

Neurological Facets of Hematological Malignancies: A Case Series

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ABSTRACT

Background: Central nerve involvement is a serious complication in hemopathies. Clinical presentations are heterogeneous; it can affect the central nervous system as well as the peripheral. The pathophysiological mechanisms are multiple.

Aims: To illustrate the diversity of these neurological manifestations affecting both the central and peripheral nervous systems. We study the pathophysiological mechanisms and diagnostic strategies. We discuss the therapeutic alternatives and the prognostic value of neurological damage.

Methods: To illustrate the clinical and etiological polymorphism, we report a series of clinical cases of seven patients followed for malignant hemopathies and who consulted for different neurological manifestations.

Results: We have seven patients followed for malignant hemopathies: Acute lymphoblastic Leukemia (ALL), Acute myeloblastic Leukemia (AML), Myelodysplastic syndrome (MDS), Chronic myeloid Leukemia (CML). Patients consult for different neurological manifestations (optic neuritis, neuropathic pain, sensory and motor deficit, myopathic syndrome).

The etiological assessment identified different causes and mechanisms: leukemic medullary infiltration (myelitis) and optic nerve (optic neuritis). Acute post infectious polyradiculoneuritis in a patient undergoing chemotherapy. The neurological manifestations related to drugs were painful peripheral neuropathy and myopathic syndrome secondary to cytarabine syndrome. The fatal outcome was associated with extensive infiltration and fulminant neurovascularitis induced by MDS.

Conclusion: We discuss here through our series the different epidemiological, physiopathological, clinical, evolutionary and prognostic aspects of neurological complications of hematological malignancies.

Keyword

Central nerve system, Peripheral nerve system, Hematological malignancies, Treatment, Evolution.

Introduction

The invasion of the nervous system in hemopathies is late and estimated at 0.5–10% to 40% during relapses [1]. The occurrence

of CNS involvement and its clinical consequences are highest in patients affected by acute lymphoblastic leukemia (ALL), then acute myeloid leukemia (AML). According to different studies [2,3], the incidence of neurological involvement in AML is varied from 1.8% to 11% in adults and 6% to 29 in children [4,5]. This result has increased about 5.1% to 32% for the patients who underwent a systematic lumb puncture [2]. However, neurological

complications occur in chronic lymphocytic leukemia in less than 1% of cases [6]. As well as primary CNS lymphomas, that involves about 2.5% of brain tumors, especially with B-cell high-grade non-Hodgkin type [7]. The clinical presentations are heterogeneous. Both central and peripheral nervous systems can be implicated. The evolution may be fatal, depending on early and appropriate treatment and health care [8].

We discuss through our series the different epidemiological,

physiopathological, clinical, evolutionary and prognostic aspects of neurological complications of hematological malignancies.

Materials and Methods

We conducted a retrospective descriptive series within the neurology department of Charles Nicolle Hospital (Tunis, Tunisia). We have seven patients followed in our neurology department for a symptomatology suggesting a central or peripheral nervous origin and followed for malignant hemopathy. We identified

Table 1: Epidemiological, clinical and paraclinical profile of the patients in our patients.

Cases	Age Sex	Background	Hemopathy	Clinical neurological symptoms	Onset mode	Cerebral and medullary MRI	Other Complementary exams
Case 1	23 ♂	—	ALL	Reduced visual acuity (left eye <1/10), Marcus Gun sign Fundus exam: macular edema, perilesional exudate, fibrous membrane on the anterior side of the papilla	acute	thickening of the left papilla with gadolinium enhancement	OCT : lesion of the left choroid and infiltration of the vitreous VEP : Severe left optic neuritis CSF : proteinorrachia 0.32 g/l, cytologie 2 elements, negative neoplastic cell research Negative Viral and tuberculosis serologies
Case 2	65 ♂	—	ALL	Neuropathic pain (electric shock in right lower limb), spastic paraparesis, brisk osteotendinous reflex of the lower right limb with hypoesthesia, posterior cordonal syndrome	Slowly progressive: 2 years (chronic)	Bipolar spinal canal,	Hypovitaminosis B12 Normal CSF : proteinorrachia, cytology, neoplastic cell research, Positive aspergillosis serology, Negative viral serologies and tumor markers
Case 3	46 ♀	Ovarian neoplasia (chemotherapy with Tascol, carboplatine)	ALL due to chemotherapy of an ovarian neoplasia)	Rapidly evolving ascending weakness, hyporeflexia, facial diplegia, swallowing impairment, dysphonia	Acute (in 1 week)	Gadolinium root enhancement (L3,L4,L5) without spinal cord compression	CSF : albuminocytological dissociation with hyperproteinorrachia 1.5 g/l, cytology= 0 elements, Electromyogram : sensitivo-motor polyradiculoneuritis with axonal form Micronodular liver with cholestasis due to Vincristine toxicity
Case 4	32 ♀	—	AML	diffuse myalgia, weakness of the 4 limbs proximal predominance	Acute (12 hours after a consolidation cure)	Normal	CSF : proteinorrachia= 0.26 g/l, cytology= 2 elements Electromyogram : normal CPK : 1 month after the symptom resolution : Normal , LDH : 350 Tumor markers, viral serologies, immunological assessment : negative
Case 5	49 ♀	—	AML	Weakness of all the lower limbs and paresthesia of the distal extremities of the lower limbs (tingling, numbness), weak achilean reflex	Slowly progressive 8 months (Chronic)	Normal	Electromyogram : sensitivomotor and axonal perepheral neuropathy
Case 6	41 ♀	Family history of breast neoplasia and fulminant (super-acute) lupus causing death of her cousine	MDS	Encephalo-meningo-radculitis: paraplegia, hypotonia, hyporelexia, multiple involvement of cranial pairs (ophtalmoplegia, (III), perepheral facial paralysis (VII), swallowing impairment (XII) + systemic manifestations and multiple visceral failure	Subacute (rapidly progressive in 6 months)	Enhancement of a right occipital lesion, Leptomeningeal enhancement and also of the acoustico-facial bundle,, neoplastic cerebral, and medullary infiltration ? or neurovascularitis ?	CSF : hyperproteinorrachia 6.33 g/l, cytology 260 elements (80% lymphocytes), negative neoplastic cell research, IEPP profile 1 Viral serology, immunological assessment, antineuronal anticorp, tumor markers are negative. Electromyogram : neuroradiculitis L2, L5, S1 TDM TAP : neoplastic pulmonary micronodule Histological result of lung biopsy : inflammatory infiltrate with ischemic necrosis suggesting vasculitis
Case 7	44 ♂	—	CML	Spastic paraparesis, vivacity of the osteotendinous reflexes, bilateral babinski, gait disorder, Parasthesia of the lower limbs, Left Marcus Gun sign, papillary edema stage 1 at the Fundus exam	Subacute (rapidly progressive in 6 months)	medullary hypersignal T2 extended to C1,2,3 and D4,7 fixing the contrast	CSF: IEPP profile 4 research for neoplastic cells in the Cerebrospinal fluide non-specific suspect cells, no lymphoblasts Viral serology, immunological assessment ,antineuronal anticorp are negative

♂ : sexe masculin, ♀ : féminin, ALL : Acute lymphoblastic Leukemia , AML : Acute myeloblastic Leukemia , MDS : Myelodysplasic syndrome , CML : Chronic myeloid Leukemia, IEPP : Protein Immunoelectrophoreses, OCT : Optical Coherence Tomography, VEP : Visual Evoked Potential, CPK : Phosphokinase Creatine, CSF : Cerebral Spinal Fluid.

Table 2: Etiologies of neurological manifestations in oncohematology and the evolutionary profile in our patients.

Cases	Hemopathy	Specefic treatment of hemopathy	Free period between the remission and neurological symptoms onset	Neurological manifestations	Etiology	Treatment	Evolution
Case 1	Acute lymphoblastic Leukemia (ALL)	Systemic chemotherapy + allogenic graft	2 years after remission	Acute Left Optic Neuritis	Leukemic infiltration	12 sessions of brain radiotherapy and systemic chemotherapy	Favorable Visual acuity 7/10, regression of edema on retinal angiography
Case 2	Acute lymphoblastic Leukemia (ALL)	Chemotherapy for one year including Methotrexate then Sprycel 70 mg/day	6 years after remission	Motor deficit, neurological pain, posterior cordonal syndrome	metabolic (Comorbidity : Hypovitaminosis B12, Bipolar spinal canal)	Vitamine B12 then Plan surgery in second line	Slow worsening
Case 3	Acute lymphoblastic Leukemia secondary to chemotherapy of an ovarian neoplasia (Tascol, carboplatine)	Induction chemotherapy (high dose of vincristine, cyclophosphamide, 1 asperginase, daunorubicine, prednisone)	One week after the induction chemotherapy, 4 days after a febril neutropenia	Acute sensitivo-motor polyradiculoneuritis with axonal form	Drug related (Vincristine+++), or Postinfectious (remains a possible etiology due to febrile neutropenia), or Both	Intravenously Immunoglobuline, vitaminotherapy, physiotherapy	Favorable : Partial improvement in gait, complete resolution of swallowing disorders, persistence of moderate dysphonia
Case 4	Acute myeloblastic Leukemia (AML)	induction Chemotherapy, then consolidation cures	2 months after remission 12 hours after the first consolidation cure	Acute myopathy	Drug related (Cytarabine syndrome)	–	Favorable spontaneous resolution in 3 days
Case 5	Acute myeloblastic Leukemia (AML)	induction Chemotherapy, then consolidation cures	1 month after remission	Chronic sensory perefheral neuropathy (possible damage of small fibre) + chronic bilateral polyradiculoneuritis L2 and L3	Drug related (Chemotherapy : cumulated dose)	Symptomatic (Pregabaline)	Stationary
Caes 6	Myelodysplasic syndrome MDS	Transfusion, antibiotherapy	Few weeks after the remission	Encephalo-meningo-radiculitis with multiple visceral failure	Immune – mediated Fulminant neurovascularitis induced by MDS with extensive infiltration	reanimation	Multiple visceral failure rapidly after 6 months => death
Case 7	Chronic myeloid Leukemia (CML)	Targeted chemotherapy for one year then Sprycel	6 months after the remission	Subacute Extensive myelitis	Leukemic infiltration	5 days of Solumedrol with chemotherapy	Favorable

the treatments received as part of the therapeutic management of hemopathy. We took the detailed history of the installation mode and evolution of neurological symptoms. Neurological examination was performed for all patients. Etiological diagnosis was based, in addition to clinical data, on cerebral and/or spinal magnetic resonance imaging (MRI), data from the cytochemical analysis of cerebrospinal fluid (CSF), flow cytometry, the search for tumor markers in blood and CSF, screening for viral and bacterial infections in the blood and CSF, neurophysiological explorations such as the electroneuromyogram and the evoked potentials. Etiopathogenic and or symptomatic treatment adapted to the etiological diagnosis retained was introduced for the patients. Evolution of clinical and paraclinical parameters of patients was evaluated in both long and short terms.

Results

Our series included 7 patients with confirmed diagnosis of malignant hemopathy. The average age is about 43 years old \pm 13 years with a sex ratio of 0.75 (4 women and 3 men). This study is about 3 cases of Acute Lymphoid Leukemia (ALL), 2 cases of Acute Myeloblastic Leukemia (AML), 1 Case of Chronic Myeloid

Leukemia (CML), and 1 case of Myelodysplastic Syndrome (MDS). The mode of onset of neurological manifestations was acute in 2 cases of ALL and in 1 case of AML. It was subacute for 1 case of MDS and 1 case of CML and slowly progressive in 1 case of LLA and 1 case of AML. The neurological damage involved the central nervous system in 4 cases, and the peripheral nervous system for the other 3 patients. Epidemiological, clinical and paraclinical data are detailed in the table1. The neoplastic origin was found in 3 cases (42,85% of all our series). There is also one case of fulminant neurovascularitis induced by myelodysplastic syndrome (indirect immune mediated hemopathy implication). The drug related to neurological manifestations was retained in 3 cases (42,85% of all cases). However, we report 1 case with uncertain etiology, namely a case of ALL with a motor deficit, neuropathic pain, hypovitaminosis B12 and bipolar spinal canal as comorbidity (Table 2). The evolution was favorable in 4 cases (3 cases with specific treatments and 1 case with spontaneous amelioration), slow worsening or stationary in 2 cases where the toxicity is chronic and cumulative, and fatal in the case of fulminant neurovascularitis leading to death.

Discussion

Neurological complications in hemopathy can occur during remission, and can even reveal the hemopathy in some cases [9]. In our series, most of our patients were in complete remission, having their cure of consolidation. In addition to the clinical symptoms and the result of CSF analysis, MRI with Gadolinium injection is the baseline exam in case of suspected CNS involvement. It can show a hyper signal of the superficial furrows, at the level of the ventricles or cranial nerve damage. Spinal MRI can help diagnose intra-dural and extra-medullary involvement. Normal MRI does not eliminate the diagnosis because there are sometimes false négatives [10]. Direct involvement of the CNS in Leukemias is due to infiltration with leukemic cells. The symptomatology depends on the location of the leukemic infiltration, which can involve the meninges, spinal roots or the cranial nerves. The mechanism of each location will be explained separately. In chronic lymphocytic leukemia, CNS involvement is also related to leukemic infiltration, but can be the first sign of Richter syndrome (evolution to an aggressive form of big cell lymphoma) [8].

However, it may also be the side effect of radiation, infection, thrombocytopenia, denutrition and neurotoxicity induced by chemotherapy (indirect mechanism). In myeloid acute leukemias, the association of cellular hyperviscosity with severe leukocytosis is frequent and can cause ischemic involvement or secondary intracranial bleeding [7]. MRI provides immediate diagnosis, and allows identifying the physiopathological mechanism. The latter is the basis of an appropriate therapeutic strategy to increase the survival [11]. Leptoeningeal metastasis is the common “direct” CNS involvement. It implicates 10% of all acute Leukemias, particularly 30 to 50% of leukemic relapse cases [8]. ALL is the type of leukemia most implicated in the invasion of the meninges, via the arachnoid veins then the CSF [12]. Acute myeloid leukemia (AML) carries also a high risk of 20% to develop leukemic meningitis [13]. After 3-6 months of the diagnosis of bone marrow damage, the occurrence of clinically objective meningeal leukemia becomes higher [14]. Cerebrospinal fluid and flow cytometric analysis can confirm the diagnosis in about 90% of cases. Many studies have proven the highest sensibility of flow cytometry (FCM) compared to conventional cytology (CC) for proving CNS damage in hemopathy [2,15]. Cases of extensive myelitis are often related to CLL [16,17], but for our seventh patient, it was about AML infiltration. No similar cases have been found in littérature according to our knowledge. Leukemia can also affect the spinal cord and roots. Isolated spinal cord injuries are exceptional in patients with leukemias. The inaugural symptoms differ depending on the location of lesions and implicate headache, radicular neuropathic pain, backpain, weakness of limbs, paraplegia, and cranial multineuritis [18]. Cranial multineuritis secondary to nerve compression or infiltration is more frequent in cases with hemopathy than with solid cancer. It is often unilateral with a tropism for the longest cranial nerve [9]. Ophthalmologic disorders of hemopathies represent from 9 to 80% of acute leukemias. However, they cause rarely optic retrobulbar neuropathy (NORB) in the elderly. An autopsy series showed that the optic nerve was affected in only 18% of cases. It implicates

optic atrophy or papillary edema [1], which are the most common signs described in ALL, AML, AMC and can cause blindness. Most of published articles reported optic neuropathy cases which occur a few months after remission or which inaugurate the hemopathy [19,7]. However, in our series acute optic neuritis occurred 2 years after remission. Therefore, this proves that the length of the free interval after remission cannot be a diagnostic criterion. The mechanisms involved are either a direct infiltration of the head of the optic nerve by the blasts, or an indirect infiltration due to the retro-laminar leukemic invasion with normal intracranial pressure, or papillary edema with intracranial hypertension [1]. Optic neuritis occurs mostly in ALL, as the case of our first patient, then AML [19]. The differential diagnostics are diverse and include inflammatory, ischemic, toxic and compressive etiologies. The infiltrative origin most often concerns tumors of the optic nerve (glioma), or tumors with orbital invasion in hematological diseases [1]. For our patient, decreased visual acuity, the absence of signs of cranial hypertension with detection of peri-vascular infiltration, asymmetric clinical symptoms, radiological data, and negativity of immunological and infectious researchs, orient towards the relapse of ALL with blastic infiltration of optic nerve, even in absence of CSF abnormalities. The efficiency of cranial radiotherapy has approved this diagnosis. The dysfunction of the hypothalamic-pituitary axis is well known. It may occur with hydrocephalus [7] and it is more common in children [9]. The first case reported was about a young patient with CLL [6]. Venous sinus thrombosis (VST) are the frequent cause of ischemic cerebral stroke at or nearly after diagnosis of hemopathy. It can be the consequence of the infiltration of the superior sagittal sinus with leukemic cells, or due to an iatrogenic effect of L-asparaginase chemotherapy for children with ALL. Some complications are more severe, such as a global encephalopathy syndrome due to multiple arterial microinfarcts [20].

Peripheral nervous system involvements are less frequent than the CNS lesions in leukemia [21]. Herpes zoster-related radiculopathies is the most common PNS involment. In fact, 7% of cases had at least one episode during the disease period, espacially in CLL cases [12]. Leukemic infiltration mechanism is rarely implicated in neuropathy. For example, axonal sensorimotor polyneuropathy is described in CLL in less than 1% of cases. It can cause also axonal polyradiculoneuropathy or severe sensory ataxic neuropathy. However, neuropathy due to the iatrogenic effect of chemotherapy is more frequent. In fact, nerve conduction abnormalities were described after more then 2 years of treatment in 30% of children with ALL disease. A monoclonal protein that can cause chronic demyelinating neuropathies was found in 8% of neuropathy cases with CLL [9]. In our series, the only patient with cranial neuropathy, radiculopathy and neuromyelitis (case 6), has no proof of Leukemic infiltration. All viral serologies were negative and he has the particularity of being diagnosed with hypovitaminosis B12 associated to AML. Infections of the CNS or peripheral nervous system can be associated with hematologic malignancies, or due to corticosteroids and chemotherapy [7]. Viral serologies must be obtained in each patient before retaining the Leukemic origin.

In some cases, the chemotherapy may activate some virus or parasites and lead to acute polyradiculoneuritis or meningitis [22]. This may explain the case of our third patient who was diagnosed with acute axonal polyradiculoneuritis associated to a positive aspergillus serology. However, Aspergillus is known to cause focal deficit, meningitis and rhombencephalitis rather than polyradiculoneuritis [23]. Symptoms related to therapy of Leukemias are diverse and depend on the type and the dose of the molecule. It includes often the peripheral system, and it is related to cumulated or high doses [24]. Different neural structures may be damaged the axons of DRG, myelin sheath, microtubules, glial structures. Most of chemotherapy agents that can induce peripheral neuropathy cannot pass the blood– brain barrier. The main damage occurs at the afferent or efferent axons and dorsal root ganglion. It manifests predominantly as sensory neuropathy. It can also cause cerebral toxicity and seizure. The recovery of neurological lesions is rare and often incomplete [25]. The most frequent is the neuropathy due to vincristine, administered during the induction and consolidation phases in acute leukemias. The most toxic molecules for CNS are Methotrexate and cytarabine. Some cases of paraplegia and neuromyelitis due to Methotrexate accumulated dose or cytarabine therapy were reported [22]. It agrees with the case of our fifth patient who carried long period of chemotherapy causing chronic axonal peripheral neuropathy and the case of our second patient with long period of Methotrexate therapy, severe denutrition and B12 hypovitaminosis. We also report the case of cytarabine toxicity (case 4) with acute toxic myopathy. Myelopathic symptoms can occur up to 2 weeks after intrathecal injection of methotrexate. No specific treatment, nor predictor factors of occurrence of myelopathic symptoms are reported. Recovery differs between patients [20]. Few case reports described a paraneoplastic progressive myelopathy due to leukemias, and not due to chemotherapy. Some non-specific biological and radiological signs may be found, such as elevated proteinorachia and the count of white blood cells in CSF with negative cytology, presence of T2 signal of white substance on MRI [26]. High-dose of systemic therapy is often prescribed to defeat the poor bioavailability of chemotherapy drugs into the CNS. The pharmacological details, toxicities, and other side effects of this approach are well described in literature [27]. In some cases as optic neuritis, the treatment should implicate emergent radiotherapy to preserve vision, in association with intrathecal therapy [1]. It is the situation for our first patient, with favorable evolution. According to a study led by Donna L Johnston and all [28], 78% of AML patient have realized total remission independently of the presence or not of CNS damage.

However, 2 studies reported that survival after remission at five years is shorter in presence of CNS damage (CNS+), with rates respectively:18% (CNS+) vs 50% in absence of CNS damage (CNS -), $P = 0.006$ and 19% (CNS +) vs 46% (CNS -), $P = 0.02$. The onset of paraneoplastic meningitis is predictive of poor prognosis, with a survival expectancy of 2-6 months [12,13]. In myelodysplastic syndrome, direct infiltration is the primary physiopathological mechanism. Nevertheless, it may happen because of induced pathologies such as hyperviscosity

and severe induced vascularities. Clinical manifestations are due to hyperviscosity, which Induce sludge and stasis in the small vessels. Treatment is based on plasmapheresis [29]. The incidence of autoimmune manifestations in myelodysplastic syndromes is estimated at 10 to 20% [30]. Vasculitis can be induced by SMD during a transformation into acute leukemia, probable situation for our patient, as it can be a comorbidity preceding or following the SMD by a few months [1]. In terms of pathophysiology, immunological abnormalities are observed during myelodysplastic syndromes. They are related to disturbances in humoral and cellular immunity, B and T lymphocyte interaction, abnormalities of NK cells and mono-nucleated phagocytes [31]. The secretion of interleukin 2, interferon-gamma, and tumor necrosis factor alpha (hematopoietic inhibitor cytokine) is the reflection of deviations in the distribution of TH (T Helper) and TC (cytotoxic T) cells. These systemic manifestations are sensitive to corticosteroid therapy, which approve the autoimmune origin. For our sixth patient, meningoencephalo-radculitis was attributed to induced vasculitis due to MDS. Particularly that she was a female, polytransfused, with multiple visceral failure and extended infiltration in cerebral MRI. She has also family history of fulminant vasculitis with rapid death without investigations of a possible MDS. The evolution is usually fatal.

Conclusion

Neurologic complications may inaugurate the hemopathy or occur with systemic involvement or at remission. It involves mostly the central nervous system, then the peripheral system. It can be the result of a direct malignant infiltration or the consequences of toxicity treatment, immunodeficiency or induced pathologies. Chemotherapy causes often peripheral sensory nerve involvement with axonal damage. The occurrence of comorbidities makes the etiological diagnosis more difficult and uncertain. We report the first case, «as our knowledge», of extensive myelitis related to AML. Our study showed that acute optic neuritis can occurred even 2 years after remission. This proves that the length of the free interval after remission cannot be a diagnostic criterion. Some conditions are rares and serious such as fulminant vasculitis in myelodysplastic syndrome. However, unfortunately they are unknown and need to be highlighted. No treatment is known to be surely safe, but early and appropriate treatment can improve the average survival.

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