Isochromosome 21q in Hematologic Malignancies

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ABSTRACT: *Isochromosome(21q) is a rare but non-random karyotypic change in hematologic diseases. We report 15 cases of i(21q) among a large group of cases, in various disorders of both myeloid and lymphoid lineage. This abnormality has been found as the sole chromosome change in two cases, the remaining cases exhibiting more or less complex karyotypes. Finally we discuss the labelling "i(21q)".*

INTRODUCTION

Isochromosome(21q) is a rare karyotypic change in hematologic diseases. Only a few well-documented cases have been reported in the literature to date. This chromosomal aberration has always been associated with secondary leukemia [1–5] or ANLL-M6 [6, 7] and recently with a possible neonatal case of acute myeloid leukemia [8], and a general rule was that other chromosome changes were present simultaneously.

To investigate its significance as a possible primary chromosome change and its occurrence in different subtypes of human leukemia, the Groupe Français de Cytogénétique Hématologique (GFCH) undertook a retrospective study, identifying 15 cases, the clinical hematologic and cytogenetic characteristics of which are presented and discussed in the present paper.

MATERIALS AND METHODS

The fifteen cases involved in this study were identified among patients referred between 1976 and 1989 to eight different cytogenetic laboratories of the Groupe Français de Cytogénétique Hématologique (see appendix). Clinical files were reviewed retrospectively.

Hematologic features were evaluated on May-Grünwald Giemsa-stained smears from bone marrow (11 cases) and peripheral blood samples (2 cases) according to the FAB recommendations [9]. Lymph node biopsies (cases 11 and 12) were analyzed following the Kiel classification [10]. Cytogenetic investigations were performed on direct preparations or after short-term cultures (16–24–48 hours) without stimulation, and G-, Q-, or R-banding techniques were used. Chromosomes were classified according to ISCN nomenclature [11].

All available data, including karyotypes, were reviewed by the members of the GFCH.

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RESULTS

The main clinical and cytogenetic data of the 15 cases with i(21q) rearrangement are shown in Table 1.

There were 10 male and 5 female patients with age ranging between 2 and 73 years. Eight patients were classified as myelodysplastic syndromes (MDS), including two refractory anemias (RA) (cases 1 and 13), one refractory anemia with excess of blasts (RAEB) (case 15), five refractory anemias with excess of blasts in transformation (cases 2, 4, 6, 8, and 14).

One patient presented a myeloproliferative disorder without a Philadelphia chromosome (case 7), 4 presented with acute non-lymphoblastic leukemia (ANLL) with M2, M4, M5, M7 subtypes (cases 10, 3, 5, 9); 1 with a Hodgkin disease (case 12) and 1 with a Lennert lymphoma (case 11).

Four patients (cases 1, 2, 3, 4) had received treatment with radiotherapy or alkylating agents from 5 to 12 years before the development of a secondary hematologic malignancy. In two additional cases (patients 5 and 6) the past history revealed a possible occupational exposure to toxic agents. Karyotypic features were as follows: 9 AN cases (normal plus abnormal metaphases), six AA cases (only abnormal metaphases), and five of the 15 cases showed karyotypic variation (1, 2, 4, 5, 12). Karyotypes were considered as complex when more than four chromosomal abnormalities were present. It was the case for seven samples (cases 2, 4, 5, 10, 11, 12, 15).

Two i(21q) main groups could be identified: a "homogeneous" one in which i(21q) was present in all the abnormal metaphases (cases 1, 3, 4, 6–15), and a "non-homogeneous" one, in which the i(21q) was present in only part of the abnormal metaphases (cases 2, 5, 12, 13). Four (cases 1, 2, 4, 6) presented an i(21q) copy number variation, with two or more i(21q) in the same metaphase. All patients but two exhibited other numerical and/or structural changes associated with i(21q).

Analysis of the additional chromosomal aberrations showed that chromosomes 5, 7, 3, 12, and 17 were often involved. Of these 13 cases, five patients had a relatively simple karyotype with involvement of only one associated chromosome change: there were two cases with del(5q), two cases with del(7q) and one case with monosomy 7. The remaining cases exhibited more than one associated chromosome aberration. Two cases (6, 7) exhibited the i(21q) as the sole abnormality. In each case the i(21q) was present in all cells, but one case (6) showed extra copies with tetrasomy or pentasomy 21q as a consequence.

Finally, all cases presented trisomy 21q or plus, since no loss of the other 21 chromosome has been observed.

DISCUSSION

Isochromosome(21q) appears to be a rather rare cytogenetic event in hematologic malignancies. It has been found in secondary leukemia, ANLL-M6, and transient leukemoid reaction. It has not been described in other de novo ANLL subtypes [1–5], in myeloproliferative syndromes, or in the various types of lymphomas or Hodgkin disease.

When present in secondary leukemia or ANLL-M6 it was part of an array of complex chromosomal rearrangements.

This study confirms the association of i(21q) with secondary hematologic malignancy. A cytotoxic treatment had been previously administered in four cases because of multiple myeloma, Waldenström disease, or non-Hodgkin malignant lymphoma. Treatments included radiotherapy and/or alkylating agents, which are known to cause ANLL and MDS. Two additional patients were occupationally exposed to potent carcinogens. The first one was a 70-year-old man who had handled chemical mutagens

Table 1. Main clinical and cytogenetic data in 15 cases with i(21q) rearrangement

Patient	Sex/Age (yr)	Occupational or cytotoxic treatment exposure	Diagnosis at time of cytogenetic diagnosis	Date of cytogenetic diagnosis	Sample/ type of culture	AN/AA	Karyotypic features		Previous disease
							Complexity (more than 4 abnormalities)	Karyotypic variation	
1	F/60	+	RA	1981	BM/24 hr /48 hr	AA	–	+	Waldenström (1976)
2	M/73	+	RAEB-T	1987	BM/24;48 hr PB 24/48 hr	AN	+	+	MM (1981)
3	M/42	+	ANLL/M4	1979	PB/24;48 hr	AN	–	–	MM (1967)
4	F/69	+	RAEB-T	1984	BM/24 hr /48 hr	AA	+	+	NHL (1974)
5	M/70	possible (gardener)	ANLL/M5	1984	BM/24;48 hr	AN	+	+	–
6	M/67	possible (carpenter)	RAEB-T	1988	BM/24;48 hr	AN	–	–	–
7	M/69	–	MPD	1976	BM direct	AA	–	–	–
8	M/43	–	RAEB-T	1980	BM direct	AN	–	–	–
9	F/2	–	ANLL/M7	1984	PB/24;48 hr	AA	–	–	–
10	F/68	–	ANLL/M2	1985	BM/24;48 hr	AA	+	–	–
11	M/66	–	Lennert lymphoma	1983	LN/17 hr	AA	+	–	–
12	F/34	–	Hodgkin	1985	LN/48 hr	AN	+	+	–
13	M/52	unknown	RA	1986	BM/24 hr	AN	–	–	–
14	M/70	gout	RAEB-T	1985	BM/48	AN	–	–	–
15	M/72	–	RAEB	1982	BM/48	AN	+	–	

Abbreviations: BM, bone marrow; PB, peripheral blood; LN, lymph node; RA, refractory anemia; MPD, myeloproliferative disorders; RAEB-T, refractory anemia with excess of blasts in transformation; RAEB, refractory anemia with excess of blasts; ANLL, acute non lymphoblastic leukemia; MM, multiple myeloma; NHL, non-Hodgkin lymphoma.

used in gardening and the other was a 67-year-old man exposed as a carpenter to organic solvents and glues. Thus, in 6 of 15 patients there was a significant association with previous exposure to external cytotoxic products.

The type of chromosome changes associated with i(21q) aberration in this study is also in favor of its secondary nature in some cases. Five patients (cases 2, 10, 5, 4, 15) had very complex karyotypes associated with more than four additional chromosome changes including chromosomes 5, 7, 3, 6, 17, and 12 abnormalities, and considered to be possibly mutagen-induced chromosomal aberrations. Besides these overt or possible secondary disorders with i(21q), new associations of i(21q) with hematologic malignancies emerge from this study, such as de novo AML-M2 in a 68-year-old woman with no known exposure to toxic agents.

We also report the case of a 2-year-old female patient who developed a de novo ANLL-M7. This subtype of ANLL is known to be associated with some cases of Down's syndrome with congenital trisomy 21q [12]. This study also reports the first association of i(21q) with Hodgkin disease and Lennert lymphoma. In all these cases i(21q) was associated with other chromosome changes. There are no indications that would allow us to consider i(21q) as a primary change in these cases. Furthermore, i(21q) was not present in all the metaphases.

On the other hand, this study revealed the presence of two cases (cases 6, 7) with i(21q) as the sole chromosomal abnormality. One case was a Philadelphia negative myeloproliferative syndrome, the other one a MDS in transformation. In these two cases i(21q) may be considered as a primary cytogenetic change.

Finally, three lines of evidence emerge from this study: 1) the i(21q) occurs in various hematologic malignancies, myeloid or lymphoid. It is not limited to secondary leukemia and ANLL-M6; 2) the i(21q) in some cases may be a primary cytogenetic event found as the sole abnormality at the diagnosis of the disease, but in most of them it is clearly not; 3) the i(21q) is a very rare cytogenetic event as it has been found in only 15 cases out of several thousand cases studied by the GFCH during the past 10 years.

The last part of our discussion will concern the labelling "i(21q)". It seems to be very difficult to call it i(21q) rather than t(21;21). We disagree with Werner-Favre and collaborators [7], who do not retain the possibility of a Robertsonian translocation which would imply a trisomy 21 followed by breakage and reunion of 21q at or near the centromere [13]. Such a mechanism could be retained and the term t(21;21) used as well as i(21q).

With regard to trisomy 21 in leukemia and lymphoma, we may be facing a situation which could be similar to that in constitutional trisomy 21 where t(21;21) or i(21q) is also rather infrequent, compared to regular trisomy 21. Thus, i(21q) may be the very rare form of trisomy 21, which is one of the most frequent acquired chromosomal changes in hematologic malignancies, either in the myeloid or in the lymphoid lineage.

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APPENDIX 1

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