A unique case of Lemierre's Syndrome and cerebral vein thrombosis in a carrier of prothrombin gene G20210A mutation

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ABSTRACT

Introduction: We describe here a case of a woman admitted to our Internal Medicine Unit for multifocal pneumonia. During the stay, she presented a few neurological symptoms: headache, nausea, emesis, photophobia, and gait disturbance.

Methodology: Chest computed tomography (CT) detected multiple areas interpreted as septic emboli. Moreover, a left internal jugular thrombosis (LIJT) was incidentally reported. A CT-angiography showed the LIJT extension to cerebral sinuses. Ear, nose, and throat consultation revealed a left medium otitis. Anticoagulation with Fondaparinux was associated to antibiotic therapy with improvement in neurological symptoms that totally remitted over the next 2 weeks.

Results: These findings confirmed the diagnosis of a Lemierre's Syndrome with thrombosis extension to cerebral sinuses. The genetic thrombophilic panel showed a heterozygosis for prothrombin gene G20210A mutation and the patient was discharged with Rivaroxaban for home continuation of anticoagulant therapy for at least 6 months.

Conclusion: The prevalence of inherited thrombophilias in Lemierre's Syndrome is unknown and to our knowledge, this article is the first to identify a prothrombin gene G20210A mutation in a patient with Lemierre's Syndrome with thrombosis extension into the cerebral venous system. Exploring patients with Lemierre's Syndrome for underlying thrombophilia could clarify whether this promotes retrograde jugular vein thrombosis extension.

Keywords: Case report, Lemierre's Syndrome, thrombophilia, cerebral vein thrombosis, DOACs.

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Introduction

In 1936, Lemierre described a rather rare syndrome that still bears his name. It consists of the triad of pharyngitis, thrombosis of the internal jugular vein (IJV), and severe metastatic infection, particularly to the lungs and large joints. His description was provided during the pre-antibiotic era and now, with the broad use of antibiotics, the defining criteria employed by Lemierre have become blurred and modified, so one might expect the disorder not to unfold as originally defined. Most cases are caused by Gram-negative anaerobe *Fusobacterium*, which are normal human microflora of the oropharynx, genitourinary tract, and gastrointestinal tract, especially *Fusobacterium necrophorum*. A systematic review encompassing 114 cases has been published and noted the main sites of infection to be the tonsils, pharynx, and chest. Rare primary sources of infection are odontogenic infection, mastoiditis, otitis media, sinusitis, and parotitis. The prevalence of inherited thrombophilias in Lemierre's syndrome is unknown, in particular, there are no reports of Lemierre's Syndrome complicated by cerebral vein thrombosis in patients with prothrombin gene G20210A mutation. We describe here a case of a woman, carrier of prothrombin gene G20210A mutation, admitted to the clinical ward of our Internal Medicine Unit because of a clinical history first consisting of aspecific clinical symptoms and signs whose evolution led to the diagnosis of Lemierre's Syndrome and cerebral vein thrombosis. Besides the clinical description of this case, we will discuss the possible relationship between inflammation and thrombophilia in the Lemierre's Syndrome.

Case Presentation

A 63-year old female presented to the Emergencies Department complying nausea, emesis, and malaise. She referred productive cough, arthro-myalgias, and fever in the past 15 days. A chest X-ray reveled multiple and bilateral round opacities and she was admitted to the internal medicine ward for "multifocal pneumonia."

She suffered from arterial hypertension, chronic autoimmune thyreopaty, and has first degree familiarity for

prothrombin gene G20210A mutation and venous thromboembolism (VTE), with no personal history of VTE or placenta-mediated pregnancy complication.

At the admission she was afebrile. Her complete blood count showed an altered formula with 81.7% neutrophils in the absence of leukocytosis. Her serum protein electrophoresis showed a mild elevation of alpha-1 an alpha-2 zone (6.1% and 17.2% respectively) with an albumin to globulin ratio of 0.9. C Reactive protein was 1.3 mg/dl.

Empiric treatment with Piperacillin/Tazobactam 4.5 g IV every 8 hours and Azithromycin 500 mg po daily was started.

Over the next few days, she presented headache, nausea, emesis, photophobia, and gait disturbance; a cranial computed tomography (CT) and a rachicentesis were performed in the suspect of a meningeal syndrome; CT was extended to include the chest, in order to better characterize the multiple opacities. Cranial CT was normal. Cerebrospinal fluid analysis showed aspecific alterations (pH = 9; total proteins 61 mg/dl; WBC 3 / mcl). Chest CT detected multiple ground-glass areas randomly distributed; some of these areas showed a solid component with cavitation and were interpreted as septic emboli (Figure 1). Moreover, a left internal jugular thrombosis (LIJT) was incidentally reported.

The clinical scenario was almost consistent with Lemierre's Syndrome (LIJT with septic embolization to the lung).

In order to study the extension of the jugular vein thrombosis and in suspicion of a cerebral sinus thrombosis a CT-angiography was performed, reveling an inflammation of the adipose tissue plans adjoining the left hypopharynx and oropharynx and extending to the IJV; moreover, the jugular vein thrombosis was cranially extended to the left sigmoid and transverse sinus. These findings confirmed the diagnosis of a Lemierre's Syndrome.

Full anticoagulation with a single, subcutaneous dose of 7.5 mg of Fondaparinux was associated to antibiotic therapy and ear, nose, and throat consultation reveled a left medium otitis.

After 2 weeks of full anticoagulation the neurologic symptoms totally remitted and the genetic thrombofilic panel showed a heterozygosis for prothrombin gene G20210A mutation.

The patient was discharged after 21 days of antibiotic therapy while Fondaparinux was substituted with Rivaroxaban 20 mg/day for home continuation of anticoagulant therapy for at least 6 months.

Discussion

How *Fusobacterium* causes septic thrombophlebitis in Lemierre's Syndrome is not known, although several mechanisms have been proposed (hematogenous, lymphatic, and connective tissue spread [1] or direct extension through fascial planes of the neck [1]).

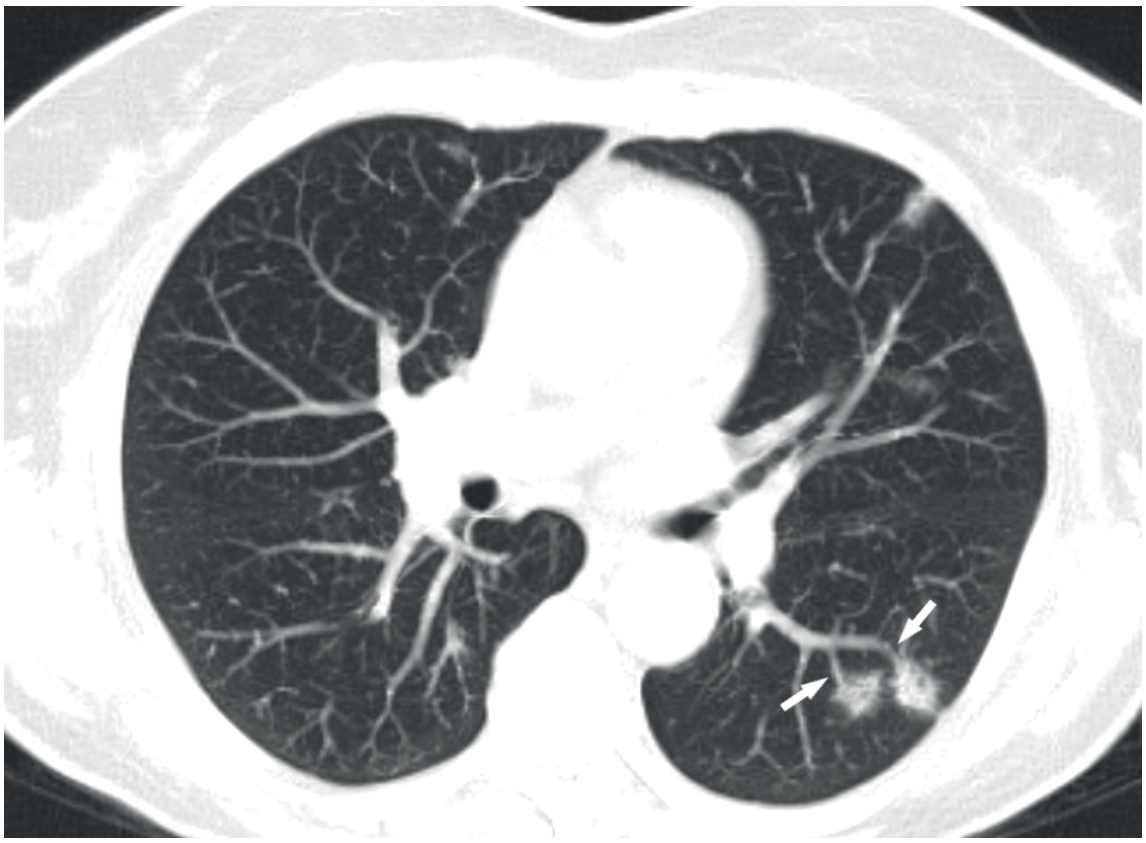

Figure 1. *Chest CT image showing septic pulmonary emboli manifesting themselves as peripheral solid and cavitary pulmonary nodules exhibiting feeding vessel sign (arrows).*

The crosstalk between innate immunity and blood coagulation has been proven to have a role in the pathogenesis of thrombosis in an inflammated environment. Both can activate each other. In particular, neutrophils, and the neutrophil extracellular traps (NET) can involve platelets and activate tissue factor (TF), a 47 kDa transmembrane glycoprotein which is the trigger of blood coagulation. It should be noted that innate immunity and blood coagulation are two ancestral defensive mechanisms. They can strongly reduce bacteria and virus dissemination by producing a fibrin network capable of trapping and killing pathogens. However, an excessive blood coagulation reaction may be dangerous, possibly leading to local thrombosis [2]. Figure 2 presents a drawing which illustrates these mechanisms.

Once infection has reached the IJV, hematogenous spread to other sites can occur, with lung the most commonly affected in up to 85% of cases [3]. The second most common site affected by septic embolization are the large joints [1]. Other metastatic presentation includes osteomyelitis, splenic and liver abscess, central nervous system complication, soft tissue abscesses, cutaneous lesions, pyomyositis, renal abscess, endocarditis, pericarditis, and hemolytic uremic syndrome [4]. Cerebral sinus thrombosis has been reported as a complication of Lemierre's Syndrome, and presumably results from retrograde intracranial extension of IJV thrombosis [4].

The prevalence of inherited thrombophilias in Lemierre's Syndrome is unknown. There are only few reports of Lemierre's Syndrome associated with inherited thrombophilia [5-8], but to our knowledge, this article is the first to identify a prothrombin gene G20210A mutation in a patient with Lemierre's Syndrome with thrombosis extension into the cerebral venous system.

Given that thrombosis of the IJV is an integral component of Lemierre's Syndrome and that mastoid infection with *F. necrophorum* is often complicated by thrombosis of the venous sinuses, it is not unreasonable to question whether thrombophilia might be a risk factor for development of these severe manifestations [1]. Moreover, it would be interesting to understand the role of prothrombin mutation in the extension of IJV thrombosis to cerebral sinus system, given that the overall relative risk for a first VTE event in carriers of prothrombin gene G20210A mutation is increased (triggered or not) compared with controls (OR 2.8, CI 2.25-3.48), especially in the case of cerebral sinus thrombosis (OR 4.4, CI 2.18-8.91) [9]. As a result, bacterial infection along with a thrombophilic risk

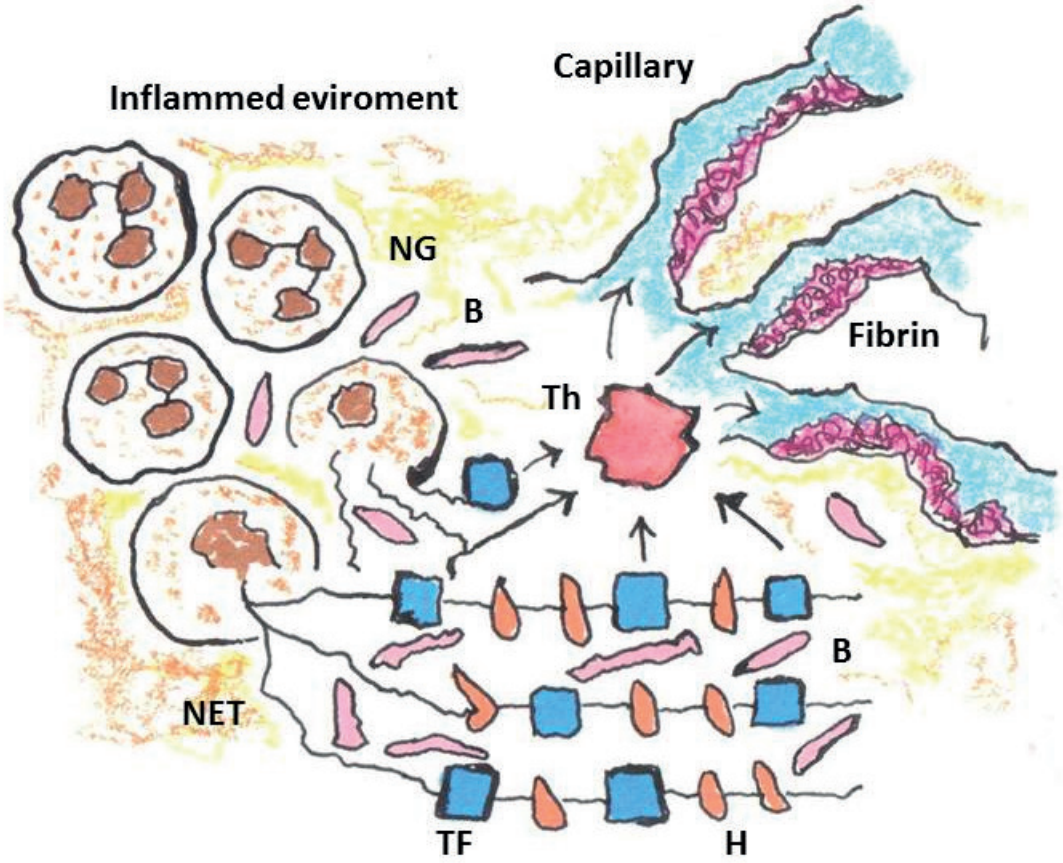

Figure 2. *The crosstalk between innate immunity and blood coagulation in an inflammed environment. In particular, neutrophils and the NET can trap bacteria and activate TF, the trigger of blood coagulation, which produces thrombin which in turn leads to fibrin deposition into capillaries. Thrombophilia may further enhance and extend the thrombotic burden. Abbreviations: Th: Thrombin, NG. Neutrophil granulocytes, NET: Neutrophil extracellular traps, TF: Tissue factor. B: Bacteria, H: Histone.*

factor could have further enhanced the vicious circle of inflammation-blood coagulation activation.

Antibiotics remain the mainstay of therapy in Lemierre's Syndrome. Most patients respond to antibiotic therapy, especially when the extent of the IJV thrombosis is limited, but the role of anticoagulant therapy is uncertain and is based on anecdotal evidence, expert opinion, and case reports. It could prevent the associated complications of respiratory failure and propagation of the septic thrombus into the intracranial sinuses, but due to the lack of randomized studies, it remains unclear if anticoagulation will reduce these complications. Some authors recommend anticoagulation for a select group of patients with lack of response despite 48 to 72 hours of adequate antimicrobial therapy, underlying thrombophilia, and progression of thrombosis or retrograde cavernous sinus thrombosis [3,10].

Concerning cerebral venous thrombosis (CVT), consensus-based guidelines recommend that warfarin therapy with a target international normalized ratio of 2.0 to 3.0 be provided for 3 to 6 months if CVT was secondary to a transient risk factor, and for 6 to 12 months if CVT was idiopathic or occurred in the setting of hereditary thrombophilia, such as protein C or protein S deficiency or heterozygosity for either factor V Leiden or the prothrombin 20210 mutation [11].

In our case, we decided to start first with Fondaparinux, a pentassacharide effective in limiting sepsis-derived coagulopathy [12] and to proceed with oral anticoagulation because of the persistence of neurological symptoms despite antimicrobial therapy and the finding of cerebral sinus thrombosis. We chose Rivaroxaban instead of a vitamin K antagonist (VKA) even if direct oral anticoagulants have not been systematically evaluated in the treatment of CVT. Indeed, a retrospective comparison of CVT patients treated with the oral factor Xa inhibitor, rivaroxaban, against those treated with VKA found no difference in efficacy or safety between the two groups, albeit the sample size was small (n = 16 total) [13]. Moreover, another study showed that in 15 patients treated with dabigatran and followed up for a median of 19 months, outcomes were rated as excellent in 87%, and recanalization was observed in 80% [14]. Finally, a single case reports on the successful use of Edoxaban in the treatment of Lemierre's Syndrome [15].

Conclusion

Given the unknown prevalence of inherited thrombophilias in Lemierre's Syndrome, we suggest exploring for underlying thrombophilia every patient with this nowadays rare syndrome for better understanding whether thrombophilias may favor retrograde thrombotic extension of the process to cerebral venous system.

What is new?

The prevalence of inherited thrombophilias in Lemierre's Syndrome is unknown and to our knowledge, this article is the first to identify a prothrombin gene G20210A mutation in a patient with Lemierre's Syndrome with thrombosis extension into the cerebral venous system.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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None.

Consent for publication

Written and informed consent was taken from patient to publish this case report.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report

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Summary of the case

1	**Patient details**	63-yo caucasian woman
2	**Symptoms**	Nausea, vomiting, headache, photophobia, gait disturbance, cough, and fever
3	**Final diagnosis**	Lemierre's Syndrome with thrombosis extension to the cerebral venous system
4	**Medication**	Fondaparinux and Rivaroxaban
5	**Clinical procedures**	CT-angiography of the central venous system, chest, and head CT
6	**Clinical specialty**	Internal Medicine, haemostasis, and thrombosis