INPLASY

Isolated del(5q) with Myeloproliferative Driver Mutations: A Systematic Review of Published Cases and Clinical Implications

INPLASY2025120046

doi: 10.37766/inplasy2025.12.0046

Received: 12 December 2025

Published: 12 December 2025

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ADMINISTRATIVE INFORMATION

Support - No.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2025120046

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 December 2025 and was last updated on 12 December 2025.

INTRODUCTION

Review question / Objective Primary Objective: To systematically identify and synthesize all published cases of adult patients with myeloid neoplasms who harbor both an isolated deletion of chromosome 5q [del(5q)] and a myeloproliferative neoplasm (MPN) driver mutation (JAK2, CALR, or MPL), and to describe their clinical, morphological, cytogenetic, molecular, and therapeutic characteristics.

PICOS Framework:

Population: Adults (≥18 years) diagnosed with myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), or MDS/MPN overlap, with confirmed isolated del(5q) and at least one MPN driver mutation (JAK2, CALR, MPL).

Intervention/Exposure: Clinical presentation, diagnostic features, and treatments received, particularly lenalidomide therapy.

Comparator: Not applicable, as the review concerns descriptive synthesis of case reports and case series.

Outcomes: Hematologic, cytogenetic, and molecular responses; phenotypic patterns; fibrosis progression; and risk of transformation to acute myeloid leukemia (AML).

Rationale Isolated deletion of chromosome 5q [del(5q)] defines a well-recognized subtype of myelodysplastic syndromes (MDS) characterized by macrocytic anemia, distinct megakaryocytic morphology, and high responsiveness to lenalidomide. In contrast, classical myeloproliferative neoplasms (MPNs) are driven by mutations in JAK2, CALR, or MPL, leading to proliferative features such as thrombocytosis, splenomegaly, and bone marrow fibrosis.

Although rare, the coexistence of isolated del(5q) with an MPN driver mutation has been increasingly reported. These cases present with overlapping dysplastic and proliferative features, challenging

the traditional distinction between MDS, MPN, and MDS/MPN overlap syndromes. The biological mechanisms underlying this dual-hit phenotype are unclear but likely involve interactions between ribosomal haploinsufficiency (from del(5q)) and constitutive JAK–STAT pathway activation. Clinically, these patients may exhibit macrocytic anemia alongside thrombocytosis and marrow fibrosis, creating d.

Condition being studied This review focuses on a rare subgroup of myeloid neoplasms in which patients simultaneously harbor an isolated deletion of the long arm of chromosome 5 [del(5q)] and a myeloproliferative neoplasm (MPN) driver mutation, specifically in JAK2, CALR, or MPL. These cases display hybrid features of both myelodysplastic syndromes (MDS) and myeloproliferative neoplasms, including macrocytic anemia, thrombocytosis, megakaryocytic dysplasia, and marrow fibrosis. Because this combination lies at the interface of MDS, MPN, and MDS/MPN overlap syndromes, it represents a diagnostically challenging and biologically ambiguous condition with uncertain prognosis and variable therapeutic responses, particularly to lenalidomide. The condition is not recognized as a distinct WHO/ICC entity, and available evidence is limited to individual case reports and small case series..

METHODS

Search strategy A comprehensive literature search was conducted using PubMed and Google Scholar from database inception to 31 December 2024. The search focused on identifying all published case reports and case series describing adult patients with myeloid neoplasms harboring both isolated deletion of chromosome 5q [del(5q)] and a myeloproliferative neoplasm (MPN) driver mutation (JAK2, CALR, or MPL).

Search terms and Boolean combinations included:

“del(5q)”

“5q deletion”

“chromosome 5q deletion”

“JAK2 V617F”

“CALR mutation”

“MPL mutation”

“myelodysplastic syndrome” OR “MDS”

“myeloproliferative neoplasm” OR “MPN”

“MDS/MPN overlap”

“case report” OR “case series”

Example PubMed search string:
("del(5q)" OR "5q deletion" OR "chromosome 5q") AND ("JAK2" OR "CALR" OR "MPL") AND ("myelodysplastic" OR "myeloproliferative" OR "MDS/MPN") AND ("case report" OR "case series").

Google Scholar was searched using broader text word combinations to ensure maximum sensitivity.

Screening process:

Duplicate records were removed.

Participant or population The review includes adult patients (≥18 years) diagnosed with any of the following myeloid neoplasms:

Myelodysplastic syndromes (MDS)

Myeloproliferative neoplasms (MPN)

MDS/MPN overlap syndromes

Myeloid neoplasms not otherwise classified

Acute myeloid leukemia only if an antecedent del(5q)+MPN-driver phase is clearly documented.

All included patients must have:

Cytogenetically confirmed isolated del(5q) (with or without one additional non–chromosome 7 abnormality), and

At least one MPN driver mutation (JAK2 V617F, CALR, or MPL).

There were no restrictions based on sex, ethnicity, comorbidities, or disease risk classification. Both de novo and secondary myeloid neoplasms were eligible if criteria were met.

Intervention This review does not evaluate a single predefined intervention but describes all treatments reported in the included cases. Interventions of interest include:

Lenalidomide therapy, which is the most frequently reported treatment in this population and a key focus of the review.

Additional therapies described across cases, such as:

Erythropoiesis-stimulating agents

Hydroxyurea or cytoreductive therapy

JAK–STAT inhibitors (e.g., ruxolitinib)

Supportive care

Hypomethylating agents

AML-directed chemotherapy in cases that transformed

Data are extracted on hematologic, cytogenetic, and molecular responses, including JAK2 V617F allele burden changes, and on disease progression (fibrosis and AML transformation).

Comparator Not applicable.

As the evidence base consists exclusively of case reports and case series without control groups, no comparator intervention is used. The review synthesizes descriptive data rather than comparative outcomes.

Study designs to be included The review includes:Case reportsCase seriesOnly peer-reviewed articles providing individual-level clinical, cytogenetic, and molecular information are included.The review excludes:Randomized trialsCohort studies without case-level detailReviews, editorials, and conference abstracts without extractable clinical dataAnimal studiesPediatric cases (<18 years)The review includes:Case reportsCase seriesOnly peer-reviewed articles providing individual-level clinical, cytogenetic, and molecular information are included.The review excludes:Randomized trialsCohort studies without case.

Eligibility criteria Inclusion Criteria:

Population: Adult patients (≥18 years) with myeloid neoplasms, including myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), MDS/MPN overlap syndromes, or acute myeloid leukemia (AML) only if an antecedent del(5q) +MPN-driver phase is documented.

Genetic requirements:

Cytogenetically confirmed isolated del(5q) (with or without one additional non–chromosome 7 abnormality).

Presence of at least one MPN driver mutation: JAK2, CALR, or MPL.

Study types: Peer-reviewed case reports and case series that provide extractable individual-level clinical, cytogenetic, or molecular information.

Language: English-language publications.

Publication type: Full-text available.

Exclusion Criteria:

Pediatric patients (<18 years).

Reports lacking adequate cytogenetic or molecular confirmation of del(5q) or MPN driver mutation.

De novo AML without a documented antecedent del(5q)+MPN-driver phase.

Reviews, editorials, conference abstracts without extractable case-level data.

Non-English publications.

Animal studies or basic science reports.

These criteria ensure inclusion of only clinically and genetically well-defined cases relevant to the research question.

Information sources The following electronic sources were used for systematic identification of eligible reports:

PubMed (MEDLINE): The primary database searched for peer-reviewed case reports and series relevant to del(5q) and MPN driver mutations.

Google Scholar: Utilized to capture grey literature, additional case reports, and articles not indexed in PubMed.

Manual Reference Checking: The reference lists of all included articles were screened to identify additional eligible publications.

Searches were performed from database inception through 31 December 2024, using combinations of terms related to del(5q), JAK2/CALR/MPL mutations, and myeloid neoplasms. Only peer-reviewed, full-text English-language publications were considered. No attempts were made to contact authors or search trial registries due to the nature of the evidence (case reports).

Main outcome(s) The review's primary outcomes include:

Clinical phenotype: Hematologic parameters, presenting symptoms, splenomegaly, and disease classification as reported.

Bone marrow and morphological features: Degree of cellularity, megakaryocytic morphology, dysplasia, and marrow fibrosis grade.

Cytogenetic and molecular findings: Characteristics of the del(5q) abnormality, presence and allele burden of MPN driver mutations (JAK2, CALR, MPL), and additional co-mutations.

Therapeutic response:

Hematologic improvement (HI)

Cytogenetic response (clearance or persistence of del(5q))

Molecular response (changes in JAK2/CALR/MPL allele burden)

Disease progression outcomes:

Development or worsening of marrow fibrosis

Transformation to acute myeloid leukemia (AML)

Treatment intolerance or failure

These outcomes collectively characterize the clinical behavior, treatment response, and prognostic implications of myeloid neoplasms with concurrent isolated del(5q) and MPN driver mutations.

Quality assessment / Risk of bias analysis Because the evidence base consists exclusively of case reports and small case series, traditional quality appraisal tools (e.g., ROBINS-I, Newcastle–Ottawa Scale) are not applicable. Instead, methodological quality and potential bias were assessed qualitatively using criteria adapted for descriptive observational evidence.

The following domains were evaluated for each included study:

Completeness of case description:

Adequacy of clinical, laboratory, bone marrow, cytogenetic, and molecular details.

Clarity in reporting the presence of isolated del(5q) and MPN driver mutation.

Diagnostic validity:

Use of established criteria for MDS, MPN, or MDS/MPN overlap.

Confirmatory cytogenetics (karyotype, FISH) and mutation testing (JAK2/CALR/MPL).

Outcome reporting:

Transparency in reporting hematologic, cytogenetic, and molecular responses.

Documentation of follow-up duration and disease progression (fibrosis, AML).

Reporting bias:

Potential for publication bias given the tendency to report unusual or favo.

Strategy of data synthesis Given the heterogeneity and descriptive nature of the included publications, a narrative (qualitative) synthesis was undertaken.

Data from each case were extracted into structured tables covering clinical features, bone marrow morphology, cytogenetic results, molecular findings, treatments, and outcomes. Variables were summarized using descriptive statistics, including:

Counts and proportions (e.g., number with thrombocytosis, number treated with lenalidomide)

Medians and ranges (e.g., hemoglobin, platelet count, JAK2 allele burden)

Simple categorical summaries (e.g., fibrosis grade, presence/absence of splenomegaly)

Where outcome data were sufficient, patterns were examined in:

Hematologic responses

Cytogenetic clearance of del(5q)

Molecular responses (e.g., JAK2 V617F reduction)

AML transformation

Fibrotic progression

No meta-analysis was performed due to:

Small sample size (24 patients total),

Non-comparative design of included studies,

Heterogeneity in diagnostic criteria, interventions, and.

Subgroup analysis Formal subgroup analysis was not feasible due to the descriptive nature and small number of available cases. However, exploratory qualitative comparisons were planned across clinically relevant categories, including:

Mutation subtype:

JAK2 V617F vs. CALR vs. MPL.

Differences in phenotype, fibrosis, and response to therapy.

Provisional disease classification:

MDS vs. MPN vs. MDS/MPN overlap.

Patterns in cytopenias, thrombocytosis, marrow morphology, and outcomes.

Treatment received:

Lenalidomide vs. other treatments vs. supportive care only.

Variation in hematologic and cytogenetic responses.

Clonal burden:

High vs. low JAK2 allele burden (where available)

Association with proliferative features or AML transformation.

Co-mutations (when reported):

Presence vs. absence of secondary mutations (e.g., ASXL1, DNMT3A).

Potential impact on progression risk.

These subgroup assessments are exploratory and qualitative only, acknowledging the limited depth and variability in reporting across cases.

Sensitivity analysis A formal sensitivity analysis could not be performed due to the absence of comparative data and the reliance on single-patient case reports. However, robustness of findings was explored by:

Re-evaluating conclusions after excluding incomplete or poorly documented cases, focusing only on those with full cytogenetic and molecular data.

Assessing whether specific high-risk cases (e.g., those with additional mutations or advanced fibrosis) disproportionately influenced outcome trends, such as AML transformation.

Comparing findings across publication years to evaluate whether evolving diagnostic methods influenced the reported phenotype.

Overall conclusions were examined for consistency when emphasizing higher-quality, more detailed case descriptions. No substantial changes in thematic findings were anticipated due to the uniformly descriptive nature of the dataset.

Country(ies) involved Qatar.

Keywords Myeloid neoplasms; del(5q); JAK2 V617F; CALR; MPL; MDS/MPN overlap.

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