Myelodysplastic syndrome with cryptic 5q deletions in young male patients showing sustained response to lenalidomide

The 5q syndrome, or myelodysplastic syndrome with isolated 5q deletion (del(5q) MDS), is a distinct MDS subtype characterized by partial deletion of chromosome 5q, typically involving regions 5q31-33.[1] It is the only MDS subtype defined by a specific cytogenetic abnormality, and typically presents with macrocytic anemia, characteristic megakaryocytes, low blast counts, and a relatively low risk of acute myeloid leukemia (AML) progression.[2] del(5q) MDS primarily affects elderly women, with a 7:3 female-to-male ratio in patients over 60.[3] Among the key genes involved, *RPS14* (ribosomal protein S14), located at 5q33.1, and *CSNK1A1*, located at 5q32 contribute to the disease through their involvement in ribosome biogenesis and function.[4]

Here, we report two young male patients diagnosed with del(5q) MDS linked to cryptic deletions involving different genomic regions: *RPS14* in one case and *CSNK1A1* in the other. These deletions were overlooked by conventional karyotyping and diagnosed through fluorescent *in situ* hybridization (FISH) and single nucleotide polymorphism (SNP) array analysis. Both patients showed sustained response to lenalidomide. French ethical rules were respected and the patients provided written informed consent.

Case 1

A 40-year-old male with no prior medical history was evaluated in October 2021 for isolated macrocytic, non-regenerative anemia (hemoglobin [Hb] 8.7 g/dL; mean corpuscular volume 112 fL), with preserved white blood cells and platelets. Initial investigations excluded secondary or inherited causes. The patient reported decreased endurance and mild exertional dyspnoea. A bone marrow (BM) aspirate revealed mild dysplastic features in the myeloid series but was insufficient (<10%) to establish a diagnosis of MDS. Cytogenetics suggested a potential deletion at 5q31 (*Online Supplementary Figure S1*), but FISH (Cytocell5q31.2/5p15.3) for *EGR1* was negative, and a myeloid panel next-generation sequencing (NGS) (NextSeq550, Illumina) showed no mutations. Imaging showed mild splenomegaly. A subsequent BM biopsy indicated hypoplastic marrow with dysplasia across all three myeloid lineages, without blast excess, and grade 1 marrow fibrosis, supporting a low-risk MDS diagnosis. A few megakaryocytes had large monolobulated nuclei with dense chromatin.

Treatment with the erythropoiesis-stimulating agent (ESA) epoetin ζ (60,000 IU/week) was initiated in January 2022 but did not elicit an erythroid response, prompting re-evaluation. In mid-February, repeated BM and karyotype analyses confirmed a small 5q31 deletion on 21 metaphases. SNP array analysis identified a 9.3 Mb deletion at 5q32–33.2, including *RPS14* and *MIR145* but neither *EGR1* or *MIR146a* (*Online Supplementary Figure S1*), supporting a diagnosis of low-blast MDS with isolated del(5q) and an IPSS-R score of 3.5.

Deletion of the RPS14 gene was confirmed using a specific FISH probe (XL 5q31/5q33/5p15 deletion probe, Metasystems) that targets this gene (*Online Supplementary Figure S1*).

Lenalidomide was initiated at 10 mg daily for 21 days per 4-week cycle in June 2022, and ESA treatment was pursued (epoietin ζ 60,000 IU weekly).[6]

This combination raised Hb from 9 to over 11 g/dL within 1 month. BM reassessment confirmed MDS under treatment, with persistent trilineage dysplasia, no blast excess, complete cytogenetic remission and no constitutional *RPS14* deletion (excluded via SNP array of skin fibroblast DNA).

With Hb normalized at 13.2 g/dL, treatment was paused after two cycles due to the patient's wish for paternity. Macrocytic anemia recurred in January 2023 (Hb 11 g/dL), prompting lenalidomide reinitiation without ESA, with Hb rising to 13 g/dL. After 26 months, the patient remained asymptomatic. In January 2025, marrow examination showed mild dysgranulopoiesis (<10%), no blast excess, no dyserythropoiesis or dysmegakaryopoiesis, cytogenetic remission on 20 metaphases and 6% *RPS14* loss by FISH.

Case 2

In 2013, a 25-year-old patient presented with progressive macrocytic anemia (Hb 9.5 g/dL, mean corpuscular volume 114 fL), with no personal or family history of hematologic disorders, malignancy, or chronic disease. Common causes of macrocytosis were excluded. Renal function was normal. Persistent unexplained anemia prompted further evaluation. A BM biopsy without cytogenetic sampling, performed in 2014, revealed megakaryocytic dysplasia without fibrosis or blast excess. No signs of paroxysmal nocturnal hemoglobinuria were found. As the anemia was well-tolerated and undiagnosed, the patient was monitored until 2016.

In 2016, due to persistent anemia and macrocytosis, the patient was referred to our center and BM aspiration was repeated. The results revealed multilineage dysplasia with dyserythropoiesis and dysmegakaryopoiesis without blast excess. Although the karyotype appeared normal, a suspected 5q microdeletion (micro del(5q) was noted in a minority (N=3/20) of metaphases (*Online Supplementary Figure S2*). Sequencing using a NGS myeloid gene panel revealed a minute *DNMT3A*- mutated clone (variant allele frequency [VAF] 1%) and a heterozygous variant in the *TERT* gene on

exon 15 (VAF 55%), the latter considered a SNP.
Additional investigations (telomere length, constitutional karyotype, fibroblast mitomycin C sensitivity) ruled out Fanconi anemia and Diamond-Blackfan anemia. FISH analysis using a 5q32 break-apart probe for *PDGFRB* (XL 5q32 PDGFRB BA, Metasystems) revealed the loss of one copy of *CSNK1A1* (*Online Supplementary Figure S2*) in the *PDGFRB* gene region.
A review of the previous karyotype raised the same microdeletion suspicion. NGS analysis revealed persistence of the *TERT* mutation and no detection of the *DNMT3A* mutation. A diagnosis of MDS with a low blast count and isolated del(5q) was made.
Treatment with epoietin α (80,000 IU weekly) was started in early 2018, but produced no response after 12 weeks. Low-dose lenalidomide (5 mg/day, 3 weeks per month) was then started to limit cumulative exposure in this young patient, leading to Hb normalization after two cycles. As Hb reached 14 g/dL, the dose was tapered in September 2018 to 5 mg every 2 days and further to twice weekly in August 2019. Treatment was interrupted for 5 months in 2024 due to paternity plans, during which Hb fell to 9 g/dL, but normalized again after resuming lenalidomide at 5 mg/day. As of February 2025, the patient remained on therapy, with a sustained response for over 83 months despite persistent dysplasia. Of note, complete cytogenetic response was never achieved, 30% to 45% of metaphases on the various marrow aspirates performed over time showing persistence of the micro del(5q), confirmed by FISH analysis.
These two cases highlight a rare clinical presentation of MDS with isolated del(5q) MDS in young male patients, diverging from the typical demographic profile, which primarily involves elderly women. Importantly, although both patients shared the same clinical syndrome and showed robust, sustained responses to lenalidomide, their underlying genetic deletions targeted different critical regions of chromosome 5q - with distinct biological implications. Patient 1 harbored a deletion encompassing *RPS14* at 5q33.1, a gene pivotal for ribosome biogenesis and erythropoiesis along with *UBE2D2* and *CTNNA1*.[4,6] Haploinsufficiency of *RPS14* is well recognized as a central driver of macrocytic anemia in classical 5q syndrome due to its role in ribosomal stress and p53 activation. Conversely, patient 2 had a deletion involving *CSNK1A1* at 5q32, a gene implicated in regulating β-catenin signaling and hematopoietic stem cell self-renewal.[7,8] Loss of *CSNK1A1* disrupts Wnt signaling pathways and contributes to stem cell expansion and ineffective hematopoiesis, potentially leading to different patterns of dysplasia or clinical progression. Persistence of macrocytosis despite an intact *RPS14* gene in patient 2 suggests that other genes, particularly *CSNK1A1*, may contribute to the erythroid phenotype, highlighting the biological and clinical heterogeneity of del(5q) MDS.
These cryptic deletions highlight the need for complementary testing beyond standard cytogenetics. Moreover, the difference in the deleted loci may also explain nuances in treatment response dynamics and long-term prognosis. While both patients achieved durable hematologic responses with lenalidomide, further follow-up is necessary to determine whether the deleted region influences the likelihood of clonal evolution, treatment resistance, or transformation. Ultimately, these cases illustrate the need for precision diagnostics in MDS and raise the possibility that individualized genomic characterization might refine prognostic assessments and therapeutic strategies even within so-called “isolated del(5q)” cases.
SNP arrays are well established for detecting copy number variations via high-throughput methods. A 2011 study showed that in 142 patients with del(5q) confirmed by metaphase cytogenetics, SNP arrays revealed cryptic lesions in 52% of cases.[7] Nonetheless, FISH remains essential for rapid detection of specific chromosomal abnormalities using targeted probes. Together, SNP array and FISH offer complementary insights into genetic architecture in both clinical and research settings. Detection of isolated del(5q) in young male patients remains exceptional. In younger patients, MDS often presents with more aggressive features, including an increased risk of progression to AML.[8] To our knowledge, only three cases of micro del (5q) have been reported (*Online Supplementary Table S1*), all in females, two occurring at unusually young ages (17 and 52 years), comparable to our two patients.
Both our patients responded well to lenalidomide, and their Hb levels normalized with treatment. We acknowledge the doses of lenalidomide were lower than the approved dose for lenalidomide in MDS with del(5q),[9] but this strategy was intentionally chosen to minimize long-term lenalidomide exposure in young patients, especially as they responded to those lower doses.
To date, no *TP53* mutation, which frequently occurs in MDS patients with isolated del(5q), has been detected in these patients, and they are regularly followed up.[10]
These cases underscore the need for repeated, comprehensive diagnostic assessment in complex MDS presentations. Because abnormalities such as del(5q) may escape standard karyotyping, an integrated approach using conventional cytogenetics, FISH, and SNP arrays is essential to refine diagnosis and guide therapy.

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Data-sharing statement

Data are available upon request to the corresponding author.

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