Review Article

A narrative review of central nervous system involvement in acute leukemias

Dalma Deak[1,2#], Nicolae Gorcea-Andronic[2#], Valentina Sas[2,3], Patric Teodorescu[1,2], Catalin Constantinescu[2,4], Sabina Iluta[1,2], Sergiu Pasca[1,2], Ionut Hotea[1,2], Cristina Turcas[1,2], Vlad Moisoiu[5], Alina-Andreea Zimta[6], Simona Galdean[1], Jakob Steinheber[2], Ioana Rus[1], Sebastian Rauch[2], Cedric Richlitzki[2], Raluca Munteanu[6], Ancuta Jurj[7], Bobe Petrushev[6], Cristina Selicean[1], Mirela Marian[1], Olga Soritau[1], Alexandra Andries[8], Andrei Roman[8,9], Delia Dima[1], Alina Tanase[10], Olafur Sigurjonsson[11], Ciprian Tomuleasa[1,2,6]

[1]Department of Hematology, Ion Chiricuta Clinical Cancer Center, Cluj-Napoca, Romania; [2]Department of Hematology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania; [3]Department of Pediatrics, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania; [4]Intensive Care Unit, Ion Chiricuta Clinical Cancer Center, Cluj-Napoca, Romania; [5]Department of Neurosurgery, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania; [6]Medfuture Research Center for Advanced Medicine, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania; [7]Research Center for Functional Genomics and Translational Medicine, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania; [8]Department of Radiology, Ion Chiricuta Clinical Cancer Center, Cluj-Napoca, Romania; [9]Department of Radiology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania; [10]Department of Stem Cell Transplantation, Fundeni Clinical Institute, Bucharest, Romania; [11]The Blood Bank, Landspitali University Hospital, Reykjavik, Iceland

Contributions: (I) Conception and design: D Deak, N Gorcea-Andronic, C Constantinescu, S Rauch, O Soritau, A Andries, A Roman, A Tanase, O Sigurjonsson, C Tomuleasa; (II) Administrative support: D Deak, N Gorcea-Andronic, S Iluta, C Turcas, S Galdean, I Rus, S Rauch, C Richlitzki, A Jurj, B Petrushev, M Marian, O Soritau, A Andries, D Dima, C Tomuleasa; (III) Provision of study materials or patients: D Deak, N Gorcea-Andronic, V Sas, S Galdean, I Rus, B Petrushev, C Selicean, O Soritau, D Dima; (IV) Collection and assembly of data: D Deak, N Gorcea-Andronic, D Deak, N Gorcea-Andronic, P Teodorescu, S Iluta, C Turcas, V Moisoiu, J Steinheber, I Rus, S Rauch, C Richlitzki, R Munteanu, A Jurj, C Selicean, O Soritau, A Roman, A Tanase, O Sigurjonsson, C Tomuleasa; (V) Data analysis and interpretation: D Deak, N Gorcea-Andronic, S Pasca, AA Zimta, J Steinheber, V Moisoiu, C Richlitzki, R Munteanu, A Jurj, M Marian, A Andries, A Roman, A Tanase, C Tomuleasa; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Ciprian Tomuleasa. Department of Hematology, Ion Chiricuta Clinical Cancer Center, Cluj-Napoca, Romania; Department of Hematology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania; Medfuture Research Center for Advanced Medicine, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania. Email: ciprian.tomuleasa@umfcluj.ro.

Abstract: Acute leukemias (both myeloid and lymphoblastic) are a group of diseases for which each year more successful therapies are implemented. However, in a subset of cases the overall survival (OS) is still exceptionally low due to the infiltration of leukemic cells in the central nervous system (CNS) and the subsequent formation of brain tumors. The CNS involvement is more common in acute lymphocytic leukemia (ALL), than in adult acute myeloid leukemia (AML), although the rates for the second case might be underestimated. The main reasons for CNS invasion are related to the expression of specific adhesion molecules (VLA-4, ICAM-1, VCAM, L-selectin, PECAM-1, CD18, LFA-1, CD58, CD44, CXCL12) by a subpopulation of leukemic cells, called "sticky cells" which have the ability to interact and adhere to endothelial cells. Moreover, the microenvironment becomes hypoxic and together with secretion of VEGF-A by ALL or AML cells the permeability of vasculature in the bone marrow increases, coupled with the disruption of blood brain barrier. There is a single subpopulation of leukemia cells, called leukemia stem cells (LSCs) that is able to resist in the new microenvironment due to its high adaptability. The LCSs enter into the arachnoid, migrate, and intensively proliferate in cerebrospinal fluid (CSF) and consequently infiltrate perivascular spaces and brain parenchyma. Moreover, the CNS is an immune privileged site that also protects leukemic cells from chemotherapy. CD56/NCAM is the most important surface molecule often overexpressed by leukemic stem cells that offers them the ability to infiltrate in the CNS. Although

asymptomatic or with unspecific symptoms, CNS leukemia should be assessed in both AML/ALL patients, through a combination of flow cytometry and cytological analysis of CSF. Intrathecal therapy (ITT) is a preventive measure for CNS involvement in AML and ALL, still much research is needed in finding the appropriate target that would dramatically lower CNS involvement in acute leukemia.

Keywords: Acute leukemias; central nervous system involvement (CNS involvement); clinical management; pathophysiology

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Background on the central nervous systems (CNS) involvement in acute leukemias

Therapy for acute leukemias, both myeloid and lymphoblastic, has become increasingly effective in the past decade (1-7). This is explained by the increasing efforts of personalizing chemotherapy treatment and supportive care that continuously adapts to initial diagnostic and progression of the disease, and which has resulted in better quality of life and higher overall survival (OS) rate in leukemic patients (8-11). Despite, improvements made to the diagnosis and treatment of both forms of acute leukemia: lymphoblastic (ALL) and myeloid (AML), the CNS involvement is still limiting long-term treatment, remaining one of the most severe complication and the primary causes of mortality (12,13). CNS involvement is detected either at the initial diagnosis or it develops at relapse. This event happens in 30% of relapse cases and it represents the main hurdle that leads to treatment failure (14).

In acute lymphoblastic leukemia (ALL), CNS involvement is more common and about 5% of adults are presenting with CNS leukemia at initial diagnosis, having a shorter OS in comparison with patients, who did not develop CNS leukemia (15,16). There is still no consensus regarding the rate of development of CNS disease in ALL even through this is a major therapeutic obstacle. It is generally accepted that a third of the relapse cases involve CNS in pediatric ALL (17,18). The established way of assessing CNS leukemia is lumbar puncture (LP). However, practitioners have to pay attention to the fact that in 10–30% of LPs there is a danger of blood entering into CSF due to the trauma caused by the needle, this is defined as traumatic LP (19). Some studies concluded that traumatic LP increases the chances of disease recurrence in ALL (20), especially in high-risk patients (21). The choice of during an LP only if symptoms are present in ALL is also a strategy to decrease the risk of recurrence. If LP should be introduced as routine check-up in adult ALL, then the procedures from childhood ALL or AML should be introduced, such as intrathecal cytarabine given from the beginning (22).

It is generally considered that AML cells rarely reach the CNS and develop tumors, (23,24), whereas in pediatric patients (25) this is a common event. This pattern might not accurately reflect the reality, as many times CNS involvement in adults remains undiagnosed (12,23). The main reasons behind undiagnosed CNS leukemia in adult AML is related to the lack of routine diagnostic LP; this procedure being performed only when CNS signs or symptoms are manifest (26,27). This is why in the case of hyperleukocytosis at diagnosis, even in the absence of other symptoms, the performance of a LP evaluation is advised (17,18). Still, attention must be paid to the risks of traumatic LP. CNS leukemia is a frequent complication of acute leukemia having some specific cytogenetic anomalies. In AML, chromosome 16 inversion (resulting core binding factor beta-myosin 11 heavy chain fusion protein) and chromosome 11 abnormalities [trisomy with gene amplification, including myeloid lymphoid leukemia (MLL)] represent risk factors for CNS leukemia (28). Still there are some reports the inv(16)/t(16;16) is a favorable prognostic marker in AML (29). In preB-ALL, t(1;19) translocation is a risk factor for CNS relapse and these cells are found to express MER kinase (30). MER positive ALL-blasts enter G0/G1 phase when co-cultured with CNS derived cells (31). In ALL with t(1;19) translocation is found the highly encountered E2A-PBX1-rearrangement (30), with increased IL7R expression on the blasts surface and CNS leukemia incidence (32).

CNS involvement during AML treatment is uncommon, and the incidence of CNS leukemia has decreased since the incorporation of high dose cytarabine, that is, as mentioned above, used as a preventive measure in AML. This drug has

beneficial effects due to its ability to penetrate the blood-brain barrier (33), however, this is also the main reason for severe CNS toxicity induced by this drug (34,35). Prior to the use of high dose cytarabine, meningeal disease was seen in up to 20% of children and 16% of adults with AML (33). In a review comprising information from 3261 adult patients enrolled in German clinical trials, CNS involvement was documented in 0.6 % of adult patients at the time of initial presentation and in 2.9% relapse cases (23). However, in infants, potential CNS involvement was identified in 29% of cases (12).

In order to better understand the development of CNS involvement in acute leukemia (both acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) it is important to analyze the problem from two perspectives: the biology of the disease and the clinical characteristics of CNS involvement.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/atm-20-3140).

Method used for literature search

In the current narrative review, we looked at the literature data on the mechanisms behind CNS invasion by ALL and AML cells and the clinical significance of CNS leukemia. All of the included studies were written in English. The vast majority of researched literature was focused on AML and ALL.

Cell biology of CNS penetration by the leukemic blast cell

CNS involvement in acute leukemias can either be occult (23) or clinically manifested as leukemic meningitis (36), or myeloid sarcoma (37); the first one being most frequently encountered.

It can be present at the initial diagnosis, but also can develop at any time during the natural course of disease, even after years of complete remission, as isolated CNS relapse (38). There is great variability in the incidence of CNS involvement between various forms of acute leukemia, but in recent years the trend has continuously increase thus stimulating a more in-depth analysis over this kind of extramedullary disease (EMD).

The role of leukemia stem cells (LSCs) in the development of CNS leukemia

Acute leukemia is maintained by a pool of self-renewing cells denominated leukemic stem cells (LSCs), that express CD34+CD38– and increased aldehyde dehydrogenase activity (39) with properties similar to other cancer stem cells (CSC) (40-44). The LSCs can originate from hematopoietic stem cells (HSCs) or from committed cells that have an inner higher self-renewal potential (45). In ALL, there is a strong possibility that these stem cells originate from fully differentiated cells that during malignant transformation re-gain stem-like properties. The LSCs in pediatric ALL were discovered committed cells (46). In AML LSCs are responsible for the maintenance of minimal residual disease which is responsible for treatment failure and disease relapse in AML. The reason behind the observed results is that the LSCs remain in G0 state and have high self-renewal capacity. Two pro-malignancy events have to happen in order for a malignant LSC to develop. The LCSs then "mature" into leukemic progenitors, then leukemic blasts, which are the most often therapeutic targets. However, as long as the LSCs pool is maintained, the therapeutic death of leukemic blasts is insufficient (47).

The pathway of CNS entering of leukemic cells

The leukemic cells, that proliferate (48) and infiltrate various tissues in the body (49), have a lot of properties in common with normal hematopoietic progenitors, especially a population of cells, called LSCs (49,50) or mature cells (e.g., activated monocytes), that are further explored. In order to access CNS, leukemic cells can move along the walls of the vascular channels connecting the bone marrow of the skull bones and vertebrae with the pachymeninges, cross the vascular endothelium by transendothelial migration or endothelium destruction, diffusely infiltrate the arachnoid, migrate and intensively proliferate in CSF and consequently infiltrate perivascular spaces and brain parenchyma (Virchow-Robin space) (51). This is caused by increased hypoxia and angiogenesis in the bone marrow microenvironment. The newly formed blood vessels are incapable to supply enough oxygen and thus cause general hypoxia, which creates a feed-back flop to sustain continuous new blood formation and increased vascular permeability (52).

The role of adhesion molecules in CNS leukemia development

Adhesion molecules in AML

Leukemic cells express high levels of adhesion molecules,

that are also expressed by normal myeloid or lymphoid lineage cells. Thus, these cells are considered "sticky cells" and have an increased ability to adhere to endothelial surfaces, a fact that can explain leukostasis in narrow blood vessels (42-45). In AML, cells can express all classes of adhesion molecules, more often identified being VLA-4 (53,54), VLA-5 (55), LFA-1 (56,57), MAC-1 (58), L-selectin (59,60), VCAM-1 (57), ICAM-1 (56), PECAM-1 (61), CD34 (62,63), CD44 (64,65) and CD56 (66).

New insides regarding blast cells extramedullary dissemination are given by the study of myeloblast endothelium interactions (67-70). Unlike normal myeloblasts or neutrophils, the AML leukemic blast cells can migrate through the endothelium when co-cultured with endothelial cells in a Transwell assay (71).

Numerous studies have demonstrated that blast cells secrete cytokines like transmembrane TNF-alpha (72) or IL-1beta (73) and induce an increase in E-selectin (74), P-selectin (75,76), ICAM-1 and VCAM-1 expression on endothelial cells (71), in a time dependent manner. Otherwise, they can also activate the migration of endothelial cells. In AML, an increased heterogeneity of adhesion molecules expression between FAB subtypes exist, that varies from patient to patient. Studies report a higher incidence of MAC-1 (CD11b/CD18) integrin expression in M4 and M5 subtypes (58), where CNS disease or other kinds of EMD are more frequent (77-80). MAC-1 has a broad binding specificity, mediating the interaction of macrophages with the extracellular matrix (81), granulocytes and collagen from extracellular matrix (82) and macrophage with other cells through ICAM-1, during activation (83). MAC1 plays major roles in transendothelial migration and tissue infiltration in the case of neutrophils (84).

Despite migration, adhesion molecules have a lot of other functions. LSCs enter a quiescent state in vascular niches in the bone marrow, but probably other niches too, and they do so by the expression of adhesion molecules like VLA-4 and CD44 (85). The integrin alpha4-beta1 (VLA-4) induces NF-kB signaling after binding to VCAM-1 molecules on the surface of stromal cells and increases the chemoresistance, while CD44 mediates the attachment of stromal cells to hyaluronic acid (86). VLA4 can also interact with other molecules as are osteopontin and fibronectin (87,88).

Adhesion molecules may also be involved in cell growth, proliferation, survival and migration (31,89,90). The most common AML adhesion molecules with pro-malignant effects are: ligand binding to integrins triggers SRC kinase (91), FAK (focal adhesion kinase) (92) and ILK (integrin-linked kinase) activation (93).

The role of adhesion molecules in ALL

Leukemic cells in ALL also express adhesion molecules, including beta-1 integrin (94), beta-2 integrin (CD18) (95) LFA-1 (96), LFA-3/CD58 (97,98), ICAM-1 (97), CD44 (99) and L-selectin (100). New research showed that ALL blasts express alpha 6-integrin and move along laminin in the microvessels connecting skull and vertebral bone marrow with the meninges (101). VE-cadherin and PECAM-1 co-expression in T-ALL cells enhances transendothelial migration (102).

Stefanidakis *et al.* showed that a supramolecular structure called invadosome is assembled at the contact points between leukemic blasts and endothelial or stromal cells. The invadosome contains proMMP-9 (gelatinase B) attached to alphaMbeta2 integrin and serves as an enzymatic machinery for tissue invasion that degrades extracellular matrix components (103).

B-cell ALL CNS leukemia is primarily a meningeal disease (104,105). The cerebrospinal fluid (CSF) of healthy humans contains mainly T cells (90%), as well as B cells (5%) and monocytes (5%) (106). ALL relapse can occur in bone marrow or extramedullary sites (less frequent), with higher incidence in ALL-blast sanctuaries and approximately 7.5–15% of relapses occur in the CNS (107). As follows, the clonal origin of CNS leukemia in ALL is called 'neurotrophic subclone' (108-110). The bone marrow of patients with CNS relapse may have contained at diagnosis small subpopulations of leukemic blasts with a CNS-prone profile, that translates into SCD (stearoyl-CoA desaturase) positiveness (111), or increased expression of SPP1 (secreted phosphoprotein 1), the gene encoding for osteopontin (112). ALL leukemic stem cells engraft in vascular niches (not in perivascular cells) expressing CXCL12 (113) and E-selectin (114).

The leukemic cells acquire irregular shapes in brain parenchyma. In CNS-derived leukemic cells, the genes related to cell cycle and oxidative phosphorylation are downregulated. They compared the transcriptome of CNS, BM and CSF-derived B-ALL leukemic cells and found that gene sets uniquely upregulated in CNS-derived leukemic cells included those associated with hypoxia and glycolysis (115). CNS-derived ALL leukemic cells are adapted to hypoxia, a mechanism that was rewarded with the 2019 Nobel Prize in Medicine or Physiology (116,117).

The acquired capacity of malignant transformed leukemic cells is related to the secretion of cytokines and overexpression of their receptors.

CXCL12/CXCR4 axis is central in physiological hematopoietic cells development (118), but it also seems to play a role in leukemic cells neurotropism. *In vitro* studies revealed that astrocytes (119), choroid plexus epithelial cells (120) and meningeal cells (121) secrete CXCL12 and B-ALL blasts move toward and adhere to them (120), CXCL12 appears to promote B-ALL blasts migration across brain-CSF barrier (120,122), but possibly also across BBB (120). CCR7/CCL19 is considered essential for CNS infiltration in Notch1-induced T-ALL, but not seem to be true for other ALL types (123). In preB-ALL, pediatric patients with IL7R overexpression have a high CNS leukemia incidence during disease evolution, especially in relapse (32). CXCR3 and PSGL-1 enhance BBB penetration as proven by *in vitro* studies. In ALL, the expression of these surface proteins is stimulated by IL-15 (124).

The role of hypoxia and VEGF secretion in the development of CNS leukemia

VEGF synthesis was identified in leukemic cells of both AML and ALL (125). In AML, high levels of VEGF-A are associated with disease diagnostic (126), and shorter OS (127). In patients with ALL, no correlation has been identified between plasma VEGF levels and CNS leukemia, but in CSF the VEGF level was significantly increased in patients with CNS involvement (128-131). VEGF expression is higher in leukemia cells already infiltrated in CNS, in comparison with cells from BM (132). Studies on CNS-derived leukemic cells found that VEGFA is one of the most upregulated hypoxia-induced genes. Despite promoting angiogenesis, VEGF can also increase endothelial permeability, including BBB disruption, by acting directly on endothelial cells (101). Indirectly, VEGF acts on its own receptors on ALL cells and stimulate MMP-2 and MMP-9 secretion (133). VEGF levels in ALL are increased in patients with relapse compared with newly diagnosed cases (134).

In vitro studies revealed that ALL-derived exosomes increase BBB permeability and VEGF secretion in astrocytes (135). When analyzing CNS-derived leukemic cells, reports show that this cell population has distinctive transcriptional signature. These cells, apart from bone marrow (BM)- and CSF-derived cells, downregulate genes involved in cell cycle and oxidative phosphorylation and increase the expression of genes related to hypoxia and glycolysis [VEGFA, hexokinase 2 (HK2), pyruvate dehydrogenase 1 (PDH1)] (115).

Brain parenchyma appears to be seeded by LSCs that adapt to hypoxic microenvironment of perivascular spaces (136). They modify the neural stem cell niches and maintain their stemness and quiescence there, also protected from chemotherapy (137). Brain microenvironment has major influence on leukemic cells transcriptome profiling.

Gaynes *et al.* found that CNS-derived leukemia cells have high PBX1 expression. Further *in vitro* assays showed that PBX1 is upregulated in a co-culture models of preB-ALL cells with BBB epithelial cells and choroid plexus epithelial cells. Moreover, these leukemic cells having increased cytarabine and methotrexate chemoresistance. Despite chemoresistance, inducing PBX1 overexpression leads to increased CNS infiltration *in vivo* (138). CNS is one of the ALL-blast sanctuaries and once LSCs get there, they are protected from chemotherapy (107) and the natural killer (NK) cells from the patient's immune system thus LSCs can persist as MRD in CNS or can rapidly develop into CNS leukemia (139). Meninges also appear to have protective effects on leukemic cells. *In vitro* studies show that adherence of ALL blasts to primary meningeal cells leads to increased chemoresistance, decreased apoptosis and quiescence (31).

The essential role of CD56 in development of CNS leukemia

Cluster of differentiation 56 (CD56), also called neural cell adhesion molecule (NCAM) is physiologically expressed by NK cells and a subset of mature T cells in the immune system (140-143). NCAM is the first adhesion molecule identified to have essential roles in both *in utero* and adult neurogenesis, synaptic plasticity and learning (144-147). When cells undergo malignant transformation, they express at a higher level CD56 and show an aggressive behavior (148). Apart from carcinomas with neuroendocrine phenotype (149) or tumors of neuroectodermal origin (150), well known for CD56 positivity, hematological malignancies can also express CD56 in various proportions. NCAM is expressed by malignant cells of NK leukemias (151), T-cell leukemias/lymphomas (152) and AML (153,154).

Through alternative splicing, the NCAM1 gene codes the synthesis of three isoforms noted as NCAM-120, NCAM-140 and NCAM-180, according to their molecular weight. All NCAM isoforms contain an N-terminal extracellular domain with five immunoglobulin-like (Ig) modules and two fibronectin type III (F3) modules (155). Except for NCAM-120, which is GAP-anchored on the

cell surface, the extracellular domains of NCAM-140 and NCAM-180 are followed by a short transmembrane segment and a C-terminal cytosolic domain, which is longer in the NCAM-180 isoform. In the immune cells, NCAM-140 is the dominant isoform, but in the neural tissue, they are differentially distributed: NCAM-120 isoform only in glia, NCAM-180 only in neurons and NCAM-140 isoform is expressed in both neurons and glia. It is the first adhesion molecule identified, but information about NCAM signaling still remains scarce, especially in immune cells. NCAM proteins form *cis* dimers on the cell surface but can also form tetramers after trans-interaction with other NCAM dimers on adjacent cells (156-158).

A link between NCAM and FGFR signaling was reported and it appears that the tetrameric form of NCAM triggers the activation of FGFR by lateral associations through the membrane. If NCAM ligands are present, spectrin mediates the colocalization of NCAM proteins with other molecules in lipid raft areas, leading to Fyn kinase activation, that in turn activates FAK (159-161).

Some of the pathways identified as being activated downstream from NCAM are Ras/MAPK (162), PLC/DAG/AA (155,163) and PI3K/Akt pathways (164), as inhibition of these key enzymes impairs the neurite outgrowth. Studies also noted the activation of PKC and PKA with consequent increase in intracellular calcium (165) and cAMP concentrations (166), following NCAM activation. The neurite outgrowth appears to depend on CREB (167,168), c-Fos (168) and NF-kB activation (169). These transcription factors are final targets in NCAM signaling.

CD56 is expressed on various cells from the immune system, not only by NK cells, but also by some populations of γδ T cells, CD8+ T cells, monocytes and monocyte-derived IL-15 dendritic cells (146). Little is known about NCAM function in the immune system, but it appears that, in NK cells, NCAM expression confers a high mobility potential (170), mediates NK cells adhesion to CD56 positive tumor cells thus amplifying the cytotoxic effects of NK cells (146) and it can also function as a pathogen recognition receptor (PRR) (171). In that context, NCAM expression on T cells positively correlates with the expression of CD16, NKG2A/D, NKp44/46, CD122, and DNAM-1 and with high intracytoplasmic perforin and granzyme B content (146). The intestinal T cell population has a high expression of CD56 and it has a stimulatory function on proliferation in CD56– T cells from peripheral blood (172).

CD56-bright NK cells only, and not the CD56dim subset, display CD117 (c-Kit) expression, high affinity receptor for IL-2 and CCR7 on their surface and express a higher level of CXCR3 (173).

The CD56 bright NK cells are more potent producers of the following cytokines: IFN gamma, TNF alpha, GM-CSF, IL10, IL13. As follows, CD56 serves as a diagnostic marker for NK-cell malignancies, but subpopulations of cells in any other hematological malignancy can also be positive for CD56. It is not completely understood whether, CD56 expression is inherited from the original normal cell, is a results of oncogenic mutations in malignant cells or the tumor microenvironment induces CD56 expression on leukemic cells (174).

Fischer *et al.* reported TRC [transfer RNA cysteine 4 (anticodon GCA)] gene rearrangements in almost all cases of CD56+ T-ALL and concluded that CD56+ leukemias could emerge from a bispecific T/NK progenitor (152).

Not known for leukemias, IL-15 serves as a powerful cytokine to boost CD56 expression in NK cells (175) and other immune cells, such as CD8+ T cells (176), the downstream signals being carried by Ras/MAPK, PI3K/Akt and JAK/STAT pathways (177). Fuhrmann *et al.* analyzed CD56 expression in a cohort of T-ALL patients. The genetic mutations found in the CD56+ group, that carry the mutations NOTCH1, PTEN and FBXW7, appear to have a similar distribution as for CD56– group such that they cannot link that immunophenotype to any genetic mutation. Also, the clinical progression of ALL showed significant differences only when patients are stratified according to CD56 expression profile (178).

Because AML show CD56 positivity in about 20% of cases and RUNX1 mutations are so frequent, Gattenloehner *et al.* also concluded that these mutations increase CD56 expression and disease aggressiveness (179). When RUNX1-coded wild-type p48 isoform is overexpressed, it exerts a potent stimulatory effect on NCAM gene promoter and, together, the two proteins increase BCL-2 expression, thus protecting the AML cell from apoptosis. New RUNX1 isoforms were characterized (p38a, p30, and p24) and they caused the underexpression of NCAM gene (179).

CD56 is expressed on a small subset of T-ALL cell population of non-thymic phenotype and frequent T receptor rearrangement. Although the patients did not show any differences at initial diagnosis, a smaller proportion of them entered into complete remission in comparison with CD56– T-ALL patients and developed resistance more often (152).

For instance, Alegretti *et al.* report a mean OS of only

4.0 months in CD56+ patients when compared with 14.5 months in CD56- patients with AML (66). CD56 expression has with a higher frequency in subtypes of AML with aggressive behaviors, such M4 and M5 types (66), or AML with t(8;21) translocation (180).

In acute promyelocytic leukemia (APL), even if it is rarely expressed, CD56 was correlated with high WBC count, lower platelet count, severe intravascular coagulation, expression of CD2, CD7, CD34 and CD117, shorter event-free survival (EFS) and increased relapse incidence (181,182). CD56 positivity in acute leukemias was also found to increase the tendency to develop EMD or relapse (183). EMD show high frequency in M4 and M5 types of AML (184) and in AML with t(8;21) translocation (185).

Many studies associated CD56 positivity with increased incidence of CNS leukemia at diagnosis, but also at any time during disease, both in myeloid (183), and lymphoblastic acute leukemias (140,186).

CD56 could serve as a predictive marker for CNS leukemia. ALL patients with CD56+ cells developed ALL more rapidly and was more severe, considering that the OS of ALL patients with CNS involvement was lower for CD56+ cases (140). CD56 presence was associated with CNS leukemia at initial presentation with 19% of cases in CD56+ ALL patients versus 4% in CD56- ALL patients. Even in the case of treatment with 8 consecutive cycles of cyclophosphamide the CNS leukemia developed more often in CD56+ ALL cases. However it should be considered that there were only 16 CD56+ cases versus 184 CD56– case (186). A study analyzing the role of CD56+ in T-ALL concluded that there was no difference in CNS leukemia between CD56+ or CD56– T-ALL cases (152). A case presentation also reported the expression of CD56, along with CD34, CD19, CD79s in B cell precursor ALL (BCP-ALL) who had *KMT2A-AFF1* gene rearrangement (187).

In AML, as stated above, there are less frequent cases of CNS involvement and the role of CD56 status is still debatable. However, CD56 positivity in AML leukemic blasts was associated with higher incidence of extramedullary involvement, including CNS infiltration (183). CNS relapse rate, and overall relapse rate too, are higher in CD56+ AML patients (180), especially second remission (188) including APL, especially if associated with high levels of WBC (189). According to a case report, in APL immunophenotype after CNS relapse, the cells express CD34 and CD56. Thorough a reanalysis of the bone marrow aspirate at the initial diagnosis a small subpopulation of CD34 and CD56 positive blasts was discovered (190). A careful analysis of CD56 expression at diagnosis could serve as a predictive marker to assess CNS relapse risk after complete molecular response. This is caused by CD56 expression on leukemic blasts that signals for the production of cytokine receptors that interact with cytokines secreted by astrocytes or other cells in the brain. Through this chemoattraction, leukemic cells infiltrate into the perivascular tissue and migrate in the neural tissue by CD56 homophilic interactions. These blasts also manipulate the microenvironment and establish neural stem cell niches. Their maintenance in such leukemic niches in a quiescent state could theoretically explain the high incidence of isolated CNS relapses, where cells show CD56 positivity (191).

Diagnosis and management of CNS disease in acute leukemias

Clinical presentation of CNS leukemia

As stated in the introduction, CNS involvement in acute leukemias remains under-diagnosed. The reason behind this is that the particularities of many cases are still overlooked, and current diagnostic tools are many times insufficient to detect the beginning of this complication. Symptomatic manifestations of CNS infiltration, although rare, are often subtle and attributed to other causes, as hyperleukocytosis, treatment related neuropathy, infections or brain parenchymal metastases (192). These symptoms depend of the leukemic infiltration and the number of sites involved.

In most cases, CNS involvement in acute leukemia is asymptomatic. Symptoms and signs on a neurological examination are present in half of patients with ≥5 leukocytes in the CSF. Moreover, 80% of patients with leukocytes in CSF below this number do not have any symptoms (193-195). The neurological symptoms depend on the localization of blasts and are many times atypical, such as headache, loss of balance, fainting, mood swings, seizures, nausea/vomiting and papilledema (12,196). Cranial nerves involvement is less common and can cause double vision (197), facial numbness, deafness, blindness, and swallowing difficulties (192). Another rare symptom, often overlooked, is the sudden onset of obesity, which can be caused by hypothalamic localization of leukemic cells (198).

Symptoms of spinal cord involvement are even more difficult to identify. Similar to CNS leukemia, different locations give different symptoms from back pain, legs or arms weakness, numbness or pain, and loss of bladder or bowel control (199,200).

Seldom, distinct tumors formed of infiltrated leukemic cells can be detected throughout the CNS (201).

CNS leukemia-diagnostic tools

At the MRI analysis, CNS leukemia can be seen as dispersed lesions in the brain with round edges and local edema that give an equal T1 signal and a long T2 signal. Typically, a contrast agent is used (202,203). However, many times it is hard to differentiate between these lesions and CNS infections or neurodegenerative disorders, which are also common in patients with acute leukemia (204,205). These imaging challenges, associated with the difficulties faced by the LP analysis oftentimes delay the diagnostic and the beginning of treatment in CNS leukemia patients, much to the disadvantage in the quality of life and survival of these patients (206,207).

The obstacles faced by pathological assessment are related to the risks of an LP analysis, especially traumatic LPs. However, nowadays new techniques are developed that may help minimize the risk, such as stereotactic biopsy (208,209). If this technique would be learned by more specialists, CNS leukemia would be diagnosed faster and more accurate (205).

Development of CNS leukemia involves a series of clinical characteristics at initial presentation or development of these characteristics over the course of the disease, in both ALL and AML. In AML, a high initial leukocyte count has been reported to be predictive of a CNS involvement (210). Sixty-eight of patients with elevated initial WBC count developed CNS leukemia, therefore screening LPs should be routinely obtained during induction therapy in these patients. Leukemia cells in the CSF at diagnosis seems to also be predictive for CNS infiltration, along with extramedullary AML without CNS localization. Men more frequently developed CNS dissemination than women at a three to one ratio. Another detected risk factor for CNS involvement is the presence of internal tandem duplication (ITD) in *FLT3* gene associated with *NPM1* gene mutations in leukemic cells (23,211).

It is essential to point out that risk factors and associations, although useful can still not replace the use of an LP and subsequent CSF pathological analysis. This remains the golden standard, which must be performed at the slightest suspicion of CNS involvement and whose technical application should be continuously improved (192). The difficulties raised by the technique start from the performance of LP, which can show high opening pressure. This is continued during sample processing, during which several indicators of CNS leukemia can be observed, but these are still not enough to put a diagnostic more than 5/mm^3 white blood cell count, less than 60 mg/dL glucose and more than 50 mg/dL protein level. The diagnostic is formulated only after leukemic cells are detected on the analyzed slides of CSF (192). Still, many times the test give false negative results (212), due to the fact that there infiltrated leukemic cells are in very small number and they all circulate in a large volume of CFS from which only a small volume is taken; as follows it is very easy to sample CSF without malignant cells. In addition, the pathologies must be very accustomed with the morphology of leukemic cells, since these can be easily confused with normal white blood cells. In order to increase the sensitivity of CSF analysis, repeated LPs are recommended. The possibility of malignant cells coming from a solid tumor that has metastasized to the brain should also be eliminated (213).

In regard to the imaging techniques the most commonly used are computed tomography (CT) and gadolinium MRI (214-216). MRI is often preferred to CT (217). During initial MRI scanning, a T1, T2 weighted sequences with fat suppression are used to scan the entire CNS. Still, it was found that this imaging analysis can only detect 44% of B-cell CNS leukemia (218).

Flow cytometry immunophenotyping (FCI) is a very reliable alternative to cytomorphology and the combination between the two can significantly increase the chances of CNS detection. This is because FCI can detect leukemic blasts even in small number (219). Flow cytometry was used successfully in the detection of CNS involvement in ALL and can successfully distinct between low risk and high risk patients (220). This technique is very useful in detecting minimal residual disease thus proving to be a powerful tool in the monitorization of leukemic patients, by being able to detect 1 abnormal cell from 10,000 events (221-223), however much attention must be paid to sampling, storage and processing (224,225). First the CSF must be collected in tubes that do not contain anti-coagulants (such as EDTA, heparin treated tubes). Secondly, analysis must be performed in maximum 72 h and prior to analysis CSF must be centrifuged and only the pellet or the bottom phase should be inserted into the flow cytometer (226-228). Besides these, it is recommended to use a combination of 6–9 antibodies (229). Due to the ability to concentrate the sample, and high sensitivity, flow cytometry is sometimes considered to be superior cu the commonly used CSF

pathology (226). FCI of the CSF increased the detection rate of CNS involvement of ALL approximately two times compared to cytomorphology. FCI of CSF is a very reliable method to determine CNS leukemia in cases of low cellularity. The status of "indeterminate cases" is low, meaning 8.3% and it includes technical flaws such as very low number of cells, inappropriate stanning, insufficient normal population of cells for appropriate comparison (230).

Histology is also predictive of a CNS involvement, with significantly higher incidence found among monocytic M4 and M5a. Among risk factors, inversion of chromosome 16, chromosome 11 abnormality, trisomy 8 (28), serum lysozyme (<30 IU) (231) and high lactate dehydrogenase activity (>25,000/mm^3) (232) was also correlated with CNS leukemia.

In ALL, the same risk factors are valid: younger age (233), presence of leukemic cells in CSF (234) or elevated lactate dehydrogenase (232). In addition, mature B-ALL and T cell phenotype is correlated with increased incidence of CNS infiltration. The presence of cytogenetic abnormalities, may it be t(9;22) or t(4;11), are also high-risk markers (235).

Therapeutic option for CNS leukemia

CNS-targeted therapy significantly increased overall and disease-free survival in hematological malignancies (236). Usually, these therapies refer to intrathecal chemotherapy (IT) or CNS targeted radiotherapy (237). Nowadays, most protocols restrict radiotherapy to high-risk patients. In addition the dose are continuously adapted to the progression of the disease, with the scope of regaining normal hematological physiology in the patient's organism as soon as possible. Elimination of MRD and monitorization of immune privileged sites, such as CNS are also incorporated.

As stated above, protection of immune privileged sites, such as CNS need careful monitorization. Because of the limited penetration of cytostatic drugs for the treatment of leukemia across the BBB, the CNS is like a protective environment for the leukemic cells. Different cell types of the neurovascular unit including vascular cells (endothelium and mural cells), glia (astrocytes, microglia), and neurons contribute to regulation of BBB permeability. The insufficient CNS accumulation of the drugs explains why CNS relapse is reported in 30% of adult patients with ALL (238) thus early measures must be taken to prevent new tumor formations in the brain (239), such as: IT, high-dose systemic chemotherapy and craniospinal irradiation. The role of cranial craniospinal radiotherapy has become controversial because of its neurologic adverse events. However, recent studies state that IT and high-dose chemotherapy are enough to prevent CNS leukemia (240-243).

When assessing initial intrathecal therapy (ITT) followed by cranial irradiation compared with further IT, there is no significant differences between the groups in the overall event rate, the annual event rate, OS at 10 years. There were fewer isolated CNS relapses in the cranial irradiation group (4.9%) than in the ITT (7.1%) (P=0.03) (242,243). When comparing the addition of intravenous methotrexate to long-term ITT (up to 12 doses) or radiotherapy with ITT (up to 9 doses), there was a significant reduction of 17% (P=0.003) in the annual event rate with intravenous methotrexate. EFS at 10 years was higher in the group given intravenous methotrexate (68.1% versus 61.9%). The OS rates at 10 years did not differ significantly. The annual rates of non-CNS relapses were 17% lower in the methotrexate group (P=0.02), while the CNS and isolated CNS rates were both non significantly lower in this group (244-249).

A randomized control study concluded that the triple ITT, in comparison with intrathecal methotrexate (IT MTX) reduces the risk of isolated CNS leukemia, but the OS of patients remains lower than in the case of IT MTX. This is reasoned by the fact that leukemia inducible tumors can also form in other sites of the body and these are often overlooked. A combination of ITT and high doses of systemic chemotherapy are recommended. When comparing cranial irradiation combined with short-term ITT versus intravenous methotrexate combined with short-term ITT, neither the 10-year survival, nor EFS was significantly different between the groups. The CNS relapse rates were 62% lower in the cranial irradiation group (P=0.00005). When comparing different doses of radiotherapy (24 versus 18 or 21 Gy) combined with short-term ITT, there were no significant differences between the doses on any measure. Still, when comparing radiotherapy combined with short-term ITT with intravenous methotrexate combined with long-term ITT, there were no significant differences between the groups on any measure (250,251). Thus, radiotherapy can be replaced by long-term ITT and intravenous methotrexate as it reduces non-CNS relapses.

It is highly important for the drugs used in CNS preventive/treatment chemotherapy to be able to cross the BBB and distribute uniformly in CNS. The best known options until now are cytarabine and methotrexate (238,252). Steroids are also frequently used in addition to

chemotherapeutic treatment. In this case dexamethasone is preferred to prednisone, because of a higher stability (253,254) and reported ability to lower CNS recurrence to 2% (255). Adequate concentration in CSF can be reached with etoposide and 6-mercaptopurine systemic administration, as well as L-asparaginase (256-258). Although the single use of chemotherapy is enough to prevent CNS relapse, this is often avoided, due to the severed side effects given by this treatment choice.

Treating a B-cell ALL with CNS disease—an example

As a proof-of-concept, of the theoretical background presented, we depict the case of a 24-year-old male presented in June 2013 for bilateral laterocervical adenopathy, associated with slight fever, dysphagia, cough, and unexplainable weight-loss. No other indications of a disease were present. Physical examination certified adenopathy, of approximately 2 cm in the laterocervical, submandibular, axillary and inguinal areas and grade II splenomegaly. Leucopenia (3.14×10^3/μL) with 22% blasts was detected upon blood analysis and the bone marrow aspirate found hypocellularity with maturation in granulocytic and erythroblastic lineages, but 60% blast cell infiltrate. The immunophenotyping analysis revealed a common Philadelphia chromosome negative (Ph-) preB-ALL (positive for: CD19, CD22, CD10, CD45, HLA-DR, CD34, CD33).

The HyperCVAD protocol was started, and the first complete remission (CR1) was obtained after the first cycle, however with MRD positivity. Clinicians decided to treat the MRD+ state with blinatumomab and the patient successfully achieved complete molecular response after 4 cycles. POMP (6-mercaptopurine, vincristine, methotrexate, prednisone) maintenance therapy was continued until December 2016, but the disease relapsed in July 2017, with 90% blasts in the bone marrow, anemia (hemoglobin =9.6 g/dL) and mild thrombocytopenia (103×10^3/μL). Chemotherapy was started again, following the same HyperCVAD protocol. However, this time a complete hematological response was not achieved, the patient remaining refractory with a low, but persistent level of blasts in the peripheral blood. Consequently, the family was tested for HLA compatibility, but were not compatible; as a consequence, he was put on the waiting-list for matched unrelated allogeneic HSCT. The Romanian National Drug Agency (ANM) approved in December 2017 the initiation of a second blinatumomab treatment, the patient being by this time in a second complete remission (CR2) after 2 cycles. Blinatumomab therapy was well tolerated, with only mild adverse effects (fever spikes, grade 1 neurotoxicity), successfully controlled with corticotherapy. A severe polyclonal hypogammaglobulinemia was present even 4 years post blinatumomab treatment (IgG =123 mg/dL, normal value 700–1,600 mg/dL), but with no severe infectious complications. Soon after CR2, the patient proceeded to an allogeneic stem cell transplantation (allo-SCT). Conditioning chemotherapy regimen consisted of busulfan and cyclophosphamide and post-transplant immunosuppression was done using methotrexate and tacrolimus (259-262). The patient rapidly recovered but developed grade 1 hepatic GVHD (graft versus host disease) that was treated with tacrolimus and methylprednisolone. He achieved complete post-transplant chimerism with no residual disease.

About one year after the allo-SCT, in July 2019, the patient presented in emergency with an episode of generalized seizures. He also associated dyspnea, sore throat and some involuntary movements of the left side of the face, but no adenomegaly or hepatosplenomegaly. The CT-scan was normal, and the CSF fluid was clean. Immunology assays and CSF virology tests for VZV, HHV-1, HHV-2, CMV and BKV were all negative, possible differential diagnoses remaining blinatumomab neurotoxicity and CNS relapse (262). A brain MRI was performed showing several millimetric demyelinating lesions scattered through the white matter, but also one bigger lesion in each precentral gyrus. The one in right precentral gyrus had 18/6 millimeters and his exact position was the superior facial area of the motor homunculus, possibly explaining the left facial involuntary movements. Both emit high signal in T2-weighted scan and are also seen in FLAIR scan, suggesting irreversible ischemic lesions. The MRI images are found in *Figure 1*. The patient state got worse, even with steroid and antiepileptic therapy, and a PET-CT performed in Vienna certified the diagnosis of isolated CNS relapse with extensive lesions. The positron emission tomography (PET-CT) images are found in *Figure 2*. He died soon thereafter, in September 2019.

Conclusions

CNS leukemia is a severe effect, that is the leading cause of acute leukemia-related deaths and that is encountered often during the progression of this disease. The leukemic cells

Figure 1 MRI of the CNS at the moment of symptom development. CNS, central nervous system.

stimulate VEGF and *de novo* angiogenesis, roll through the bone marrow endothelial cells through adhesion molecules (the most important being CD56) and enter into the CNS through the blood vessels connecting bone marrow to the CNS. In the brain parenchyma, these malignant cells can travel to different locations thus they give a high variety of neurological symptoms.

Early diagnostic through a more common application

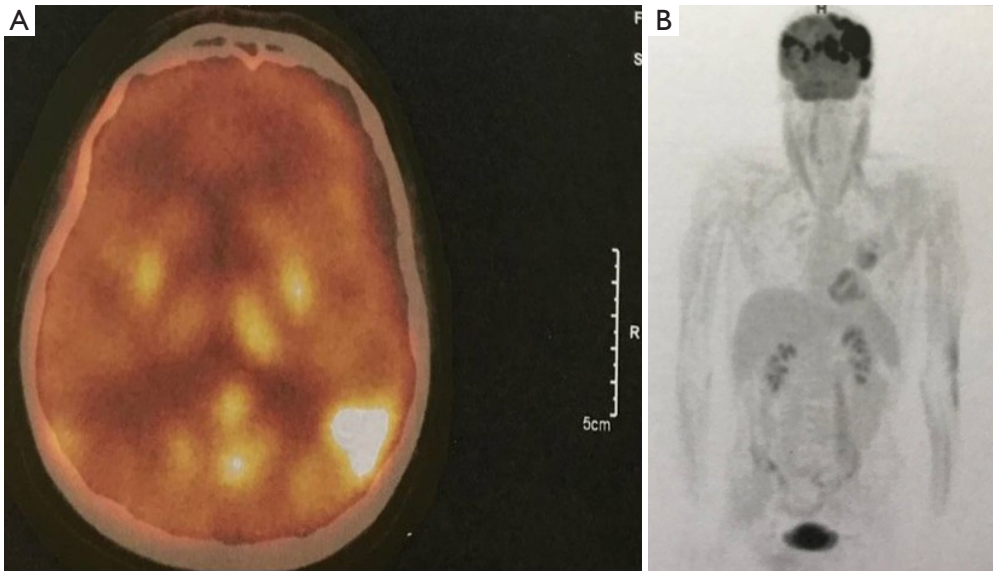

Figure 2 PET-CT images of the CNS relapse, at symptom worsening despite therapy. CNS, central nervous system.

of CSF analysis, improved MRI techniques and flow cytometry is the first step to an early detection of the disease. Practitioners should improve their techniques of LP and keep up-to date this the latest developments that would prevent complications. At the same time, the role of prophylaxis and early treatment is still underestimated. The best types of treatment are: targeted chemo-or radiation therapy to the CNS and high doses of systemic chemotherapy.

We have decided to show the case presented as a proof-of-concept. All the modern diagnostic protocols were used but physicians still failed to properly establish whether the immunocompromised patient has a CNS relapse or infection. Thus, a better, more targeted early diagnosis is crucial, for instance a combined use of flow cytometry and cytomorphology analysis of CSF.

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