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A novel translocation t(2;6)(p12;q23) appeared during the transformation from follicular lymphoma with t(18;22)(q21;q11) to diffuse large cell lymphoma

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Abstract

Follicular lymphoma is characterized genetically by t(14;18)(q32;q21), whereas t(18;22)(q21;q11), a rare variant form of t(14;18), has been preferentially observed in chronic lymphocytic leukemia (CLL). We describe here an unusual case of follicular lymphoma with t(18;22)(q21;q11), that progressed to diffuse large cell lymphoma with a novel translocation t(2;6)(p12;q23). A 53-year-old woman was initially diagnosed as follicular lymphoma, grade 2. Chromosome analysis showed near-tetraploid karyotype as follows: 45,X,-X,t(3;14)(q27;q32),i(6)(p10),t(18;22)(q21;q11)/92,idemx2,+5,+5/90, idemx2,-1,+5,-8,+12. After 18 months, the disease relapsed and evolved to diffuse large cell lymphoma with follicular lymphoma grade 3. The karyotype was converted as follows: 45,X,-X,add(2)(p12),t(3;14)(q27;q32),i(6)(p10),add(6)(q23),del(9)(q?),t(18 ;22)(q21;q11). Spectral karyotyping revealed that add(2)(p12) and add(6)(q23) were derived from t(2;6)(p12;q23). Fluorescence *in situ* hybridization analysis confirmed the rearrangements of the *BCL2* gene at 18q21 and the *BCL6* gene at 3q27. It has been shown that chromosomal deletions at 6q23-26 in follicular lymphoma are associated with a significantly higher risk of transformation. Our results indicate that a reciprocal translocation involving 6q23 could be implicated in the progression of follicular lymphoma and that t(18;22) may have a specific role in the pathogenesis of follicular lymphoma as well as CLL.

1. Introduction

The t(14;18)(q32;q21) translocation is found in about 80 to 90% of follicular lymphoma and up to one third of diffuse large lymphoma [1-3]. This translocation juxtaposes the *BCL2* gene at 18q21 with the immunoglobulin heavy chain (*IgH*) gene joining region at 14q32 and results in deregulated expression of the *BCL2* gene encoding a 26-kd protein that prolongs cell survival by blocking programmed cell death. Besides the major translocation t(14;18), variant translocations, t(2;18)(p11-12;q21) and t(18;22)(q21;q11), that involve the *BCL2* and either immunoglobulin kappa (*Igk*) or lambda (*Igλ*) genes, have also been observed in lymphoid malignancies [4-6]. The majority of cases with t(2;8) were follicular lymphoma [5, 6], whereas most reported cases of t(18;22) were chronic lymphocytic leukemia (CLL) and lymphocytic lymphoma, a counterpart of CLL [6-9]. That is, only a few cases of follicular lymphoma with t(18;22) have been reported to date [6, 10-12].

In addition to t(14;18), secondary chromosomal alterations, such as +X, +1q21-q44, +7, +12q, +18q, del(1)(p36), del(6q), del(10)(q22-q24), i(17q) and der(18)t(14;18), are detected in almost all cases of follicular lymphoma at initial diagnosis [2, 3]. Patients with follicular lymphoma have an initial indolent course, but more rapid progression by histological transformation to diffuse large cell lymphoma finally occurs in many patients. The disease progression was shown to be associated with some of the secondary abnormalities, including del(6q), although a consistent pattern of cytogenetic evolution in follicular lymphoma has not been completely elucidated [3, 13].

We describe here a rare case of follicular lymphoma with t(18;22)(q21;q11) and t(3;14)(q27;q32). Furthermore, a novel reciprocal translocation t(2;6)(p12;q23) appeared during the transformation to diffuse

large cell lymphoma. The results indicated that t(2;6) may be implicated in the progression of the disease.

2. Materials and methods

2.1. Case History

A 53-year-old woman was referred to our hospital for left cervical lymphadenopathy and a swelling of her left tonsil in November 2000. A cervical lymph node biopsy was consistent with a follicular center lymphoma, grade 2, according to the World Health Organization (WHO) classification. Peripheral blood showed hemoglobin 14.7 g/dl, platelets 211 x 10^9/l and white blood cells 6.2 x 10^9/l with 77% segmented neutrophils, 2% monocytes, 1% eosinophils, 1% basophils and 19% lymphocytes. Atypical lymphocytes were not detected. Serum levels of lactate dehydrogenase (LDH) and soluble interleukin-2 receptor (sIL-2R) were 221 IU/l (normal range, 117-205) and 766 U/ml (normal range, 135-483), respectively. Surface marker analysis of the cells from lymph nodes revealed that they were positive for CD10, CD19, CD20, and surface (Sm-) IgM and λ chain. Southern blot analysis demonstrated the rearrangement of the *IgH* gene, but neither T-cell receptor β chain (TCRβ) gene nor major breakpoint cluster region (mbr) of the *BCL2* gene were rearranged. Computed tomography, Ga-67 citrate scintigraphy and bone marrow biopsy showed no evidence of lymphoma cell infiltration except for the left tonsil and cervical lymph nodes. Therefore, she was diagnosed as clinical stage IIA and treated with irradiation for her throat and neck. Local irradiation (2 Gy/fraction, total dose 46 Gy) induced a complete remission (CR).

In May 2002, a left inguinal lymphadenopathy appeared. Histological examination of inguinal lymph nodes biopsy showed the diagnosis of diffuse large cell lymphoma with follicular center lymphoma, grade 3. Serum levels of LDH and sIL-2R elevated to 252 IU/l and 1030 U/ml, respectively. Immunophenotypic analysis of the cells from lymph nodes revealed that they were positive for CD10, CD19, CD20, CD25 and Sm-λ.

Computed tomography and Ga-67 scintigraphy also disclosed the swelling of para-aortic lymph nodes. She was treated with R-CHOP regimen (Rituximab 375 mg/m^2 day1, cyclophosphamide 750 mg/m^2 day2, doxorubicin 50 mg/m^2 day2, vincristine 1.4 mg/m^2 day2, prednisolone 100 mg/body day2-6). She received a total of 4 cycles of R-CHOP and 4 cycles of CHOP regimens and remained in CR.

2.2. Chromosome analysis and Spectral Karyotyping (SKY)

Chromosome analyses were performed on short-term culture of the cells obtained from cervical (at the initial diagnosis, November 7, 2000) or inguinal (at the relapse, May 28, 2002) lymph nodes by the G-banding technique. Karyotypes were described according to the International System for Human Cytogenetic Nomenclature (ISCN 1995) [14]. Spectral karyotyping (SKY) was carried out with SkyPaint^{TM} kit (Applied Spectral Imaging, Migdal Ha'Emek, Israel) according to the manufacturer's instructions. A total of 5 metaphase spreads at the relapse were analyzed for spectral karyotyping.

2.3. Fluorescence in situ hybridization (FISH) analysis

Probes used in these studies were LSI BCL6 Dual Color, Break Apart Rearrangement Probe and LSI IGH/BCL2 Dual Color, Dual Fusion Translocation Probe (Vysis, Downers Grove, IL, USA). Ten and 6 metaphase spreads at the relapse were analyzed by BCL6 and IGH/BCL2 probes, respectively. The BCL6 probe is a mixture of an approximately 300 kb labeled SpectrumOrange 5' LSI BCL6 probe and a 600 kb labeled SpectrumGreen 3' LSI BCL6 probe. In a normal cell hybridized with the BCL6 probe, the expected signal pattern is two orange/green fusion signals. In a cell with a translocation breakpoint within the gap region between the 5' and 3' BCL6 probe, one orange, one green and one fusion signals are

observed.

The IGH/BCL2 probe is a mixture of the LSI IGH probe labeled with SpectrumGreen spanning approximately 1.5 Mb containing the entire IGH locus and LSI BCL2 probe labeled with SpectrumOrange covering an approximately 750 kb region including the entire BCL2 gene. The expected pattern in a normal nucleus is the two orange and two green signals. In a nucleus harboring a t(14;18)(q32;q21), the most common pattern is one orange signal, one green signal (representing normal homologue) and two orange/green (yellow) fusion signals representing the two derivative chromosomes resulting from the reciprocal translocation.

3. Results

Chromosome analysis at the initial diagnosis showed the hypodiploid stemline and near-tetraploid sidelines as follows (Fig. 1A): 45,X,-X,t(3;14)(q27;q32),i(6)(p10),t(18;22)(q21;q11)[8]/92,idem x2,+5,+5[1]/90,idem x2,-1,+5,-8,+12[4]/46,XX[7]. At the relapse, the karyotypes converted as follows: 45,X,-X,add(2)(p12),t(3;14)(q27;q32),add(6)(q23),i(6)(p10),del(9)(q?),t(18;22)(q21;q11)[11] (Fig. 1B).

To identify the origin of additional chromosomes, we applied SKY analysis on metaphase spreads of the same sample preparation obtained at the relapse. SKY analysis revealed that add(6)(q23) and add(2)(p12) were derived from a reciprocal translocation t(2;6)(p12;q23). Therefore, the karyotype at the relapse was revised as follows (Fig. 2): 45,X,-X,t(2;6)(p12;q23),t(3;14)(q27;q32),i(6)(p10),del(9)(q?),t(18;22)(q21;q11).

For further characterization of t(3;14)(q27;q32) and t(18;22)(q21;q11) translocations, we performed FISH analyses with BCL6 and BCL2/IgH probes on metaphase spreads at the relapse. The BCL6 probe at 3q27 was split and located on the der(3)t(3;14) and der(14)t(3;14) (Fig. 3A). The BCL2 probe at 18q21 was also split to der(18)t(18;22) and der(22)t(18;22). Furthermore, the IgH probe at 14q32 was split to der(3)t(3;14) and der(14)t(3;14) by t(3;14)(q27;q32) (Fig. 3B). These results confirmed the rearrangements of the *BCL6* and *BCL2* genes.

4. Discussion

On the basis of G-banding and SKY analyses, we defined a novel translocation t(2;6)(p12;q23) appeared during the transformation from follicular to diffuse large cell lymphoma. Furthermore, the present case showed several interesting cytogenetic findings other than t(2;6). Namely, dual translocations t(18;22) and t(3;14), i(6p) and near-tetraploidy were observed at the initial diagnosis and del(9q) was found at the relapse. All 3 loci of the immunoglobulin genes (2p11-12, 14q32 and 22q11) were involved in these translocations.

It has been shown that secondary karyotypic changes that correlated with morphologic progression of follicular lymphoma include del(6q), del(1)(p36), del(10)(q22-q24), +7, the total number of abnormalities, the number of markers and additions and the presence of polyploidy [3]. Among these cytogenetic abnormalities, del(6q) is one of the most common secondary aberrations in non-Hodgkin's lymphoma (NHL) and has been observed in 15 to 20% of all NHL patients [1, 15]. Isochromosome 6p, detected in the present case, also results in the loss of 6q and is most often associated with follicular lymphoma with t(14;18) [1]. Offit et al. identified three 6q regions of minimal cytogenetic deletions (RCD) by loss of heterozygosity analysis, that is, RCD1 at 6q25-27 with intermediate-grade NHL, RCD2 at 6q21 with high-grade NHL and RCD3 at 6q23 with low-grade NHL without t(14;18) [15]. Zhang et al. revealed by FISH that deletions of 6q23-24 are more frequent in low-grade follicular lymphoma with t(14;18) than other types of low-grade B-cell lymphoma [16]. Moreover, Tilly et al. reported that 9 follicular lymphoma with breaks at 6q23-26 (and 7 patients with 17p abnormalities) had a significantly higher risk of transformation into a diffuse large cell lymphoma and a shorter survival [13]. All 9 patients showed interstitial 6q deletions, but not

translocations. Therefore, these findings suggest that chromosomal deletions at 6q23 are specifically associated with the transformation from follicular lymphoma with/without t(14;18) and that tumor suppressor genes may be located around 6q23.

In contrast to the high frequency of del(6q), as shown in Table 1, only 11 cases of follicular or diffuse large cell lymphoma with translocations involving 6q23 have been described so far [3, 6, 17-24]. Partner sites of translocations are heterogeneous except for 1q21 observed in 3 cases, indicating that t(1;6)(q21;q23) may be a non-random aberration in NHL. Only one case had breakpoint at 14q32, the locus of the *IgH* gene [18]. The relations between these translocations and transformation remain to be elucidated. However, our results indicated that translocations at 6q23, similar to del(6q), could contribute to the histological transformation. It is possible that t(2;6)(p12;q23) may result in the deregulated expression of novel gene(s) at 6q23 by the *Igκ* gene at 2p11-12.

On the other hand, deletions of 9q are extremely rare abnormalities in follicular lymphoma. They were observed in only one out of 165 cases and appear to have no specific association with follicular lymphoma [3]. Then, the pathological significance of del(9q) at the relapse of the present case is unclear.

Polyploidy has been detected in about 10% of follicular lymphoma. Clonal evolution by the development of polyploidy is associated with the morphological progression from follicular small cleaved cell to follicular large cell lymphoma [3, 25], but polyploidy does not affect overall survival [25]. Interestingly, in the present case, near-tetraploid clones were observed at the initial diagnosis, but did not develop at the relapse. Tetraploid clones were eradicated by local irradiation but not related to histological transformation. The clinical course of the patient may reflect little prognostic significance of polyploidy.

Translocations involving 3q27 and *BCL6* rearrangement have been observed in about 15% of follicular lymphoma [1]. The present case also had dual translocations t(3;14)(q27;q32) and t(18;22)(q21;q11) and rearrangements of the *BCL6* and *BCL2* genes. However, it is reported that *BCL6* rearrangement has no effect on clinical features and is not associated with progression in follicular lymphoma [1, 2]. This finding seems to be applicable to the present case.

Among the complex karyotypes of the present case, t(18;22)(q21;q11) is supposed to be a primary event. A total of 11 cases of lymphoid malignancies with t(18;22) have been reported and 7 of them were diagnosed as CLL [6], suggesting that t(18;22) might have a specific role in the pathogenesis of CLL [7]. It has been shown that t(18;22) results in the juxtaposition of the 5' region of the *BCL2* gene and *Igλ* gene in CLL [7-9]. As a result, follicular lymphoma and CLL are characterized by the same *BCL2* gene but different *Ig* genes. Adachi et al. supposed that the *BCL2* gene might be activated in different ways by *IgH* and *Igλ* genes at the transcriptional level or through mutations of the protein coding region.

As shown in Table 2, 4 cases of NHL with t(18;22)(q21;q11) have been described [10-12]. Common clinical features could not be found, because only limited information was available. We first confirmed the *BCL2* involvement in the variant translocation t(18;22) by FISH, whereas the *BCL2* rearrangement was not confirmed in other 4 cases. The patient reported by Au et al. [12] also had t(3;14)(q27;q32) as well as t(18;22)(q21;q11), but Southern blot analyses with mbr and mcr probes of the *BCL2* gene and MTC probe of the *BCL6* gene did not detect rearrangements. In contrast to CLL, breakpoints of these NHL cases with t(18;22) have never been molecularly characterized. Unfortunately, in the present case, it was not clarified whether the breakpoint at 18q21 was 5' *BCL2* region or not. It is of interest whether there might be molecular

heterogeneity at the 5' *BCL2* or *Igλ* breakpoints between CLL and NHL including follicular lymphoma. Further cytogenetic and molecular analyses are needed to elucidate the pathogenesis of t(18;22) and t(2;6) in follicular lymphoma.

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Figure legends

Fig.1. G-banded karyotypes of the lymphoma cells (A) at the initial diagnosis and (B) relapse. (A) The karyotype of near-tetraploid clone is shown. Arrowheads indicate rearranged chromosomes.
(A)92,XX,-X,-X,t(3;14)(q27;q32)x2,+5,+5,i(6)(p10)x2,t(18;22)(q21;q11)x2.
(B)45,X,-X,add(2)(p12),t(3;14)(q27;q32),add(6)(q23),i(6)(p10),del(9)(q?),t(18;22)(q21;q11).

Fig.2. Spectral karyotype of the metaphase spread after spectra based classification (left side, reverse DAPI; right side, SKY). Chromosomes were assigned a pseudocolor according to the measured spectrum. Arrowheads indicate rearranged chromosomes.

Fig.3.
(A) Dual-color FISH analysis with BCL6 probe. BCL6 signals are located on [1] der(3)t(3;14) (green), [2] chromosome 3 (green and red) and [3] der(14)t(3;14) (red).
(B) Dual-color FISH analysis with IgH/BCL2 probes. BCL2 signals (red) are split and located on [1] der(18)t(18;22), [2] chromosome 18 and [3] der(22)t(18;22). IgH signals (green) are also split and located on [4] der(14)t(3;14), [5] der(3)t(3;14) and [6] chromosome 14.

Table 1. Reported cases of follicular or diffuse large cell lymphoma with translocations involving 6q23

Age/Sex	*Diagnosis*	*Karyotypes*	*References*
59/F	DLCL	51,X,-X,t(3;11)(q29;p13),+5,t(6;11)(q23;p15),+der(7)t(7;11)(p15;p15),+8,+9,-21,+mar	[17]
59/M	DLCL	46,XY,der(1)t(1;1)(p32;q25),t(6;14)(q23;q32)	[18]
73/M	DLCL	52,XY,+2,t(2;6)(q36;q23),+5,+11,+15,+19,+22	[18]
60/F	DLCL	48,XX,+1,t(1;6;11)(p31;q23;q13),t(1;13)(q25;q22),del(6)(q21),+7,t(8;14)(q24;q32),+9,del(11)(p13),-20	[19]
17/M	DLCL	43-47,t(1;6)(q21;q23),-6,-9,-11,+13,-17,inc	[20]
64/F	FL	47,XX,+3,der(6)t(1;6)(q21;q23),t(8;14)(q24;q32)/48,idem,+mar	[21]
59/F	FL	86,XXXX,t(1;6)(p36;q23)x2,t(8;14)(q24;q32)x2,inc	[21]
67/M	FL	43-49,XY,+X,add(1)(p36),add(7)(q22),+del(11)(q13),+12,add(14)(q13),add(18)(q21)/ 49,idem,t(6;10)(q23;q24)/50,idem,+5,t(6;10)(p23,q24)	[22]

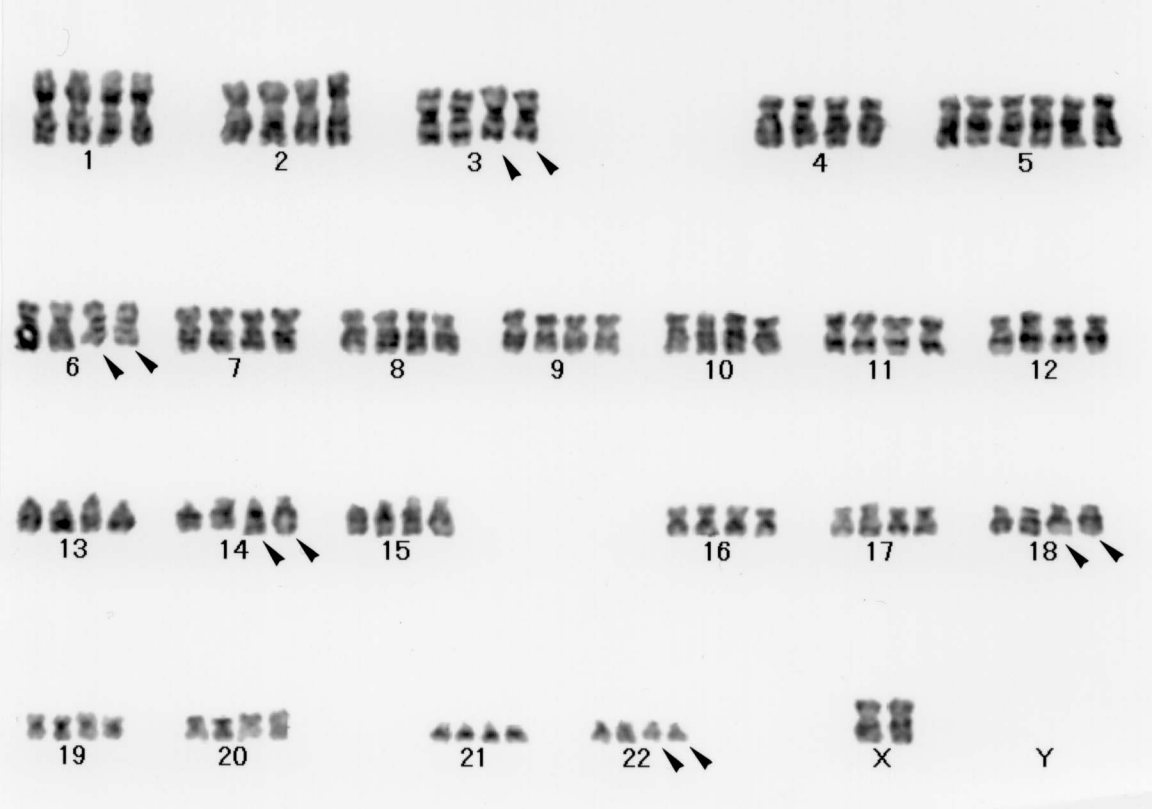
NA/F	FL	46-47,XX,t(1;5)(p36;q13),t(5;6)(q13;q23),t(14;18)(q32;q21)	[23]
59/F	FL	46,XX,t(6;13)(q23;q13),add(8)(p23),dup(12)(q13q24),t(14;18)(q32;q21)	[24]
39/M	FL	47,XY,add(3)(q27-28),der(6)t(1;6)(q21;q23),+12,t(14;18)(q32;q21),-22,+mar	[3]

DLCL, diffuse large cell lymphoma; FL, follicular lymphoma; NA, not available.

Table 2. Reported cases of non-Hodgkin's lymphoma with t(18;22)(q21;q11)

Age/Sex	*Diagnosis*	*Karyotypes*	*BCL2*	*References*
43/M	Peripheral B-cell neoplasm	49,XY,t(1;14)(q21;q32),+3,t(7;12)(p11;p12),t(8;14)(q24;q32),+der(12)t(7;12),+del(13)(q12q21),t(18;22)(q21;q11)	NA	[10]
51/M	Follicular lymphoma	50,XY,t(1;5)(p36;q31),+8,+der(18)t(18;22)(q21;q11),t(18;22)(q21;q11),+20,+21/50,idem,der(2)t(1;2)(q21;q37)/50,idem,der(3)t(1;3)(q21;p26)/50,idem,der(4)t(1;4)(q21;q35)/50,idem,der(5)t(1;5)(q21;p15)/50,idem,der(8)t(1;8)(q21;q24)/50,idem,der(9)t(1;9)(q21;p24)/50,idem,der(17)t(1;17)(q21;q25)	NA	[11]
38/M	Diffuse large lymphoma	47,XY,+add(1)(q24),t(3;14)(q27;q32),del(8)(q24),add(13)(q14),t(18;22)(q21;q11)	G	[12]
56/F	Follicular lymphoma	47-49,XX,+7,ins(12;?)(q13;?),+14,der(15)t(1;15)(q23;p11),+16,t(18;22)(q21;q11),+21,-22,+2-4mar	NA	[3]
53/F	Follicular lymphoma, grade 2	45,X,-X,t(3;14)(q27;q32),i(6)(p10),t(18;22)(q21;q11)[8]/92,idemx2,+5,+5[1]90,idemx2,-1,+5,-8,+12[4]/46,XX[7]	R	Present case

A case of lymphocytic lymphoma is excluded [9]. NA, not available; G, germ line by Southern blot analysis with mbr and mcr probes; R, rearranged by FISH.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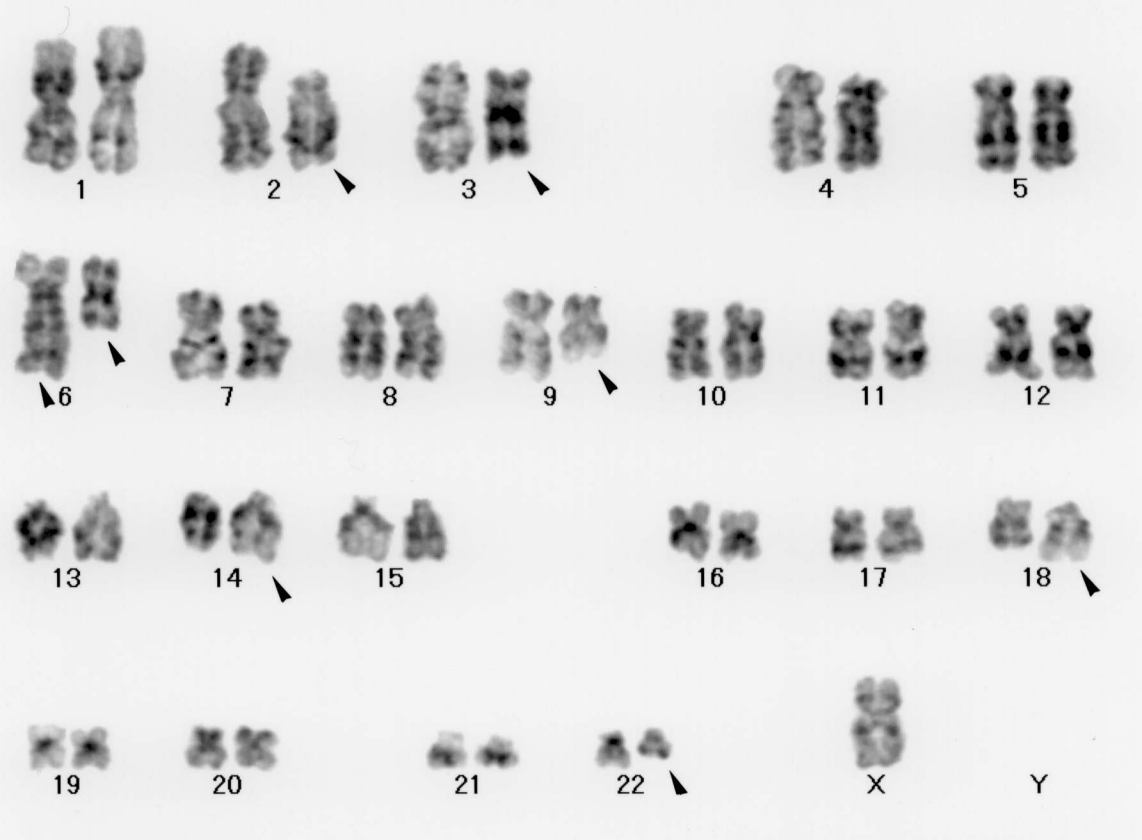
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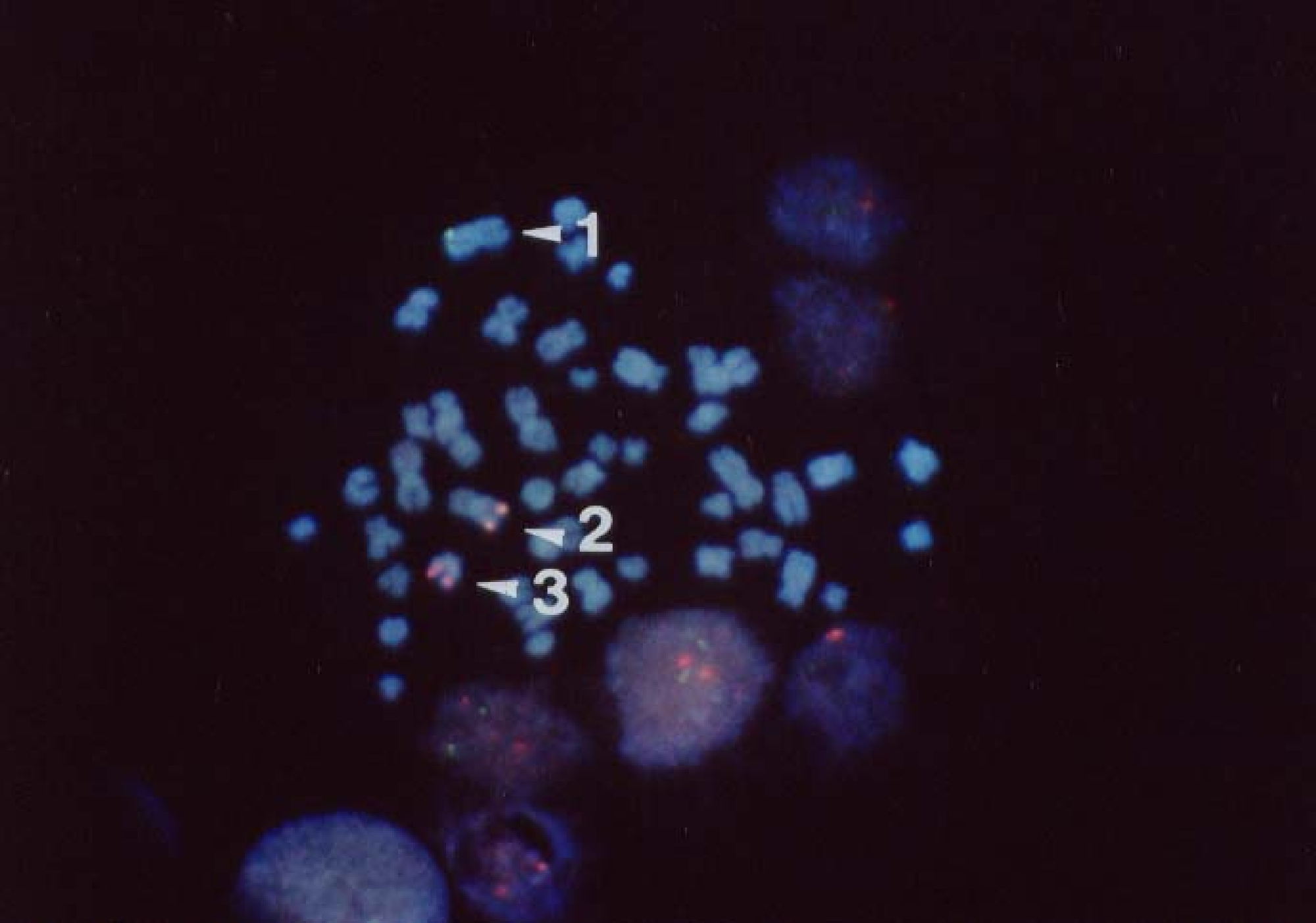
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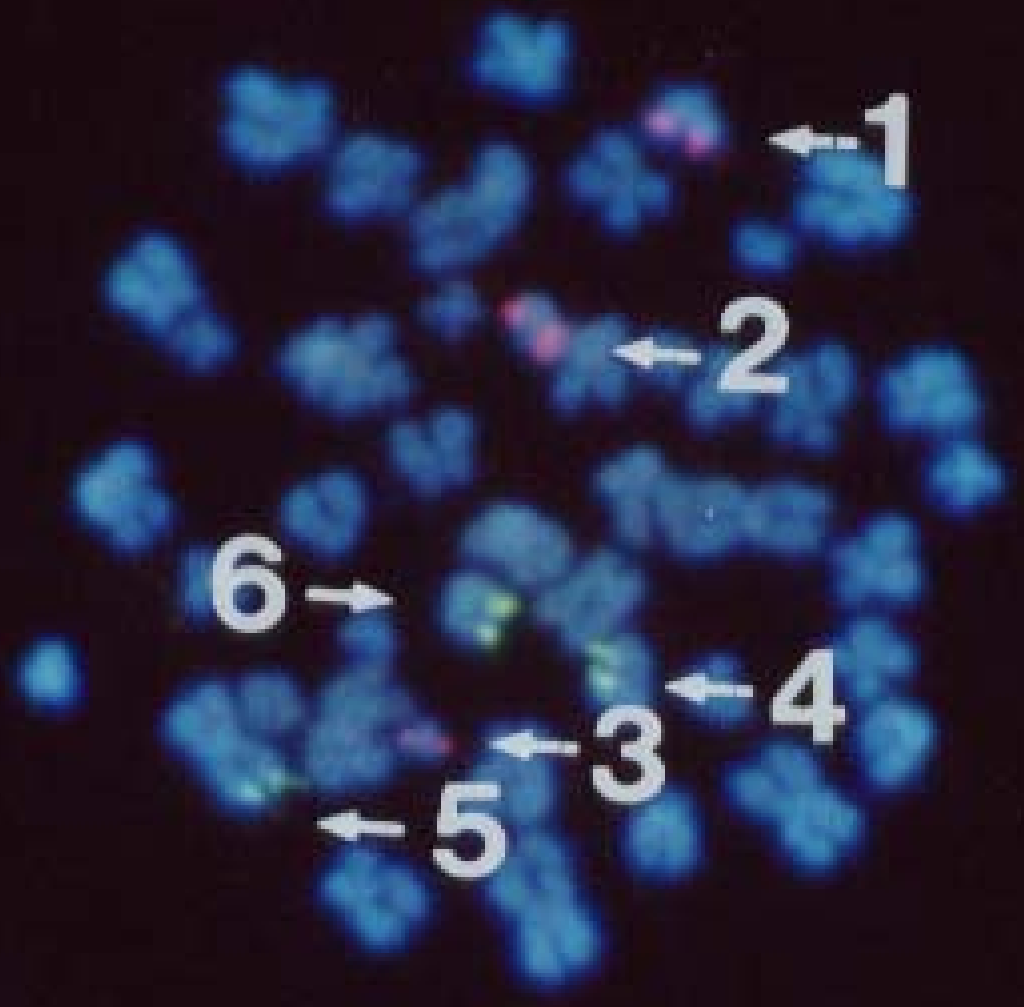
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