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Case Report

Lemierre's Syndrome Caused by *Streptococcus pneumoniae* in a Patient with Carbimazole-Induced Severe Neutropenia

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INTRODUCTION

Lemierre's syndrome is characterized by septic thrombophlebitis of the internal jugular vein, typically originating from oropharyngeal infection and accompanied by surrounding soft tissue inflammation, septic emboli, and persistent bacteremia.[1] This rare condition had a higher incidence of 1/1,000,000 in the pre-antibiotic era, but its occurrence has significantly diminished since the introduction of antibiotics in the 1960s.[2] In recent times, there is a renewed focus on Lemierre's syndrome, possibly influenced by changes in antibiotic prescription patterns for conditions like pharyngitis or tonsillitis.[3] The primary causative agent is often *Fusobacterium necrophorum*, a normal human oropharyngeal microflora. Other implicated organisms include *Fusobacterium nucleatum*, Streptococcus species (such as *Streptococcus pyogenes* and the *Streptococcus milleri* group), *Hemophilus influenzae*, *Escherichia coli*, *Eikenella corrodens*, and *Bacteroides*.[4,5] Methicillin-resistant *Staphylococcus aureus* (MRSA) has also been identified as a rare cause of Lemierre's syndrome.[6]

We present a case involving a 22-year-old female with Graves' disease undergoing anti-thyroid drug treatment. The patient developed drug-induced neutropenia, subsequently leading to Lemierre's syndrome secondary to *Streptococcus pneumoniae* and an underlying lower respiratory tract infection.

CASE REPORT

A 22-year-old female, previously diagnosed with Graves' disease and currently on a regimen of Carbimazole 10mg twice daily for the past three months, presented to the emergency department with complaints of fever, neck pain, neck swelling, multiple oral ulcers, and odynophagia persisting for four days. Upon arrival, the patient exhibited a fever of 103°F, tachycardia (heart rate: 133/min), tachypnea, and low blood pressure measuring 60/30 mm Hg. Physical examination revealed diffuse neck swelling with induration, tenderness, and erythema.

Meeting the criteria for severe sepsis, the patient received intravenous fluid resuscitation following standard guidelines. However, as blood pressure did not respond to fluid resuscitation, she was diagnosed with septic shock, prompting the initiation of vasopressors. Two sets of blood cultures were obtained, and broad-spectrum antibiotics were promptly administered. Further investigations revealed leukopenia with an absolute neutrophil count (ANC) of 10, elevated inflammatory markers (including an increased erythrocyte sedimentation rate and C-reactive protein), and elevated procalcitonin values (Table 1).

Table 1. Results of laboratory and radiological investigations.

Investigation	Findings
Hemoglobin	10.0 g/dL (13-16 g/dL)
Total Leucocyte count	0.21 x 10^3 cells/uL (4000-11000/ul)
Absolute Neutrophil count	10 cells/ ul
Platelet count	418 x 10^3 /ul (150 x 10^3 – 450 x 10^3/ul)
Blood film morphology	RBC-Microcytic hypochromic RBC picture with many pencil cells and few target cells and elliptocytes WBC-Marked leucopenia and neutropenia DLC (%)-25 cells counted: Neutrophil = 0, Lymphocyte = 25, Monocyte = 0 Platelets- Increased in smear (5,30,000)
Urea	63 mg/dL (6-24 mg/dL)
Creatinine	0.74 mg/dl (0.7-1.4 mg/dL)
Bilirubin – Total	1.46 mg/dL (0.3-1.2 mg/dL)
Bilirubin- conjugated	0.76 mg/dl (<0.2 mg/dL)
Aspartate transaminases (AST)	45 IU/L (8-33 IU/L)
Alanine transaminases (ALT)	32 IU/L (8-48 IU/L)
Alkaline phosphatase (ALP)	96 IU/L (30-120 IU/L)
Total Protein	6.94 g/dL (6.6 -8.3 g/dL)
Serum Albumin	2.97 g/dL (3.5-5.2 g/dL)
Serum Globulin	3.97 g/dl (2.0-3.5g/dL)
Procalcitonin	20.4 ng/dl (<0.02ng/dL)
CRP	358.9 mg/dl (less than 5 mg/dL)
ESR	74 mm/hr (0-20 mm/hr)
Serum cortisol	44.38 ug/dL
Prothrombin time	22.6 seconds (11-14 seconds)
INR	1.77
Thyroid profile	TSH - 0.1mIU/L (0.35-5.50 mIU/L) FREE T3 - 1.19pg/ml (2.2-4.20 pg/ml) FREE T4 - 0.58ng/dl (0.89-1.70 ng/dL)
CECT NECK	Left IJV thrombosis with bilateral multilevel cervical lymphadenopathy and diffuse retropharyngeal and parapharyngeal edema

Abbreviations: DLC: Differential leucocyte count; RBC: Red blood cells; WBC: White blood cells; ESR: Erythrocyte sedimentation rate; CRP: C- reactive protein; INR: International Normalized Ratio; TSH: Thyroid Stimulating Hormone; CECT: Contrast-enhanced computed tomography; IJV: Internal Jugular Vein

The patient was suspected to have oropharyngeal infection, leading to the addition of metronidazole to the treatment plan. A contrast-enhanced computed tomography (CECT) of the neck with thorax was performed, revealing left internal jugular vein thrombosis with diffuse retropharyngeal and parapharyngeal edema extending from C2-C6 levels. The imaging also showed multi-level cervical lymphadenopathy and bilateral pneumonia (Figure 1).

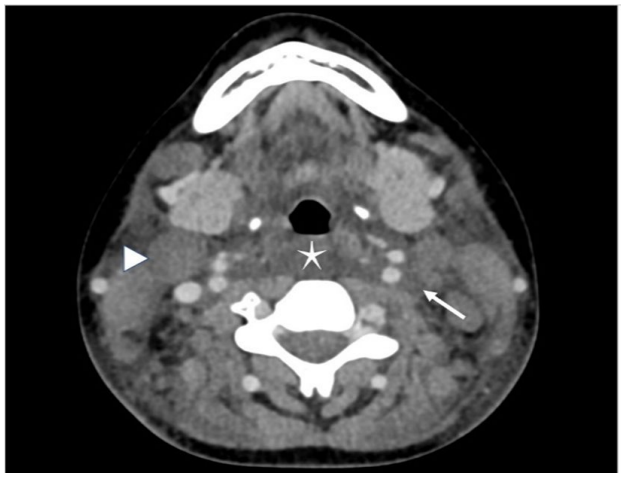

Figure 1. CECT Neck axial section. It shows diffuse hypodensity in retropharyngeal region (*), left IJV thrombosis (arrowed), enlarged right level II cervical lymph node (arrowhead).

The thyroid gland exhibited diffuse enlargement. Thyroid function tests indicated significantly low levels of thyroid-stimulating hormone, free T3, and free T4, collectively suggestive of hypothyroidism, raising the possibility of drug-induced hypothyroidism. Transthoracic echocardiography revealed a collapsed inferior vena cava alongside normal cardiac contractility.

As the patient gradually improved, vasopressors were tapered over a span of three days. On the third day, blood culture results identified *Streptococcus pneumoniae*, susceptible to Ceftriaxone, Levofloxacin, Linezolid, and Vancomycin. Ceftriaxone was continued, while vancomycin and metronidazole were discontinued on the fourth day of hospitalization. To address the low ANC, Injection Filgrastim was administered for three days. A PET-CT scan conducted revealed the presence of septic emboli in the lungs and kidneys, with no involvement observed in the brain or other organs (Figure 2).

An Ear, Nose, and Throat (ENT) surgeon was consulted and determined that surgical intervention was unnecessary. Intravenous ceftriaxone was continued for a total of 14 days. Subsequent cultures sent on day 7 and day 10 yielded sterile results. The patient's condition improved gradually with intravenous antibiotics (ceftriaxone), and no surgical intervention was required. She was discharged on day 14 of her hospital stay.

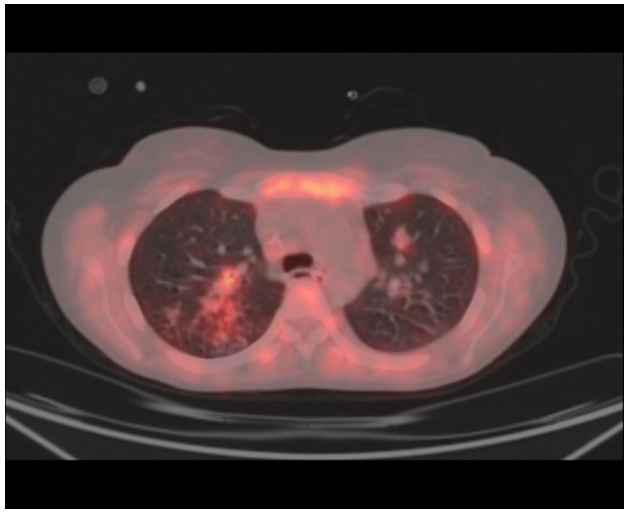

Figure 2. PET-CT with Thorax (axial section). It is suggestive of hypermetabolic lesions in parapharyngeal areas and bilateral lung fields.

DISCUSSION

Lemierre's syndrome, initially described by French physician Andre Lemierre in 1936 as post-pharyngitis anaerobic sepsis, is a rare and potentially fatal condition characterized by septic thrombophlebitis of the internal jugular vein resulting from oropharyngeal bacterial infections.[2] *Fusobacterium necrophorum* is the most commonly implicated organism, with *Fusobacterium nucleatum* following closely behind, and pharyngitis or tonsillitis serving as the causative focus in over 85% of cases.[7] Other causative organisms encompass *Staphylococcus* (including MRSA), *H. influenzae*, *Eikenella corrodens*, *Porphyromonas asaccharolytica*, *Bacteroides*, and Enterobacteriaceae. While Streptococci can contribute to Lemierre's syndrome, infections are generally associated with *Streptococcus viridans*, *Streptococcus pyogenes*, and *Streptococcus milleri* species. It is exceptionally rare for Lemierre's syndrome to be secondary to *Streptococcus pneumoniae*. In our patient, the diagnosis of Lemierre's syndrome was established based on clinical manifestations including fever, neck swelling, internal jugular vein thrombosis, and positive blood cultures.

Streptococcus pneumoniae, typically regarded as a commensal in the nasal mucosa, occasionally presents as clinically significant skin and soft tissue infections (SSTIs). These SSTIs, attributed to *Streptococcus pneumoniae*, constitute less than 2% of all streptococcal infections but can lead to severe conditions, including necrotizing fasciitis.[8,9] Such SSTIs are predominantly observed in immunocompromised individuals, encompassing those with haematological malignancies, Systemic Lupus Erythematosus, and diabetes. In our case, the patient exhibited a significant state of immunocompromise, characterized by a persistently low total leukocyte count and ANC. The diminished ANC was identified as the primary risk factor contributing to the *Streptococcus pneumoniae* infection and the subsequent development of Lemierre's syndrome in our patient.

Lemierre's syndrome can give rise to various complications, including internal jugular vein (IJV) thrombosis and septic emboli affecting organs such as the lungs, joints, and brain. Additionally, this syndrome has the potential to induce bacteremia, leading to severe conditions like osteomyelitis, acute respiratory distress syndrome, and septic shock.[10] In our patient's case, the presence of both IJV thrombosis and septic shock was observed, indicating the progression of Lemierre's syndrome.

The management of Lemierre's syndrome involves systemic administration of antibiotics and surgical intervention if necessary. Antibiotic therapy plays a pivotal role and should be guided by microbiological etiology and antimicrobial susceptibility. Effectiveness has been noted with the use of penicillin, carbapenem, or piperacillin/tazobactam, often combined with metronidazole. While the optimal treatment duration remains uncertain, a regimen of intravenous antibiotics lasting two weeks, followed by a total of four to six weeks, appears sufficient. However, the duration should be personalized considering disease severity and ongoing evaluations.[11] There is no specific recommendation regarding the use of anticoagulation therapy in the treatment of Lemierre's syndrome.

A high suspicion of disease is crucial for prompt diagnosis. Pneumonia or empyema is the most common primary site of infection in *Streptococcus pneumoniae*-associated Lemierre's syndrome.[12] Early initiation of antibiotics and the management of complications are key components in patient care and are associated with improved outcomes. While Lemierre's syndrome secondary to *Streptococcus pyogenes* and the *Streptococcus milleri* group have been reported, Lemierre's syndrome secondary to *Streptococcus pneumoniae* has not been documented in the literature. This case is likely the first reported instance. Although *Streptococcus pneumoniae* commonly causes skin, lung, and central nervous system infections, the consideration of life-threatening Lemierre's syndrome as a rare manifestation is essential. Prompt treatment with sensitive intravenous antibiotics and timely de-escalation are crucial for early recovery and to prevent antimicrobial resistance.

CONCLUSIONS

Lemierre's syndrome, marked by septic thrombophlebitis of the internal jugular vein, is a rare and potentially life-threatening condition linked to oropharyngeal infections. Our case involves a young immunocompromised female who developed Lemierre's syndrome due to an *Streptococcus pneumoniae* infection originating from the lower respiratory tract, underscoring the unusual etiology and significance of this condition. Timely diagnosis, prompt initiation of appropriate antibiotics, and effective management of complications are imperative for favorable outcomes.

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