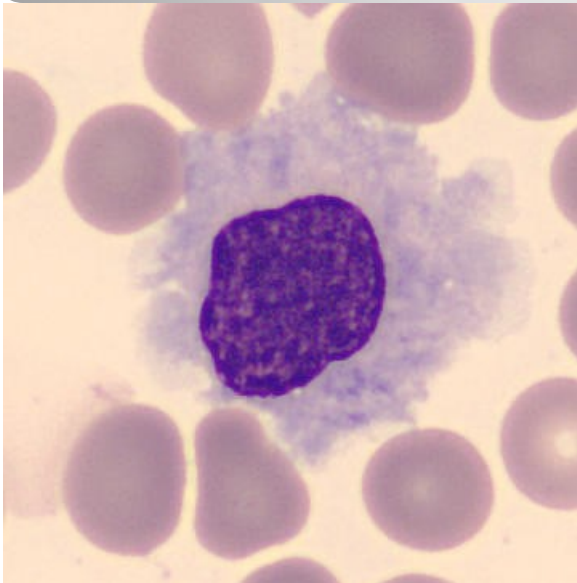


Diagnóza leukemie s vlasatými buňkami

v součinnosti morfoložického pracoviště OKL VN Brno, OKH FN Brno a laboratoře průtokové cytometrie OLM MOÚ Brno



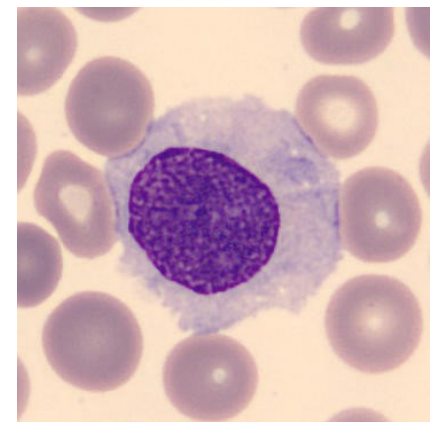
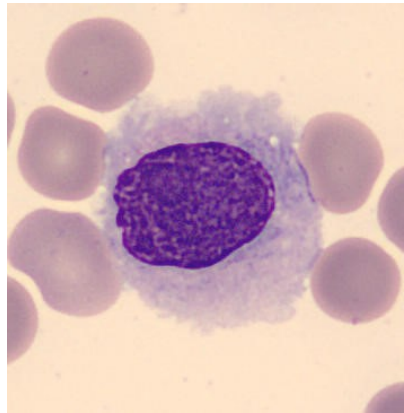
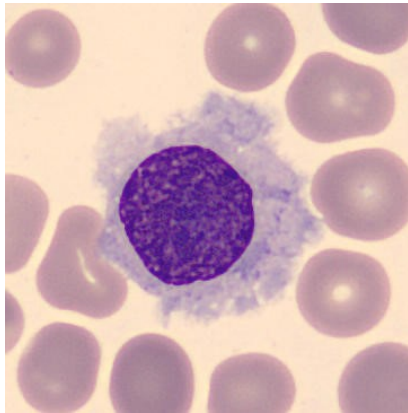
Soňa Vytisková

**FAKULTNÍ
NEMOCNICE
BRNO**

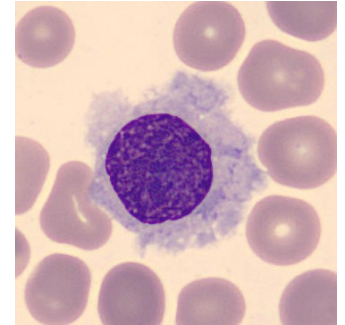


Cíle

1. Kazuistika – představení dg leukémie s vlasatými buňkami

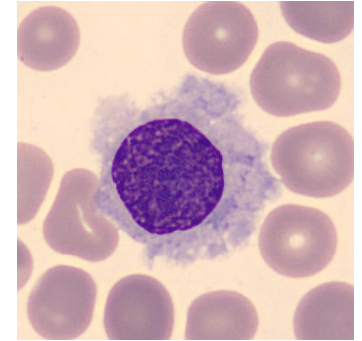


Leukémie s vlasatými buňkami



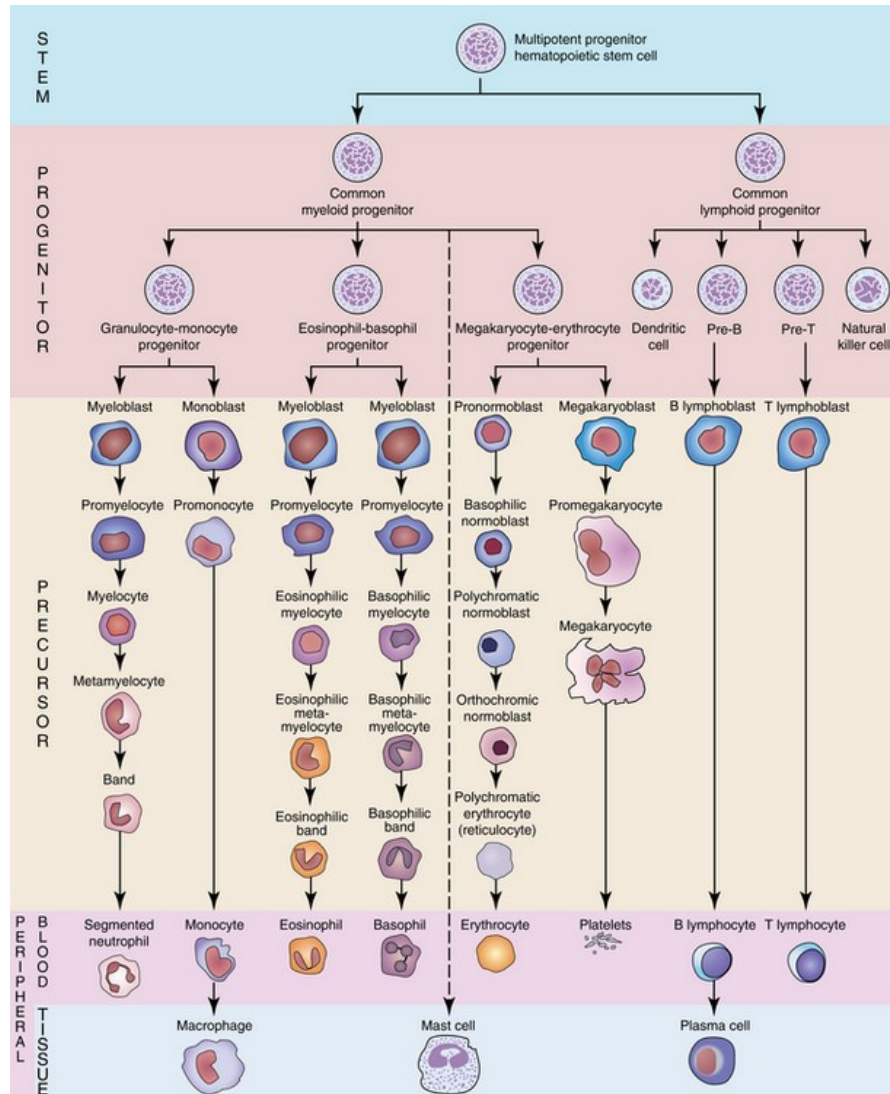
- Dle WHO 2016 je řazena k **nádorovým lymfoproliferacím ze zralých B buněk**
- **Incidence**
 - 2% z maligních lymfoproliferaticních onemocnění
 - 2% ze všech leukémií
- Průměrný věk 50 let (muži 4x častěji než ženy)
- **Pomalou progredující lymfoproliferativní onemocnění, pro něž je typická**
 - Přítomnost charakteristických vlasatých lymfocytů v PK a KD
 - Pancytopenie
 - Různě vyjádřená splenomegalie (různě vyjádřená - infarkty sleziny, ruptury)
 - Závažné infekce a febrilní stavy (defekt imunity)

Leukémie s vlasatými buňkami

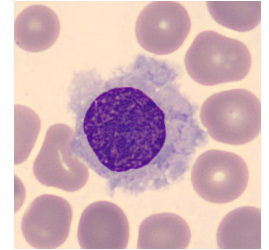


- Anémie normocytární normochromní (hraniční makrocytosa)
- Leukopenie je provázena hlavně neutropenií a monocytopenií
- Aspirace KD bývá obtížná, někdy až nemožná (dřeňová fibróza)
- Dg potvrzuje v souladu s klinickým obrazem **cytochemické vyšetření TRAP** a zejména imunocytologické vyšetření **průtokovou cytometrií** (CD19, CD20, CD22, CD11c, slg)
- Pokud se provádí biopsie KD, tak histologické a imunohistochemické vyšetření může být klíčové pro stanovení dg
- Molekulární biologie: **BRAF mutace**

Hematopoeza



Leukémie s vlasatými buňkami



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Review Series

THE UPDATED WHO CLASSIFICATION OF HEMATOLOGICAL MALIGNANCIES

The 2016 revision of the World Health Organization classification of lymphoid neoplasms

Steven H. Swerdlow,¹ Elias Campo,² Stefano A. Pileri,³ Nancy Lee Harris,⁴ Harald Stein,⁵ Reiner Siebert,⁶ Ranjana Advani,⁷ Michele Ghielmini,⁸ Gilles A. Salles,⁹ Andrew D. Zelenetz,¹⁰ and Elaine S. Jaffe¹¹

¹Division of Hematopathology, Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA; ²Department of Pathology, Hospital Clinic, University of Barcelona, August Pi i Sunyer Biomedical Research Institute, Barcelona, Spain; ³Haematopathology Unit, European Institute of Oncology, Milan, and Department of Experimental, Diagnostic and Specialty Medicine, Bologna University Medical School, Bologna, Italy; ⁴Department of Pathology, Harvard Medical School and Massachusetts General Hospital, Boston, MA; ⁵Pathodiagnostik, Berlin, Germany; ⁶Institute of Human Genetics, Christian Albrechts University Kiel, Kiel, Germany; ⁷Division of Oncology, Department of Medicine, Stanford University, Stanford, CA; ⁸Department of Medical Oncology, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; ⁹Department of Hematology, Hospices Civils de Lyon, and Université Claude Bernard Lyon-1, Lyon, France; ¹⁰Department of Medicine, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY; and ¹¹Hematopathology Section, Laboratory of Pathology, National Cancer Institute, Bethesda, MD

A revision of the nearly 8-year-old World Health Organization classification of the lymphoid neoplasms and the accompanying monograph is being published. It reflects a consensus among hematopathologists, geneticists, and clinicians regarding both updates to current entities as well as the addition of a limited number

of new provisional entities. The revision clarifies the diagnosis and management of lesions at the very early stages of lymphomagenesis, refines the diagnostic criteria for some entities, details the expanding genetic/molecular landscape of numerous lymphoid neoplasms and their clinical correlates, and refers to

investigations leading to more targeted therapeutic strategies. The major changes are reviewed with an emphasis on the most important advances in our understanding that impact our diagnostic approach, clinical expectations, and therapeutic strategies for the lymphoid neoplasms. (*Blood*. 2016;127(20):2375-2390)

Leukémie s vlasatými buňkami

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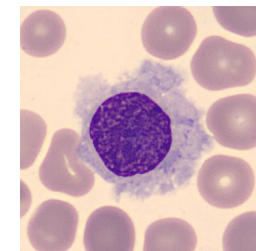


Table 1. 2016 WHO classification of mature lymphoid, histiocytic, and dendritic neoplasms

Mature B-cell neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis ¹
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic B-cell lymphoma/leukemia, unclassifiable
Splenic diffuse red pulp small B-cell lymphoma
Hairy cell leukemia-variant
Lymphoplasmacytic lymphoma
Waldenström macroglobulinemia
Monoclonal gammopathy of undetermined significance (MGUS) IgM ²
μ heavy-chain disease
γ heavy-chain disease
κ heavy-chain disease
Monoclonal gammopathy of undetermined significance (MGUS) IgG/A ²
Plasma cell myeloma
Solitary plasmacytoma of bone
Castles disease plasmacytoma
Monoclonal immunoglobulin deposition disease ³
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma
Diffuse large B-cell lymphoma
Follicular lymphoma
In situ follicular neoplasia ⁴
Dusky-type follicular lymphoma ⁴
Posttransplant follicular lymphoma ⁴
Large B-cell lymphoma with IRF1 rearrangement ⁴
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
In situ mantle cell neoplasia ⁴
Diffuse large B-cell lymphoma (DLCL) NOS
Germinal center B-cell type ⁴
Activated B-cell type ⁴
T-cell/histiocytic large B-cell lymphoma
Primary DLCL of the central nervous system (CNS)
Primary cutaneous DLCL, leg type
CD30 ⁺ DLCL, NOS ⁴
EBV ⁺ mucocutaneous ulcer ⁴
DLCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK ⁺ large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
ANHR ⁺ DLCL, NOS ⁴
Burkitt lymphoma
Burkitt-like lymphoma with t(8;24) aberration ⁴
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangement ⁴
High-grade B-cell lymphoma, NOS ⁴
B-cell lymphoma, unclassifiable, with features intermediate between DLCL and classical Hodgkin lymphoma
Mature T and NK neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
Systemic CD30 ⁺ T-cell lymphoma of childhood
Hyaline vacuolization-like lymphoproliferative disorder ⁴
Adult T-cell leukemia/lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma

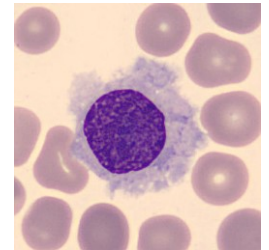
Table 1. (continued)

Monoclonal epitheliotropic (nodal) T-cell lymphoma ⁴
Anaplastic T-cell lymphoproliferative disorder of the GI tract ⁴
Hepatocytic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30 ⁺ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous CD30 ⁺ aggressive epitheliotropic cytotoxic T-cell lymphoma
Primary cutaneous anaplastic T-cell lymphoma ⁴
Primary cutaneous CD30 ⁺ anaplastic T-cell lymphoproliferative disorder ⁴
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
Follicular T-cell lymphoma ⁴
Nodal peripheral T-cell lymphoma with TCR phenotype ⁴
Anaplastic large-cell lymphoma, ALK ⁺
Anaplastic large-cell lymphoma, ALK ⁻
Great vessel-associated anaplastic large-cell lymphoma ⁴
Hodgkin lymphoma
Nodular lymphocyte predominant Hodgkin lymphoma
Classical Hodgkin lymphoma
Nodular sclerosing classical Hodgkin lymphoma
Lymphocyte-rich classical Hodgkin lymphoma
Mixed cellularity classical Hodgkin lymphoma
Lymphocyte depleted classical Hodgkin lymphoma
Posttransplant lymphoproliferative disorders (PTLD)
Plasmacytic hyperplasia PTLD
Infectious mononucleosis PTLD
Follicular hyperplasia PTLD ⁴
Polyclonal PTLD
Monoclonal PTLD (B- and T-follicular types)
Classical Hodgkin lymphoma PTLD
Histiocytic and dendritic cell neoplasms
Histiocytic sarcoma
Langerhans cell histiocytosis
Langerhans cell sarcoma
Indeterminate dendritic cell tumor
Immunoblastic dendritic cell sarcoma
Follicular dendritic cell sarcoma
Fibroblastic reticular cell tumor
Disseminated large cell angiohistiocytosis
Erdheim-Chester disease ⁴

Provisional entities are listed in italics.
⁴Change from the 2008 classification.

small population, but is often associated with a lymphocytosis.⁴ Whereas in 2008 it was unknown whether MBL was a precursor of CLL, we now know that MBL precedes virtually all cases of CLL/small lymphocytic lymphoma (SLL).⁴⁶ The updated WHO will retain the current criteria for MBL, but will emphasize that “low-count” MBL, defined as a PB CLL count of $<0.5 \times 10^9/L$, must be distinguished from “high-count” MBL because low count MBL has significant differences from CLL, an extremely limited, if any, chance of progression, and, until new evidence is provided, does not require routine follow-up outside of standard medical care.⁴⁷ In contrast, high-count MBL requires routinely follow-up, and has very similar phenotypic and genetic/molecular features as Rai stage 0 CLL, although immunoglobulin heavy chain variable region (IGHV)-mutated cases are more frequent in MBL.⁸ Also impacting our diagnostic criteria, the revision will eliminate the option to diagnose CLL with $<5 \times 10^9/L$ PB CLL cells in the absence of extramedullary

Leukémie s vlasatými buňkami



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Table 1. 2016 WHO classification of mature lymphoid, histiocytic, and dendritic neoplasms

Mature B-cell neoplasms

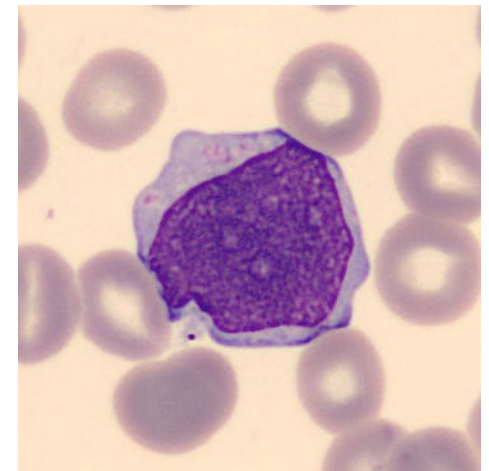
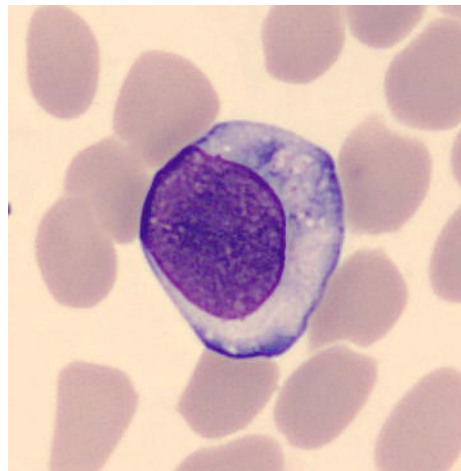
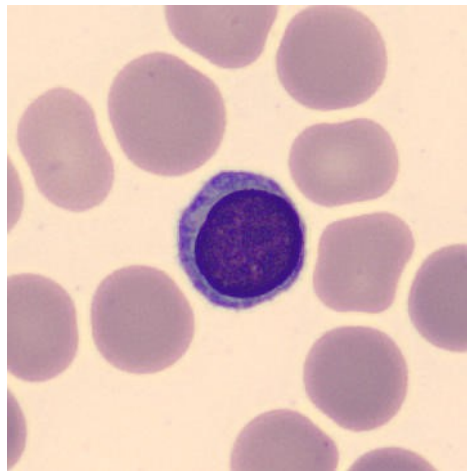
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis*
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
<i>Splenic B-cell lymphoma/leukemia, unclassifiable</i>
<i>Splenic diffuse red pulp small B-cell lymphoma</i>
<i>Hairy cell leukemia-variant</i>
Lymphoplasmacytic lymphoma
Waldenström macroglobulinemia
Monoclonal gammopathy of undetermined significance (MGUS), IgM*
μ heavy-chain disease
γ heavy-chain disease
α heavy-chain disease
Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*

Table 1. (continued)

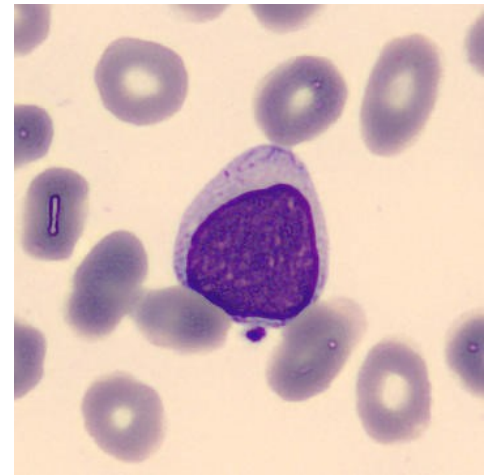
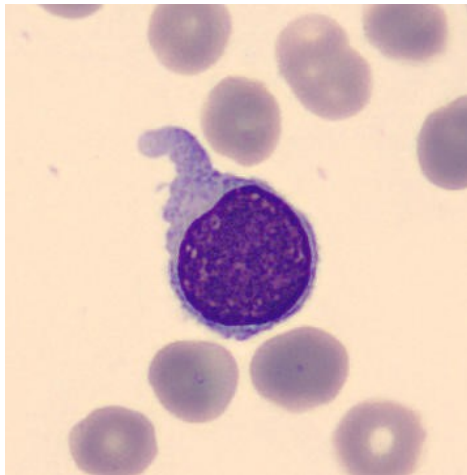
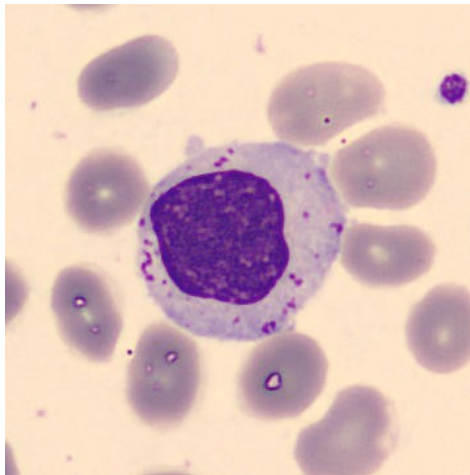
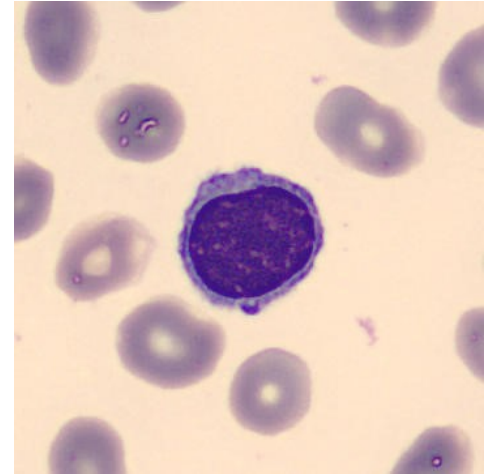
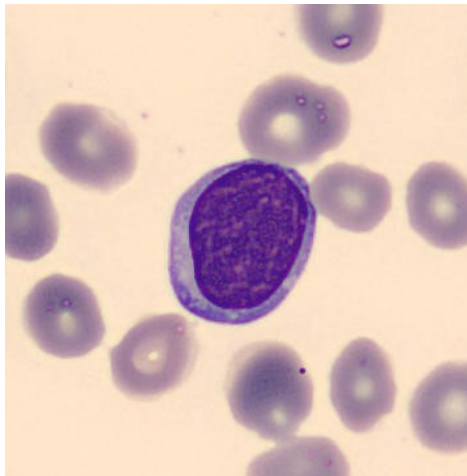
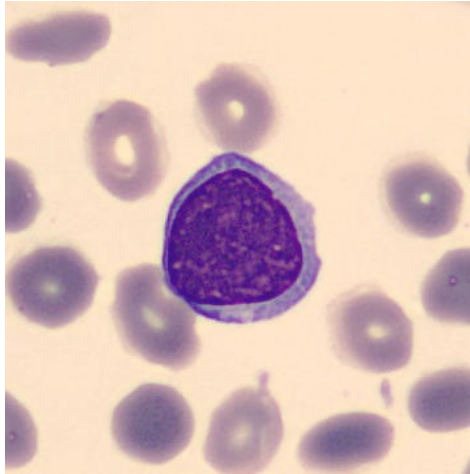
Monomorphic epitheliotropic intestinal T-cell lymphoma*
<i>Indolent T-cell lymphoproliferative disorder of the GI tract*</i>
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30 ⁺ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
<i>Primary cutaneous CD8⁺ aggressive epidermotropic cytotoxic T-cell lymphoma</i>
<i>Primary cutaneous acral CD8⁺ T-cell lymphoma*</i>
<i>Primary cutaneous CD4⁺ small/medium T-cell lymphoproliferative disorder*</i>
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
<i>Follicular T-cell lymphoma*</i>
<i>Nodal peripheral T-cell lymphoma with TFH phenotype*</i>

Cíle

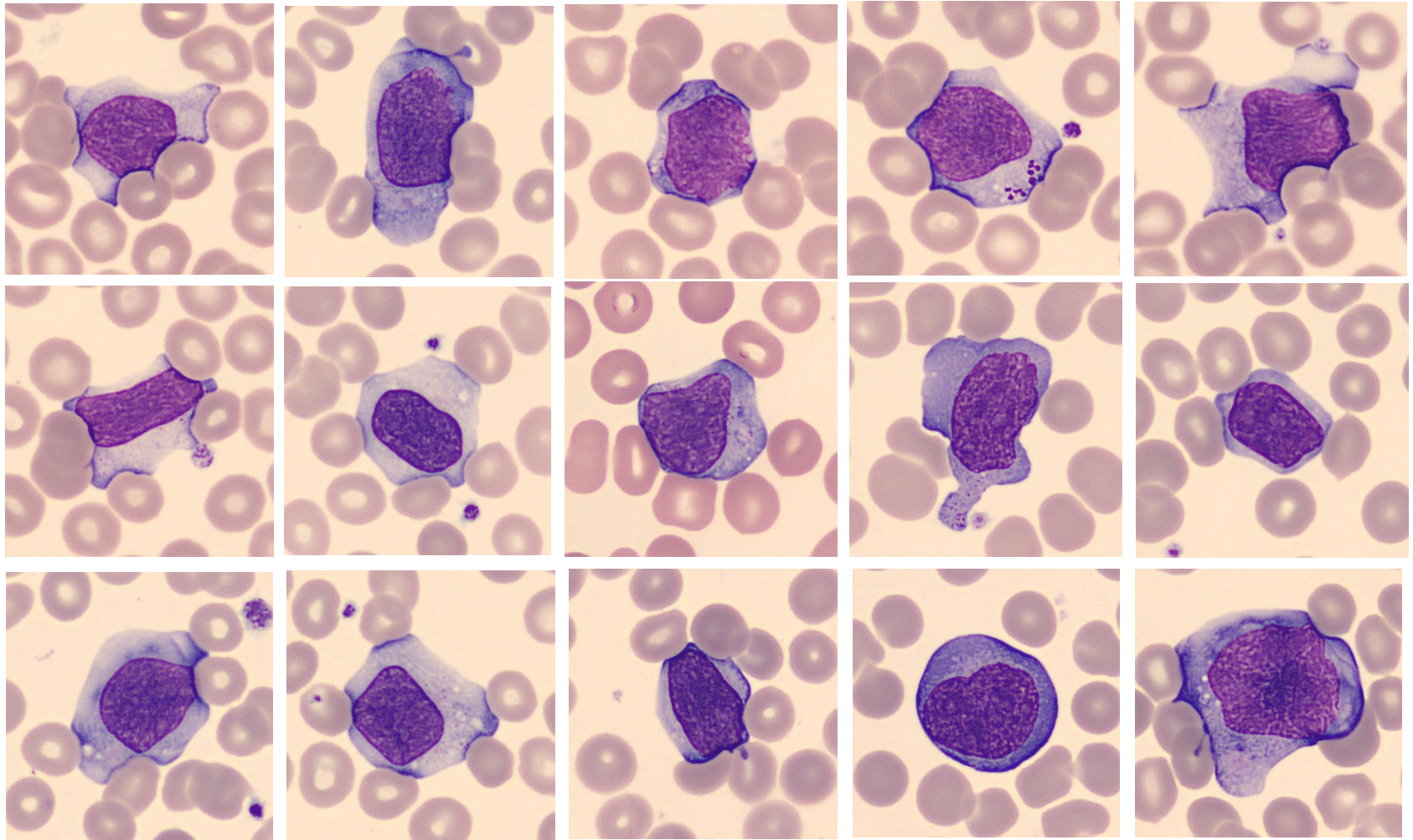
2. Lymfocyty – morfologické trápení



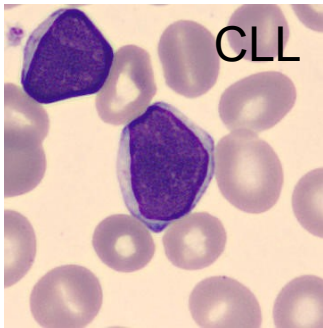
Fyziologické lymfocyty



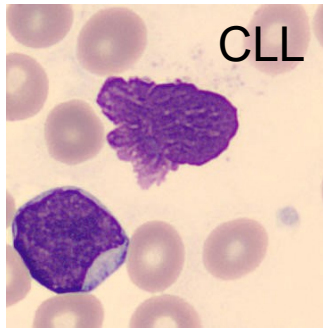
Reaktivní lymfocyty



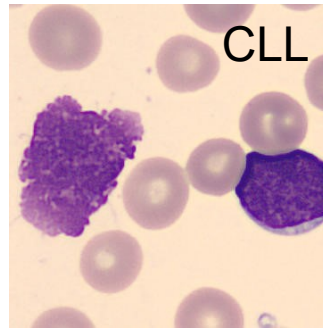
Nádorové lymfocyty



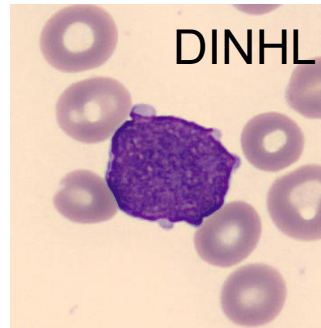
CLL



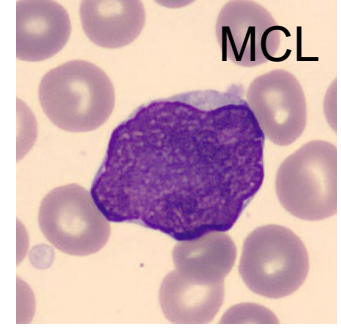
CLL



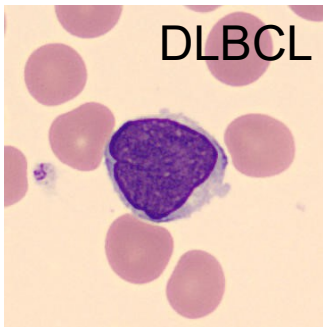
CLL



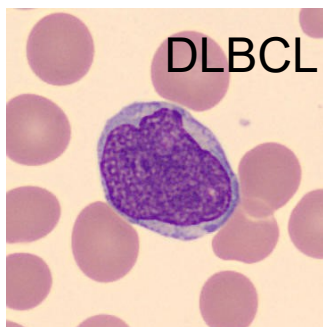
DLNHL



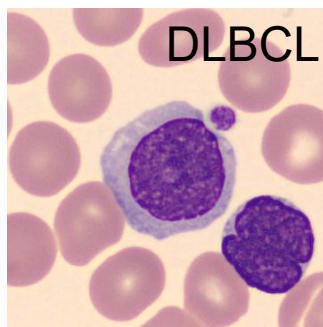
MCL



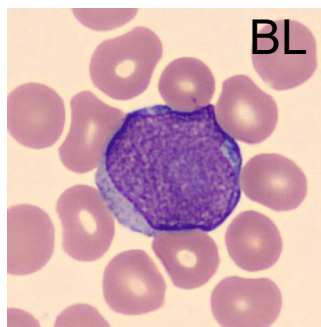
DLBCL



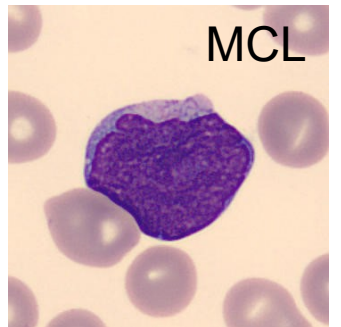
DLBCL



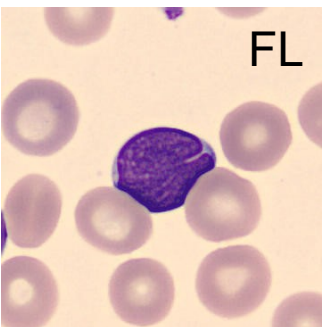
DLBCL



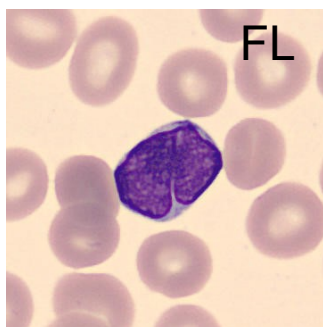
BL



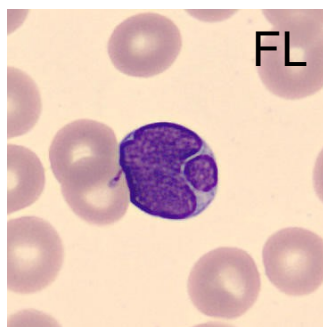
MCL



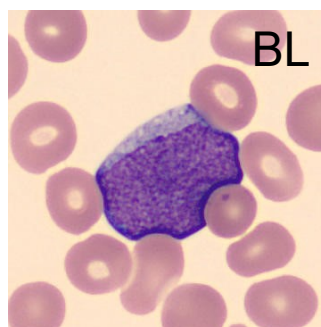
FL



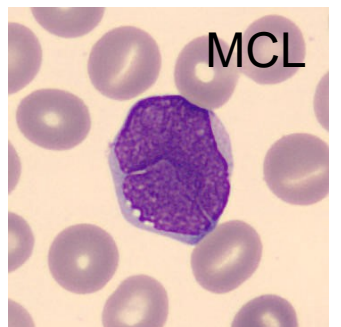
FL



FL



BL



MCL

Cíle

3. Mezioborová spolupráce



Pacient muž *33



- SA:
 - jedná se na svůj věk (86 let) o velmi vitálního muže, váha 75 kg, výška 167 cm
 - bývalý vojenský pilot proudových letadel
 - žije sám, má přítelkyni
- RA
 - otec zemřel v 73 letech na CA plic, matka v 79 letech na stáří
 - 2 děti, dcera má 10 let cukrovku (transplantace slinivky a ledvin), syn neví
- Alergie
 - alergická rýma, léková zpočátku není (později na penicilin)
- Abusus
 - nekuřák, alkohol v poslední době velmi málo

Pacient muž *33 - OA



- Od r. 1989 je sledován pro ICHS v ÚVN Praha (tehdy spíše arytmie) – pacient nic trvale neužívá
- Od r. 1995 první záznam v dokumentaci VN Brno (pracovní lékařství)
 - v anamnéze úraz DKK bil. popáleniny II. stupně (pracovní úraz)
 - TK 140/90 P 68/min ICHS zatím bez pravidelné léčby
- 1996
 - Abnormální zátěžový test při těžké poruše rytmu při fyzické zátěži, porucha srdečního rytmu odpovídá dle Lowna stadiu IVa
 - Nasazen Vasocardin
 - RTG (pro bolest zad) – degenerativní spondylosa, osteochondrosa (C), degenerativní spondyloarthrosa s osteochondrosami disků (Th)
- 1997
 - Vyšetřeny EBV a CMV – pozitivní IgG, negativní IgM, KO v normě
- 1999
 - Steatosa slinivky, lehce zvětšená prostata, vertebrogenní algie
 - TK 140/80 P 66/min
- 2003
 - Haemoroidy, hemoglobin 144 g/l, **MCV 109 fl**



Pacient muž *33 - OA

- 2004
 - HGB **111 g/l**, MCV **132 fl**
 - Anémie makrocytární
 - Haemoroidy aa, varixy bil.
 - ISCH dysrytmická forma
 - Vertebrogeně algický
 - Hy prostaty

- 2005
 - Gastroskopie, rectoskopie, onkomarkery negativní
 - Vit B12 **97 ng/l ↓**, HGB **112 g/l ↓**, MCV **132 fl ↑↑**
 - Anémie z nedostatku vit. B12
 - Substituce B12 inj. formou cestou PL, pyridoxin

 - Předán do péče hematologa VN Brno
 - B12 **1429 ↑**, HGB **158 g/l**, MCV **93,9 fl**

Pacient muž *33 - OA

- 2008
 - Stále substituce B12 a 6 týdnů, KO zcela v normě
 - Opakovaně vyšší TK, 160 /90 – Micardis
 - Hypertenze II
- 2014/2015
 - Před operací katarakty, první záchyt trombocytopenie
 - 13.10.2014: trombo **133** ↓, KO jinak zcela v normě
 - 7.4.2015: trombo **120** ↓, KO jinak zcela v normě
 - 6.10.2015: trombo **102** ↓, LEU **3,79** ↓, KO včetně diff v normě
 - Doplněno vyšetření protilátky proti trombo a granulo, ANA, ACLA, AB2GP, LA, celiakie, štítnice, CT, elfo, vit B12, metabolismus železa
- Leden 2016
 - trombo **108** ↓, LEU **3,20** ↓, NEU **38%** ↓ (1,22 ↓ abs), LYM **51%** ↑ (1,62 abs)
 - Mikroskop. diff: morfologicky v normě – oj. LGL lymfocyty
- 19.4.2016
 - Provedena sternální punkce: hypocelulární KD s redukcí granulopoezy a megakaryopoezy, lymfopoeza **4,8%**, bez elevace blastů a bez významných dysplastických změn
 - UZ břicha BPN

Pacient muž *33



- Listopad 2017

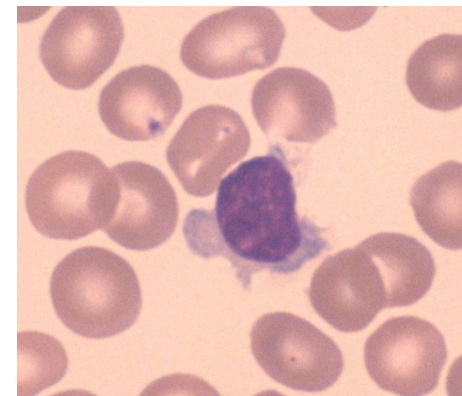
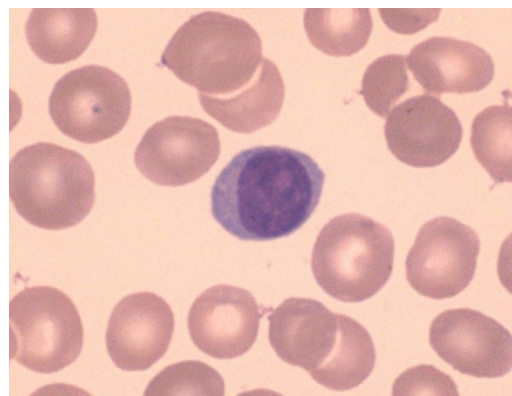
- Vzhledem k prohlubování trombocytopenie, leukopenie a neutropenie indikována opět SP na leden 2018
- V mikroskopickém preparátu PK popisujeme variantní formy lymfocytů, LGL formy lymfocytů
- Klinicky je pacient asymptomatický, bez lymfadenopatie, bez splenomegalie

	7.11.2017		11.1.2018	
LEU	2,14	↓	1,65	↓
ERY	3,38	↓	3,03	↓
HGB	113,2	↓	99,5	↓
HCT	0,35	↓	0,31	↓
TROMBO	47,7	↓	43,8	↓
MCV	102,2	↑	102,2	↑
MCH	33,5		32,9	
MCHC	327,5		322	
NEU %	23	↓	28	↓
LYM %	71	↑	60	↑
MONO %	3		7	
EO %	3		4	
BASO %	1		0	
NEU abs	0,48	↓	0,46	↓
LYM abs	1,52		1,00	
MONO abs	0,06	↓	0,12	
EO abs	0,07		0,07	
BASO abs	0,01		0	
RETI %	1,58		1,62	
RETI abs	53,3		49,1	

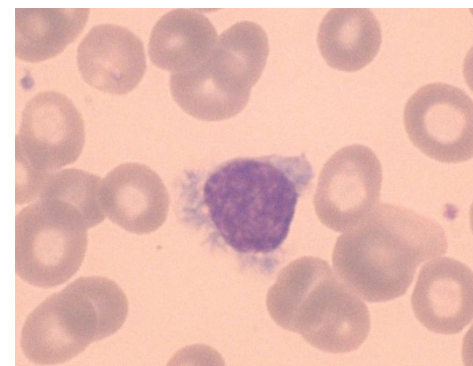
Výsledky mikroskopického hodnocení periferní krve 11.1.2018:



- Tyče 3%
- Neutrofilní segmenty 20%
- Lymfocyty 70%
- Monocyty 3%
- Eosinofily 3%
- Bazofily 1%



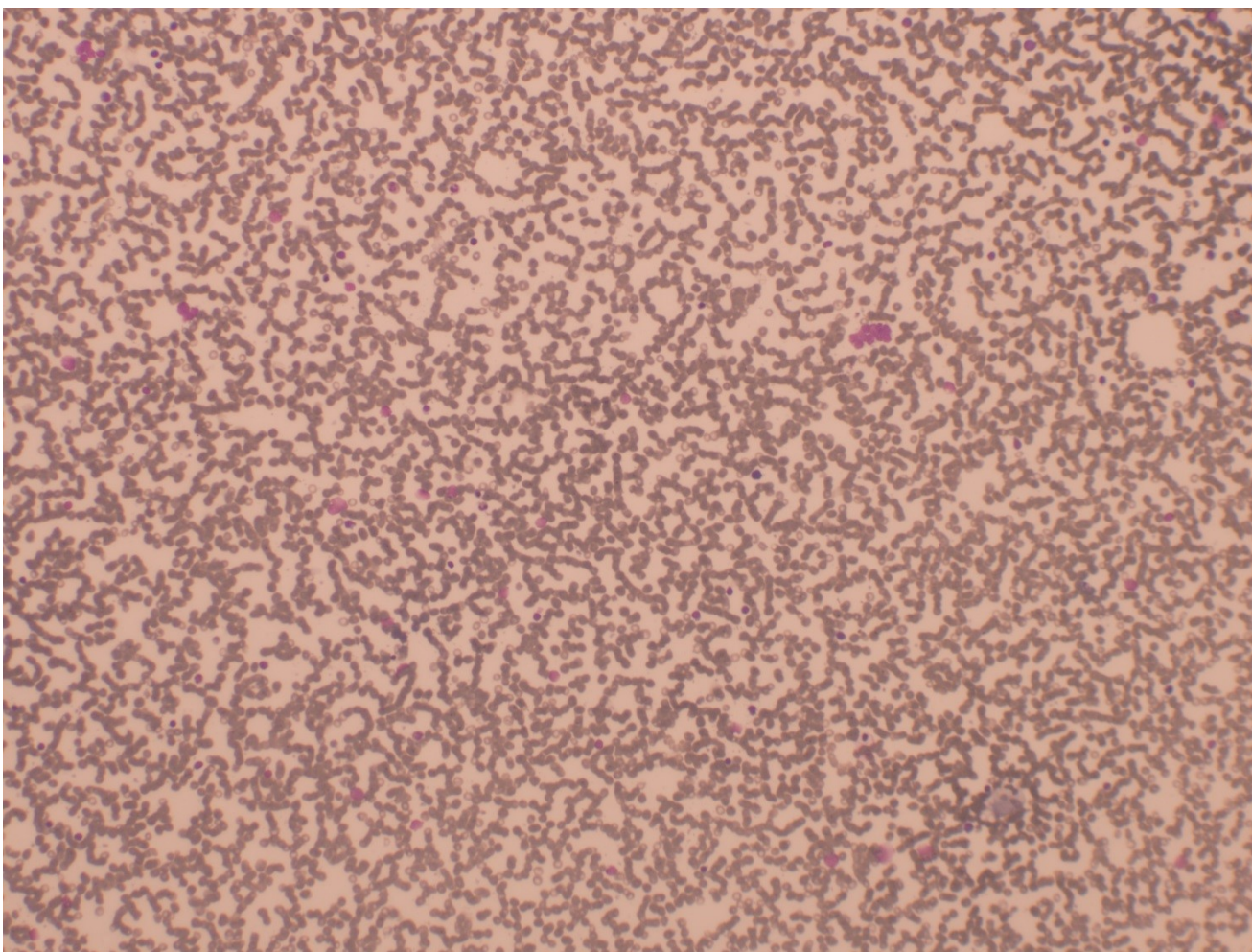
- LEU: zastiženy atypické lymfocyty se světle bazofilní nepravidelnou cytoplazmou a jemnými projekcemi cytoplazmy
- ERY: makrocyty, mírná anizocytosa, oj. ovalocyty
- PLT: hypogranulace, anizocytosa, makrotrombocyty



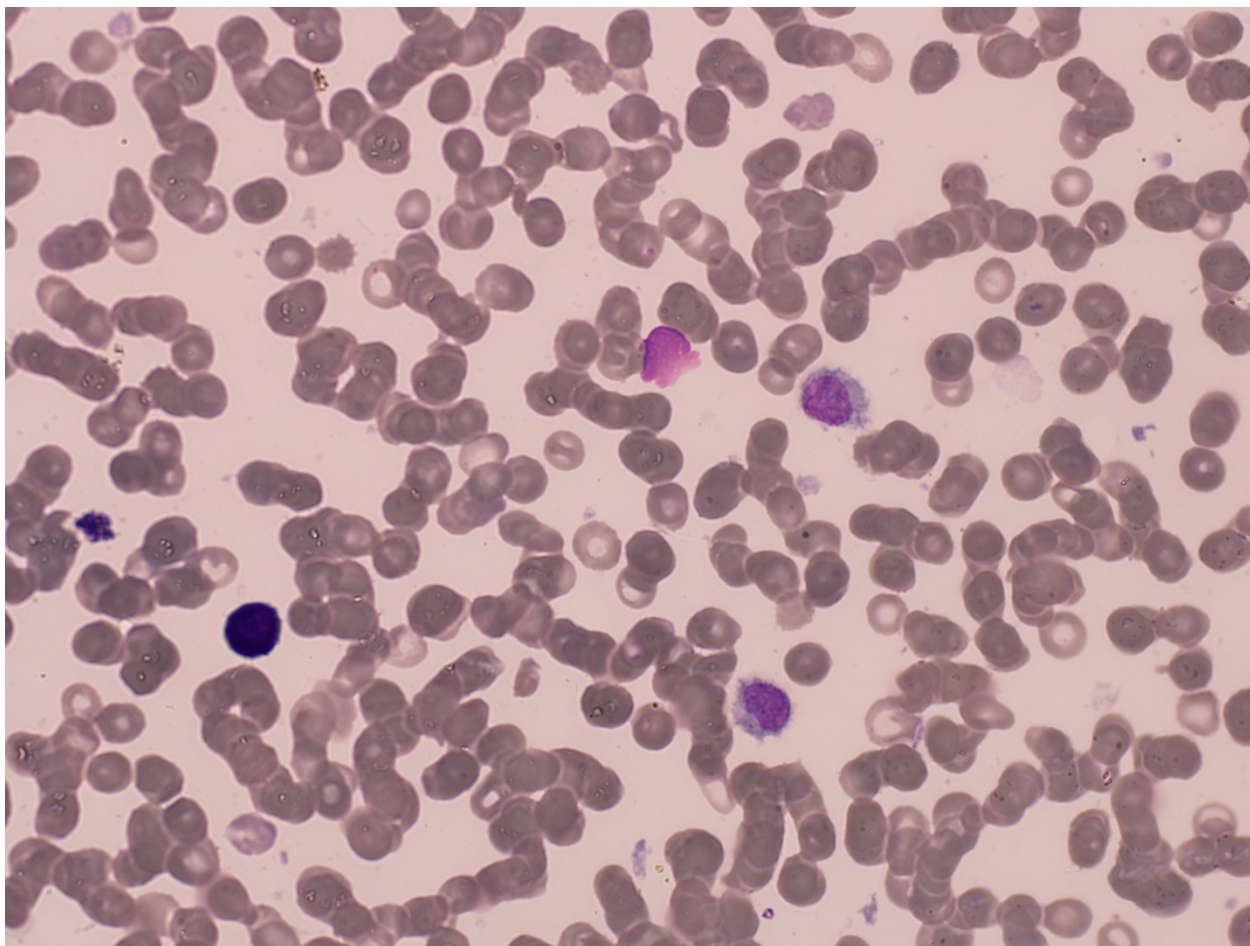
Výsledky mikroskopického hodnocení kostní dřeně 11.1.2018:

- Granulocytární řada: 10,2% (55-70%)
 - Červená řada: 34,8% (15-35%)
 - Lymforetik. řada: 53,4% (5-20%)
 - **Lymfocyty** **52,2%** **(5-20%)**
 - Monocytární řada: 1,6% (0-3%)
 - Megakaryocyty: zastiženy ojediněle, holá jádra MGKCT
-
- Jedná se o buněčně chudý preparát s výrazně disproporcionálním zastoupením jednotlivých řad
 - V nátěru zastiženy atypické lymfocyty se světle bazofilní cytoplazmou s výběžky, charakteru HCL

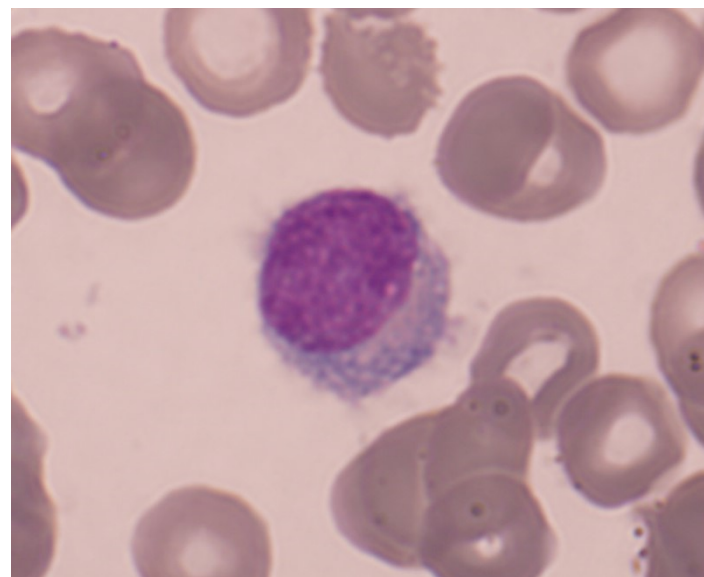
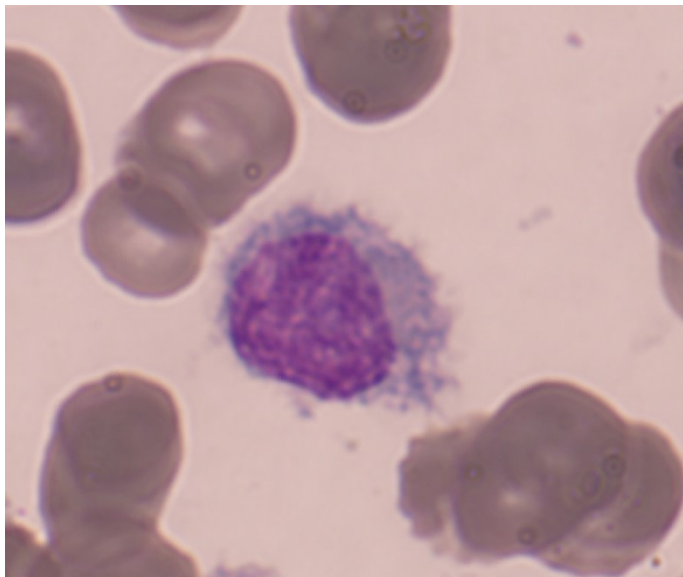
Výsledky mikroskopického hodnocení kostní dřeně 11.1.2018:



Výsledky mikroskopického hodnocení kostní dřene 11.1.2018:



Výsledky mikroskopického hodnocení kostní dřeně 11.1.2018:



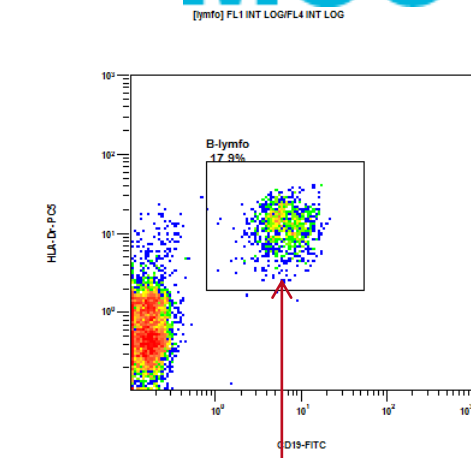
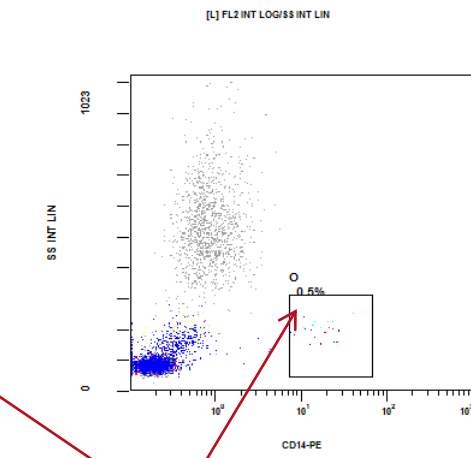
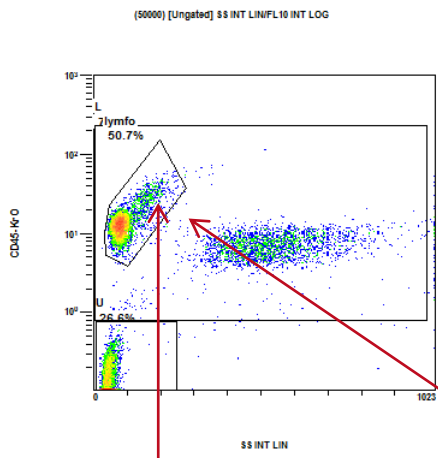
Patologické lymfocyty

Průtoková cytometrie kostní dřeně 11.1.2018:

- vzorek kostní dřeně je zaslán do laboratoře průtokové cytometrie OLM MOU
- zde je provedena imunofenotypizace
- nálezem z průtokového cytometru je záchyt

abnormálních B-lymfocytů s imunofenotypem CD19+ CD20++
sIg(kappa)+ FMC7+ CD79b(low)+ CD5- D23- CD11c+ CD103+
CD25+ CD38- CD10- CD200+ bez elevace absolutního počtu B-
lymfocytů

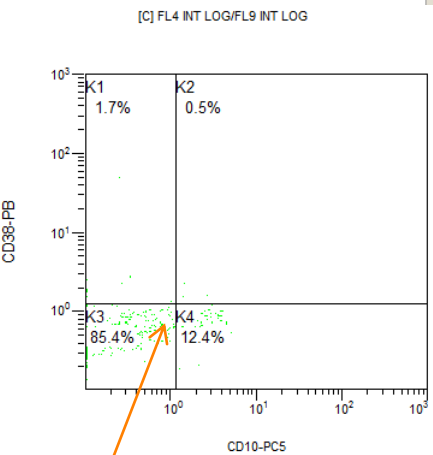
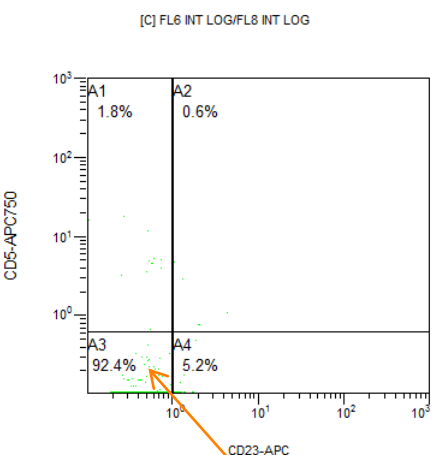
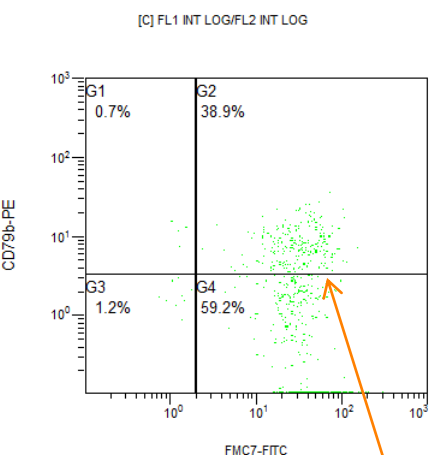
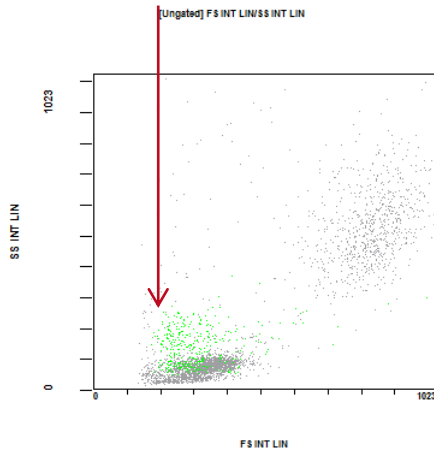
- Nález potvrzuje dg. Leukémie s vlasatými buňkami



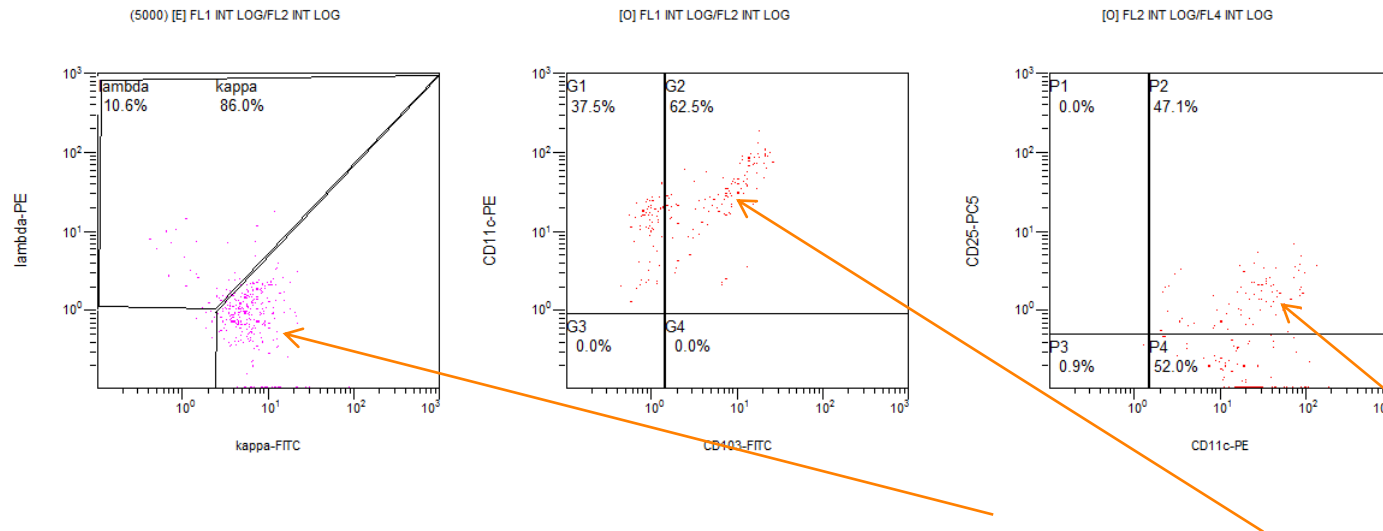
monocytopenie

bez elevace B-lymfocytů
abnormální exprese CD19 (2 populace)

Abnormální optické vlastnosti části
lymfocytů, patologických B-lymfocytů
(jsou mimo lymfo-gate)



CD19+ FMC7+ CD79b-/+ CD5- CD23- CD38- CD10-/+



CD19+ FMC7+ CD79b-/ + CD5- CD23- CD38- CD10-/ + sIg(kappa)+ CD11c + CD103+ CD25+/-

Výsledky, hodnocení, jednotlivé scattergramy a závěr vyšetření z průtokové cytometrie mi laskavě poskytla **doc. RNDr. Lenka Zdražilová Dubská, Ph.D.**



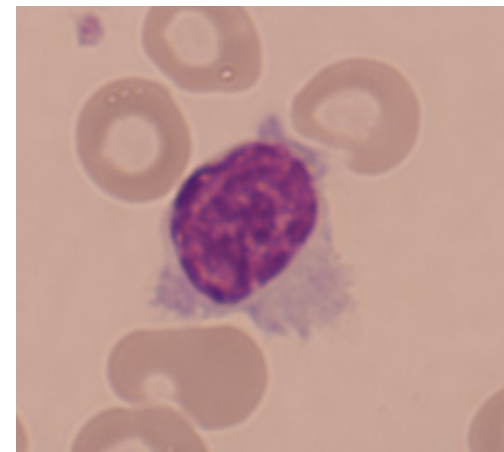
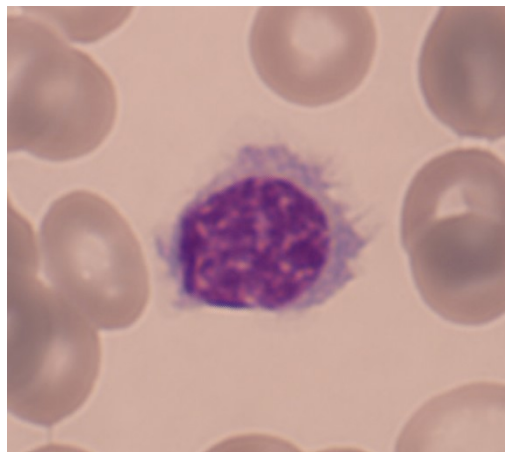
Pacient muž *33



- 16.1.2018 – IHOK
 - Periferní pancytopenie – susp. HCL
 - Lucidní, afebrilní, hlava BPN, dýchání alveolární čisté bez vf, eupnoe, SA reg, srdeční ozvy bez šelestů, břicho klidné, bez hepatosplenomegalie, DKK bez otoků, na bérkách jizvy po spáleninách
 - LU bez hmatné lymfadenopatie
 - Indikována SP na stacionáři IHOK
 - Myelogram
 - Flow
 - Molekulární biologie (BRAF)
 - Ostatní nelze, obtížná aspirace ze 2 vpichů

Výsledky mikroskopického hodnocení periferní krve 16.1.2018:

- Neutrofilní segmenty 31%
- Lymfocyty 62%
- Monocyty 3%
- Eosinofily 3%
- Bazofily 1%



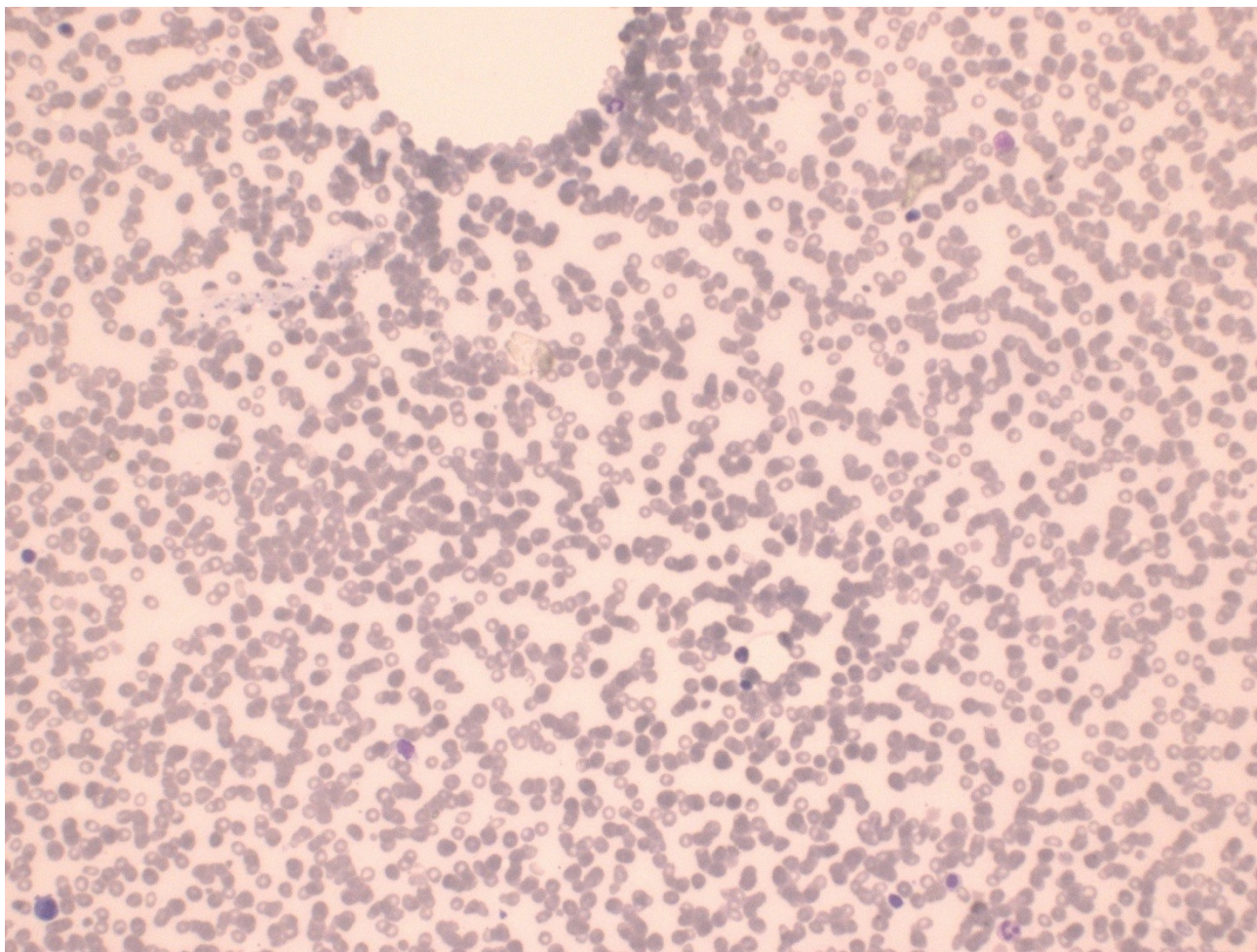
- LEU: zastiženy oj. atypické lymfocyty se světle bazofilní cytoplazmou a jemnými projekcemi cytoplazmy
- ERY: makrocyty, anizocytosa, hypochromie, ovalocyty
- PLT: anizocytosa, makrotrombocyty, nalezen gigatrombocyt

Výsledky mikroskopického hodnocení kostní dřeně 16.1.2018:

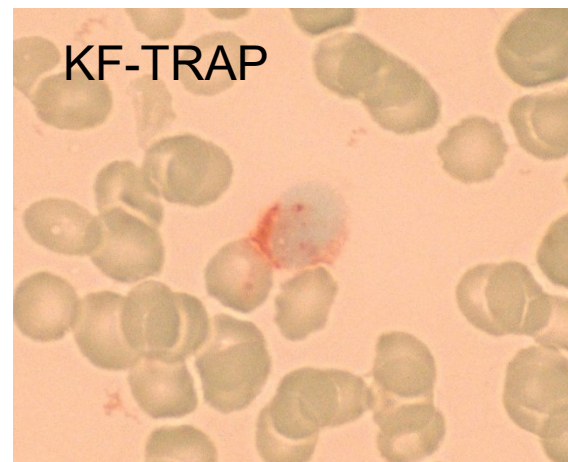
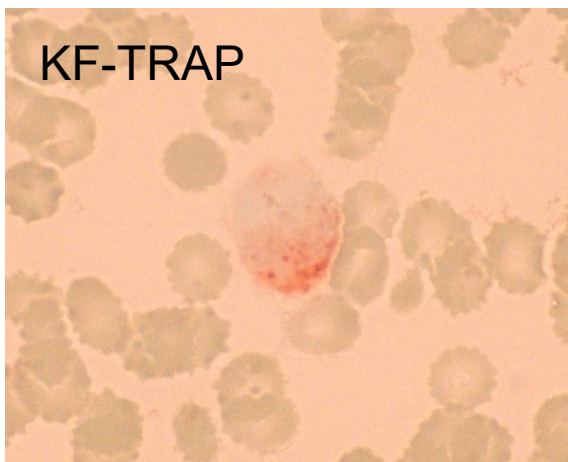
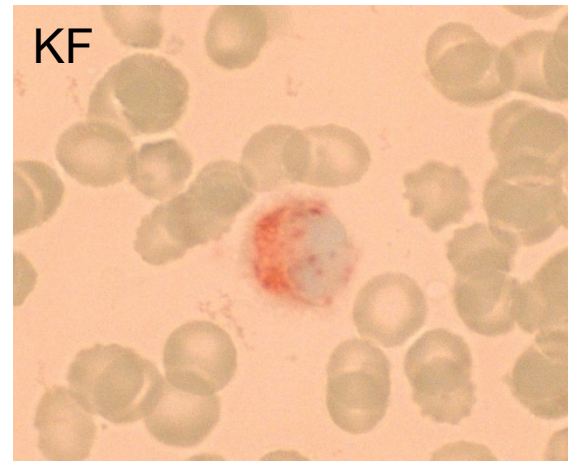
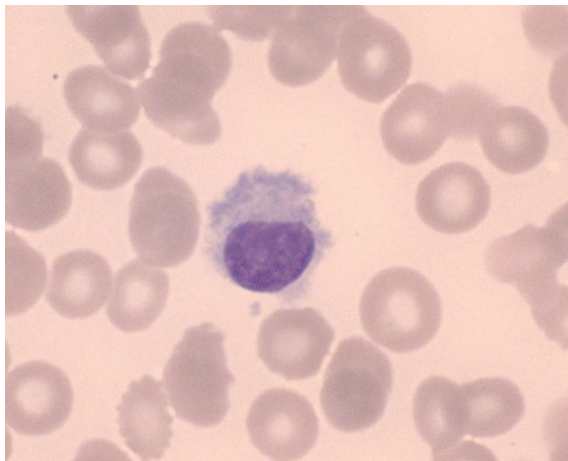


- Granulocytární řada: 29,8% (55-70%)
 - Červená řada: 22,8% (15-35%)
 - Lymforetik. řada: 47,0% (5-20%)
 - **Lymfocyty** **40,4%** (5-20%) z toho **11,4% atyp. lymfo**
 - Monocytární řada: 0% (0-3%)
 - Megakaryocyty: nalezeny, ojediněle
-
- Jedná se o buněčně chudý preparát s výraznou redukcí granulopoezy a megakaryopoezy, naopak zmnožení lymfopoezy
 - Nacházíme jednak zralé lymfocyty, jednak LGL a výraznou frakci nádorových lymfocytů s nepravidelným okrajem s jemnými cytoplazmatickými protruzemi, jemnějším chromatinem a jadérkem, vs. vlasatobuněčné lymfocyty
 - KF: zvyklá pozitivita buněčných elementů
 - **KF-TRAP: patol. silná granulární pozitivita** některých lymfocytů

Výsledky mikroskopického hodnocení kostní dřeně 16.1.2018:



Výsledky mikroskopického hodnocení kostní dřeně 16.1.2018:



Pacient muž *33



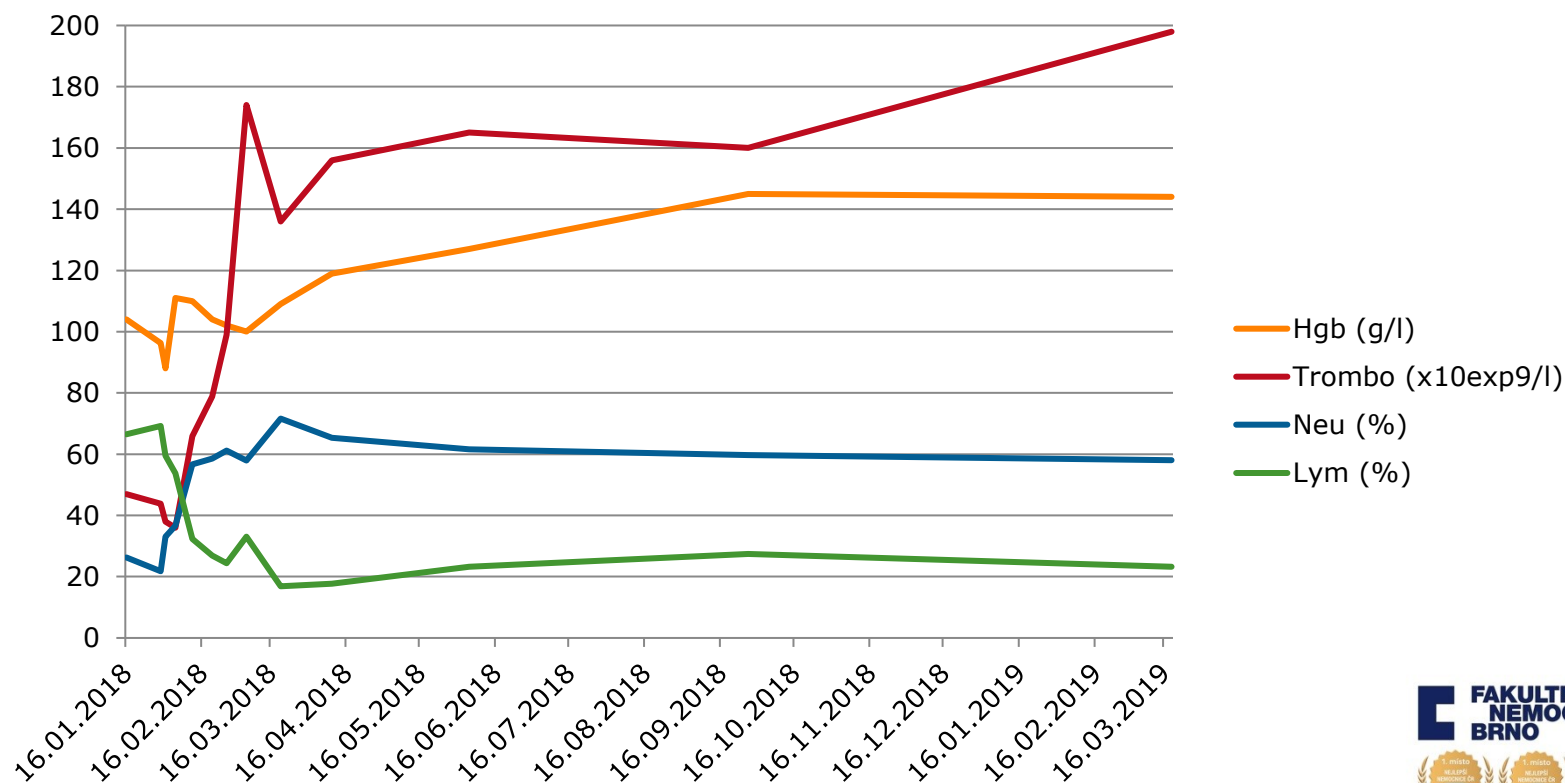
- 30.1.2018- 1.2.2018 – hospitalizace IHOK
 - Morfologicky dg. Leukémie s vlasatými buňkami
 - Potvrzeno mol. geneticky: BRAF pozitivní
 - Výsledky flowcytometrie– nejsou k dispozici

 - V první linii s ohledem na těžkou trombocytopenii a dobrý biologický věk pacienta byla zvolena terapie kladribinem (redukovaný), start 30.1.2018, bez komplikací
 - Podána 1 TU ERY TP
 - Ambulantní kontrola á týden

- 10.4.2018
 - Již plná restituce krvetvorby, hodnocen klinický efekt jako CR
 - S ohledem na věk pacienta není indikováno přešetření KD

- Remise trvá dosud
 - Poslední kontrola hematolog VN Brno: 30.5.2019
 - Poslední kontrola IHOK FN Brno: 17.9.2019

	16.1.2018	30.1.2018	1.2.2018	5.2.2018	12.2.2018	20.2.2018	26.2.2018	6.3.2018	20.3.2018	10.4.2018	5.6.2018	27.9.2018	19.3.2019
Leu (x10exp9/l)	2,35	2,15	1,21	0,41	0,642	0,68	0,9	1,24	1,39	2,42	4,01	4,71	5,37
Ery (x12exp9/l)	3,14	2,98	2,69	3,51	3,44	3,21	3,14	3,18	3,3	3,56	3,86	4,57	4,4
Hgb (g/l)	104	96,3	88	111	110	104	102	100	109	119	127	145	144
Trombo (x10exp9/l)	47	43,8	38	36	65,9	78,8	99	174	136	156	165	160	198
Neu (abs)	0,62	0,47	0,4	0,15	0,36	0,4	0,55	0,75	1	1,58	2,47	2,81	3,11
Neu (%)	26,3	21,8	33	36,6	56,7	58,5	61,2	57,9	71,6	65,3	61,6	59,7	58
Lym (abs)	1,56	1,49	0,72	0,22	0,21	0,18	0,22	0,41	0,23	0,43	0,93	1,29	1,24
Lym (%)	66,5	69,2	59,5	53,7	32,3	26,9	24,4	33	16,8	17,7	23,2	27,4	23,2



ORIGINAL ARTICLE

BRAF Mutations in Hairy-Cell Leukemia

Enrico Tiacci, M.D., Vladimir Trifonov, Ph.D., Gianluca Schiavoni, Ph.D., Antony Holmes, Ph.D., Wolfgang Kern, M.D., Maria Paola Martelli, M.D., Alessandra Pucciarini, Ph.D., Barbara Bigerna, B.Sc., Roberta Pacini, B.Sc., Victoria A. Wells, B.Sc., Paolo Sportoletti, M.D., Valentina Pettirossi, Ph.D., Roberta Mannucci, Ph.D., Oliver Elliott, M.Sc., Arcangelo Liso, M.D., Achille Ambrosetti, M.D., Alessandro Pulsoni, M.D., Francesco Forconi, M.D., Livio Trentin, M.D., Gianpietro Semenzato, M.D., Giorgio Inghirami, M.D., Monia Capponi, M.D., Francesco Di Raimondo, M.D., Caterina Patti, M.D., Luca Arcaini, M.D., Pellegrino Musto, M.D., Stefano Pileri, M.D., Claudia Haferlach, M.D., Susanne Schnittger, Ph.D., Giovanni Pizzolo, M.D., Robin Foà, M.D., Laurent Farinelli, Ph.D., Torsten Haferlach, M.D., Laura Pasqualucci, M.D., Raul Rabadan, Ph.D., and Brunangelo Falini, M.D.

ABSTRACT

BACKGROUND

Hairy-cell leukemia (HCL) is a well-defined clinicopathological entity whose underlying genetic lesion is still obscure.

METHODS

We searched for HCL-associated mutations by performing massively parallel sequencing of the whole exome of leukemic and matched normal cells purified from the peripheral blood of an index patient with HCL. Findings were validated by Sanger sequencing in 47 additional patients with HCL.

RESULTS

Whole-exome sequencing identified five missense somatic clonal mutations that were confirmed on Sanger sequencing, including a heterozygous mutation in *BRAF* that results in the BRAF V600E variant protein. Since BRAF V600E is oncogenic in other

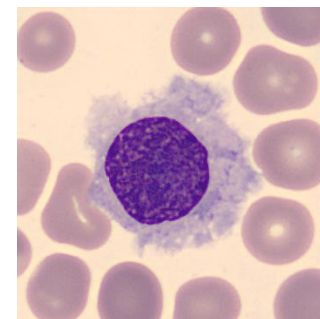
The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Falini at the Institute of Hematology, University of Perugia, Ospedale S. Maria della Misericordia, S. Andrea delle Fratte, 06132 Perugia, Italy, or at faliniem@unipg.it.

Drs. Rabadan and Falini contributed equally to this article.

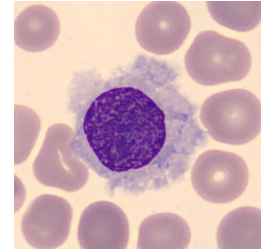
This article (10.1056/NEJMoa1014209) was published on June 11, 2011, at NEJM.org.

N Engl J Med 2011;364:2305-15.

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Leukémie s vlasatými buňkami



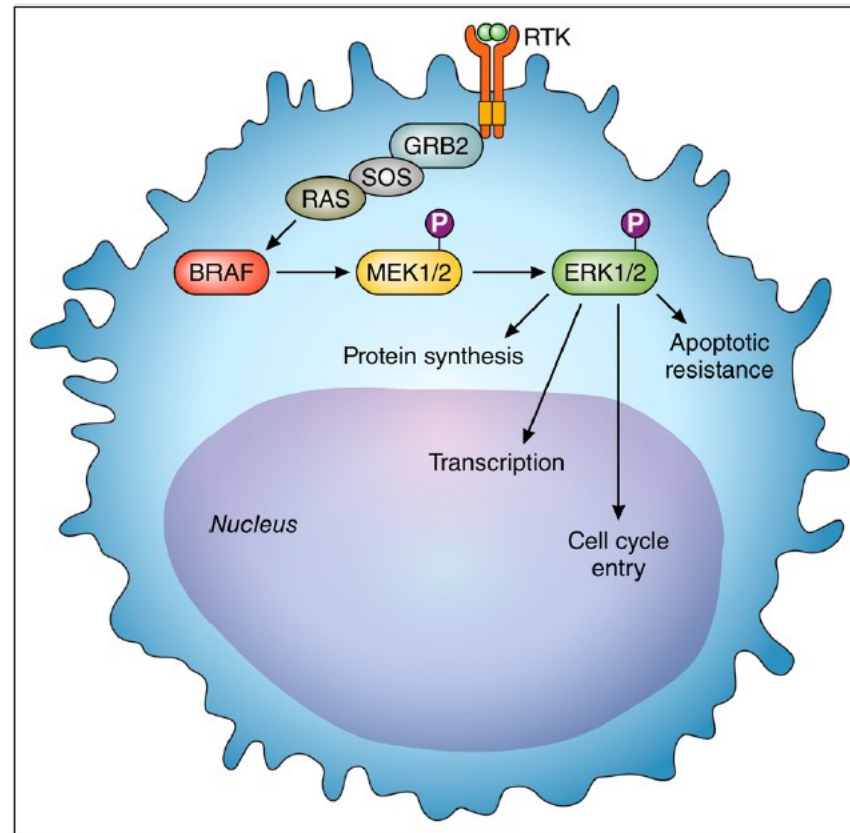
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BLOOD, 19 MAY 2016 • VOLUME 127, NUMBER 20

Table 2. Highlights of changes in 2016 WHO classification of lymphoid, histiocytic, and dendritic neoplasms

Entity/category	Change
CLL/SLL	<ul style="list-style-type: none">• Cytopenias or disease-related symptoms are now insufficient to make a diagnosis of CLL with $<5 \times 10^9/L$ PB CLL cells.• Large/confluent and/or highly proliferative proliferation centers are adverse prognostic indicators.• Mutations of potential clinical relevance, such as <i>TP53</i>, <i>NOTCH1</i>, <i>SF3B1</i>, <i>ATM</i>, and <i>BIRC3</i>, have been recognized.
Monoclonal B-cell lymphocytosis	<ul style="list-style-type: none">• Must distinguish low-count from high-count MBL.• A lymph node equivalent of MBL exists.
Hairy cell leukemia	<ul style="list-style-type: none">• <i>BRAF</i> V600E mutations in vast majority of cases with <i>MAP2K1</i> mutations in most cases that use IGHV4-34 and lack <i>BRAF</i> mutation.
Lymphoplasmacytic lymphoma (LPL)	<ul style="list-style-type: none">• <i>MYD88</i> L265P mutation in vast majority of cases impacting diagnostic criteria even though finding is not specific for LPL.• IgM MGUS is more closely related to LPL and other B-cell lymphomas than to myeloma.
Follicular lymphoma (FL)	<ul style="list-style-type: none">• Mutational landscape better understood but clinical impact remains to be determined.
In situ follicular neoplasia	<ul style="list-style-type: none">• New name for in situ follicular lymphoma reflects low risk of progression to lymphoma.
Pediatric-type FL	<ul style="list-style-type: none">• A localized clonal proliferation with excellent prognosis; conservative therapeutic approach may be sufficient.• Occurs in children and young adults, rarely in older individuals.

BRAF mutace



The activated BRAF pathway provides oncogenic signaling to the leukemic hairy cell through the MEK-ERK cascade. Vemurafenib is an inhibitor of BRAF in this pathway. The activity of pERK is reduced as a consequence of BRAF inhibition. The reduced pERK results in decreased cell proliferation. This is measured by immunohistochemical analysis and is used as a pharmacodynamics biomarker of BRAF inhibition. P, indicates a phospho-group; RTK, receptor tyrosine kinase. Professional illustration by Patrick Lane, ScEYence Studios.

Cílená terapie

● ● ● LYMPHOID NEOPLASIA

Comment on Dietrich et al, page 2847

BRAF inhibitor: targeted therapy in hairy cell leukemia

Michael R. Grever THE OHIO STATE UNIVERSITY COMPREHENSIVE CANCER CENTER

In this issue of *Blood*, Dietrich et al report that the low-dose BRAF inhibitor, vemurafenib, is highly effective in refractory hairy cell leukemia.¹

BLOOD, 9 JUNE 2016 • VOLUME 127, NUMBER 23

Závěr – lymfoproliferativní onemocnění

Pro diagnostiku nutná spolupráce nejen hematologů a imunologů!!!

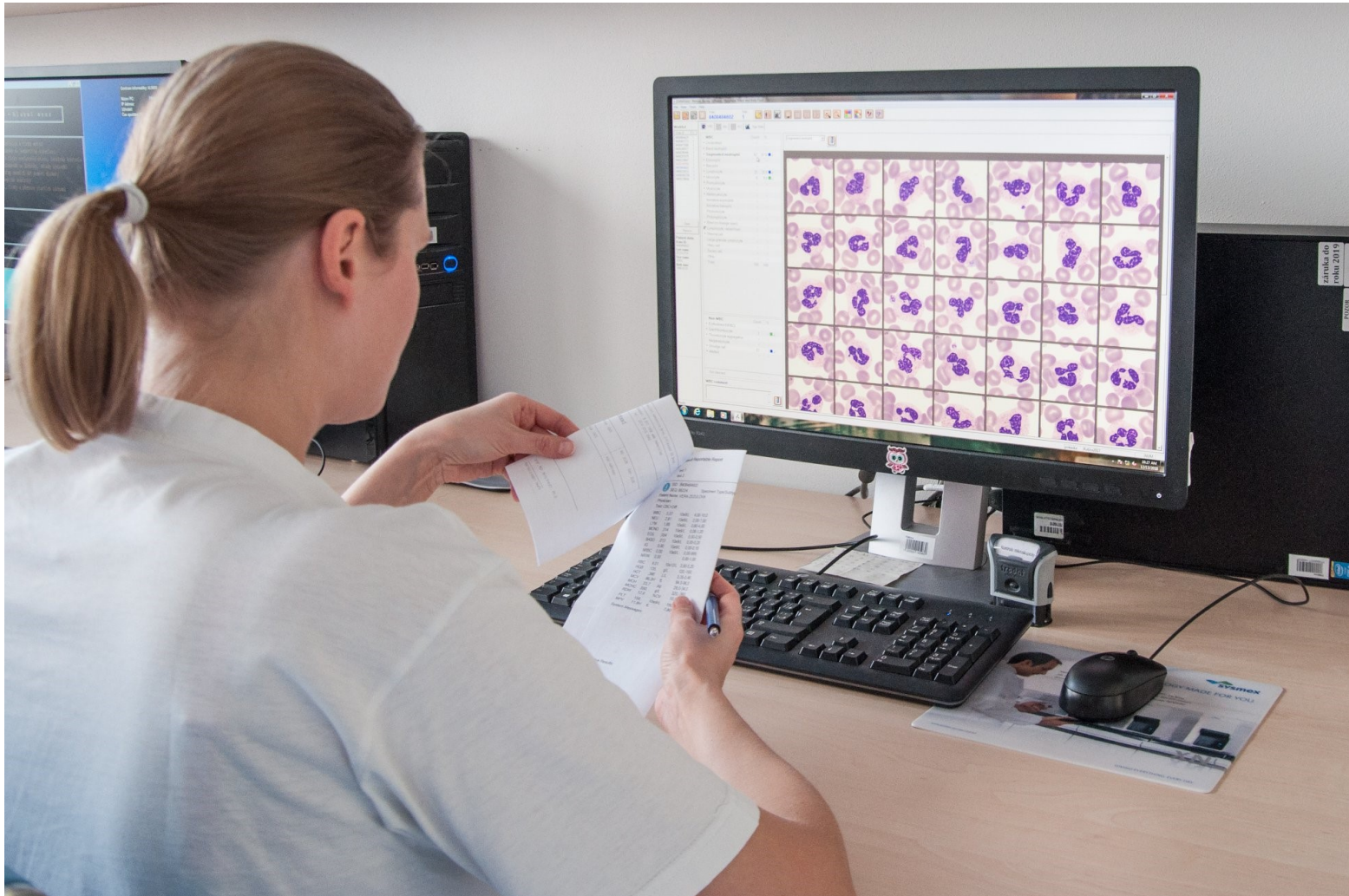


Hematologická linka



Podpořeno MZ ČR – RVO (FNBr, 65269705)

Digitální morfologie



Podpořeno MZ ČR – RVO (FNBr, 65269705)

Děkuji za pozornost



Podpořeno MZ ČR – RVO (FNBr, 65269705)