Pearls & Oy-sters: Case of Atypical Peripheral Nerve Findings Following Paclitaxel for Breast Cancer

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Abstract

Neuromuscular ultrasound (NMUS) is a valuable tool in establishing a diagnosis of carpal tunnel syndrome (CTS) and can be particularly helpful in patients with clinical CTS but normal nerve conduction studies (NCSs). This case involves the uncommon presentation of enlarged median nerves on NMUS with normal NCS in a patient with breast cancer who developed chemotherapy-induced peripheral neuropathy and CTS after taxane treatment. This case demonstrates that CTS should not be excluded based on electrodiagnostic studies alone, and comorbid CTS should be considered in patients receiving neurotoxic chemotherapy, even in the setting of normal NCS.

Pearls

- Nerve conduction studies (NCSs) may be normal in some cases of carpal tunnel syndrome (CTS), although this is not common.
- CTS can be confirmed in patients with enlarged median nerves at the wrist on neuromuscular ultrasound (NMUS).
- Comorbid CTS should be considered in patients receiving neurotoxic chemotherapy when symptoms do not fit chemotherapy-induced peripheral neuropathy (CIPN).
- CTS can be associated with chemotherapy, and this combination may be more common than the literature suggests.

Oy-sters

- A diagnosis of CTS should not be excluded based on NCS alone; NMUS may be a valuable additive tool in establishing the diagnosis.

Case

A 39-year-old woman was referred for evaluation of numbness and tingling in the bilateral hands. She had a history of chemotherapy-related paresthesia after receiving dose-dense doxorubicin and cyclophosphamide and taxol (paclitaxel) to treat stage IIB, BRCA2 positive, triple-negative breast cancer. She initially received 4 weekly doses of taxol but transitioned to every 3-week Abraxane (paclitaxel) because of development of presumed neuropathy in the bilateral feet. She completed 7 cycles of Abraxane with continued symptoms in her feet and minimal new paresthesias in her hands.

Approximately a year after her initial symptoms, she reported worsening of the pain, numbness, and tingling in her bilateral hands. Her symptoms were consistent with Common Terminology Criteria for Adverse Events Grade 2 peripheral sensory neuropathy and were symmetric and in the median nerve distribution. On physical examination, the patient had normal strength in both upper extremities. She had decreased sensation to light touch bilaterally in the first 3 digits. She had a positive Tinel sign at her left wrist and 1+ reflexes in both upper extremities.

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The patient had a normal hemoglobin A1c, vitamin B12, folate, thyroid stimulating hormone, free thyroxine, and rapid plasma reagin. NCS of the right median and ulnar nerves, at skin temperature of 32°C, revealed normal amplitudes and velocities in the motor and sensory divisions (Table 1). Upper limb EMG was not included in her diagnostic workup because her presentation did not involve proximal upper limb or neck symptoms, and bilateral cervical radiculopathy was believed to be an unlikely cause of her symptoms. Transcarpal mixed studies were performed to evaluate for CTS and were normal bilaterally. However, NMUS revealed moderate bilateral enlargement of median nerve cross-sectional areas at the wrists and palms compared with the forearms (Table 2). Both nerves were hypoechoic, had slightly reduced mobility, and had normal vascularity. She declined interventional treatments and had some benefit from wrist splints and anti-inflammatory medications.

Discussion

CTS occurs secondary to a mononeuropathy of the median nerve at the wrist.[1,2] CTS should be considered in patients reporting pain, paresthesia, or weakness in the median nerve distribution. Diagnosis of CTS is important for making informed treatment decisions because various treatments may offer symptom relief, including wrist braces, steroid injections, and surgical carpal tunnel release.[3] CTS is likely underreported after chemotherapy, leading to worsened disability, lost productivity, and increased health care costs.[1,2]

CIPN is a common complication of treatment with taxanes and other neurotoxic chemotherapy. CIPN can result in dose reductions, delays in treatment, reduced cancer survival, and functional disabilities.[4,5] CIPN symptoms frequently start within months of initiating therapy and often persist for years after treatment.[5] Taxanes cause sensory-predominant neuropathy that presents with paresthesias, numbness, or pain in the distal extremities. CTS has been documented with CIPN but is not a commonly described finding.[6]

Electrodiagnostic testing, including NCSs, may be used to complement history and physical examination in evaluating patients with symptoms of CTS or CIPN.[4,5] NCS may also be used to assess severity and determine prognosis of a mononeuropathy. In CTS, expected NCS findings include decreased nerve conduction velocity across the carpal tunnel.[3] The slowed conduction is reflective of damage to the myelin sheath from nerve compression in the carpal tunnel. In taxane CIPN, NCS often shows a reduction in amplitudes, consistent with an axonal process.[7] Median nerve conduction velocities may also be slow across the carpal tunnel in CIPN, suggesting median mononeuropathies may be caused or worsened by taxane exposure.[7] In this case, the patient's median and ulnar nerves did not display electrodiagnostic evidence of CIPN, suggesting her CIPN symptoms were from small fiber involvement.

A small population of patients with clinical CTS symptoms will show normal NCS, as seen in this case.[1,2] In these patients, NMUS is a cost-effective and noninvasive option to assess for anatomic abnormalities in the median nerve and

Table 1 Motor, Sensory, and Transcarpal Mixed Nerve Conduction Studies

Study	Nerve	Site	Muscle	Latency, msec	Amplitude, μV	Velocity, m/s
Motor	R Median	Wrist	APB	2.9 (<4.4)	13 (>5.9)	—
		Elbow	APB	6.3 (<4.4)	13 (>5.9)	54 (>53)
	R Ulnar	Wrist	ADM	2.5 (<3.7)	12.1 (>7.9)	—
		B. Elbow	ADM	5.3 (<3.7)	12.2 (>7.9)	62 (>52)
		A. Elbow	ADM	7.0 (<3.7)	11.5 (>7.9)	58 (>52)
Study	**Nerve**	**Site**	**Rec. site**	**Peak latency, msec**	**Amplitude, μV**	**Velocity, m/s**
Sensory	R Median	Wrist	Digit II	3.3 (<3.3)	45 (>17)	56 (>42)
	R Ulnar	Wrist	Digit V	3.3 (<3.1)	38 (>14)	58 (>45)
Study	**Nerve**	**Site**	**Rec. site**	**Peak latency, msec**		
Transcarpal mixed	R Median	Palm	Wrist	2.2		
	R Ulnar	Palm	Wrist	2.0		
	L Median	Palm	Wrist	2.1		
	L Ulnar	Palm	Wrist	2.1		

Abbreviations: ADM = abductor digiti minimi; APB = abductor pollicis brevis.
Findings are expressed as "result (reference value)." The reference values are from the Wake Forest Diagnostic Neurology Laboratory. For the Transcarpal Mixed studies, the normal peak latency difference is <0.4 milliseconds for both the median and ulnar palms.

Table 2 NMUS Findings of the Bilateral Median Nerve

Nerve	Location	Area	Mobility	Echogenicity	Vascularity
R. Median	Palm	17 mm^2			
	Distal wrist crease	13 mm^2	Slightly reduced	Hypoechoic	Normal
	Forearm	5 mm^2			
	Wrist-to-forearm ratio	2.6			
L. Median	Palm	11 mm^2			
	Distal wrist crease	11 mm^2	Slightly reduced	Hypoechoic	Normal
	Forearm	7 mm^2			
	Wrist-to-forearm ratio	1.6			

Abbreviation: NMUS = neuromuscular ultrasound.
Normal NMUS values include median nerve cross-sectional area at the palm of <13.0 mm^2, at the wrist of <13.0 mm^2, at the forearm of <10.7 mm^2, and wrist-to-forearm ratio of <1.5. These reference values are from the Wake Forest Diagnostic Neurology Laboratory.

surrounding structures.[1,2] NMUS should be considered in all patients with clinical CTS but normal or atypical NCS findings or when patients may have an underlying neuropathy such as CIPN, with potential superimposed CTS.[8]

In patients with CTS, NMUS evaluation should include measurement of the median nerve cross-sectional area at the site of maximal nerve enlargement within the carpal tunnel.[8] The sensitivity of median nerve cross-sectional area for the diagnosis of CTS ranges from 65% to 97% and specificity from 72.7% to 98%.[9] In addition, the wrist-to-forearm ratio should be used to demonstrate enlargement of the nerve focally at the wrist.[8] In CTS, NMUS of the median nerve may have a normal area at noncompressive sites, and this finding has been reported in CIPN as well.[4] There is limited literature on NMUS in patients with CIPN, and median nerve enlargement may be more common in CIPN than expected.

Other uses of NMUS include assessing for complete transection of the transverse carpal ligament in failed carpal tunnel release surgery and evaluating for focal enlargement suggestive of superimposed mononeuropathies in individuals with severe polyneuropathy. While user dependence influences the accuracy and reproducibility of NMUS and variability exists across devices, scanning protocols, and reference ranges, these limitations are not unique to NMUS and must be considered with electrodiagnostic techniques as well.[9]

Nerve enlargement in the setting of normal NCS is not commonly reported with typical idiopathic CTS or CIPN. However, this combination of findings may be more common than the sparse literature would suggest because NMUS is not frequently used to assess the median nerves in CIPN. While CTS is common, the pathophysiology is not completely understood. In particular, the sequence of changes, including nerve enlargement, nerve echogenicity and vascularity changes, and nerve conduction slowing, is not known. This case suggests that perhaps nerve enlargement occurs before changes in NCS, and this finding may be exacerbated by chemotherapy or unique to CTS associated with chemotherapy. Therefore, CTS cannot be excluded in patients with clinical symptoms and normal NCS, and the combination of findings from NCS and NMUS may be more informative than either modality alone.[8]

CTS treatment in a patient with nerve enlargement on NMUS and normal NCS should be the same as in other settings. Treatment may begin with wrist splinting in patients with mild symptoms and may progress to oral anti-inflammatories, steroid injection into the carpal tunnel, or surgical carpal tunnel release. In severe cases of CTS, initial treatment may be steroid injection or surgical release. Using NMUS to clarify the diagnosis of CTS is important for guiding treatment because worsening symptoms could indicate the need for injections or surgery. The choice of treatment should be a shared decision-making process between the patient and the treating physician.

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