Lemierre Syndrome: Case Report

Lemierre Sendromu: Olgu Sunumu

Dr. Ertan YÜCEL,[a]
Dr. Aydan EROĞLU,[b]
Dr. Işık CONKBAYIR,[c]
Dr. Şahin ŞAHİNALP,[a]
Dr. Kanat ÖZIŞIK[a]

Departments of
[a]Cardiovascular Surgery,
[c]Radiyology,
Ankara Dışkapı Yıldırım Beyazıt Education and Research Hospital,
[b]Department of General Surgery,
Ankara University Faculty of Medicine,
Ankara

Geliş Tarihi/*Received:* 16.07.2012
Kabul Tarihi/*Accepted:* 16.09.2012

Yazışma Adresi/*Correspondence:*
Dr. Kanat ÖZIŞIK
Ankara Dışkapı Yıldırım Beyazıt Education and Research Hospital,
Departmant of Cardiovascular Surgery,
Ankara,
TÜRKİYE/TURKEY
sozisik2002@yahoo.com

ABSTRACT Lemierre syndrome (LS) is a very rare disease presenting with thrombosis of internal juguler vein (IJV) and septic embolia following orophrangeal infection. The common complaint in LS is pain in the throat and the usual findings are unilateral swelling and decrease in range of motion of neck. For diagnosis, Doppler ultrasonography can be used. The case presented here is 29 years old healthy multipar woman. In this case, following postphrangial infection, thrombosis of the right IJV and partial thrombosis of internal carotid artery (İCA) were found. The laboratory findings of the case revealed high homosistein levels and mutation in the metilentetrahidrofolat (MTHFR) 677 CT and MTHFR 1298AC genotype. Moreover, the other laboratory findings confirmed antiphospholipid syndrome (APS). The patient was treated with antibiotics and anticoagulants. Due to repetation of the postphrangial infection this case is LS, a very rare cause of thrombosis with accompanying hereditary trombophilia mutations and APS . The patient was suggested to keep away from infections and continue taking anticoagulants and stop taking contraceptive pills.

Key Words: Thrombophilia; Lemierre syndrome; thrombosis; polymorphism

ÖZET Lemierre sendrom (LS), klasik olarak orofaringeal infeksiyonu takiben internal juguler venin (IJV) trombozu ve septik emboli gelişimiyle karakterize olup nadir bir hastalıktır. LS sıklıkla genç sağlıklı bireyde boğaz ağrısı, tek taraflı boyunda ağrı ve şişlik ile kendini gösterir. Tanı için renkli Doppler ultrasonografi kullanılabilir. Burada 29 yaşında bir kadında postfaringeal enfeksiyonu takiben sağ IJV'de tam tıkanma ve sağ internal karotis arterde (IKA) sıvanma tarzında trombüs gelişmiş, serum homosistein düzeyi yüksek, metilentetrahidrofolat (MTHFR) 677 CT ve MTHFR 1298AC genotipine sahip, anti-phospholipid sendromu (APS) laboratuar bulguları olan, tekrarlayan postfaringeal enfeksiyonlu, trombofili yatkınlığı bulunan bir olgu sunulmaktadır. Genetik mutasyonu, APS olan ve enfeksiyonu tekrarlayan hastaya, devamlı antikoagülan, uzun etkili benzatin penisillin kullanımı önerilmiştir. Kontraseptif alımı durdurulmuştur.

Anahtar Kelimeler: Trombofili; Lemierre sendromu; tromboz; polimorfizm

Damar Cer Derg 2012;21(3):289-93

In 1936, Andre Lemierre reported 18 lethal sepsis cases caused by an anaerobic bacteria, *Basillus funduliformisa (Fusobacterium necroforum).*[1] Lemierre syndrome (LS), is a rare complication of oropharangial or odontogenic infections generally occurring in young individuals, characterized by thrombophlebitis of internal jugular vein (IJV) and sepsis caused by gram negative bacteria confirmed by blood culture for Fusobacterium necroforum (necrobasillozis). Before the antibiotics were available, LS occurred as a com-

doi: 10.9739/uvcd.2012-31357

plication of phrangitis accompanying paraphryngeal abscess. After clinical use of penicilline, LS was defined as *forgotton disease.*[2,3] Today this syndrome is very rare with an incidence of 0.8 per million occuring due to less use and possible resistance to antibiotics in pharyngeal infections.[3]

LS is defined as fever, increase in pain with the motion of the neck, postpharyngitis IJV thrombosis, septic pulmoner embolia, abscess in the liver and arthralgia.[2] The thrombosis in inferior vena cava, cavernous and lateral sinus has also been reported.[4] In very few cases, thrombosis in carotid artery and ischemic stroke were present.[2,5] According to Sinave and colleagues,[6] LE is defined as primary infection of oropharynx, blood culture positive septicemia and thrombosis in IJV, and presence of septic metastases. Although, the mechanism causing thrombosis in blood vessels adjacent to infection/inflammation is unclear, hypercoagulability might be due to anaerobic infection causing thrombosis, Fusobacterium necroforum causing platelet aggregation, the presence of APS, or high levels of Factor V activity.[7] Whether the thrombus formation in LS is a temporary hypertrombotic situation or the present thrombophilia is triggered by acute infection is not known.

CASE REPORT

The patient (K.E.) was a healthy multiparous woman. The complaints like headache, fatigue, weakness, loss of appetite, swelling, pollakuria, fever, irritation in the throat, palpitation started one year before the diagnosis was made. She had transient ischemic attack, chilling, restricted motion of the neck, and oral lesions before and after the admission to our clinic. After the blaze out of the infection the pain in the neck increased, the motion of the head was limited while numbness in her left arm and visual problems occurred. The patient was treated with antibiotics and anticoagulants. Therefore, isolation of bacteria may not be possible in our case. At initial admission to our clinic smoking and oral contraceptive pills were quitted. On first, third and fifth months of the treatment the infection in the pharynx recurred. The personal and family history of the patient was unremarkable.

Laboratuary findings: All the serum parameters are given in Table 1. The antiphospholipid antibodies were positive. The high homocysteine levels declined after the treatment. The hereditary thrombophilia analyses showed MTHFR 677CT, MTHFR 1298 AC mutations.

Doppler Ultrasound: At the level of right ICA proximal region approximately 12.3x4.6 mm thrombus was present. The IJV was occluded with thrombus (Figure 1, 2). After 12 days of initiation of the treatment the thrombus in right ICA decreased to 8.1 x 3.5 mm in size and recanalization started in IJV (Figure 3). The lymphadenopathies regressed to 13 mm which was 26 mm in initial evaluation before the medication (Figure 4).

TABLE 1: Laboratory finding.

Blood Test; (Initial Evaluation)	
Hemoglobin: 12.8	
White Blood Count: 5.9 K/ul	
Hematocrit: 36.7	
Mean Corpuscular Volume: 81.4	
Trombocyte: 160 000/ul	
Peripheral Blood Smear;	
Neutrophils: %68	
Monocytes: %12	
Sedimentation Test:: 50 mm /S	
Coagulation Test:	
Protein-C,:70.516 (70-140%)	
Protein S: 55.980 (58-130%),	
Antithrombin III : 88.452 (75-125%)	
Homocysteine-1	14.2 (5-12)
Homocysteine -2	8.60 (12-15)
Fibrinogen	451.8 mg/dl (180-350)
Genetic Mutation	
Prothrombin F20210A	Mutation (-)
Factor V Leiden	Mutation (-)
MTHFR A120C-DL	Heterozigot Mutation (+)
MTHFR C677T-DL	Heteozigot Mutation (+)
Anti-Phospholipid antibodies sendrome	
Lupus antigen LA1/LA2	<2.0 pozitif (0.8-1.2)
Anti Nuclear Antibody (ANA)	(+)
Anti-cardiolipin IGG :	84 IU/mL(0-48)
Anti-cardiolipin IGM	142 IU/mL (0-44)

MTHFR: Methylene Tetra Hydrofolate Reductase.

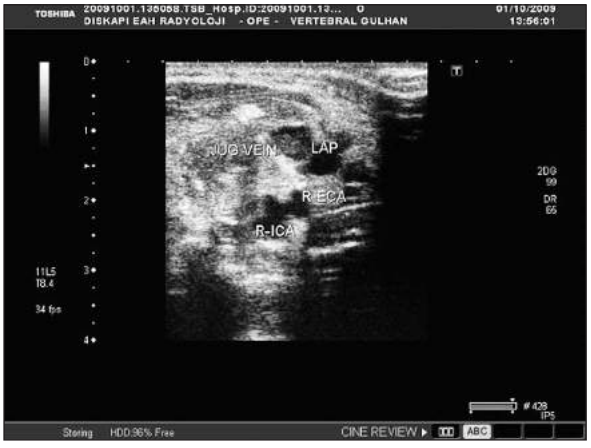

FIGURE 1: Carotid Doppler 1: Thrombosis of internal jugular vein, hypertrophic lymphadenopathies and partial thrombosis of right internal carotid artery at the bifurcation.

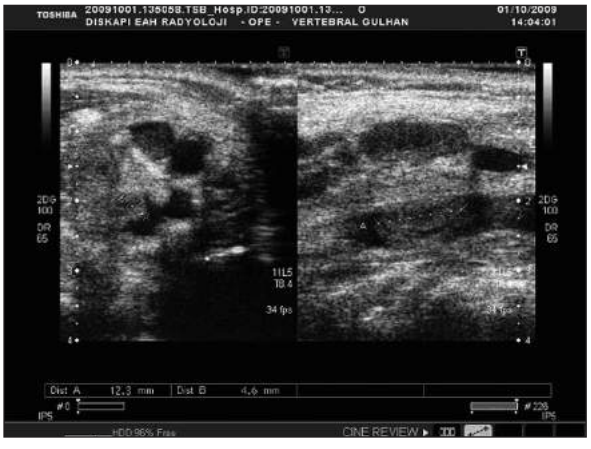

FIGURE 2: Carotid Doppler 2:Thrombosis of internal jugular vein, hypertrophic lymphadenopathies and partial thrombosis of right internal carotid artery at the bifurcation. Carotid Doppler USG showed 12.3x4.6 mm huge thrombus at the level of right ICA.

DISCUSSION

The patients with LS syndrome usually are healthy young adults and they suffer from fever with shivering, bad general status, pain, swelling and decreased range of motion along the sternocleidomastoid muscle due to draining abscess of tonsillar and peri-tonsillar venous supurative thrombophlebitis to IJV. Although LS is usually caused by *Fusobacterium necroforum* which is a non-pathogen obligatory anaerobic bacteria from the oral flora, *Streptococcus viridans*, *Bacteroides spp*, *Peptostreptococcus*, *Enterococcus spp* can be the reason[8] and the symptoms of odontojenic infection, mastoiditis, parotitis or sinusitis can be present. In the classical form of LS the primary infection site is the oropharynx but the thrombosis in the IJV may lead to metastatic infection. Pain and swelling in the anterior cervical region; thrombosis in IJV, embolism may lead to diagnosis.

The physio-pathology of LS is contraversial. It is unknown why *Fusobakterium necroforum* which is normally found in the flora of oropharynx; gastro-intestinal system and genito-urinary system becomes pathogenic. The insufficiency of the immune defense which may be seconder to an infection may produce an anaerobic atmosphere fa-

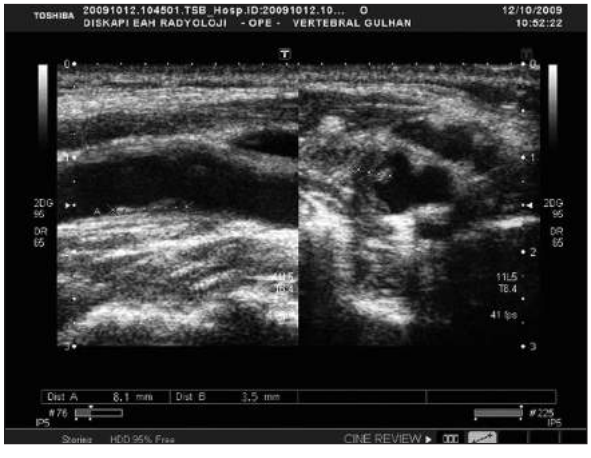

FIGURE 3: Carotid Doppler 3: After 12 days of initiation of the treatment the thrombus in the partial right ICA decreased to 8.1x3.5 mm in size and recanalization started in IJV.

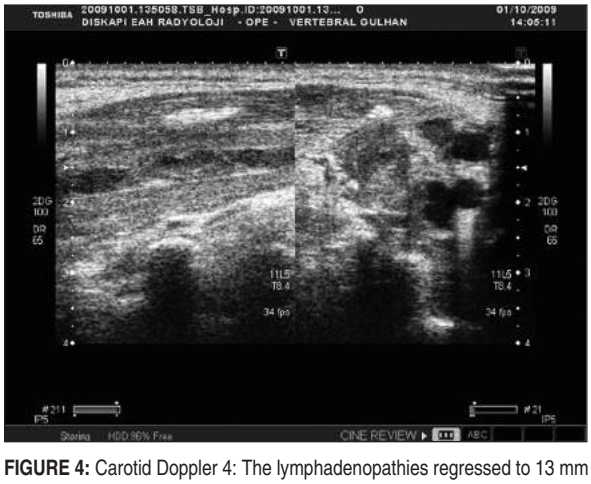

FIGURE 4: Carotid Doppler 4: The lymphadenopathies regressed to 13 mm which was 26 mm in initial evaluation. Also the partial thrombus in the right ICA and IJV decreased.

cilitating the invasion of the microorganism. The bacteria may cause fibrin and plattelet aggregation, micro-abscess formation and release hemolysin, hemaglutinin and leukosidin.[9]

The initiation of the syndrome is infection in the throat. In the seconder phase the invasion of the lateral phrangeal space, IJV thrombophlebitis or as in our case it may cause thrombosis in the artery of carotid. The metastatic spreading of the bacteria may cause systemic coagulopathy. In 95% of the cases, pleuro-pulmonary involvement was reported. Metastatic abscess may be in joints, bones, soft tissues, liver, spleen, kidney and brain.[4,10] The syndrome is usually seen in young adults with mean age of 22 years. ICA thrombosis was reported in 2 cases and cerebral infarct in one.[2]

The thrombosis in the adjacent vessels may be due to endothelial damage and platelet aggregation which is caused by the bacteria itself. From the perspective of Virchow, inflammation, systemic hypercoagulability which is altered by infection, venous stasis and endothelial damage may have acted in collaboration.[7] It has been reported that hypercoagulapathy may be related to anti-phospholipid antibodies and elevated factor VIII levels but it is unclear if the formation of the thrombus is caused by temporary hyperthrombotic status or trombophilia which is aggravated by infection. Factor V leiden (FVL) heterozygosity,[10] prothrombin (PT) 20210GA mutation, the polymorphims of MTHFR 677 CT was reported in cases with LS syndrome.[11] In a LS case previously reported by Constantin and colleagues,[12] heterozygote tissue factor (TF 603) associated with protrombogenic factor and homozygote mutation of plasminogen activator inhibitor-1 (PAI-1 4G/4G) was found. In another case, PT G20210A, FVL ve MTHFR C677T polymorphisms were normal.[8] Deficiency of Factor XII (F XII), one of the major factor in intrinsic pathway of coagulation may lead to thromboembolia.[13] In the case reported here, FVL and PT G20210A were normal, while heterozygote mutations of MTHFR C677T CT and MTHFR A1298C AC were found. Even if the association between high plasma homocysteine levels and VTE is well known,[14] the reported relationship between arterial trombosis and hyperhomocysteinemia in meta-analyses is incompatible according to some studies.[15]

Fusobacterium necroforum is sensitive to penicilline, clindamycin, metranidazole and cloramfenikol.[16] In every case, isolation of *Fusobacterium necroforumun* may not be possible. Therefore, response to antibiotics may indicate it as possible microorganism in the etiology.[10] Before the clinical availability of antibiotics, LS were 90% mortal. Today, with modern antimicrobial treatments this rate declined to 4-12%.[16] Hence, the infection is endovascular and carries the risk of distant metastases, long term antibiotics are required. Although, the use of anticoagulants is suggested by some authors,[13,17] others only used antibiotics.[18] Therefore, use of anticoagulants still under debate.[3] Adding anticoagulants to medical treatment with antibiotics is recommended as this combined treatment provides rapid resolution of bacterial infection and thrombophlebitis which in this manner minimizes the formation of new metastatic focuses. The case presented here claims that LS still exists as sporadic cases. The repetitive postpharyngeal infections, arterial and venous thrombosis in this case support the diagnosis. Moreover, hereditary thrombophilia and markers of APS were also positive in this case. All the preventive measures should be taken to avoid infections in LS. Prescription of anticoagulants for lifelong in cases with genetic mutations and APS is strongly suggested.

REFERENCES

1. Lemierre A. On certain septicaemias due to anaerobic organisms. Lancet 1936;227:701-3.
2. Karkos PD, Asrani S, Karkos CD, Leong SC, Theochari EG, Alexopoulou TD, et al. Lemierre's syndrome: A systematic review. Laryngoscope 2009;119(8):1552-9.
3. Hagelskjaer LH, Prag J, Malczynski J, Kristensen JH. Incidence and clinical epidemiology of Necrobacillosis, including Lemierre's syndrome, in Denmark 1990-1995. Eur J Clin Microbiol Infect Dis 1998;17(8):561-5.
4. Razonable RR, Rahman AE, Wilson WR. Lemierre syndrome variant: Necrobacillosis associated with inferior vena cava thrombosis and pulmonary abscesses after trauma-induced leg abscess. Mayo Clin Proc 2003;78(9): 1153-6.
5. Goyal MK, Kumar G, Burger R. Necrobacillosis resulting in isolated carotid thrombosis and massive stroke: A unique Lemierre variant? J Neurol Sci 2009;287(1-2):108-10.
6. Sinave CP, Hardy GJ, Fardy PW. The Lemierre syndrome: suppurative thrombophlebitis of the internal jugular vein secondary to oropharyngeal infection. Medicine (Baltimore) 1989; 68(2):85-94.
7. Goldenberg NA, Knapp-Clevenger R, Hays T, Manco-Johnson MJ. Lemierre's and Lemierre's-like syndromes in children: survival and thromboembolic outcomes. Pediatrics 2005; 116(4):e543-8.
8. Boga C, Ozdogu H, Diri B, Oguzkurt L, Asma S, Yeral M. Lemierre syndrome variant: Staphylococcus aureus associated with thrombosis of both the right internal jugular vein and the splenic vein after the exploration of a river cave. J Thromb Thrombolysis 2007;23(2):151-4.
9. Tan ZL, Nagaraja TG, Chengappa MM. Fusobacterium necrophorum infections: virulence factors, pathogenic mechanism and control measures. Vet Res Commun 1996;20(2):113-40.
10. Warabi YS, Yoshikawa H, Idezuka J, Yamazaki M, Onishi Y. Cerebral infarctions and brain abscess due to Lemierre syndrome. Intern Med 2005;44(6):653-6.
11. Schmid T, Miskin H, Schlesinger Y, Argaman Z, Kleid D. Respiratory failure and hypercoagulability in a toddler with Lemierre's syndrome. Pediatrics 2005;115(5):e620-2.
12. Constantin JM, Mira JP, Guerin R, Cayot-Constantin S, Lesens O, Gourdon F, et al. Lemierre's syndrome and genetic polymorphisms: a case report. BMC Infect Dis 2006;6: 115.
13. Hlibczuk V. Lemierre's syndrome complicating bacterial pharyngitis in a patient with undiagnosed factor XII deficiency. J Emerg Med 2007;32(4):365-9.
14. Falcon CR, Cattaneo M, Panzeri D, Martinelli I, Mannucci PM. High prevalence of hyperhomocyst(e)inemia in patients with juvenile venous thrombosis. Arterioscler Thromb 1994;14 (7):1080-3.
15. Ozmen F, Ozmen MM, Ozalp N, Akar N. The prevalence of factor V (G1691A), MTHFR (C677T) and PT (G20210A) gene mutations in arterial thrombosis. Ulus Travma Acil Cerrahi Derg 2009;15(2):113-9.
16. Vohra A, Saiz E, Ratzan KR. A young woman with a sore throat, septicaemia, and respiratory failure. Lancet 1997;350(9082):928.
17. Lustig LR, Cusick BC, Cheung SW, Lee KC. Lemierre's syndrome: two cases of postanginal sepsis. Otolaryngol Head Neck Surg 1995;112(6):767-72.
18. Nadal CF, Creus A, Beatobe S, Moraga F, Pujol M, Vazquez E. Lemierre syndrome in a previously healthy young girl. Acta Pediatr 2003;92(5):631-3.