Clinical Neurology and Neurosurgery 184 (2019) 105340

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Neuroleukemiosis: Diagnosis and management

Christine Mau[a], Michael G.Z. Ghali[a,b,c,d,e,*], Michael Styler[c,d], Jozef Malysz[e], Charles S. Specht[a,e], Elias Rizk[a]

[a] Department of Neurological Surgery, Penn State Health Milton S. Hershey Medical Center, 500 University Drive Hershey, PA, 17033, United States
[b] Department of General Surgery, Penn State Health Milton S. Hershey Medical Center, 500 University Drive Hershey, PA, 17033, United States
[c] Department of Hematology and Oncology, Philadelphia, PA, 19102, United States
[d] Hahnemann University Hospital, Philadelphia, PA, 19102, United States
[e] Department of Pathology, Penn State Health Milton S. Hershey Medical Center, 500 University Drive Hershey, PA 17033, United States

ARTICLE INFO

Keywords:
Leukemia
Neuroleukemiosis
NLK
Chloroma
Peripheral
Nerve
PNS
Infiltration

ABSTRACT

An exceedingly rare manifestation of leukemia, termed neuroleukemiosis, involves peripheral nerve infiltration by leukemic cells. Patients with neuroleukemiosis typically present with a peripheral neuropathy and/or chloromatous masses. The diagnosis is supported by, and established with, electrophysiologic testing, imaging, histopathology, and immunophenotyping. We present the case of 21 year old male with multiply relapsed M4 type of acute myelogenous leukemia (AML) who presented with extremity pain and was subsequently found to have multiple cervical, thoracic, and lumbosacral nerve root masses. A diagnosis of neuroleukemiosis was established via CT-guided biopsy and immunophenotyping. The patient's neuroleukemiosis responded well to chemotherapy, donor lymphocyte infusions, and spinal irradiation. The literature is reviewed regarding this interesting and rare clinical condition.

1. Introduction

Leukemia has a propensity to infiltrate the leptomeninges, cranial nerves, and nerve roots. Though an exceedingly rare phenomenon, leukemic blasts may also infiltrate peripheral nerves, a process termed neuroleukemiosis (NLK) [5,11–15,19,29]. NLK may occur with or without central nervous system involvement and is generally considered a predictor for systemic relapse and a poor prognostic marker [1,3,5,6,9,13–15,17,20,21,25,26,29,31].

NLK characteristically presents as a peripheral neuropathy, with or without a nerve mass, the former termed myeloid sarcoma or historically as chloroma – used to denote extramedullary leukemic masses in general [7]. Occurring in approximately 1% of cases of leukemia, the presence of myeloid sarcoma (chloroma) portends poor outcome and those involving the peripheral nervous system were rarely reported prior to the advent of treatment [4,8,18,27]. Here, we present a rare case of NLK and discuss the diagnostic and management considerations.

Case Presentation

The patient is a 21 year old male who initially presented when he was 14 years old with several enlarged, painful lymph nodes and scrotal pain. He was diagnosed with M4 Type (myelomonocytic with eosinophilia) acute myeloid leukemia (AML). He underwent chemotherapy and went into remission for one year. He underwent a second course of chemotherapy and an allogeneic bone marrow transplant at age 15 after he was found to have a relapse, presenting with thrombocytopenia. He did well after this second course, but required transfusions to maintain acceptable platelet counts. One year following his relapse he received four donor lymphocyte infusions over the course of 3 months given his favorable chromosomal mutation (inversion 16). However, he did not respond to this and ultimately underwent a course of re-induction chemotherapy at age 16. He responded well to treatment but was found to have graft versus host disease, initially affecting his intestines, skin, and joints but subsequently causing contractures affecting multiple joints from progression of skin involvement. He was treated for this and was eventually maintained on low dose Plaquenil.

He remained in remission for another 4 years, but started to endorse left shoulder pain at age 20. He initially attributed this pain to falling off his motorcycle, but, when it persisted, sought out a chiropractor who referred him for cervical spine magnetic resonance imaging (MRI). He was found to have left C7-T1 foraminal nerve tumor with widening of the neural foramina. The patient underwent a left transforaminal epidural steroid injection which relieved the pain temporarily. However, pain distribution extended to include the left hand and midportion of the neck, with additional new right posterior hamstring

* Corresponding author.
E-mail address: mgzghali@gmail.com (M.G.Z. Ghali).

https://doi.org/10.1016/j.clineuro.2019.04.019
Received 11 August 2018; Received in revised form 29 March 2019; Accepted 16 April 2019
Available online 17 April 2019
0303-8467/

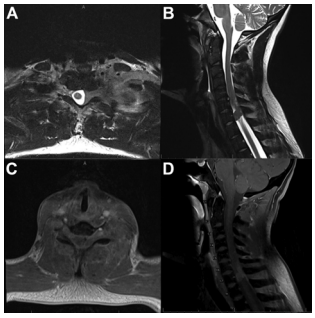

Fig. 1. Cervical neuroleukemiosis. A: Axial T2 weighted MRI demonstrating left C7-T1 foraminal nerve tumor. B: Sagittal T2 weighted MRI demonstrating lower cervical nerve tumor and cervical stenosis. C: Axial T1 weighted MRI showing cervical nerve tumors bilaterally in C5-6 neuroforamen. D: Sagittal T1 contrast enhanced MRI demonstrating contrast enhancing lesion at the C7 level.

region pain worsened with flexion and extension. At this time, the patient underwent cervical, thoracic, and lumbar spine MRI which revealed multiple dumbbell-shaped masses traversing the right C4-5 and C5-6 foramina, the left C6-7, C7-T1, T1-T2, and T2-3 foramina, and right L5-S1 neural foramina (Fig. 1).

The patient underwent computed tomography (CT) guided biopsy of the left C5-6 mass. Fine needle aspiration demonstrated occasional blast-like cells and core biopsy revealed myeloid sarcoma. Myeloid blasts were confirmed by immunophenotyping using flow cytometry. He immediately underwent systemic chemotherapy and reported significant reduction in his pain. On radiographic analysis, his chloromas had significantly decreased by 3 weeks after the initiation of treatment, most markedly in the cervicothoracic region. He subsequently received four donor lymphocyte infusions and underwent radiation to his spine. On the patient's most recent imaging, 9 months following administration of systemic chemotherapy for chloromas, there is minimal enhancement at the right C5-6 and right L5-S1 neural foramina without any tumor recurrence or progression.

2. Discussion

We present a rare case of a 21 year old male with acute myelomonocytic leukemia in remission for 4 years after his last course of chemotherapy. Neuroleukemiosis is exceedingly rare with only a handful of case reports having been previously described [1,3,5,6,9–15,19,20,22,23,25,29–31,33]. This is only the second case reported in a patient with acute myelomonocytic leukemia. In this patient, axial and extremity pain represented the only manifestations of neuroleukemic relapse, whereas the patient's previous and initial relapse was indicated by isolated thrombocytopenia. NLK is thought to arise as a consequence of use of peripheral nerves by leukemic cells as sanctuary sites, due to the blood-nerve barrier, analogous to the blood-brain barrier. Additionally, differential effects of graft-versus-leukemia effect, systemically versus in areas protected by the blood-nerve barrier, may be implicated in the pathogenesis of NLK [3,16]. Although rare, NLK should be considered in a patient with acute leukemia in remission presenting with isolated peripheral neuropathy. Electromyography (EMG), imaging, and the response to treatment help to confirm diagnosis if a biopsy cannot be obtained.

3. Clinical features

NLK may occur in the setting of acute lymphocytic leukemia or acute myelogenous leukemia and is often diagnosed during remission [1,6,10,12,30,31]. NLK may occur following a previous systemic or solid organ relapse and may predict concurrent or subsequent systemic relapse [6,9,14]. Alternatively, treatment of NLK may be followed by many years of sustained remission [30].

NLK presents as a peripheral neuropathy and/or a subcutaneous mass/chloroma [1,3,5,6,9,11–15,19,20,22,25,29–31,33]. Reported deficits have included those characteristic for peripheral neuropathies, including weakness, paresthesias, numbness, and pain [1,3,5,6,9,12–15,19,20,22,29–31,33]. Cases of NLK have been reported involving the axillary, peroneal, ulnar, median, radial, and sciatic nerves, as well as brachial and lumbar plexi [1,3,5,6,9,12–15,19,20,22,25,29–31,33]. Cases describing multiple nerve involvement and multiple recurrences have also been reported [1,3,5,6,12,15,19,29].

The differential diagnosis for a patient suspected to have NLK includes, but is not limited to, vasculitic neuropathy, chemotherapeutic neurotoxicity, and Guillain-Barre syndrome [6,24] Vasculitic neuropathy presents as asymmetric polyneuropathy or mononeuritis multiplex, in contrast to NLK, which typically manifests as mononeuropathy [24]. Moreover, vasculitic neuropathy has a more acute to subacute presentation, in contrast to NLK, which may be slowly progressive over several months. Guillain Barre syndrome (GBS) is distinguished from NLK clinically by diffuse and symmetric involvement, an acute/subacute presentation, and absence of a mass.

Unusual presentations of neuroleukemiosis may result in diagnostic delay [12,31]. For instance, abscess may be a confounding diagnosis as NLK has occasionally presented with concurrent signs and symptoms of acute inflammation and this population of patients is frequently neutropenic [31]. Disseminated NLK may also masquerade as high cervical cord pathology, presenting in one 66 year old gentleman with AML as acute quadriplegia, dysautonomia, and respiratory insufficiency; autopsy confirmed disseminated blast infiltration of peripheral nerves without leptomeningeal dissemination [12]. Appropriate clinical judgment and adjunct testing aid in distinguishing amongst these alternate diagnoses.

4. Diagnosis

Early diagnosis of neuroleukemiosis is critical in optimizing patient response to treatment and requires a high index of suspicion. Upon suspecting NLK, it is first necessary to establish the diagnosis with biopsy and/or imaging. Second, it is requisite to identify concurrent or subsequent systemic relapse, as this changes both management and prognosis [9].

EMG may be useful in confirming the presence of a peripheral neuropathy and distinguishing axonal (consistent with NLK) from demyelinating neuropathy (consistent with GBS) [1,30]. The role of imaging is principally to identify and localize NLK, when a myeloid sarcoma (chloroma) or gross invasion is present. MRI has been used successfully in the diagnosis and subsequent follow-up of NLK [1,9,14,20,30]. When a mass is present, it characteristically enhances and is T1 isointense and FLAIR/T2 hyperintense [1,30]. In one small series, 80% of patients with NLK had an MRI-identifiable mass [20]. Gallium scanning and FDG-PET are alternative modalities, the latter demonstrating hypermetabolism of leukemic blasts [1,23].

Nerve biopsy remains the gold standard for diagnosis of NLK, but should not be performed if neurologic deficit from the procedure is anticipated. Biopsy of NLK reveals monoblastic nerve infiltration, as well as involvement of the surrounding muscle on occasion [30]. Immunophenotyping can be used to more confidently support the diagnosis [32]. In cases where biopsy is deemed not feasible, the clinical features along with imaging findings and response to treatment strongly supports, if not confirms, a diagnosis of NLK. Biopsy, while specific, may yield false negatives, missing the diagnosis in cases with patchy or proximal nerve involvement and those lacking a mass consistent with myeloid sarcoma (chloroma) [2,20,28]. For example, Reddy and colleagues (2012) identified leukemic infiltration in only 2 of 3 likely cases of NLK using biopsy and van den Bent and colleagues (1999) report on two patients with neurolymphomatosis and negative biopsies, despite clinical and electrophysiologic evidence of neuropathy [20,28].

5. Management

Patients found to have concurrent systemic relapse may undergo conventional or myeloablative chemotherapy with rescue allogenic bone marrow transplantation. In the absence of systemic relapse, NLK typically responds to local fractionated radiation therapy without or with systemic chemotherapy. [1,3,14,20,31] Among five patients with NLK presenting with a mass, four responded readily to combined chemotherapy and radiation [20]. Either surgical resection or radiation treatment may be used in rare cases where urgent decompression proves necessary [31].

When selecting a chemotherapeutic regimen, it is necessary to select agents which penetrate the blood-nerve barrier. There has been some success in treating NLK with use of cytarabine, fludarabine, methotrexate, etoposide, mitoxantrone, and hyperfractionated cyclophosphamide. [1,3] Good response to radiation therapy alone has been described in several cases [3,14,30]. Bakst and colleagues (2011) describe the case of a 21 year old female with AML in remission following allogenic bone marrow transplant, who developed multiple (> 5) brachial plexus, lumbar plexus and peripheral nerve leukemic infiltrates treated with fractionated radiation (1375–3000 cGy in 11–15 fractions for each lesion; the first lesion was also treated with etoposide/mitoxantrone), with clinical and radiographic resolution. She was able to resume triathlon competitions. Most of the lesions were treated with 2400 cGy in 12 fractions and successfully effected resolution of symptoms and mass effect, in contrast to the previously common practice of using 3000 cGy in the treatment of myeloid sarcoma (chloroma) [27]. Surgical resection alone of a distal sciatic myeloid sarcoma (chloroma) proved ineffective in relieving symptoms in a 9 year old male with AML [25].

6. Conclusion

Isolated peripheral nerve involvement as the first sign of relapse from leukemia is exceedingly rare. It can lead to a delay in diagnosis given its unusual presentation and rarity. Here, we present a case of neuroleukemiosis involving several nerve roots in the cervical, thoracic and lumbar spine which was diagnosed by CT-guided biopsy and confirmed with immunophenotyping. To our knowledge, this is only the second case of neuroleukemiosis described in the literature in a patient with M4 subtype acute myelomonocytic leukemia. He showed clinical and radiographic improvement within one month of reinitiating systemic chemotherapy and continues to do well after subsequent donor lymphocyte infusions and radiation therapy to the spine. The rapid response to treatment once initiated makes early diagnosis critical in order to avoid permanent numbness or paralysis of the involved nerve.

Funding

None.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Acknowledgments

None.

References

[1] D.G. Aregawi, et al., Neuroleukemiosis: case report of leukemic nerve infiltration in acute lymphoblastic leukemia, Muscle Nerve 38 (3) (2008) 1196–1200.
[2] J.M. Baehring, et al., Neurolymphomatosis, Neuro Oncol. 5 (2) (2003) 104–115.
[3] R. Bakst, A. Jakubowski, J. Yahalom, Recurrent neurotropic chloroma: report of a case and review of the literature, Adv. Hematol. 2011 (2011) 854240.
[4] A.N. Bekassy, et al., Granulocytic sarcoma after allogeneic bone marrow transplantation: a retrospective European multicenter survey. Acute and Chronic Leukemia working Parties of the European Group for Blood and Marrow Transplantation, Bone Marrow Transplant. 17 (5) (1996) 801–808.
[5] R. Billstrom, A. Lundquist, Acute myelomonocytic leukaemia with infiltrative peripheral neuropathy, J. Intern. Med. 232 (2) (1992) 193–194.
[6] J.M. Boiron, et al., Isolated peripheral nerve relapse masquerading as Guillain-Barre syndrome in a patient with acute lymphoblastic leukemia, Leuk. Lymphoma 10 (6) (1993) 489–491.
[7] A. Burns, G.S. Pattison, Observations on the Surgical Anatomy of the Head and Neck : Illustrated by Cases and Engravings, 1st american ed., (1823) Baltimore: F. Lucas … [et al.]. 512 p., 10 leaves of plates.
[8] R.A. Henson, H. Urich, Cancer and the Nervous System: the Neurological Manifestations of Systemic Malignant Disease, Blackwell Mosby Book Distributors, Oxford; Boston, 1982, p. 657 ix.
[9] J.H. Hsu, et al., A rare case of peripheral neuropathy from relapse of acute lymphoblastic leukemia to the brachial plexus, J. Pediatr. Hematol. Oncol. 34 (2) (2012) e77–9.
[10] C. Karam, A. Khorsandi, D.J. MacGowan, Clinical reasoning: a 23-year-old woman with paresthesias and weakness, Neurology 72 (2) (2009) e5–10.
[11] S. Kesari, et al., Recurrent acute promyelocytic leukemia presenting as a sacral nerve root mass, J. Clin. Oncol. 26 (19) (2008) 3279–3281.
[12] D.A. Krendel, R.E. Albright, D.G. Graham, Infiltrative polyneuropathy due to acute monoblastic leukemia in hematologic remission, Neurology 37 (3) (1987) 474–477.
[13] A. Lekos, et al., Mononeuritis multiplex. A harbinger of acute leukemia in relapse, Arch. Neurol. 51 (6) (1994) 618–622.
[14] H.C. Liu, et al., Acute sciatica: an unusual presentation of extramedullary relapse of acute lymphoblastic leukemia, Int. J. Hematol. 86 (2) (2007) 163–165.
[15] Y. Nishi, et al., Polyneuropathy in acute megakaryoblastic leukemia, Cancer 68 (9) (1991) 2033–2036.
[16] Y. Olsson, Studies on vascular permeability in peripheral nerves. IV. Distribution of intravenously injected protein tracers in the peripheral nervous system of various species, Acta Neuropathol. 17 (2) (1971) 114–126.
[17] A. Paterson, et al., Granulocytic sarcoma (chloroma) presenting as a dumbbell tumor, Pediatr. Radiol. 32 (5) (2002) 391–392.
[18] S. Paydas, S. Zorludemir, M. Ergin, Granulocytic sarcoma: 32 cases and review of the literature, Leuk. Lymphoma 47 (12) (2006) 2527–2541.
[19] M. Platten, et al., Painful neuropathy due to intraneural leukemic spread in a patient with acute myeloid leukemia, Neurology 69 (7) (2007) 707.
[20] C.G. Reddy, et al., Neuroleukemiosis: an unusual cause of peripheral neuropathy, Leuk. Lymphoma 53 (12) (2012) 2405–2411.
[21] D. Roig-Vilaseca, et al., L5 sciatica as first symptom of a granulocytic sarcoma, Acta Oncol. 33 (1) (1994) 83–84.
[22] C.G. Romo, P. Jain, J.E. Cortes, Numb chin syndrome by precursor B acute lymphoblastic leukemia, Am. J. Hematol. 89 (8) (2014) 860–861.
[23] A. Sabate-Llobera, et al., Diagnosing neuroleukemiosis: is there a role for 18F-FDG-PET/CT? Rev. Esp. Med. Nucl. Imagen Mol. (2017).
[24] G.A. Schaublin, et al., An update on the classification and treatment of vasculitic neuropathy, Lancet Neurol. 4 (12) (2005) 853–865.
[25] M.J. Stillman, et al., Leukemic relapse presenting as sciatic nerve involvement by chloroma (granulocytic sarcoma), Cancer 62 (9) (1988) 2047–2050.
[26] J.A. Sweet, et al., Relapsed acute myelogenous leukemia of brachial plexus after marrow transplant, Muscle Nerve 45 (3) (2012) 440–444.
[27] A. Szomor, et al., Myeloid leukemia and myelodysplastic syndrome relapsing as granulocytic sarcoma (chloroma) after allogeneic bone marrow transplantation, Ann. Hematol. 75 (5-6) (1997) 239–241.
[28] M.J. van den Bent, et al., Negative sural nerve biopsy in neurolymphomatosis, J. Neurol. 246 (12) (1999) 1159–1163.
[29] A. Vital, et al., Malignant infiltration of peripheral nerves in the course of acute myelomonoblastic leukaemia: neuropathological study of two cases, Neuropathol. Appl. Neurobiol. 19 (2) (1993) 159–163.
[30] T. Wang, et al., Isolated leukemic infiltration of peripheral nervous system, Muscle Nerve 51 (2) (2015) 290–293.
[31] B. Warme, et al., Chloroma of the forearm: a case report of leukemia recurrence presenting with compression neuropathy and tenosynovitis, Iowa Orthop. J. 29 (2009) 114–116.
[32] C.S. Wilson, L.J. Medeiros, Extramedullary manifestations of myeloid neoplasms, Am. J. Clin. Pathol. 144 (2) (2015) 219–239.
[33] X. Zhu, Wan K.S, Liu Y. L, Y. Wu, Isolated peripheral neuropathy as an unusual presentation for an extramedullary relapse of acute leukemia, Neuro Asia 19 (2) (2014) 4.