Lymphome B agressif avec double réarrangement *MYC* et *BCL6* associé à un profil d'aberration 11q

Christine Lefebvre

GFCH du 1er février 2024

Mr A. 77 ans

Pancytopénie fébrile

Antécédents :

- Décompensation cardiaque, dysfonction biventriculaire rythmique et ischémique
- Flutter commun
- Coronarographie : lésions tritronculaire
- Hypertension artérielle
- Dyslipidémie
- Diabète type 2
- Insuffisance rénale chronique
- Pneumopathie base droite en 2020

Clinique :

Altération de l'état général, hyperthermie 39°5,
Toux, dyspnée, pas d'adénopathie, pas de splénomégalie

Scanner TAP : bronchiolo-alvéolite étendue,
pas d'adénopathie profonde, pas de splénomégalie, pas de masse tumorale

Patient transféré en réanimation

Bilan sanguin

CYTO HEM

NUMERATION

Leucocytes		4,4	G/l	(4,1 - 9,9)
Erythrocytes	B	3,19	T/l	(4,28 - 5,57)
Hémoglobine	B	101	g/l	(134 - 167)
Hématocrite	B	0,30	l/l	(0,39 - 0,49)
VMC		93,1	fl	(82,1 - 97,0)
TCMH		32	pg	(27 - 33)
CCMH		340	g/l	(324 - 363)
IDR	H	14,8	%	(11,0 - 14,2)
Plaquettes	B	25	G/l	(161 - 393)
VMP		9,5	fl	(8,0 - 13,0)
Erythroblastes		0,4	G/l	
COM. NUMERATION				
Com. NUM 1		Identification et prélèvement vérifiés		
Com. NUM 2		Plaquettes vérifiées sur frottis sanguin		

FORMULE

PN %		12,5	%	
PN G/l	B	0,6	G/l	(1,8 - 6,1)
PE %		0,0	%	
PE G/l	B	0,0	G/l	(0,1 - 0,6)
PB %		4,2	%	
PB G/l	H	0,2	G/l	(0,0 - 0,1)
Lympho %		49,4	%	
Lympho G/l		2,2	G/l	(1,2 - 3,6)
Monocytes %		24,0	%	
Mono G/l	H	1,1	G/l	(0,2 - 0,7)
Promyélocytes		2,6	%	
Myélocytes		4,2	%	
Métamyélocytes		3,1	%	
Micromégacaryocytes		0,5	%	
TOTAL		100,0		

COM. FORMULE	
Contrôle Micro	Formule

BILAN DE COAGULATION

TP

Technique TP		1		
TQP		43,4	sec.	
TQP témoin		13,1	sec.	
TP	B	21	%	(> 70)
INR		3,39		
RC		AVK		
RD		.....		

TCA

Technique TCA		1		
TCA		47,4	sec.	
TCA témoin		33,4	sec.	
RATIO TCA	H	1,42		(< 1,20)
RC		AVK		
RD		.....		
Fibrinogène	H	9,0	g/l	(2,1 - 4,1)
TQP FACT AVK				
Monomères de fibrine	H	54,8	µg/ml	(< 10,0)
COMBC		Prélèvement vérifié		

Bilan Hépatique

Transaminases

TGO (ASAT)	H	846	UI/l	(13 - 40)
TGP (ALAT)	H	77	UI/l	(7 - 40)
Phos.alcaline	H	458	UI/l	(46 - 116)
GGT	H	80	UI/l	(< 73)
LDH	H	19895	UI/l	(120 - 246)
Albumine	B	27,5	g/l	(35,0 - 52,0)
Ferritine	H	>16500	µg/l	(22 - 322)

CRP = 321 mg/L

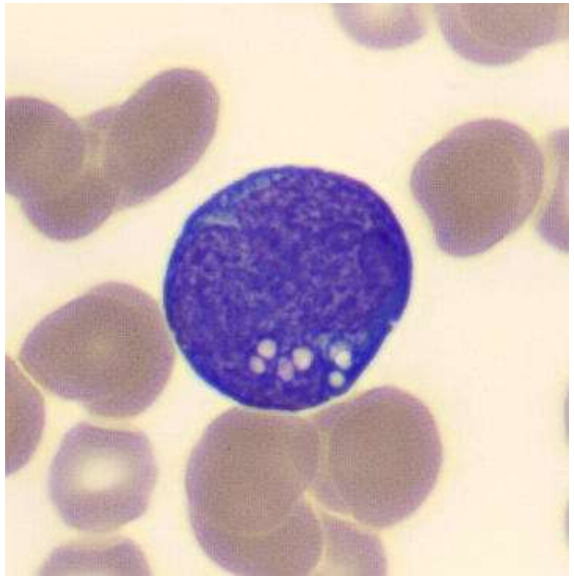
Hémoculture positive à Streptocoque

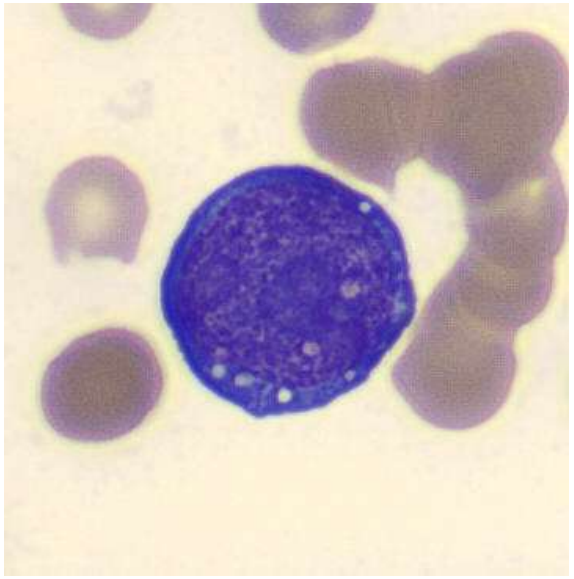
Frottis sanguin :

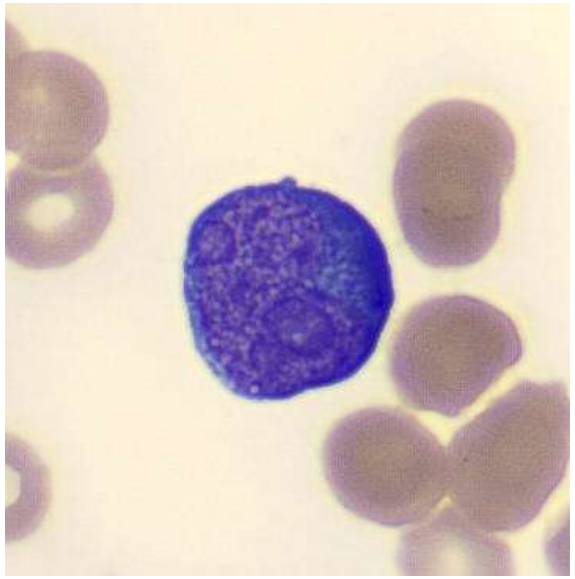
5% de cellules lymphoïdes anormales :

taille moyenne, rapport N/C élevé, noyau rond ou un peu irrégulier, 1 ou 2 nucléoles cerclés, cytoplasme très basophile avec vacuoles

Myélogramme : cellules altérées, 7% de cellules lymphoïdes anormales



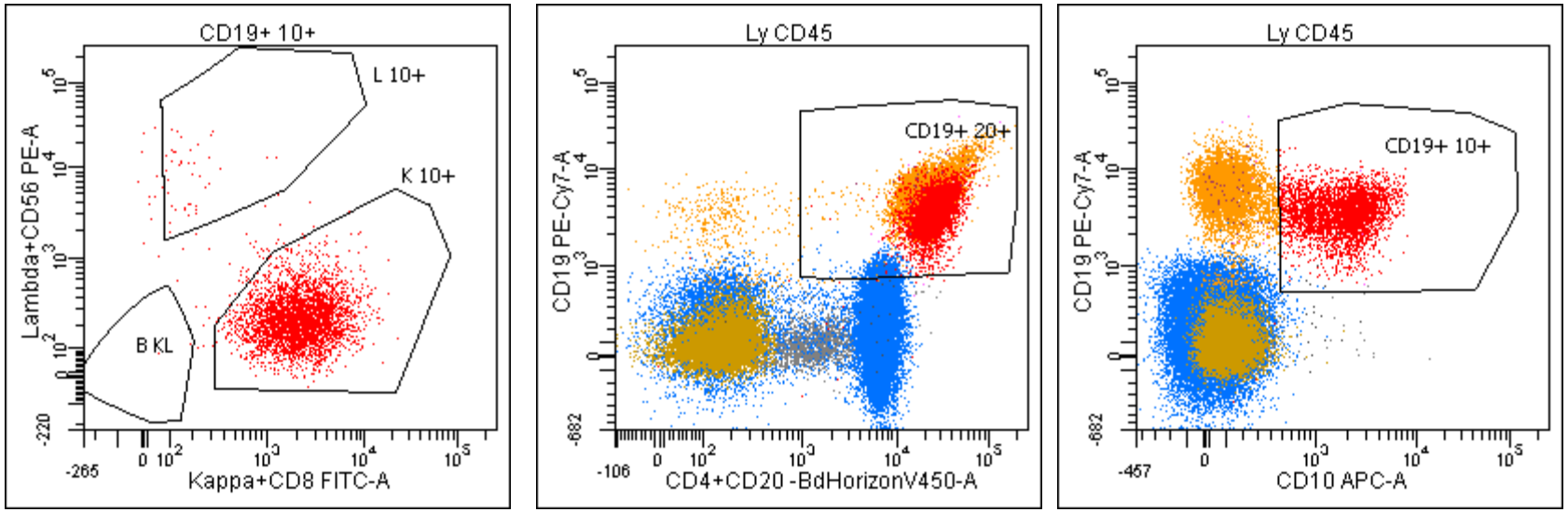




Hypothèses diagnostiques :

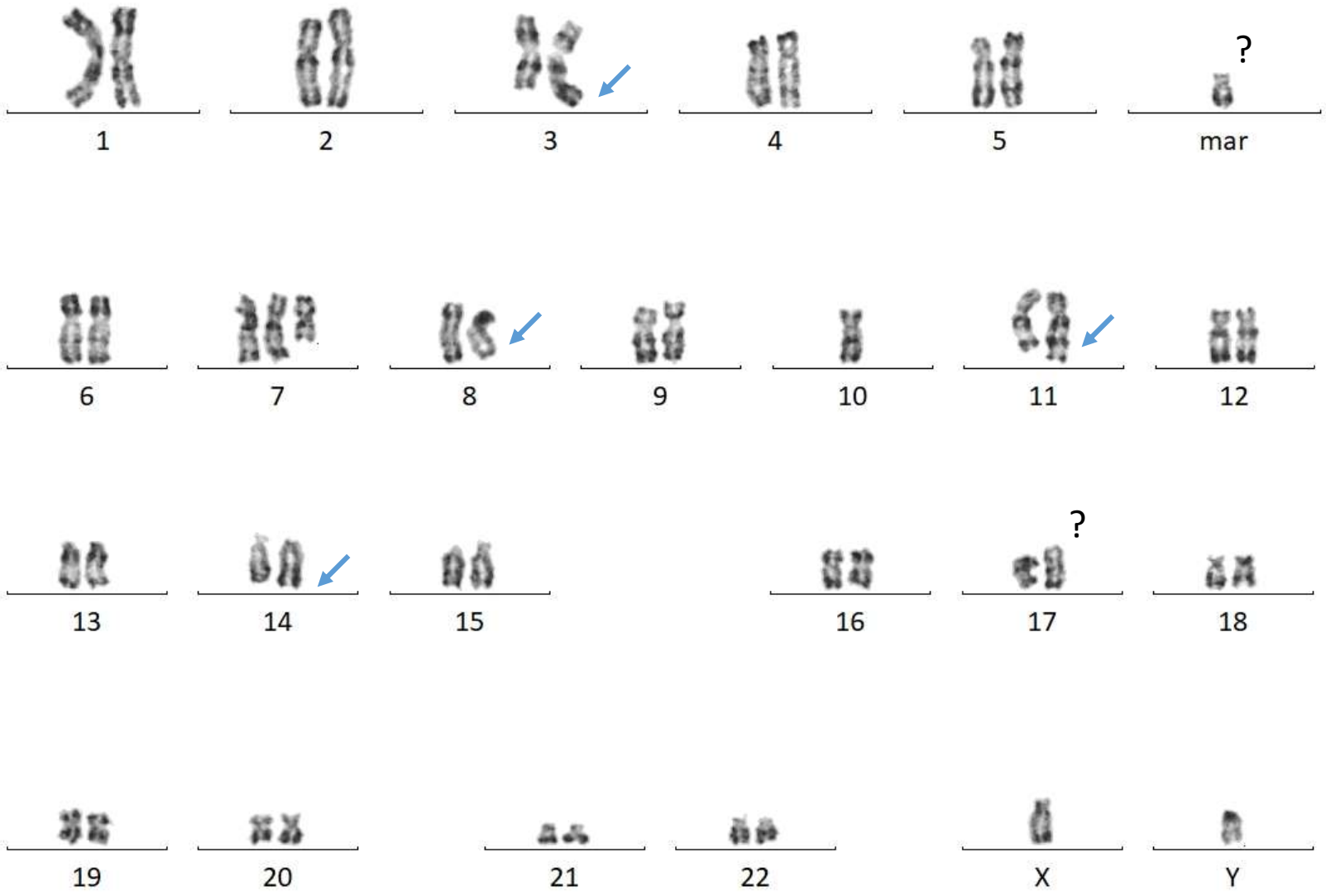
- Lymphome de Burkitt
- Lymphome B de haut grade
- ? « double/triple hit »

Immunophénotypage (moelle) :



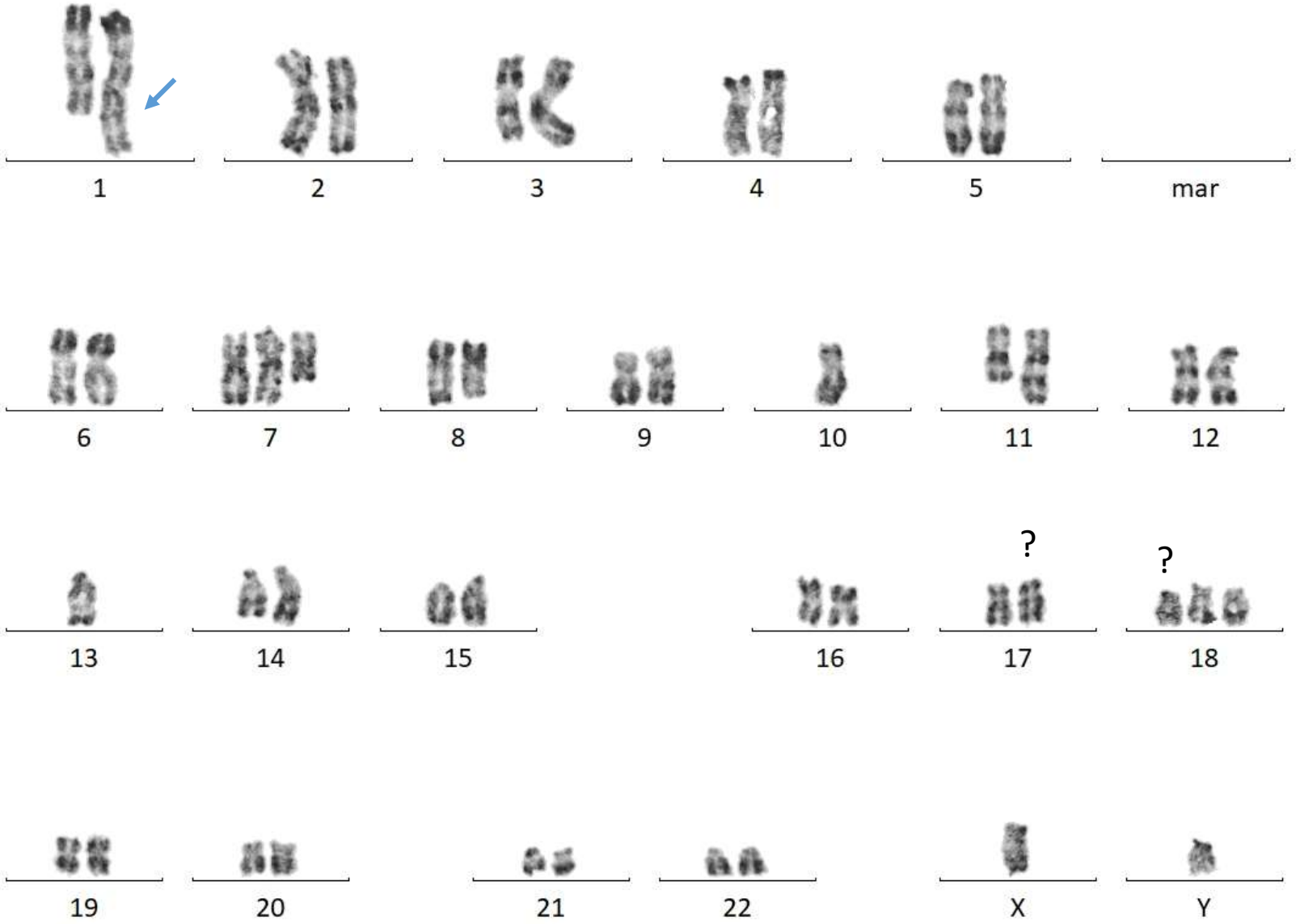
Présence d'une population homogène de lymphocytes B (restriction isotypique des chaînes légères d'Ig de type kappa).
Ces cellules sont de taille moyenne en CMF, IgKappa, CD20+, CD5-, CD24+, CD10+, CD44+ phénotype compatible avec un diagnostic de lymphome B mature.
Ces cellules représentent 5% de la population totale.

Caryotype sur moelle
Culture non synchronisée 1h



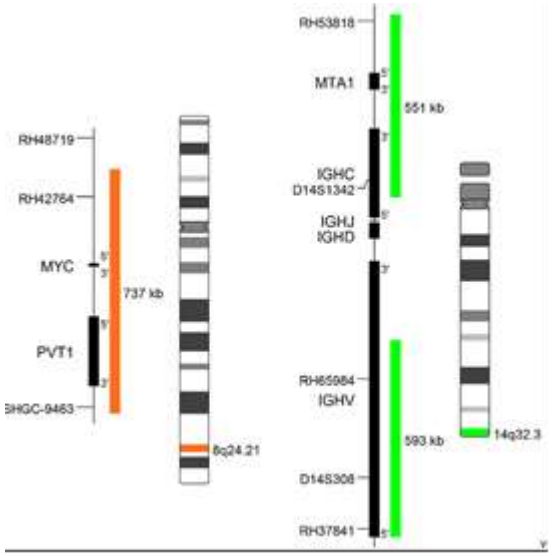
Caryotype sur moelle
Culture non synchronisée 1h

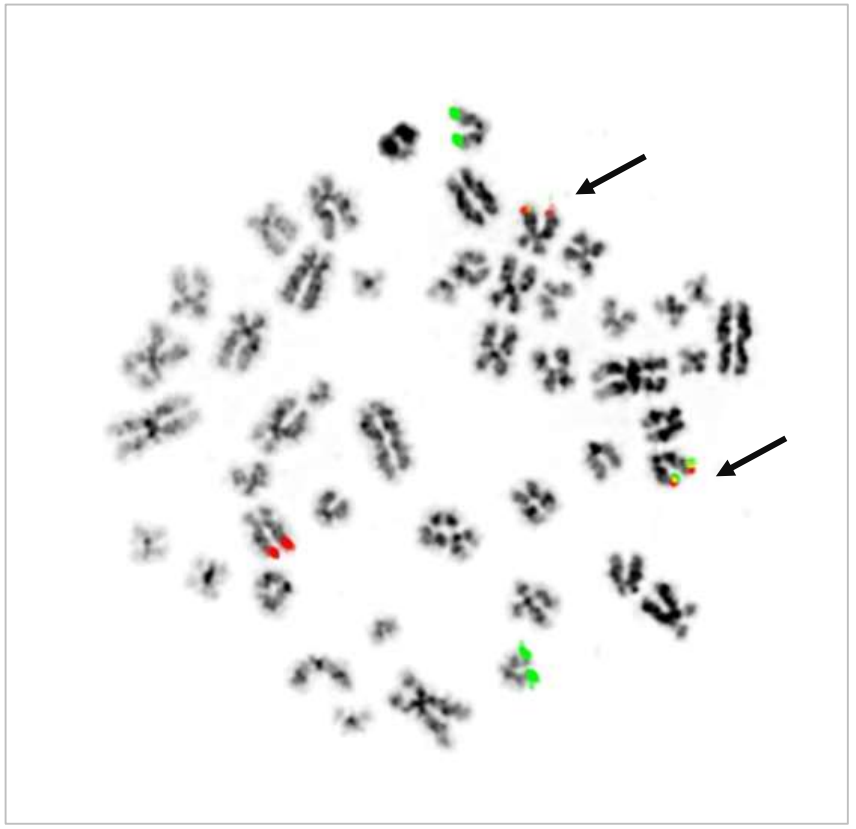
47,Y,del(X)(p12p23),der(3)t(3;?10)(q27;q?21),+7,del(7)(q21q35),
t(8;14)(q24;q32),-10,add(11)(q24),-13,?21,+mars[6]/
46,sl,dup(1)(q12q43),-13[6]

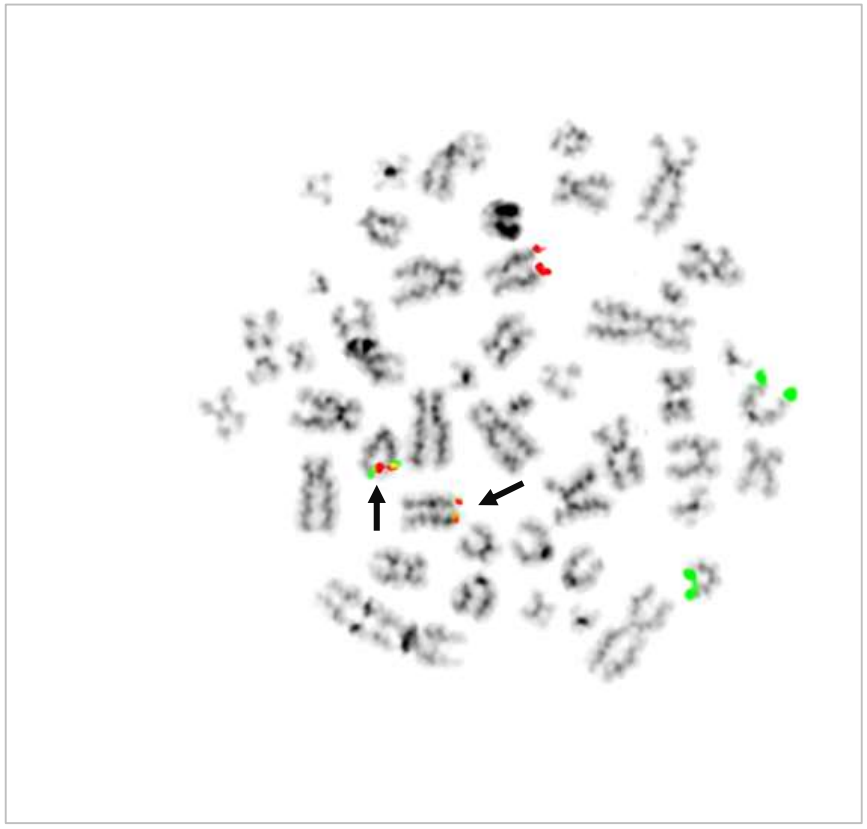


FISH

Sonde IGH/MYC DF



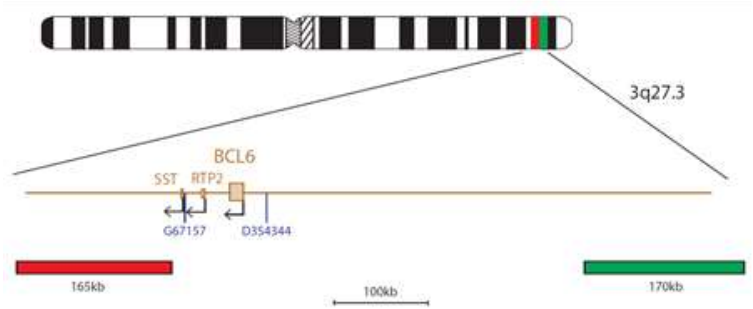


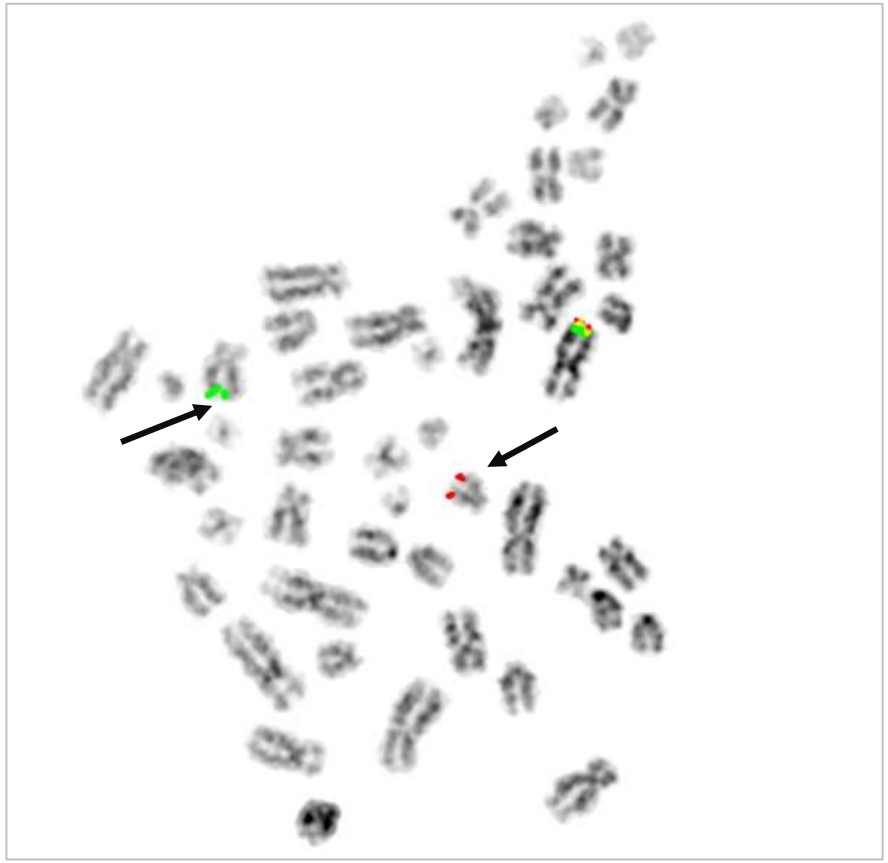


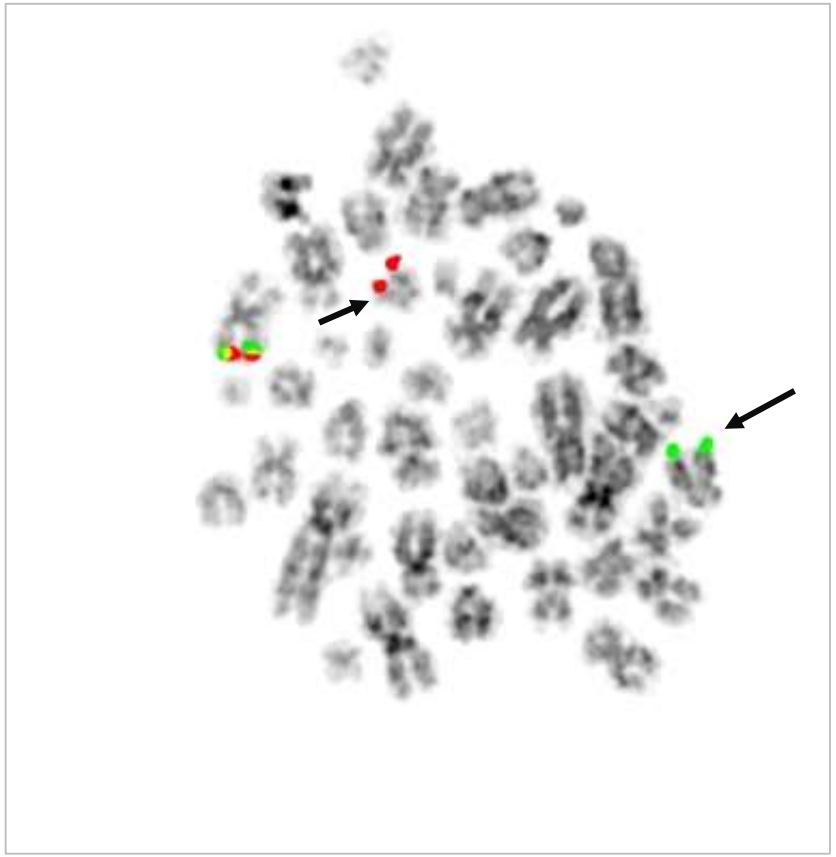
Réarrangement IGH*::MYC* par t(8;14)(q24;q32)
Signal IGH surnuméraire sur marqueur

FISH

Sonde BCL6 BA



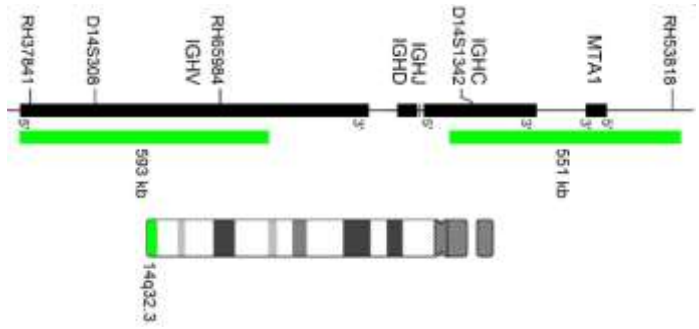


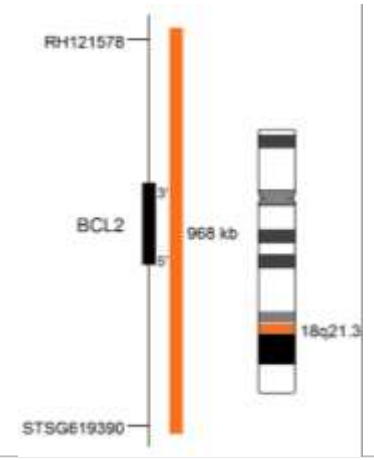


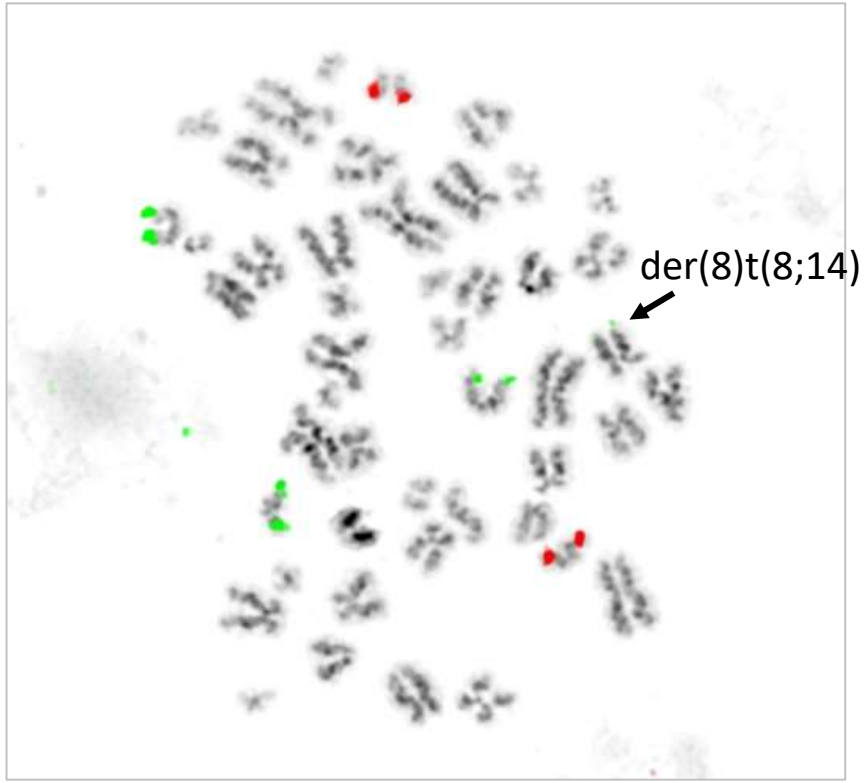
Réarrangement *BCL6* : partenaire ?

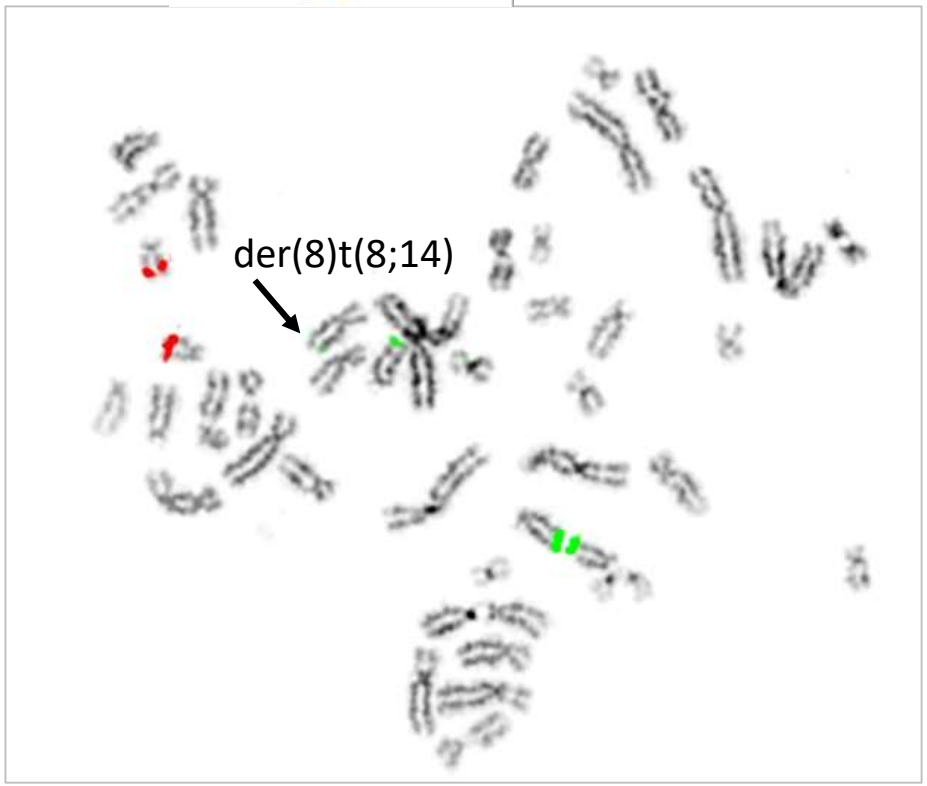
FISH

Sonde IGH/BCL2 DF





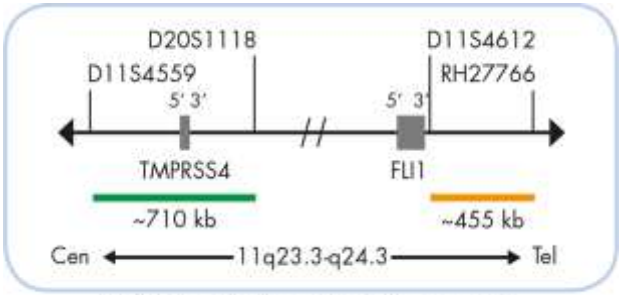




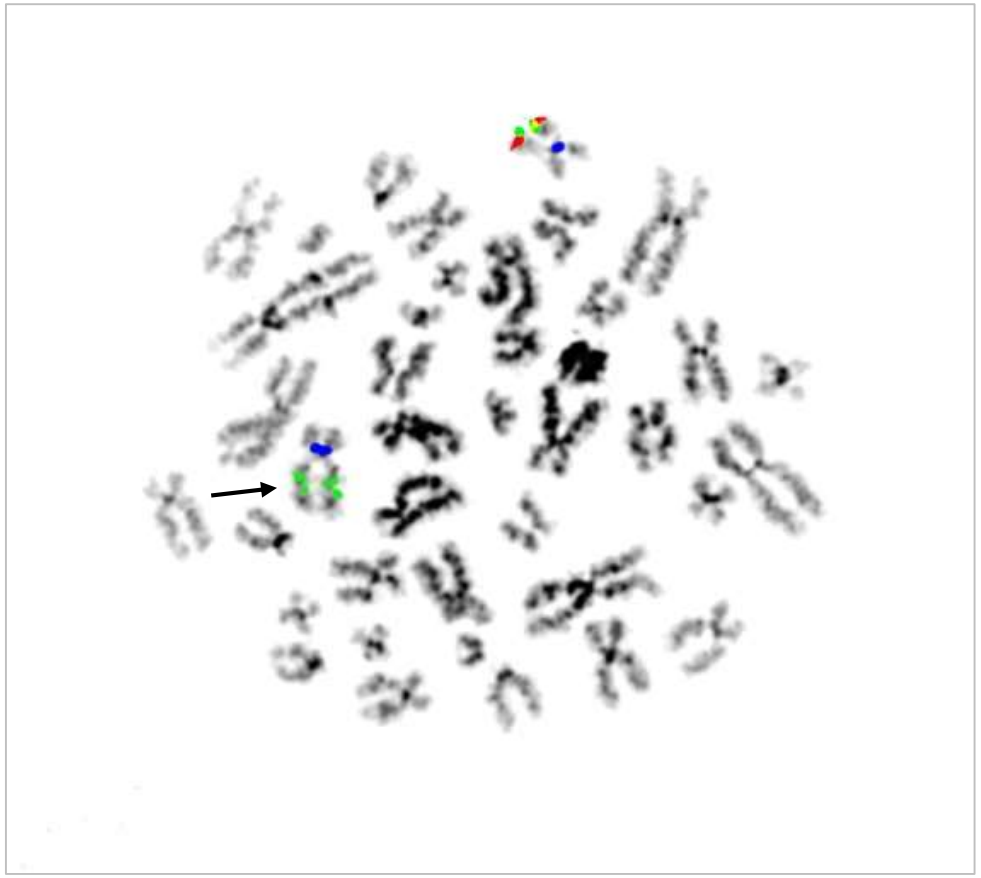
Absence de réarrangement IGH*::BCL2*, absence de gain *BCL2*

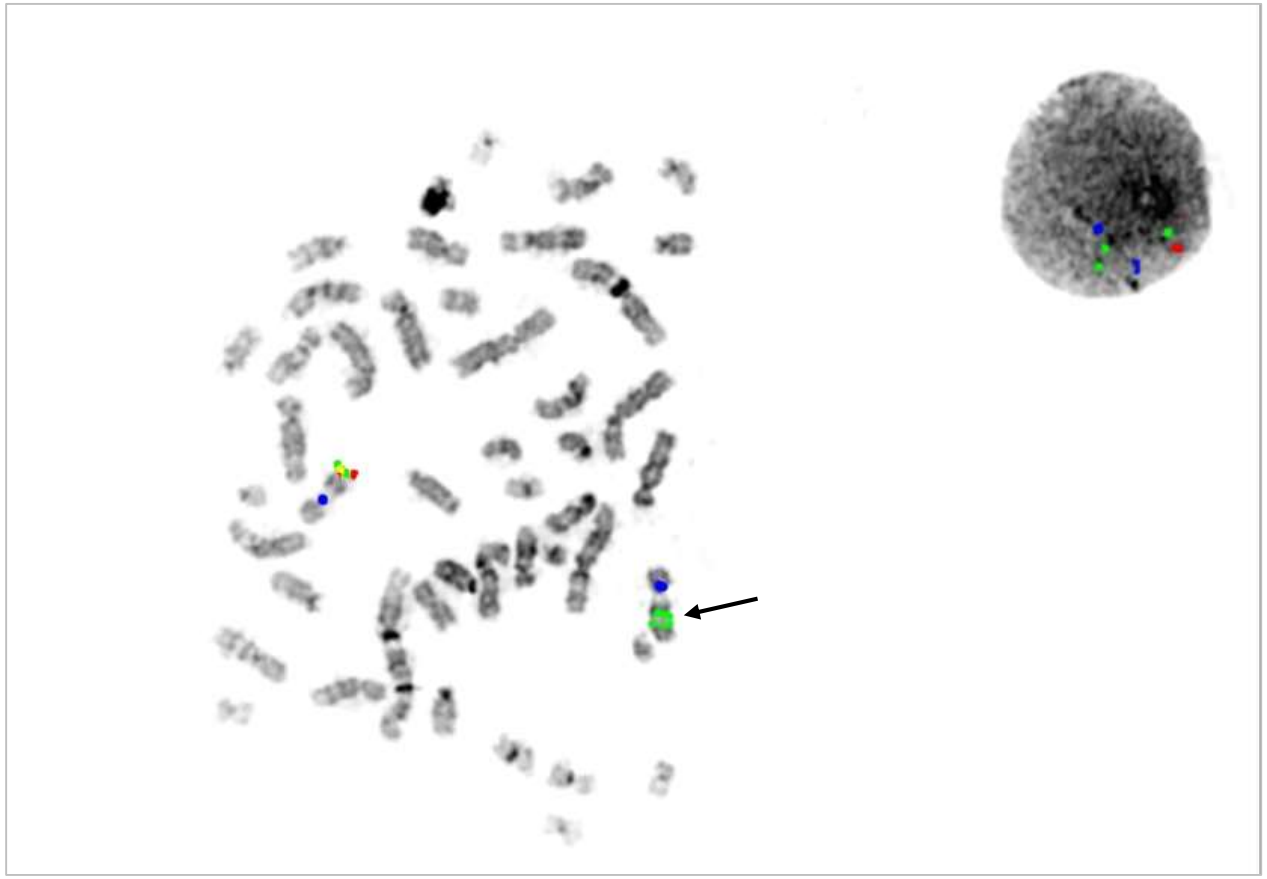
FISH

Sonde 11q23.3 / 11q24 / CEN11



SPEC 11q Probe map (not to scale).

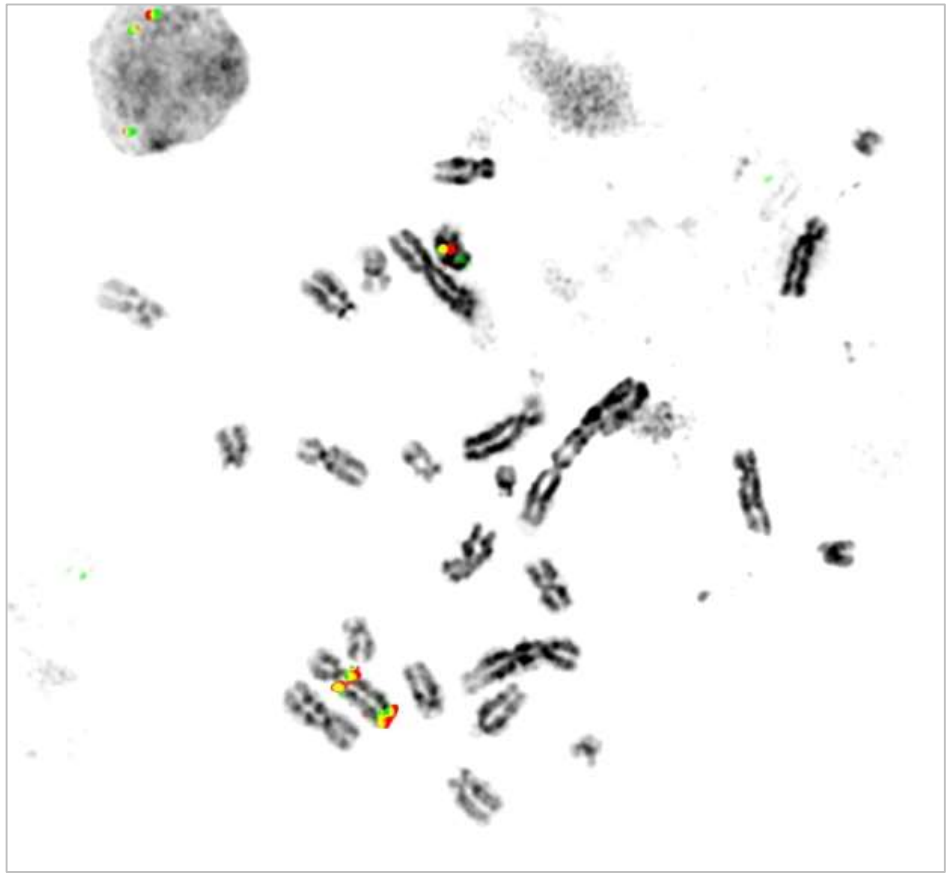




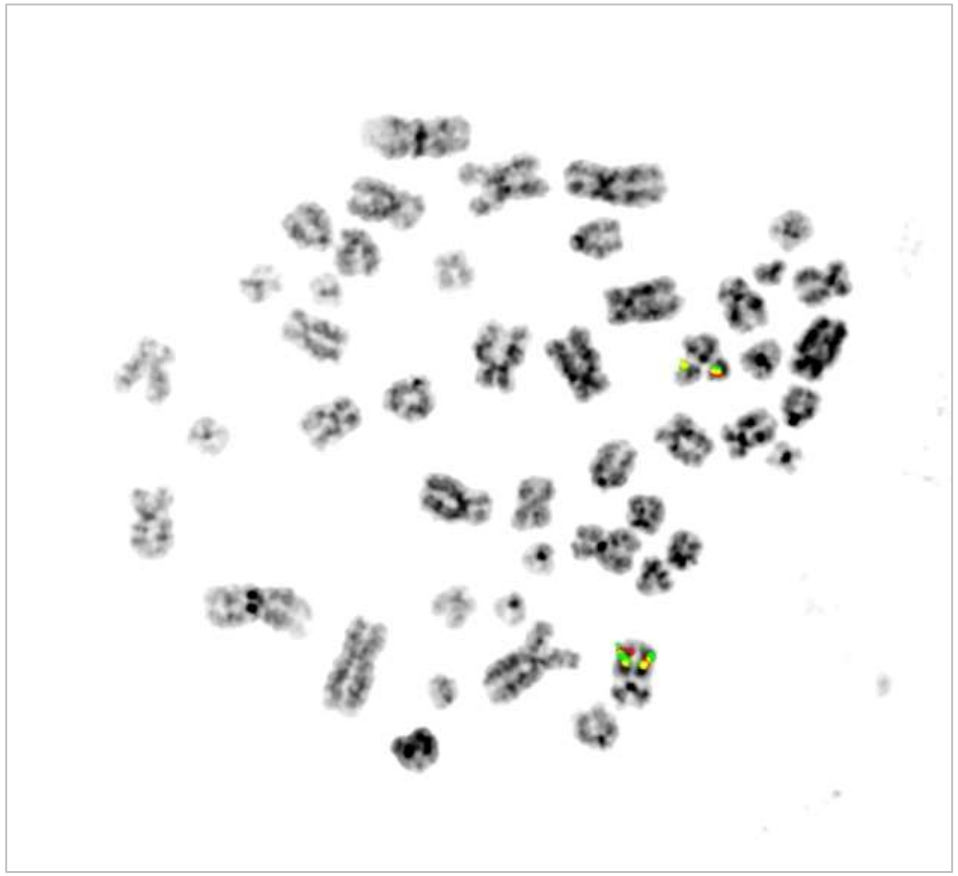
Profil de gain 11q23.3 / délétion 11q24 → aberration 11q

FISH L’anomalie 11q est le résultat d’une duplication segmentaire avec inversion

Sonde CCND1 ba (11q13.3)



Sonde KMT2A ba (11q23.3)



→ der(11)dup(11)(q23q12)del(11)(q24q25)

DIAGNOSTIC

Diagnostic de lymphome B agressif avec double réarrangement *MYC* et *BCL6*
Réarrangements IGH*::MYC et BCL6::?*
Accompagné d'un profil d'aberration 11q : gain 11q23.3 et délétion 11q24.
Présentation clinique : extra-ganglionnaire.

Les lymphomes B de haut grade/ à grandes cellules avec réarrangement *MYC/BCL2* ou *MYC/BCL6* peuvent s'accompagner d'un profil d'aberration 11q.

Le diagnostic d'un lymphome B à grandes cellules avec aberration 11q doit nécessairement être associé à un profil non réarrangé pour les cibles *MYC, BCL2, BCL6*.
La sonde KMT2A seule ne peut être utilisée pour établir le diagnostic de lymphome B avec aberration 11q.

Intérêt d'une culture minimale (« direct ») : métaphases déjà présentes, noyaux préservés.

Dénomination

WHO 2023 (site officiel blue books) → ne constitue pas une entité
mais un sous-type de HGBL, NOS ou DLBCL, NOS (LBCL/HGBL avec réarrangements *MYC* et *BCL6*)

Diffuse large B-cell lymphoma / high grade B-cell lymphoma with MYC and BCL2 rearrangements

Definition

Diffuse large B-cell lymphoma/High-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements (DLBCL/HGBL-MYC/BCL2) is an aggressive mature B-cell lymphoma with structural chromosomal aberrations with breakpoints at both *MYC* and *BCL2* loci.

Pathogenesis …

Large B-cell lymphoma/High-grade B-cell lymphoma with MYC and BCL6 rearrangements

DLBCL/HGBL-MYC/BCL2 represent a homogeneous pathological entity with close relationship to FL pathogenesis and related molecular DLBCL subtypes { 29475959 ; 30523716 ; 31844144 ; 32289277 }. In contrast, DLBCL/HGBL with *MYC* and *BCL6* translocations, but lacking *BCL2* translocation, diverge from DLBCL/HGBL-*MYC/BCL2* in patterns of presentation { 23348205 ; 30113335 ; 29581544 ; 33548250 }, frequent non-GCB IHC phenotypes, and ABC-like gene expression profiles { 24179151 ; 26565895 ; 29475959 ; 31844144 }. In addition, they show infrequent mutations of epigenetic regulators linking DLBCL/HGBL-*MYC/BCL2*, FL and EZB-DLBCL cluster, but instead show a more varied pattern including mutations in genes such as *PIM1* and *CD79B* that have been linked to ABC-DLBCL { 29713087 ; 31844144 }. Since current evidence points to a heterogeneous category with variable gene expression profiles and mutational spectra, these cases are excluded from the DLBCL/HGBL-*MYC/BCL2* category and included in DLBCL, NOS or HGBL, NOS. Their presence, however, should be reported to allow for their inclusion into ongoing clinical trials. In addition, such cases have shown variable risk association in different series { 26373676 ; 26426741 ; 26565895 ; 26573234 ; 27347428 ; 29903764 ; 31498031 }.

ICC 2022 : catégorie provisoire → HGBL avec réarrangements *MYC* et *BCL6*

High-grade B-cell lymphoma with *MYC* and *BCL2* rearrangement	The category is redefined to exclude patients with only *MYC* and *BCL6* rearrangements. Some neoplasms may express terminal deoxynucleotide transferase without being considered a B-lymphoblastic neoplasm.
High-grade B-cell lymphoma with MYC and BCL6 rearrangements	With the change in the definition of high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements, this provisional category was added.

Campo, Blood, 2022

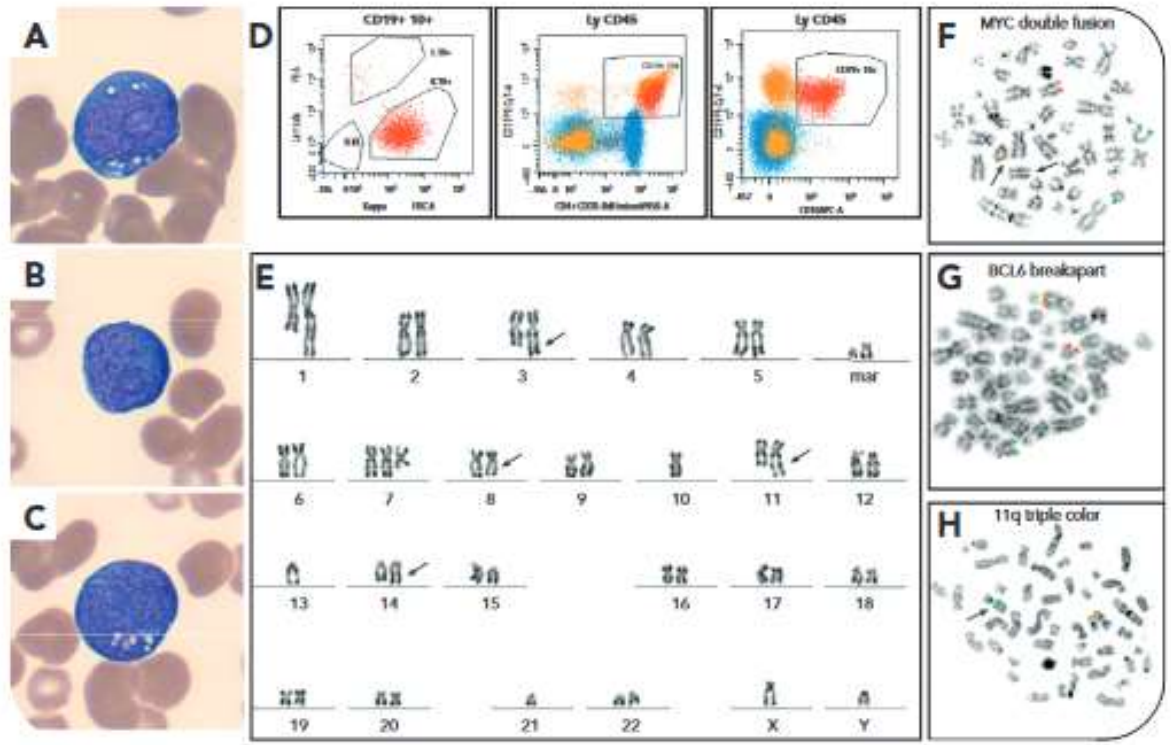
Table 3: Distribution and frequency of cytogenetic abnormalities in aggressive B-cell lymphomas (excluding primary mediastinal B-cell lymphoma).

Entities	Karyotype	*MYC* rearrangement	*BCL2* rearrangement	*BCL6* rearrangement	*IRF4* rearrangement	11q23 gain/ 11q24 loss d	References
BL	Simple [a]	100% Always IG*::MYC*	No	No	No	Rare	[1,67,92,98]
DLBCL, NOS	Complex	8-12%	15-20%	30%	Rare [b]	Rare	[1,5,71,75,100,101]
HG/DLBCL-*MYC/BCL2*	Complex	100% : 60% IG::*MYC* 40% non-IG*::MYC*	100%, mostly IGH*::BCL2*	10-15%	Rare [c]	Rare	[1,2,74,96]
HG/DLBCL, NOS-*MYC/BCL6*	Complex	100% 30% *BCL6::MYC*	No	100% 30% *BCL6::MYC*	Unknown	Rare	[1,2,75,77,97]
HG/LBCL-11q	Complex	No	No	No	No	100% [d,e]	[92,93]
LBCL-*IRF4*	Unknown	No	No	~10%	100% [c]	No	[1,92,100,101]

blood work
images in hematology

Extranodal presentation of a *MYC/BCL6* double-hit lymphoma with 11q aberration in an older patient

Christine Lefebvre and Gautier Szymanski, Centre Hospitalier Universitaire Grenoble Alpes



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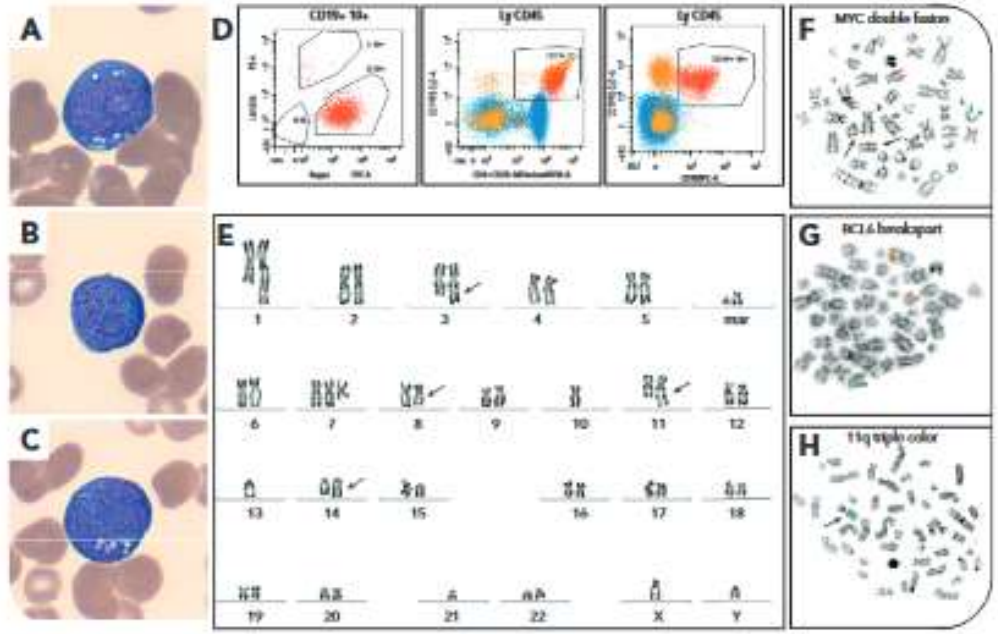

A 77-year-old man presented with weakness and pancytopenia. His laboratory values showed a white blood cell count of 4 × 10^9/L; neutrophils, 0.6 × 10^9/L; hemoglobin, 101 g/L; and platelet count, 25 × 10^9/L. Physical examination and computed tomography revealed no adenopathy or organomegaly. Peripheral blood smears showed 7% of medium-sized lymphoid cells with basophilic cytoplasm, round or irregular nuclei, finely clumped chromatin, and various-sized nucleoli (panels A-C; May-Grünwald-Giemsa stain; 100× objective, original magnification ×1000). Bone marrow was massively infiltrated. Flow cytometric analysis demonstrated a $CD20^+/CD10^+/CD5^-$ population with K chain restriction (panel D). The karyotype was complex with t(8;14) translocation, 3q abnormality, and 11q duplication-inversion (panel E; 46~47,Y,del(X)(p11p22),dup(1)(q12q43),der(3)t(3;?10)(q27;q22),+7,del(7)(q21q36),t(8;14)(q24;q32),-10,dup(11)(q23q12),add(12)(p11),-13,-21,+2mars[cp13].ish der(3)(BCL6-),t(8;14)(MYC+,IGH+;IGH+,MYC+),der(11)(11pter->11q23::11q23->11q13::11q25->11qter)(D11Z1+,FAHAH1B2++,ETS1-),der(12)(5'BCL6+),mar(3'BCL6+,IGH+)[10]). Fluorescence in situ hybridization confirmed the co-occurrence of *IGH::MYC* rearrangement (panel F, double fusion); *BCL6* rearrangement (panel G, split); and 11q23 gain and 11q24 loss targeting *FAHAH1B2* and *ETS1* loci, respectively (panel H, 3 green signals, 1 red signal), without *BCL2* rearrangement (panels F-H; 63× objective, original magnification ×630). The patient quickly died.

This leukemic case was diagnosed as high-grade B-cell lymphoma with *MYC* and *BCL6* rearrangements (HGBL-*MYC/BCL6*). The 11q23 gain/11q24 loss pattern constitutes the cytogenetic hallmark of the "large B-cell lymphoma with 11q aberration" that diagnostically lacks *MYC* rearrangement. However, 11q aberration and *MYC* rearrangement may occasionally co-occur in HGBL. This is the first report of HGBL-*MYC/BCL6* with 11q aberration.

Dénomination

WHO 2023 (site officiel blue book) → ne constitue pas une entité
Est considéré comme sous-type de HGBL, NOS ou DLBCL, NOS (DLBCL/HGBL avec réarrangements *MYC* et *BCL6*)

ICC 2022 : catégorie provisoire → HGBL avec réarrangements *MYC* et *BCL6*

Table 1. continued

WHO Classification, revised 4th edition	WHO Classification, 5th edition	ICC 2022
High grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements	Diffuse large B-cell lymphoma/High grade B-cell lymphoma with *MYC* and *BCL2* rearrangements	High grade B-cell lymphoma with *MYC* and *BCL2* rearrangements
Not included as an entity	Not included as an entity	High grade B-cell lymphoma with MYC and BCL6 rearrangements (provisional entity)

Caryotype sur moelle
Culture non synchronisée 1h