

Research Article

Neurological complications of hematological neoplasms: Characterization in a referral hospital between 2018-2024Santiago Pérez Gil¹, Dionis M. Vallejo Mesa^{1,2}, Jorge A. Jiménez Arango², Sandra P. Isaza Jaramillo¹***Corresponding author**

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¹Department of Neurology, Universidad de Antioquia²Neuroclínica, Medellín**Abstract**

Introduction: Neurological complications in hematological neoplasms severely impact morbidity and mortality. Their characterization is usually limited to critical care settings. The objective of this study was to describe the clinical spectrum in general ward and outpatient clinic patients between 2018-2024 with hematological malignancies, specifically: non-Hodgkin lymphomas (NHL), acute lymphoblastic and myeloid leukemias (ALL, AML), multiple myeloma (MM), and Hodgkin lymphoma (HL).

Methods: A retrospective observational study was conducted on 334 adults with MM, ALL, AML, HL, and NHL. Sociodemographic, clinical, and temporal variables were analyzed using descriptive statistics.

Results: The prevalence of neurological complications was 42.2%. MM was the most frequent malignancy (46.4%), mainly presenting with vertebral fractures (22.2%), peripheral neuropathy (20.5%), and compressive myelopathy (17%). In acute lymphoblastic leukemias, headache (28.9%) and meningeal infiltration (15.7%) predominated. Spinal involvement preceded treatment (median -25 days), whereas neuropathies were mostly post-chemotherapy (median +34 days). A high prevalence of neurological complications was documented in hematological patients, both in general wards and the ICU, with percentages exceeding those described in previous studies. Mortality was observed in 50% of subjects who had meningeal infiltration and hemorrhagic events as a neurological complication. Only 18.6% of the cases received a neurological assessment.

Conclusion: Complications such as spinal involvement and polyneuropathies were the most relevant in our study, appearing prior to treatment and with a pattern suggestive of treatment-related toxicity, respectively. However, other relevant complications were also identified. Additionally, a low participation of neurologists was identified when compared to multicenter Neuro-Oncology registries. Although consultations are usually limited to urgent cases such as epileptic seizures or ischemic stroke, the study highlights the need for a specialized approach in less acute, but equally severe, pathologies such as neuropathies.

Keywords: Hematologic Neoplasms, Neurologic Manifestations, Multiple Myeloma, Peripheral Nerve Diseases, Neurotoxicity Syndromes

INTRODUCTION

Cancer represents one of the leading burdens of disease and mortality worldwide, accounting for 1 in 6 deaths and 25% of deaths from non-communicable diseases, according to GLOBOCAN data [1]. Although solid tumors have the highest incidence rates, hematological neoplasms—specifically non-Hodgkin lymphomas (NHL), acute lymphoblastic and myeloid leukemias (ALL, AML), multiple myeloma (MM), and Hodgkin lymphoma (HL)—maintain a critical epidemiological relevance. They are grouped among the top 20 newly diagnosed cancers, with a higher prevalence observed in the male population [1].

Morbidity and mortality in these hemato-oncological patients can derive from complications secondary to the cancer affecting vital organs, highlighting the involvement of the central nervous system (CNS). Furthermore, it is noted that neurological involvement can precede the oncolog-

ical diagnosis, resulting in functional sequelae that exceed the disability generated by the neoplasm itself [2,3]. These complications include direct neoplastic infiltrations, cerebrovascular events, metabolic-type encephalopathies or infectious processes, and treatment-associated neurotoxicity. In high-dependency units such as the intensive care unit (ICU), the incidence of these alterations ranges between 15% and 22% [4,5]. Moreover, complications such as delirium and even meningeal infiltrations in patients with these hematological neoplasms increase mortality in the critical care unit and are markers of a worse prognosis [6,7].

Considering the above, current scientific literature presents limitations, as most studies jointly analyze solid and hematological tumors [8-11] or are restricted exclusively to the ICU setting [3,11], in addition to finding no data for Colombia. Consequently, there is a knowledge gap regarding the evolution of these complications in settings different from those previous-

ly mentioned and within the local hospital environment. Therefore, this study aims to characterize the neurological complications in patients with acute leukemias, MM, and lymphomas in a referral hospital in Medellin, Colombia, who attended the outpatient clinic and/or general hospitalization service between the years 2018 and 2024.

MATERIALS AND METHODS

A descriptive, retrospective, observational study was conducted in a high-complexity hospital care center. Between January 1, 2018, and December 31, 2024, in the city of Medellin.

Eligible subjects were those with a confirmed diagnosis of hematological neoplasms, specifically acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), multiple myeloma (MM), Hodgkin lymphoma (HL), and non-Hodgkin lymphoma (NHL) treated in inpatient or outpatient settings. Individuals under 18 years of age or not evaluated by hematology were excluded. Only those who authorized the use of their information for studies approved by the institutional ethics committee upon admission to the Hospital Alma Mater de Antioquia were included, as is the case for this study.

The principal investigator extracted the information by reviewing the institutional medical records identified by filtering the institution's system during that period using the following ICD-10 codes: C91.9 (Acute lymphoblastic leukemia, Lymphoid leukemia, unspecified, without mention of complete remission. Lymphoid leukemia, unspecified, in remission), C92.9 (Acute myeloid leukemia), C81.9 (Hodgkin lymphoma), C85.9 (Non-Hodgkin lymphoma), C90.0 (Multiple myeloma without mention of remission, Multiple myeloma in relapse). Variables collected included sociodemographic data, type of hematological neoplasm, start and end dates of hematology care, chemotherapy and radiotherapy, date of diagnosis of the neurological alteration, type of neurological alteration reported by neurology or hemato-oncology, evaluation (or lack thereof) by neu-

rology, and vital status (alive or deceased) according to the last recorded clinical encounter. Each variable was defined and coded as explained in the protocol approved by the institutional ethics committee. Furthermore, compliance with the eligibility criteria was verified, and the subjects to be included were identified with their medical record number to avoid data duplication. The principal investigator verified the quality of the data collected from the first 10 medical records and the recording of such information in the database.

Given that the Kolmogorov-Smirnov test ($p<0.001$) showed a negative skewness (-0.599), qualitative variables were presented with their absolute and relative frequencies. The quantitative variables of age and time between the start and end of hematology care, chemotherapy, and time between the diagnosis of the neurological alteration, the start of chemotherapy, and the first hematology evaluation were presented as median and interquartile range (IQR). Data were recorded during their collection in an Excel® format and analyzed using the R® software.

The study adhered to bioethical principles considered in the Declaration of Helsinki, the CIOMS guidelines, and complied with Colombian Resolution 8430. Information was handled following these principles and maintaining confidentiality, subsequent to approval by the corresponding bioethics committees, registered under Record Number: FR-DV-3420 Version 07 of 08/25/2022. It was considered a risk-free study, and therefore informed consent was not required.

RESULTS

A total of 334 subjects met the eligibility criteria, the majority being men at 53.9% ($n=180$); with a median age of 61.5 years (IQR 47-72). The majority of individuals had comorbidities at 72.7% ($n=243$), and a single subject could have multiple comorbidities. The clinical characteristics are summarized in Table 1.

Table 1: Clinical characteristics of the patients

Category / Variable	n (%)	Median Age in Years	IQR
Hematological Disorder			
(n=334)			
Multiple Myeloma (MM)	155 (46.4%)	65	58-74
Acute Myeloid Leukemia (AML)	92 (27.5%)	64	50-75
Acute Lymphoblastic Leukemia (ALL)	70 (21.0%)	42	26-59
Hodgkin Lymphoma (HL)	10 (3.0%)	35	29-65
Non-Hodgkin Lymphoma (NHL)	7 (2.1%)	-	-
Comorbidity Profile (n=243)			
Arterial Hypertension	141 (58.0%)		
Diabetes	52 (21.4%)		
Dyslipidemia	46 (18.9%)		
Thyroid Disease	38 (15.6%)		
Heart Disease	30 (12.3%)		
Kidney Disease	30 (12.3%)		
Lung Disease	25 (10.3%)		
Musculoskeletal Disease	13 (5.3%)		
Multimorbidity (≥2 diagnoses)	164 (67.5%)		

Most Frequent Neurological Alterations

Out of the 334 subjects, 42.2% (n=141) presented diverse neurological alterations as observed in Table 2. Onconeural antibodies in cerebrospinal fluid (CSF) and blood were measured in 3 subjects; none were positive. Vertebral fractures and ischemic strokes presented more frequently in women, while neuropathies, myelopathy/radiculopathy, meningeal infiltration, Parkinsonism, epileptic seizures/epilepsy, and other neurological complications presented more frequently in men. The distribution of complications by hematological neoplasm is summarized in Table 3.

Of the total patients with neurological complications, 18.6% (n=62) were assessed by neurology. Of the 62 assessed by neurology, the majority had MM at 61.3% (n=38); ALL at 19.3% (n=12), and AML at 17.7% (n=11); Subjects who were not assessed by neurology had neurological alterations including myelopathy, vertebral fracture, hemorrhagic stroke, neuropathy, and meningeal infiltration. The reasons for consultation with neurology can be seen in Table 4.

Table 2: Neurological alterations in subjects with hematological disorder

Neurological Alteration	N	%
Vertebral fractures	22	15.6
Other neurological complication*	18	12.8
Neuropathy	17	12.1
Headache	13	9.2
Cancer-related compressive myelopathy/radiculopathy	12	8.5
Hemorrhagic stroke/CNS bleeding	8	5.7
Ischemic stroke	6	4.3
Meningeal infiltration	4	2.9
Parkinsonism	4	2.9
Symptomatic epileptic seizures	4	2.9
Cancer-related compressive myelopathy/radiculopathy and vertebral fracture	2	1.4
Vertebral fracture and neuropathy	3	2.1
Meningeal infiltration	2	1.4
Neuropathy and other alteration	2	1.4
Neuropathy and cancer-related compressive myelopathy/radiculopathy	2	1.4
Symptomatic epileptic seizures and hemorrhagic stroke/CNS bleeding	2	1.4
Neuropathy and myelopathy	1	0.7
Neuropathy and headache	1	0.7
Neuropathy and hemorrhagic stroke/CNS bleeding	1	0.7
Myopathy and meningeal infiltration	1	0.7
Autoimmune encephalitis and epilepsy	1	0.7
Parkinsonism and meningeal infiltration	1	0.7
Parkinsonism, neuropathies, and meningeal infiltration	1	0.7
Symptomatic epileptic seizures and other neurological alteration	1	0.7
Epilepsy	1	0.7
Non-compressive myelopathy	1	0.7
Cancer-related compressive myelopathy/radiculopathy and neuropathy	1	0.7
Cancer-related compressive myelopathy/radiculopathy and epilepsy	1	0.7
Headache, Parkinsonism, hemorrhagic stroke/CNS bleeding	1	0.7
Headache and meningeal infiltration	1	0.7
Inflammatory polyradiculopathy	1	0.7
Vertebral fracture, symptomatic epileptic seizures, and hemorrhagic stroke/CNS bleeding and epilepsy	1	0.7
Lambert-Eaton	1	0.7
Meningeal infiltration and other	1	0.7
Meningeal infiltration, cancer-related compressive myelopathy/radiculopathy	1	0.7
Symptomatic epileptic seizures, epilepsy, and neuropathy	1	0.7
Total	141	100

*Other neurological complication: includes delirium, toxic, metabolic or sepsis-related encephalopathy.

Table 3: Distribution of complications by hematological malignancy

Hematological Neoplasm	Total Patients (N=334)	Neurological Complication By Hematological Neoplasm (%) *	Predominant Clinical Profile
Multiple Myeloma (MM)	155	117 (75.4%)	1. Vertebral Fractures (22.2%) 2. Peripheral Neuropathy (20.5%) 3. Myelopathy / Compression (17%)
Acute Lymphoblastic Leukemia (ALL)	70	38 (54.2%)	1. Headache (28.9%) 2. Other neurological complication (18.4%) 3. Meningeal/ Central nervous system (CNS) Infiltration (15.7%)
Acute Myeloid Leukemia (AML)	92	22 (23.9%)	1. Other neurological complication (36.3%) 2. Peripheral Neuropathy (18.1%) 3. Hemorrhagic stroke/CNS bleeding (13.6%)
Hodgkin Lymphoma (HL)	10	4 (13.3%)	1. Peripheral Neuropathy (50%) 2. CNS Bleeding (25.0%) 3. Hemorrhagic stroke/CNS bleeding (25%)
Non-Hodgkin Lymphoma (NHL)	7	0 (0.0%)	None documented in this cohort.

*Calculated considering the number of neurological complications presented per person, which can be ≥ 1 per subject.

Table 4: Temporal relationship of each neurological complication with the start of chemotherapeutic treatment and most frequent reason for neurology consultation.

Neurological Complication:	Number	Time between first chemotherapy and diagnosis of neurological alteration*	Assessed by neurology (% for each neurological alteration)
Vertebral fractures	28	Median -25 days (IQR -35 days and -9 days)	6 (21.4%)
Other neurological complication	36	Median 5.5 days (IQR -17 days and 37.5 days)	20 (55.6%)
Neuropathy	30	Median 34 days (IQR -20 days and 108 days)	10 (33.3%)
Headache	16	Median 36 days (IQR -16 days and 307.5 days)	8 (50.0%)
Cancer-related compressive myelopathy/radiculopathy	21	Median -26.5 days (IQR -87 days and -15 days)	5 (23.8%)
Hemorrhagic stroke/CNS bleeding	13	Median 27 days (IQR 1 day and 567 days)	6 (46.2%)
Ischemic stroke	6	Median 252.5 days (IQR 28 days and 639 days)	6 (100%)
Meningeal infiltration	12	Median -3.5 days (IQR -250 days and 40 days)	6 (50.0%)
Parkinsonism	7	Median 8 days (IQR -19 days and 97 days)	5 (71.4%)
Symptomatic epileptic seizures / Epilepsy	12	Median 12 days (IQR -18 days and 35 days)	10 (83.3%)

*Negative data indicate that the neurological alteration occurred prior to chemotherapy.

Chronology of Consultation and Treatment

Clinical follow-up was calculated using the first hematology consultation and the last one recorded by said specialty. For the entire cohort, it was 4.7 months (IQR 1.1-14.2); for MM, it was 6.3 months (IQR 1.2-20.3); AML 2.9 months (IQR 1.2-11.9); ALL 5.2 months (IQR 1.2-8.6); HL 3.0 months (IQR 1.0 - 11.0); NHL 3.3 months (IQR 0.8 - 24.7). The time in days between the first chemotherapy and the diagnosis of the neurological alteration was known in 132 subjects; the date of the first chemotherapy could not be clearly established in 7 individuals (only the year was available), of those, only 4 had the month, and 6 individuals had no data. Temporality was calculated for the main neurological complications as observed in Table 4.

Mortality During Follow-up

121 subjects died: MM 38.0%, AML 37.2%, ALL 21.5%, HL 1.7%, NHL 1.7%. Of these, $n=71$ presented at least one neurological complication. Twenty-four subjects presented epileptic seizures, 16 had meningeal in-

filtration, 13 had peripheral neuropathy, 9 had delirium, and 9 had cerebrovascular attacks. Mortality was greater than 50% among those with meningeal infiltration, other neurological complications, and hemorrhagic stroke/CNS bleeding. Of the 121 subjects who died, 21.5% were assessed by neurology; 53.8% ($n=14$) had MM, 30.8% AML ($n=8$), and 15.4% ($n=4$) ALL.

DISCUSSION

Our findings reveal a notable prevalence of neurological complications, exceeding the ranges of 15% to 22% previously reported in studies conducted in ICUs [4,5,11]. This suggests that neurological involvement is more extensive and frequent in outpatient and general ward practices than traditionally estimated when evaluating only critically ill patients; a difference explained by our methodology, which encompassed outpatient care and incorporated peripheral nervous system (PNS) pathologies.

We identified, for example, spinal involvement in MM with frequencies very similar to those of classical series, where it is described as the initial

manifestation in 52% of cases and in up to 45% of patients with a known diagnosis [12]. Similarly, we observed a significant tendency toward peripheral neuropathy in MM, which in our cohort predominantly appeared post-chemotherapy; although the frequency was lower than the 40-70% reported in the literature—associated with the use of thalidomide and bortezomib [13], the temporality in our subjects was very similar to that described by authors who report the highest rate of neuropathy after the fifth treatment cycle, with a median of 53 days [14]. This suggests that these findings primarily correspond to neurotoxicity, akin to the behavior observed in patients with ALL, where agents with neurotoxic potential are also employed [15].

Among other complications, we highlight headaches and meningeal infiltration; the latter occurring with a frequency similar to the 5-10% described in other studies regarding direct CNS involvement [7,16]. However, the percentages of headaches in the literature are highly variable depending on patient selection and oncological diagnosis, with prevalences of 56% in breast cancer [17], compared to averages of 12% in mixed cohorts (grouping solid and hematological tumors) [18]. Due to the temporal behavior identified, with an onset mainly post-chemotherapy in the ALL group, this symptom could be attributed to the toxicity of intrathecal agents or the post-lumbar puncture effect [18]. The behavior of AML was similar when compared to other centers, with CNS bleeding frequencies between 6-17% (19,20), and delirium up to 40% [6,11], based on data discussing these entities in this group of neoplasms.

Of the patients with complications, 18.6% were evaluated by neurology; a percentage higher than the 12.6% in previous reports [10], but much lower than the 42% seen in large neuro-oncology cohorts, where even 20% of consultations to this specialty originate from both the oncology and hematology groups [21]. The reasons for consultation were consistent with the literature regarding motor symptoms and epileptic seizures; nevertheless, entities such as neuropathies did not frequently prompt consultations, despite being among the most common complications in our cohort.

It is imperative to highlight that somatic neuropathy can appear concomitantly with autonomic neuropathy [22], either due to the systemic involvement of cancer (AL amyloidosis) or from treatment with bortezomib, manifesting symptoms such as orthostatic hypotension or paralytic ileus [13,23,24]. These autonomic neuropathies reduce survival by 50% [25], and pose a diagnostic challenge as they are frequently asymptomatic, detected only through specialized electrodiagnostics like Sudoscan® [26]. This reinforces the necessity of the neurologist's insight to contribute to management and improve outcomes—an intervention that has already been evaluated in other scenarios [27].

Because lymphomas had a minor representation, generalization about them is limited, although the observed trend contrasts with other authors [28]. Finally, mortality exceeded 50% in those who presented meningeal infiltration and hemorrhagic stroke, with diagnoses such as delirium and metabolic encephalopathies present in 19 of our 121 deceased patients, as has been seen in critical care settings [6,7,20,21]. This reinforces the notion that they impact the prognosis and outcomes of these patients.

Strengths and Limitations

The retrospective design entails limitations, such as the underreporting of minor symptoms (mild paresthesias or subtle cognitive dysfunction) and a lack of precise temporal data in a smaller subgroup. Furthermore, we found a potential overrepresentation of MM (46%) compared to the maximum of 6% usually described in the literature summarizing various studies [10,21], where NHL and acute leukemias predominate. This difference is likely due to the study being conducted in a high-complexity center that serves as a national referral center for these types of blood dyscrasias. Another limitation is that the study was conducted at a single center.

When comparing our work with other studies, such as that by Larrañaga et al. [21], it is evident that including multiple centers facilitates drawing conclusions on diseases like lymphomas.

Nevertheless, our strengths reside in the cohort size, which was much larger than most prior studies, except for multicenter ones [8,9]. Additionally, the study by Hovestadt et al. [10], although slightly exceeding our sample size, did not evaluate longitudinal follow-up as we did, which allowed us to observe the neurological evolution outside the critical care setting, evaluating both the CNS and PNS.

Conclusion

We documented a high frequency of neurological complications in patients with hematological malignancies across different contexts, not limited to the ICU. We identified relevant complications, both early and late (probably toxic), such as spinal involvement and polyneuropathies in MM. Despite this frequency, only 18% were evaluated by neurology. Although seizures or strokes were the primary reasons for consultation, it is worth considering the approach a neurologist can offer for other entities, such as neuropathies.

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