Clinical Reasoning:

A 23-year-old woman with paresthesias and weakness

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SECTION 1

A 23-year-old woman presented with a 6-month history of progressive left hand weakness associated with left ulnar distribution numbness and paresthesias. At the onset of these symptoms, she recalled shooting pain up and down the medial left forearm. She denied any neck pain.

The patient had been diagnosed with acute myeloid leukemia (AML) type 5a and appendicitis 9 months previously. At that time lumbar puncture and brain and spine MRI were negative for CNS involvement. A right Hickman catheter was placed. She was treated with cytarabine and idarubicin and was thought to be in complete remission after re-

peated bone marrow biopsies showed no blasts. No intrathecal chemotherapy was given. The appendicitis was treated for 1 month with moxifloxacin prior to an elective appendectomy.

Bone marrow examination and peripheral blood smear were normal at the time of neurologic presentation.

Questions for consideration:

1. Where can the lesion be localized and what could be its nature in the context of this patient's history?
2. How could the differential diagnosis be narrowed further?

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SECTION 2

The evaluation of a patient with hand weakness, numbness, and paraesthesias would start with localizing the lesion. A lesion in the CNS, involving the contralateral precentral gyrus and anterior aspect of the postcentral gyrus,¹ is highly unlikely, especially with the shooting pain up and down the medial left forearm.

In the peripheral nervous system, radiculopathy, plexopathy, or a nerve lesion could be responsible for combined motor and sensory impairment in the hand. Minor repetitive trauma can cause nerve damage, resulting in carpal tunnel syndrome or ulnar neuropathy at the elbow. The radial, ulnar, or median nerve could have been damaged during the patient's recent surgery. Other causes of isolated neuropathy in this patient include a mononeuritis multiplex caused by blast cell infiltration of the left ulnar nerve. The brachial plexus may also be compressed or infiltrated by an extramedullary myeloid tumor (EMT) in the setting of leukemia. Neurotoxicity secondary to the chemotherapy is more likely to be bilateral, symmetric, and ascending.

In this patient, the neurologic examination showed 4/5 strength of the left interossei, flexor carpi ulnaris, ulnar flexor digitorum profundus, and adductor pollicis. There was no other weakness. There was reduced pin sensation in the medial aspect of the 4th digit, entire 5th digit, hypothenar eminence, and medial one third of the dorsal hand. Tinel sign was positive in the left ulnar cubital tunnel. Sensation of the left medial forearm was intact. Tone, reflexes, vibration, coordination, and gait were normal. There was no Horner syndrome.

The neurologic examination indicates that the lesion is localized to the peripheral nervous system. The symptoms can be explained by left ulnar neuropathy, left C8 radiculopathy, or a lower trunk/medial cord plexopathy. The absence of neck pain argues against a nerve root lesion.

Questions for consideration:

1. What are the clinical findings in an ulnar neuropathy and a lower trunk/medial cord plexopathy?
2. What is the role of an EMG/NCS study?

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SECTION 3

Patients with ulnar neuropathy usually present with numbness and paresthesias involving the 5th finger and the ulnar half of the 4th digit. Some patients may notice a dull ache down the ulnar border of the forearm. The symptoms can be elicited by having the patient flex the elbow or by tapping over the ulnar nerve at the cubital tunnel (Tinel sign). C8 radiculopathy causes pain and numbness of the 4th and 5th digits. T1 root pain causes pain in the shoulder joint radiating down the medial side of the upper arm and forearm with numbness of the medial arm and forearm. Atrophy and weakness reflect motor axon or anterior horn cell loss. A proximal ulnar neuropathy at the elbow (UNE) results in weakness in the interosseous muscles, adductor pollicis, and long flexors of the 4th and 5th digits. Usually it spares the flexor carpi ulnaris (FCU).² A T1 root lesion will preferentially involve the abductor pollicis brevis (APB) and opponens. A C8 root lesion will cause weakness in the flexor carpi ulnaris, deep finger flexors, flexor pollicis longus, interossei, adductor pollicis, and extensor indicis proprius muscles. Medial cord brachial plexopathy would result in weakness of the muscles innervated by the ulnar nerve in addition to the median-innervated intrinsic hand muscles, i.e., opponens and APB. Thus in order to differentiate UNE from C8/T1 radiculopathy and lower trunk/medial cord brachial plexopathy, one would search for sensory loss extending into the medial forearm

and assess for weakness of C8/T1 non-ulnar innervated muscles such as flexor pollicis longus, extensor indicis proprius, opponens and abductor pollicis brevis.

This patient had sensory symptoms of an ulnar neuropathy at the elbow, with a positive Tinel sign, which is suggestive of UNE. However, the shooting pain up and down her medial forearm is atypical. This distribution of pain fits a C8 and T1 radiculopathy or a lower trunk/medial cord plexopathy. The motor findings suggest an ulnar pattern of weakness, although FCU weakness is atypical.

EMG/NCS studies could help determine the affected muscles and sensory nerve deficits, thus indicating if her symptoms are secondary to UNE secondary to minor elbow trauma or positioning at the time of her surgery vs a lower trunk/medial cord brachial plexopathy. In 1999, the American Association of Electrodiagnostic Medicine (AAEM) issued a Practice Parameter for Electrodiagnostic Studies in Ulnar Neuropathy at the Elbow. The strongest evidence of ulnar neuropathy at the elbow includes an absolute motor nerve conduction velocity (NCV) from above elbow (AE) to below elbow (BE) of less than 50 m/s and an AE-to-BE segment greater than 10 m/s slower than BE-to-wrist (W) segment. Other findings include a decrease in compound muscle action potential (CMAP) negative peak amplitude from BE to AE greater than 20% suggesting a conduction block or temporal dispersion indicative of focal demyelination and a significant change in CMAP configuration at the AE site compared to the BE site. Ulnar sensory responses should be recorded from the fifth fingers and dorsal ulnar palm.

In this patient, the left ulnar distal motor response latency was prolonged. There was diffuse left ulnar forearm and across elbow slowing with reduced left ulnar motor response amplitudes. The ulnar F-waves done with supramaximal stimulation at the wrist were prolonged. There was no conduction block, focal area of slowing, or temporal dispersion. The left ulnar and dorsal digital ulnar cutaneous sensory response amplitudes were very reduced. The bilateral medial cutaneous nerve of forearm sensory responses were normal. Median motor and sensory conduction studies and F-waves were normal.

Needle EMG of muscles in the left upper extremity showed spontaneous fibrillations and positive sharp waves with reduced recruitment of prolonged and polyphasic motor units in all left ulnar innervated muscles including the FCU. All other muscles were normal, including APB, flexor pollicis longus, and extensor indicis proprius (table).

The findings are consistent with subacute, proximal, and axonal left ulnar neuropathy. The pro-

Table Motor and nerve conduction studies of the ulnar nerve			
	Latency, ms	Amplitude, mV	Conduction velocity, m/s
Motor nerve conduction studies			
L ulnar/ADM			
Wrist	4.55	3.8	
Below the elbow	9.3	3.2	42.1
Above the elbow	11.7	1	41.7
L ulnar/FDI			
Wrist	4.4	4.2	
Below the elbow	8.85	2.7	44.9
Above the elbow	11.95	2.1	32.3
Sensory nerve conduction studies			
R ulnar-V-antidromic	2.7	70.3	50
L ulnar-V-antidromic	4.45	4.9	27
R ulnar-dorsal-antidromic	1.45	14.4	55.2
L ulnar-dorsal-antidromic	2.3	3.7	37

The moderately prolonged left distal ulnar motor response latency and conduction velocity slowing in the forearm and across the elbow reflects a loss of left ulnar large fiber axons. There is no evidence of selective slowing in the left ulnar nerve across the elbow. These findings were felt to be consistent with a proximal, axonal left ulnar neuropathy rather than a lower trunk plexopathy since the medial antebrachial cutaneous sensory, median motor conduction studies, and needle EMG of the abductor pollicis brevis were normal.

longed ulnar F-waves were thought to be due to large fiber axon loss in the ulnar nerve.

The normal left medial antebrachial cutaneous sensory response and needle EMG of the abductor pollicis brevis favors isolated ulnar neuropathy. However, the involvement of the flexor carpi ulnaris (FCU) fibers is unusual in UNE.

The patient had a left ulnar nerve transposition procedure but postoperatively developed worsening of the left hand weakness with new right toe extension weakness and right dorsal foot numbness. Her neurologic examination showed weakness in the following muscles on the left: APB and opponens 4/5, wrist and finger extensors 4+/5, FCU 4/5, FDP

IV/V 4/5, interossei and adductor pollicis 2/5; and on the right: extensor hallucis longus (EHL) 2/5 and extensor digitorum brevis (EDB) 4/5. All other muscles were normal. Pin sensation was reduced in the left hypothenar eminence, 5th and medial 4th digits, and medial forearm. Vibration and proprioception were normal. Reflexes were intact apart from trace right and absent left ankle jerks. Plantar responses were flexor.

Questions for consideration:

1. What is the next step in assessing the plexopathy and why is there progression of the patient's symptoms with multifocal weakness?
2. What is the best approach and management?

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Figure 1 Coronal spin echo T1 and postcontrast FMSPGRs demonstrate a bulky, enhancing lesion involving the divisions of the left brachial plexus surrounding the distal left subclavian and axillary arteries (arrows)

Figure 2 Postgadolinium fat suppressed T1-weighted image enhancement of the right lumbosacral trunk (arrows)

SECTION 4

Subsequent EMG/NCS showed evolution consistent with lower trunk brachial plexopathy evidenced by new absence of the left medial cutaneous nerve of forearm sensory response denervation in the extensor indicis proprius, flexor pollicis longus, and abductor pollicis brevis. The right lower extremity showed absent right and reduced left superficial peroneal sensory responses, absent right and prolonged left H-reflexes, and denervation activity in the right more than left EHL and EDB.

MRI is the best neuroimaging technique for the assessment of plexopathies. MRI demonstrated bilateral brachial and lumbosacral plexus thickening and enhancement consistent with chloromas, worst in the left brachial plexus (figures 1 and 2). MRI with and without gadolinium of the brain and entire spine were negative. The peripheral blood smear now showed AML relapse. A second lumbar puncture was negative, with no leukemic cells in the CSF after cytocentrifugation, flow cytometry, and immunocytochemistry.

The patient was treated with reinduction and consolidation therapy. Total body irradiation with a boost to the left brachial plexus provided marked improvement in her symptoms, with complete resolution of the chloromas on imaging. She underwent allogeneic bone marrow transplantation that was complicated by graft vs host disease. One year later the patient was found to have imaging recurrence of the left brachial plexus chloroma without clinical worsening. This resolved completely following repeated local irradiation. She is now believed to be in complete remission.

DISCUSSION In this patient the initial EMG and NCS study showed normal left medial antebrachial cutaneous sensory response and needle EMG of the left abductor pollicis brevis. This led to the diagnosis of UNE.

Plexopathies may initially present with selective fascicular involvement or sparing that may lead to a misdiagnosis of a peripheral nerve lesion, such as ulnar neuropathy as in this case. The FCU weakness with radiating pain up and down the medial arm and forearm was a clue to plexopathy in this case since the FCU is usually spared in UNE. The false reassurance provided by evidence of hematologic remission at neurologic presentation also led to missed consideration of the diagnosis of plexopathy. The explanation for the apparent ulnar neuropathy in this case of lower trunk brachial plexopathy resides in the nature of the plexus lesion. Extramedullary myeloid tumors (EMT) are depositions of blasts outside the blood vessels. They can compress or infiltrate surrounding tissue as in the lower brachial plexus in this patient's case, resulting in progressive symptoms as different fascicles are compressed and infiltrated earlier than others.

Peripheral nervous system involvement in acute myeloid leukemia has different manifestations. Most commonly, leptomeningeal metastasis with nerve root involvement results in radiculopathy.³ Plexus compression by EMT is rare⁴ as is infiltration of peripheral nerves resulting in mononeuritis multiplex.⁵ Gadolinium enhanced MRI of the spine is useful for showing radicular infiltrations, while mononeuritis can be diagnosed by biopsy of the involved nerve. Chloromas, more correctly called EMT, were first

described by Burns in 1811. They occur most frequently in AML type M2, M4, and M5, the latter being the type in our case.⁶ Although these tumors commonly have an indolent course, they can present as true neurologic emergencies. Controversies exist regarding whether EMT affect the prognosis of AML.⁷ The diagnosis can be suspected clinically if the lesion is superficial as in a cutaneous chloroma or orbital myeloblastoma. EMT can be seen on CT and MRI.⁸ These tumors usually respond rapidly to irradiation. However, they often recur. Other treatment options include surgical decompression, IV chemotherapy, or any combination of these treatments. There are no studies showing superiority of any treatment modality.

The blood–nerve barrier shares some similarities with the blood–brain barrier.⁹ It has a protective role toward the endoneurium, isolating it from the extracellular fluid, making metastases to peripheral nerves a rare incident.¹⁰ At the same time, malignant cells that have succeeded in infiltrating this barrier would be protected from systemic chemotherapy. Malignant cells can then nest in the peripheral nervous system and relapse after treatment of the primary tumor, often preceding hematologic relapse.⁵ In summary, chloromatous infiltration of plexi and nerves should be considered in patients with AML who have neurologic symptoms, even in the presence of hematologic remission.

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