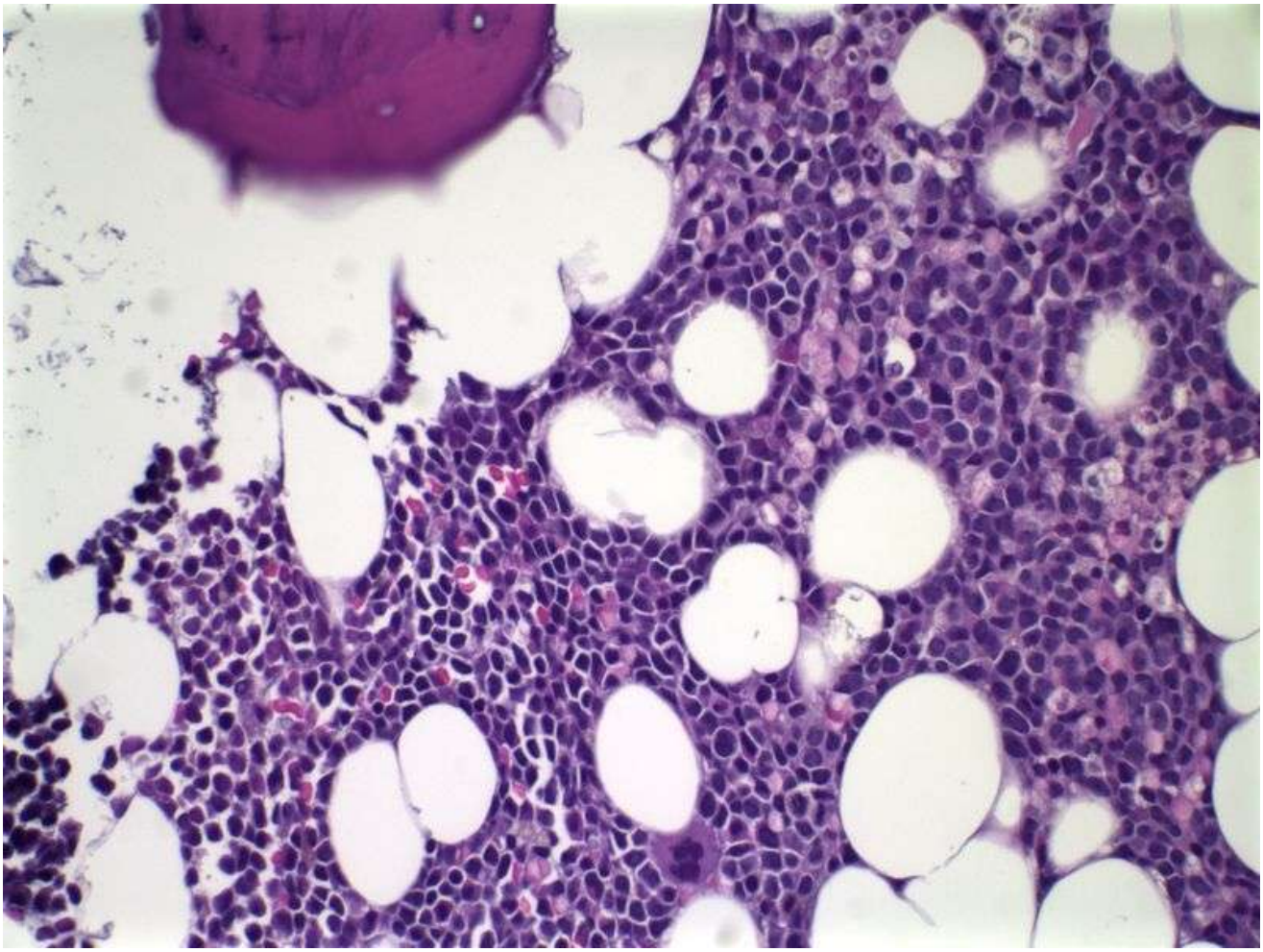
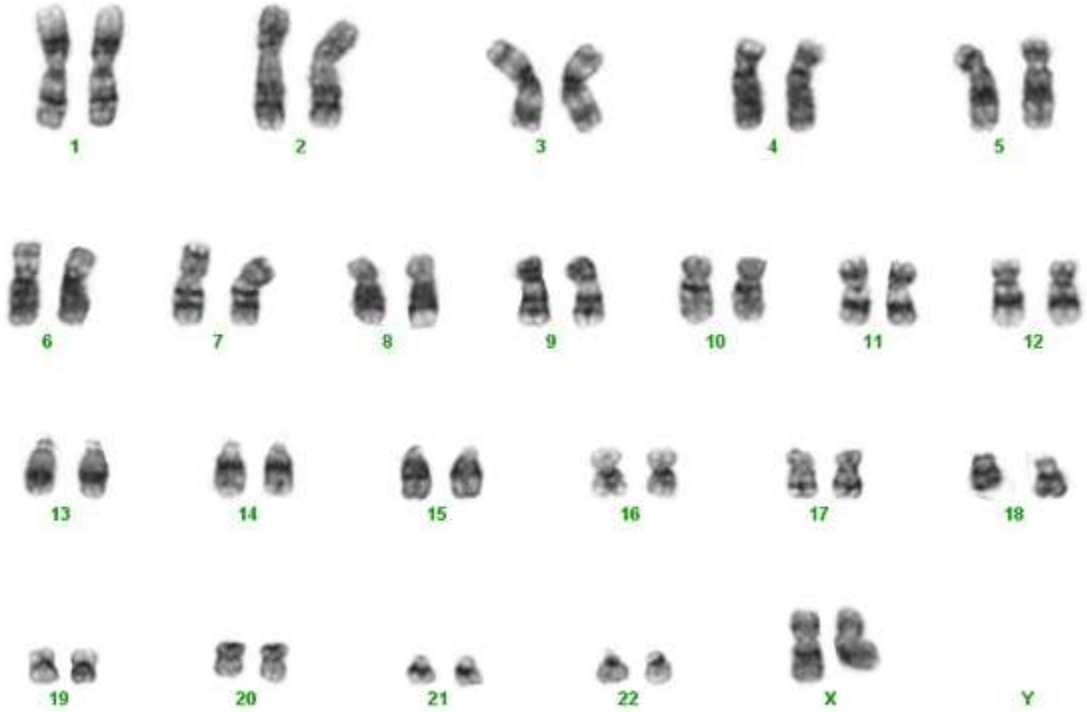


Figure 4: Conventional karyotype with t(8;19)(q24;q13.1) as the sole cytogenetic abnormality (found at diagnosis and relapse, but not in remission) is depicted.



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