

## Leukemia and the Peripheral Nervous System: A review

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### Abstract

The fate of patients with leukemia has greatly improved in the past decades. Survival has been increased and the once stereotypic pattern of Cerebrospinal fluid (CSF) infiltration and diffuse infiltration of nerves and muscles has entirely changed.

Peripheral nervous structures as cranial nerves, nerve roots, plexus and peripheral nerves can be affected in different types of leukemia, by different mechanisms and at different time points.

Treatment side effects become more apparent, as the number of long term survivors increases. In some cases also isolated relapses of leukemia in the nervous system occurs and effects of stem cell transplantation on the nervous system became apparent.

Diagnostically the cranial nerves, nerve roots, cauda equina, nerve plexus and the peripheral nerves have become more accessible to investigation due to improved imaging methods as ultrasound and MRI, thus facilitating the earlier diagnosis and treatment of nerve involvement.

**Keywords:** Leukemia; Peripheral nerve; Mononeuropathy; Plexopathy; CSF; Neuroleukemiosis; Imaging

### Introduction

The peripheral nervous system is commonly classified into intra- and extra cranial/medullary parts. It consists of cranial nerves, nerve roots, the cauda equina, nerve plexus, peripheral nerves, the area of the neuromuscular transmission and muscles.

The cranial nerves and nerve roots as well as the cauda equina can be involved in neoplastic involvement of the CSF. Within the CSF space several types of nerve involvement occur: meningeal leukemia causes CN deficits and polytopic radicular symptoms. In particular the CN and the cauda equina can be affected [1]. Rarely ascending multiradicular involvement can be observed mimicking Guillain Barre syndrome. The spinal cord can be affected by epidural deposits, dural leukemia [2] and granulocytic sarcoma, or chloroma which can result additionally in spinal compression.

Peripheral nerve involvement in leukemia does not necessarily involve the CSF [3].

Various mechanisms of neoplastic nerve damage as infiltration, compression by leukemic masses and hemorrhage into nerves occur and in addition toxicity of drug treatment, and rarely autoimmune and paraneoplastic cases [4].

The mechanisms of nerve infiltration in neoplastic disease have been elucidated in cancer [5], several types of lymphoma [6] neurolymphomatosis [7,8], intravascular lymphoma and combinations thereof [9]. Leukemic infiltration has been described [10,11] and also the term neuroleukemiosis has been introduced [12]. Also muscles can be diffusely infiltrated [13-15].

### Materials and Methods

The work was based on previous reviews on peripheral nerve lesions in cancer [16,17] lymphoma and leukemia. In addition databases were screened for search terms.

**Search strategy:** Pubmed and Pubmed central, Google scholar and DOAJ were searched for acute and chronic leukemia and nerve infiltration, plexus lesions and chloroma, mononeuropathy and neuropathy; also a search for bone marrow/stem cell transplant and neurological complications was done.

Additionally searches for "leukemia" and nerve infiltration with "MRI" and/or "ultrasound" and for "drug treatment" of leukemia were launched.

For practical issues nerve lesions in leukemia are subdivided in 2 groups. A neoplastic lesions and B others.

## A ) Neoplastic lesions in leukemia

- 1 Meningeal involvement with CN and polyradicular spread and dural leukemia
- 2 Head and skull involvement with cranial nerve lesions
- 3 Symmetric or asymmetric neuropathy (multiplex type)
- 4 Focal nerve lesions occurring in the nerve plexus and individual nerves
- 5 Peripheral nerve involvement following Bone marrow (BMT) and Stem cell transplantation (SCT)
- 6 Sanctuary and dormant cells

## B) Others

- 7 Neurotoxicity
- 8 Paraneoplastic diseases
- 9 Other mechanisms: immune mediated, vasculitis, infection (eg herpes)

The results of the review will be subsequently reported in this order.

## 1) Neoplastic Involvement

**Meningeal involvement with CN and polyradicular spread and dural leukemia:** Several analogies exist with lymphoma, where various types of nerve infiltration have been termed neurolymphomatosis and intravascular lymphoma and have been subject to several reviews [7,8,11,16].

In leukemia several types of neoplastic nerve involvement occur: within the CSF space most commonly meningeal infiltration of CN and nerve roots and also focal deposits, commonly termed chloroma. Chloromas occur most frequently in myeloid leukemias harbouring monocytic markers, e.g. M4 and M5.

The precise type of nerve infiltration in malignancies varies and has been described by [5] recently reviewed [18,19]. Cranial nerves, with the exception of the olfactory nerve and optic nerve, which are considered as a part of the brain, are usually considered as part of the PNS. Generally the course of the CN is considered as intracranial, transition through the base of the skull and the extracranial course.

**Meningeal, dural and intraspinal leukemia:** Meningeal involvement in acute leukemia, rarely in chronic leukemia, is the most frequent and well described occurrence. Involvement of the optic nerve seems to be most frequent site, and involves leukemic infiltration in all parts of the optic nerve as well as the papilla [20,21].

Other CN most commonly affected are the facial nerve or the optomotor nerves often in a combination with CNS symptoms and single or multiple spinal radicular symptoms. Typically CN lesions in meningeal leukemia do not appear isolated, but are accompanied by other multifocal CNS and spinal symptoms.

In addition to multiradicular spinal root involvement also isolated involvement of the cauda equina [22] and the dura [23] have been described.

Rarely a focal leukemic deposit as chloroma can cause CN or radicular symptoms or spinal compression [24,25]. Isolated thickening due to nerve infiltration of the trigeminal nerve in leukemia has been described [26] (Dura Image: Figure 1).

**Head and skull involvement with cranial nerve lesions:** Local leukemic deposits appearing usually in recurrence of leukemia can involve the orbit [27], the skull (mastoid and jaw: resulting in numb chin syndrome) [28,29], the nasopharyngeal space [30,31] and cause focal cranial nerve damage. Several types of peripheral facial nerve lesion usually at the site of the parotid gland have been described [32,33,34]. The focal leukemic lesion is considered to produce nerve damage by compression and infiltration. An antero- or retrograde spread via the cranial nerves as in solid tumors has been rarely described [35,36] (Cranial nerve infiltration: Figure 2).

**Symmetric or asymmetric neuropathy (multiplex type):** Neuropathies are usually classified symmetric or asymmetric types. Focal peripheral nerve lesions involve the nerve plexus and individual nerves (mononeuropathies).

Symmetric generalized neuropathies are rarely caused by leukemic infiltration of peripheral nerves. Symmetric weakness should rather rise the suspicion for myelopathy, polyradicular meningeal involvement, or if occurring during treatment for chemotherapy-induced neuropathy. Rarely dysimmune neuropathies such as Guillain-Barré-Syndrome (GBS) or Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) occur. Their relation to leukemia is not well defined. However rarely symmetric infiltration of nerves has been observed [37,38] and their course can mimic GBS [39].

Conversely asymmetric multifocal or multiplex neuropathies are suggestive of neoplastic nerve infiltration. Several reports have identified mono M4/5 leukemias which seem to have a particular affinity to peripheral nerve infiltration [40,41,42].

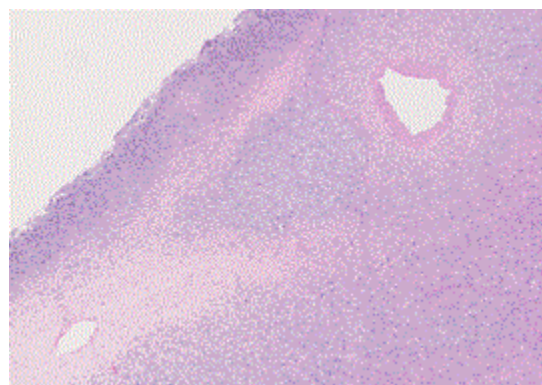


Figure 1A: Dura of a patient with hairy cell leukemia

## Focal nerve lesions occurring in the nerve plexus and individual nerves

**Nerve plexus:** Several cases of focal nerve infiltration of the brachial plexus have been described, also as an isolated recurrence of leukemia in remission [43]. Observations of leukemic involvement the lumbar or the sacral plexus were not found in our search. Several reports have described leukemic local mass lesions termed chloroma which can also compress nerves [44,46].

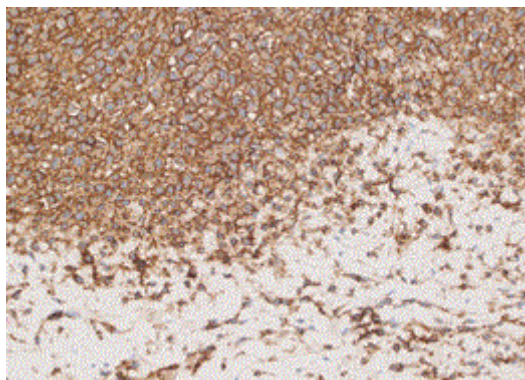


Figure 1B: CD 20 staining of leukemia cells

**Mononeuropathies:** The occurrence of mononeuropathies due to leukemic infiltration has been reported in small numbers, typically as case reports. Clinically they are difficult to distinguish from other causes of mononeuropathies but most reports describe associated pain. Rarely mononeuropathies appear in chronic leukemias [47].

**Neuroleukemiosis:** several nerve lesion due to leukemia have been described by Aregawi et al. [12] and Reddy et al [48] and this type of lesion has been termed neuroleukemiosis. Diagnosis has been facilitated by imaging techniques as MR and ultrasound. Sciatica can be the first presentation of nerve infiltration [49].

In addition to diffuse infiltrating lesions, also focal compression by chloromas or extramedullary sarcomas have been observed.

Coagulopathies In leukemia can be severe and can cause focal hemorrhages into peripheral nerves resulting in painful mononeuropathies [50].

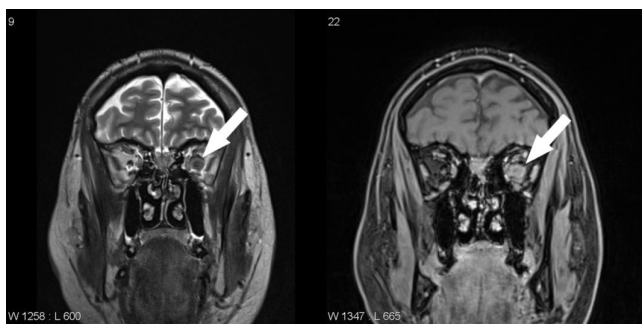


Figure 2A: Leukemic infiltration of the left optic nerve. A1 Left: T2 weighted, coronal MRI scan of the orbit. Thickened optic nerve (arrow). A2 Right; T1 weighted, coronal MRI scan with fat suppression with gadolinium contrast enhancement of the orbit. The thickened optic nerve is markedly enhancing indicating the infiltration.



Figure 2B: Leukemic infiltration of the left trigeminal nerve. B1 Left: T2 weighted, axial MRI scan of the trigeminal nerve at the entrance to the trigeminal cave at the parasellar region. Significant thickening of the trigeminal roots and ganglion in the trigeminal cave (arrow). B2 Right: T2 weighted, coronal MRI scan of the trigeminal ganglion in the trigeminal cave (arrow).

**Peripheral nerve involvement following Stem cell transplantation (SCT):** Nerve damage due to local recurrence of leukemia has been observed, either as polyneuropathy [42], or focal nerve lesions by chloromas [49,51,52,53,54] during remission.

Several other neurological complications following bone marrow transplant have been described [55] and dysimmune inflammatory neuropathies as CIDP [56,57] or GBS [58] can occur.

In addition several peripheral neurologic effects have been described in graft versus host disease [56,59,60,61]. Rarely also multiple entrapment neuropathies, due to tissue fibrosis have been observed [62].

Direct injection of neural stem cells into the CSF can cause focal inflammatory changes of the cauda equina [63].

**Sanctuary and dormant cells:** CSF sanctuaries and dormant leukemia, have to be considered in relapse.

Relapses of leukemias in the CSF space occur and are considered in several treatment protocols by prophylactic intrathecal treatment. Isolated relapse of the brachial plexus in a case of AML was described [51]. Cranial nerves can be effected by local leukemic relapse in their entire course as the facial nerve passing the parotid gland [32].

Leukemic stem cells may have immature or mature phenotypes, be multipotent or restricted to a lineage, quiescent or cycling. Leukemia can only be eradicated when complete eradication of the leukemic stem cells succeeds [64]. Dormant cells can cause disease progression. Their stem cell properties such as low metabolism, expression of efflux pumps at the cell membrane as well as poor penetration of the drugs to sanctuary sites like the central nervous system or even peripheral nerves protected by the blood-nerve barrier may protect these cells from the effects of chemotherapy and enable them to cause recurrence of the leukemia [65].

## 2) Other Conditions

### Neurotoxicity:

**Systemic drug delivery:** Neurotoxicity of leukemia treatment appears usually after several cycles of chemotherapy. Vinca alkaloids

and arsenic trioxide are potential neurotoxic agents [66,67,68]. Combination of arsenic trioxide with retinoids can result in a retinoic acid syndrome [69,70,71].

Several new drugs are used in leukemia and lymphoma treatment, which need to be mentioned due to peripheral neurotoxic side effects:

A liposomal vinca alkaloid formulation has been used which seems however equally neurotoxic than conventional vinca alkaloid treatment [72,73].

Brentuximab vedotin is a CD 30 antibody, which is coupled with the microtubule agent monomethyl auristatin E which as a microtubule agent is neurotoxic on peripheral nerves [74,75] and has also been used in leukemia as well as in lymphoma.

Nelarabine is used in the treatment of acute lymphoblastic leukemia and T cell lymphoblastic lymphoma. Severe neuropathies, resembling GBS, have been observed [76,77].

The proteasome inhibitor bortezomib, and the VEGF inhibitor lenalidomide have been described in the treatment of leukemia. Bortezomib has a high risk of inducing peripheral neuropathy [78], lenalidomide [79] is less toxic than its predecessor thalidomide.

**IT drug delivery:** Also intrathecal treatment can potentially cause severe neurotoxicity as subacute combined degeneration [80]. This has been described in methotrexate and cytosine arabinoside. Long acting cytosine arabinoside can result in aseptic meningitis and arachnitis. Rapidly ascending paraparesis due to toxic myelopathy has been observed both in conventional drugs as MTX and cytosine arabinoside, and severe irreversible polyradiculopathies by accidental IT application of vinca alkaloids [81,82].

Also potential contaminations with solvents, preservation fluids of potentially neurotoxic agents have to be considered [83].

The effect of biological drugs on the PNS is less well defined. Imatinib mesylate causes papilledema in rare cases [84].

**Radiotherapy:** Neurotoxic effects on the CNS of radiation therapy have been extensively described. The peripheral nerves are usually not the target unless for specific local aspects. Peripheral nerves are rarely affected by acute radiation effects, but usually late radiation effects as fibrosis or the development of secondary tumors have been described [85].

**Paraneoplastic effects:** Rarely peripheral nerve lesions can be considered paraneoplastic in leukemia. Some singular cases have been described [86,87]. There are several reports in considering immune mediated neuropathies in CLL [88,89] and in the myelodysplastic syndrome [90] as of paraneoplastic origin.

#### Others:

**Immune mediated, Vasculitis, Infection:** Immune neuropathies as GBS or CIDP can appear at any time of the course of the disease and also following BMT. Severe neurotoxicity from vincristine, potentially also from nelarabine, can resemble GBS [91].

**Vasculitic neuropathy [92] and anti-MAG paraproteinemic demyelinating neuropathy [93] has been described in association with hairy cell leukemia.**

**Infection:** Herpes zoster occurs in all types of leukemia and in particular in CLL. Dissemination may occur and can cause meningeal and motor symptoms. Post post-herpetic neuralgia can develop into a chronic pain syndrome.

#### Diagnosis:

The involvement of the PNS in patients with leukemia has changed due to improved treatments, longer survival and also better diagnostic methods, which can be applied. In particular imaging has allowed the structural diagnosis or abnormalities of the peripheral nervous system suggesting malignancy.

**Imaging:** Various imaging modalities can be used in the detection of leukemic infiltration in different locations:

Due to its availability Magnetic Resonance Imaging (MRI) with the additional application of gadolinium contrast media is the mainstay in the detection of infiltrated segments of the peripheral nervous system. MRI allows the examination of all relevant parts of the peripheral nervous system, as well as of the surrounding structures. The enlargement of a nerve can be indicative of a focal leukemic infiltration [94]. An increased contrast enhancement after administration of a gadolinium contrast medium should also raise the suspicion of neuroleukemiosis [94,26]. It is also possible to perform the follow-up during and after therapy in order to verify the remission or to detect a possible relapse [51,26]. Based on the information of the infiltration obtained by MRI it is possible to guide the surgeon to a potential biopsy position (51).

Especially the in-line combination of a Positron-emission Tomography (PET) and a Computed Tomography (CT) within one machine has the advantage of a high confidence level of lesion localization. Traditionally the detection of lesions with 2-[F18]-fluoro-2deoxy-D-glucose (FDG) uptake is very sensitive, but lacks specificity and spatial resolution whereas the combination with CT allows the good correlation of PET CT and neurological clinical findings. The lack of specificity is reflected in the limited distinction of true malignant infiltration and (benign) inflammatory processes. Though the latter could be excluded by the clinical course [96].

High resolution ultrasound of the peripheral nerve system is quite a new method which allows the visualization of peripheral nerves with the surrounding tissue in a superior spatial resolution than MRI [97]. Clearly, the commonly known disadvantages of conventional ultrasound, as obstruction of the scan by gas or bone, also apply for the high resolution neuromuscular ultrasound. Consequently the spinal nerves, parts of the lumbar plexus, the sacral plexus and some cranial nerves cannot be routinely examined with ultrasound. However in those regions, where ultrasound can be applied, it is possible to examine the entire length of a nerve in one single ultrasound scan sweep. With the commonly available color doppler function it is possible to depict also a hypervascularized segment of the nerve [98]. Ultrasound contrast media are also a new tool in neuromuscular ultrasound. The role in the detection of neuroleukemiosis is not evaluated.

#### Therapy

The decision for therapeutic intervention depends on the type of leukemia and most of all on the certainty of neoplastic disease, which can be local or diffusely spread. In some cases a confirmation by biopsy may be needed. Local infiltration and local tumors are most frequently treated with local RT.

Symptomatic treatment is targeted at symptoms as neuropathic pain, physiotherapy and occupational therapy to overcome motor and sensory deficits of peripheral nerve lesions.

Long term effects of CIPN affect the quality of life.

**Relapse:** The involvement of the PNS in patients with leukemia has changed due to improved treatments, longer survival and also better diagnostic methods, which can be used. In particular imaging has allowed the structural diagnosis or abnormalities suggesting malignancy. However also new drugs causing potential neurotoxic effects and late relapses, and recurrences after stem cell and bone marrow transplants need to be considered.

## Discussion

Unlike lymphoma where neurolymphomatosis and intravascular lymphoma in its various presentations has been subject to reviews [7,8], the involvement of the PNS in leukemia is less well defined. This may result from different and radically improved survival, new treatments as well as the more heterogeneous classification.

In addition to the classic infiltration of nerve and muscle, which has been observed in the untreated patients with acute leukemia, several different types of PNS lesions are clinically relevant and have been described.

For the practical issues of care, a symmetrical sensory or sensorimotor neuropathy is the least suspicious for leukemic infiltration. If sensorimotor neuropathy develops during treatment it is most likely treatment related, and can usually be explained by the neurotoxicity of the drugs used. In more advanced stages, in particular after severe weight loss, or severe infection, in particular sepsis, a distal sensorimotor neuropathy can develop.

Rapidly ascending types of neuropathy, resembling a GBS during any time raise the suspicion of neoplastic involvement of the CSF. This suspicion is even increased if cranial nerves are involved and CNS symptoms appear. Immune mediated acute neuropathies have been described to occur at random, or as an immunological sequel of BMT.

The multiplex type of neuropathy in a patient with leukemia at any time rises the suspicion of a neoplastic neuropathy (Table 1). The term neuroleukemiosis has been designed for this in the past years, and a peculiar affinity of M4 and M5 type of leukemia has been observed. The peripheral nerve involvement can occur with a tumor cell free CSF.

Several types of mononeuropathies of individual nerves and plexus have been observed in leukemia. They are either infiltrative in nature, but also local tumor like deposits (chloromas) occur. The imaging either shows tumor like lesions, enlarged nerves either in ultrasound or combined MR and PET studies. An identical development can be expected in brachial plexus lesions.

This review distinguishes between neoplastic and non-neoplastic lesion of cranial and peripheral nerves. A distinction which implies different treatment strategies. Definitely the natural disease of leukemia is undergoing changes by prolongation of survival, treatment types with additional involved toxicity, and new presentations after BMT or stem cell therapy.

Type of neuropathy	At diagnosis of leukemia	Acute stage during treatment	During remission	After BMT
Symmetric sensorimotor		toxicity	toxicity	toxicity
Ascending quadraparetic neuropathy	neoplastic or	neoplastic		dysimmune
Facultative with CN involvement	dysimmune	dysimmune		
Multiplex type	neoplastic	neoplastic	neoplastic	
Individual mononeuropathy	neoplastic or	neoplastic	neoplastic	neoplastic
	unrelated	rarely toxic	toxic	toxic
Plexopathy (brachial, lumbal or sacral)	neoplastic	neoplastic	neoplastic	neoplastic – “dormant” cells in recurrence

**Table 1:** Likelihood of different causes of neuropathy at different stages of the disease: This table correlates the likelihood of specific types of neuropathy in regard to the time course of leukemia. This time course is defined as time at the diagnosis, during the acute stage of treatment, in remission and after BMT.

The classification has been made according to the most common peripheral nerve lesions as symmetric sensorimotor neuropathy, ascending quadraparetic neuropathy with facultative cranial nerve lesions, a multiplex (multifocal) type, and focal neuropathies as mononeuropathies or lesion of the nerve plexus.

As an example, the most common sensorimotor type of neuropathy is unlikely to appear at diagnosis but can be expected due to toxicity during the course of treatment.

Whereas ascending quadraparetic neuropathies with or without CN involvement can appear late the time of diagnosis either as a dysimmune neuropathy, or due to meningeal/radicular neoplastic

infiltration. This can occur also in the course of acute treatment, but is not likely in remission.

The diagnosis of peripheral nerve lesion is undergoing significant changes.

Classical electrophysiology is supported with imaging techniques as MRI, PET and ultrasound. These techniques allow a better approach to peripheral nerves and combinations with fusion techniques allow precise identification of local lesions.

This development of combining diagnostic tools as electrophysiology and imaging, has proven beneficial in detecting lesions in the neuromuscular system, and is increasingly applied in oncology.

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