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Triplication of Chromosome 1q in Myelodysplastic Syndrome: A Case Report Emphasizing Cytogenetic Complexity and Prognostic Implications

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Abstract

Myelodysplastic syndrome (MDS) is defined by inadequate hematopoiesis and a risk of progression to acute myeloid leukemia (AML). This case report describes a 59-year-old individual with MDS who has a complicated karyotype that includes chromosomal 1q triplication (q21q32) and grade 2 myelofibrosis (MF-2). The patient had severe cytopenias, recurring infections, and inflammatory lesions suggestive with pyoderma gangrenosum. A bone marrow biopsy indicated myelofibrosis and dysplastic characteristics. Cytogenetic investigation revealed a triplication of 1q, as well as an inversion of chromosome 9 and a deletion at 3q25, which could indicate genomic instability and a poor prognosis. Next-generation sequencing revealed an *ETV6* gene variation of unknown significance, which had previously been linked to poorer outcomes in MDS patients. The presence of 1q triplication suggests a potential early indication for disease advancement, especially in patients with complex karyotypes. This case highlights the significance of chromosomal and molecular profiling in determining prognosis and guiding treatment regimens in MDS, emphasizing the necessity for targeted treatment to improve patient outcomes.

Keywords: Myelodysplastic syndrome; MDS; acute myeloid leukemia; AML; chromosome 1q triplication; myelofibrosis; cytogenetics

Abbreviations: MDS: myelodysplastic syndrome; AML: acute myeloid leukemia; MF-2: grade 2 myelofibrosis; BL: Burkitt lymphoma; FA: Fanconi anemia; FL: follicular lymphoma; ALL: acute lymphoblastic leukemia; MM: multiple myeloma; MPN: myeloproliferative neoplasms; PMF: primary myelofibrosis; PG: pyoderma gangrenosum; CRP: C-reactive protein; ASI: applied spectral imaging; FISH: fluorescence in situ hybridization; NGS: next generation sequencing; VAF: variant allele frequency; VUS: variant of uncertain significance

Introduction

Myelodysplastic syndrome (MDS) refers to a group of hematologic illnesses marked by dysplastic hematopoiesis and a proclivity to proceed to acute myeloid leukemia (AML) [1]. The three main symptoms of MDS are usually anemia, leukopenia, and thrombocytopenia, which are caused by a disruption in the development and synthesis of red blood cells. MDS patients can range in severity from those with no symptoms to those with serious morbidity and consequences. The advancement of the disease can lead to consequences including myelofibrosis, a condition marked by aberrant fibrotic tissue in the bone marrow affecting normal hematopoiesis.

Triplication of 1q is a rare event in the realm of myeloid neoplasms, with only a few cases recorded in the literature. This triplication is regarded as a secondary karyotypic event in a variety of hematological malignancies, including Burkitt lymphoma (BL), Fanconi anemia (FA), follicular lymphoma (FL), acute lymphoblastic leukemia (ALL), multiple myeloma (MM), MDS, AML, myeloproliferative neoplasms (MPN), and primary myelofibrosis (PMF). The most often affected region is 1q21-q32, which accounts for approximately 33% of cases, with a 71% male preponderance and a median age of 41.5 years. Most instances have complicated karyotypes [2]. The chromosomal region 1q21-q32 region encompasses a gene-rich locus that includes several critical regulators of hematopoietic proliferation, apoptosis, and differentiation, notably *CKS1B*, *MCL1*, *BCL9*, and *IL6R*. Aberrations involving 1q, most commonly segmental gains, amplifications, or triplications have been recurrently documented in high-risk MDS cohorts, where their presence correlates with clonal evolution, disease progression, and inferior clinical outcomes. Studies have suggested that overexpression of *CKS1B* contributes to cell cycle dysregulation via the degradation of p27^Kip1^, while *MCL1* upregulation promotes anti-apoptotic signaling, potentially conferring resistance to hypomethylating agents and conventional chemotherapeutics. Additionally, *BCL9*, a coactivator in the Wnt/β-catenin pathway, may further potentiate leukemic transformation through stemness-related transcriptional activation [3]. While 1q abnormalities are not yet incorporated into standardized prognostic frameworks such as IPSS-R or IPSS-M, their frequent co-occurrence with adverse cytogenetic markers suggests a compounding effect on genomic instability and therapeutic refractoriness. Emerging data advocate for the inclusion of 1q21-q32 aberrations in future stratification models and highlight the need for mechanistic studies that delineate their functional contribution to MDS pathobiology. As our understanding of these lesions deepens, they may serve not only as biomarkers of high-risk disease but also as rational targets for precision therapeutics aimed at disrupting aberrant survival and proliferation pathways in clonal hematopoiesis. We report a case of MDS with a complex karyotype featuring triplication of 1q (q21q32) and grade-2 myelofibrosis (MF-2), possibly linked to inflammation, with further investigation suggesting pyoderma gangrenosum (PG). PG is a rare, ulcerative neutrophilic dermatosis characterized by rapid dermal infiltration of dysregulated neutrophils, resulting in painful, necrotic ulcers with undermined borders. While its precise pathogenesis remains incompletely understood, PG is increasingly recognized as an autoinflammatory condition driven by innate immune dysfunction and aberrant cytokine signaling. In the context of MDS, PG represents a paraneoplastic manifestation linked to the proinflammatory milieu associated with clonal hematopoiesis. This intersection underscores the systemic and inflammatory nature of MDS, where chronic immune activation not only facilitates autoinflammatory manifestations like PG but also contributes to clonal expansion and leukemic progression. In this case, cytogenetic findings further support the presence of advanced disease biology. While conventional karyotyping revealed a complex chromosomal architecture, FISH analysis was negative for recurrent MDS-associated aberrations such as del(5q), -7/del(7q), and trisomy 8. This discordance highlights the locus-specific limitations of targeted FISH probes, which may overlook non-canonical, cryptic, or structurally complex rearrangements often present in high-risk MDS [2]. Together, these findings reinforce the importance of comprehensive cytogenetic assessment in capturing the full genomic and immunologic landscape of MDS.

Case Report

A 59-year-old male with a history of MDS, diagnosed in 2021, presented with fever, chills, and progressive ulcerative lesions on his lower limbs. Initial tests showed anemia (Hb: 9.3 g/dL), leukopenia (WBC: 4.54 x 10^3/μL), thrombocytopenia (platelet count: 51 x 10^3/μL), and elevated CRP (6.8 mg/L). His clinical condition worsened with deteriorating cytopenias (Hb: 8.8 g/dL, WBC: 2.75 x 10^3/μL, platelets: 50 x 10^3/μL) and high CRP (38 mg/L). Examination revealed grade III ulcers with erythema and discharge. Ultrasound indicated hepatomegaly and bilateral renal cortical cysts. A bone marrow biopsy, chromosomal analysis, FISH, and NGS panel were performed for diagnosis.

Bone Marrow Biopsy

The bone marrow sample indicated diffuse myeloid growth and dispersed blasts, which are consistent with myelofibrosis. The biopsy revealed fibromuscular tissue and fragmented cellular marrow gaps in a fibrotic backdrop, together with an increased number of megakaryocytes grouped in loose clusters, indicating dyspoiesis. The myeloid lineage is adequately represented, while the erythroid series is largely suppressed. There is no morphologic evidence of blast excess, and immunohistochemistry reveals no significant increase in CD34+ or CD117+ blasts. CD41 indicates an increase in megakaryocytes, including micromegakaryocytes. Reticulin staining reveals grade-2 myelofibrosis (MF-2), which is consistent with myelofibrosis in the context of a recognized myelodysplastic syndrome. The findings point to progressive illness in the context of pre-existing myelodysplastic syndrome.

Cytogenetic Analysis

Cytogenetic studies were performed on bone marrow samples after short-term (24 and/or 48 hour) on unstimulated cultures and GTC banding was performed, the image of metaphases were captured and at least 20 metaphases were analysed using Applied Spectral Imaging (ASI) software, karyotype was described according to the criteria of the International System for Human Cytogenetics Nomenclature (ISCN 2020). The resultant was a complex karyotype interpretated as 46,XY,trp(1)(q21q32),inv(9)(p12q13)c[21]/46,idem,del(3)(q25)[3]. [Figure 1.a] The chromosomal analysis identified a male karyotype with a pericentric inversion of chromosome 9 with breakpoints at p12 and q13 in all metaphases analysed, a deletion on the q arm of chromosome 3 at band 3q25 in 3/25 metaphases, and a triplication of chromosome 1 (between bands q21 and q32) in 25 metaphases. There is no known clinical significance for the polymorphic variant represented by the chromosome 9 inversion. Figure 1.b highlights the G-banded metaphase chromosomes depicting the triplicated region. The cytogenetic results support AML advancement along the myeloid lineage.

FISH Analysis

Interphase FISH was performed on directly harvested 200 nuclei cells using the MDS probe panel, with an Applied Spectral Imaging software and Olympus BX51 fluorescence microscope. The probes utilised were MetaSystems XL 5q31/5q33, XL del(7)(q22q31),XL del(20q) plus, XL TP53/17cen and XCE 8 orange. However, no abnormalities were detected and the results were negative.

Sequential FISH was performed on G-banded metaphases using MetaSystem XL CDKN2C/CKS1B locus specific probe to detect the amplification of the long arm of chromosome 1, the chromosomal breakpoint region being q21q32 (Figure 1.c). The FISH on metaphase confirmed the triplication of this region. FISH was carried out according to the manufacturer's instructions, with slight modification.

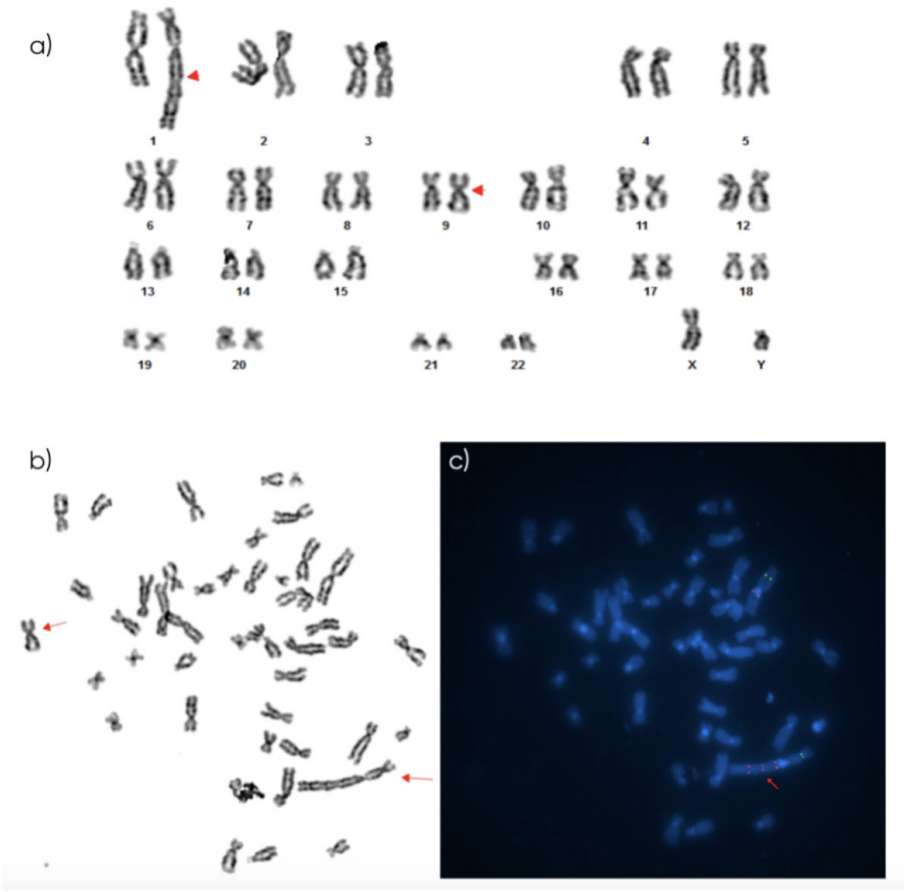

Figure 1: Cytogenetic Findings a) Karyotype showing 46,XY,trp(1)(q21q32),inv(9)(p12q13); b) G-banded metaphase; c) Sequential FISH image showing triplication of 1q (q21-q32) with three distinct orange signals, indicating the triplication of the 1q arm

Next-Generation Sequencing (NGS)

The NGS analysis revealed a variant of uncertain clinical significance (VUS) in the *ETV6* gene. With a variant allele frequency (VAF) of 39.26% in exon 6, the particular variation, c.1103T>G (p.Phe368Cys), was discovered and has been classified as tier 3. No clinically significant mutations or fusions were discovered in other genes. The *ETV6* variant, which is found on chromosome 12, is classified as VUS, although its clinical implications are unknown.

Treatment

Initially, the patient was treated with intravenous antibiotics (Meropenem, Targocid, and Voriconazole) for infection, with additional antibiotics added later (Cefepime and Tazobactam). Dexamethasone and cyclosporine were prescribed due to the clinical suspicion of pyoderma gangrenosum. Supportive therapies, including blood transfusions, pain control, and wound care, were provided. Azacitidine therapy was planned for MDS progression. Topical antibiotics were used regularly, and hematologic parameters were closely monitored.

Discussion

Triplication of chromosome 1q is a rare cytogenetic anomaly found in myeloid neoplasms, such as MDS, and has been linked to a variety of hematologic malignancies, including FA, MM, and AML. Table 1 depicts the reported cases in literature with this anomaly in MDS. To the best of our knowledge, this is the first documented case from India detailing the clinical characteriza-

tion of MDS with triplication of chromosome 1q, highlighting its potential role in disease progression; our findings are consistent with international reports but underscore its relevance within the Indian clinical context. Several studies have shown that 1q triplication is most usually associated with a complex karyotype and is frequently associated with a poor prognosis. [2] In our study, triplication of 1q (q21q32) was seen in 25 metaphases, indicating that it could be a primary or secondary cytogenetic alteration in MDS, potentially impacting progression to AML. The q21-q32 region is frequently impacted, containing genes that may promote tumor development and adversely influence patient outcomes. [1]

Table 1: Summary of triplication 1q (q21q32) in MDS cases reported in literature

Case No.	Patient, age /sex	Diagnosis	Triplication region	Another chromosomal abnormalities	Technique Employed	References
1	52Y/M	MDS	trp(1)(q21q32) [40]	Trisomy 8 observed in 20% of metaphases	Karyotyping	Papenhausen PR et al
2	51Y/M	MDS (RA)	trp(1)(q21q32) [2]	Dup(1)(q21q32)×2[5], dup(1)(q21q32),trp(1)(q21q32)[2]	Karyotyping followed by CGH	Choi JR et al
3	38Y/M	FA → MDS	trp(1)(q12-21q31-q32)	Two markers: add(11)(p15) and add(21)(q22), with extra material from chromosome 3	Karyotyping	Ferro MT et al
4	55Y/F	MDS	trp(1)(q21q32)[21]	tri(1)(q21q32),+8[19]	Karyotyping followed by FISH	Cho HS et al
5	64Y/M	Refractory Cytopenia with MDS	trp(1)(q21q32)[20]	No additional chromosomal changes detected	Karyotyping followed by aCGH	Ha JS and Choi MS
6	66Y/M	MDS	trp(1)(q21q32)[20]	add(3)(p25)[20]	Karyotyping followed by FISH	Nakagawa M et al
7	58Y/F	MDS	trp(1)(q21q32)[20]	No additional chromosomal changes detected	Karyotyping followed by FISH	Nakagawa M et al
8	55Y/M	MDS (RAEB), transformed from ET	trp(1)(q21q32)[16]	dup(1)(q21q32)[4]	Karyotyping	Knuutila S et al
9	ND	MDS	trp(1)(q21q32)	add(3)(q26),add(19)(p13)	Karyotyping followed by FISH	Ashok V et al
10	31Y/M	FA → MDS	trp(1)(q21q32) in all metaphases	del(5)(q22q35) in 50% of the metaphases	Karyotyping followed by FISH	Rajendra N et al
11	59Y/M	MDS	trp(1)(q21q32) [25]	inv(9)(p12q13)[26], del(3)(q25)[3], dup(1)(q21q32)[1]	Karyotyping,FISH and NGS	Present Case

Abbreviations: M, male; F, female; MDS, myelodysplastic syndrome; RA, refractory anemia; RAEB, refractory anemia with excess blasts; FA, Fancomi Anemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; FA, Fanconi anemia; ET, essential thrombocythaemia; FISH, Fluorescence in situ hybridization; CGH, comparative genome hybridization; aCGH, array comparative genome hybridization; NGS, next generation sequencing; ND, not described.

The presence of MF-2 in the bone marrow biopsy, together with triplication 1q, indicates advanced-stage MDS. Myelofibrosis in MDS is frequently accompanied with inflammatory cytokine production, which accelerates disease development by establishing a pro-inflammatory bone marrow microenvironment. Inflammation is critical in the dysregulation of hematopoiesis in MDS, resulting in poor differentiation and proliferation of hematopoietic stem cells (HSCs) [3] and contributing to consequences including pyoderma gangrenosum, which was clinically suspected in this case. This inflammation-driven deregulation

of hematopoiesis could explain the patient's development to AML. Cytogenetic findings, including the inversion of chromosome 9 and deletion on 3q, along with triplication 1q, support the potential progression toward AML [4]. Chromosome 9 inversion is a common polymorphic variant without known pathogenic significance, but the deletion of 3q25, reported in some hematologic disorders, suggests genomic instability and a poor prognosis. [5] Moreover, while the ETV6 gene mutation found in this case is classified as a VUS, mutations in *ETV6* are found in <5% MDS cases and known to correlate with worse outcomes. *ETV6* is a hematopoietic transcriptional repressor critical for megakaryocyte differentiation and platelet production. Mutations or deletions in *ETV6* have been associated with MDS, contributing to thrombocytopenia through impaired megakaryopoiesis and are often correlated with poor prognosis and genomic instability. [6] Genomic amplification of the 1q21-q32 results in overexpression of key oncogenic drivers, notably *MCL1*, *CKS1B*, and *BCL9*, which collectively contribute to a proliferative, anti-apoptotic phenotype. *MCL1*, an anti-apoptotic BCL-2 family member, is frequently amplified in hematologic malignancies and has been mechanistically linked to resistance against hypomethylating agents (HMAs) such as azacitidine and decitabine through impaired mitochondrial priming and evasion of apoptosis. Similarly, *CKS1B* amplification promotes accelerated cell cycle progression via degradation of p27^Kip1^ and has been associated with inferior survival and reduced treatment responsiveness in myeloid neoplasms. Clinical studies have demonstrated that patients with 1q gains exhibit diminished response rates to HMAs, rapid clonal evolution, and shorter overall survival, particularly when occurring alongside complex karyotypes [7]. These findings underscore the need for risk-adapted therapeutic strategies, including early allogeneic hematopoietic stem cell transplantation or enrollment in trials targeting *MCL1* or other 1q-driven pathways, to overcome the intrinsic chemoresistance conferred by this cytogenetic lesion. Though rare, triplication of 1q arm in MDS may indicate early disease progression, particularly in complex karyotypes. 1q abnormalities are associated with poorer outcomes and a higher risk of progression to AML. This underscores the importance of chromosomal profiling in MDS prognosis and treatment planning. Further research is needed to explore its clinical implications.

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