Scope

The Atlas of Genetics and Cytogenetics in Oncology and Haematology is a peer reviewed on-line journal in open access, devoted to genes, cytogenetics, and clinical entities in cancer, and cancer-prone diseases. It is made for and by: clinicians and researchers in cytogenetics, molecular biology, oncology, haematology, and pathology. One main scope of the Atlas is to conjugate the scientific information provided by cytogenetics/molecular genetics to the clinical setting (diagnostics, prognostics and therapeutic design), another is to provide an encyclopedic knowledge in cancer genetics. The Atlas deals with cancer research and genomics. It is at the crossroads of research, virtual medical university (university and post-university e-learning), and telemedicine. It contributes to "meta-medicine", this mediation, using information technology, between the increasing amount of knowledge and the individual, having to use the information. Towards a personalized medicine of cancer.

It presents structured review articles ("cards") on:
1- Genes,
2- Leukemias,
3- Solid tumors,
4- Cancer-prone diseases, and also
5- “Deep insights” : more traditional review articles on the above subjects and on surrounding topics.
It also present
6- Case reports in hematology and
7- Educational items in the various related topics for students in Medicine and in Sciences.
The Atlas of Genetics and Cytogenetics in Oncology and Haematology does not publish research articles.

See also: http://documents.irevues.inist.fr/bitstream/handle/2042/56067/Scope.pdf

Editorial correspondence

Jean-Loup Huret, MD, PhD,
Genetics, Department of Medical Information,
University Hospital
F-86021 Poitiers, France
phone +33 5 49 44 45 46
jlhuret@AtlasGeneticsOncology.org or Editorial@AtlasGeneticsOncology.org

Editor, Editorial Board and Publisher


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Mailing Address: Catherine Morel, 2, Allée du Parc de Brabois, CS 10130, 54519 Vandoeuvre-lès-Nancy France.
Email Address: catherine.morel@inist.fr
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Gene Section
Short Communication

TYRP1 (tyrosinase-related protein 1)

Kunal Ray, Mainak Sengupta, Sampurna Ghosh

Academy of Scientific and Innovative Research (AcSIR), Campus at CSIR - Central Road Research Institute, Mathura Road, New Delhi - 110 025, kunalray@gmail.com (KR); University of Calcutta, Department of Genetics, 35, Ballygunge Circular Road, Kolkata - 700 019, sengupta.mainak@gmail.com; sampurna_ghosh@yahoo.in (MS, SG) India.

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Abstract

TYRP1 gene, having a chromosomal location of 9p23, encodes a melanosomal enzyme belonging to the tyrosinase family. TYRP1 catalyses oxidation of 5,6-dihydroxyindole-2-carboxylic acid (DHICA) into indole-5,6-quinone-2-carboxylic acid. TYRP1 is also thought to play a role in stabilizing tyrosinase and modulates its catalytic activity, in maintenance of melanosome structure, affecting melanocyte proliferation and melanocyte cell death. Defects in this gene cause oculocutaneous albinism type III; OCA III (also known as rufous oculocutaneous albinism).

Keywords
TYRP1, albinism, OCA III

Identity

Other names: CATB, TRP1, CAS2, TYRP 3, TRP 3, EC 1.14.18.1, b-PROTEIN
HGNC (Hugo): TYRP1

Location: 9p23

DNA/RNA

Description
In Chromosome 9, the 24,852 bases long gene starts from 12,685,439 bp from pter and ends at 12,710,290 bp from pter; Orientation: Plus strand. The gene contains 8 exons and spans ~24.8 kb of the genome.

Transcription
The gene encodes a 2876 bp mRNA. This gene has been reported to have 7 transcripts (splice variants) of which 3 have been found to be protein coding (http://asia.ensembl.org/Homo_sapiens/Gene/Summary?g=ENSG00000107165;r=9:12685439-12710290). Microphthalmia-associated transcription factor (MITF) stimulates melanin synthesis by up-regulating expression of TYRP1 acting as a transcription factor.

Cytogenetic band showing TYRP1 locus (Ref: http://www.genecards.org/cgi-bin/carddisp.pl?gene=TYRP1)

Protein
**Description**

The gene encodes a protein, containing 537 amino acids, of molecular mass 60724 Da; it is an enzyme needing Cu++ as cofactor (binds 2 copper ions per subunit).

**Expression**

TYRP1 is mainly expressed in two cell types: (a) Melanocytes that are derived from neural crest cells colonizing within iris, cochlea, skin and choroids, and (b) Retinal pigment epithelial (RPE) cells that are derived from the optic cup. It has also been reported to be expressed in heart and ear (http://genatlas.medecine.univ-paris5.fr/fiche.php?symbol=TYRP1). Interestingly, expression of the gene in the following tissue types are evident by its existence in the corresponding cDNA libraries: brain, cerebrum, ear, embryonic tissue, eye, fetus, gastrointestinal tract, heart, kidney, mammary gland, nervous, retina, skin, stem cell and stomach (http://cgap.nci.nih.gov/Genes/GeneInfo?ORG=Hs LLNO=7306).

**Localisation**

TYRP1 is a melanosomal membrane protein.

**Function**

TYRP1 acts a 5,6-dihydroxyindole-2-carboxylic acid (DHICA) oxidase converting DHICA to Indole 5,6-quinone carboxylic acid in the melanin biosynthesis pathway. It is also involved in maintaining the stability of tyrosinase protein, modulating its catalytic activity in eumelanin synthesis, in maintenance of melanosome structure and affects melanocyte proliferation and cell death.

**Homology**

Interspecies: Homolog to murine brown locus. Intraspecies : Homolog to tyrosinase family of proteins comprising of TYR, TYRP1 and DCT (TYRP2)

**Mutations**

**Germinal**

A small number of mutations in the TYRP1 gene have been found to cause oculocutaneous albinism III. Seventeen mutations have been reported in Albinism Database (http://www.ifpcs.org/albinism/oca3mut.html). It is to be noted that Albinism Database has been updated till 2009. OCA3 has been described primarily in dark-skinned people from Southern Africa. Affected individuals have reddish-brown skin, ginger or red hair, and hazel or brown irises. OCA3 or Rufous oculocutaneous albinism has been estimated to affect 1.8500 individuals in Africa; however, it is very rare in any other populations as per published literature.

**Somatic**

Somatic mutations in TYRP1 have been identified in different cancers (https://dcc.icgc.org/genes/ENSG00000107165, http://cancer.sanger.ac.uk/cosmic/search?q=TYRP1), but no causality has been reported.

**Implicated in**

**Melanoma**

TYRP1 expression has been found to be significantly correlated with distant metastasis-free survival (DMFS), overall survival and Breslow thickness in melanoma patients (F Journe et al., 2011). Polymorphisms in 3’UTR of TYRP1 mRNA: rs683 and rs910 have been found to affect TYRP1 mRNA regulation by miR-155 and its subsequent translation into protein (El Hajj P et al., 2015). These SNPs have been hypothesized to render TYRP1 expression nonsusceptible to miR-155 activity and disclose a prognostic value for TYRP1 protein in a subgroup of melanoma patients. TYRP1 SNP rs1408799 has been found to be associated with melanoma risk (OR, 0.77; 95% CI, 0.60-0.98) (Nan H et al., 2009).

**References**


This article should be referenced as such:

HMGN5 (High Mobility Group Nucleosome binding domain 5)

Michael Bustin, Takashi Furusawa

National Cancer Institute, NIH, Building 37, Room 3122, 37 Convent Drive, Bethesda, MD 20892, US.
bustinm@mail.nih.gov; furusawt@mail.nih.gov; http://irp.nih.gov/pi/michael-bustin

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Abstract

HMGN5 is a member of the high mobility group nucleosome binding domain (HMGN) protein family. HMGN proteins are ubiquitously expressed in vertebrate cells. They are nuclear proteins that bind specifically to nucleosomes without specificity for the DNA sequence and affect the structure and function of chromatin. HMGN5 sequences have been detected in all vertebrate tissues examined. HMGN5 differs from the other members of the HMGN family in that it is significantly larger and its amino acid sequence varies significantly between different vertebrate species.

Keywords: HMGN5, NSBP1, Chromatin

Identity

Other names: NSBP1, NBP-45

HGNC (Hugo): HMGN5

Location (base pair): Starts at 81113701 and ends at 81201942 bp from pter (according to NCBI 11-Apr_2016)

HMGN5 (High Mobility Group Nucleosome binding domain 5)  Bustin M and Furusawa T


DNA/RNA

**Description**
NCBI Reference Sequence: NC_000023.11; Coding positions from 81,113,701 to 81,201,942 (length: 88,242 bp). Both human and mouse Hmgn5 genes are composed of 6 exons and 5 introns.

**Transcription**
849 bp cDNA for Human HMGN5. No splicing isoforms are reported as of April 2016.

**Protein**

**Description**
Reference sequence for HMGN5 protein: NP_110390.1. HMGN5 contains 282 amino acid residues with a molecular weight of 31525 Da. HMGN5 belongs to the HMGN protein family.

HMGN5 contains a Nucleosome Binding Domain (residue 12-36) for chromatin interaction.

**Expression**
Expressed at low levels in most vertebrate cells.

**Localisation**
Nucleus.

**Function**
Modulates chromatin structure.

**Homology**
HomoloGene (NCBI) Genes identified as putative homologs: NP_110390.1 HMGN5, Homo sapiens; XP_001144951.2 Hmgn5, Pan troglodytes; XP_001103630 Hmgn5 Macaca mulatta; XP_002699982.3 Hmgn5, Bos taurus.

Implicated in

**Clear cell renal cell carcinoma (ccRCC)**

HMG5 expression is detected in renal tissues from clear cell renal cell carcinoma (ccRCC) patients and in ccRCC cell lines, and its expression level is associated with tumor grade. Knockdown of HMG5 induced cell cycle arrest and apoptosis, and inhibited invasion in ccRCC cell line 786-O. (Ji et al, 2012).

**Prostate Cancer**

Knock down of HMG5 inhibits the in vitro and in vivo growth of the human prostate cancer cell line DU145 by inducing cell cycle arrest and apoptosis (Jiang et al, 2010). Similar effect is also observed in the LNCaP prostate cancer cell line, too (Zhang et al, 2012). HMG5 knockdown exhibit increased apoptosis rate in response to ionizing radiation (Su et al, 2015). The normal prostate epithelial cells which are induced Ectopic HMG5 expression results in oncogenic phenotype such as colony formation and invasion (Guo et al, 2015). Tumorogenic activity of the cells which overexpress HMG5 is suppressed by MIR340 (microRNA-340) (Wei et al, 2015).

**Gliomas**

HMG5 is highly expressed in both low-grade and high-grade glioma tissue samples than normal brain tissues. The down regulation of HMG5 expression in human glioma cell line (U251 and U87) caused cell cycle arrest and apoptosis. (Qu et al, 2011).

**Bladder cancer**

The protein level of HMG5 in surgically removed bladder cancer specimens and human bladder cell lines is correlated with the increased tumor grade and pathologic stage. Knock down of HMG5 reduced cell viability and cell cycle promotion (Wahafu et al, 2010; Gan et al, 2015). The expression level of HMG5 is suppressed by MIR186 in human bladder cancer cells (Yao et al, 2015).

**Lung cancer**

HMG5 is highly expressed in lung cancer cell lines A549 and H1299. Downregulation of HMG5 inhibits cell proliferation and colony formation (Chen et al, 2012). MIR326 downregulated HMG5 expression in the non-small cell lung cancer (NSCLC) cell and inhibited cell proliferation and invasion of NSCLC (Li et al, 2016).

**Osteosarcoma**

Both HMG5 RNA and HMG5 protein are highly expressed in human osteosarcoma tumor. The expression level is also upregulated in osteosarcoma cell lines SaOS2 and MG63 while other cell lines U-2OS and MG63 showed lower expression level. HMG5 expression is induced by anticancer agents in these cell lines. Overexpression of HMG5 in U-2OS and MG63 cells increased drug resistance by upregulating autophagy (Yang et al, 2014).

**Breast cancer**

HMG5 is highly expressed in breast cancer tissues when compared with the adjacent non-cancerous tissues. Clinical and histopathologic analysis revealed that HMG5 expression level is correlated to the tumor grade and staging. Using the human breast cancer cell line MCA-MB-213 as a model, HMG5 knockdown resulted in inhibition of migration and invasion, and induced cell death (Weng et al, 2015).

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LMDRA (leucine rich melanocyte differentiation associated)

Kunal Ray, Mainak Sengupta, Sampurna Ghosh

Academy of Scientific and Innovative Research (AcSIR), Campus at CSIR - Central Road Research Institute, Mathura Road, New Delhi - 110 025, kunalray@gmail.com (KR); University of Calcutta, Department of Genetics, 35, Ballygunge Circular Road, Kolkata - 700 019, sengupta.mainak@gmail.com; sampurna_ghosh@yahoo.in (MS, SG) India.

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Abstract

C10orf11 encodes a leucine-rich repeat protein having a role in melanocyte differentiation. Mutations in this gene have been associated with autosomal recessive oculocutaneous albinism 7 (OCAVII).

Keywords: OCAVII, albinism, C10orf11

Identity

Other names: C10orf11, CDA017
HGNC (Hugo): LRMDA
Location: 10q22.3

DNA/RNA

Description
In Chromosome: 10, the 1,128,715 bases long gene starts from 75,431,453bp from pter and ends 76,560,167 bp from pter; Orientation: Plus strand. It contains 6 exons.

Transcription
C10orf11 encodes 16 splice variants of which 4 are protein coding and the remaining are processed transcripts.

Protein

Description
The gene encodes a 198 amino acids long leucine-rich repeat-containing protein of molecular mass 22568 Da.

Expression
The gene is expressed in embryonic melanoblasts and fetal melanocyte and has not been detected in retinal pigment epithelial cells. In addition the expression of the gene in the following tissue types are evident by its existence in the corresponding cDNA libraries: adrenal cortex, brain, cartilage, cerebellum, endocrine, eye, fetus, heart, kidney, liver, lung, muscle, nervous, pancreas, pancreatic islet, placenta, pooled tissue, prostate, skin, stem cell, testis and uterus (http://cgap.nci.nih.gov/Genes/GeneInfo?ORG=HsCID=118161LLNO=83938).

Localisation
10q22.3

**Function**
The precise function of C10ORF11 is not yet known. However, there is some evidence that the protein might have a role in melanocyte differentiation.

**Mutations**
C10orf11 mutations are responsible for Oculocutaneous Albinism type 7 (OCA7). Nine Faroese patients and one Danish patient of Lithuanian origin were found to have mutations in C10orf11 gene representing OCAVII (Gronskov et al., 2014). These patients have a light skin pigmentation that is reported to be lighter than their relatives. Hair color ranges from light blond to dark brown. Eye findings include nystagmus, iris transillumination, visual acuity ranging from 6/9 to 3/60 and very sparse peripheral ocular fundus pigmentation.

**Implicated in**

**Breast Cancer**
To identify genetic polymorphisms associated with clinical outcomes of breast cancer patients with tamoxifen treatment, genome-wide association study was conducted using 462 Japanese patients with hormone receptor-positive, invasive breast cancer receiving adjuvant tamoxifen therapy. The study revealed that rs10509373 in C10orf11 gene to be significantly associated with recurrence-free survival in the replication study (log-rank P= 2.02 × 10⁻⁴).

Hazard ratio per C allele of rs10509373 was found to be 4.51 [95% confidence interval (CI), 2.72–7.51; P= 6.29 × 10⁻⁹].

In a combined analysis of rs10509373 genotype with previously identified genetic markers, CYP2D6 and ABCC2, the number of risk alleles of these three genes was reported to have cumulative effect on recurrence-free survival among 345 patients receiving tamoxifen monotherapy (log-rank P= 2.28 × 10⁻¹²) (Kiyotani et al., 2011).

**References**


This article should be referenced as such:

Classical Hodgkin lymphoma

Samir Dalia, Luis Miguel Juarez Salcedo

Department of Pathology Centro di Riferimento Oncologico Aviano (CRO), Istituto Nazionale Tumori, IRCCS, Aviano, Italy; acarbone@cro.it (AC); Department of Diagnostic Pathology and Laboratory Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; annunziata.gloghini@istitutotumori.mi.it (AG)

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Abstract

Hodgkin lymphoma (HL) was one of the earliest cancers to be cured with multiagent chemotherapy even before its biology was understood. Over the past 50 years, a relevant progress has been made toward our understanding of HL pathology, cell biology and treatment options. Histologic classification of HL evolved through different systems, starting from the modern histologic classifications by Jackson and Parker in 1944 and Lukes and Collins in 1966, to the 2008 World Health Organization (WHO) classification. Classical HL is a distinct neoplastic entity with typical clinical, epidemiological, pathological, genetic, and virological features. It accounts for approximately 10% of all malignant lymphomas.

Phenotype/cell stem origin

Cell origin: Hodgkin and Reed-Sternberg (HRS) cells, the tumour cells of cHL, derive from preapoptotic crippled germinal center (GC) B cells. In fact, molecular features of HRS cells in cHL demonstrate that they are derived from GC B cells that have acquired disadvantageous immunoglobulin variable chain gene mutations and normally would have undergone apoptosis (Kuppers et al., 2012). As shown in gene expression profiling (GEP) studies, HRS cells have lost the expression of most B-cell genes and acquired expression of genes that are typical for other types of immune cells (Greaves and Gribben 2012; Steidl et al. 2012; Tiacci et al., 2012).

Phenotype: Phenotypically, HRS cells of cHL are consistently positive for CD30, CD15, CD40, and IRF4/MUM1 (Stein et al., 2008). Expression of molecular markers in cHL include (Younes et al., 2014)
- B-cell markers (CD20 and CD79) usually negative
- GC B-cell markers (BCL6 and AID) usually negative
- Plasma cell markers (MUM1/IRF4) usually positive
- Molecules involved in Ag presentation (MHC class II, CD40, CD80, CD86) positive
A surfaceoma study by TMA analysis indicated that gamma-glutamyltranspeptidase 1 is a potential additional marker for differential diagnosis of cHL versus non-Hodgkin lymphoma (Hofmann et al., 2015).
Cellular components of the cHL microenvironment express molecules involved in cancer cell growth and survival (such as CD30L or CD40L), and in immune escape (programmed death 1 (PD-1)). For example, CD30L+ eosinophils and mast cells, and proliferation-inducing ligand (APRIL)+ neutrophils, are consistently admixed to HRS cells, whereas CD40L-expressing CD4+ T lymphocytes rosette HRS cells. A fraction of infiltrating CD4+ T cells are regulatory T (Treg) cells. Treg cells and PD-1+ T cells also interact with HRS cells (Aldinucci et al., 2010; Liu et al., 2014; Carbone et al., 2015).

**Epidemiology**
Classical HL is the most common cancer in patients under 20 years (adolescents and younger adults). The first peak of incidence can be observed in patients under 35 years of age, whereas a second incidence peak can be observed in the elderly (Hjalgrim et al., 2008; Stein et al., 2008).

**Cytology**
Binucleated and multinucleated HRS cells are giant cells with binucleation and huge nucleoli. These cells and their mononuclear variant, the so-called Hodgkin cells, are pathognomonic for cHL identification.

**Pathology**
HRS cells reside in an inflammatory cell microenvironment.
Based on the characteristics of the HRS cells (lacunar cells, multinucleated giant cells, pseudosarcomatous cells) and of the reactive infiltrate, four histologic subtypes have been distinguished: lymphocyte-rich cHL (LRCHL), nodular sclerosis (NS) cHL, mixed cellularity (MC) cHL, and lymphocyte depletion (LD) cHL. Most cHL can be classified as NS or MC subtypes. The remaining LRCHL and LD subtypes are uncommon. LRCHL cases display histological and clinical features intermediate between those of cHL and NLPHL (Poppema et al., 2008; Stein et al., 2008; Swerdlow et al., 2016).
In cHL, microenvironmental cell types include T- and B-reactive lymphocytes, eosinophils, granulocytes, histiocytes/macrophages, plasma cells, mast cells. In addition, a great number of fibroblast-like cells and fibrosis are frequently found (Aldinucci et al., 2010).
Figure 2. Mononucleated giant cells, the so called Hodgkin cells

Figure 3. The schema shows a Reed-Sternberg within its cell microenvironment.
Other features

EBV infection

The immunophenotypic and genetic features of HRS cells are identical in the different histologic subtypes of cHL. Conversely, the association with EBV shows differences. EBV is found in HRS cells preferentially in cases of MC and LD cHL, and less frequently in NS and LRCHL. Notably, EBV is found in HRS cells in nearly all cases of cHL occurring in patients infected with HIV (Younes et al., 2014; Dolcetti et al., 2016). The virologic characteristics of cHL vary according to the immunocompetence status of the host and cHL subtype (IARC, 2012) as follows:

- cHL of the general population
  - NS cHL, usually EBV negative
  - MC cHL, usually EBV positive
  - LRCHL, variably EBV positive
  - LD cHL, variably EBV positive
- Immune deficiency-associated cHL
- HIV-associated cHL, EBV positive
- Post-transplant cHL, EBV positive
- Iatrogenic (methotrexate), variably EBV positive

Treatment

Cure rates approaching 80% have been achieved in patients undergoing chemo-radiotherapy, qualifying cHL as a chemosensitive disease (Santoro et al., 1987, Canellos et al., 2014). However, 25% to 30% of these patients show either primary refractoriness to chemotherapy, early disease relapse or late disease relapse (Canellos et al., 2014; Carbone et al., 2015).

Prognosis

The implementation of novel agents for the treatment of multi-relapsed cHL patients has improved the outcome of these patients and will significantly impact the history of multi-relapsed cHL in the near future when the results of combination studies become available. For example, the synergistic effect of Dehydroxymethylepoxyquinomicin (DHMEQ) with three chemotherapeutic drugs widely used in cHL treatment, doxorubicin, gemcitabine and cisplatin, has recently been demonstrated (Locatelli et al., 2014).

Genetics

Recurrent genetic alterations have been identified in HRS cells of cHL. These lesions affecting members of the NF-kappaB or JAK/STAT signalling pathways include inactivating mutation in NFKBIA (10-20% of cases), NFKBIE (10%), TNFAIP3 (40%), SOCS1 (40%), genomic gains of RELA (30%) and JAK2 (30%) and rare BCL3 translocations. TNFAIP3 mutations are found in Epstein-Barr virus-negative cases of cHL. Mutations have been found in the tumour suppressor genes FAS (CD95) and TP53.

Further genomic imbalances, identified by comparative genomic hybridization studies include gains of IKKBKB, CD40 and MAP3K14 that are regulators of NF-kappaB signaling (Küppers and Re, 2007; Hartmann et al., 2008; Steidl et al., 2010; Küppers 2011; Küppers et al., 2012; Pasqualucci and Dalla Favera, 2014).

Interestingly, HRS cells show aberrant somatic hypermutation of several proto-oncogenes (PIM1, RHOH (TTF), MYC, PAX5) in a considerable fraction of cases (Küppers et al., 2012; Pasqualucci and Dalla Favera, 2014).

Cytogenetics

HRS cells are clonal with variable modal chromosome numbers as indicated from direct chromosome analysis and DNA measurements and shown by the detection of clonal immunoglobulin V gene rearrangements in single HRS cells. The modes are about twice as frequently in the triploid-tetraploid as near diploid region. Translocations involving the immunoglobulin loci have been found in about 20% of cHL; deletions and duplications, common in other types of tumour, have also been described in cHL.

Diploid as well as aneuploid metaphases are commonly found in chromosome studies, both direct and after culturing. Using FISH 1-12% of "normal" nuclei in cHL exhibit abnormalities, especially trisomies for various chromosomes (Atkin, 1998; Jensen et al., 1998; Hartmann et al., 2008; Schmitz et al., 2009; Steidl et al., 2010; Küppers 2011).

References


Classical Hodgkin lymphoma

Carbone A and Gloghini A


Sorafenib in Hodgkin lymphoma cell line xenografts mediate the antitumor effects of the HDACi Givinostat and Stella C. BIM upregulation and ROS-dependent necroptosis Locatelli SL, Cleris L, Stirparo GG, Tartari S, Saba E, Pierdominici M, Malorni W, Carbone A, Anichini A, Carlo-Stella C. BIM upregulation and ROS-dependent necroptosis mediate the antitumor effects of the HDACi Givinostat and Sorafenib in Hodgkin lymphoma cell line xenografts Leukemia 2014 Sep;28(9):1861-71

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Lymphocyte depletion classical Hodgkin lymphoma

Antonino Carbone, Annunziata Gloghini

Department of Pathology Centro di Riferimento Oncologico Aviano (CRO), Istituto Nazionale Tumori, IRCCS, Aviano, Italy; acarbone@cro.it (AC); Department of Diagnostic Pathology and Laboratory Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; annunziata.gloghini@istitutotumori.mi.it (AG)

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Abstract

The lymphocyte depletion classical Hodgkin lymphoma (LDCHL) is the less common subtype of cHL. In LDCHL, Hodgkin and Reed-Sternberg (HRS) cells grow within a background depleted in reactive lymphocytes. LDCHL subtype accounts for only a small fraction of all HL cases in Western countries. It also occurs in people with HIV/AIDS. The HRS cells show the same immunophenotype as in the other subtypes of cHL.

Keywords

Lymphocyte depletion; classical Hodgkin Lymphoma; Hodgkin Lymphoma; LDCHL.

Identity

Other names

Lymphocyte depletion Hodgkin Lymphoma
Lymphocyte-depleted classical Hodgkin lymphoma
Lymphocyte depletion Hodgkin disease.

Clinics and pathology

Disease

Hodgkin Lymphoma (HL) includes classical Hodgkin lymphoma (CHL) which accounts for 95% of all cases (Stein et al. 2008). Lymphocyte depletion classical Hodgkin lymphoma (LDCHL) is the less common subtype of cHL (Benharroch et al., 2008). LDCHL is a subtype of cHL rich in Hodgkin and Reed-Sternberg (HRS) cells. These cells reside within a background depleted in non-neoplastic lymphocytes. In the past few decades, a fraction of these cases have been reclassified into different non-Hodgkin lymphoma entities (Benharroch et al., 2008).

Phenotype/cell stem origin

LDCHL involves a clonal expansion of germinal center B-cell derived lymphocytes which mimic those observed in the other subtypes of cHL.

Epidemiology

LDCHL accounts for only a small fraction, less than 1%, of all HL cases in Western countries. There is a male predominance. The median age ranges from 30 to 40 years. LDCHL is often seen in people infected with HIV/AIDS and more often in developing countries (IARC, 2012). People with HIV/AIDS are at increased risk of HL in the highly active antiretroviral therapy era. In HIV-infected people cHL is presently the most common non-AIDS defining cancer (Carbone et al., 2014).

Clinics

Patients affected by LDCHL present with an advanced stage (III-IV stage) and with B symptoms more often than those affected by the other subtypes. LDCHL usually involves retroperitoneal lymph-nodes and extranodal sites including abdominal organs and bone-marrow (Younes et al., 2014).
Lymphocyte depletion classical Hodgkin lymphoma

Carbone A and Gloghini A

Atlas Genet Cytogenet Oncol Haematol. 2017; 21(1)

Figure 1. Involvement of lymph node by HIV-associated classic Hodgkin lymphoma (cHL) of the lymphocyte depletion subtype. Large Hodgkin Reed-Sternberg (HRS) cells with multiple nuclei and prominent nucleoli are present. HRS cells express the typical phenotype with intense staining for CD30.

Figure 2. Involvement of lymph node by HIV-associated classic Hodgkin lymphoma (cHL) of the lymphocyte depletion subtype. Large Hodgkin Reed-Sternberg (HRS) cells are Epstein-Barr virus-infected as demonstrated by EBER in situ hybridization (brown) with latent membrane protein 1 expression (red).
Pathology
A consistent feature is the predominance of HRS cells in relation to the cell density of the background. The HRS cells are pleomorphic with a sarcomatous appearance. A proportion of HRS cells may resemble anaplastic forms of tumour cells observed in some large cell non-Hodgkin lymphoma. The background is characterized by diffuse fibrosis and depletion in reactive lymphocytes.

Phenotype
The HRS cells show the same immunophenotype as in the other subtypes of CHL (Carbone and Gloghini, 2016); the immunophenotype is the following: CD30+, CD15 usually+, MUM1/IRF4+, PAX5 usually+, CD20-/+.

Other features
Virology
Tumour tissue is characterized by an unusual large proportion of HRS cells infected by EBV. EBV is found in nearly all cases of LDCHL occurring in patients infected by HIV. EBV infected tumour cells contain LMP1 which can activate critical signaling pathways including NF-κB. It seems appropriate to mention here that the virologic characteristics of HL vary according to the immunocompetence status of the host and cHL subtype (IARC, 2012; Swerdlow et al., 2008) as follows:
- cHL of the general population
- NS cHL, usually EBV negative
- MC cHL, usually EBV positive
- LRCHL, variably EBV positive
- LD cHL, variably EBV positive

Immunodeficiency-associated cHL
- HIV-associated cHL, EBV positive
- Post-transplant cHL, EBV positive
- Iatrogenic (methotrexate), variably EBV positive

Etiology
LMP1 expression is observed in virtually all HIV associated LDCHL cases; it suggests that EBV play an etiological role in the pathogenesis of these tumours.

Cell microenvironment
HRS cells are usually seen in a microenvironment where several histiocytoid cells are admixed with few small lymphocytes. These lymphocytes predominantly express the CD3+, CD4+, CD8-/+ phenotype. It has been recognized that EBV has the capability to modulate the tumour microenvironment (Dolcetti, 2015; Dolcetti et al., 2016).

Treatment
The combination of cART with better supportive therapy has made standard ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), used for LDCHL occurring in the general population, feasible in patients with HIV-associated Hodgkin lymphoma (Carbone et al., 2014).

Prognosis
Most patients affected by LDCHL have a worse prognosis than do patients affected by other cHL subtypes (Younes et al., 2012). Poor prognosis have been observed in patients affected by HIV-associated LDCHL. The outcome of HIV-associated cHL has dramatically improved since the introduction of cART with intensive chemotherapy regimens (Carbone et al., 2014).

Genetics
Due to the small number of LDCHL cases analysed for genetics/cytogenetics characteristics and to the reclassification of cases into different lymphoma categories, the previously described genetics and cytogenetics findings are not unquestionably acknowledged.

References

This article should be referenced as such: Carbone A, Gloghini A. Lymphocyte depletion classical Hodgkin lymphoma. Atlas Genet Cytogenet Oncol Haematol. 2017; 21(1):14-16.
Lymphocyte-rich classical Hodgkin lymphoma

Annunziata Gloghini, Antonino Carbone

Department of Diagnostic Pathology and Laboratory Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; annunziata.gloghini@istitutotumori.mi.it (AG); Department of Pathology Centro di Riferimento Oncologico Aviano (CRO), Istituto Nazionale Tumori, IRCCS, Aviano, Italy; acarbone@cro.it (AC)

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Lymphocyte-rich classical Hodgkin lymphoma. Atlas Genet Cytogenet Oncol Haematol

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Abstract

Lymphocyte-rich classical Hodgkin lymphoma accounts for a small fraction of all Hodgkin lymphomas.
Lymphocyte-rich classical Hodgkin lymphoma is a rare variant of classical Hodgkin lymphoma which resembles nodular lymphocyte predominance Hodgkin lymphoma, in terms of nodular growth and lymphocyte-richness, and mimics cHL, in terms of the immunophenotype of the tumour cells. Lymphocyte-rich classical Hodgkin lymphoma tumour cells have lost the B-cell phenotype and express CD30 and the B-cell transcription program. As regards to genetics and cytogenetics findings please refer to the general features described in the CARDS related to nodular lymphocyte predominance Hodgkin lymphoma and classical Hodgkin lymphoma.

Keywords
Lymphocyte-rich classical Hodgkin lymphoma; LRCHL; Pathology; Phenotype; Clinics

Identity

Other names
Nodular lymphocyte-rich classical Hodgkin lymphoma
LRCHL
Nodular lymphocyte-rich classical Hodgkin disease

Clinics and pathology

Disease
Hodgkin lymphoma (HL) has been classified into classical HL (cHL) (Stein et al., 2008), which accounts for 95% of all cases, and the less common nodular lymphocyte predominant HL (NLPHL) (Poppema et al., 2008). A variant of cHL which resembles NLPHL, in terms of nodular growth and lymphocyte-richness, and mimics cHL, in terms of the immunophenotype of the tumour cells, was originally designated nodular lymphocyte-rich classic Hodgkin disease (Anagnostopoulos et al. 2000), now called lymphocyte-rich cHL (LRCHL). LRCHL displays histologic and clinical features intermediate between those of cHL and NLPHL (Nam-Cha et al., 2009; Anagnostopoulos et al., 2008; Swerdlow et al., 2016).

Phenotype/cell stem origin
Cell origin: LRCHL involves a clonal expansion of B lymphocytes which mimic those observed in the outer zone of germinal centers of lymphoid follicles (Nam-Cha et al., 2009). Tumour cells have partly lost the B-cell phenotype and coexpress CD30 and the B-cell transcription program.
 Phenotype: The tumour cell phenotype, which is characterized by the expression of CD30, also shows the expression of CD20 and B-cell transcription factors.
The phenotype is the following (Nam-Cha et al., 2009):
MUM1/IRF4 + (100%)
PAX5 + (94%)
BOB1 + (62%)
CD15+ (56%)
OCT2 + (56%)
OCT1 + (50%)
BCL6 + (36%)
CD20+ (31%)

**Cell microenvironment**
LRCHL tumour cells reside in a microenvironment resembling expanded mantle zones, where numerous small B lymphocytes displaying a mantle cell phenotype (IgD+, CD20+) are admixed with meshworks of dendritic reticulum cells (CD21+, CD23+). LRCHL tumour cells are rosetted by CD4+, PD1+ T cells.

**Epidemiology**
LRCHL accounts for only a small fraction (3% to 5%) of all HLs (Younes et al., 2014), in similar frequency to NLPHL. The median age is similar to NLPHL and significantly higher than in other subtypes of cHL. There is a male predominance (Shimabukuro-Vornhagen, et al., 2005).

**Pathology**
Among the four histological subtypes of cHL, nodular sclerosis and mixed cellularity are the most common subtypes, whereas the lymphocyte-depleted and lymphocyte-rich subtypes are the less common (Stein et al., 2008).
LRCHL exhibits a nodular growth pattern.
The nodules are composed of small lymphocytes and may harbour germinal centers that are usually eccentrically located and relatively small or regressed.
The neoplastic cells, the Hodgkin Reed-Sternberg (HRS) cells, are predominantly found within the nodules, but consistently outside of the germinal centers.
The HRS cells show broad morphologic spectrum: a proportion of the HRS cells may resemble lymphocyte predominant (LP) cells or mononuclear lacunar cells.
However, the demonstration of an immunophenotype typical for classical HRS cells may permit their precise recognition as LRCHL tumour cells.

**Other features**

**Virology**
At variance with NLPHL the neoplastic cells in LRCHL appear to be permissive for an EBV infection. EBV infection is observed in LRCHL tumour cells less frequently than in mixed cellularity cHL but more frequently than in nodular sclerosis cHL (Carbone et al., 2016).
It seems appropriate to mention here that the virologic characteristics of HL of the general population vary according to the immunocompetence status of the host and cHL subtype (IARC, 2012) as follows:

cHL of the general population
- Nodular sclerosis cHL, usually EBV negative
- Mixed cellularity cHL, usually EBV positive
- LRCHL, variably EBV positive
- Lymphocyte depletion cHL, variably EBV positive
- NLPHL usually EBV negative

**Evolution**

Clinically, patients with NLPHL and LRCHL show similar disease presentation but differ in the frequency of multiple relapses and prognosis after relapse. Patients with NLPHL and LRCHL differ from patients with cHL with nodular sclerosis or mixed cellularity, as they present with an earlier disease stage (Anagnostopoulos et al. 2000).

**Prognosis**

Most LRCHLs have a better prognosis than do other cHLs.

**Genetics**

See the pertinent sections within the CARDS describing the general features of NLPHL and cHL (Küppers, 2011; Carbone and Gloghini, 2016; Gloghini and Carbone, 2016).

**References**


This article should be referenced as such:

Nodular lymphocyte-predominant Hodgkin lymphoma

Annunziata Gloghini, Antonino Carbone

Department of Diagnostic Pathology and Laboratory Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; annunziata.gloghini@istitutotumori.mi.it (AG); Department of Pathology Centro di Riferimento Oncologico Aviano (CRO), Istituto Nazionale Tumori, IRCCS, Aviano, Italy; acarbone@cro.it (AC)

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Abstract

Diagnostic characteristics of nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL): nodular or nodular and diffuse proliferation of scattered lymphocyte predominant (LP) tumour cells within a background reminiscent of primary or secondary lymphoid follicles. Six different patterns: A) 'classical' nodular, B) serpiginous/interconnected nodular, C) nodular with prominent extra-nodular LP cells, D) T-cell-rich nodular, E) diffuse with a T-cell-rich background, and F) diffuse, B-cell-rich pattern.

Typical histopathologic patterns in NLPHL include patterns A and B. Both of these patterns show a predominantly nodular growth, with LP cells located within the nodules. So called "histopathologic variants" are defined by prominent extranodular LP cells associated to patterns C to F. "Histopathologic variants" may be associated with advanced stage disease and higher relapse rate. Assessing "histopathologic variants" patterns in NLPHL may be useful for the management of the patients.

Keywords
Nodular lymphocyte-predominant Hodgkin lymphoma; NLPHL; Immunohistological patterns; Clinics; Pathology

Identity

Other names: Lymphocyte-predominant HL

Disease

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) is a distinct subtype of Hodgkin lymphoma (HL), usually associated with an indolent course and presenting in the early stages of the disease (Anagnostopoulos et al., 2000).

Phenotype/cell stem origin

Cell origin

Tumour cells are antigen-selected mutating germinal center (GC) B cells. This origin is supported by The expression of BCL6 and CD40 by tumour cells (Carbone et al., 1995; Liso et al., 2006). The presence of CD4+, CD57+, PD1+ T cells surrounding the tumour cells (Poppema et al., 2008). The expression of a follicular dendritic cell meshwork within the tumour nodules (Mason et al., 1994; Carbone and Gloghini, 2012). The gene expression profile (Brune et al., 2008). Rearranged, clonal and mutated (ongoing) Ig genes of tumour cells (Marafioti et al., 1997; Küppers, 2011).

Phenotype

LP cells profile: CD45+, CD20+, CD40+, CD79a+, CD75+, BCL6+, IRF4/MUM1+, and OCT2+, BOB1+, PAX5+, PU.1+, epithelial membrane antigen+, CD15 and CD30 are usually negative (Poppema et al., 2008). Nodules composition: CD20+ and IgD+ small B cells, CD3+ and CD4+ T cells and histiocytes.
The background of the nodules also includes an increase in GC-derived CD57+, IRF4/MUM1+, and PD-1+ T-cells populations which form a rim around LP cells (Carbone and Gloghini, 2012).

**Epidemiology**

About 5% of all HL cases are classified as NLPHL. Males are more commonly affected than females (male-female ratio, 3:1). The median age at presentation is about 40 years.

**Clinics**

NLPHL is a neoplasm usually associated with a favourable clinical course despite a tendency for local recurrences.

**Cytology**

NLPHL tumour cells are termed lymphocyte predominant (LP) cells. LP cells are large cells with multilobated nuclei and scant cytoplasm. They contain multiple, not prominent, nucleoli in contrast with typical Reed Sternberg cells of classical HL that contain huge eosinophilic nucleoli.

**Pathology**

LP tumour cells proliferate within a nodular or nodular and diffuse background (Anagnostopoulos et al., 2000). The tumour nodules are reminiscent of a primary follicle containing spherical meshworks of follicular dendritic cells (FDCs) admixed with inflammatory cells (Mason et al., 1994).

On morphologic and immunohistologic grounds, six patterns are recognizable in NLPHL (Fan et al., 2003): A) ‘classical’ nodular, B) serpiginous/interconnected nodular, C) nodular with prominent extra-nodular LP cells, D) T-cell-rich nodular, E) diffuse with a T-cell-rich background, and F) diffuse, B-cell-rich pattern.

Typical histopathologic patterns in NLPHL include patterns A and B. Both of these patterns show a predominantly nodular growth, with LP cells located within the nodules.

So called "histopathologic variants" include patterns from C to F and are associated to prominent extranodal LP cells or to B-cell depletion of the microenvironment (Hartmann et al. Blood, 2013). An additional nodular pattern in which LP cells proliferate within a background reminiscent of a secondary follicle without invasion of the extranodal space has been recognized (Carbone and Gloghini, 2012; Gloghini et al., 2015).
Other features

Virology
The neoplastic cells are usually EBV negative (Anagnostopoulos et al., 2000).

Treatment
Early stage disease: treatment with local radiation provides disease control and good overall survival (Advani and Hoppe, 2015).
Locally extensive or advanced stages: paradigms used for classical HL with similar outcomes (Advani and Hoppe, 2015). Excellent response rates (but increased relapse rates) observed with single agent rituximab. Promising data observed with R-CHOP (Advani and Hoppe, 2013; Younes et al., 2014).
Relapsed disease: single agent rituximab is a reasonable choice because of excellent tolerability (Advani and Hoppe, 2015).

Evolution
Transformation to diffuse large B-cell lymphoma (T-cell/histiocyte rich large B-cell lymphoma).

Prognosis
Favourable clinical course despite a tendency for local recurrences (Advani and Hoppe, 2013). Compared with "typical NLPHL", "histopathologic variants" are associated with more advanced disease and a higher relapse rate (Hartmann et al. Blood, 2013).

Genetics
Translocation involving the BCL6 protooncogene (Liso et al., 2006). Strong NFKB activity (Küppers, 2011). Aberrant somatic hypermutation of multiple proto-oncogenes (PIM1, RHOH (TTF), MYC, and PAX5) in a fraction of cases. Most of mutations are on the 5′ untranslated regions of the genes (Liso et al., 2006). Mutation in SOCS1 (Küppers, 2011). Mutation in the 5′ untranslated regions of the genes (Liso et al., 2006). Strong NFKB activity (Küppers, 2011). Translocation involving the BCL6 protooncogene (Liso et al., 2006). Strong NFKB activity (Küppers, 2011). Translocation involving the BCL6 protooncogene (Liso et al., 2006). Strong NFKB activity (Küppers, 2011). Translocation involving the BCL6 protooncogene (Liso et al., 2006). Strong NFKB activity (Küppers, 2011). Translocation involving the BCL6 protooncogene (Liso et al., 2006). Strong NFKB activity (Küppers, 2011). Translocation involving the BCL6 protooncogene (Liso et al., 2006). Strong NFKB activity (Küppers, 2011).

References
Leukaemia Section
Short Communication

**t(7;21)(p22;q22) RUNX1/USP42**

Carlos A. Tirado

UCLA Pathology and Laboratory Medicine, Los Angeles, CA. ctirado@mednet.ucla.edu

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**Abstract**

Review on t(7;21)(p22;q22) RUNX1/USP42, with data on clinics, and the genes involved.

**Clinics and pathology**

**Disease**
Acute myeloid leukemia M0 (M0 AML)

**Phenotype/cell stem origin**
M0 AML

**Epidemiology**
Three cases to date; a 7-year old male, a 32-year old male, and a 52-year old female

**Evolution**
The 7-year old male patient relapsed; however, he is still alive, with a bone marrow graft, 10 years after diagnosis. The 32-year old male died of alternative causes shortly after diagnosis. The female patient did not relapse, and is still alive.

**Disease**
Acute myeloid leukemia M4 (M4-AML)

**Phenotype/cell stem origin**
M4-AML

**Epidemiology**
Three cases to date, with the possibility of a fourth. Excluding fourth: 2 males (ages 39 and 13), and 1 female (age 57). The fourth case was a 54-year old male with either M4 or M5 subtype.

**Evolution**
39-year old male is dead from alternative causes, no relapse; 57-year old female and 13-year old male are both alive, with no evidence of relapse.

**Disease**
Acute myeloid leukemia M5 (M5-AML)

**Phenotype/cell stem origin**
M5/M5a-AML

**Epidemiology**
Two cases with the possibility of a third (overlap with aforementioned M4 cases). First case is a 33-year old male; second case is a 68-year old female. The third case is, as mentioned, a 54-year old male.

**Evolution**
The 33-year old male had no relapse and is still alive. The 68-year old female is dead, 5 years after diagnosis. The 54-year old male is, as mentioned, dead 3 months after diagnosis.

**Genes involved and proteins**

**USP42 (ubiquitin specific peptidase 42)**

**Location**
7p22.1

**Protein**
USP42 (ubiquitin specific protease 42), belongs to the ubiquitin specific protease family. Ubiquitins are
highly conserved proteins. Ubiquitins target proteins for degradation in the proteasome. Some USPs, however, act in the opposite reaction. These ubiquitin specific proteases (cysteine proteases) are also called deubiquitinating enzymes. They cleave ubiquitin from ubiquitin-conjugated target proteins and may lead to protein stabilization. Usp42 can cleave ubiquitin from ubiquitinated substrates. Usp42 seems to be a deubiquitinating enzyme. It may play an important role in mouse embryogenesis.

**RUNX1** *(runt-related transcription factor 1 (acute myeloid leukemia 1; aml1 oncogene))*

**Location**  
21q22.12

**Protein**  
Transcription factor (activator) for various hematopoietic-specific genes, which expression is limited to hematopoietic stem cells, and endothelial cells and mesenchymal cells in the embryo; core binding factor family member which forms heterodimers with CBFB; binds to the core site 5’-PyGPyGGTPy 3’ of promoters and enhancers

**Result of the chromosomal anomaly**

**Hybrid gene**

**Description**  
5’ RUNX1- 3’ UPS42

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HIV-associated lymphomas

Annunziata Gloghini, Antonino Carbone, Liron Pantanowitz

Department of Diagnostic Pathology and Laboratory Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy. annunziata.gloghini@istitutotumori.mi.it (AG); Department of Pathology Centro di Riferimento Oncologico Aviano (CRO), Istituto Nazionale Tumori, IRCCS, Aviano, Italy. acarbone@cro.it (AC); Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania. pantanowitzl@upmc.edu (LP)

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Abstract

Lymphoma remains the most frequent neoplastic cause of death among HIV-infected individuals. Lymphomas in patients infected with HIV are heterogeneous, not only pathologically but also in terms of pathogenetic pathways and cellular derivation. This CARD summarizes the association of the different types of HIV-associated lymphomas with known genetic lesions and/or oncogenic viruses. In the setting of HIV infection different, but not mutually exclusive, pathogenic pathways might occur. For a distinct pathway of AIDS-related lymphomagenesis there can be multiple associated genetic lesions in the tumor. Several of the HIV-associated lymphomas are also related to EBV and/or KSHV (HHV-8) infection.

Keywords: AIDS-related lymphoma; HIV-associated lymphoma; HIV; lymphoma, gamma herpesviruses

Identity

Other names: AIDS-related lymphomas, HIV-related lymphomas; Lymphomas associated with HIV infection

Clinics and pathology

Disease

The most common lymphomas arising in HIV-infected individuals include Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL). Classical Hodgkin lymphoma (cHL) is also common. Other lymphomas include primary effusion lymphoma (PEL) and its solid variants, lymphoma associated with Kaposi sarcoma herpesvirus (KSHV)-related multicentric Castleman Disease (MCD), and plasmablastic lymphoma (PBL) (Table 1) (IARC 2012; Dolcetti et al., 2016;). The latter three types of lymphomas rarely occur in the general population.

Epidemiology

Lymphoma is still the most frequent neoplastic cause of death among HIV-infected individuals (Grulich et al., 2015). Young and middle-aged people afflicted with HIV infection are most often affected. The age of lymphoma occurrence is dependent on the patient's age of HIV infection. Although the incidence of HIV-associated non-Hodgkin lymphomas has declined after the introduction of combination antiretroviral therapy (cART), these lymphomas remain the main type of cancer to be detected in HIV-infected people. Curiously, the incidence of cHL has increased since the Highly Active Antiretroviral (HAART) era whereas the incidence of other HIV-associated lymphomas remains stable. This high incidence of lymphomas, despite the immunoreconstitution promoted by cART, strongly suggests that factors other than HIV-related immunosuppression are probably still acting as lymphomagenic factors in the HIV setting (Pantanowitz et al., 2015; Dolcetti et al., 2016;).
Table 1. Categories of HIV-associated lymphomas

<table>
<thead>
<tr>
<th>Lymphoma Type</th>
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<tr>
<td>Burkitt lymphoma- mostly plasmacytoid</td>
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<tr>
<td>Primary central nervous system lymphoma</td>
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<tr>
<td>Diffuse large B-cell lymphoma, including primary central nervous system lymphoma (immunoblastic, plasmacytoid and centroblastic)</td>
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<tr>
<td>Plasmablastic lymphoma</td>
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<tr>
<td>Primary effusion lymphoma (PEL) and its solid variant (Classic PEL - in the absence of tumor masses; Solid PEL with or without serous effusion)</td>
</tr>
<tr>
<td>Multicentric Castleman Disease (MCD)-associated large cell lymphoma</td>
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<tr>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td>Other histotypes (rare)</td>
</tr>
<tr>
<td>Marginal zone lymphoma</td>
</tr>
<tr>
<td>Unclassifiable lymphomas with features intermediate between Burkitt lymphoma and diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td>Polymorphic B-cell lymphoma (PTLD-like)</td>
</tr>
</tbody>
</table>

**Clinics**

Sex. There is an apparently higher risk of HIV-associated lymphomas in men than women.

Site. Lymphomas that develop in HIV-infected patients are predominantly aggressive B-cell malignancies. These lymphomas display a marked propensity to involve extra-nodal anatomic sites such as the central nervous system, gastrointestinal tract, liver, bone marrow, and perinodal soft tissue. At diagnosis, most patients with HIV-associated HL present with advanced stages of disease with involvement of such extranodal sites.

**Pathology**

**Macroscopy.**

Most HIV-associated lymphomas present with extra-nodal tumour masses, lymphadenopathy with necrosis, and/or effusion.

**Microscopy**

Burkitt lymphoma (BL). HIV-associated BL includes cases that exhibit classic BL features, as well as cases that show plasmacytoid differentiation (Gloghini et al., 2013).

Diffuse large B-cell lymphoma (DLBCL). DLBCL can be morphologically heterogeneous. The different morphological variants of DLBCL include the centroblastic variant, immunoblastic variant (which requires there to be at least 90% of immunoblasts with plasmacytoid features), and the anaplastic variant (Carbone et al., 2001; Gloghini et al., 2013).

Primary DLBCL of the central nervous system (PCNSL) associated with HIV infection usually belongs to the immunoblastic type.

Primary effusion lymphoma (PEL). Lymphoma cells range from large tumor cells showing anaplastic morphology to cells with immunoblastic or plasmablastic morphology. These lymphomas frequently display a certain degree of plasma cell differentiation (Carbone et al., 2001; Cesarman et al., 1995).

Plasmablastic lymphoma (PBL). These lymphomas can be subdivided into two morphologic subgroups: 1) lymphomas comprised of a monomorphic population of plasmablasts with no/minimal plasmacytic differentiation, and 2) lymphomas with plasmacytic differentiation, composed of plasmablasts and cells showing plasma cell differentiation (Delecluse et al., 1997; Stein et al., 2008).

Classical Hodgkin lymphoma (cHL). cHL is currently the most common type of non-AIDS-defining cancer.

Common encountered histological subtypes in HIV-positive patients include mixed cellularity and lymphocyte depleted cHL (Carbone et al., 2014; Uldrick and Little, 2015).
HIV-associated lymphomas

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Figure 1. HIV-associated Burkitt lymphoma involving the colon (H&E stain, 40x magnification).

Figure 2. HIV-associated pericardial primary effusion lymphoma (cell block preparation, H&E stain, 40x magnification).
**Immunophenotype**

BL: CD45+, CD20+, CD10+, BCL6+, BCL2-, MYC+, Ki67+ 100%

DLBCL (CB): CD45+, CD20+, BCL6+, MUM1/IRF4-, CD138-

DLBCL (IB): CD45+, CD20-/+, BCL6-, MUM1/IRF4+, CD138-

DLBCL (IB with plasmacytoid features): CD45+/-, CD20-/+, BCL6-, MUM1/IRF4-, CD138-

PEL: CD45+, CD20-, T/NK markers+/-, CD30+, CD138+, EMA+/-, LNA-1+

PBL: CD45+/-, CD20+/-, CD79a+/-, PAX5-, CD138+, EMA+/-, CD31-/+, LNA-1-

cHL (Reed Sternberg cells): CD45-, CD20-/+, PAX5+, CD30+, CD15+/-, OCT-2+, BOB.1-, LMP1+

**Prognosis**

The outcome of HIV-associated lymphomas including Non-Hodgkin and Hodgkin lymphomas has dramatically improved since the introduction of cART with intensive chemotherapy regimens (Carbone et al., 2014; Uldrick and Little, 2015). Immunodeficiency states usually increase susceptibility to cancer as a result of reduced immune surveillance and enhanced chances for viral-driven oncogenesis. The viral contribution to the development of HIV-associated malignancies has been extensively studied (IARC 2012); but only two oncogenic viruses -i.e., Epstein Barr virus (EBV) and Kaposi sarcoma-associated herpesvirus (KSHV)/Human Herpesvirus-8 (HHV8) - have been pathogenically associated with specific lymphomas occurring in the HIV setting (Carbone et al., 2009).

Table 2 lists those lymphoid proliferations occurring in HIV-infected patients that are known to be associated with infection by EBV and/or KSHV. Importantly, these co-infected lymphomas are frequently associated with single or multiple genetic lesions, as shown in Table 2 (Carbone et al., 2001; Chadburn et al., 2013). The HIV virus itself is thought to contribute to lymphomagenesis through induction of chronic B-cell activation, due to HIV-mediated immune dysfunction. In summary, the pathogenesis of HIV-associated lymphomas is the result of different factors including impaired immune surveillance, genetic alterations, viral infection and chronic B-cell activation.
Table 2. Co-infected lymphomas in people with HIV/AIDS

<table>
<thead>
<tr>
<th>Histotype</th>
<th>BL</th>
<th>DLBCL-CB</th>
<th>DLBCL-IB</th>
<th>PBL</th>
<th>PEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral Infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBV</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>KSHV</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Genetic abnormalities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCL2</td>
<td>-</td>
<td>-</td>
<td>30%</td>
<td>20%</td>
<td>-</td>
</tr>
<tr>
<td>BCL6</td>
<td>100%</td>
<td>&gt;75%</td>
<td>-</td>
<td>&lt;10%</td>
<td>-</td>
</tr>
<tr>
<td>TP53</td>
<td>50-60%</td>
<td>Rare</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MYC</td>
<td>100%</td>
<td>0-50%</td>
<td>-</td>
<td>40%</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations. BL, Burkitt lymphoma; CB, centroblastic; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein Barr virus; HIV, human immunodeficiency virus; IB, immunoblastic; KSHV, Kaposi sarcoma-associated herpesvirus; PEL, primary effusion lymphoma; PBL, plasmablastic lymphoma; +, positive in 100% of cases; -, negative in 100% of cases; +/-, positive in less than 50% of cases; +/-, positive in more than 50% of cases.

References


This article should be referenced as such:

Second case of t(2;21)(q11.2;q22.3) in a child with T-cell acute lymphoblastic leukemia

Aurelia Meloni-Ehrig, Nathan Bohls, Sean Mahoney, Christine A. Curtis, Lorraine Pare, Martin Johnston, Lalarukh Aftab, Lawrence Hertzberg

Department of Cytogenetics, CSI Laboratories, 2580 Westside Parkway, Alpharetta, GA, USA (AME, NB, SM, CAC); Departments of Hematopathology, Flow Cytometry, CSI Laboratories, 2580 Westside Parkway, Alpharetta, GA, USA (LA, LH); Department of Hematology/Oncology, The Children’s Hospital at Memorial University Medical Center, 4700 Waters Ave., Savannah, GA, USA(LP, MJ) / e-MAIL: ameloni@csilaboratories.com

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Abstract
Case report on second case of t(2;21)(q11.2;q22.3) in a child with T-cell acute lymphoblastic leukemia.

Clinics
Age and sex: 10 years old female patient.
Previous history: no preleukemia, no pertinent past medical history, no previous malignancy, no inborn condition of note
Organomegaly: no hepatomegaly, no splenomegaly, no enlarged lymph nodes, no central nervous system involvement

Blood
WBC: 29.8X 10^9/l
HB: 13.4g/dl
Platelets: 184X 10^9/l
Blasts: 0% none seen in peripheral blood.
Bone marrow: 70%. The bone marrow shows partial involvement of the marrow by blasts with abnormal T-cell phenotype similar to the patient's mediastinal mass. The blasts represent 72% of cells by flow cytometry. Reduced trilineage hematopoiesis is present in the background. No dysplasia is identified. Megakaryocytes are present in normal numbers and show normal morphology. Monocytes are not increased. Plasma cells are not increased. No iron is identified on Prussian blue stain. Differential: Blasts: 70%; Promyelocytes: 4%; Myelocytes: 2%; Metamyelocytes: 2%; Neutrophils: 5%; Eosinophils: 1%; Monocytes: 1%; Erythroblasts: 15%

Cyto-Pathology Classification
Cytology L1 ALL
Immunophenotype Flow cytometric analysis of the mediastinal mass shows mostly a T-lineage immature cell population (99% of analyzed events) expressing: cytoplasmic CD3, CD5, CD7, small subset CD11c, CD38, CD45, CD71 and TdT. Significantly negative for CD2, surface CD3, CD4, CD8, CD10, CD19, CD20, CD13/CD33 and CD34. Based on light scatter characteristics the cells are enlarged to medium in size and have no increase in side scatter.
Rearranged Ig Tcr Unknown.
Diagnosis T-cell lymphoblastic acute leukemia.

Survival
Date of diagnosis 04/2015
Treatment Chemotherapy per children oncology group (cog) protocol aall1231: induction with vincristine, daunorubicin, prednisone, peg-asparaginase; intrathecal cytarabine/methotrexate.
Second case of t(2;21)(q11.2;q22.3) in a child with T-cell acute lymphoblastic leukemia

Meloni-Ehrig A, et al.

Atlas Genet Cytogenet Oncol Haematol. 2017; 21(1)

GTW-banded abnormal karyogram showing the t(2;21)(q11.2;q22.3) and other rearrangements:
46,XX,t(2;21)(q11.2;q22.3),ins(3;?)(q21;?),del(5)(q15q31),del(6)(q13q21).

Interphase FISH showing the splitting of one of the RUNX1 signals due to the t(2;21). ETV6 (12p13) is labeled in SpectrumGreen and RUNX1 (21q22) in SpectrumOrange. Arrows point to the split RUNX1.
Flow cytometric remission after four weeks. Consolidation therapy with cyclophosphamide, cytarabine, vincristine, peg-asparaginase; intrathecal methotrexate. More therapy to follow.

**Complete remission:** Yes (still on therapy)

**Treatment related death:** no

**Relapse:** no

**Status Alive**

**Last follow up** 08/2015

**Survival** 3 months

### Karyotype

**Culture time:** 24 and 48 hours unstimulated

**Banding:** GTW t

**Results:** 46,XX,t(2;21)(q11.2;q22.3),ins(3;?)q21(?), del(5)(q15q31),del(6)(q13q21) [cp21]

**Karyotype at Relapse:** N/A

### Other Molecular Studies

**Technics:** FISH ETV6-RUNX1 (12;21) dual-color ES translocation probe. Abbott Molecular, Des Plains, IL, USA.

**Results:** nuc ish(ETV6x2,RUNX1x3)[98/100].

### Comments

This is the second case of T-ALL with t(2;21)(q11.2;q22.3) and involvement of RUNX1. The first case, which was reported in 2008, affected a 6-year-old boy (Chinen et al. 2008). In the previous report, the authors demonstrated that the t(2;21) resulted in a fusion between the AFF3 (aka., LAF4) and the RUNX1 (aka., AML1) genes located at 2q11.2 and 21q22.3, respectively. In the present case, we used FISH to demonstrate the involvement of RUNX1 in the t(2;21). It is, therefore, reasonable to assume that the t(2;21) observed here leads to an AFF3-RUNX1 fusion as well. AFF3 belongs to a family of putative transcription factors also comprising AFF1 (4q21), AFF2 (Xq28), and AFF4 (5q31). In both previous and present cases, the t(2;21) is present together with other chromosome abnormalities.

Both patients responded well to the therapeutic approach. According to Chinen and coauthors, their patient was treated on the Tokyo Children's Cancer Study Group (TCCSG) L04-16 extremely high-risk (HEX) protocol, including stem cell transplantation. He achieved complete remission after the induction phase. After the early consolidation phase and two courses of the consolidation phase, he received allogeneic bone marrow transplantation from an unrelated HLA-matched donor 4 months after diagnosis. At the time of the case report in 2008, he was in complete remission for 17 months. Our patient also responded favorably to the therapeutic protocol (induction with vincristine, daunorubicin, prednisone, peg-asparaginase; intrathecal cytarabine/methotrexate; flow cytometric remission after four weeks; consolidation therapy with cyclophosphamide, cytarabine, vincristine, peg-asparaginase; intrathecal methotrexate). She is in complete remission for 5 months.

The present case report provides further support that the t(2;21) is a rare but recurrent finding in pediatric T-ALL. This translocation seems to occur together with other chromosome abnormalities. Patients have responded favorably to the therapy and have achieved complete remission.

### References


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