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Percutaneous ultrasound-guided laser ablation for the treatment of cervical tuberculous lymphadenitis: a pilot study

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Abstract

Objective: This study was performed to assess the feasibility, effectiveness, and safety of percutaneous ultrasound (US)-guided laser ablation (LA) for the treatment of cervical tuberculous lymphadenitis (CTBL).

Methods: We retrospectively reviewed 11 patients with CTBL (mean age, 32.0 ± 8.6 years; range, 18–47 years) who underwent percutaneous US-guided LA from June 2014 to December 2016 with a subsequent 12-month follow-up. We assessed the mean volume reduction and contrast-enhanced US (CEUS) changes of the target lymph nodes as well as the tolerability and adverse effects of LA.

Results: The mean ablation energy was 522 ± 312 J (range, 204–1317 J). All 17 enrolled target lymph nodes were completely non-enhanced after LA treatment as detected by CEUS, indicating complete ablation of all lymph nodes (100%). The target lymph nodes significantly decreased in volume by a mean of 74.0% ± 15.6% from baseline to 12 months after LA. The LA procedure was well tolerated, and none of the 11 patients developed severe complications during the 12-month follow-up.

Conclusion: Percutaneous US-guided LA for the treatment of CTBL exhibits good tolerability, minimal invasiveness, and few adverse effects. Further investigations with larger sample sizes and longer follow-up periods are warranted to confirm these findings.

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Introduction

According to the recent Global Tuberculosis Report, tuberculosis (TB) is one of the 10 leading causes of death, and approximately 1.7 million people died of TB worldwide in 2016.[1] Extrapulmonary TB, which is a form of TB involving organs other than the lung, accounts for a crucial proportion (8%–24%) of cases of TB.[1] Lymph node TB is considered to be the most common form of extrapulmonary TB, and cervical tuberculous lymphadenitis (CTBL) accounts for 60% to 90% of all cases of lymph node TB.[2] Combination treatment with various anti-tuberculous drugs is currently the first-choice treatment for CTBL. However, an increasing number of drug-resistant *Mycobacterium tuberculosis* strains and low blood flow in the vessels near lymph nodes affected by CTBL may cause the pathogenic bacteria to remain in a latent state for a long time, thereby inducing several complications including enlargement of the original lesions, infection of other important tissues, and the formation of sinus tracts.[3–7] When severe complications occur, patients with CTBL may require surgical treatment, resulting in a large surgical wound that does not readily heal.[3–7] Thus, the development of a novel approach with minimal invasiveness and high efficacy for the treatment of CTBL would be of great clinical value.

Ultrasound (US)-guided thermal ablation including laser ablation (LA) has gained broad attention and widespread acceptance as a minimally invasive technique for the treatment of various disorders in recent decades.[8–11] Although good therapeutic outcomes of LA for the treatment of metastatic retroperitoneal lymph nodes have been obtained,[12] the therapeutic feasibility and effect of LA on CTBL remains unclear. We performed percutaneous US-guided LA on 17 cervical lymph nodes of 11 patients with CTBL and investigated the feasibility, treatment outcome, and safety of this technique with the aim to facilitate clinical treatment of CTBL.

Patients and methods

Patients

We retrospectively reviewed patients who were diagnosed with CTBL and underwent percutaneous US-guided LA of the cervical lymph nodes in the Department of Ultrasonography of Hangzhou Red Cross Hospital, Hangzhou, China from June 2014 to December 2016. This study was approved by the institutional review board of Hangzhou Red Cross Hospital, Hangzhou, China, and written informed consent was voluntarily provided by all patients. Preoperative routine examinations of coagulation function were performed on all patients. For those who were undergoing anticoagulant therapy, drug withdrawal was requested 1 week before LA treatment.

Methods

We used a MyLab 90 ultrasound system (Esaote, Genova, Italy) with an LA523 probe and an iU22 ultrasound system (Philips, Amsterdam, The Netherlands)

with L12-5 and L9-3 probes. LA was performed with a Nd:YAG laser ablation system (EchoLaser X4; Elesta s.r.l., Florence, Italy) in a continuous mode with a wavelength of 1064 nm, in which the penetration of light in the infrared spectrum is optimal.

All patients were kept in the supine position with their neck fully exposed. Before LA, conventional US and contrast-enhanced US (CEUS) examinations were conducted to measure the three diameters (largest diameter and other two perpendicular diameters) and blood supply of the lymph node, respectively. LA was then conducted according to a previous report.[13] After local anesthesia of the skin, a 21-gauge needle was inserted into the target lymph node along its long axis under US guidance. After correct positioning of the needle, the needle core was extracted. A 300-μm quartz bare fiber was then introduced and advanced into the tip of the needle through the needle sheath. A 0.5-cm distance between the tip of the laser fiber and distal borderline of the target lymph node was kept to ensure safety. LA was performed at a fixed output power of 3 W. The lighting time of LA was modified based on the size of the lesion. The LA procedure did not end until the gas produced completely covered the entire lesion during LA. If the target lymph node was close to vital tissues or organs, ≤30 mL of normal saline was pre-injected between the target lymph node and these important structures.

After LA treatment, CEUS was performed to assess the size of the ablation zone. In cases of residual enhancement as detected by CEUS, an additional LA procedure was conducted during the same treatment session.[13] SonoVue (59 mg SF6 powder dissolved in 5 mL saline) was applied for CEUS.

During and after the LA procedure, postoperative reactions and potential adverse effects such as pain, hemorrhage, and peripheral tissue lesions were monitored and recorded. Both CEUS and LA were performed by two sonographers with more than 5 years of experience. At 1, 3, 6, and 12 months after the procedures, the volume and blood supply of the target lymph node were detected by conventional US and CEUS, respectively. Complications were also recorded and followed. The volume of the lymph node was calculated as $V = \pi/6abc$ (where V is volume, a is the largest diameter, and b and c are the other two perpendicular diameters), and the the volume reduction percentage was calculated as $([\text{initial volume} - \text{final volume}] \times 100)/\text{initial volume}$.[14]

Statistical analysis

Values are presented as mean ± standard deviation and were compared with a paired Student's t test, if appropriate. All data were analyzed with IBM SPSS Statistics, version 23 (IBM Corp., Armonk, NY, USA). A P value of <0.05 was considered statistically significant.

Results

Ultrasound guidance and LA

We evaluated 17 lymph nodes of 11 patients (4 male, 7 female; mean age, 32.0 ± 8.6 years; range, 18–47 years). At baseline, the mean maximum diameter of the 17 lymph nodes ranged from 1.4 to 2.0 cm (mean, 1.62 ± 0.2 cm), the mean short-axis diameter ranged from 0.6 to 1.6 cm (mean, 0.9 ± 0.3 cm), and the mean volume ranged from 0.4 to 2.1 mL (mean, 1.05 ± 0.44 mL) (Table 1). The total energy applied for each lymph node ranged from 204 to 1317 J (mean, 522 ± 312 J). At the time of post-LA treatment, CEUS demonstrated that 88.2% (15/17) of the lymph nodes achieved complete non-enhancement, while the remaining 11.8% (2/17) exhibited local residual enhancement and thus underwent

Table 1. Mean volume and volume reduction percentage of the lymph node before and after ultrasound-guided laser ablation.

	Baseline	1 month	3 months	6 months	12 months
Mean volume	1.05 ± 0.44 mL	0.91 ± 0.38 mL	0.78 ± 0.33 mL	0.64 ± 0.29 mL	0.30 ± 0.24 mL
Volume reduction percentage	0.0% ± 0.0%	12.9% ± 8.7%	23.9% ± 13.8%	38.3% ± 12.5%	74.0% ± 15.6%
P value (*vs.* baseline)		0.001	<0.001	<0.001	<0.001

Data are presented as mean ± standard deviation.

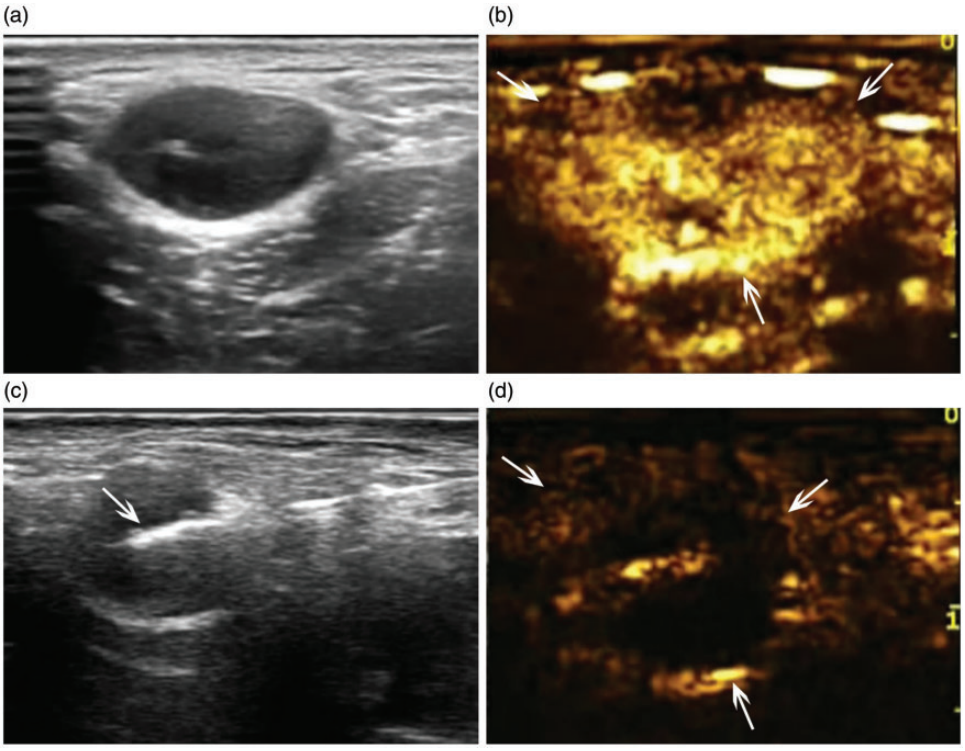

Figure 1. A 23-year-old female patient with cervical tuberculous lymphadenitis undergoing ultrasound (US)-guided laser ablation (LA) treatment. (a) Longitudinal conventional US of the neck demonstrates a tuberculous lymph node with a well-defined margin and internal heterogeneous echogenicity. (b) Contrast-enhanced US (CEUS) before LA treatment demonstrates heterogeneous enhancement of the entire lymph node (arrows). (c) Conventional US during LA treatment demonstrates that the fiber is accurately inserted into the center of the lymph node, with hyperechoic gas microbubbles produced at the tip of the optical fiber (arrow). (d) After LA treatment, CEUS demonstrates that the ablation zone is non-enhanced (arrows) and that the internal hyperechogenicity indicates gas microbubbles generated by tissue heating (arrowhead).

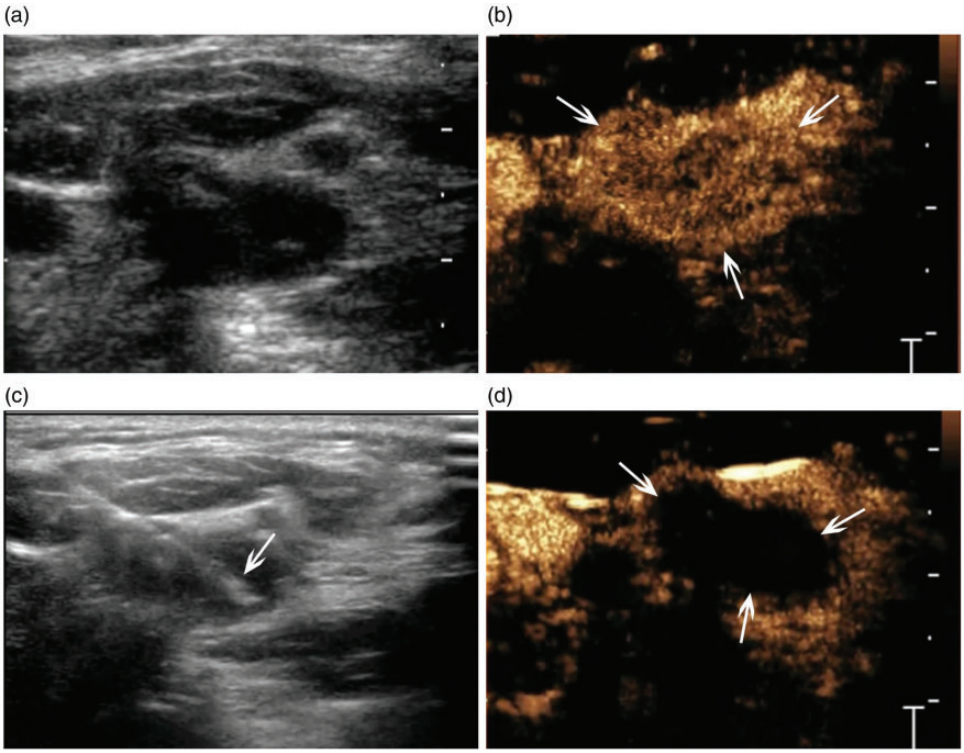

Figure 2. A 35-year-old male patient with cerivial tuberculous lymphadenitis undergoing ultrasound (US)-guided laser ablation (LA) treatment. (a) Longitudinal conventional US of the neck demonstrates a tuberculous lymph node with a well-defined margin and internal heterogeneous echogenicity. (b) Before LA treatment, contrast-enhanced US (CEUS) demonstrates heterogeneous enhancement of the entire lymph node, containing internal punctate non-enhancement (arrows). (c) During LA treatment, conventional US demonstrates accurate positioning of the fiber with gas microbubble-induced hyperechogenicity at the tip (arrow). (d) After LA treatment, CEUS demonstrates complete non-enhancement of the ablation zone (arrows).

an additional LA treatment. Ultimately, all 17 lymph nodes (100%) achieved complete non-enhancement after LA treatment as detected by CEUS (Figures 1, 2), indicating complete ablation in all target lymph nodes.

Clinical follow-up

LA treatment induced progressive shrinkage of the target lymph nodes. The mean volume of the lymph nodes decreased from 1.05 ± 0.44 mL at baseline to 0.91 ± 0.38 mL at 1 month, 0.78 ± 0.33 mL at 3 months, 0.64 ± 0.29 mL at 6 months, and 0.30 ± 0.24 mL at 12 months. The mean volume reduction percentage was markedly increased by $12.9\% \pm 8.7\%$ at 1 month, $23.9\% \pm 13.8\%$ at 3 months, $38.3\% \pm 12.5\%$ at 6 months, and $74.0\% \pm 15.6\%$ at 12 months (all $P \leq 0.001$ *vs.* baseline). One of the 17 lymph nodes nearly disappeared at the 12-month follow-up as detected by conventional US. The mean volume and mean volume reduction percentage of the lymph nodes are summarized in Table 1.

Adverse effects

During and after LA treatment, none of the 11 patients (0%) developed severe adverse effects such as hemorrhage, nerve injury, or sharp pain. Of the 11 patients, only 1 (1%) developed mild cervical pain (grade 3) on the day of LA treatment but soon recovered during the following few days, and 1 (1%) had a low-grade fever of 38.0°C for 2 days that decreased to normal during the following few days.

Discussion

LA treatment has gained increasing attention worldwide during the past few decades because of its minimal invasiveness and good cosmetic outcome. It has been broadly accepted as a valid thermal technique for the treatment of hepatic and thyroid disorders; however, it is still in the prototype stage for the treatment of lymph node diseases.[8–12] Accumulating evidence demonstrates that percutaneous US-guided LA is a feasible, effective, and minimally invasive approach for the treatment of metastatic lymph nodes.[13–15] Therefore, we hypothesized that LA may also be feasible and effective for the treatment of patients with CTBL who cannot undergo surgery or are unresponsive to anti-tuberculous drugs.

Mauri et al.[13] performed percutaneous US-guided LA on 46 fluorodeoxyglucose positron emission tomography/computed tomography–positive cervical nodal metastases using a single optical fiber for nodal metastases with a short-axis diameter of $\leq$1 cm and two fibers for those of >1 cm. They achieved technical success in all 46 lymph nodes; moreover, 1-year local control was obtained in 40 of 46 (87%) lymph nodes and 3-year local control in all 25 actively followed lymph nodes (100%),[13] indicating the high efficacy of LA for treating lymph node disease. Although the short-axis diameter of the lymph nodes in the present study ranged from 0.6 to 1.6 cm, a single fiber was chosen for all of the target lymph nodes. The CEUS guidance during the LA procedure indicated that complete ablation was achieved in all lymph nodes. Thus, our results indicate that percutaneous US-guided LA treatment with a single fiber is likely to achieve effective ablation of CTBL.

In the present study, we found that the US-detected hyperechoic rim was clear in the short term after LA treatment but that it became blurred as time went on. This indicated that conventional US might be unable to accurately assess the ablation zone after a long period of LA treatment.[16] Due to the favorable characteristics of CEUS in detecting the microcirculation of lymph nodes, CEUS has been widely used as an objective tool to guide thermal ablation treatment.[13,17] In the present study, we found that the size of the non-enhanced, well-defined LA zone detected by CEUS was smaller than that measured by conventional US. This was probably due to the evaporation of lymph node necrosis or to the penetration of microbubbles in the blood vessels into the surrounding tissues.[18] Therefore, CEUS can more accurately reflect the ablation zone, evaluate the degree of thermal damage in real time, and determine whether additional ablation is needed.[19,20]

Mauri et al.[21] also used CEUS to assess the therapeutic effect of percutaneous US-guided LA on 24 cervical metastatic lymph nodes and performed an additional ablation for 2 lymph nodes based on the results of CEUS. Thus, CEUS might be of high clinical value in the real-time evaluation of the treatment outcome of LA and in making proper decisions regarding the LA procedure. With the use of CEUS, we optimized the needle insertion path and performed an additional ablation for the residual enhanced regions in 2 of 17 lymph nodes (11.8%). Ultimately, after the

additional ablation, these two lymph nodes exhibited complete non-enhancement as detected by CEUS, indicating the achievement of complete ablation. Of the two lymph nodes, one was closely adjacent to the carotid artery. The excessive injection of sealing liquid to protect the artery and the flow of blood in the artery might account for incomplete ablation of this lymph node. However, the other lymph node was not next to an artery, and the reason for the lack of complete ablation in this node was inconclusive. Nevertheless, CEUS clearly plays a crucial role in determining complete ablation.

The volume reduction percentage of lymph nodes is considered a significant indicator of the therapeutic effects of LA treatment. In one study, LA induced progressive volume reductions of cervical lymph nodal metastases in patients with papillary thyroid cancer, with a significant mean volume reduction of $87.7\% \pm 0.11\%$ at the 12-month follow-up ($P < 0.01$ *vs.* baseline).[22] Similarly, our study showed that the volume of the target lymph nodes was markedly reduced by about 70% at the 12-month follow-up ($P < 0.001$ *vs.* baseline). At the 1-month follow-up, the mean volume of the 17 lymph nodes was also significantly reduced by $12.9\% \pm 8.7\%$ (P value approached 0.001 *vs.* baseline), whereas the mean volume of 3 of 17 (17.6%) lymph nodes was not altered at the 1-month follow-up. The reason for this phenomenon might be the slow absorption of the LA-induced necrosis or the presence of residual/recurrent lesions. Some investigators have proposed that CEUS can assess the blood supply to the lesions in a more convenient, more powerful, and highly repeatable manner and that CEUS changes can be used as another indicator to evaluate the effects of LA treatment and identify residual/recurrent lesions.[23] In the present study, the volume of 3 of the 17 lymph nodes remained unchanged or not obviously changed at the 1-, 3-, and 6-month follow-ups, while the volume was significantly reduced by >50% at the 12-month follow-up compared with baseline. Notably, CEUS revealed no enhancement in these lesions at any of these follow-up time points, indicating slow absorption of the lesions rather than residual or recurrent lesions in these three lymph nodes at the initial follow-up. Thus, CEUS can allow for more accurate and earlier evaluation of the therapeutic effects of LA than calculation of the change in lymph node volume.

No patients in our study developed severe complications, Only one developed mild pain in the neck and one developed a low-grade fever after the LA procedure. One possible reason for the absence of severe complications is the correct positioning of the fiber under US guidance and accurate control of the output energy. Another possible reason is the continuous injection of normal saline to guarantee adequate supplementation of liquid when peripheral tissues were undergoing LA treatment.

Several limitations of the present study should be taken into account. First, the sample size of our study was relatively small. Second, we did not include lymph nodes with bulky calcifications or large areas of necrosis; however, both of these are common characteristics of lymph node TB. Third, we only collected data during a short-term follow-up period of 12 months. Fourth, we used an US-only approach rather than combining US with other imaging modalities such as computed tomography and magnetic resonance imaging to evaluate the efficacy of LA treatment on the target lymph nodes. Fifth, we did not correlate our imaging findings with pathological results. Finally, previous research has shown that ablation might stimulate the immune system, resulting in a systematic response to a local treatment.[8] Ablation-induced cavitation, which does not result in thermal destruction and denaturation of

proteins, is likely to be a potential mechanism of ablation-stimulated immunomodulation.[8] Immunomodulation is thought to play a significant role in tumor control. However, the mechanisms underlying the onset of immune responses to *M. tuberculosis* remain poorly understood.[24] The immunomodulatory effects and mechanisms of local ablation therapy for CTBL require further investigation.

Despite these limitations, our pilot study indicates that percutaneous US-guided LA is a feasible approach to the effective treatment of CTBL and is characterized by minimal invasiveness, few adverse effects, and a good cosmetic outcome. Thus, percutaneous US-guided LA may be regarded as an alternative to surgery for the management of CTBL. Further studies with larger sample sizes, longer follow-ups, and multiple imaging modalities are necessary to confirm the efficacy of LA for treatment of CTBL.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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