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Relation Between CSF Infiltration and Clinical, Laboratory and Radiological Finding in Acute Leukemia Patients: A Single Center Study

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Abstract:

Background: Acute leukemia, including 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 leukemia cells in the central nervous system (CNS) and the subsequent formation of brain tumors.

Methods: This is a prospective study of acute leukemia patients at diagnosis, at re-evaluation or at time of medullary relapse. The study aim was to mention the correlation of CSF infiltration with clinical, laboratory and radiological findings in acute leukemia cases. The study is approved by the Institutional Review Board at the Mansoura University Hospital.

Results: 53 cases included in the study. 2 cases were isolated CNS relapse without medullary relapse. CSF infiltration was found in 5 cases. CSF infiltration was significantly associated with Acute lymphoblastic leukemia (ALL) and LL parathesia and showed higher incidence among relapsed cases.

Conclusion: Detailed physical examination including neurological examinations of acute leukemia patients is critical in driving the physician for possibility of CNS extension of the disease that has an impact on treatment plans. CSF examination is a cornerstone in investigational plans, especially in ALL patients.

Keywords: Acute leukemia, cerebrospinal fluid infiltration, central nervous system infiltration, whole body MR imaging

1. Introduction

Acute leukemias are a group of aggressive hematological diseases characterized by clonal proliferation of immature progenitor cells in the bone marrow. This infiltrate causes severe thrombocytopenia, anemia, and leukopenia that, if left untreated, can lead to death within weeks (Kibler and Chabot-Richards, 2023).

There are three main groups of acute leukemias subtypes: acute myeloid leukemia, acute lymphocytic leukemia, and a third rare subtype mixed phenotype acute leukemia. The presentation of the patients usually share the same symptoms and signs, although the management plans are different, and the diseases can only be cured by intensive chemotherapeutic agents, possibly in combination with allogeneic hematopoietic cell transplantation (Allo-HCT).(Arber et al., 2022).

The World Health Organization classification and definition of "myeloid sarcoma" is inaccurate and misleading. A more accurate term is "extramedullary acute myeloid leukemia tumor (eAML)". The pathogenesis of eAML has been associated with aberrancy of cellular adhesion molecules, chemokine receptors/ligands and RAS-MAPK/ERK signaling. eAML can present with or without synchronous or metachronous intramedullary acute myeloid leukemia(Shallis et al., 2021).

Lymph node enlargement, which is usually painless, liver and spleen enlargement, which occurs in 68% of patients, and in most of cases be asymptomatic, the central nervous system (CNS), skin, renal and orbital affection all are extramedullary manifestations due to infiltration of leukemic cells. Abnormal persistence of any of these common signs and symptoms should be considered as a part of the disease(Masi et al., 2023).

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(Johnston et al., 2017).

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 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(Deak et al., 2021).

Whole body MR imaging can identify asymptomatic chloromas. If organ-specific imaging is used, asymptomatic chloromas can be missed. There is no doubt that a treatment plan should be set based on the exact extent of disease involvement. Therefore, whole body MR scans may be needed for the accurate evaluation of disease involvement in patients with AML(Yoon et al., 2017).

Whole body MR imaging can provide additional information, including not only the presence of unexpected chloromas but also clinically occult non chloroma lesions(Ilaslan and Sundaram, 2016).

The anatomical site of relapses is the second most important factor after timing in acute lymphocytic leukemia relapses. Anatomical site of relapse categories are marrow relapse alone (worst prognosis), extramedullary alone (best prognosis), and combined relapses (intermediate prognosis)(Zhao et al., 2020).

Central nervous system leukemic infiltration can present itself as increased intracranial tension manifestations such as persistent headache, confusion, emesis, attacks of fits and stiffness of the neck. In less occasions, cranial nerve affection may be the patient presentation such as trigeminal neuralgia, facial nerve palsy, and neuropathy(Shahriari et al., 2020).

Material and Methods

Study Design:
This is a prospective study in which morphological CSF examination done to acute leukemia patients at diagnosis, at re-evaluation or at time of medullary relapse.
The study is approved by the Institutional Review Board at the Mansoura University Hospital.
Acute leukemia patients fulfilling the inclusion and exclusion criteria in oncology center Mansoura University involved. 53 patients included in the current study calculated using Raosoft sample size calculator.

Study Population:
Inclusion Criteria
Patients aged 18 years or above
Both genders are eligible
Newly diagnosed or relapsed Acute leukemia (including de-novo and secondary cases)
Acute leukemia patient with suspected extramedullary infiltration during course of treatment
Exclusion Criteria
Patients did not accept intrathecal and CSF analysis

All patients subjected to the following: Detailed history taking with attention to the presence or absence of neurological or systemic symptoms and history suggestive of other medical disease or organ failure. Careful physical examination.
Investigational Plan:
The enrolled subjects performed the following investigations:
1) Complete Blood Count (CBC): using the electronic counter.
2) Blood film and Differential leucocyte Count (DLC).
3) Immunophenotyping.
4) Bone Marrow Aspiration and Trephine Biopsy (BMA & BMB)
5) Cancer Cytogenetic Analysis either conventional karyotyping or
FISH (Fluorescence Institute Hybridization) analysis and molecular genetics.
6) Chemistry Profile including:
Liver function test (ALT, AST, Total bilirubin and serum Albumin)
Kidney function tests (Serum creatinine and Serum uric acid)
7) Coagulation Profile: as PT and APTT
8) Virology Markers: HCV, HBV and HIV
9) Cerebrospinal Fluid Analysis by Lumbar Puncture.
10) Radiological Investigations: Chest X-Ray, Pelvi-abdominal ultrasound and whole-body MRI.
Statistical analysis:
The statistical analysis is carried out using SPSS18.0 software (SPSS Inc., Chicago, IL, USA). Descriptive statistics used to characterize the patients. Associations between variables, prognostic factors and response analyzed with the chi-square test and Fisher's exact test. The level of statistical significance setted at 5% (p-value <0.05).

Results

The study was conducted on 53 acute leukemia cases. Their median age was 38, ranged from 16 to 68 years. 29 male 54.7% , 24 female 45.3% as shown in table 1.

Table (1). Demographics of all studied cases.

			Cases N=53	
Age (years)		Median (range)	38	(16-68)
Gender	Male	N, %	29	54.7%
	Female	N, %	24	45.3%

Among all studied cases, 64.2% "34 case" had AML, 34% "18 case" had ALL and 1.9% "one case" had biphenotypic leukemia as shown in table 2.

Table (2). Diagnosis of all studied cases.

			Cases N=53	
Diagnosis	AML	N, %	34	64.2%
	ALL	N, %	18	34.0%
	Biphenotypic leukemia	N, %	1	1.9%

AML cases classification according to FAB classification was 6.1% had M0, 15.2% had M1, 15.2% had M2, 12.1% had M3 and 51,5% had M4-5. While 17.6% of AML cases were Secondary AML as shown in table 3.

Table (3). The classification of AML cases.

			Cases N=34	
AML (FAB)	M0	N, %	3	6.1%
	M1	N, %	5	15.2%
	M2	N, %	5	15.2%
	M3	N, %	4	12.1%
	M4-5	N, %	17	51.5%
AML (origin)	De novo	N, %	28	82.4%
	Secondary	N, %	6	17.6%

Among ALL cases, 38.9% had B ALL and 61.1% had T ALL as shown in table 4.

Table (4). The classification of ALL cases.

			Cases N=18	
ALL	B-ALL	N, %	7	38.9%
	T-ALL	N, %	11	61.1%

Most of studied cases were Newly diagnosed 64.2%, in 11.3% "6 cases "Whole body MRI performed after complete remission, 15.1% were relapsed, and 9.4% were newly diagnosed secondary AML cases as shown in table 5.

Table (5). The disease status at time of enrollment among all studied cases.

		Cases N=53	
Newly diagnosed	N, %	34	64.2%
Complete remission	N, %	6	11.3%
Relapsed	N, %	8	15.1%
Newly diagnosed secondary AML	N, %	5	9.4%

Headache was found in 5.7%, LL parasthesia was found in 11.3%, Fatigue was found in 9.4%, Dyspnea or orthopnea was found in 11.3%, Axillary, cervical or inguinal swelling was found in 9.4%, Abdominal pain was found in 24.5%, bone aches was found in 45.3%, musculoskeletal back pain was found in 13.2% as shown in table 6.

Table (6). Symptoms among all studied cases.

		Cases N=53	
Headache	N, %	3	5.7%
LL parathesia	N, %	6	11.3%
Fatigue	N, %	5	9.4%
Dyspnea or orthopnea	N, %	6	11.3%
Axillary, cervical or inguinal swelling	N, %	5	9.4%
Abdominal pain	N, %	13	24.5%
Bone aches	N, %	24	45.3%
Musculoskeletal back pain	N, %	7	13.2%

Median BMA blasts were 80%, ranging from 0 to 98%. Regarding BMB, median blasts were 80%, ranged from 20 to 95%, 35.5% were Normocellular, 21.6% were Hypocellular and 43.1% were Hypercellular. Isolated CNS relapses were found in 3.8% as shown in table 7.

Table (7). BM aspiration and biopsy and CNS relapse among all studied cases.

			Cases N=53	
Bone marrow aspiration, blasts (%)		Median (range)	80	(0-98)
Bone marrow biopsy, blasts (%)		Median (range)	80	(20-95)
Bone marrow cellularity	Normocellular	N, %	18	35.3%
	Hypocellular	N, %	11	21.6%
	Hypercellular	N, %	22	43.1%
Isolated CNS relapse without medullary relapse		N, %	2	3.8%

According to laboratory parameter median WBC was 21, ranged from 1 to 399, median lymphocytes was 11, ranged from 1 to 233, median ANC was 2, ranged from 0 to 60, median Hb was 9, ranged from 5 to 14, median platelet count was 30, ranged from 5 to 1000, median ALT was 20, ranged from 2 to 100, median AST was 20, ranged from 2 to 150, median total bilirubin was 1, ranged from 0.3 to 4, median direct bilirubin was 0.3, ranged from 0.1 to 0.8, median Serum creatinine was 1, ranged from 0.5 to 5, median Serum uric acid was 5, ranged from 1 to 15, median LDH was 550, ranged from 120 to 2800, positive HCV was found in 15.1% of cases as shown in table 8.

Table (8) Laboratory parameters among all studied cases.

		Cases N=53	
WBCs	Median (range)	21	(1-399)
Lymphocytes	Median (range)	11	(1-233)
Neutrophil (ANC)	Median (range)	2	(0-60)
Hb (gm/dl) *109	Median (range)	9	(5-14)
Platelet count	Median (range)	30	(5-1000)
ALT	Median (range)	20	(2-200)
AST	Median (range)	20	(2-150)
Total bilirubin	Median (range)	1	(0.3-4)
Direct bilirubin	Median (range)	0.3	(0.1-0.8)

Serum creatinine	Median (range)	1	(0.5-5)
Serum uric acid	Median (range)	5	(1-15)
LDH	Median (range)	550	(120-2800)
Positive HCV	N, %	8	15.1%

CSF infiltration was found in 5 cases as shown in table 9.

Table (9). CSF infiltration among all studied cases.

		Cases N=53	
CSF infiltration	N, %	5	9.4%

Among all studied cases, 42.3% achieved CR, induction death in7.7% of cases and 50.9% were refractory as shown in table 10.

Table (10). Remission status among all studied cases.

			Cases N=53	
Remission status	Complete remission	N, %	22	42.3%
	Induction death	N, %	4	7.7%
	Refractory	N, %	27	50.9%

Extensive bone marrow infiltration of all scanned bone was observed in 81.1% (43 case), BM infiltration of bones of UL, LL was found in 20.8%, BM infiltration of bones of clavicle, neck was noticed in 9.4%, L3 leukemic infiltration was observed in 1.9% and Bone marrow reconversion was found in 1.9% as shown in table 11.

Table (11). Medullary infiltration among all studied cases by whole body MRI.

		Cases N=53	
Extensive bone marrow infiltration of all scanned bone	N, %	43	81.1%
BM infiltration of bones of UL, LL	N, %	11	20.8%
BM infiltration of bones of clavicle, neck	N, %	5	9.4%
L3 leukemic infiltration	N, %	1	1.9%
Bone marrow reconversion	N, %	1	1.9%

CSF infiltration was significantly associated with ALL and showed higher incidence among relapsed cases as shown in table 12.

Table (12). Association of CSF infiltration with diagnosis and disease status at time of enrollment among all studied cases.

	CSF infiltration				p
	Absent N=48		Present N=5		
	Median/N	Range/%	Median/N	Range/%	
AML	34	70.8%	0	0.0%	0.003
ALL	13	27.1%	5	100.0%	
Biphenotypic	1	2.1%	0	0.0%	

M0	2	6.1%	0	0.0%	-
M1	5	15.2%	0	0.0%	
M2	5	15.2%	0	0.0%	
M3	4	12.1%	0	0.0%	
M4-5	17	51.5%	0	0.0%	
Secondary AML	6	17.6%	0	0.0%	-
B	6	42.9%	2	40.0%	0.912
T	8	57.1%	3	60.0%	
Newly diagnosed	32	66.7%	2	40.0%	0.029
complete remission	6	12.5%	0	0.0%	
Relapsed	5	10.4%	3	60.0%	
Newly diagnosed secondary AML	5	10.4%	0	0.0%	

CSF infiltration was significantly associated with higher incidence of LL parasthesia. Otherwise, no significant association was found regarding CSF infiltration with clinical presentation among all studied cases as shown in table 13.

Table (13). Association of CSF infiltration with clinical presentation among all studied cases.

	CSF infiltration				p
	Absent N=48		Present N=5		
	Median/N	Range/%	Median/N	Range/%	
Headache	3	6.3%	0	0.0%	0.565
LL parasthesia	4	8.3%	2	40.0%	0.033
Fatigue	4	8.3%	1	20.0%	0.403
Dyspnea or orthopnea	6	12.5%	0	0.0%	0.401
Axillary or cervical inguinal swelling	5	10.4%	0	0.0%	0.448
Abdominal pain	13	27.1%	0	0.0%	0.317
bone aches	21	43.8%	3	60.0%	0.649
musculoskeletal Back pain	7	14.6%	0	0.0%	0.359

No significant association was found regarding CSF infiltration with medullary findings by MRI among all studied cases as shown in table 14.

Table (14). Association of CSF infiltration with medullary findings by MRI among all studied cases.

	CSF infiltration				p
	Absent N=48		Present N=5		
	Median/N	Range/%	Median/N	Range/%	
Extensive bone marrow infiltration of all scanned bone	38	79.1%	5	100.0%	.571
BM infiltration of bones of UL, LL	10	20.8%	1	20.0%	.965
BM infiltration of bones of clavicle, neck	5	10.4%	0	0.0%	.448
L3 leukemic infiltration	1	2.1%	0	0.0%	.745
Bone marrow reconversion	1	2.1%	0	0.0%	.745

No significant association was found regarding CSF infiltration with outcome among all studied cases as shown in table 15.

Table (15). Association of CSF infiltration with outcome among all studied cases.

		CSF infiltration				p
		Absent N=48		Present N=5		
		Median/N	Range/%	Median/N	Range/%	
Remission status	Complete remission	20	41.7%	2	50.0%	.746
	Induction death	4	8.3%	0	0.0%	.548
	Refractory	24	50.0%	3	60%	1

No significant association was found regarding CSF infiltration with OS among all studied cases with impact shown between 6 months and 12-month OS as shown in table 16 and figure 1.

Table (16). Association of CSF infiltration with OS among all studied cases.

	CSF infiltration		
	Absent N=48	Present N=5	P
Median OS	14.877	7.6	
95% CI	12.3 -17.455	7.28- 7.92	
6 months OS	100	100	
12 months OS	100	66.7	

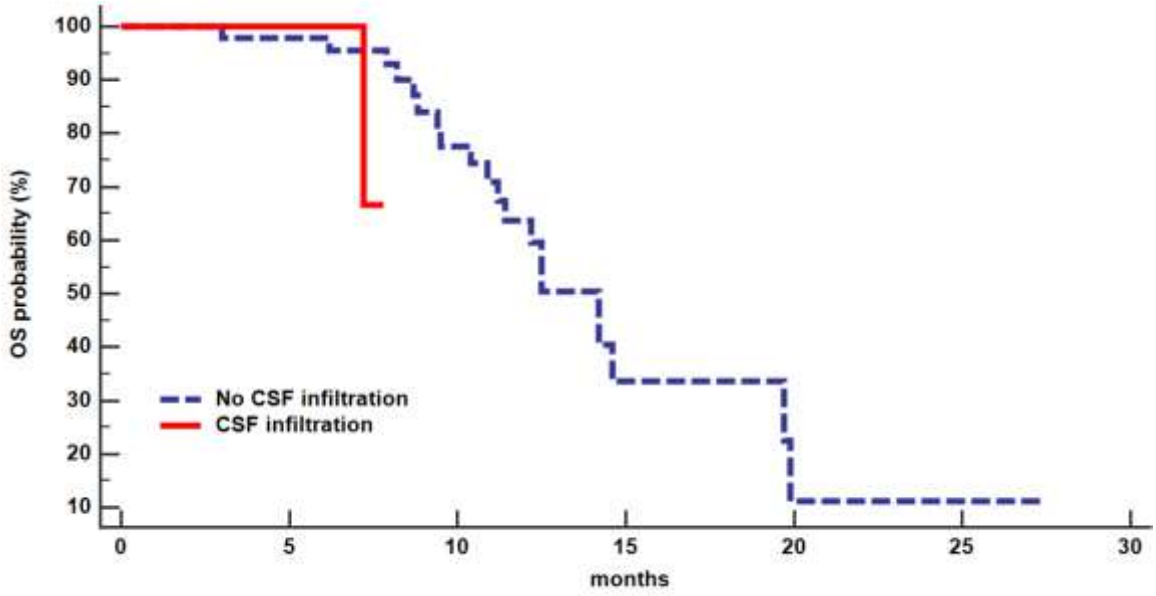

Figure (1). OS according to CSF infiltration among all studied cases.

Discussion

Leukemia is one of the most common malignant disorders affecting the world population. Globally, in 2018, leukemia ranked as the fifteenth most common diagnosed cancer with 437,033 cases and 309,006 mortalities, amounting to the eleventh cause of death due to malignant disorders(Tebbi, 2021).

Median age of present study cases was 38, ranging from 16 to 68 years. 29 male 54.7%, 24 female 45.3%. Guenette et al study conducted on 34 patients 19 women, 15 men; mean age, 51 years; range, 18–72 years(Guenette et al., 2016).

In current study, patients diagnosed with acute myeloid leukemia (AML) were categorized using the FAB classification. The distribution was as follows: 6.1% had M0, 15.2% had M1, 15.2% had M2, and 12.1% had M3. Additionally, 17.6% were identified as having Secondary AML. In Zhou et al study M2 and M4 FAB subtypes showed the highest percentage of 36% and 22% respectively and also M0 and M6 showed the lowest frequencies; 0.8% and 2.4% respectively, while they showed that M1 and M5 were in 6.5 and 8.1%, respectively of their 122 enrolled AML patients(Zhou et al., 2015).

ALL cases are broadly classified as B-ALL or T-ALL based on immunophenotyping, with B-ALL comprising approximately 85% of cases, although this percentage can differ depending on age at diagnosis, race, or ethnicity (Inaba and Pui, 2021). Among ALL cases in present study, 38.9% had B ALL and 61.1% had T ALL.

Based on the findings of Shahverdi et al study, Fever (70%) and hepatomegaly (60%) were the most common signs and symptoms in patients. 23% of patients had bone pain, 14% had arthralgia, and 16% complained of weakness and early fatigue (Shahverdi et al., 2020). In present cases, hepatomegaly was present in 43.4%. Other symptoms identified included headache in 5.7% of cases, lower limb paresthesia in 11.3%, fatigue in 9.4%, dyspnea or orthopnea in 11.3%, abdominal pain in 24.5%, bone aches in 45.3%, and musculoskeletal back pain in 13.2%.

Upon presentation at our institution, median WBC was 21×109/L, median lymphocytes was 11, median ANC was 2, median Hb was 9, median platelet count was 30, median BMA blasts were

80%. Regarding BMB, median blasts were 80%, 35.5% were normcellular, 21.6% were hypocellular and 43.1% were hypercellular. Close to our results a study which enrolled 65 AML patients demonstrated that median WBC count at diagnosis was 19.8×109/L. As regards blast cells percentage; 48 patients had BM blast percentage more than 70% and 28 had PB blasts more than 70% (Chenga et al., 2018).

A study of liver function tests in 50 patients with Acute Leukemia at diagnosis by Tahmidul Islam and his colleague show that the mean serum total bilirubin at diagnosis/before chemotherapy was 0.89 mg/dl. The mean serum alanine transaminase (ALT) at diagnosis was 47.46 U/L. The mean serum aspartate transaminase (AST) at diagnosis was 38.00 U/L(Islam et al., 2020). Current research cases number were 53 very close to Islam et al study and liver functions study in them at diagnosis show that median ALT was 20, ranged from 2 to 100, median AST was 20, ranged from 2 to 150, median total bilirubin was 1, ranged from 0.3 to 4, median direct bilirubin was 0.3, ranged from 0.1 to 0.8.

In our study CSF infiltration was found in 5 cases among the 53cases (9.4%) and was significantly associated with ALL among aother types P value 0.003. Deak et al study show that 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 (Deak et al., 2021).

In Baehring and Chan study about 0.3% of acute leukemia patients, epidural deposits or vertebral destruction results in spinal cord compression. Early warning signs include localized pain from infiltration of the richly innervated periosteum, excruciating radicular pain from nerve root compression, motor paresis and spasticity (“leg heaviness,” difficulty climbing stairs) followed by segmental sensory deficits and alarming symptoms of urinary retention and flaccid paresis (Baehring and Chan, 2018).Our study prove that CSF infiltration was significantly associated with higher incidence of LL paresthesia and this prove the importance of detailed examination of acute leukemia patients that drive us to the extent of the disease at presentation that affect treatment plan.

No significant association was found regarding CSF infiltration with outcome and OS among all studied cases with impact shown between 6 months (100%) and 12-month OS (decrease to 66,7% of cases).

Conclusion

Detailed physical examination including neurological examination of acute leukemia patients is critical in driving the physician for possibility of CNS extension of the disease that has an impact on treatment plan. CSF examination is a cornerstone in investigational plan, especially ALL patients.

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N.A

Author contributions

MS, MT, EA, MN equally participated in collecting clinical, and radiological data,
All authors contributed to the study design, participated in writing and editing the final version of the manuscript, and read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of the Medical Research Ethics Committee of Mansoura Faculty of Medicine, Mansoura University (Code Number: MD.21.04.259)

Consent for publication

Not applicable.

Availability of data and materials

All the clinical, radiological, and pathological data used in this manuscript are available at Mansoura University medical system (Ibn Sina Hospital management system).

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Conflicts of interest

The authors declare that they have no competing interests.

References

- ARBER, D. A., ORAZI, A., HASSERJIAN, R. P., BOROWITZ, M. J., CALVO, K. R., KVASNICKA, H.-M., WANG, S. A., BAGG, A., BARBUI, T. & BRANFORD, S. 2022. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood, The Journal of the American Society of Hematology, 140, 1200-1228.
- BAEHRING, J. M. & CHAN, A. M. 2018. Neurological Complications of Leukemia. Cancer Neurology in Clinical Practice: Neurological Complications of Cancer and its Treatment, 559-569.
- DEAK, D., GORCEA-ANDRONIC, N., SAS, V., TEODORESCU, P., CONSTANTINESCU, C., ILUTA, S., PASCA, S., HOTEA, I., TURCAS, C. & MOISOIU, V. 2021. A narrative review of central nervous system involvement in acute leukemias. Annals of Translational Medicine, 9.
- GUENETTE, J. P., TIRUMANI, S. H., KERALIYA, A. R., SHINAGARE, A. B., RAMAIYA, N. H. & JAGANNATHAN, J. P. 2016. MRI findings in patients with leukemia and positive CSF cytology: a single-institution 5-year experience. American Journal of Roentgenology, 207, 1278-1282.
- ILASLAN, H. & SUNDARAM, M. 2016. Pediatric and Adult MRI Atlas of Bone Marrow. Normal Appearances, Variants and Diffuse Disease States.
- INABA, H. & PUI, C.-H. 2021. Advances in the diagnosis and treatment of pediatric acute lymphoblastic leukemia. Journal of clinical medicine, 10, 1926.

- ISLAM, T., RAHMAN, A. S., HASAN, M. K., JAHAN, F., MONDAL, M. C., FERDOUSHI, S., ALAM, S., AHSAN, M. K., TASNIM, J. & TOHURA, S. 2020. Liver function tests in patients of acute leukemia before and after induction chemotherapy. Journal of Biosciences and Medicines, 8, 110-121.
- JOHNSTON, D. L., ALONZO, T. A., GERBING, R. B., APLENC, R., WOODS, W. G., MESHINCHI, S. & GAMIS, A. S. 2017. Central nervous system disease in pediatric acute myeloid leukemia: a report from the Children's Oncology Group. Pediatric blood & cancer, 64, e26612.
- KIBLER, C. E. & CHABOT-RICHARDS, D. S. 2023. Molecular Pathology of Leukemia. Molecular Surgical Pathology. Springer.
- MASI, A., HUNDER, G. & LIE, J. 2023. 11.6 Acute leukaemia. Textbook of Paediatric Emergency Medicine-E-Book, 33, 290.
- SHAHRIARI, M., SHAKIBAZAD, N., HAGHPANAH, S. & GHASEMI, K. 2020. Extramedullary manifestations in acute lymphoblastic leukemia in children: a systematic review and guideline-based approach of treatment. American Journal of Blood Research, 10, 360.
- SHAHVERDI, E., SHAHRIARI, M., ZARE, S., RAHIMINEJAD, M. S., SOLEIMANI, F. H., MAKI, M., MANOUCHEHRI, R. & ABDO, M. H. 2020. Common presenting signs and symptoms in children with acute lymphoblastic leukemia. Basic & Clinical Cancer Research, 12, 26-33.
- SHALLIS, R. M., GALE, R. P., LAZARUS, H. M., ROBERTS, K. B., XU, M. L., SEROPIAN, S. E., GORE, S. D. & PODOLTSEV, N. A. 2021. Myeloid sarcoma, chloroma, or extramedullary acute myeloid leukemia tumor: a tale of misnomers, controversy and the unresolved. Blood Reviews, 47, 100773.
- TEBBI, C. K. 2021. Etiology of acute leukemia: A review. Cancers, 13, 2256.
- YOON, H. M., KIM, J. R., JUNG, A. Y., CHO, Y. A., IM, H. J. & LEE, J. S. 2017. Whole body MR imaging: a useful imaging modality in the management of children with acute myeloid leukemia. Clinical Lymphoma Myeloma and Leukemia, 17, 231-237.
- ZHAO, Z., HU, Y., LI, J., ZHOU, Y., ZHANG, B. & DENG, S. 2020. Applications of PET in diagnosis and prognosis of leukemia. Technology in Cancer Research & Treatment, 19, 1533033820956993.
- ZHOU, J., TEWARI, A., NASSIRI, M. & CZADER, M. 2015. Changes in Antigen Expression in a Follow-up of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. J Leuk, 3, 2.