Lemierre's Syndrome in an Aseptic Patient with Systemic Lupus Erythematosus

Hymie H. Chera MD[1], Max Cohen BS[2], Robert Ishakis BS[3], Yitzhak Rosen, MD[1] and David J. Ozeri MD FACR[4]

[1]Department of Medicine and Rheumatology, State University of New York, Downstate Medical Center, Brooklyn, NY, USA
[2]College of Osteopathic Medicine, New York Institute of Technology, Glen Head, NY, USA
[3]Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel
[4]Department of Medicine, Division of Rheumatology, New York Presbyterian Brooklyn Methodist Hospital, Brooklyn NY, USA

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Lemierre's syndrome describes the combination of internal jugular vein (IJV) thrombus and mediastinitis and is usually associated with an invasive infection. We report the case of IJV thrombus and mediastinitis in an aseptic patient with systemic lupus erythematosus (SLE). We postulate that Type III hypersensitivity reactions in SLE can induce a localized inflammatory response leading to Lemierre's syndrome. To the best of our knowledge, this is the first report of Lemierre's syndrome due to SLE that was successfully treated with low-molecular weight heparin, hydroxychloroquine, and mycophenolate mofetil.

PATIENT DESCRIPTION

We present a 30 year old African American woman with a 4 year history of SLE maintained by prednisone 20 mg daily and hydroxychloroquine 400 mg daily. She presented to the emergency department complaining of severe, sharp, and constant midsternal chest pain. Pain was associated with odynophagia, supraclavicular neck swelling, left upper extremity swelling exacerbated by movement, and swallowing. She denied experiencing any fevers, cough, drooling, exertional chest pain, chills, arthritis, rash, vision changes, lower extremity swelling, dysuria, or oral or nasal ulcers.

Pertinent physical examination revealed a young woman in mild distress due to pain. Her blood pressure was 196/92 mmHg, pulse rate was 121 beats per minutes, and respiratory rate was 25 breaths per minute. She was afebrile. She had a cushingoid appearance with moon facies, central obesity, and diffuse alopecia. She had edema of the left lateral aspect of the neck extending to the anterior aspect of chest and upper extremity. Her edematous area was cool to the touch, without induration, erythema, tenderness to palpation, or fluctuance. She had no pharyngeal erythema, tonsillar hypertrophy, or tonsillar exudates. She had diffuse cervical lymphadenopathy. No malar rash or discoid lesions were noted. Cardiovascular and pulmonary auscultation revealed no abnormalities.

Initial lab results were positive for a normocytic anemia with a hemoglobin of 10.4 g/dl and serum creatinine of 0.85 mg/dl. Urinalysis revealed proteinuria with 10–20 red blood cells per high-power field (HPF) and 5–10 white blood cells per HPF in the absence of urinary casts. A computed tomography scan of the neck was performed with contrast and revealed left IJV thrombosis from the level of the hyoid bone to the subclavian vein with extensive inflammatory changes surrounding the subcutaneous fat extending to the superior anterior mediastinum, along with lymphadenopathy [Figure 1].

The patient was admitted to the hospital for presumed septic IJV with mediastinitis

Figure 1. Computed tomography with intravenous contrast. The orange arrow shows the left internal jugular vein thrombosis from the level of the hyoid bone to the subclavian vein and left brachiocephalic vein. The red arrows show extensive inflammatory changes surrounding the subcutaneous fat extending to the superior anterior mediastinum with lymphadenopathy and edema.

(Lemierre's syndrome). Her blood cultures and a procalcitonin were sent to the laboratory, and treatment was started on broad spectrum intravenous antibiotics (vancomycin and piperacillin-tazobactam) as well as a full dose anticoagulation with low molecular weight heparin.

The patient's other test results revealed negative blood cultures, procalcitonin < 2.0 pg/ml, erythrocyte sedimentation rate (ESR) 77 mm/h, C-reactive protein (CRP) 94.25 mg/L, C3 45 mg/dl, C4 4 mg/dl, antinuclear antibody (ANA) positive, anti-DNA positive, anti-Smith positive, and anti-Sjögren's syndrome A positive. Antiphospholipid antibodies were negative. A spot urine protein was 469 mg/dl, spot urine creatinine was 254.75 mg/dl, and renal sonogram showed normal appearing kidneys.

Given the patient's negative blood cultures, negative procalcitonin, hypocomplementemia, and proteinuria, SLE was strongly considered as the etiology of presentation. The patient was treated with 1 gram of intravenous methylprednisolone sodium succinate daily for 3 days in addition to low molecular weight heparin and antibiotics. She improved rapidly with decreased swelling and resolution of chest pain. Antibiotics were stopped after hospital day 3 and the patient was treated with low molecular weight heparin, prednisone 60 mg daily, and hydroxychloroquine 400 mg daily. Mycophenolate mofetil treatment was initiated. On hospital day 7, the patient had down trending ESR and CRP (40 mm/hr and 7.62 mg/L) and complement levels were up trending (C3 69, C4 5 mg/dl). The patient was discharged from the hospital on day 8.

COMMENT

A systematic search was performed using an electronic database (PubMed–NCBI). We used the following search terms in all possible combinations: systemic lupus erythematosus, arterial thrombosis, internal jugular venous thrombosis, vein thrombosis, antiphospholipid antibodies, antiphospholipid syndrome, and mediastinitis. No cases were found to demonstrate IJV thrombosis along with mediastinitis in SLE patients.

SLE is a multifaceted heterogeneous autoimmune inflammatory disease that can affect nearly every system in the body. The reported prevalence of SLE in the United States is 20 to 150 cases per 100,000 individuals. This disease can affect individuals of all ethnic groups, ages, and genders, but predominantly affects women of childbearing age [1]. The systemic pleomorphic nature of SLE produces challenges both in diagnosis and treatment. The discovery of antinuclear antibody, and more specific serologic tests, has aided diagnostics in complex atypical presentations. Still, often the diagnosis and treatment of SLE relies on clinical judgment and experience.

Although the exact etiology of this disease remains elusive, it is evident that SLE is the product of failed self-tolerance by the body's immune system. A vast array of autoantibodies, particularly ANAs, including anti-phospholipid antibody, have been shown to be mediators of this disease process. In addition, the formation of immune complexes as a function of type III hypersensitivity reactions represents the heterogeneity of SLE in its ability to colonize in various organs [2].

Type III hypersensitivity reactions are caused by the formation of immune complexes composed of immunoglobulin G and soluble antigens. In SLE plasma cell release, antibodies form immune complexes. The immune complexes that are not cleared propagate inflammation via their interaction with complement receptors and leukocytes. The inflammation occurs where the immune complexes aggregate contributing to the heterogeneity of this condition [2,3].

The immune and coagulation systems share many of the same molecular components, allowing cross talk, in which the function of one system directly impacts the other. Inflammation has been shown to mediate the coagulation cascade and even lead to thrombus formation. Inflammatory cytokines induce many downstream components of the coagulation cascade. For example, the release of the following inflammatory cytokines interleukin (IL)-1α, IL-1β, IL-6, or IL-8 increases the expression of tissue factor on endothelial cells and macrophages leading to coagulation and thrombus formation [4].

The formation of an abnormal mass arising from blood constituents and residing within the vascular system is called a thrombus [4]. Thrombotic events are of greater risk in patients with SLE compared to the general population. The incidence of thrombosis in SLE is more than 50% higher compared to the general population [4]. Thrombosis is also the leading cause of death in patients with SLE.

Lemierre's syndrome is a rare infection of the head and neck characterized by thrombophlebitis of the IJV. This rare condition highlights the connection between thrombus formation and disease-induced inflammation. Lemierre's syndrome follows the progression of an oropharyngeal infection forming a peritonsillar abscess, which then ruptures and spreads through nearby soft tissue. Surrounding infection of the IJV induces an inflammatory response, resulting in compression of the IJV and thrombus formation. Patients with Lemierre's syndrome often present with symptoms such as chest pain, fever, shortness of breath, chills, and overall discomfort, which indicate the spread of infection that can induce life threatening mediastinitis [5]. The dual presentation of IJV thrombus and mediastinitis has been a unique feature of Lemierre's syndrome, specifically with *Fusobacterium necrophorum*. Our case represents the first reported case of IJV and mediastinitis in a patient without oropharyngeal infection, but rather with active SLE.

In Lemierre's syndrome, the presence of both IJV thrombus and mediastinitis is primarily due to the robust inflammatory response caused by an invasive bacterial infection. We postulate that, in our case, active SLE led to a robust inflammatory response that caused both IJV thrombus formation and mediastinitis. To the best of our knowledge this is the first report of IJV thrombus and mediastinitis as a manifestation of SLE.

Correspondence
Dr. D.J. Ozeri
Dept. of Medicine, Division of Rheumatology, New York Presbyterian Brooklyn Methodist Hospital, Brooklyn, NY 11215, USA
Phone: 1-917-445-9963
email: davidozeri@gmail.com

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Capsule

Uncomplicating malaria

Severe malaria is caused by the parasite *Plasmodium falciparum*. Infections can result in organ failure and life-threatening hematological or metabolic abnormalities. **Lee** et al. sequenced patient and parasite transcriptomes from 46 *P. falciparum*-infected Gambian children to better understand host–pathogen interactions. The immune response in severe malaria, compared with that in uncomplicated malaria, was not necessarily dysregulated but instead reflected high parasite loads, although there was a distinct neutrophil response.

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Eitan Israeli

Capsule

Metastatic cancers promote cachexia through ZIP14 upregulation in skeletal muscle

Patients with metastatic cancer experience a severe loss of skeletal muscle mass and function known as cachexia. Cachexia is associated with poor prognosis and accelerated death in patients with cancer, yet its underlying mechanisms remain poorly understood. **Wang** et al. identified the metal-ion transporter ZRT- and IRT-like protein 14 (ZIP14) as a critical mediator of cancer-induced cachexia. ZIP14 is upregulated in cachectic muscles of mice and in patients with metastatic cancer and can be induced by TNF-α and TGF-β cytokines. Strikingly, germline ablation or muscle-specific depletion of *Zip14* markedly reduces muscle atrophy in metastatic cancer models. The authors found that ZIP14-mediated zinc uptake in muscle progenitor cells represses the expression of *MyoD* and *Mef2c* and blocks muscle-cell differentiation. Importantly, ZIP14-mediated zinc accumulation in differentiated muscle cells induces myosin heavy chain loss. These results highlight a previously unrecognized role for altered zinc homeostasis in metastatic cancer-induced muscle wasting and implicate ZIP14 as a therapeutic target for its treatment.

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Eitan Israeli

Capsule

Using subcutaneous methotrexate to prolong duration of methotrexate therapy in rheumatoid arthritis

Harris and co-authors aimed to determine whether the use of subcutaneous methotrexate (SC MTX) is associated with prolonged MTX use and lower incidence of hepatotoxicity in rheumatoid arthritis (RA) patients on MTX monotherapy and multiple drug therapy. For MTX monotherapy, SC MTX was associated with a significantly lower likelihood of therapeutic change (hazard ratio [HR] 0.64, 95% confidence interval [95%CI] 0.52–0.78). With multiple DMARD therapy, SC MTX was not associated with a lower risk of adding a biologic (HR 1.13, 95%CI 0.97–1.31). With regard to liver enzymes, there was no significant association between the use of SC MTX and decreased frequency of abnormal LFTs [$P = 0.09$ for alanine aminotransferase (ALT), $P = 0.924$ for aspartate aminotransferase (AST)]. The authors concluded that use of SC MTX is associated with longer duration of MTX monotherapy before the addition of other DMARDs/biologic agents in RA patients. Use of SC MTX is not associated with significantly longer duration of multiple DMARD therapy before the addition of biologic agents. Use of oral MTX is not significantly associated with increased frequency of elevated LFTs.

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Eitan Israeli