

Senile Lemierre syndrome complicated with descending necrotizing mediastinitis

A case report

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Abstract

Rationale: Senile patients with LS complicated with DNM are rarely seen in clinical practice, and extensive cervical incision and drainage plus administration of effective antibiotics are the basis for treatment. Currently, the treatment controversy mainly has focused on whether mediastinal incision and drainage is necessary for patients with type I DNM, and whether anticoagulation therapy is required for jugular venous emboli and distant metastatic emboli induced by LS.

Patient concerns: A female, 76 years old, developed pain of tonsil on right side 5 days ago, and felt that the pain aggravated complicated with dysphagia and swelling pain of neck on both sides since then.

Diagnoses: She was diagnosed with LS complicated with type I DNM.

Interventions: Tazobactam and Piperacillin 4.5 q8h and Ornidazole 100 ml q6h ivgtt were administered empirically, and secondary extensive cervical incision and drainage was performed under general anesthesia, after which low molecular weight heparin 4250 U q12h SC was administered. G test was performed 3 days later, which showed (1,3)- β -D-glucan >1000 pg/ml. Bridging anticoagulation therapy, low molecular weight heparin 4250 U q12h SC, and Warfarin 2.5 mg qd po were given one week later. Low molecular weight heparin SC was discontinued and only Warfarin po was administered after treatment of bridging therapy for 3 days.

Outcomes: CT of head and neck was reexamined on post-admission d24 and revealed that neck infection was improved on both sides, jugular vein distension on right side was restored to normal, abscess and pneumatosis of superior mediastinum were improved, distension of pulmonary artery on both sides was normalized, WBC was $9.94 \times 10^9/L$, neutrophil count was $4.43 \times 10^9/L$, CRP level was 9.8 mg/L, D-D level was 0.81 mg/L, PCT level was 0.800 ng/mL and G test suggested (1,3)- β -D-glucan pf 27.1 pg/mL.

Lessons: Concomitant use of anticoagulants on the basis of repeated cervical incision and drainage + administration of effective antibiotics can obtain excellent therapeutic efficacy in the treatment of patient with LS complicated with type I DNM.

Abbreviations: BP = blood pressure, CNF = cervical necrotizing fasciitis, CRP = C-reactive protein, CT = computer tomography, D-D = D-dimer, DNM = descending necrotizing mediastinitis, ICU = intensive care unit, INR = international normalization ratio, LS = Lemierre syndrome, PCT = procalcitonin, WBC = white blood cell count.

Keywords: anticoagulant, descending necrotizing mediastinitis, infectious thrombophlebitis, Lemierre syndrome

1. Introduction

Lemierre syndrome (LS) is a kind of clinical syndrome that has potential fatal risks, and it is secondary to acute oropharyngeal infection. The most common pathogenic bacterium is anaerobic necrophorum (a kind of fastidious bacteria *Fusobacterium*), which can spread through parapharyngeal space, or invade jugular vein by way of lymphatic circulation system and tonsillar venous

system, thereby resulting in infectious thrombophlebitis. After the bacterial emboli enter into lung circulation system, the disease is mainly marked by pulmonary septic embolism, pulmonary abscess and pleural effusion, etc. In 1936, LS was initially named by Lemierre in his report. Moreover, under the action of multiple factors like gravity, respiration, and intrathoracic negative pressure, the infection can also develop into cervical necrotizing fasciitis (CNF) along carotid sheath or deep cervical fascia through connective tissue space, and spread to mediastinum through substernal space, consequently triggering descending necrotizing mediastinitis (DNM).^[1-3] Clinically, senile patients with LS accompanied by DNM have been rarely reported, for whom the current treatment has highlighted radical cervical incision and drainage plus administration of effective antibiotics, while mediastinal incision and drainage plus administration of anticoagulants is still controversial.^[3] This study mainly reported on a senile patient with LS accompanied by DNM who was treated with radical cervical incision and drainage plus administration of effective antibiotics and anticoagulants, with favorable efficacy obtained. The details are reported as follows.

2. Case description

A female, 76-years old, developed pain of tonsil on right side 5 days ago, and felt that the pain aggravated complicated with

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The authors declare no conflicts of interest.

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dysphagia and swelling pain of neck on both sides since then. She was healthy at usual, and denied of history of infectious diseases. The prophylactic inoculation was conducted as required. She denied history of surgical trauma, blood transfusion, or allergies to food or drugs. No history of surgery was recorded. She denied history of smoking or drug addiction. She had no contact with infected water or life in an epidemic region, and had no history of contacting with industrial poisons, dust, or radioactive substances. She had no history of feculent sexual intercourse. She got married and had birth at proper age. Her mate and children were healthy. She had menophania at the age of 14 years, and had had amenorrhea already. She denied history of any familial genetic diseases. Physical examinations on admission: she complained of pain, hoarseness, dysphagia, polypnea, cyanosis of mouth and lips, diffusive swelling pain of neck on both sides, high skin temperature, local crepitus (which was more significant on right side), swelling of tonsil and pharynx on right side with severe haphalgnesia, and congestion and edema of epiglottis. White blood cell count (WBC) was $12.5 \times 10^9/L$, neutrophil count was $10.23 \times 10^9/L$, C-reactive protein (CRP) level was 72.8 mg/L, temperature was 39°C, respiratory rate was 24/minute, pulse was 118/minute, and blood pressure (BP) was 88/50 mmHg. As the patient had suffered asphyxia, extensive incision, and drainage + tracheotomy were conducted for cervical abscess under general anesthesia immediately, with lots of purulent fluid drained. Blood and purulent fluid were collected from multiple body parts for the conduction of blood and pus culture. The patient was transferred to intensive care unit (ICU) after operation. Computer tomography (CT) of neck was conducted on post-admission day 2, which revealed diffusive swelling combined with pneumatosis in submandibular space, parapharyngeal space, and anterior tracheal space on both sides (Fig. 1). CNF induced by tonsillitis on right side was considered. Tazobactam and piperacillin 4.5 q8 hours and ornidazole 100 mL q6 hours intravenous glucose tolerance test (IVGTT) were administered empirically, after which blood and pus cultures were performed and showed *F necrophorum* infection. Surgical field on neck was washed repeatedly to remove necrotic tissues after operation. Although patient's respiration had been stabilized, purulent fluid on neck was not reduced prominently, and no decrease of temperature or WBC was found. On day 10 after admission, flushing of anterior cervical triangle was found, anterior edge of sternocleidomastoid

on right side was streaky in shape complicated with haphalgnesia and pain of thoracic wall, temperature was 39.2°C, respiratory rate was 23/minute, pulse was 122/minute, BP was 100/65 mmHg, blood WBC was $28.3 \times 10^9/L$, neutrophil count was $26.43 \times 10^9/L$, CRP level was 26.5 mg/L, procalcitonin (PCT) level was 15.080 ng/mL, and D-dimer (D-D) level was 18.74 mg/L. CT of neck and chest was conducted and suggested that the cervical abscess and pneumatosis were not improved on either side, and extensive filling defect was found in jugular vein on right side from basis cranii to the level of thyroid cartilage; abscess and pneumatosis were found in superior mediastinum, pleural effusion, and inflammatory nodes were noticed on both sides, and filling defect was observed in pulmonary artery on both sides (Fig. 2). Therefore, the patient was diagnosed with LS complicated with type I DNМ. Color ultrasound of deep and superficial veins of lower limbs on both sides was conducted on bedside, which excluded phlebothrombosis of both lower limbs. After consultation of all doctors in our hospital, it advised that the primary antibiotic regimen was continued, and secondary extensive cervical incision and drainage was performed under general anesthesia, after which low molecular weight heparin 4250 U q12 hours SC was administered. G test was performed 3 days later, which showed (1,3)- β -D-glucan >1000 pg/mL. Bridging anticoagulation therapy, low molecular weight heparin 4250 U q12 hours SC, and Warfarin 2.5 mg qd po were given 1 week later. Low molecular weight heparin SC was discontinued and only Warfarin po was administered after treatment of bridging therapy for 3 days. International normalization ratio (INR) was monitored constantly and controlled in 2-3. CT of head and neck was reexamined on post-admission day 24 and revealed that neck infection was improved on both distension of jugular vein on right side was restored to normal, abscess and pneumatosis of superior mediastinum were improved, distension of pulmonary artery on both sides was normalized (Fig. 3), WBC was $9.94 \times 10^9/L$, neutrophil count was $4.43 \times 10^9/L$, CRP level was 9.8 mg/L, D-D level was 0.81 mg/L, PCT level was 0.800 ng/mL, and G test suggested (1,3)- β -D-glucan pf 27.1 pg/mL. After discharge, Penicillin po and Warfarin po were continued for 4 weeks and 12 weeks respectively, and INR was monitored and controlled in 2-3. Twelve weeks after discharge, CT of chest was reexamined and demonstrated that pulmonary arterial emboli never reoccurred, and color ultrasound of jugular vein was

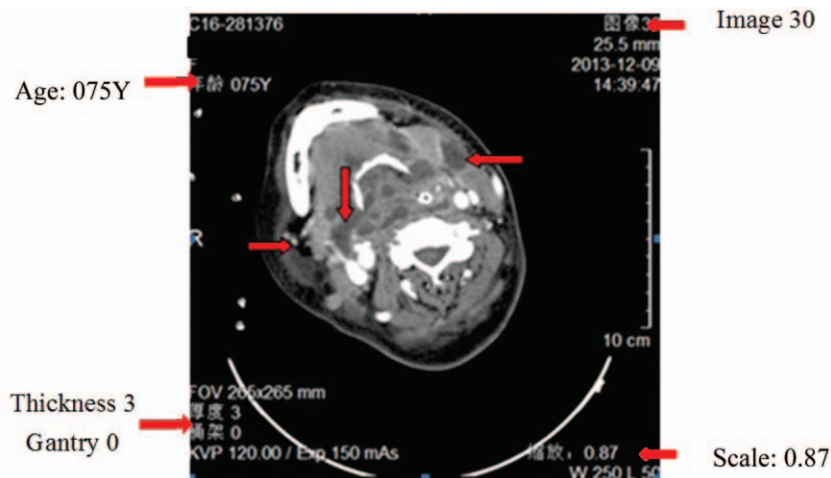


Figure 1. CT images on post-admission day 2: Pneumatosis and effusion in multiple cervical spaces.

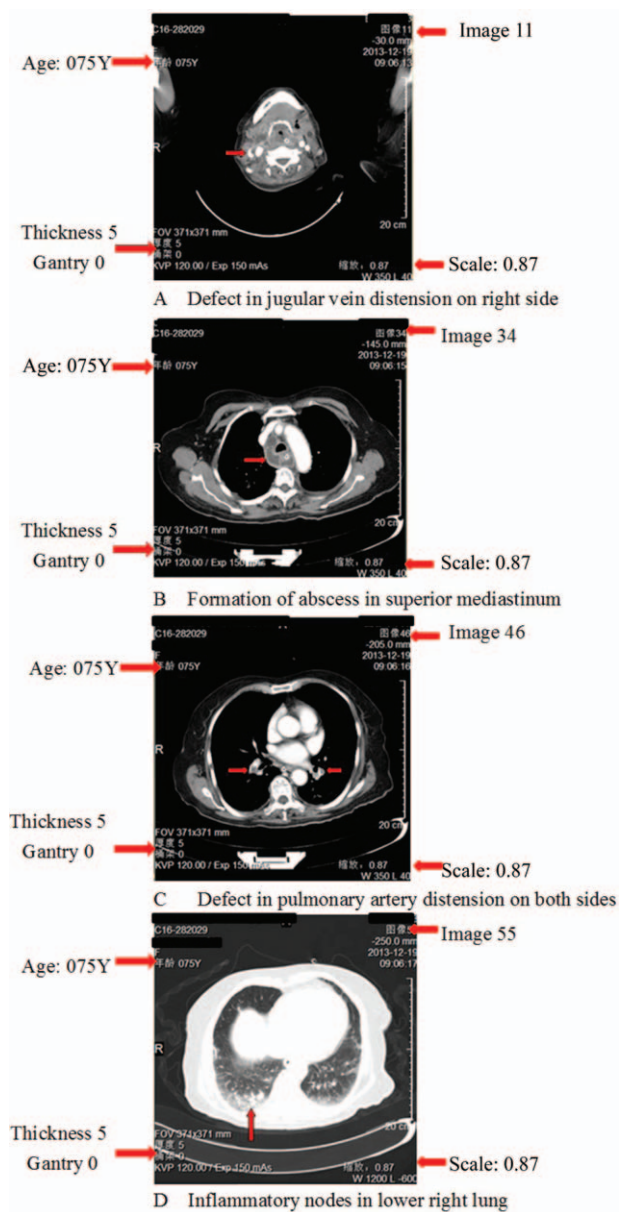


Figure 2. CT images of neck and chest on post-admission day 10.

reexamined and indicated that thrombi disappeared completely. This study had been approved by the Ethics Committee in our hospital and the patient had signed the informed consent form of surgery. The patient had provided informed consent for publication of the case.

3. Discussion

CNF, as a serious soft tissue inflammation of neck induced by mixed infection of multiple bacteria, occurs more frequently in odontogenic infection and pharyngeal infection, and is characterized by necrosis of subcutaneous tissues as well as deep and superficial fascia of neck.

DNM is a serious complication of CNF.^[4] It can result in extensive phlegmon and formation of abscess, or even complication of septicopyemia in mediastinum.^[2,4-12] Its morbidity was between 16.7% and 30.4%.^[6,7] Sarna et al^[2] pointed out that mediastinitis and septicopyemia were primary causes for the death

of patients with CNF, and the mortality in patients with CNF complicated with DNM plus septicopyemia was up to 64%. There is still controversy specific to the surgical protocol for CNF complicated with type I DNM.^[2,4-12] Endo et al^[9] based on local mediastinal anatomy, classified DNM into following types: type I: infection of superior mediastinum with above bronchial bifurcation; type IIA: infection invading lower anterior mediastinum; and type IIB: infection invading lower posterior mediastinum. As to the treatment, extensive neck incision and drainage is advised for type I DNM while extensive cervical drainage and thoracotomy drainage for type II DNM. Estrera et al^[10] believed that single cervical incision for mediastinal drainage was effective in the treatment of type I mediastinitis above juga or parallel to the 4th thoracic vertebra. Sakamoto et al^[11] believed that cervical incision and drainage was the golden standard for the treatment of DNM as it was small in trauma and easy to be accepted by patients, and only when DNM had been controlled by cervical incision and drainage could radical thoracotomy for thoracic drainage be performed. However, Osiwa et al^[12] considered that single cervical incision could not radically open the fascia separation around trachea even when the infection was above bronchial bifurcation as the infection around trachea was often separated by fascia, and that the cured rate of both cervical and thoracic drainage was evidently higher than that of single cervical drainage. Hudorovic et al^[13] presented that early conduction of trans-thoracic mediastinal drainage and cervical and thoracic drainage had significant advantages in cured rate. Patients' mortality was 47% after cervical incision and drainage, and was 19% after combined trans-thoracic drainage. Above relevant studies demonstrated that relative to traditional thoracoscopic mediastinal drainage, radical cervical incision, and drainage has least surgical trauma and short in surgical duration and can greatly relieve patients' pain, avoid serious postoperative complications like sternal osteomyelitis and shorten the length of hospital stays.

In this study, although tazobactam and piperacillin plus ornidazole sensitive to *F necrophorum* were administered, patient's cervical infection was not controlled, and instead, it spread to superior mediastinum. The reasons were that the cervical incision and drainage required opening of all cervical spaces to radically eliminate necrotic fascia tissues to the greatest extent, but cervical fascia system was complex and contained important structures like carotid arteries, trachea, esophagus, and nerves, which might also be damaged during disposable elimination of necrotic tissues, consequently bringing about fatal results. Therefore, it was impossible to radically eliminate cervical inflammation by surgery for once. In addition, although the infection of this patient spread of superior mediastinum, the anatomical structure of oropharynx and neck had certain consistency and superior mediastinum did not have structure separated with cervical fascia, thus single large incision and extensive radical drainage of neck could achieve target of inhibiting the spread of infection to the whole mediastinum and preventing drainage in superior mediastinum. Considering above reasons, patient's cervical fascia systems were opened radically and lots of necrotic tissues were eliminated by repeated operations, after which patient's mediastinal infection was effectively controlled. Therefore, it was concluded that repeated cervical incision and drainage not only could safely open the cervical spaces, but also can radically eliminate unceasingly formed necrotic fascia tissues, thus achieving the target of upper mediastinal drainage. Meanwhile, it was also small in surgical trauma and short in surgical duration, and could effectively alleviate patients' pain.

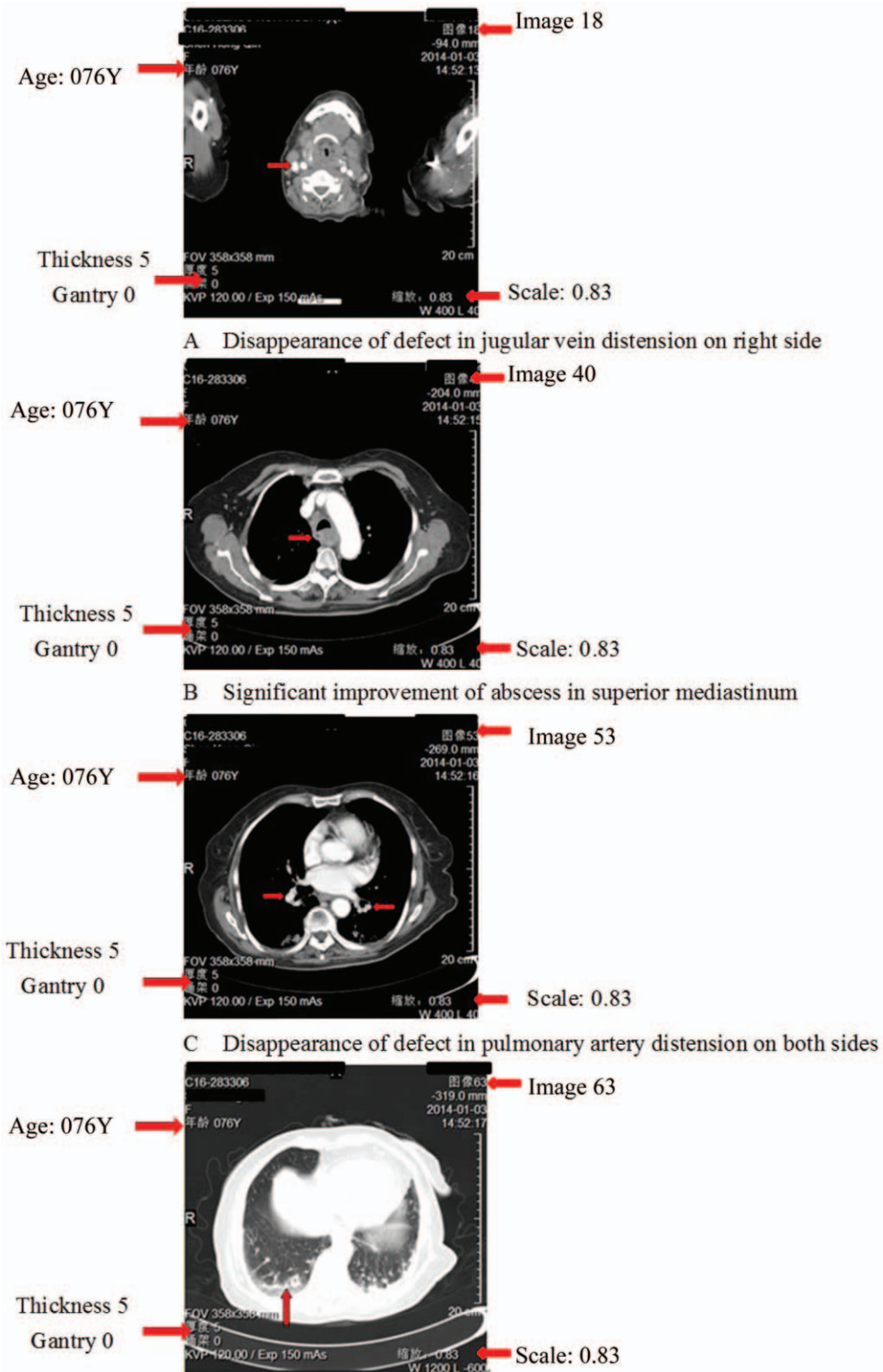


Figure 3. CT images of neck and chest at post-anticoagulation week 2.

LS occurs more frequently in children and young populations. A study from Denmark shows that LS morbidity was 14.4 per million in populations at the age of 14 to 24 years. In 2007, Riordan analyzed the clinical data of 222 LS patients with mean age of 19 years, and the results indicated that LS occurred in 89% patients at the age of 10 to 35 years, but rarely occurred in senile

patients, and the reasons were unknown.^[14] LS symptoms start from tonsillitis, oropharyngeal swelling pain, and fever, followed by high fever and unilateral enlargement of cervical lymph nodes. It's typical manifestations are marked by streaky vascular swelling and epidermal congestion with positive haphalgnesia along the running way of sternocleidomastoid, infectious cervical

thrombophlebitis as well as local or hematogenous-spread pyogenic infection, which is closely associated with deep cervical infection.^[1,14–16] If CNF is complicated, it will lead to diffusive swelling pain in cervical soft tissues and subcutaneous pneumatosis with significant crepitus, and CT of neck can clearly show jugular space-occupying bacterial thrombi which can enter into pulmonary circulation through brachiocephalic veins, superior vena cava and right cardiac atrium, hence CT examinations of lung and mediastinum should also be strictly considered.^[1,15,16]

F necrophorum, as a primary pathogenic bacterium for LS, often produces β -lactamase which is resistant to penicillin. Therefore, enzymatic inhibitor β -lactam antibiotics like ticarcillin/clavulanic acid, ampicillin/sulbactam piperacillin/tazobactam should also be added.^[1–3,15–20] The disease course of using antibiotics has not been concluded currently because the antibiotics cannot easily achieve effective antibacterial concentration locally as the pathogenic bacteria in vomicae and bacterial emboli. Therefore, some scholars advise to consecutively use antibiotics IVGTT for 1 to 2 weeks and sequentially administer isodose β -lactam antibiotics po for about 3 to 6 weeks after symptoms are improved.^[18] As to patients with acute respiratory distress syndrome secondary to septicopyemia, imipenem can be administered for consecutive 12 weeks.^[19]

Some pathological studies have found that lectins, hematoxins, endotoxins, and leukotoxins released by *F necrophorum* can result in purulent phlebitis and platelet aggregation, which can lead to vascular endothelial injury and local hypercoagulability at site of lesions.^[2,18,20,20] Although anticoagulation therapy is an important method for the treatment of deep venous thrombosis, its use for LS is still controversial, and there has been no randomized controlled study currently.^[1,16–18,20,21] However, the dissenters believe that as to early thrombophlebitis, the administration of effective antibiotics can exert the function of eliminating bacterial emboli, while anticoagulants are only advisable for a few patients with infectious thrombophlebitis insensitive to antibiotics not only because the use of anticoagulants will result in the systematic spread of infection and increases patients' risk of potential hemorrhage, but also because the treatment complexity has been increased as the drugs administered should be adjusted based on the results of patients' anticoagulation function that should also be re-examined during treatment.^[1] However, the studies consider that although the antibiotics cannot easily effective antibacterial concentration for the treatment of pathogenic bacteria in vomicae and bacterial emboli, early thrombolytic therapy can expose the bacteria in high-concentration antibiotics, which is beneficial to shortening the use time of antibiotics and reducing the risk of distal spread of bacterial emboli from lung.^[3,17,20] In this study, endotoxin quantitative assay showed that lipopolysaccharide (LPS) was 245.3 pg/mL after treatment with anticoagulants for 3 days, which was considered to be an evidence of plenty of *F necrophorum* being released into blood and exposed in high-concentration antibiotics following dissolution of bacterial emboli in jugular vein and pulmonary artery on both sides. Ten days later, endotoxin quantitative assay was re-conducted and showed that LPS was <5 pg/mL, indicating that administration of antibiotics plus anticoagulants had excellent therapeutic efficacy and the use of anticoagulants did not cause systematic spread of infection.

Lots of studies have proved that administration of anticoagulants on the basis of close monitoring of INR in the treatment of LS rarely trigger any hemorrhagic complications.^[20] However, there still lacks of international uniform standard on how to use anticoagulants for the treatment of IS currently. Wright et al.^[21] advised to use low molecular weight heparin SC

followed by Warfarin po for anticoagulation, and control INR in 2–3, for consecutive ≥ 3 months, but did not describe the time for the alternation of low molecular weight heparin into Warfarin in details. Combing with the therapeutic experiences for this case, the possibility of secondary surgery should also be considered during anticoagulation therapy for the patient with LS complicated with DNM. Therefore, selection of low molecular weight heparin with half-life period of 3 to 5 hours for early anticoagulation could maximally reduce surgery-induced potential hemorrhage. Bridging anticoagulation therapy, that is, low molecular weight heparin SC plus Warfarin po, was conducted 1 week later, and 3 days later after Warfarin played its anticoagulating role, low molecular weight heparin SC was discontinued and only long-term Warfarin was continued for anticoagulation, while INR was closely monitored and controlled in 2–3, after which hemorrhage never reoccurred.

In conclusion, senile patients with LS complicated with DNM are rarely seen in clinical practice, and extensive cervical incision and drainage plus administration of effective antibiotics are the basis for treatment. Currently, the treatment controversy mainly has focused on whether mediastinal incision and drainage is necessary for patients with type I DNM, and whether anticoagulation therapy is required for jugular venous emboli and distant metastatic emboli induced by LS. In this study, concomitant use of anticoagulants on the basis of repeated cervical incision and drainage plus administration of effective antibiotics obtained excellent therapeutic efficacy in the treatment of patient with LS complicated with type I DNM, demonstrating that this therapeutic protocol worthy of being clinically referred. However, this study also has its disadvantages that there has been no randomized controlled study to date as the patients of same kind are less in number and their disease conditions are serious and proceed fast.

Author contributions

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Methodology: Xu Yang, Yi-Fei Yang, Zhi-Chao Zhu.

Project administration: Zhi-Chao Zhu.

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Supervision: Tian-Shu Xu, Yi-Nan Cheng, Zhao-Yao Sun.

Validation: Tian-Shu Xu, Yi-Nan Cheng, Zhao-Yao Sun.

Visualization: Xu Yang, Yi-Fei Yang, Yi-Nan Cheng.

Writing – original draft: Xu Yang.

Writing – review & editing: Xu Yang.

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