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Case Report

Genetic complexity in myelodysplastic syndromes: Insights from a case with complex karyotype and renal manifestations

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ABSTRACT

Myelodysplastic syndrome (MDS) is a heterogeneous disorder with a significant risk of progression to acute myeloid leukemia. We present a case initially suspected of acute leukemia, subjected to comprehensive cytogenetic, immunophenotypic, and molecular evaluations. Cytogenetic analysis revealed a complex karyotype including translocation t (1;3) (q42;q21), near-tetraploidy, and deletions on chromosomes 5q and 20q. Fluorescence *in situ* hybridization confirmed the 5q and 20q deletions, along with trisomy 8. Immunophenotyping identified 7.5% abnormal myeloid blasts. Next-generation sequencing detected pathogenic TP53 mutations: c.569 (p.Pro190LeufsTer57) and c.464C>A (p.Thr155Asn). In addition, renal imaging showed mildly raised echotexture. This case underscores the value of integrated multimodal analysis for precise diagnosis and management of MDS, offering insights into its complex genetic landscape.

Keywords: Cytogenetics, Fluorescence *in situ* hybridization, Karyotype, Next-generation sequencing, Myelodysplastic syndrome

INTRODUCTION

Myelodysplastic syndrome (MDS) represents a heterogeneous group of clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis, leading to peripheral blood cytopenias and a predisposition to acute myeloid leukemia (AML) transformation.[1] The pathogenesis of MDS involves various genetic and epigenetic alterations, such as mutations in genes encoding transcription factors, splicing machinery components, and chromatin modifiers, which disrupt normal hematopoietic differentiation and proliferation.[2] Clinically, MDS manifests with symptoms of anemia, bleeding, and infections due to decreased production of functional blood cells. Diagnosis relies on the presence of cytopenias, dysplastic morphologic features in bone marrow, and the exclusion of other causes of hematologic abnormalities. The World Health Organization classification system categorizes MDS based on morphological, cytogenetic, and molecular features into several subtypes, each with distinct prognostic implications and therapeutic considerations.[3] Cytogenetic abnormalities are common in MDS and play a crucial role in risk stratification and treatment decisions. High-risk cytogenetic abnormalities, such as complex karyotype and abnormalities involving chromosomes 7 and 5q, are associated with poor prognosis and a higher risk of leukemic transformation, whereas favorable cytogenetic abnormalities, such as isolated del(5q), are associated

with better outcomes.[4] Treatment strategies range from supportive care measures, such as transfusion support and growth factors, to disease-modifying therapies, including hypomethylating agents, immunomodulatory agents, and allogeneic stem cell transplantation,[5] aiming to ameliorate symptoms, delay disease progression, and potentially achieve cure in eligible individuals.

CASE REPORT

A 74-year-old male presented with severe headache, giddiness, blurred vision, and seizures, escalating to hypertension and gum bleeding. In view of the presenting symptoms, magnetic resonance imaging was performed, revealing benign pre-mesencephalic and prepontine subarachnoid hemorrhage (World Federation of Neurosurgical Societies grade 1). Complete blood count showed low counts of hemoglobin: 6.5 g/dL, red blood cell: $2.3 \times 10^6/\mu L$, platelets: $69 \times 10^3/\mu L$, and white blood cell: $3.27 \times 10^3/\mu L$. Ultrasound revealed mildly raised renal echotexture. Immunophenotyping using BC Navios EX identified 7.5% of viable cells as abnormal myeloid blasts, expressing moderate CD33, HLA-DR, CD34, CD123, CD117, CD56, and myeloperoxidase, with negative lineage-specific markers.

The bone marrow biopsy revealed cellularity of over 20%, indicating hypocellularity and dyspoiesis with increased megakaryocytes, left-shifted myeloid maturation, 15–18% CD34-positive blasts, and Grade-2 myelofibrosis. Moreover, initial workup showed 3% blasts on peripheral smear. Bone marrow aspiration revealed 8–12% myeloid blasts. These findings suggested a myelodysplastic neoplasm with increased blasts-2.

Cytogenetic analysis of bone marrow aspirates identified a complex karyotype with near-tetraploidy: 44~52,XY,t(1;3)(q42;q21),del(5)(q15),-12,+19,del(20)(q11.2q13.3),add(21)(q22),+1~6mar [cp16]/79~92,idem,+X,+Y,+1,+2,+3,+4,+4,+5,+5,+6,+7,+8,+9,+10,+11,+12,+12,+13,+14,+14,+15,+15,+16,+17,+18,+19[cp4] [Figure 1].

Fluorescence *in situ* hybridization confirmed 5q and 20q deletions and trisomy 8 [Figure 2]. Next-generation sequencing (NGS) targeting key genes revealed pathogenic TP53 mutations: c.569 (p.Pro190LeufsTer57) deletion and c.464C>A (p.Thr155Asn) missense mutation, indicating a poor prognosis.

The patient was counseled for treatment with hypomethylating agents but was lost to follow-up.

DISCUSSION

The mildly raised renal echotexture suggests underlying renal pathology, potentially linked to MDS-associated immune dysregulation, predisposing to conditions like tubulointerstitial nephritis.[6] MDS is associated with aberrant cytokine signaling and dysfunctional immune cells, leading to autoimmune reactions targeting renal tissues.[7] While subarachnoid hemorrhage is not directly correlated with MDS, thrombocytopenia-related bleeding diathesis may contribute to such hemorrhagic events.

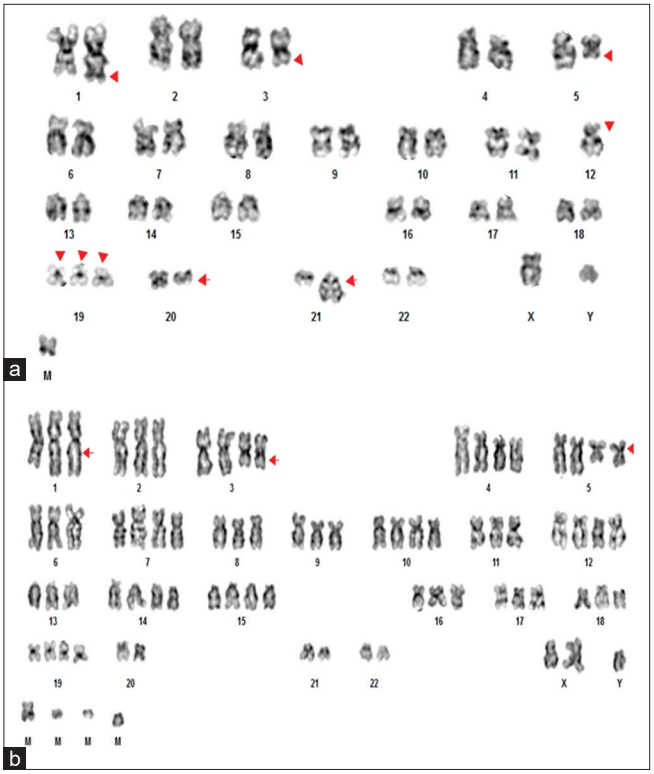

Figure 1: (a) Karyotype showing 47,XY,t(1;3)(q42;q21),del(5)(q15),-12,+19,del(20)(q11.2q13.3),add(21)(q22),+mar (red arrows) (b) Karyotype showing 79,XY,+X,t(1;3)(q42;q21)x2,+1,+2,+3,+3,+4,+4,del(5)(q15)x2,+5,+5,+6,+7,+7,+8,+9,+10,+10,+11,+12,+12,+13,+14,+14,+15,+15,+16,+17,+18,+19,+19,+4mar (red arrows).

Bone marrow biopsy and immunophenotyping indicated advanced MDS with blast proliferation and disrupted hematopoiesis reflected in the abnormal immunophenotypic profile and increased CD34-positive blasts. The presence of myelofibrosis further indicates a high disease burden and potential progression to AML.[8]

TP53 mutations identified by NGS are critical, as TP53 is a tumor suppressor gene associated with poor prognosis, therapy resistance, and rapid disease progression in MDS.[9] These mutations contribute to genomic instability, underscoring the poor prognosis.

The complex karyotype, including near-tetraploidy, deletions on chromosomes 5q and 20q, trisomy 8, and translocation between chromosomes 1 and 3, suggests significant genomic instability. Tetraploidy and multiple marker chromosomes indicate aberrant cell division and are common in cancer.[10]

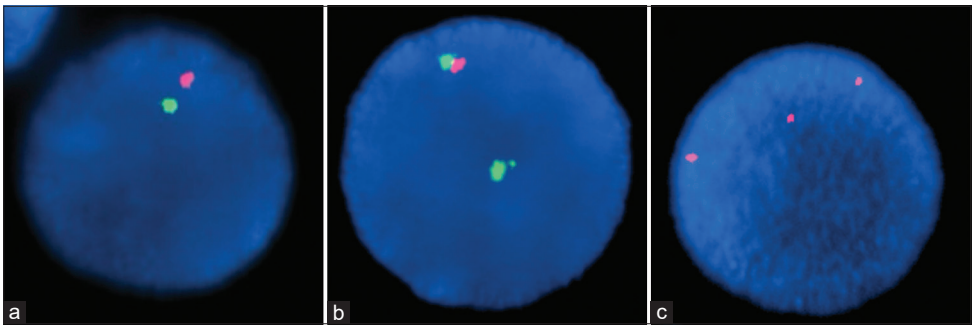

Figure 2: (a) An interphase cell showing one green and one orange signals interpreted as positive for 5q31.2/5q32-33.1 deletion. (b) An interphase cell showing two green and one orange signals interpreted as positive for 20q12-q13.3 deletion. (c) An interphase cell showing three orange signals interpreted as positive for trisomy 8.

Deletions on 5q and 20q suggest loss of tumor suppressor genes, contributing to oncogenesis.[11,12] The novel t(1;3)(q42;q21) translocation may have implications for gene expression and cellular function, warranting further investigation.[13]

CONCLUSION

This case highlights the importance of integrating bone marrow biopsy, immunophenotyping, NGS, and cytogenetic analyses in understanding MDS's genetic complexity. Advanced MDS with significant blast proliferation and TP53 mutations points to severe genomic instability, poor outcomes, and the need for comprehensive management approaches. Recognizing and managing renal involvement and hemorrhagic events in MDS are crucial for holistic patient care, ensuring optimal treatment and monitoring strategies.

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