deletion of αCGRP partially, but not completely, inhibited thermal hyperalgesia, suggesting the contribution of other molecules to thermal hyperalgesia after CFA injection.

Because deletion of the TRPV1 gene completely abolished CFA-induced thermal hyperalgesia,[35] it is proposed that TRPV1 is primarily activated in the inflamed area, and then excitatory amino acids and CGRP are released from TRPV1-positive primary afferents in the spinal cord, resulting in thermal hyperalgesia. However, CFA-induced guarding behavior is not inhibited by a selective TRPV1 antagonist[36] although desensitization of TRPV1-positive afferents by resiniferatoxin completely inhibits CFA-induced guarding behavior. These findings suggest that CFA-induced spontaneous pain depends on TRPV1-positive fibers but not on TRPV1 itself, whereas it is unknown what receptors or channels expressed in TRPV1-positive afferents are responsible for such spontaneous pain. Spinal release of CGRP after activation of TRPV1-positive afferents would be one of the mechanisms underlying CFA-induced spontaneous pain and thermal hyperalgesia.

Our results finally indicate that, although inflammatory pain and postoperative pain share common behavioral phenotypes, the mechanisms of inflammatory pain differ in the involvement of αCGRP from those of postoperative pain. Previous studies have shown different pharmacological responses between the two types of pain.[28,37] Thus, even if the phenotypes of pain-related behavior are the same, the effects of drugs depend on the etiology of pain.

Study Limitations

A previous study showed that the expression level of βCGRP in DRG neurons is much lower than that of αCGRP.[2] In addition, because CGRP immunoreactivity in the SDH of αCGRP knockout mice was below the detection level and was not changed at 24 h after incision and CFA injection in the current study, it is likely that βCGRP played little role in CFA- and incision-induced pain in the spinal cord. However, we could not completely exclude the effects of βCGRP in our results.

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Competing Interests

The authors declare no competing interests.

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特集「CRPS診療の現況と進歩」－5

複合性局所疼痛症候群に対するインターベンション治療*

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要旨　複合性局所疼痛症候群（complex regional pain syndrome：CRPS）は、四肢の痛みに加えて、感覚異常、血管運動異常、発汗障害、萎縮性変化を伴い、重篤な場合には運動機能障害に至ることもある。CRPSの病態は複合的であり、薬物療法やリハビリテーションだけでは、痛みを緩和できないことが多い。

CRPSに対するエビデンスレベルの高い治療法は確立されていない。保存的治療で症状が緩和しない場合には、異なる鎮痛メカニズムを有するインターベンション治療を考慮する。インターベンション治療としては、交感神経ブロックと脊髄電気刺激療法（spinal cord stimulation：SCS）が挙げられ、その効果と副作用・合併症のバランスを考慮し、適応を判断する。星状神経節ブロックや腰部交感神経節ブロックのような交感神経ブロックは、交感神経活動に依存した痛みのあるCRPS患者に対して、鎮痛効果が期待できる。交感神経ブロックが無効な場合には、SCSが選択肢になる。SCSは硬膜外腔に電極を留置し、脊髄に電気刺激を与える方法であり、CRPS type I患者に対する鎮痛効果と患肢機能改善効果が示されている。

こうしたインターベンション治療を薬物療法や理学療法に組み合わせて、複合的なCRPSの痛み治療に対処する。

Key Words：複合性局所疼痛症候群，交感神経ブロック，脊髄電気刺激療法

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はじめに

複合性局所疼痛症候群（complex regional pain syndrome：CRPS）患者の四肢の痛み、運動機能障害、浮腫、関節可動域制限、発汗異常などの多彩な症状には、自律神経系の異常だけでなく、感覚神経系、運動神経系、免疫系、そして中枢神経系の病的機能変化も関与すると考えられている[1)]。CRPSの病態は複合的で、症状・徴候も多彩であり、エビデンスレベルの高い治療法はなく[2,3)]、画一的な保存的治療に反応しないケースも多い。

CRPSの治療目標は、リハビリテーションにより患肢機能の維持・回復をし、日常の生活の質を高めることにある。薬物療法などの保存治療のみで痛みが緩和されず、リハビリテーションが進まない時には、鎮痛のメカニズムが異なる様々な治療法を組み合わせて鎮痛を図り、リハビリテーションの促進に努める[4,5)]。本稿では、ペインクリニックの領域で実施される低侵襲なインターベンション治療の中で、CRPSの痛みに対して鎮痛効果が期待できる、交感神経ブロック[6)]と脊髄電気刺激療法（spinal cord stimulation：SCS）[7)]について概説する。

1．交感神経ブロック

（1）交感神経ブロックによる鎮痛のメカニズム

慢性痛の病態の一つとして、交感神経活動に依存して痛みが惹起されている病態が考えられている。外傷などを契機とし、侵害受容器にα-アドレナリン受容体が発現し、ノルエピネフリンに対して反応するようになり、交感神経系と侵害受容器の機能的な結合が生じるという病態が考えられている[1,8)]。交感神経ブロックは、交感神経系の活動を抑制することにより鎮痛をもたらす。また、交感神経遠心性信号の遮断による末梢組織の血行改善効果もある。

（2）CRPSに対する交感神経ブロックの効果と適応

CRPS type I患者の痛みや、血管運動異常による血管収縮・拡張、発汗障害は、交感神経活

* Interventional pain management for complex regional pain syndrome.

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動の異常により生じると考えられてきた。そのため、交感神経を遮断する治療として、交感神経終末でノルアドレナリンの遊離を抑制するグアネチジンを用いた局所静脈内ブロックや、局所麻酔薬による交感神経（節）ブロックが多用されてきた。しかし、グアネチジンによる局所静脈内ブロックは鎮痛効果が否定的で[2]、星状神経節ブロック（stellate ganglion block：SGB）や、腰部交感神経節ブロック（lumbar sympathetic ganglion block：LSGB）は一部の患者に鎮痛効果を示す[6]。保存的治療により痛みが緩和されないCRPS type Ⅰ患者の約1/3が、SGBにより鎮痛効果が得られる。下肢に痛みのあるCRPS患者に対するLSGBは、半数の患者に鎮痛効果を示す[9]。一方、アロディニアと感覚鈍麻のあるCRPS患者では、交感神経ブロックによる鎮痛効果が得られにくいとされる[10]。アロディニアは、中枢神経系の感受性亢進状態と考えられ、感覚鈍麻は末梢神経障害が原因とされており、CRPS患者の痛みのメカニズムが交感神経の過緊張や末梢組織の虚血と関連が無い時には、交感神経ブロックは無効となる。

リハビリテーションや薬物療法による保存的治療が無効な上肢や下肢のCRPS患者に対して、まずはそれぞれSGBやLSGBを考慮する（図1）。最初に、短時間作用型の局所麻酔薬を用いて診断的交感神経ブロックを行う。鎮痛効果がみられたら、数回交感神経ブロックを繰り返す、あるいは高周波熱凝固による交感神経ブロックを実施する。交感神経ブロックは重篤な合併症を生じうるため、長期にわたり漫然とブロックを繰り返すことは避けるべきである。

（3）SGBの方法と合併症

星状神経節は、下頚神経節と胸神経節が融合したものであり、C7横突起からT1横突起の高さで、横突起基部の腹側に位置する。星状神経節の節前線維は第1～第5胸部交感神経節に由来し、頭頚部と上肢を支配する。C7横突起、あるいはC6横突起を目標として、ブロック針を刺入する。図2Aに示すように、C7横突起前方を椎骨動脈が走行することが多いため、C7横突起基部を目標にすると椎骨動脈を穿刺しやすい。椎骨動脈穿刺を避けるため、C6横突起前方の頚長筋を目標としたSGBを実施することが多い（図2B）。局所麻酔薬を横突起基部の腹側に位置する頚長筋内に投与すると、浸潤作用により交感神経節をブロックできる。超音波ガイド下にブロック針を進め、針先端が頚長筋に到達したら、吸引テストを行い血液の逆流がないことを確認してから、局所麻酔薬を少量ずつ

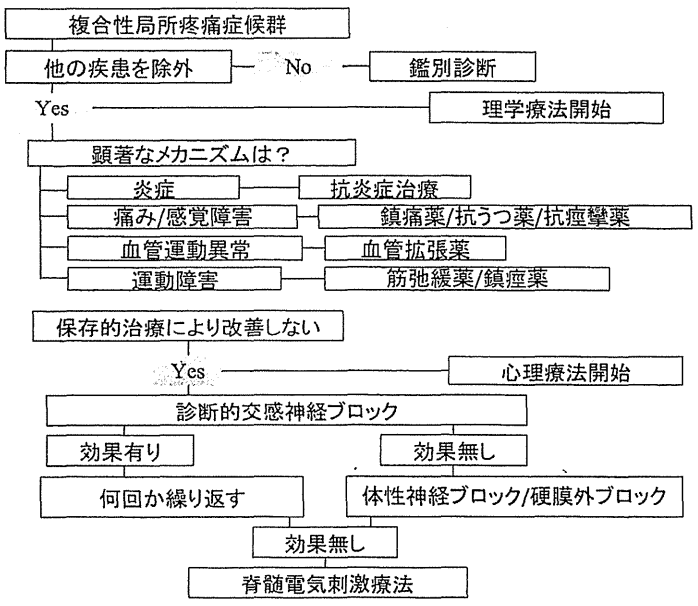

図1 複合性局所疼痛症候群の治療アルゴリズム
治療の目的は、鎮痛を図り理学療法・リハビリテーションを促進し、患肢機能を維持・回復することにある。初期には、薬物療法を実施する。保存的治療に抵抗性に場合に、交感神経ブロックを考慮する。交感神経ブロックや知覚神経ブロックによっても症状の緩和がない場合には、脊髄電気刺激療法が選択肢になる（文献4より翻訳して作成）。

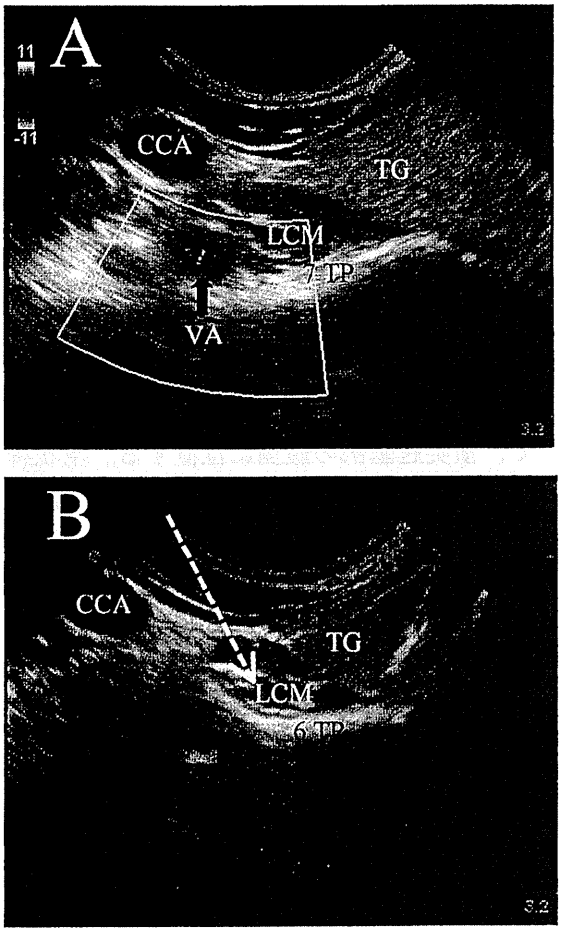

図2 星状神経節近傍の超音波画像
C7横突起レベルの、マイクロコンベックスプローブによる超音波画像。椎骨動脈（黒矢印）がC7横突起前面を走行している（A）。C6横突起レベルの、マイクロコンベックスプローブによる超音波画像。マイクロコンベックスプローブで軽く圧排することにより、総頸動脈と甲状腺の間にブロック針（白矢印）を刺入するスペースができる（B）。交感神経は頸長筋の近傍を走行しており、薬液を頸長筋内に投与すると、浸潤作用により星状神経節をブロックできる。CCA，総頸動脈；TG，甲状腺；LCM，頸長筋；6TP，C6横突起；7TP，C7横突起；VA，椎骨動脈。

合計5～6ml投与する。SGBが成功すると、頸部交感神経幹ブロックにより、眼瞼下垂、縮瞳、眼球陥凹、顔面の紅潮がみられ、上胸部交感神経幹ブロックにより手掌の発汗停止と上肢の温度上昇がみられる。ブロック後に生じる上記の徴候は、SGBによる鎮痛持続時間と相関がある[11]。

表1にSGBとLSGBの合併症を示す。SGBは本邦のペインクリニック外来処置で頻繁に実施されるブロックの一つであるが、重篤な合併症が生じることもあるため、施行後少なくとも30分間は、モニターを装着し厳重に経過観察をする。重篤な合併症を減らすために、超音波ガイド下に周囲の構造物を観察しながらブロック針を進めることが望ましい。正確な位置に針を誘導することにより、少量の局所麻酔薬で効果的なブロックが可能になるという利点もある[12]。頸部正中付近は平面部分が少なく、リニアプローブの使用は制限されるが、ヒト母指頭大のマイクロコンベックスプローブを用いた超音波ガイド下SGBは、総頸動脈や甲状腺を圧排し、ブロック針の穿刺スペースを拡大でき有用である[13]。

表1 交感神経ブロックの合併症

星状神経節ブロックの合併症	腰部交感神経節ブロックの合併症
腕神経叢ブロック	神経根障害
横隔神経ブロック	臓器穿刺
気　胸	血管穿刺
椎骨動脈内に誤投与	射精障害
脊髄くも膜下腔・硬膜外腔への誤投与	発汗障害
出血・血腫	
反回神経麻痺	

（4）LSGBの方法と合併症

腰部交感神経幹は椎体前外側を走行しており、大腰筋筋膜と椎体、腎筋膜後葉により囲まれた狭いコンパートメント内にある。LSGBは通常、第2～4腰椎レベルで行う。棘突起を正中とし、6～8cm外側からブロック針を刺入し、透視下でブロック針を椎体から離れないようにしながら椎体前縁まで誘導する（図3）。造影剤を投与し、椎間孔、血管、大腰筋に造影効果が無いことを確認し、局所麻酔薬を投与する。ブロック成功により、下肢の皮膚温度上昇や発汗の減少がみられる。局所麻酔薬を用いたLSGBの効果は短期間であるが、効果を持続させるために、高周波熱凝固を行うこともある。高周波熱凝固は、先端だけ熱伝導を有する針を用いて、近傍のタンパク質を熱凝固する方法である。CRPS type I 患者に対するLSGB高周波熱凝固（80℃、90秒）により、3～4ヶ月間の鎮痛効果が得られる[14]。高周波熱凝固はアルコールによるブロックと比較し副作用は少ないが、針周囲の狭い範囲内しか熱凝固をできないため、ブロック針先端を正確な位置に誘導する必要がある。

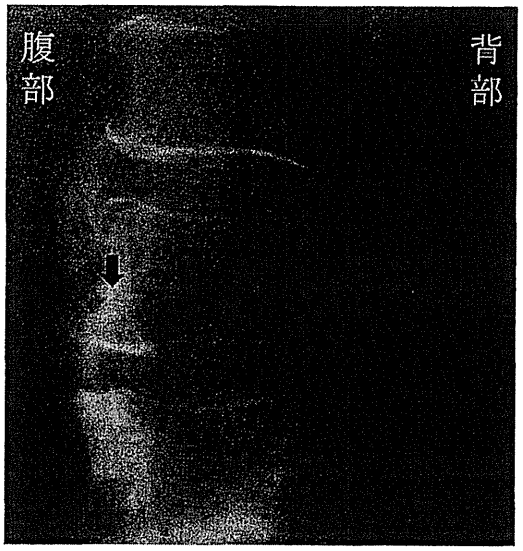

図3 腰部交感神経節ブロック時のX線側面像
L2椎体レベルの単純X線側面像。腰部交感神経節は椎体前外側に位置しており、背部から刺入したブロック針（黒矢印）を、椎体から離れないようにしながら椎体前縁まで進める。

LSGBでは、椎間孔近傍をブロック針先端が通過する時に、神経根を障害する可能性がある。下肢の放散痛がある場合には、刺入方向を変更する。ブロック針が外側にそれると腎臓や尿管を穿刺するので、透視下に椎体に沿ってブロック針を進める。両側のL1交感神経節ブロックにより射精障害を来すことがあるため、L1の交感神経節ブロックは片側にとどめる。

2．脊髄電気刺激療法
（spinal cord stimulation：SCS）

（1）SCSによる鎮痛のメカニズム

脊髄に電気的刺激を与えることによる鎮痛のメカニズムは、ゲートコントロール理論、下行性疼痛抑制系の活性化、交感神経活動の抑制、カルシトニン遺伝子関連ペプチド（CGRP）の放出による局所血流の改善、抑制性神経伝達物質の産生増加といった多くの説が提唱されている[15]。しかし単一の機序では説明が困難で、SCSの鎮痛メカニズムの詳細は不明である。

（2）CRPSに対するSCSの効果と適応

1960年代に臨床応用が始まったSCSは、硬膜外腔に刺激電極（リード）を留置し、脊髄後索を電気刺激することにより、鎮痛を図るものである。本邦では1992年に難治性慢性疼痛に対して保険適応になり、脊髄より末梢側に病因のある慢性痛や虚血性の痛みに有効性が示されている（表2）[16,17]。CRPS type I 患者が、SCSを併用しながらリハビリテーションを実施すると、リハビリテーション単独よりも、痛みが緩和され生活の質が向上する[7]。SCSの鎮痛効果と患肢機能の改善は長期間持続する[18]。実際には、痛みが心地よい電気刺激に置き換わったと表現する患者が多い。SCSのリードは、頚部・胸部・腰部硬膜外腔のいずれにも挿入可能であり、上肢あるいは下肢に痛みがあるCRPS患者に対して鎮痛効果が期待できる[19]。

表2 脊髄電気刺激療法により、鎮痛がえらえる病態・疾患（文献16，17より引用）

脊椎手術後の難治性の痛み
複合性局所疼痛症候群Ⅰ型
末梢血管障害による虚血痛
末梢性の神経障害性痛
狭　心　痛

図1に示すように保存的治療により鎮痛が図れず、リハビリテーションが進まない時、そして交感神経ブロックや知覚神経ブロックが奏功しない時にSCSを考慮する[4]。SCSは早期のCRPS患者により有効なため、保存的治療が無効な早期CRPS患者での実施が推奨されている。とはいえ、SCS単独での鎮痛は困難であり、薬物療法やリハビリテーションとの併用が必要である。SCSの鎮痛効果を確認するために、低侵襲な試験刺激から実施する。

（3）SCS装置植え込みの方法

試験刺激のためのリードは、局所麻酔下での経皮的な操作のみで挿入可能である。透視下で、上肢の痛みに対しては頚部硬膜外腔に、下肢の痛みに対しては下位の胸部硬膜外腔から腰部硬膜外腔にかけて、リードを挿入する。リードによって与えられた電気刺激が、患者の痛みの部位と一致するように、硬膜外腔に留置したリード先端の位置を微調整する。1週間その状態で生活し、SCSの効果を患者と医療者で判定する。試験刺激が無効であればリードを抜去する。試験刺激によるSCSが奏功し、患者の満足感が得られるならば、二期的にリードを硬膜外腔に、刺激装置を前胸部あるいは腹部に留置する（図4）。刺激装置留置のためには小切開が必要であり、全身麻酔下で行うこともある。

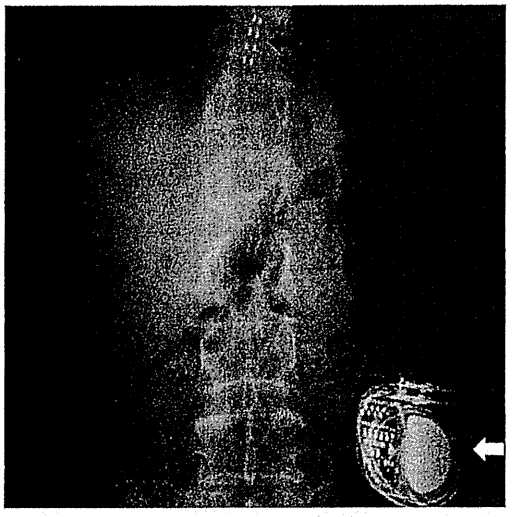

図4 脊髄電気刺激装置植え込み後のX線正面像
硬膜外腔に挿入された2本の刺激電極（黒矢印）は、皮下トンネルを走行するエクステンションにより、下腹部の刺激装置に接続されている（白矢印）。

（4）SCS装置植え込み後の注意点と合併症

SCS植え込み後の生活上の注意点を、患者には事前に十分に説明しなければならない。刺激法は、患者用プログラムを操作することにより、一定の範囲内で自己設定をする必要がある。リードが硬膜外腔内で移動すると効果が減弱することがあるため、激しい運動は控える。核磁気共鳴画像（MRI）、心臓ペースメーカー、除細動、電気メスの使用により、リードの移動やSCS刺激装置の誤作動や故障が発生することがある。SCSが不要になった場合には、装置の抜去はいつでも可能である。

表3に示すとおり、生命の危機に至る合併症は非常に稀であるが、SCS装置の抜去が必要になることもなる[17,20]。

表3 脊髄電気刺激療法の合併症とその頻度
（文献17,20より引用）

合　併　症	頻　度
リードの移動	13～21%
リードの断線	5～9%
ハードウェアの故障	3～5%
皮下血腫	4%
感　染	3%
刺激装置留置部位の疼痛	1%
脳脊髄液の漏れ	<1%
接続部の緩み	<1%

おわりに

CRPSの治療の目標は痛みを消失させることではなく、リハビリテーションにより身体機能を維持・回復させ、充実した日常生活を送ることにある。CRPSの病態の進行による患肢機能障害を防止するためには、リハビリテーションの重要性を説明し、能動的な態度を引き出す。CRPS患者は、他の慢性痛患者よりも生活の質の低下が大きく、それは痛みの程度と相関している[21]。激しい痛みのためリハビリテーションができない場合、まず薬物治療を行う。薬物療法によっても痛みが緩和されずリハビリテーションが進まない時に、交感神経ブロックやSCSといったインターベンション治療を考慮する。CRPSの痛みのメカニズムは、個人や病期により異なる。個々の患者の病態、痛みの程度や性質に応じて、鎮痛効果と副作用・合併症のバランスを考慮しながら、様々な治療法の組み合わせを患者に提供していく必要がある。

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Interventional pain management for complex regional pain syndrome.

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Complex regional pain syndrome (CRPS) is a painful debilitating condition characterized by sensory, vasomotor, sudomotor, and trophic changes usually in the hand or foot, and it is a potential cause of disability. The pathophysiology of CRPS is unknown but is likely to be multifactorial. The pain seen in patients with CRPS often becomes refractory to conservative treatments including physical rehabilitation and pharmacological pain management.

If conservative therapies do not show sufficient analgesia, interventional technique, which produce pain relief via different mechanisms from those of conservative therapies, need to be considered. Sympathetic blocks such as stellate ganglion and lumbar sympathetic ganglion blocks are the first choice for interventional treatment. Sympathetic blocks show different degrees of analgesia in patients with CRPS. For patients with CRPS who do not respond to sympathetic blocks, spinal cord stimulation (SCS) is another option for interventional therapy. SCS is a minimally invasive procedure that applies mild electrical stimulation to the spinal cord using electrodes implanted in the epidural space. SCS has been validated for the treatment of CRPS type I.

Evidence-based treatment guidelines for CRPS have not been established yet. Treatment for CRPS should be flexible and individualized according to severity and progression of symptoms. The decision to undertake interventional procedures is based on the balance between the inherent risks and benefits. Interventional pain management such as sympathetic blocks and SCS could be an alternative treatment to provide patients with pain relief and enhance functional restoration when conservative therapies are not sufficiently efficacious.

Key Words: complex regional pain syndrome (CRPS), sympathetic block, spinal cord stimulation (SCS)

特集「CRPS診療の現況と進歩」－6

CRPSのリハビリテーション*

有野　浩司

要旨　複合性局所疼痛症候群（Complex Regional Pain Syndrome: CRPS）は原因が明らかでなく治療は難渋する。CRPSは疼痛症候群であり，治療は疼痛・機能障害の改善である。種々の治療法を合わせた集学的な治療が行われる。中枢神経系の画像検査の発達に伴い脳の可塑性や神経のネットワークの再構築を目指す治療が行われるようになってきた。

Key Words：複合性局所疼痛症候群，リハビリテーション，脳の可塑性

Peripheral Nerve 2014; 25(1): 40–45

はじめに

複合性局所疼痛症候群（Complex Regional Pain Syndrome: CRPS）は原因や発生機序が明らかでなく、様々な治療を行うも難渋することが多い。確立した治療法はなく、各々の治療の効果は不確かである。患者の症状の訴え、治療への要求も強く有効な治療法の確率が望ましいが、難しい。

CRPSは疼痛症候群であり、治療の目標は疼痛の軽減、併発または続発する関節可動域制限、筋力低下、巧緻運動障害などに対する機能回復であり、薬物療法、神経ブロック療法、リハビリテーション療法、心理学的療法などが行われる。

CRPSに対するリハビリテーションの目的は疼痛に対するリハビリテーションと機能障害に対するリハビリテーションの2つに大別される。疼痛に対しては温熱・光線・電気刺激療法などがあり、機能障害に対しては関節可動域訓練・筋力強化訓練・作業療法・装具療法などがある。

疼痛に対する治療の効果が機能回復に対するリハビリテーションを促進し、逆に機能回復の治療の効果が疼痛を軽減するので両者を合わせて行う。

初期のCRPSでは疼痛を軽減し機能回復訓練を行えれば良好な結果を得ることもできるが、進行した例では疼痛をなくすことは非常に困難であり、機能障害の改善も困難となる。完全な除痛でなく疼痛のコントロール、機能障害の改善を治療目標とすることも必要と思われる。

予防の重要性

日常診療でよく遭遇する外傷、それほど重症と思わないものにCRPSは発症することが多い。機能回復が通常予想される程度より進まないことや、通常の経過でみられる程度以上の腫脹・痛みが存在することに気づくことが重要である。元の外傷に対するリハビリテーションなどを十分に行うことで関節拘縮や骨萎縮の発生を抑制し、二次的な器質的な障害を予防する。一度瘢痕などで膠原線維の線維化がおこると治療は長期化し、軽快は困難となり、CRPSの発症リスクが高まる。もちろんリハビリテーションのみで対処するのではなく、他の治療法も合わせて行う。少しover diagnosis, over treatmentでも，早期にCRPSを疑い、早期治療した方が治療のためには良いが[1]、疾病利得が絡む後遺症診断に大きな影響を及ぼす可能性があるため安易にCRPSの病名をつけるべきではない。

* Rehabilitation of complex regional pain syndrome.

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ORIGINAL ARTICLE

Reliability of peripheral intraneural microhemodynamics evaluation by using contrast-enhanced ultrasonography

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Abstract
Purpose The purpose of the study was to validate the reliability of quantitative intraneural enhancement patterns by using contrast-enhanced ultrasonography (CEUS).
Methods Nine asymptomatic wrists underwent a total of three CEUS examinations each conducted at 1-month intervals. The CEUS enhancement pattern of median nerves was quantitatively evaluated. The area under the time–intensity curve was calculated by placing the regions of interest at the proximal, center, and distal regions of the median nerve. An intra-class correlation coefficient for intra-observer, inter-observer, and inter-examination reproducibility was calculated.
Results The intra- and inter-observer reproducibility was almost perfect. Inter-examination reproducibility of the proximal, center, and distal regions was 0.891, 0.614, and 0.535, respectively. In this study, we found that the reproducibility of the distal and center regions of the median nerve in the carpal tunnel was lower than that of the proximal region.
Conclusion High intra-observer, inter-observer, and inter-examination reproducibility of CEUS was obtained in the evaluation of the intraneural enhancement pattern when the region of interest was placed in the proximal region of the median nerve.

Keywords Contrast-enhanced ultrasound · Median nerve · Intraneural vascularity · Reproducibility

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Introduction

Nerve entrapment syndrome is thought to be caused by both local physical compression of the nerve and abnormal microvascularization [1, 2]. However, the abnormal changes in microhemodynamics remain unproven. Several studies have reported using color or power Doppler ultrasound (DUS) to evaluate intraneural blood flow in carpal tunnel syndrome (CTS), one of the typical entrapment neuropathies [3–6]. However, DUS is not sensitive or reproducible enough to detect the microcirculation of the median nerve. Establishing accurate and reproducible methods for the clarification of pathological conditions requires an evaluation of the intraneural microcirculation.

While contrast-enhanced ultrasonography (CEUS) has been widely used to diagnose hepatic tumors [7, 8], it has not been used commonly in the field of orthopedics. Only a few studies have evaluated intratendinous vascularity [9, 10]. We attempted to evaluate the median nerve vascularity quantitatively by performing CEUS. Sonazoid™ (Daiichi-Sankyo, Tokyo, Japan; GE Healthcare, Milwaukee, WI, USA) is an ultrasound contrast agent consisting of perfluorobutane microbubbles and lipid shells. It has been

approved in Japan for diagnosing liver tumors since 2007 [11]. We can obtain stable real-time vascular imaging with CEUS even for hypovascular tissue such as peripheral nerves; however, the reliability and validation of CEUS have not been reported. The purpose of this study was to validate the reliability of intraneural vascularity of the median nerve by using CEUS.

Materials and methods

Subjects

Nine patients (1 man, 8 women; age range, 49–80 years; average age 63.7 years) with a diagnosis of CTS were enrolled in this study. All of the patients underwent carpal tunnel release, and the opposite asymptomatic wrists of these patients underwent CEUS between July 2012 and July 2013. In our study, we considered that there would be almost no effect on the blood flow of the study side wrists by the contralateral side that underwent carpal tunnel release. Six out of the nine wrists had no surgical history, and the rest had undergone carpal tunnel release more than 2 years prior to study enrollment. CTS was ruled out in all the studied wrists by a board certified orthopedic surgeon (M.M.) based on the absence of the following common criteria for CTS: predominantly nocturnal hand numbness, the presence of sensory and motor deficits of the median nerve, and a positive Phalen test. Our institutional review board approved the study design, and written informed consent was obtained from all subjects.

Nerve conduction study

The patients initially underwent two nerve conduction studies (NCS) with a Neuropack 230B (Nihon Kohden, Tokyo, Japan) and later a CEUS examination. Four experienced medical technologists performed the electrophysiological tests in the same room with the temperature maintained at 25 °C with an air conditioner and the hand skin temperature maintained between 31 and 34 °C, as measured by using an infrared thermometer. The active electrode was placed over the abductor pollicis brevis muscle to record compound muscle action potentials (CMAP). The reference electrode was placed just distal to the first metacarpophalangeal joint. The median nerves were stimulated supramaximally at the wrist at a distance of 6 cm from the wrist to the active electrode. Median nerve distal latency (MDL) and the amplitude of CMAP were measured. Antidromic sensory responses were obtained. Ring electrodes were used to obtain sensory nerve action potentials (SNAP) and were placed over the index finger. The surface electrode was placed 14 cm proximal to the proximal ring electrode. Sensory nerve conduction velocity (SCV) was calculated by dividing the distance of 14 cm by the measured latency.

Contrast-enhanced ultrasound

The CEUS scans were conducted a total of three times at monthly intervals. All of the CEUS scans were performed by one sonographer (K.I.). The images were corrected by using an ultrasound unit (Aplio^{TM} 500, 2012, Toshiba Medical Systems Corp., Tochigi, Japan) with a linear transducer, with a center frequency of 8.0 MHz (PLT-805AT). The hand was positioned with the wrist in neutral and with full forearm supination on an arm stand (Fig. 1a). The scaphoid tubercle, pisiform, and hook of the hamate were marked on the skin surface after palpation. Sagittal views of the median nerve were obtained at the middle point between the scaphoid tubercle–pisiform line and hook of hamate (Fig. 1b, c). Contrast harmonic imaging (commercially called advanced pulse subtraction) with a reception frequency of 5.5 MHz was used. The microbubble contrast agent, Sonazoid^{TM}, was injected as a 0.015 mL/kg/body bolus into an antecubital vein via a 22-gauge needle, followed by a 10-mL saline flush. The focus point was set at the deeper end of the median nerve, which was 1.25–1.50 cm below the skin surface, at a rate of 17 frames per second and with a dynamic range of 50 dB. The mechanical index was set as 0.25–0.26. Ten seconds after the injection of Sonazoid^{TM}, enhanced signals from the CTS were recorded continuously for 80 s as raw data on the hard drive of the ultrasound unit.

Evaluation

The time–intensity curves using continuous raw data (1,190 frames) were drawn with the help of software (time curve analysis) equipped with an ultrasound unit (Fig. 1d). Oval regions of interest (ROIs) with a fixed size of 2.26 × 1.41 mm were placed proximally (the scaphoid tubercle and pisiform line), at the center (within the carpal tunnel), and distally (the hook of hamate) to the median nerve. The area under the time–intensity curves (AUCs) was calculated (Fig. 1e). Normalized data were obtained for each wrist relative to a baseline value by using an average from the first 250 frames (about 15 s). The AUCs were used for the statistical analysis and were expressed as acoustic units.

Intra-observer reproducibility was evaluated by having one investigator (K.I.) place the ROIs three different times by using the first examination data from nine wrists; inter-observer reproducibility was evaluated by having two investigators (K.I. and M.M.) place ROIs using the first examination data from nine wrists; and inter-examination

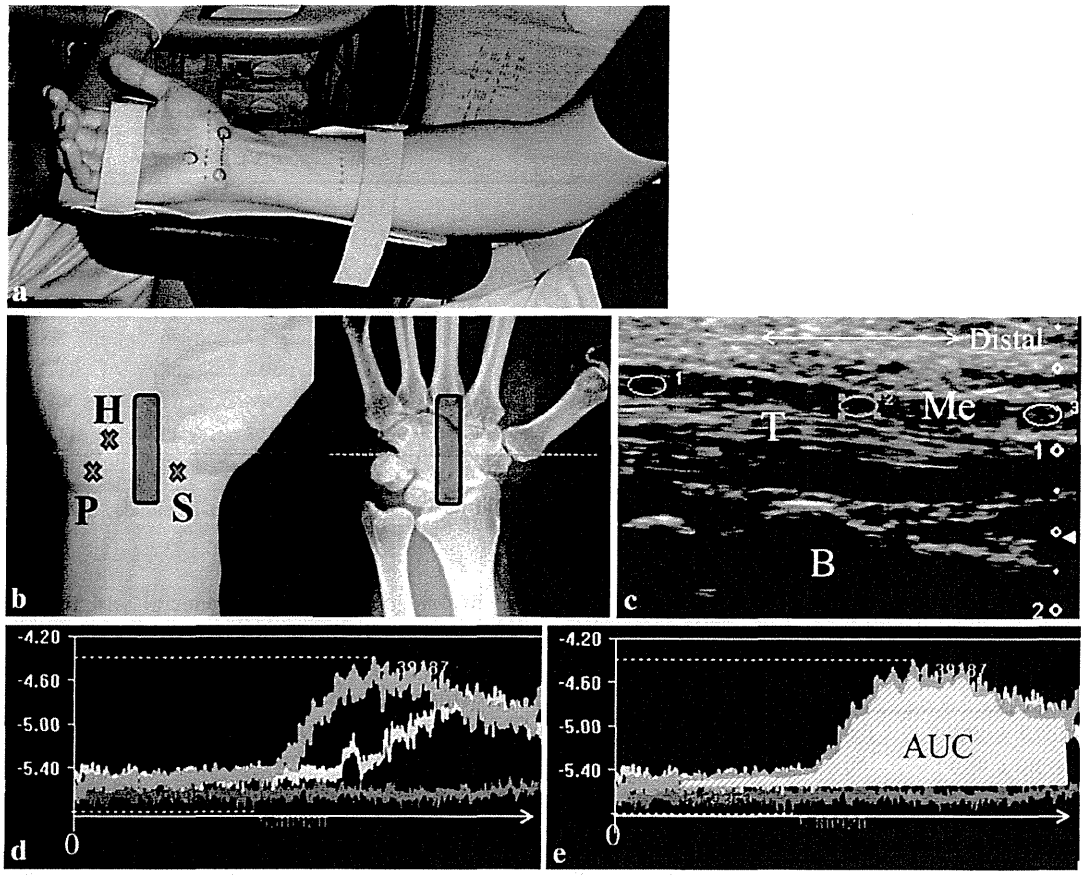

Fig. 1 **a** Patient's forearm position during the ultrasound study. Scaphoid tubercle, pisiform, and hook of hamate were marked on the skin surface by palpation. **b** The probe position was determined to be at the center of the scaphoid tubercle–pisiform line and hook of hamate, and a scan of the median nerve long axis view was performed. *H* hook of hamate; *P* pisiform; *S* scaphoid tubercle. **c** B-mode ultrasonography of median nerve long axis view. ROIs are placed at the proximal (*1*), center (*2*), and distal (*3*) regions of the median nerve. *Me* median nerve; *T* flexor tendon; *B* carpal bone. **d** The time–intensity curves of the proximal (*sky blue*), center (*violet*), and distal (*yellow*) regions of the median nerve obtained by CEUS. The *vertical line* shows the intensity and horizontal axis time after injection of Sonazid™. **e** The area under the time–intensity curve calculated by the time–intensity curves

reproducibility was evaluated by having one investigator (K.I.) place ROIs on three different occasions. The analyses were performed randomly and blinded to subject data. All statistical analyses were performed using SPSS 20.0. An intra-class correlation coefficient (ICC) and 95 % confidence intervals (CI) were calculated.

Results

CEUS data were successfully acquired, and no side effects occurred in any of the subjects. Table 1 shows the NCS results. The mean MDL of all the subjects at the initial examination was 4.2 ± 0.6 ms. There was no major change in the SCV and MDL values (<10 m/s and <1.0 ms, respectively) between the initial and the final examinations in eight subjects. The mean AUC values in each of the three different CEUS studies are shown in Table 2. The AUC values in the center region of the median nerve in the carpal tunnel tended to be low. The standard deviation of the proximal region was lower than that of the center and the distal regions. Intra-observer reproducibility of the proximal, center, and distal regions of the median nerve was 0.974, 0.997, and 0.991, respectively. The 95 % CI of the ICC for intra-observer reproducibility at the proximal, center, and distal regions of the median nerve was 0.923–0.994, 0.992–0.999, and 0.972–0.998, respectively. Inter-observer reproducibility of the proximal, center, and distal regions of the median nerve was 0.928, 0.920, and 0862, respectively. The 95 % CI of the inter-observer reproducibility at the proximal, center, and distal regions of the median nerve was 0.677–0.984, 0.661–0.982, and 0.366–0.969, respectively. Inter-examination reproducibility of the proximal, center, and distal

Table 1 Patient characteristics and nerve conduction study data

No.	Sex	Age	Surgical history (years before)	First examination				Last examination			
				SNAP		CMAP		SNAP		CMAP	
				Amp (μV)	SCV (m/s)	Amp (mV)	MDL (ms)	Amp (μV)	SCV (m/s)	Amp (mV)	MDL (ms)
1	F	80	–	12.3	46.9	4.5	5.0	14.7	49.7	3.8	4.5
2	F	62	30	27.9	51.6	10.5	3.5	30.0	54.4	11.1	3.4
3	M	60	–	20.6	57.5	12.5	3.5	28.2	58.9	9.6	3.8
4	F	49	–	26.1	54.1	11.1	3.8	27.3	58.5	11.9	3.9
5	F	63	3	6.7	42.6	8.6	4.7	7.7	46.5	8.8	4.6
6	F	59	–	24.0	48.6	8.4	4.8	30.3	50.8	11.2	4.4
7	F	74	–	14.3	50.2	11.4	3.7	NA		NA	
8	F	60	2	16.0	35.3	11.6	4.7	12.8	43.9	11.1	3.8
9	F	66	–	23.8	48.5	10.4	3.7	32.6	50.9	11.3	3.9

M male; *F* female; *SNAP* sensory nerve action potential; *CMAP* compound motor action potential; *Amp* amplitude; *SCV* sensory nerve conduction velocity; *MDL* median nerve distal latency; *NA* not available

Table 2 The mean AUC of three contrast-enhanced ultrasounds

No.	Mean AUC ± SD		
	Proximal	Center	Distal
1	167.7 ± 2.0	120.3 ± 65.5	152.0 ± 68.9
2	123.9 ± 32.9	79.6 ± 56.5	105.6 ± 31.6
3	27.2 ± 7.6	23.6 ± 30.3	43.7 ± 35.1
4	108.7 ± 3.0	16.3 ± 14.5	112.7 ± 92.2
5	110.6 ± 42.4	52.2 ± 25.6	44.3 ± 39.9
6	136.0 ± 28.7	5.3 ± 6.3	86.5 ± 64.6
7	77.9 ± 17.0	22.5 ± 54.8	10.6 ± 28.0
8	115.2 ± 17.0	14.4 ± 9.7	120.0 ± 59.2
9	97.1 ± 12.2	66.0 ± 71.5	126.9 ± 33.7

AUC area under the curve; *SD* standard deviation

regions of the median nerve was 0.891, 0.614, and 0.535, respectively. The 95 % CI of the inter-examination reproducibility at the proximal, center, and distal regions of the median nerve was 0.670–0.973, 0.160–0.904, and 0.398–0.885, respectively. We found high reproducibility at the proximal region of the median nerve, while ICC (1.3) of the center and distal regions of the median nerve showed a low value.

Discussion

Previous studies have reported that there was almost no blood flow signaling in healthy nerves [4, 6]. In our study, all quantitative evaluations of intraneural vascularity were performed on the asymptomatic wrists. There were adequate enhancement patterns in the median nerve in all subjects. Ghasemi-Esfe et al. [4] reported that only 10 % of the healthy controls had intraneural vascularity. CTS is considered to have a tendency to be bilateral [12], and the MDL was slightly prolonged in our subjects [4, 13]. According to these reports, it is suspected that these subjects might have subclinical or early-stage CTS, even though all subjects were asymptomatic. The aim of our study was to validate the quantitative reliability of intraneural vascularity. There should be adequate intraneural vascularity for the evaluation of reliability, and no changes in clinical symptoms and NCS data during the 3-month study periods were needed. There is only slight vascularity in healthy wrists, and it would not be enough for evaluation. While in CTS patients, unstable symptoms would be a factor. Therefore, we thought that asymptomatic wrists, i.e., the opposite side of the CTS wrists, would be suitable as subjects in a reproducibility evaluation. Also, postoperative cases were included in this study. However, more than 2 years had passed since the surgery, ensuring that intraneural vascularity would be stable since symptoms were absent and NCS values were stable [14].

We evaluated intra-observer, inter-observer, and inter-examination reproducibility for intraneural vascularity of the median nerve in each region. Several ultrasound studies on the assessment of reproducibility of CTS by measuring cross-sectional area and flattening ratio of the median nerve have been reported [15, 16]. Evaluation of inter-examination reproducibility of quantitative values for intraneural vascularity of the median nerve has not been reported. Both intra-observer and inter-observer reproducibility were almost perfect with the ICCs over 0.9. The size of the ROI and median nerve thickness are factors in analyzing intraneural vascularity, because median nerve thickness is different in each wrist [17]. Also, the median nerve is swollen in CTS wrists [18, 19]. In our study, the ROI was set as

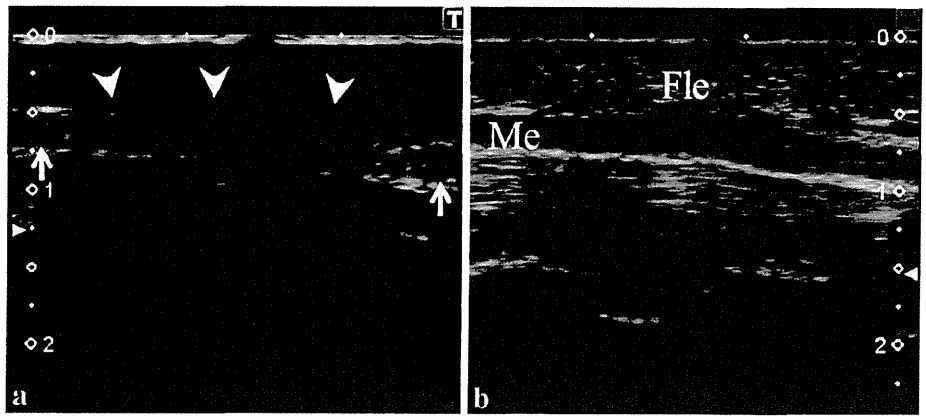

Fig. 2 Images of contrast mode (**a**) and conventional B-mode (**b**) in subject 9. Relatively favorable contrast enhancement patterns at the proximal and distal regions of the median nerve (*white arrow*) and a poor enhancement pattern at the *center* are shown. The poor enhancement pattern is caused by attenuation of ultrasound by the flexor retinaculum (*white arrow head*). *Me* median nerve; *Fle* flexor retinaculum

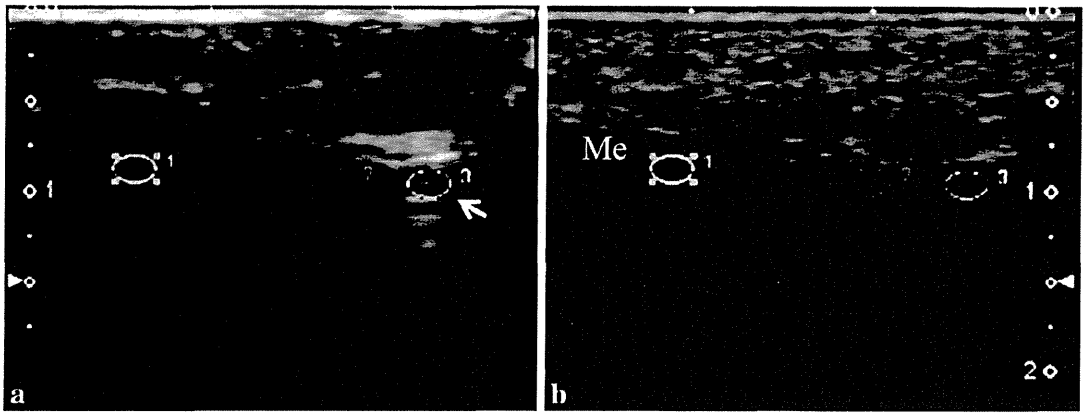

Fig. 3 Images of contrast mode (**a**) and conventional *B*-mode (**b**) in subject 1. An artifact caused by the palmar arterial arch running parallel on the anterior aspect of the median nerve in the distal region is shown in the contrast mode (*white arrow*). *Me* median nerve

smaller than the median nerve thickness in all cases. And all subjects were evaluated using the same ROI size. According to this method, high intra-observer and inter-observer reproducibility were achieved in this study. This way, a difference in the ratio of the ROI and the thickness of the median nerve would not affect this result in a major way. On the other hand, inter-examination reproducibility of the center and distal regions of the median nerve in the carpal tunnel was relatively low. There are several reasons for the low reproducibility in the center region of the median nerve in the carpal tunnel. One of the reasons was attenuation of the ultrasound by the flexor retinaculum, which was located ventral to the median nerve (Fig. 2). It is thought that subtle differences in the fixed angle of the probe in each examination caused varying degrees of ultrasound attenuation. Another reason was the difference in the degrees of compression. The probe was raised by the prominent flexor retinaculum and thenar muscle group in some subjects; this difference in the physical anatomy caused an unstable probe position. The reason for low reproducibility at the distal region of the median nerve in the carpal tunnel was thought to be signal contamination or artifact due to its proximity to the palmar arterial arch (Fig. 3). Therefore, we should remember that the reproducibility in a nerve differs according to the region.

The high ICC value for inter-examination in this study could be due to several reasons. The median nerve runs along the body surface linearly and stays still. Placing the regions of interest is easy in the thin median nerve. Therefore, it is possible to achieve a high reproducibility.

Diagnosis of CTS by NCS, gray scale ultrasonography, and DUS would be sufficient in most cases. However, previous studies reported that ischemic changes in micro-hemodynamics might be one of the causes of entrapment neuropathy [20, 21]. DUS is not capable of detecting microcirculation. Sugimoto et al. [2] reported that dynamic magnetic resonance imaging (MRI) detects several enhancement patterns in CTS wrists caused by ischemia or collapse of blood–nerve barrier in the nerve vessels. CEUS has a high spatial and temporal resolution. It would be expected to provide enough information equivalent to or greater than that of dynamic MRI. We expected that CEUS would be helpful to diagnose early-stage CTS or assist diagnosis when the NCS result is borderline. CEUS is also

expected to be available to assess microhemodynamics in various regions.

This study has some limitations. One of them is the difficulty in distinguishing contrast enhancement signals from the background tissue as the contrast effect is visualized with gray scale. This problem can be resolved by placing the ROI carefully before the contrast agent flows into the nerve. In addition, the dual mode, which permits simultaneous display of a conventional image on one side and the contrast mode on the other side, might be effective in placing the ROI in baseline images on the same exact place as that on the contrast images. This will ensure that the evaluation of the exact intraneural enhancement pattern can be performed. The other limitation is a lack of evaluation of inter-examination with inter-examiner reproducibility. Further investigation with a larger sample size will solve this problem.

Conclusion

We demonstrated high intra-observer, inter-observer, and inter-examination reproducibility for the evaluation of median nerve vascularity using CEUS.

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Conflict of interest None.

Human rights statements and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

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Intraosseous neurilemmoma of the proximal ulna

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ABSTRACT

INTRODUCTION: Neurilemmoma is a benign nerve sheath neoplasm commonly located in the soft tissue. Intraosseous neurilemmoma is rare, constituting less than 1% of primary bone tumors.
PRESENTATION OF CASE: A 21 year-old woman was presented with left elbow pain of 1-month duration. Plain radiographs showed a well-defined, lytic and expansile lesion of the proximal ulna. Computed tomography revealed cortical destruction and soft tissue extension. Because the tissue of origin for the tumor was uncertain, an open biopsy was performed. The specimens demonstrated a benign spindle cell tumor suggestive of a neurilemmoma, similar to a soft tissue neurilemmoma. The diagnosis of intraosseous neurilemmoma was established. Marginal excision of the soft tissue component and curettage of the lesion in the bone were performed. After 3.5 years of follow up, there is no clinical or radiographic finding to suggest any recurrence.
DISCUSSION: The major site of intraosseous neurilemmoma is the mandible. Occurrence in the long bone is particularly rare. Only two cases of intraosseous neurilemmoma involving the bones around the elbow have been reported to our knowledge; these cases arose in the distal humerus. We describe the first case of intraosseous neurilemmoma of the proximal ulna of the left elbow. The recommended treatment is conservative resection and bone grafting, as malignant change is extremely rare.
CONCLUSION: Although very rare, intraosseous neurilemmoma should be taken under consideration in the differential diagnosis of painful, radiographically benign-appearing osseous tumor around the elbow.

1. Introduction

Neurilemmoma (schwannoma) is a benign neoplasm that arises from the myelinating schwann cells of the nerve sheath.[1–3] It is a relatively common tumor, comprising approximately 5% of all benign soft tissue tumors, and shows a predilection to affect the sensory nerves.[3] Intraosseous neurilemmoma, however, is very rare, accounting for less than 1% of benign bone tumors.[4,5] It shows no sex-, race-, or age-dependant predilections.[6] The mandible is the most frequently affected site, followed by the sacrum; this tumor rarely arises in the bones of the extremities.[5,7,8] Only 2 cases of intraosseous neurilemmoma around the elbow have been described in literature[6,9]; these cases arose in the distal humerus. We present the first case report of an intraosseous neurilemmoma affecting the proximal ulna.

2. Presentation of case

A 21-year-old woman was referred to our orthopedic unit with a 1-month history of pain in the left elbow. The initiating factor, such as trauma, was not clear. On physical examination, the overlying skin was intact, and there was no evidence of warmth, erythema, or induration. No other masses were palpable. The elbows and forearms had a normal range of motion (ROM). No evidence of lymphadenopathy or neurovascular involvement was found.

Plain radiographs revealed a well-defined, lytic, and expansile lesion, with thin marginal sclerosis and trabeculation in the proximal ulna (Fig. 1). Computed tomography (CT) showed considerable destruction of the cortex of the ulna, which connected with a mass of soft tissue. At the edge of the destructed cortex overhung a soft tissue mass (Fig. 2a), which had invaded into the cortex, and no periosteal reaction was seen (Fig. 2b). Magnetic resonance imaging (MRI) showed the well-defined and lobulated lesion to be isointense to skeletal muscle on T1-weighted images, and heterogeneous and hyperintense on T2-weighted images. The lesion revealed uniform enhancement following Gd-DTPA administration.

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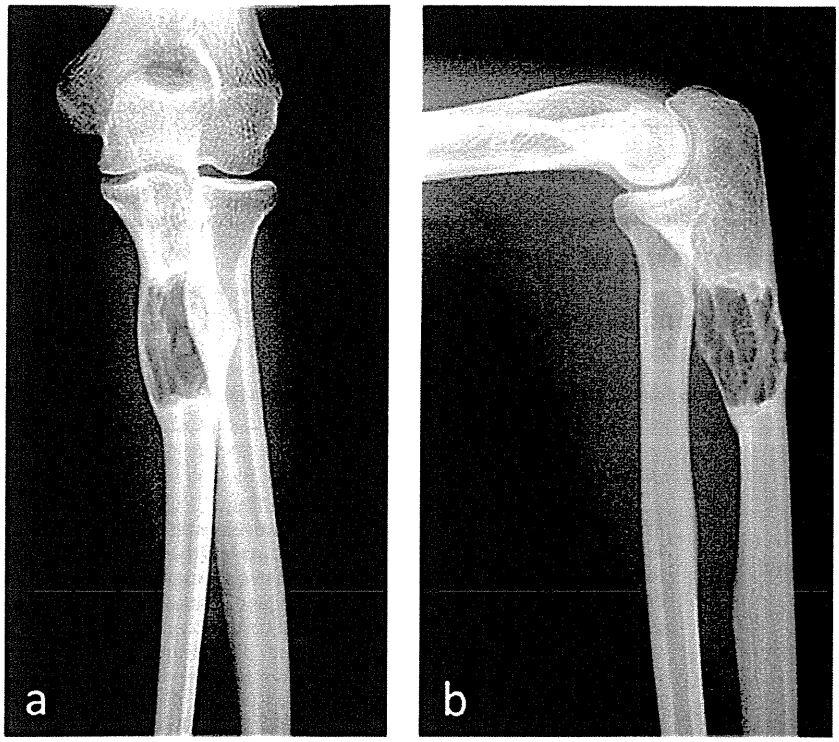

Fig. 1. Anteroposterior (a) and lateral (b) plain radiographs, showing a well-defined, lytic, and expansile lesion, with marginal thin sclerosis and trabeculation in the proximal ulna.

Because of uncertainty regarding the histological origin of the tumor, we performed an open biopsy. The pathologic specimen consisted of hypercellular regions with palisading nuclei (Antoni type A), and hypocellularity regions with myxoid background (Antoni type B). Almost all of the area was Antoni type A (Fig. 3). We could not observe nuclear atypia, necrosis, or mitosis. Immunohistochemical studies showed strong, diffuse reactivity for S-100 protein within the lesional cells. Microscopic findings were consistent with a diagnosis of neurilemmoma.

The diagnosis of intraosseous neurilemmoma was established. We surgically excised the soft tissue component of the mass by marginal resection. Curettage was performed on the bone lesion, and the resulting deficit was grafted with beta-tricalcium

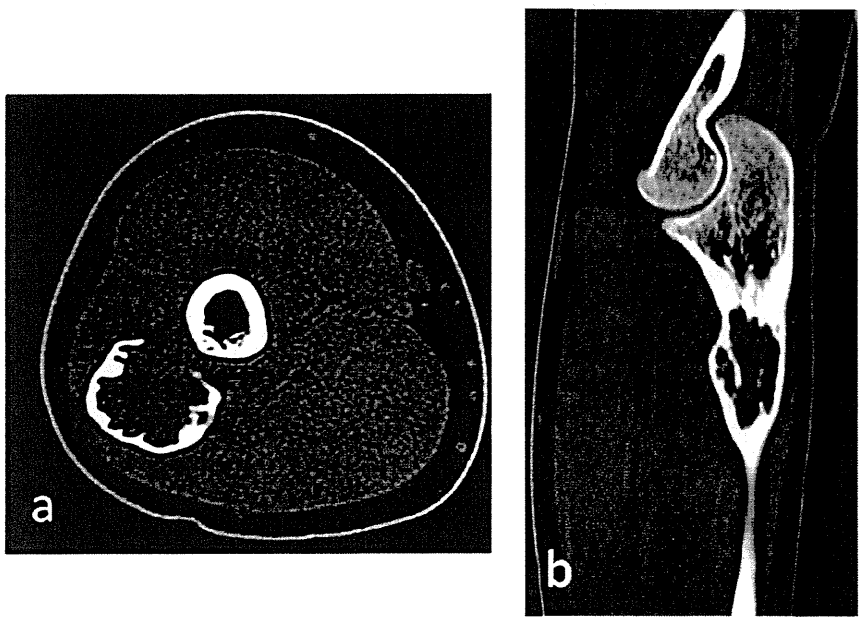

Fig. 2. Axial computed tomography scan (a) and sagittal reconstruction (b) of the ulna, demonstrating destruction of the cortex of the ulna, with extension into the adjacent soft tissue. At the edge of the destructed cortex overhung a soft tissue mass (arrows), which had invaded into the cortex (arrowhead).

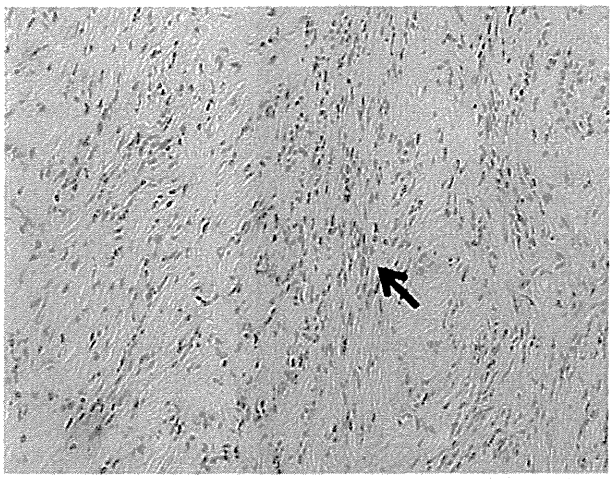

Fig. 3. Photomicrograph of the tumor specimen, showing the highly cellular Antoni type A pattern of growth. Nuclear palisading is noted (arrows) (hematoxylin–eosin staining; magnification, 200×).

phosphate (Fig. 4). The pathologic tissue that was removed was yellow-to-brownish. After 3.5 years of follow up, the patient is clinically asymptomatic, and the radiographs show complete graft incorporation (Fig. 5). There is no clinical or radiographic finding to suggest any recurrence.

The patient was informed that the case would be submitted for publication and her consent was obtained.

3. Discussion

We present the case of an intraosseous neurilemmoma affecting the proximal ulna. This tumor rarely arises in the bones of the extremities.[5,7,8] Only two cases have previously been reported around the elbow. These cases arose in the distal humerus.[6,9] This is the first report of its origin in the proximal ulna.

Neurilemmomas may involve bone tissue via 3 mechanisms: (1) they may be intramedullary, producing rarefaction of the bone; (2) they may be located within the nutrient canal, with the formation of a dumbbell-shaped tumor; or (3) they may be extraosseous, eroding into the bone.[5,7,10] With regard to the comparatively high incidence of intraosseous neurilemmoma in the mandible, it has been speculated that the long intraosseous path of the mandibular nerve may predispose to metaplasia of the schwann cells in its nerve sheath.[5] However, some authors have refuted this theory, noting that the nerves innervating the long bones through the nutrient foramina are longer than the mandibular nerve; nevertheless, the frequency of intraosseous neurilemmoma in the long bones is several times lower than that in the mandible.[7,8] Neurilemmoma shows a predilection to the myelinated nerves, especially the sensory nerves. However, most intraosseous nerves are non-myelinated and participate in vasomotor functions.[11] de la Monte and colleagues have suggested that the death of sensory nerve fibers within bone tissue may account for the exceedingly rare occurrence of intraosseous neurilemmoma.[8] We think that the high frequency of neurilemmoma in the mandible is not because of the long intraosseous course, but because the mandibular nerve consists of sensory nerves of the trigeminal nerve origin.

The characteristic radiographic features of intraosseous neurilemmoma include the following: (1) a well-defined lytic

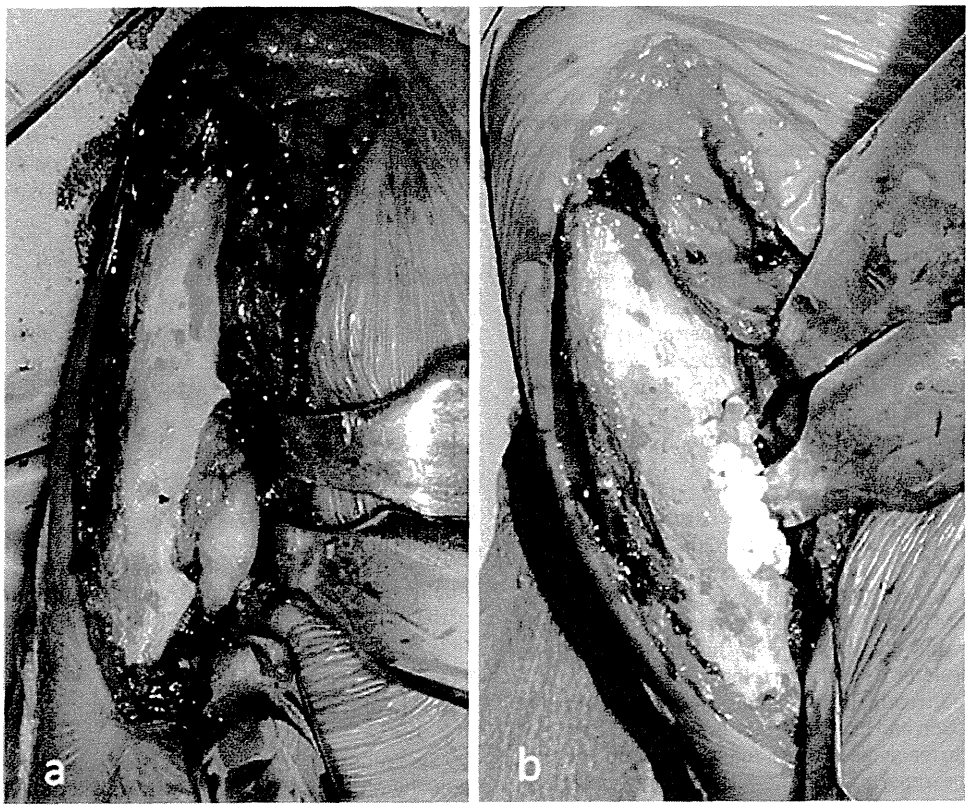

Fig. 4. (a) Intraoperative photograph shows that the tumor destructed the cortex of the ulna. (b) Curettage was performed on the bone lesion, and the defect was filled with beta-tricalcium phosphate.

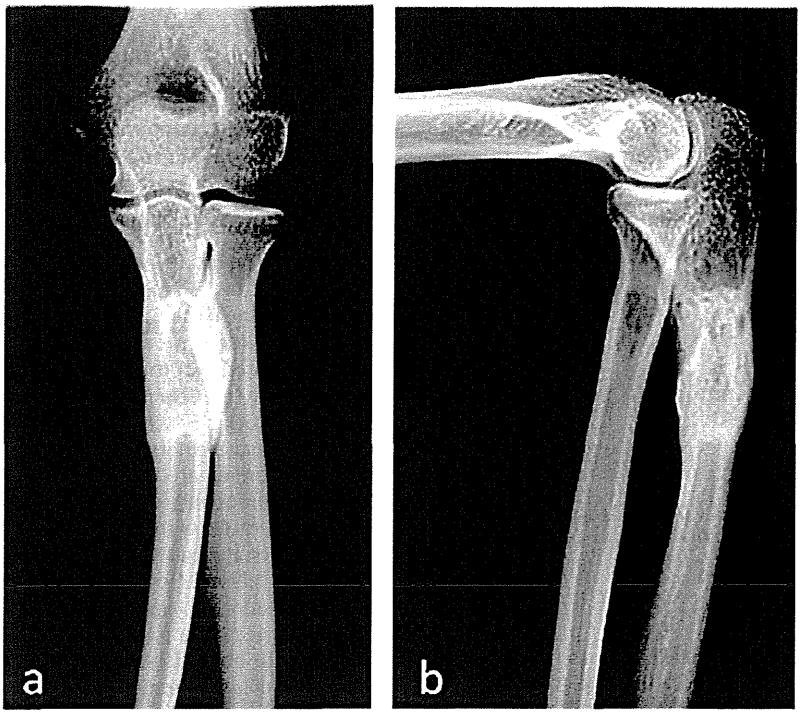

Fig. 5. Anteroposterior (a) and lateral (b) plain radiographs after 3.5 years of surgery, showing complete graft incorporation and no recurrence.

lesion, (2) sclerotic margins, (3) lobulated or trabeculated contours, (4) cortical expansion, and (5) absence of central calcification.[7–9] However, the radiographic findings are non-specific. It is difficult to differentiate intraosseous neurilemmoma from other benign neoplasms of such osseous lesions, including solitary bone cyst, aneurysmal bone cyst, giant cell tumor, non-ossifying fibroma, benign fibrous histiocytoma, desmoplastic fibroma, fibrous dysplasia, chondromyxoid fibroma, and enchondroma. On CT, we can confirm the origin of the tumor when there is soft tissue extension of the tumor. If the origin is intraosseous instead of periosteal, no periosteal reaction is seen, and the edge of the destructed cortex will be overhung by a soft tissue mass. Young and colleagues pointed out that the aspect of the overhanging edges of cortical bone can assist in distinguishing between an intraosseous desmoplastic fibroma versus a periosteal desmoplastic fibroma.[12] Similarly, intraosseous neurilemmoma is considered to originate from intraosseous nerves rather than from periosteal nerves, if CT shows overhanging edges of cortical bone. In our case and in others,[13–15] CT showed that the tumor had invaded into the cortex. This may be the characteristic finding of intraosseous neurilemmoma provided the tumor expands within the nutrient canal of the cortex.

The final diagnosis of intraosseous neurilemmoma was not made until after histologic examination of tissue obtained during excision. The histologic features of intraosseous neurilemmoma are similar to those of soft tissue neurilemmoma. Microscopically, neurilemmoma has identifiable Antoni A and Antoni B regions. The diffuse immunoreactivity for S-100 protein is indicative of a Schwann cell origin, and helps distinguish this tumor from other benign spindle cell lesions of similar histology.

The recommended treatment for intraosseous neurilemmoma is conservative resection and bone grafting, as malignant change is extremely rare. Recurrence also is rare following complete local excision. In previous reports, after performing only curettage, curettage and bone grafting, or en block resection, local recurrence only occurred in 2 cases.[16,17] These authors did not refer to the reason for local reference, but recurrence of the tumor is not evidence of malignant transformation. In our case, there was no evidence of recurrence.

4. Conclusion

Owing to the infrequency of an intraosseous neurilemmoma, the diagnosis is often not even suspected until histologic evaluation after a biopsy. Although very rare, intraosseous neurilemmoma should be taken under consideration in the differential diagnosis of painful, radiographically benign-appearing osseous tumor around the elbow.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical approval

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contributions

Case report writing, data collection, and discussion writing were done by Munehisa Kito and Yasuo Yoshimura. Discussion writing was carried by Ken'ichi Isobe, Kaoru Aoki, Takashige Momose, and Hiroyuki Kato.