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Cytogenetics in the management of clonal chromosomal abnormalities of undetermined significance and persistent polyclonal B-cell lymphocytosis: Guidelines from the Groupe Francophone de Cytogénétique Hématologique (GFCH)

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ABSTRACT

Acquired clonal chromosomal abnormalities (CAs) are usually considered to be disease-related. However, when a CA of this type is the only abnormality present (and especially in small clones), the clinical significance is unclear. Here, we review the literature on recurrent CAs whose significance is regularly subject to debate. Our objective was to help with their interpretation and develop guidelines for sex chromosome loss, trisomy 15, trisomy 8, deletion 20q and other isolated non-myelodysplastic neoplasm (MDS)-defining CAs. We suggest that non-MDS-defining CAs correspond to clonal hematopoiesis of indeterminate potential (CHIP) in the absence of cytopenia and clonal cytopenia of undetermined significance (CCUS) in the presence of cytopenia. Lastly, we review the literature on persistent polyclonal binucleated B-cell lymphocytosis; although usually benign, this condition may correspond to a premalignant state.

Introduction

A clone is defined as a cell population derived from a single progenitor. In cytogenetics, a clone must have at least two cells with the same aberration (for a chromosome gain or a structural rearrangement) or at least three cells with the same aberration (for the loss of whole chromosome) [1]. The presence of clonal chromosomal abnormalities (CAs) is usually indicative of a malignant or premalignant state. However, some CAs are of uncertain significance and are difficult to interpret [2]. Not all CAs are proven markers of malignancy [3], particularly when they are the sole abnormality in a small clone [4,5] and when the morphological features of a myeloid neoplasm are absent. Here, we discuss several situations in which the significance of clonal CAs remains elusive. Our observations and guidelines are summarized in Table 1.

Recurrent clonal CAs

Sex chromosome loss

Sex chromosome mosaicism is more frequent than autosomal mosaicism [6] and is the largest source of aneuploidy [7]. Loss of sex chromosomes as a sole abnormality has long been considered as an age-related event. Loss of chromosome Y (-Y) is more frequent in the bone marrow (BM) in older men, while -X occurs more frequently in the blood in older females [8].

Age-related -Y was first observed more than 50 years ago and is considered to be a neutral event [9]. However, several studies conducted during the last few decades have shown an association between –Y and a wide range of diseases, including cancer (both hematopoietic and non-hematopoietic), Alzheimer disease, and cardiovascular disease [6]. Moreover, –Y is associated with clonal hematopoiesis (CH; see below) and an elevated risk of all-cause mortality [10]. Loss of Y in aging men is thought to be multifactorial: the risk factors include age, genetic predispositions, prior chromosome Y structural aberrations, and sources of environmental stress (such as smoking and pollution) [6]. The mechanisms underlying -Y's contributions to disease development are not currently understood and have yet to be investigated in detail [11]. It has been shown that chromosome Y not only imparts male characteristics but also serves as a major regulator of gene expression [6]. Sano et al. provided evidence from mouse models and human cohort analyses to show that in men, hematopoietic –Y cells contribute to fibrosis, cardiac dysfunction, and mortality [12].

At the individual level, it can be difficult to determine whether –Y is a disease-associated alteration or just an incidental, age-associated somatic mosaicism. Wong et al. reported a 3.8-fold increase in the risk of developing myelodysplastic neoplasm (MDS) with –Y [13]. Populations with a percentage of –Y cells $\geq$ 75 % probably correspond to disease-associated clones [14,15]. Ouseph et al. demonstrated also that a proportion of metaphases with $-Y \geq 75$ % in the BM was associated with (i) a high frequency of molecular alterations in genes commonly mutated in myeloid neoplasia and (ii) a diagnosis of MDS. Accordingly, $-Y < 25\%$ was associated with a normal BM and a lower likelihood of progression to MDS [15].

The clinical significance of –X as a sole abnormality in the BM remains unknown. Tang et al. showed that acquired –X was usually disease-related when present as a major clone in patients with myeloid neoplasm [16]. In contrast, –X was either age-related or a benign finding when present as a minor clone in patients with normal BM [16]. No

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Table 1
Characteristics of clonal chromosomal abnormalities of undetermined significance.

CAs[¤]	Sample	Frequency	Main associated features	Main associated genomic features	Recommendation[$]	References
-Y (isolated or with +15)	BM PB (less frequent)	**age-dependent (BM)** 21-40 y: 0% 70 y: 40% 93 y: 57%	- Older males -Cancer (hematopoietic and non-hematopoietic) -Common diseases (e.g. Alzheimer disease and cardiovascular disease)	CH (predominantly in major clones)	**minor clone** (<25%): probably incidental or age-related - *Normal PB, normal BM, no CH* ⇨ no follow-up - *Cytopenia or CH:* risk of disease progression ⇨ follow-up **major clone** (> 75%): probably disease-related ⇨ follow-up	[6,7,12,15]
-X	PB BM (rare)	**age dependent (PB)** < 16 y: 0.07% < 50 y: 3.2% > 50 y: 5.1% > 65 y: 7.3%	- Older females -Wide spectrum of human diseases		**minor clone***: probably incidental or age-related - *Normal PB, normal BM, no CH* ⇨ no follow-up - *Cytopenia or CH*: risk of disease progression ⇨ follow-up **major clone***: probably disease-related ⇨ follow-up	[16]
+15 (Isolated or with –Y)	BM	0.01-0.3%	-Older people, with male predominance -Wide spectrum of human diseases			[4,8,19]
+8	BM	not specified	Wide spectrum of human diseases			[30]
del(20q)	BM					[31–34]
+i(3)(q10)	PB	rare, probably underestimated	-Young to middle-aged female smokers -Persistent polyclonal B-cell lymphocytosis (binucleated lymphocytes in PB) -High level of polyclonal IgM -HLA-DR7 expression -*Culture specifications*: 72 h CpG-ODN+IL2	-*ATR* (3q23) and *MECOM* (3q26) amplification -*ACA* (rare): +3 -Chromosome instability with CAs (del(6q), +8,…) and non-clonal CAs	- Usually indolent - Low risk of malignant transformation ⇨ follow-up	[44,46,50,51]

+: trisomy, -: monosomy, i: isochromosome, CH: clonal hematopoiesis (somatic gene mutation)
CA: chromosomal abnormality; ACA: additional CA; BM: bone marrow; PB: peripheral blood; y: year-old; CpG-ODN + IL2: CpG-oligodeoxynucleotide (DSP30) + interleukin 2
$: FISH is highly recommended for evaluating the number of cells with CA in a large number of metaphases and interphase nuclei.
¤: these CAs are of undetermined significance when isolated
*: threshold not specified

clearly pathogenic genes have been identified on the X chromosome [16] but *XIST* (located in band Xq13) might be a potent suppressor in hematologic disease. Thus, –X might give cells a selective advantage [7].

In conclusion, FISH is highly recommended for evaluating the number of cells with sex chromosome loss in a large number of metaphases and interphase nuclei. As a minor clone, sex chromosome loss appears to be age-related and the frequency increases regularly with age (Table 1). Clinical and laboratory follow-up is required in cases of isolated sex chromosome loss present as a major clone (> 75 % for -Y) or associated with an unexplained CH or cytopenia.

Trisomy 15

Trisomy 15 (+15) as a single autosomal abnormality is a rare event (0.01–0.3 %) in hematological disorders [17]. It is usually described in older patients and has male predominance. Trisomy 15 is frequently associated with -Y in older males [3] but not with -X in older females [8]. Trisomy 15 and -Y can be present in the same mitoses or in different ones. Moreover, +15 has never been identified in conventional and FISH-based analysis of non-BM samples, which rules out a constitutional origin [18].

Typically, +15 is present as a minor clone (5–35 %) [4] and may be transient [3]. In some cases, isolated +15 is described as a major clone (80–85 %) and, notably, in patients referred for acute myeloid leukemia (AML) [19]. Thus, trisomy 15 can be divided into two categories, depending on the size of the clone: a minor clone (more likely to be a benign, age-related abnormality or a transient phenomenon) [19] or a major clone (which might be disease-related) [4].

Trisomy 15 has been reported in the BM of patients referred for a wide range of hematological and non-hematological diseases [19]. A few patients with no hematological diseases remained disease-free; in a few cases, the +15 disappeared [3]. In hematological malignancies, isolated + 15 appears mainly in myeloid disorders but may also occur in lymphoid disorders [17]; even then, however, +15 is restricted to myeloid cells [4,19].

The group of diseases reportedly associated with isolated +15 is too large for this CA to be considered as a truly disease-specific finding. The only feature that all these diseases have in common is that they occur in older people [18]. Thus, it is more likely that +15 (like – Y) reflects an age effect [3,18]. Apart from leukemic patients and especially in cases with +15 as a minor clone, long-term clinical follow-up appears to be more appropriate than immediate treatment [19].

Trisomy 8

Trisomy 8 (+8) is found as a constitutional mosaicism (mos +8c) in healthy people, and is not considered to be a tumor marker by some experts [20]. However, the incidence of mos +8c is very low. Nielsen and Wohlert detected one case of mos +8c among approximately 35,000 live births [21], and Seghezzi et al. found two cases out of 40,140 [22]. Patients with +8c can develop hematologic malignancies [23] and

cytopenia in the absence of neoplasia [24]. Trisomy 8 has been reported in the BM of patients referred for hematological and non-hematological diseases (24). When the +8 is not clearly somatic [26], investigations for a constitutional CA may be indicated.

Isolated +8 is one of the most frequent cytogenetic abnormalities in MDS: it accounts for 9–11 % of *de novo* cases of MDS with a CA, and 5 % of all cases of MDS. Trisomy 8 is not, however, specific to MDS and is also frequent in chronic myelomonocytic leukemia, in some myeloproliferative neoplasms (especially primary myelofibrosis and, to a lesser extent, polycythemia vera), and even in lymphoid pathologies (in about 5 % of cases of acute lymphoblastic leukemia) [25,27].

In the absence of sufficient morphologic dysplasia and cytological signs, finding +8 is not currently considered to be MDS-defining [28,29]. Petrova-Drus et al. [30] compared two groups with +8 as the sole CA: one group had early or low-risk MDS, and the other did not meet the morphologic criteria for dysplasia and was referred to as "idiopathic cytopenia of undetermined significance" (ICUS) - despite the presence of +8. In the ICUS group, 36 % of the patients progressed to MDS or AML; these individuals did not show any morphological differences but had a higher percentage of metaphases with +8 (65 %, versus 20 % in ICUS patients who did not progress) in the initial BM, neutropenia, and a higher median platelet count. The median interval between the initial identification of +8 and the subsequent MDS/AML diagnosis was more than 2 years but this variable varied markedly (from 12.2 to 61.2 months) - suggesting that the clinical course was indolent in this group.

To our knowledge, no study has been published comparing the molecular profile in patients with isolated +8 without evidence of myelodysplasia. Based on these results, patients with cytopenia and isolated +8 but who do not meet the morphologic diagnostic criteria for MDS require close clinical and laboratory monitoring. In addition to cytogenetic analysis, a molecular profile may be performed.

Deletion 20q

Deletion of the long arm of chromosome 20 [del(20q)] is a frequent finding in the BM karyotype, and is mainly associated with myeloid neoplasms [31]. Isolated del(20q) can be incidentally observed in the absence of morphological features [32] and in non-neoplastic conditions [33]. Therefore, del(20q) as the sole CA in a normal BM is not definitive evidence of a myeloid neoplasm in patients with unexplained cytopenia [34,35]. Although the clinical course in patients with isolated del(20q) is usually indolent, some progress into myeloid neoplasms. Jawad et al. showed that only patients with del(20q) and cytopenia developed a myeloid neoplasm; they concluded that close follow-up is not required in individuals with isolated del(20q) and a normal blood count [31]. According to Ravindran et al.'s 10-year follow-up study of patients with an isolated del(20q), only those with clonal mutations in myeloid malignancy-associated genes progressed to myeloid neoplasia [33]. Indeed, this progression was particularly associated with the presence of clonal mutations in non-DTA (i.e. not *DNMT3A, TET2* and *ASXL1*) epigenetic modifier/spliceosome mutations (IDH1, IDH2 and BCOR, the kinases CBL, PTPN11 and JAK2, the tumor suppressors TP53 and PHF6, and the transcription factor RUNX1) [33]. Therefore, clinical and laboratory follow-up is probably only necessary when an isolated del(20q) is associated with unexplained cytopenia or CH.

CAs and clonal hematopoiesis

CH refers to an expanded blood cell population derived from a single clone. The clonal origin of cancer was first demonstrated in blood cancers in general and chronic myeloid leukemia in particular. Later studies of non-random X-chromosome inactivation in women concluded that CH could also occur outside the context of cancer [36]. Among CH, clonal hematopoiesis of indeterminate potential (CHIP), and clonal cytopenia of undetermined significance (CCUS) are now formally defined in the fifth edition of the World Health Organization Classification (WHO—HAEM5) [29].

In WHO—HAEM5, CHIP is defined as the presence of at least one somatic mutation in a myeloid malignancy-associated gene detected in the blood or the BM at a variant allele fraction (VAF) $\geq$ 2 % ($\geq$4 % for X-linked gene mutations in males); -Y may be also indicative of CHIP. Furthermore, CHIP is an age-related phenomenon: the prevalence is close to zero in people under the age of 40 but rises to 10–20 % of individuals over the age of 70. Individuals with CHIP have an increased risk of disease progression to hematological disorders, when compared with individuals lacking detectable mutations [37]. A patient's risk of progression depends on the age of the patient, the size of the somatic clone, the number of mutations identified, and the mutation profile [38,39]. The annual rate of progression to an hematological malignancy is between 0.5 and 1 % per year [32]. CHIP is not only associated with the risk of developing a hematological neoplasm but has also emerged as a risk factor for cardiovascular diseases [38,40]. The mechanism by which CHIP contributes to cardiovascular complications is not completely understood but it may be linked (at least in part) to its contribution to chronic inflammation. As these patients are at risk of disease progression, clinical and laboratory follow-up (including molecular and cytogenetic testing) is necessary [38].

CCUS is defined as CHIP associated with one or more unexplained cytopenias but does not meet all the diagnostic criteria for MDS. In WHO—HAEM5, clonality is defined as the presence of a somatic mutation or clonal CA in myeloid cells [41]; the CAs considered for CCUS are those "that do not define other myeloid neoplasms." In parallel, the International Consensus Classification of Myeloid Neoplasms and Acute Leukemias [28] states that CAs should be taken into account as a marker of clonality and that "aside from del(5q), −7/del(7q), or a complex karyotype, the previous MDS-defining CA in cytopenic patients lacking dysplasia are now considered as CCUS".

In conclusion, we suggest defining CHIP as the presence of at least one somatic mutation or a non-MDS-defining CA, including –Y, +15, +8 and del(20q). In cytopenic patients, the presence of a non-MDS-defining CA falls within the scope of CCUS, as suggested by Brett et al. [42]. Lastly, MDS-defining CA (as described by the WHO-2017)[35] corresponds to overt MDS in cytopenic patients (Table 2).

Table 2
Clonal chromosomal abnormalities defining CHIP/CCUS/MDS.

PB	cytopenia		no cytopenia
BM	Little or no dysplasia (<10 %)		Little or no dysplasia (<10 %)
cytogenetic abnormalities	MDS-defining CAs,* including del(5q), −7/del(7q), del(17p), CK	Non-MDS-defining CAs, including -Y, +15, +8, del(20q)	Non-MDS-defining CAs, including -Y, +15, +8, del(20q)
Entities	MDS	CCUS	CHIP

PB: peripheral blood, BM: bone marrow, CK: complex karyotype; MDS: myelodysplastic neoplasm; CCUS: clonal cytopenia of undetermined significance; CHIP: clonal hematopoiesis of indeterminate potential.
* as defined by the WHO-2017 [35].

Persistent polyclonal B-cell lymphocytosis

Persistent polyclonal binucleated B-cell lymphocytosis (PPBL) was first described by Gordon in 1982 and is characterized by chronic, stable, and moderate lymphocytosis (5–15.109/L) with a variable percentage (1–40 %) of binucleated lymphocytes in peripheral blood (PB) [43]. This condition results from the expansion of functional IgD+CD27+ memory B-cells resembling marginal zone B-cells. An associated polyclonal increase in serum IgM levels and HLA-DR7 expression are also observed in most cases. Typically, PPBL occurs in young to middle-aged women who smoke. PPBL is a rare entity who incidence is probably underestimated because most patients complain of non-specific symptoms (weakness and fatigue) [44,45], and the only immediate physical sign in some cases is mild splenomegaly [46].

The presence of binucleated lymphocytes is characteristic of (but not specific for) PPBL. In cases mimicking lymphoproliferative disorders [44], a comprehensive morphological study is essential [47]. The polyclonal nature of the B-cell proliferation can be demonstrated by immunophenotyping and immunoglobulin gene rearrangement analysis [43].. A cytogenetic analysis can be performed on CpG-ODN + IL2-stimulated lymphocytes cultured for 72 h.

PPBL is characterized by a recurrent cytogenetic profile that includes an additional isochromosome for the long arm of chromosome 3 (+*i*(3)(q10)) and premature chromosome condensation [48]. The +*i*(3)(q10) is restricted to B-cell lymphocytes, independently of the light chain phenotype and the binuclear aspect [49]. Trisomy 3 can be detected in addition to extra +*i*(3)(q10), which suggests that PPBL is associated with chromosome 3 instability [46]. Instability of other chromosomes is also common, with the presence of other clonal abnormalities (like del(6q) and +8) and/or non-clonal CAs [50]. The consequences of tetrasomy 3q due to +*i*(3)(q10) have not been defined. To determine whether or not 3q is involved in the pathogenesis of PPBL, Cornet et al. used single-nucleotide polymorphism arrays to highlight the amplification of the 3q26 genomic region (including the *MECOM* gene) in the majority of patients [51]. *MECOM* abnormalities are mainly described in myeloid neoplasms but are also involved in lymphoid disorders [52]. Likewise, the *ATR* gene (located on band 3q23) is amplified in PPBL (43). *ATR* has a role in the G2/M checkpoint, and its overexpression leads to sensitivity to DNA-damaging agents and defects in cell cycle checkpoints [53,54]. Thus, +*i*(3)(q10) is probably involved in chromosomal and genomic instability, and might be part of the multistep process leading to the emergence of a malignant disease [51].

Several studies showed the absence of driver mutations in PPBL by next generation sequencing [55–57].

Despite genetic instability, most patients have an uneventful clinical course and no changes in laboratory variables - suggesting that PPBL is a benign disorder. It is therefore important to distinguish this syndrome from other malignant lymphoproliferative diseases, in order to avoid unnecessarily aggressive therapy. However, Cornet et al. reported the occurrence of subsequent lymphoma in 3 % of the patients, justifying an accurate diagnosis and a careful follow-up, including prospective immunological and genetic studies at different stages of the disease to detect the evolution toward malignant lymphoma or a secondary solid cancer [51].

Conclusion

Here, we reviewed clonal CAs of uncertain significance. In case of a recurrent, single CA, we can distinguish three situations. Firstly, in a minor clone, sex chromosome loss and +15 (alone or associated with –Y) are probably age-related. Isolated del(20q) and +8 in a minor clone might be incidental [32] and do not constitute definitive evidence of a myeloid neoplasm. Moreover, +8 present as a small clone may be constitutional. Although the definition of a “minor clone” is subject to debate, we suggest that close follow-up is not required when sex chromosome loss, +15, +8 or del(20q) are present as a single CA in a minor clone and the patient’s blood counts are normal [31]. Secondly, when present in a major clone, sex chromosome loss, +15, +8, and del(20q) are presumed to be disease-related and require follow-up. Thirdly, when associated with unexplained cytopenia or a somatic gene mutation, all CAs (including sex chromosome loss, +15, +8, and del(20q)) are association with a risk of disease progression, and clinical and laboratory follow-up is necessary.

For most CAs, there are no thresholds for defining minor and major clones. We recommend using FISH to more accurately assess the number of cells with a CA in metaphases and interphase nuclei. One can reasonably consider that follow-up should be suggested if non-MDS-defining CAs are present in 25 % or more cells (5 out of 20 metaphases and/or 25 % of interphase nuclei).

In contrast, when sex chromosome loss, +15, +8 or del(20q) are found in association with other CAs, they might be involved in the oncogenic process and so must be included in the chromosome counts used to define karyotype complexity. Lastly, in cases of PPBL, long-term follow-up is necessary because malignancies may subsequently arise.

Declaration of Competing Interest

We have no Conflict of Interest.

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N. Nadal[a,*], N. Auger[b], A. Bidet[c], F. Nguyen-Khac[d,e]
[a] *Service de génétique chromosomique et moléculaire, CHU Dijon, Dijon, France*
[b] *Génétique des tumeurs, Gustave Roussy, Villejuif, France*
[c] *Laboratoire d'hématologie, CHU Bordeaux, Bordeaux, France*
[d] *Drug Resistance in Hematological Malignancies, Centre de Recherche des Cordeliers, UMRS 1138, INSERM, Sorbonne Université, Université Paris Cité, Paris, France*
[e] *Service d'Hématologie Biologique, Hôpital Pitié-Salpêtrière, AP-HP, Paris, France*

[*] Corresponding author at: Service de génétique chromosomique et moléculaire, CHU Dijon-Bourgogne, Plateforme de Biologie Hospitalo-Universitaire, BP 37013, F-21070 Dijon cedex, France.
E-mail address: nathalie.nadal@chu-dijon.fr (N. Nadal).