SUPERIOR MESENTERIC VEIN THROMBOSIS AND CYTOMEGALOVIRUS: A DIAGNOSTIC DILEMMA. A CASE REPORT AND REVIEW OF THE LITERATURE.

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Introduction
Superior mesenteric vein thrombosis (SMVT) is a rare condition, usually caused by infections, intra-abdominal inflammatory diseases, portal hypertension, hypercoagulable states, or contraceptive therapy. Due to its vague symptomatology, SMVT is often diagnosed only after an abdominal contrast-enhanced computed tomography (CT) scan. In this article, we present a case of SMVT in a patient with a history of contraceptive drug use and a recent cytomegalovirus infection.

A 36-year-old female was admitted to our department with the clinical symptoms of an acute appendicitis. The patient was a smoker and had been using hormonal contraceptives for over a year. Surgery was deemed the best course of action. Before the operation, blood tests showed a mild lymphocytosis and altered liver enzyme levels, while coagulation values were normal. A contrast-enhanced CT scan revealed a complete superior mesenteric vein thrombosis without signs of bowel ischemia. Anticoagulants were immediately administered. A thrombophilia panel did not highlight any noteworthy elements. Cytomegalovirus (CMV) tests resulted positive.

Since CMV is a rare, but potentially significant cause or precipitating factor for thrombosis in immunocompetent hosts, all patients with an unexplained fever and seemingly spontaneous thrombosis should be screened for CMV infection.

SUMMARY
Superior mesenteric vein thrombosis (SMVT) is a rare condition, usually caused by infections, intra-abdominal inflammatory diseases, portal hypertension, hypercoagulable states, or contraceptive therapy. Due to its vague symptomatology, SMVT is often diagnosed only after an abdominal contrast-enhanced computed tomography (CT) scan. In this article, we present a case of SMVT in a patient with a history of contraceptive drug use and a recent cytomegalovirus infection. A 36-year-old female was admitted to our department with the clinical symptoms of an acute appendicitis. The patient was a smoker and had been using hormonal contraceptives for over a year. Surgery was deemed the best course of action. Before the operation, blood tests showed a mild lymphocytosis and altered liver enzyme levels, while coagulation values were normal. A contrast-enhanced CT scan revealed a complete superior mesenteric vein thrombosis without signs of bowel ischemia. Anticoagulants were immediately administered. A thrombophilia panel did not highlight any noteworthy elements. Cytomegalovirus (CMV) tests resulted positive. Since CMV is a rare, but potentially significant cause or precipitating factor for thrombosis in immunocompetent hosts, all patients with an unexplained fever and seemingly spontaneous thrombosis should be screened for CMV infection.

Introduction
Superior mesenteric vein thrombosis (SMVT) is a rare condition that causes intestinal ischemia, and can be quite difficult to diagnose. SMVT diagnoses have increased in the last two decades, probably due to the increased use and availability of contrast-enhanced computed tomography (CT) scans for diagnosing patients with portal hypertension or abdominal pain. SMVT frequently occurs in young adults, and may be caused by infection (e.g., cytomegalovirus in immunocompetent patients) 1, intra-abdominal inflammatory diseases (acute cholecystitis, pancreatitis or appendicitis) 2, portal hypertension, splenectomy, sepsis, hypercoagulable states (thrombophilia or myelodysplastic syndrome), or contraceptive therapy (oral contraceptive use has been shown to increase the risk of thrombosis) 3.

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SMVT often presents with nonspecific symptoms such as nausea, vomiting and abdominal pain, sometimes mimicking an acute abdomen. The vague symptoms and lack of distinct findings on physical examination (the abdomen is usually non-tender on palpation), despite the severe pain, make the disease difficult to diagnose; conclusive diagnosis is generally delayed, and it can even be an incidental finding during an abdominal computerized tomography (CT) or ultrasound (US) scan. Furthermore, like in the present case, abdominal US does not always detect any of the abnormalities caused by SMVT, and in such cases, contrast-enhanced CT scan seems to be the most sensitive investigation method.

This article describes the case of a patient suffering from SMVT with a history of hormonal contraceptive use and a recent cytomegalovirus (CMV) infection.

Case report
A 36-year-old Caucasian woman was admitted to our department with a one week history of postprandial abdominal pain, located around the area of the right iliac fossa and responsive to paracetamol, and a one month history of evening rise low-grade fever (37-38°C) with chills, malaise and weakness, that had been treated at home with intramuscular 500 mg injections of ciprofloxacin for 6 days. The patient described her pain as a dull ache, turning crampy in the immediate postprandial period. The patient was diagnosed with Darier’s disease in 1999, and had undergone a laparoscopic cholecystectomy five years prior to the present admission. Furthermore, the patient referred a history of jugular vein thrombosis in her immediate family (mother), in addition to a case of spontaneous miscarriage and a twin pregnancy with threatened abortion. Medication history included the use of transdermal contraceptives (norelgestromin/ethinyl estradiol 6mg/600mcg) for about one year, followed by oral contraceptives (drospirenone/ethinyl estradiol 3mg/0.03mg) for five months prior to being interrupted during the present hospital admission. The patient had been smoking 15-20 cigarettes per day for the past 18 years. At physical examination, the patient presented a distended but non-tender abdomen, although deep palpation in the proximity of the right iliac fossa resulted in minor pain. McBurney’s sign resulted positive and Blumberg sign weakly positive. Blood tests showed elevated gamma-glutamyl transferase (103 IU/L) and alkaline phosphatase (107 IU/L) serum levels. Aspartate transaminase (AST) levels were 47 IU/L, while those of alanine transaminase (ALT) were 45 IU/L. Coagulation parameters fell within normal values (INR: 0.87) and no leukocytosis was observed (7030 cells/μL), while only a mild degree of relative lymphocytosis was detected (50.4%). Suspecting an appendicitis, but with the clinical picture still remaining unclear, we decided to perform an abdominal US and contrast-enhanced CT scan immediately preceding the intervention. The US scan did not evidence any abnormalities, whereas the contrast-enhanced CT scan revealed a complete superior mesenteric vein thrombosis without discernible signs of bowel ischemia (Figure 1). Furthermore, the CT scan showed a small intramural uterine leiomyoma with a diameter of three centimeters. Anticoagulation therapy was immediately commenced, administering 4000 IU of enoxaparin sodium twice per day. The hematologist prescribed an additional anticoagulant therapy of warfarin (5 mg per day) in order to maintain an INR of 2.5. Paroxysmal nocturnal haemoglobinuria clone, Jak-2, Factor V Leiden (R506Q), and Prothrombin (G20210A) mutations resulted negative, while the patient presented a mutation in one of the two alleles of methylenetetrahydrofolate reductase (MTHFR) gene, and a 4G/5G polymorphism was detected in the PAI-1 gene. Due to the fever, and considering past experiences recorded in literature, an enzyme-linked immunosorbent serologic assay (ELISA) for CMV was performed. CMV IgM levels resulted 3.1 times higher than normal; CMV IgG levels were 147.0 AU/ml. Crucially, the patient had undergone routine blood exams during her pregnancy one year earlier, and tested negative for CMV.

Six months after admission, the patient was found to be in good health and free of any residual symptoms.

Discussion
SMVT can be a severe condition that could lead to irreversible intestinal necrosis if not promptly identified and properly treated. It
may be caused by local factors, such as trauma, infection, or venous obstruction, or be associated with hypercoagulable states, such as polycythemia rubra vera and carcinomatosis. SMVT is insidious and difficult to diagnose, since it often presents with nonspecific symptoms, such as nausea, diarrhea, vomiting, abdominal pain, or, as in our case, the physical signs of an acute abdomen caused by appendicitis. Treatment should be initiated while the patient is still in the reversible ischemia phase, before irreversible necrosis occurs. In the latter situation, an extensive surgical resection of the necrotic intestinal loops is required. The mortality rate for this condition ranges from 20% to 50%.

Survival depends on several factors, mostly on the timing of diagnosis and surgical intervention. Short bowel syndrome is a major complication of SMVT surgery, subject to the extent of resection necessary. There are currently no reported laboratory findings specific for the diagnosis of SMVT; however, increased plasma lactate levels and metabolic acidosis may help to identify an irreversible bowel infarction, but this is usually a late-stage finding, and as such not useful for early diagnosis.

Contrast-enhanced CT scan is the diagnostic method of choice for suspected cases of mesenteric venous thrombosis. Unfortunately, this technique is not as sensitive for thrombosis of the smaller mesenteric vessels: in these patients, a mesenteric angiography should be performed.

Hormonal oral contraceptive (OC) therapy has been available since the 1960s. To date, it is estimated that more than 100,000 women use this contraceptive method.

Figure 1. Contrast-enhanced CT scan. Complete thrombosis of the superior mesenteric vein and its distal branches, associated with hyperdense congestive perivascular fat deposition.
method. In the beginning of the 1970s, many studies showed an increased risk of thromboembolic and cardiovascular diseases among the users of oral contraceptives. The risk has since been shown to be further increased in women who smoke or have a family history of deep vein thrombosis, like in the present case. It has been demonstrated that estrogens increase the hepatic production of factors VII and X, and fibrinogen. Moreover, they decrease the levels of antithrombin III and protein S. In the fibrinolytic cascade, they increase the levels of plasminogen and tissue plasminogen activator (t-PA), and lead to a reduction in plasminogen activator inhibitor-1 (PAI-1) levels. Estrogens also determine an increase in platelet levels, induce intimal hyperplasia and are responsible for changes in lipid profiles. The risk of a thromboembolic complication declines within one month of discontinuing oral contraceptives. In the reported case, no coagulation alterations or particularly significant gene mutations were registered; however, the patient’s medical history included a case deep vein thrombosis in the immediate family, and a previous miscarriage for unknown causes. Furthermore, she was a heavy smoker. All these elements point towards a diagnosis of OC-related SMVT. Interestingly, in this case, an intermittent fever that had lasted for a month, and hepatic serum enzyme anomalies were also present. In immunocompetent hosts, primary CMV infections, when carefully evaluated at the clinical level, are mostly associated with mild clinical symptoms, such as headache, fatigue, fever, or sore throat. Symptoms, when perceptible, develop 9-60 days after the primary infection. CMV can cause a wide range of infections in immunocompetent hosts. Most commonly affected sites include the lung (severe community-acquired viral pneumonia), liver (transaminasemia), spleen (splenomegaly), gastrointestinal tract (colitis), central nervous system (encephalitis), hematologic system (cytopenias), and multisystemic infection (fever of unknown origin). A possible role for CMV in adrenal gland tumorigenesis has also been postulated. In the present case, the previous miscarriage and/or the threatened abortion could have been caused by the presence of the intramural fibroid, which are thought to be one of the main causes of subfertility. CMV may also result in atypical lymphocytes in the blood. Other typical findings include negative heterophile antibody tests, mildly or moderately elevated levels of aspartate transaminase, and evidence of subclinical hemolysis. Hepatitis and atypical lymphocytes usually resolve within six weeks. CMV-associated thrombosis has been extensively reported in medical literature, mainly in immunocompromised patients. A meta-analysis showed that deep venous thrombosis/pulmonary embolism (DVT/PE), splanchnic vein thrombosis and splenic infarction were the most prevalent types of thrombosis associated with acute CMV infection. Cytomegalovirus-related superior mesenteric vein thrombosis is extremely rare, especially in immunocompetent patients. In the few previously reported cases, all patients presented with a high body temperature, mild abdominal pain, altered liver enzyme levels, mild lymphocytosis and a negative thrombophilia panel. The exact pathologic mechanisms through which CMV triggers thrombosis are still unclear. Several theories have been proposed, such as inhibition of p53-mediated apoptosis, and platelet-derived growth factor β-receptor escalation. It has also been suggested that the procoagulant effect of CMV may arise from the infection of endothelial cells. As a result of either one or a combination of these mechanisms, CMV infection can induce vascular changes that may trigger a cascade of events that lead to inflammation and thrombosis. Regardless of the exact causative mechanism, there is growing evidence that CMV may induce potentially life-threatening vascular damage with associated thrombosis.

Conclusions
Mesenteric venous thrombosis is a major cause of intestinal ischemia and necrosis. Its diagnosis is often significantly delayed due to the generally vague clinical presentation of this condition, frequently causing it to be mistaken for other diseases (appendicitis, Crohn’s disease, salpingitis, peritonitis etc.); modern imaging techniques enable an early diagnosis, thus avoiding the need for surgery. Prompt treatment with anticoagulants drastically improve the quality of life and the survival rate of patients. Surgical resection of the
bowel loops should only be resorted to in patients with irreversible necrosis following a delayed diagnosis or anticoagulant therapy failure. Since CMV is a rare, but potentially significant cause or precipitating factor for thrombosis in immunocompetent hosts, all patients with an unexplained fever and spontaneous thrombosis should be screened for CMV infection.

References
25. Ofotokun I, Carlson C, Gitlin SD, Elta G, Singleton TP, Markovitz DM: Acute cytomegalovirus infection complicated by...