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Case Report

Lemierre Syndrome Associated with Ipsilateral Recurrent Laryngeal Nerve Palsy: A Case Report and Review

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Lemierre syndrome (LS) is a rare life-threatening disease that is often caused by an acute oropharyngeal infection with a secondary thrombophlebitis of the internal jugular vein. LS rarely manifests as cranial nerve palsy. To the best of our knowledge, this is the second case report of LS associated with recurrent laryngeal nerve palsy. A 66-year-old female presented to a dental clinic with gingivitis and sore throat. Due to moderate periodontitis, her left first upper molar was extracted. A few days later, she subsequently developed a coarse voice and occipital headaches, and was referred to an otolaryngologist. She was diagnosed with left recurrent laryngeal nerve palsy and subsequent left-sided otitis media, and was referred to us for persistent headaches. She intermittently presented with high-grade fever and complained of salty taste disturbance. Her head magnetic resonance imaging (MRI) revealed left mastoiditis, thrombosis in the left transverse and sigmoid sinus, and left internal jugular vein. Her laboratory tests revealed an elevated white blood cell count, levels of C-reactive protein, and D-dimer. No endogenous coagulopathy was confirmed. Although, blood and cerebrospinal fluid culture grew no microorganisms, respectively, the empirically determined antibiotic therapy was initiated. In a week, the patient defervesced and had no headaches despite persistent thrombosis. Early diagnosis and an immediate antibiotic treatment are crucial for LS patients. Anticoagulation therapy was not needed for our patient and is still controversial for LS.

Keywords: Lemierre syndrome, oropharyngeal infection, recurrent laryngeal palsy, sinovenous thrombosis, antimicrobial therapy

Introduction

Lemierre syndrome (LS) or postanginal sepsis, is a rare but well-characterized life-threatening disease, so called as "the killer sore throat" and proved to be fatal in up to 90% of the patients in the pre-antibiotic era.[1,2)] This disease is often caused by an acute oropharyngeal infection with a secondary thrombophlebitis of the internal jugular vein,[3,4)] and is sometimes followed by a dental extraction,[5)] mastoiditis,[6)] and otitis media.[6)] The postanginal septic infection was first reported by Courmont and Cade in 1890.[7)] but it was Lemierre who defined the clinical entity of the disease describing a series of 20 cases of throat infections with anaerobic septicemia in 1936.[2,8–10)]

After the advent of the antibiotics, the disease has dramatically decreased and only 40 cases were reported from 1950 to 1995.[11)] Although LS was once known as "the forgotten disease," the incidence recently seems to increase again due to more judicious antibiotic prescribing habits or its growing resistance to antibiotics,[4,12,13)] and 9% of the LS patients are still fatal in this century.[3)]

The most frequently implicated microorganism of LS has been reported to be *Fusobacterium necrophorum*, a Gram-negative anaerobic rod that is a part of the normal oropharyngeal flora.[9)] However, the detail in the mechanism of the LS remains poorly understood.

LS rarely manifests as a cranial nerve palsy, and only few cases have been reported to date.[14–18)] To the best of our knowledge, this is the second case report of LS associated with recurrent laryngeal nerve palsy.

Case Presentation

A previously healthy 66-year-old Japanese female presented to a local dental clinic with pain in the swollen left upper gingiva. She was diagnosed with moderate periodontitis, and her left first upper molar was extracted (Fig. 1A). Three days later, she subsequently developed coarse voice and occipital headaches, and visited a neurosurgeon at a nearby hospital (day 0). She underwent a non-enhanced head computed tomography (CT) that showed no abnormal findings.

She was referred to an otolaryngologist at a local hospital for her coarse voice on the same day. The fiberoptic laryngoscope revealed a left recurrent laryngeal nerve palsy with pooling of saliva in the left piriform fossa (Fig. 1B, C), and she was placed on prednisolone and valacyclovir hydrochloride. Two weeks later, the patient returned to the doctor's office with left-sided hearing loss and moderate headaches. The audiogram demonstrated that pure-tone average (PTA) was 23.3 dB on the left and 13.3 dB on the right (Fig. 2A), and the tympanometry showed type B on the left (Fig. 2B). As the otoscope revealed a left-sided serous otitis media, clarithromycin was added to the prescription. Because of persistent headaches and an unknown cause of recurrent laryngeal nerve palsy, the patient was referred to us for further managements.

On examination, the patient persistently complained of left-sided occipital headaches, blockage in her left ear, and dull hearing. She intermittently had high-grade fever with malaise, chills, and rigors, presenting with 37.8°C. She was fully alert, but presented with coarse voice and left-sided

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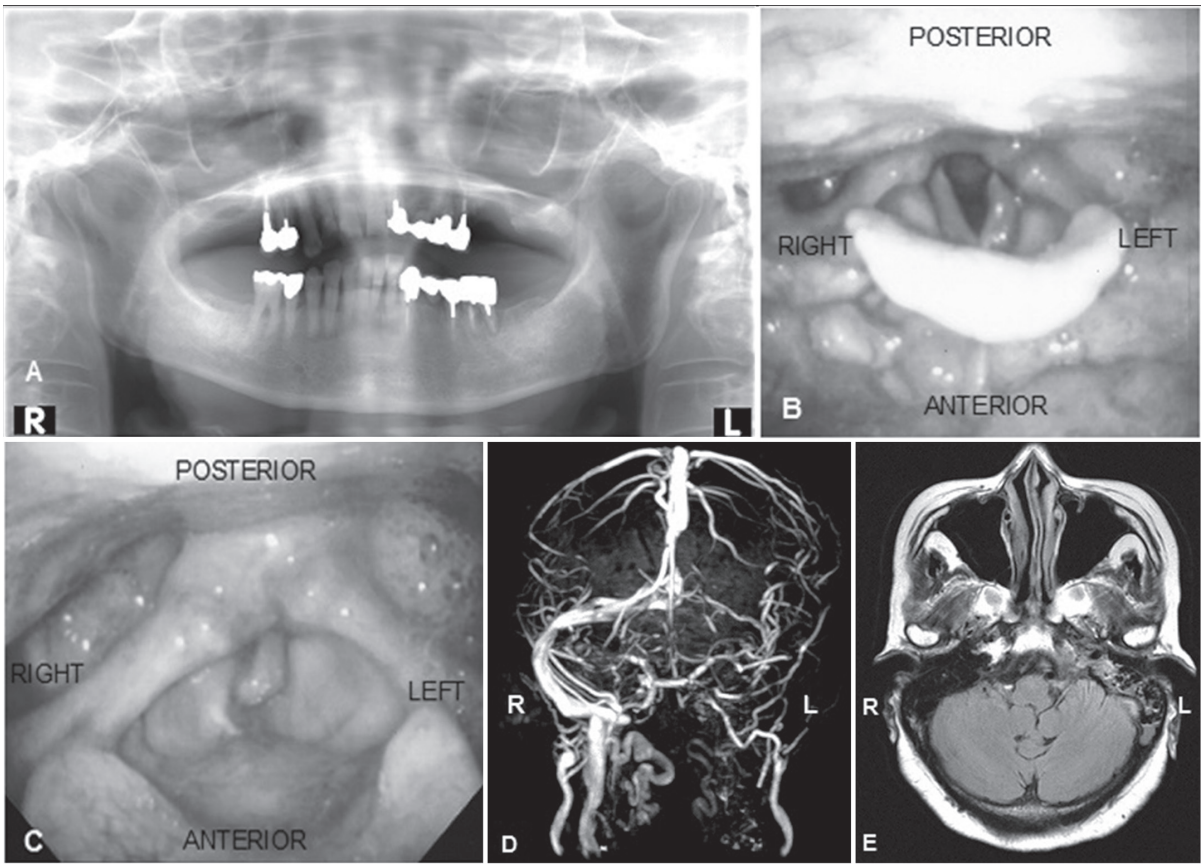

Fig. 1 A: Dental pantomography on day 39 showing notable bone loss and teeth defects in the moderate periodontitis. B, C: Vocal cords abducted (B) and vocal cords adducted (C). Flexible fiberoptic laryngoscopy imaging on day 0 showing incomplete motion of the left vocal cord and pooling of saliva in the left piriform fossa. D: Magnetic resonance venography of the head on day 22 showing a diminished perfusion of the left internal jugular vein, the left sigmoid sinus, and the left transverse sinus as a sign of thrombosis. E: Transversal fluid attenuation inversion recovery (FLAIR) image on day 22 revealing fluid collection within the left mastoid air cells and the middle ear.

hearing loss. She also complained of a salty taste disturbance though the electrogustometry demonstrated no apparent abnormalities.

Her past medical history was asymptomatic pulmonary tuberculosis and pneumonia at around 40 years of age, and her family history was unremarkable. She used to smoke 20 cigarettes a day for 40 years from 20 years of age. She also admits to daily alcohol use.

Her laboratory testing revealed white blood cell count (WBC) of 15,800 cells/μL with 82.0% neutrophils and elevated levels of C-reactive protein (CRP, 15.6 mg/dL) (Fig. 2C). Blood cultures were obtained twice but grew no microorganisms.

The enhanced cervical and chest CT showed neither abscess, thoracic aortic aneurysm, nor a thyroid tumor that could be the cause of left recurrent laryngeal nerve palsy, but showed a number of inflammatory changes in the peripheral regions of the bilateral lungs. No septic pulmonary emboli were confirmed. However, head magnetic resonance imaging (MRI) and magnetic resonance venography (MRV) revealed thrombosis in the left transverse sinus, the sigmoid sinus, left internal jugular vein, as well as in the left-sided mastoiditis. No reflux to the cerebral veins were demonstrated (Fig. 1D, E).

The level of protein-C, protein-S, lupus antibody, antilipid antibody, anticardiolipid antibody, and anti-CLb GPI complex antibody were normal. The genomic sequence analysis showed no mutant Factor V Leiden [1691nt G: codon 506 CGA (Arg)]. Thus, no endogenous coagulopathy was confirmed.

Although blood and cerebrospinal fluid (CSF) culture grew no microorganisms, respectively, the empirically determined antibiotic therapy was initiated using intravenous sulbactam sodium with ampicillin sodium followed by oral sitafloxacin against the suspected bacteremia or sepsis following periodontitis, dental extraction, otitis media, mastoiditis, and thrombophlebitis. In a week, the patient defervesced and all her laboratory data turned to be normal, including WBC 4,100 cells/μL and CRP less than 0.3 mg/dL (Fig. 2C). Although the repeat CT venography showed persistent thrombosis in the left transverse sinus, left sigmoid sinus and left internal jugular vein, her headaches had completely dissolved. The patient was discharged on the 17th hospital day, 6 weeks after the onset.

Discussion

I. Epidemiology

LS is a rare entity especially in this century and was once known as the forgotten disease. Although only 0.8–1.5

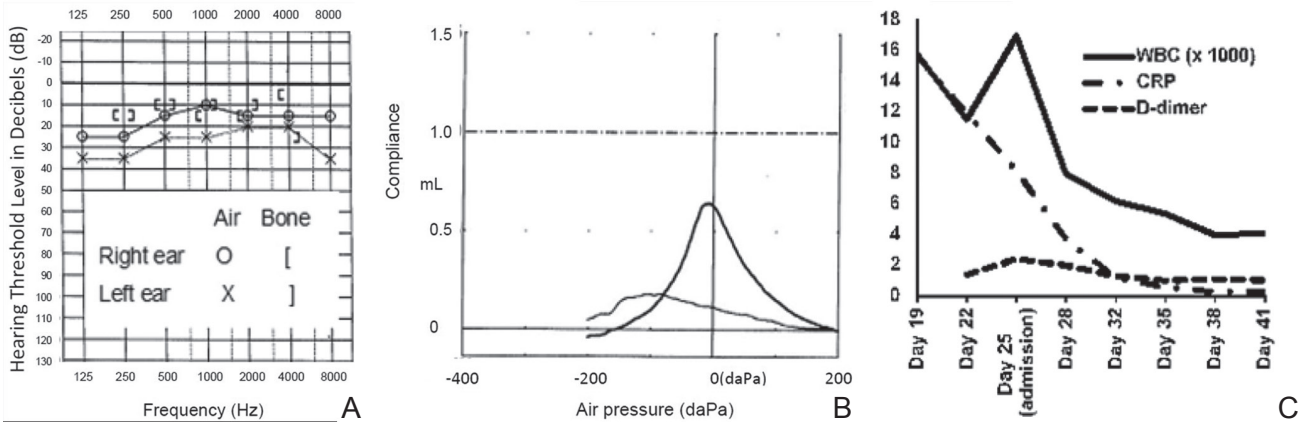

Fig. 2 A: Pure tone audiogram on day 0 showing the 23.3 dB level of the conductive hearing loss on the left side. B: Tympanogram on day 0 showing type B on the left side, suggesting the fluid collection in the left middle ear. C: The level of white blood count, C-reactive protein, and D-dimer showing a remarkable decrease with the intravenous antimicrobial therapy after admission.

per million population was estimated to develop LS per year,[4,12,13] a number of recent studies have reported that the incidence of LS has increased again.[3,4,9,13] A PubMed search, using the term "Lemierre syndrome" as the keyword, hit only 41 related articles between 2000 and 2004, 76 relevant articles between 2005 and 2009, and 192 articles in the last 5 years (2010–2014). The reason for the rapid increase is not clear, but is speculated to be due to an increased antibiotic resistance of anaerobic bacteria, less prescription of antibiotics for uncomplicated sore throats, inappropriate use of antibiotics and/or nonsteroidal anti-inflammatory drugs for infection with *F. necrophorum,* or easier diagnosis of the disease with the advanced imaging technology.[3,9,13] Nevertheless, the current mortality rate of LS ranges from 5% to 22%,[1,8,9,19] in contrast, 90% in Lemierre's initial series.[1,2] This remarkable decrease in the mortality can also be attributable to the advent of antibiotics and the latest imaging devices.

II. Cranial nerve palsy

LS rarely complicates a cranial nerve palsy and only seven previous LS patients with a cranial palsy were reported. The previous LS patients with a cranial palsy were all young and the average age of the patients was 17.9 ± 10.2 years of age (Table 1). And 73.4% of the total LS occurred in patients aged 16–25 years.[19] Young people are generally susceptible to pharyngitis and otitis media that may easily spread to the surrounding tissue. This is the main reason why majority of the LS patients are young children or adolescents.

Our patient was the oldest LS patient with cranial palsy, 66-year-old, ever reported. The patient had a moderate periodontitis and underwent left upper first molar extraction as shown in the pantomography (Fig 1A). LS can be precipitated by dental procedures at 1.8%,[19] mastoiditis at 2.7%,[19] intravenous drug abuse, infectious mononucleosis, and possibly cigarette smoking.[19,20] Our patient is a former cigarette smoker; smoking a pack a day for 40 years. Cigarette smoking may weaken the mucosal barrier and allows *F. necrophorum* to enter the bloodstream and/or invade the surrounding tissue. The LS progresses in several steps, primary infection, invasion of the lateral pharyngeal space, thrombophlebitis, and metastatic complications.[19] The time interval between the oropharyngeal infection and the onset of the invasion of the lateral pharyngeal space was usually less than 1 week.[19]

Given the patient's history of the present illness, imaging studies and laboratory data, poor oral hygiene caused periodontitis and dental extraction followed by oropharyngeal infection. The infection had spread to the surrounding tissue due to the weakened mucosal barrier by smoking, developing the ipsilateral otitis media through the Eustachian tube and the ipsilateral mastoiditis. The inflammation spread further to the carotid sheath, developing thrombophlebitis in the transverse sinus, sigmoid sinus, and internal jugular vein. The thrombophlebitis finally caused infection and inflammation of the vagus nerve, developing left laryngeal recurrent nerve palsy.

Additionally, our patient complained of a salty taste disturbance. This salty taste was mainly carried to the solitary nucleus in the medulla oblongata via the fiber that courses in the lingual nerve, chorda tympani, and facial nerve.[21] Since the chorda tympani courses in the middle ear close to the mastoid air cells, the nerve might be infected in our patient, developing a salty taste disturbance. Despite the negative results in the electrogustometry, the patient's persistent complaint of salty taste disturbance was suggestive of a mild chorda tympani palsy below the threshold of the electrogustometer.

III. Microbiology

The most common etiologic agent of LS based on blood cultures has been the obligate anaerobic, nonmotile, nonspore-forming Gram-negative rod *F. necrophorum* at 81.7%.[19] Up to 10.1% of the previously reported cases involved *F. necrophorum* in combination with another agent, while 5.5% of cases have involved an organism other than *F. necrophorum*.[19] It is notable that 12.8% of cases grew negative cultures as in our case.[6,19] Although we obtained blood cultures twice while the patient had fever, both the cultures grew no organisms. The CSF cultures grew no organisms, either. The negative cultures could be attributed

Table 1 Lemierre syndrome patients with cranial nerve palsy

Case no.	Authors	Year	Age/ Sex	Cranial nerve palsy	Symptoms	Occluded vessels	Surgery	Causing agent	Anticoagulation/ antiplatelet	Antibiotics
1	Jones et al.	1990	26/M	3rd, 4th, 5th, 6th, 12th	pharyngitis, diplopia	bilateral ICA stenosis	No	*F. necrophorum*	No	cefotaxime, chloramphenicol, erythromycin, cefotaxime, chloramphenicol, metronidazole
2	Agarwal et al.	2000	37/F	10th, 11th	left vocal fold palsy	left IJV to sigmoid sinus thrombosis	No	*F. necrophorum*	intravenous anticoagulation	penicillin, metronidazole
3	Jaremko et al.	2003	12/F	5th, 7th, 8th	meningitis, pharyngitis, mastoiditis	left sigmoid sinus	left tympanostomy, mastoidectomy	*F. necrophorum*	subcutaneous low-molecular-weight heparin	vancomycin, cefotaxime, ciprofloxacin, piperacillin-tazobactam
4	Jones et al.	2006	18/F	6th, 12th	tonsilar enlargement, meningitis, metastatic abscesses, articulation, and mastication difficulties	left IJV	No	N/A	subcutaneous tinzaparin, warfarin	metronidazole, cefotaxime, amoxicillin
5	van Dijk et al.	2007	17/M	5th, 6th, 10th, 11th, 12th	somnolence, dysphagia, dysarthria, meningitis, hemiparesis, Horner's syndrome, cerebral infarct	left ICA, subtotal right ICA stenosis	opening of ethmoid and sphenoid sinuses	*F. necrophorum*	Aspirin	cephotaxim, ciprofloxacin, penicillin, metronidazole
6	Lee et al.	2009	3/M	4th	sore throat, intermittent headaches, right head tilt, diplopia	left IJV, left EJV	inferior oblique recession	*Streptococcus viridans, S. salivarius*	Yes	ceftriaxone, clindamycin
7	Blessing et al.	2013	12/M	12th	deviation of the tongue, septic shock, impaired kidney and liver function, mastoiditis, otitis media	left IJV	mastoidectomy	*F. necrophorum* (PCR)	Low-dose heparin	cefuroxime, meropenem, clindamycin, amoxicillin and sulbactam
Present case	Miyamoto et al.	2015	66/F	10th	left mastoiditis, left otitis media, left vocal fold palsy, salty taste disturbance	left transverse sinus, left sigmoid sinus, left IJV	No	N/A	No	clarithromycin, sulbactam sodium-ampicillin sodium, sitafloxacin

EJV: external jugular vein, F: female, IJV: internal jugular vein, M: male.

to clarithromycin that had been administered beforehand by the otolaryngologist. Although numerous previous reports documented that *Fusobacterium* species and other several microorganisms are the agents causing LS, no direct evidence has ever been shown to elucidate how the microorganism invades the surrounding tissue and causes angiophlebitis, finally developing LS. Since the diagnosis of LS is primarily clinical,[4] the negative cultures do not rule out the diagnosis of LS.[6]

IV. Therapy

The mainstay of the treatment for LS is the intravenous antimicrobial therapy. The antibiotics with anaerobic coverage such as clindamycin, metrodinazole, carbapenems, amoxicillin plus β-lactamase inhibitor, antipseudomonal penicillin, and penicillin-sulbactam have been recommended for *Fusobacterium* species.[5,8,19] Despite the negative cultures in our case, we used sulbactam sodium with ampicillin sodium and sitafloxacin empirically because the laboratory data strongly suggested an infection. The antibiotics remarkably ameliorated the symptoms and improved the laboratory data in a week (Fig. 2C). Thus, in a case where LS is strongly suspected, an immediate initiation of the antimicrobial therapy is crucial despite negative blood cultures.

Use of anticoagulation in LS remains controversial and no consensus exists.[4,22,23] A routine use of anticoagulation in LS is not recommended as a standard of care due to the limited evidence and no randomized controlled trials due to low incidence.[4,13,14] Only 21–30% of patients were treated with anticoagulation therapy in the literature.[14,24,25] Some clinicians advocate the use of anticoagulation in patients complicated by distant emboli, cerebral infarcts, thromboses extending into the cavernous sinuses, or a lack of improvement despite 48–72 hours of adequate antimicrobial therapy.[22,26] However, the optimal anticoagulant and the duration of the therapy remain unclear. Our patient was not treated with an anticoagulant because of her relatively mild clinical symptoms and lack of distant septic emboli or due to the extension of the thromboses. Despite persistent sinovenous thromboses, her headache was completely resolved for unknown reasons.

Conclusion

We presented a rare LS case with recurrent laryngeal nerve palsy. The early diagnosis and intervention were the key contributing factors to the good outcome and survival of the patients. Neurosurgeons should reconsider LS in differential diagnosis in patients presenting with poor oral hygiene, a sore throat, headaches, fever, a recent history of a dental procedure, and/or a cranial palsy.

Conflicts of Interest Disclosure

The authors have no financial disclosures to declare and no conflict of interests to report. Neither a whole or a portion of the contents of the article has been presented previously.

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