Lemierrov sindrom: primer bolnice s septičnim tromboflebitisom notranje jugularne vene in septično embolizacijo perifernih arterij z ishemičnimi zapleti

Peripheral arterial embolization and limb ischemia complicating septic internal jugular vein thrombosis: a case report of Lemierre's syndrome

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Izvleček

Namen: *Septični tromboflebitis, v tem primeru notranje jugularne vene (Lemierrov sindrom), je bolezenska slika, ki ogroža bolnikovo življenje. Pogosto se pri zdravljenju poleg antibiotikov uporablja heparin. Zdravljenje s heparinom pri bolnikih z Lemierrovim sindromom je protislovno. Vendar zamujanje s pričetkom dajanja heparina lahko povzroči periferne embolizacije z gangreno udov. Namen prikaza primera bolnice z Lemierrovim sindromom je prikazati, kako obsežne so lahko posledice opustitve zgodnjega dajanja heparina pri bolniku z Lemierrovim sindromom. Doslej ni bilo poročila o akutni ishemiji udov kot posledici septičnih embolizacij pri bolniku z Lemierrovim sindromom.*

Poročilo o primeru: *Prikazan je neobičajen primer 23 letne bolnice z Lemierrovim sindromom, kjer se je zaradi septičnih embolizacij hitro pojavila gangrena prstov vseh okončin, kar je neobičajno tudi pri streptokokni sepsi. Paci-*

Abstract

Purpose: *Septic thrombophlebitis of the internal jugular vein is a life-threatening complication of venous thrombosis. While heparin is frequently added to antimicrobial therapy, its usefulness in patients with Lemierre's syndrome is controversial. In this case report, we demonstrate that delayed use of intravenous heparin may be associated with septic embolization of peripheral arteries. Limb ischemia has rarely been reported in patients with Lemierre's syndrome.*

Case presentation: *Lemierre's syndrome is a complex and unusual clinical entity, characterized by septic thrombophlebitis of the internal jugular vein and accompanied by sepsis. We present an unusual case of a young female with Lemierre's syndrome who developed peripheral arterial embolization and Streptococcus pyogenes sepsis, complicating septic internal jugular vein thrombosis. The patient was ini-*

entka je imela najprej bolečine v desnem ušesu s temperaturo. Zdravljena je bila ambulantno. Po dveh dnevih so jo z visoko temperaturo pripeljali v bolnišnico, kjer so ugotovili septični šok in jo premestili v našo ustanovo. Že ob sprejemu je bila vidna huda ishemija prstov vseh okončin, ki je kasneje prešla v gangreno obeh dlani in obeh goleni. CTA preiskava je pokazala trombozo notranje vene jugularis, v hemokulturah pa je bil izoliran Streptococcus pyogenes. Kasneje je dobila gnojni meningitis, pojavila pa se je tudi gljivična sepsa. Šest tednov po sprejemu je umrla zaradi večorganske odpovedi. Pacientka je od začetka dobivala antibiotike, terapevtskih odmerkov heparina pa ne. Pacientka je umrla šest tednov po sprejemu zaradi mnogo organske odpovedi.

Zaključek: *Avtorja ob primeru razpravljata o prednostih in morebitnih slabih straneh takojšnje uporabe heparina v terapevtskih odmerkih pri odraslih bolnikih z Lemierrovim sindromom in sodita, da je pri takih bolnikih smiselno takoj pričeti z dajanjem terapevtskih odmerkov heparina.*

tially treated with antibiotics without therapeutic heparin. The patient developed digital gangrene in all four extremities, septic meningitis, and a severe fungal infection; she died 6 weeks after admission secondary to multisystem organ failure. We discuss the importance of rapid diagnosis of disease extent in directing heparin treatment in patients with Lemierre's syndrome.

Conclusion: *It may be advisable to treat Lemierre's syndrome with anticoagulation in the acute setting.*

INTRODUCTION

In 1936, Andre Lemierre described 20 patients of internal jugular vein thrombophlebitis (IJVT) who developed postanginal sepsis. This entity would later become known as Lemierre's syndrome (1). Septicemia was primarily associated with anaerobic oropharyngeal infection extending to the neck, with disseminated, and mostly pulmonary, abscesses (1, 2). The mortality rate in Lemierre's series was 90% (1). The syndrome is usually characterized by a history of recent oropharyngeal infection, clinical or radiologic evidence of internal jugular vein thrombosis, including remote septic emboli, and isolation of anaerobic pathogens—primarily Fusobacterium necrophorum, although other pathogens have been reported (2-7). Reports of Lemierre's syndrome significantly declined after the discovery and widespread use of antibiotics. It was considered to be a rare and forgotten disease, with an estimated incidence of approximately one per million (5). However, an increase in frequency over recent years implies changes in antibiotic usage (8). Lemierre's syndrome usually affects previously healthy children and young adults, but can be seen at any age (3, 6, 9). While heparin is frequently added to antimicrobial therapy, its usefulness in patients with Lemierre's syndrome is controversial (10). We present an unusual case of a previously healthy young female with Lemierre's syndrome who developed peripheral arterial embolization and Streptococcus pyogenes sepsis, with gangrene of all four extremities complicating septic internal jugular vein thrombosis. We demonstrate that delayed use of intravenous heparin may be connected with septic embolization of peripheral arteries.

CASE REPORT

A 23-year-old, previously healthy, intubated female was transferred from an outside hospital with a diagnosis of septic shock. Four days prior to admission, she presented to her family physician with a pharyngeal pain, fever, and right ear pain. She was diagnosed with viral pharyngitis and discharged. She presented to the emergency department 2 days later with worsening ear pain, persistent fever (38°C), and neck swelling. Within an hour of arrival, she reported difficulty breathing. Laboratory testing revealed a white blood cell count

of 28,100/μL. An arterial blood gas showed a pH of 7.51, a pCO_2 of 40, a pO_2 of 95, and a HCO_3- of 32, consistent with a mixed respiratory and metabolic alkalosis. The patient was intubated and admitted to the intensive care unit (ICU), where she was empirically started on ciprofloxacin and cefotaxime. No heparin treatment was initiated. There was no clinical improvement and she continued to have high fevers (41°C) and decreased urine output over the following 2 days. When she displayed acute digital ischemia on all four extremities, she was transferred to our hospital. At admission, she had developed digital gangrene in both upper and lower extremities (Figure 1, 2). Doppler ultrasound of her peripheral arteries demonstrated occluded palmar and plantar arterial arches.

Her blood culture on admission was positive for Streptococcus pyogenes, which was started intravenously. Contrast-enhanced computed tomography (CT) was performed, and showed right internal jugular vein thrombosis, multiple septic pulmonary emboli, and bilateral necrotizing pneumonia (Figure 3, 4). The diagnosis of Lemierre's syndrome was made and metronidazole was added to her antibiotic regimen. Anticoagulation was initiated with prophylactic low molecular weight heparin. Additionally, she developed acute renal failure (serum creatinine 2.1 mg/dL) and hypokalemia (serum potassium 2.3 mmol/L). Laboratory testing revealed a white blood cell count of 18,600/μL, a hemoglobin of 9.8 g/dL, a red blood cell count of 4.2 × 10^6/mL, a platelet count of 282 × 10^3/mL, a prothrombin time of 19.2, a partial thromboplastin time (PTT) of 44.6; an international normalized ratio (INR) of 1.56 and a C-reactive protein level of 168 mg/L. A thrombophilia workup, including antiphospholipid antibodies, factor V Leiden, and prothrombin G20210A mutation, was negative. In the ICU, her condition deteriorated due to severe fungal infection, purulent meningitis, renal insufficiency, hepatic failure, and disseminated intravascular coagulation (DIC). Her antibiotic regimen was changed to meropenem and linezolid. She required bilateral lower limb amputation. On the thirtieth hospital day, multiple organ failure (MOF) followed by cardiopulmonary arrest ensued.

DISCUSSION

The two leading causes of IJVT are iatrogenic trauma secondary to jugular vein catheterization and repeated intravenous injections by drug users (11). Lemierre's syndrome was previously thought to be a rare and almost forgotten disease, with a suggested incidence of approximately one per million (5). However, an increase in frequency over recent years implies changes in antibiotic usage (8). Unfortunately, widespread antibiotic use has changed the clinical picture of Lemierre's syndrome and it is often difficult to recognize this unusual illness in the emergency setting (12). Systemic septic complications may range from deep neck infection to septic arthritis and meningitis, and may involve

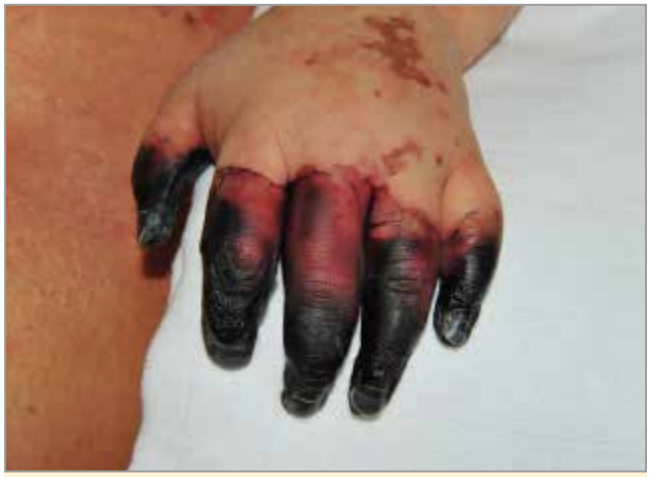

Figure 1. *Ischemic lesions of left upper limb. Similar clinical picture was present on right side.*

Figure 2. *Ischemic lesions of both lower limbs.*

every organ system (13). Delays in diagnosis, even up to 11 days after admission have been reported (14, 15). The reason for this is multifactorial; however, it is true that most clinicians have never seen a case of Lemierre's syndrome and patients often present to subspecialists who are inexperienced at diagnosing and managing this disease (14, 15). Our patient was admitted to the hospital 4 days after symptom onset.

Lemierre's syndrome has classically been associated with Fusobacterium necrophorum (82%). However, polymicrobial infection can occur (10%) and other organisms such as Fusobacterium nucleatum, Bacteroides species, Peptostreptococcus species, Staphylococcus aureus including community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA), Streptococci viridans species, Eikenella corrodens, and Enterococcus species have been reported (3, 6). Lemierre's syndrome due to Streptococcus pyogenes is very rare (6), with only two cases in adults reported in the literature (16, 17). These patients presented initially with pharyngitis and subsequently developed sepsis, Streptococcus pyogenes bacteremia, and internal jugular vein thrombosis on ultrasound or neck CT scan. They were treated with prolonged intravenous antibiotics, as well as anticoagulation therapy. One patient died, while the other case developed diffuse infection but survived. In our case, this patient had all the classic manifestations of Lemierre's syndrome, but also developed a rare physical manifestation of streptococcal sepsis: limb ischemia. Limb ischemia has been reported in streptococcal sepsis; it has been connected with meningococcal sepsis in pediatric patients (18, 19). Surgical arteriolysis has been suggested (microsurgical periarterial tissue lysis) to restore blood flow to an ischemic limb. This approach is successful only in cases where arteries are still patent or ischemic lesions are not irreversible, which was not the case in our patient (18, 19).

The role of anticoagulation in patients with Lemierre's syndrome is not well defined (2, 10, 20, 21, 22). Theoretically, these patients have a risk of venous septic embolism. In cases of retrograde extension of thrombus where stroke or pulmonary embolus is a potential risk, anticoagulation is recommended to prevent these complications. A wide range of recommendations regarding anticoagulation has been reported, including no coagulation to extended therapy with warfarin (2, 20, 21, 22). Due to the rarity and heterogeneity of presentations of Lemierre's syndrome, a direct outcome analysis

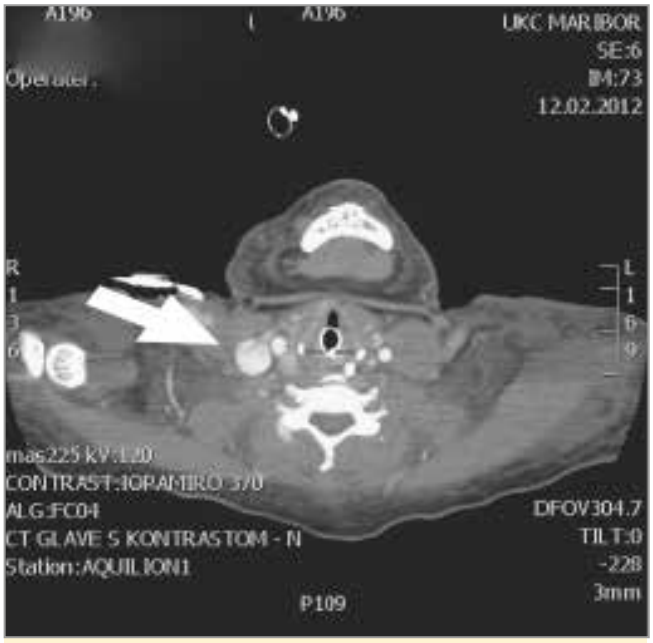

Figure 3. *Computed tomography with contrast (CTA) of neck vessels. Arrow denotes dilated and thrombosed right internal jugular vein.*

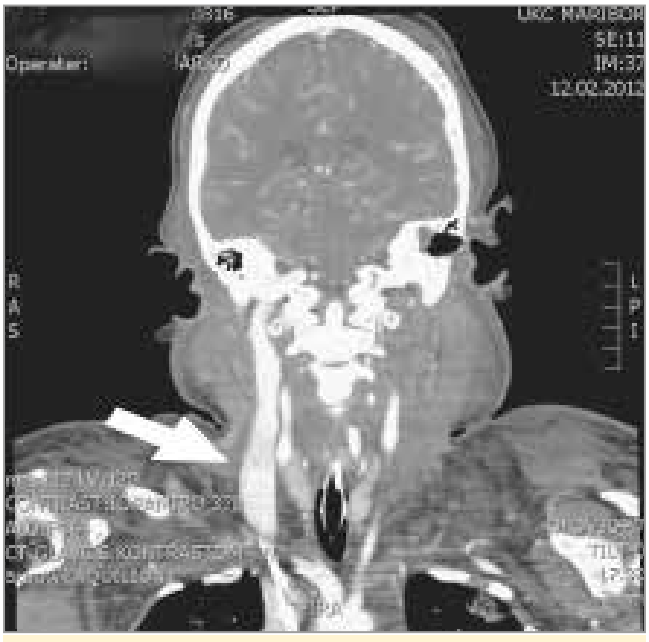

Figure 4. *Computed tomography with contrast (CTA) of neck vessels – sagittal view. Arrow denotes dilated and thrombosed right internal jugular vein.*

based on anticoagulation therapy alone is difficult (22). Inferences have to be made from similar conditions that involve septic thrombophlebitis (22).

Joey and Staggers studied the clinical course of 46 patients with deep septic thrombophlebitis (23), all of whom were immediately treated with heparin; a complete clinical response was documented in 42 patients in a mean of 2.5 days. Eleven patients (24%) had pulmonary emboli before initiation of heparin and none developed embolism thereafter. Akol et al. reported the successful resolution of ischemic lesions in a patient with pneumococcal sepsis treated with recombinant tissue plasminogen activator (24). Based upon the literature and our own experience (9, 20, 22, 23, 24), we find it reasonable to treat Lemierre's syndrome with anticoagulation in the acute setting. When the acute illness has resolved, heparin can be discontinued, thereby minimizing the risk of side effects.

There are limited data from comparative trials regarding the use of heparin in septic thrombophlebitis. Falagas et al. found only one randomized control trial in their systematic review; the remainder of the evidence comes from case series and case reports (10, 25). Fourteen articles describing 216 patients were included for analysis (10). Heparin was added to the therapeutic regimen immediately after septic thrombophlebitis was suspected, or after a few days. Low molecular weight heparin was the chosen anticoagulant in one of 14 studies and its use was not uniform. Although the lack of comparative trials did not allow them to draw definitive conclusions, heparin was thought to be a useful addition to antimicrobial treatment, especially as some patients may have concurrent antiphospholipid antibody syndrome and elevated factor VIII levels (26).

Early diagnosis, complete radiologic assessment, and no delays in treatment are vital. It has been suggested that bedside ultrasound of the internal jugular vein before other radiologic imaging, may lead to rapid diagnosis and treatment of Lemierre's syndrome (11). However, ultrasound examination will not reveal the extent of spread of disease which is needed to direct the treatment in patients with Lemierre's syndrome (4, 27). We believe that in patients with Lemierre's syndrome a rapid whole body CT is indicated.

The mainstay of treatment of Lemierre's syndrome is a prolonged course of high-dose, intravenously administrated antibiotics (penicillin type, or 2nd or 3rd generation cephalosporins) and metronidazole, or clindamycin monotherapy initially, and adapted as necessary, for at least 6 weeks (27). In rare cases, surgical treatment with the ligation or even excision of the jugular vein is needed (4, 27).

CONCLUSION

Lemierre's syndrome is a complex and potentially lethal illness arising from both oropharyngeal and extrapharyngeal sources. Early recognition of disease extent and high-dose antibiotics are critical elements in reducing mortality. Immediate anticoagulation may play a part in preventing septic embolic events as in the presented case.

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