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Review Article

Clonal Haematopoiesis and Progression to Myelodysplastic Syndrome in Patients with Unexplained Cytopenias

Lorenzo Gallo^{1*}, Marek Tamme² and Katarina Hrabovsky³

¹Department of Haematopathology, University of Turin, Turin, Italy

²Department of Cardio-Oncology, University of Tartu, Tartu, Estonia

³Department of Cancer Epidemiology, Comenius University, Bratislava, Slovakia

*Address for Correspondence: Lorenzo Gallo, Department of Haematopathology, University of Turin, Turin, Italy

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Summary

A patient with unexplained cytopenia and no dysplasia used to be told there was nothing to find. Targeted sequencing now identifies a clone in a substantial minority of them, and the clone changes the answer: myeloid neoplasm becomes fourteen times more likely, and which mutations are present predicts how likely.

Objectives: To review the published evidence on clonal haematopoiesis in patients investigated for unexplained cytopenia: how often a clone is found, what proportion progress to a myeloid neoplasm, over what timescale, which mutation patterns carry the risk, and what follows for surveillance.

Material and Methods: Narrative review of prospective cohorts, sequencing studies, comparative analyses and consensus definitions indexed in PubMed and the major haematology journals. Studies were eligible if they reported the prevalence, mutation profile or outcome of clonal haematopoiesis in a defined population investigated for cytopenia of unknown cause. No new patient data were generated and no patients were recruited; every estimate quoted is one published by the original investigators.

Results: Among patients investigated for unexplained cytopenia, 8 to 36 per cent are found to carry a clone at a variant allele frequency of 2 per cent or above without diagnostic dysplasia, meeting the definition of clonal cytopenia of undetermined significance. Myeloid neoplasm is approximately fourteen times more likely in that group than in patients whose cytopenia is non-clonal. In a prospective cohort of 400 such patients, 20 per cent developed a myeloid neoplasm within ten years, predominantly myelodysplastic syndrome (46 per cent of progressions) and overlap syndromes (32 per cent), and 84 per cent of all progressions occurred within the first five years. The number of mutated genes was the strongest single predictor. Spliceosome mutations, RUNX1 and JAK2 predict progression specifically, as does the combination of a DNA methylation gene mutation with at least one other lesion.

Conclusion: Sequencing converts an undiagnosable presentation into a risk-stratified one, and the stratification is meaningful enough to guide surveillance interval. What it does not yet do is identify anyone who benefits from treatment before progression occurs.

Abbreviations: CCUS – Clonal Cytopenia of Undetermined Significance, ICUS – Idiopathic Cytopenia of Undetermined Significance, CUS – Cytopenia of Undetermined Significance, CHIP – Clonal Haematopoiesis of Indeterminate Potential, CHRS – Clonal Haematopoiesis Risk Score, MDS – Myelodysplastic Syndrome, MPN – Myeloproliferative Neoplasm, AML – Acute Myeloid Leukaemia, VAF – Variant Allele Frequency, NGS – Next-Generation Sequencing, PPV – Positive Predictive Value.

Keywords: *Clonal Cytopenia of Undetermined Significance; Clonal Haematopoiesis; Myelodysplastic Syndrome; Somatic Mutation; Risk Prediction*

Introduction

Persistent cytopenia without an identifiable cause is a common reason for haematological referral, particularly in older patients. Where myeloid neoplasms and reactive or secondary causes have both been excluded, the presentation was historically labelled idiopathic cytopenia of undetermined significance and followed without further characterisation [1,2].

Sequencing changed that. Myeloid malignancies are now understood to be preceded by a long preclinical phase during which somatic mutations accumulate in haematopoietic stem cells [3,4], and the same mutations found in overt myelodysplastic syndrome can be detected

years earlier in people who appear well [5,6]. Where a clone is present without cytopenia, the term clonal haematopoiesis of indeterminate potential applies [5,7].

The intersection of the two, persistent unexplained cytopenia together with a demonstrable clone and without diagnostic dysplasia, is defined as clonal cytopenia of undetermined significance [1,8]. It is diagnosed by variant allele frequency of 2 per cent or above in one or more myeloid-associated genes, with dysplasia below 10 per cent and no MDS-defining cytogenetic abnormality [8,9].

This review sets out how often the clone is found, what proportion progress, over what interval, which mutation patterns carry the risk, and what should follow clinically.

Material and Methods

Search strategy: PubMed and the archives of the major haematology journals were searched for studies of clonal haematopoiesis in cytopenic patients. Search terms combined clonal cytopenia of undetermined significance, idiopathic cytopenia, clonal haematopoiesis and unexplained cytopenia with progression, myelodysplastic syndrome, somatic mutation, variant allele frequency and risk score. Reference lists of retrieved cohorts and consensus documents were screened by hand.

Eligibility: Studies were included if they reported prevalence, mutation profile, progression rate or outcome in a defined population investigated for cytopenia of unknown cause, or established the diagnostic definitions used. Studies of clonal haematopoiesis in non-cytopenic populations are cited where they establish the biological background and are identified as such.

Data extraction and handling: Design, cohort size, sequencing panel, variant allele frequency threshold, dysplasia criteria and reported progression estimates were extracted as published. The variant allele frequency threshold is stated alongside every prevalence figure, because prevalence scales directly with assay sensitivity and the reported range reflects that as much as it reflects population differences. No pooling or re-analysis was performed and no patient-level data were obtained. Figures 1 to 4 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

How often a clone is found: Across studies of patients investigated for unexplained cytopenia, 8 to 36 per cent were identified as having clonal cytopenia of undetermined significance (Figure 4) [8,9]. That range is wide because it depends on the sequencing panel applied and the variant allele frequency threshold accepted, both of which have moved as technology has improved [8,10].

The clinical significance of finding a clone is substantial. Myeloid neoplasm is approximately fourteen times more likely to develop in

patients with clonal cytopenia than in those whose cytopenia is non-clonal (Figure 3) [8,11]. Clonality, rather than the cytopenia itself, is what separates the two groups prognostically [1,8].

Mutations recur in a recognisable set of pathways: DNA methylation (DNMT3A, TET2, IDH1 and IDH2), chromatin modification (ASXL1, KDM6A, PHF6), RNA splicing (SF3B1, SRSF2, U2AF1, ZRSR2), transcription (RUNX1, BCOR), signalling (NRAS, KRAS, KIT, CBL) and DNA damage response (TP53, ATM) [8]. These are the same genes recurrently mutated in overt myelodysplastic syndrome [3,4].

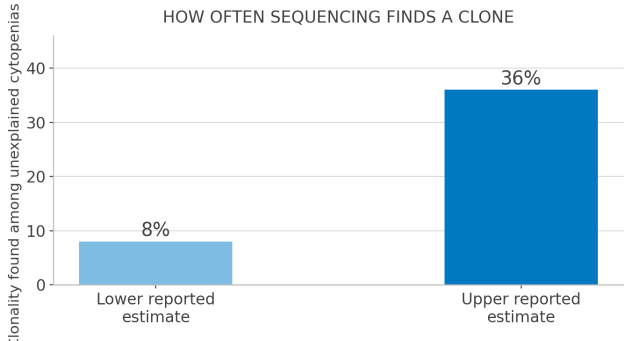


Figure 4: Reported prevalence of clonality among patients investigated for unexplained cytopenia [8,9]

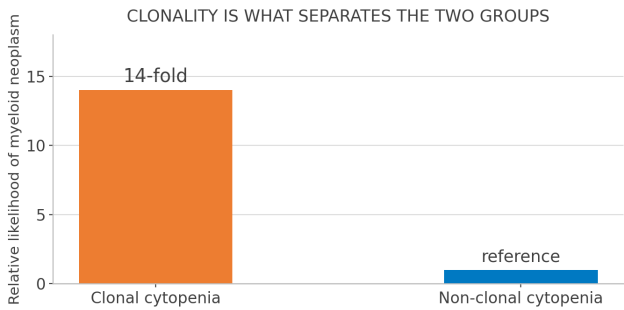


Figure 3: Relative likelihood of myeloid neoplasm by clonality status [8,11]

What proportion progress, and when: The largest prospective follow-up enrolled 400 patients with clonal cytopenia and reported that 20 per cent developed a myeloid neoplasm within ten years. Among those who progressed, 46 per cent developed myelodysplastic syndrome and 32 per cent an overlap syndrome of myelodysplastic and myeloproliferative features (Figure 1) [12].

The timing is clinically important. Eighty-four per cent of all progressions occurred within the first five years after diagnosis (Figure 2) [12], which means surveillance intensity should be front-loaded and can reasonably be relaxed in patients who remain stable beyond that point. In the progression analysis, the number of mutated genes proved the strongest single predictor [12].

An earlier prospective analysis reported a progression risk of approximately 20 per cent per year for patients carrying specific

high-risk mutation patterns, which is an order of magnitude above the cohort average and illustrates how much the aggregate figure conceals [9,13].

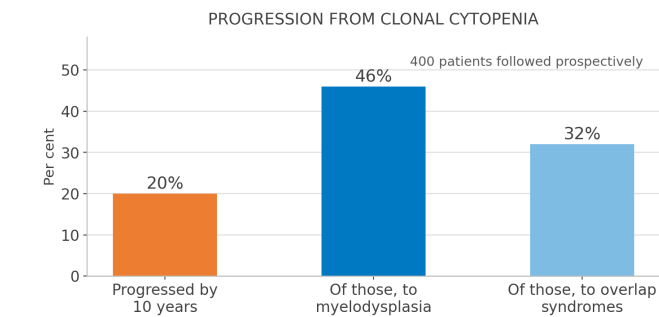


Figure 1: Progression to myeloid neoplasm and its distribution by diagnosis in 400 patients [12]

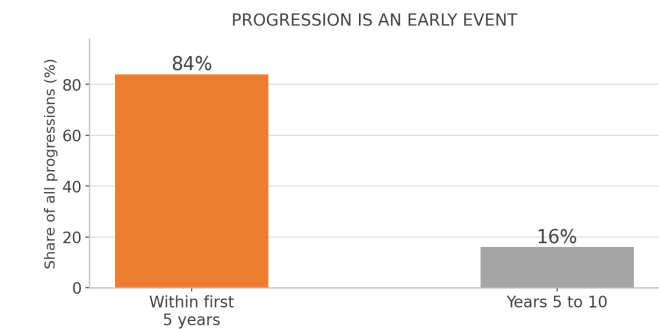


Figure 2: Timing of progression relative to diagnosis [12]

Study	n	Design	Principal reported finding
Malcovati et al. 2017 [9]	—	Prospective	Mutation patterns predictive of myelodysplasia
Shanmugam et al. 2019 [14]	—	Sequencing	Spliceosome mutations carry the strongest signal
Galli et al. 2021 [13]	—	Prospective	Mutation pattern refines progression estimate
Cargo et al. 2023 [10]	Cohort	Prospective	Mutation profile predicts cytopenias and survival
Weeks et al. 2023 [15]	—	Model	Clonal haematopoiesis risk score developed
Cargo et al. 2025 [12]	400	Prospective	20% progression at ten years; 84% within five

Table 1: Principal studies reviewed, with design and the finding as reported by the original investigators

Which mutations carry the risk: Not all clones behave alike, and the distinction is well characterised. Mutations in the spliceosome factors SF3B1, SRSF2, U2AF1 and ZRSR2 are specifically

predictive of myelodysplastic syndrome, as are RUNX1 and JAK2 [9,13,14]. Where DNMT3A, TET2 or ASXL1 mutation occurs in combination with at least one other lesion, that pattern is also predictive [9,13].

Two quantitative features raise the positive predictive value further. A higher variant allele frequency, at 10 or 20 per cent and above, and the presence of two or more mutated genes each increase the likelihood that a myeloid neoplasm is present or will develop [9,12]. The number of mutated genes was the strongest predictor in the largest prospective analysis [12].

These observations have been formalised. A clonal haematopoiesis risk score provides a framework for estimating progression risk from the mutation profile, and it separates patients whose annual risk is negligible from those in whom it approaches that of low-risk myelodysplastic syndrome [15,16].

Feature	Effect on risk	Source
Spliceosome mutation	Specifically predictive of MDS	Prospective cohorts [9,13,14]
RUNX1 or JAK2 mutation	Predictive of MDS	Prospective cohort [9]
Methylation gene plus one other	Predictive of MDS	Prospective cohorts [9,13]
Two or more mutated genes	Strongest single predictor	400-patient cohort [12]
Variant allele frequency ≥10%	Raises positive predictive value	Multiple series [9,12]
Isolated DNMT3A or TET2	Lower risk	Prospective cohorts [9,13]

Table 2: Mutation features and their reported effect on progression risk

Where the boundary with myelodysplasia sits: The distinction between clonal cytopenia and low-risk myelodysplastic syndrome rests on morphological dysplasia and cytogenetics, both of which are less reproducible than the sequencing that identifies the clone [1,2]. Direct comparison found that patients with clonal cytopenia carrying certain clinical or genetic features had outcomes resembling lower-risk myelodysplastic syndrome, and the investigators suggested they should be regarded and treated accordingly [17].

Supporting evidence comes from other modalities. Flow cytometric assessment of CD13 and HLA-DR expression on myeloblasts predicts progression [18], and aberrant DNA methylation is detectable in clonal cytopenia as well as in overt myelodysplasia, consistent with a continuous rather than a categorical relationship [19]. In patients aged 80 and above, overall survival with unexplained cytopenia and specific mutations did not differ from that of patients with a diagnosed myeloid neoplasm [20].

What happens after progression: Once myelodysplastic syndrome is diagnosed, prognosis is assigned by established scoring systems

based on blast percentage, cytogenetics and depth of cytopenia [22], and more recently by molecular scores incorporating the same mutations that defined the preceding clonal phase [23]. A patient therefore moves from a framework where mutations predict whether disease will develop to one where the same mutations predict how it will behave.

Current classifications have absorbed the precursor states formally, with both the World Health Organization and the consensus classification recognising clonal cytopenia as an entity distinct from myelodysplastic syndrome rather than an early form of it [24,25]. Whether that boundary survives is uncertain, given the finding that some patients with clonal cytopenia behave like lower-risk myelodysplasia [17].

Discussion

Sequencing has converted a non-diagnosis into a stratified one. A patient with unexplained cytopenia and no clone has a substantially lower risk than one with a clone, by a factor of roughly fourteen [8,11], and within the clonal group the mutation profile separates a negligible annual risk from one approaching 20 per cent per year [9,12,13].

The timing finding is the most directly actionable. With 84 per cent of progressions occurring within five years [12], surveillance can be concentrated where the events are and relaxed thereafter, which is a concrete change to follow-up scheduling that the data support without requiring any new intervention.

What the risk stratification cannot yet do

Identifying a high-risk patient is useful only if something can be offered to them. At present nothing can. There is no evidence that treating clonal cytopenia before progression alters outcome, and the available data on treatment in this population are limited to a single institution's retrospective experience of patients requiring intervention beyond transfusion [21].

That leaves risk stratification serving surveillance and counselling rather than therapy. Both are worth something, but the gap between prediction and intervention is wider here than in most areas where molecular risk scores have been introduced, and it should be described honestly when the result is discussed with a patient [15,21].

Why the prevalence range is so wide

A reported prevalence of 8 to 36 per cent spans more than fourfold, and most of that is methodological rather than biological [8,9]. Prevalence scales with the number of genes on the panel, with the variant allele frequency threshold accepted, and with the depth of sequencing, none of which is standardised across the studies compared [8,10].

The practical consequence is that a negative result means different things in different laboratories. Reporting the panel composition and the limit of detection alongside the result would allow a clinician to interpret a negative finding, which at present is difficult to do [8,10,15].

Study limitations

The limitations belong to the underlying literature. Cohorts are assembled from patients referred for investigation of cytopenia, so they are selected by referral practice and are not population-representative [10,12]. Sequencing panels and variant allele frequency thresholds differ between studies, which affects both prevalence and the composition of the clonal group [8,9]. The distinction from low-risk myelodysplastic syndrome depends on morphological dysplasia assessment, which carries known interobserver variability [1,17]. Follow-up in most cohorts is shorter than the interval over which progression occurs, so ten-year estimates rest on relatively few completed observations [12]. And progression is diagnosed by the same morphological criteria whose limitations define the entity, which makes the endpoint partly circular [1,2,17].

Two gaps deserve naming. No trial has tested whether any intervention in clonal cytopenia delays or prevents progression, so the risk score guides observation rather than treatment [15,21]. And no study reviewed here reports whether patients identified as low risk can safely be discharged from haematological follow-up, which is the question most often asked in clinic [12,15].

Conclusion

Targeted sequencing identifies a clone in 8 to 36 per cent of patients investigated for unexplained cytopenia, and finding one raises the likelihood of a myeloid neoplasm approximately fourteenfold. Twenty per cent of those patients progress within ten years, most commonly to myelodysplastic syndrome, and 84 per cent of progressions occur within the first five years. The number of mutated genes is the strongest single predictor, with spliceosome, RUNX1 and JAK2 mutations and combinations involving a methylation gene carrying particular weight, while an isolated DNMT3A or TET2 mutation carries less. The stratification is good enough to set a surveillance interval and poor enough to offer nothing else, since no intervention has been shown to alter the trajectory before progression occurs. Reporting the panel and limit of detection alongside a negative result, and concentrating surveillance in the first five years, would both improve current practice without requiring new evidence [8,10,12].

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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