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Venous Thromboembolism in Ulcerative Colitis: a clinical case report

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VENOUS THROMBOEMBOLISM IN ULCERATIVE COLITIS: A CLINICAL CASE REPORT

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

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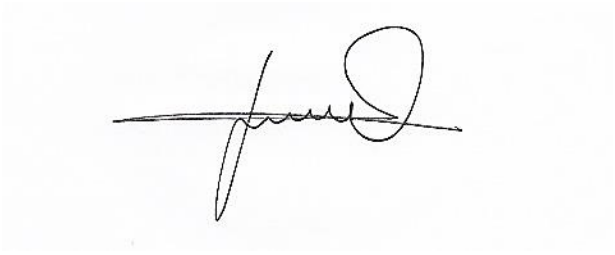

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Resumo

Introdução: O tromboembolismo venoso é a segunda manifestação extraintestinal mais prevalente na doença inflamatória intestinal. O seu risco é cerca de 3 vezes maior em comparação com a população geral e numa exacerbação aguda, o risco aumenta até 15 vezes. A trombose venosa cerebral ocorre em cerca de 0,5% a 6,7% na doença inflamatória intestinal e constitui um fator importante no prognóstico e na morbilidade do doente.

Revisão da Literatura: O estado inflamatório da colite ulcerosa é pró-trombótico. Do mesmo modo, os corticosteroides, que são primeira linha no tratamento das exacerbações moderadas a graves, também têm um risco acrescido de tromboembolismo. Por estas razões, os doentes hospitalizados com agudização de colite ulcerosa devem receber tromboprofilaxia. Por outro lado, os doentes tratados em ambulatório têm indicação para profilaxia apenas se história prévia de tromboembolismo.

Caso Clínico: O caso relata um homem de 27 anos de idade com exacerbação da colite ulcerosa, sob corticosteroides orais, que se apresentou ao serviço de urgência com cefaleia, vómitos e fotofobia. Foi-lhe diagnosticada uma trombose cerebral do seio venoso lateral direito e da veia jugular ipsilateral, tendo sido internado sob terapêutica anticoagulante. Dada boa evolução clínica teve alta medicado com dabigatrano, que manterá por pelo menos 12meses, até confirmação da restauração total do fluxo sanguíneo cerebral.

Discussão: Quanto à prevenção do evento, o doente não tinha indicação de tromboprofilaxia, dado não ter critérios de internamento nem história prévia de eventos trombóticos. As recomendações atuais de tromboprofilaxia aplicam-se a doentes internados. Tal é aparentemente justificado porque que se sabe que o risco absoluto de tromboembolismo em ambulatório é baixo e a prática de tromboprofilaxia em ambulatório provou não ser custo-efetiva. No entanto, embora os corticosteroides sejam a primeira linha para induzir a remissão da doença, os seus efeitos pró-trombóticos não podem ser negligenciados e devem ser vistos como potenciadores do evento trombótico.

Conclusões: Não existem diretrizes que esclareçam uma abordagem específica na trombose cerebral no doente com doença inflamatória intestinal. Assim, é necessária mais investigação para avaliar a melhor gestão e tratamento desta complicação. Além disso, deve-se compreender melhor se alguns dos doentes em ambulatório com doença ativa poderão beneficiar de tromboprofilaxia.

Palavras-Chave: Colite Ulcerosa; Tromboembolismo venoso.

Abstract

Introduction: Venous thromboembolism is the second most prevalent extraintestinal manifestation in inflammatory bowel disease. Its risk is about 3 times higher compared to the general population and in an acute exacerbation, the risk increases up to 15 times. Cerebral venous thrombosis occurs in about 0.5% to 6.7% in inflammatory bowel disease and is an important factor in patient prognosis and morbidity.

Literature Review: The inflammatory state of ulcerative colitis is pro-thrombotic. Similarly, corticosteroids, which are first line in the treatment of moderate to severe exacerbations, also have an increased risk of thromboembolism. For these reasons, hospitalized patients with acute ulcerative colitis should receive thromboprophylaxis. On the other hand, patients treated in outpatient settings are indicated for prophylaxis only if there is history of thromboembolism.

Clinical Case: The case reports a 27-year-old man with exacerbation of ulcerative colitis, on oral corticosteroids, who presented to the emergency department with headache, vomiting and photophobia. He was diagnosed with cerebral thrombosis of the right lateral venous sinus and the ipsilateral jugular vein and was admitted under anticoagulant therapy. Given the good clinical evolution, he was discharged with dabigatran, which will be maintained for at least 12 months, until confirmation of total restoration of cerebral blood flow.

Discussion: Regarding the prevention of the event, the patient had no indication for thromboprophylaxis, as he had no admission criteria and no previous history of thrombotic events. Current recommendations for thromboprophylaxis apply to inpatients. This is apparently justified because the absolute risk of outpatient thromboembolism is known to be low and the practice of outpatient thromboprophylaxis has proven not to be cost-effective. However, although corticosteroids are the first line to induce disease remission, their pro-thrombotic effects cannot be neglected and should be seen as enhancers of the thrombotic event.

Conclusions: There are no guidelines clarifying a specific approach in cerebral thrombosis in the patient with inflammatory bowel disease. Thus, more research is needed to evaluate the best management and treatment of this complication. In addition, it should be better understood whether some of the outpatients with active disease may benefit from thromboprophylaxis.

Key words: Ulcerative colitis; Venous thromboembolism.

Abbreviations list

5-ASA - 5-Aminosalicylic Acid

AHA/ASA - American Heart Association and American Stroke Association

BWT - Bowel Wall Thickness

CD – Crohn's Disease

CD40L – CD40 Ligand

CRC - Colorectal Cancer

CRP – C-Reactive Protein

CT - Computed Tomographic

CVST - Cerebral Venous Sinus Thrombosis

ER – Emergency Room

ESR - Erythrocyte Sedimentation Rate

FC - Faecal Calprotectin

GIUS - Gastrointestinal ultrasound

IBD - Inflammatory bowel disease

ICP - Intracranial Pressure

INR - International Normalised Ratio

LMWH - Low Molecular Weight Heparin

NOAC´s - Novel Oral Anticoagulants

PAI-1 - tPA Inhibitor

TAFI - Thrombin Activatable Fibrinolysis Inhibitor

TNF - Tumor Necrosis Factor

tPA - Tissue Plasminogen Activator

UC - Ulcerative Colitis

UFH - Unfractionated Heparin

VTE - Venous Thromboembolism

vWF - Von Willebrand Factor

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Introduction

Inflammatory bowel disease (IBD) is a global health problem with a steadily increasing incidence. It includes two major forms, Crohn's Disease (CD) and Ulcerative Colitis (UC), which are distinct chronic idiopathic bowel inflammatory disorders, with a relapsing course.[1] UC affects mostly the colon[2], however about 20%-30% of IBD cases are associated with manifestations in other organs.[3] Extra-intestinal manifestations adversely impact upon patients' quality of life and some, such as venous thromboembolism (VTE), can be life-threatening[4]. The prevalence of VTE ranges from 1%-7% among IBD patients and is the second most prevalent extraintestinal manifestation, only spondyloarthropathies are more frequent than thrombosis.[5] Thrombosis usually occurs in the form of deep vein thrombosis of the legs and pulmonary embolism[5], however cerebral thrombosis may also occur. Cerebral venous sinus thrombosis (CVST) occurs in around 0.5%-6.7% of all IBD patients[6], usually in young patients with UC and with a mean age of <29 years.[7] IBD patients have a risk of VTE about 3 times higher compared to the general population[8], and the absolute risk is much higher in the hospital setting (about 6 times higher) compared to the non-hospital setting[4]. Disease activity plays an important role in risk, so moderate to severe disease should be considered as a triggering factor[8]. In an acute exacerbation, the risk increases as much as 15 times when compared to the general population[4].

Literature review

Ulcerative Colitis

DEFINITIONS

UC is a condition that causes mucosal inflammation of the colon. The inflammation characteristically starts in the rectum and it extends proximally in a continuous fashion affecting a variable length of the colon, or its entire mucosal surface.[9]

EPIDEMIOLOGY

The typical age of disease onset is between 30-40 years of age[10], and there is no gender predominance[11]. About 8–14% of patients with ulcerative colitis have a family history of IBD and first-degree relatives are 4 times more likely to develop the disease[12]. Prevalence rates are highest in Europe[13], with countries located in the western and northern regions having higher incidences than eastern countries.[14] A meta-analysis showed that smoking is protective against ulcerative colitis[15].

PATHOLOGY

A widely accepted framework suggests a complex contribution of environmental and internal factors that increase susceptibility to develop UC, and that disease onset is triggered by events that disrupt the mucosal barrier, alter the balance of the gut microbiota, and stimulate abnormal gut immune responses.[16] In this way, the pathogenesis is multifactorial, involving genetic predisposition, epithelial barrier defects, dysregulated immune responses, and environmental factors.[10]

CLINICAL PRESENTATION AND DIAGNOSIS

A "gold standard" for the diagnosis of ulcerative colitis does not exist. It is established by clinical, laboratory, imaging, and endoscopic parameters, including histopathology.

Symptoms of UC are dependent upon extent and severity of disease. The classic presentation of UC includes symptoms of bloody diarrhoea with or without mucus, rectal urgency, tenesmus, and variable degrees of abdominal pain.[17] However, other intestinal or systemic symptoms can occur, such as weight loss, fever, fatigue, nausea or vomiting.[18]

Laboratory analysis

The full blood count may reveal thrombocytosis, anaemia or leucocytosis which raises the possibility of an infectious complication. C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) are valuable markers of severity but are not specific to differentiate UC from other causes of colitis. Albumin levels play an important role, since hypoalbuminemia (defined as ≤ 3.5 gm/dl), at the time of disease diagnosis is a poor prognostic indicator.[19]

Fecal calprotectin (FC) and lactoferrin levels are helpful to assess the degree of inflammation[17]. FC is a marker of intestinal inflammation, however in can be elevated in non-inflammatory conditions like bowel infections. So, the specificity of this biomarker is relatively low, opening a range of differential diagnoses. The lack of guidelines and data regarding optimal FC cut-offs makes intermediate FC concentrations of 150-250µg/g often challenging to interpret in IBD, while <40µg/g excludes IBD and >250µg/g should lead to rapid assessment for IBD.[20] Despite these limitations this is a valuable marker to monitor disease activity, as fluctuations may predict relapse of disease.

Imaging

Ultrasound

Gastrointestinal ultrasound (GIUS) is relevant in the assessment of the disease extent and follow-up of UC. The assessed parameters are bowel wall thickness (BWT), parietal blood flow, doppler signal, wall layer stratification, and fatty wrapping. Of these, BWT has proven to correlate well with clinical, endoscopic, and histological activity.[21]

Computed tomography

Computed tomographic (CT) enterocolonography is used to stratify the severity of UC and to detect intramural, extra-intestinal involvement and intestinal complications. Common inflammatory features are hyperenhancement, bowel wall thickening, loss of haustrations and luminal narrowing.[22]

Endoscopy

Endoscopy plays an essential role in establishing the diagnosis, as well as ruling out other etiologies. It is also key in monitoring disease activity, response to treatment and assessing complications.[23]

In patients with clinical presentation suggestive of IBD, the initial evaluation should include a colonoscopy with ileoscopy and biopsies.[23] However, colonoscopy is generally not feasible in the acute setting of severe colitis and contraindicated if complications are suspected, like toxic megacolon. In these cases flexible sigmoidoscopy is a useful and safe alternative that allows examination of the left or distal colon and the acquisition of biopsies.[23]

The endoscopic features of mild inflammation are erythema, vascular congestion, and a partial loss of the visible vascular pattern. Moderate colitis is characterized by a complete loss of the vascular pattern, adherence of blood to the mucosal surface, erosions, and friability of the mucosa. Severe colitis is characterized by spontaneous bleeding and ulceration.[24]

Histologically, UC is characterised by diffuse inflammatory cell infiltration of the mucosa with basal plasmacytosis, crypt architectural changes (with cryptic abscess and cryptitis lesions) and a reduction of mucus-secreting goblet cells.[25] Absence of a histological acute inflammatory infiltrate predicts quiescent course of disease.

CLASSIFICATION

UC should be classified by its extent and severity.

Extent of Ulcerative colitis

As to its extent, the Montreal classification of IBD classifies UC as proctitis, left-sided colitis, or extensive colitis, as described in Table I.[26] Proctitis is defined as involvement limited to the rectum, left-sided colitis is defined by an involvement distal to the splenic flexure, while in extensive colitis the disease extends proximal to the splenic flexure (including pancolitis).

Extent should be assessed at diagnosis, because knowledge of the anatomic extent of mucosal inflammation is essential for selection of treatments.[27] In addition to this, the extent of colitis influences the risk of development of colorectal cancer (CRC), and thus the frequency of colonoscopic surveillance.[28]

Severity of Ulcerative colitis

Additionally, it is important to assess its severity (Table II[29] and III[30]) since it influences treatment decisions, modality and route of administration.[9]

For this purpose, one of the most used tools is the Truelove and Witts Severity Index, presented in Table II[29], which analyses objective clinical features, like bloody stool and frequency, body temperature and heart rate, but also some analytical criteria such as the acute phase CRP, ESR and haemoglobin.

The Mayo Score (Table III)[30] is a combined endoscopic and clinical scale, from 0 to 3, that is also used to assess the severity of UC.

TREATMENT

The goal of maintenance therapy in UC is to maintain steroid-free remission, defined as stool frequency ≤ 3/day, no rectal bleeding, and an endoscopically normal mucosal pattern. The treatment strategy for UC is based on the severity, distribution, and pattern of disease. The latter includes relapse frequency, disease course, response to previous medications, side effects of medication, and extra-intestinal manifestations.

Mild to moderate Disease

For induction and maintenance of remission in mild proctitis, topical 5-aminosalicylic acid (5-ASA) are effective and are the preferred initial treatment.[31] Patients who required an oral 5-ASA to achieve remission or have multiple relapses on topical therapy should be treated with oral 5-ASAs to maintain remission. [17]

Mild left-sided or extensive ulcerative colitis should initially be treated, for induction of remission, with a 5-ASA enema 1 g/day combined with oral mesalazine (5-ASA) ≥ 2.4 g/day. Systemic corticosteroids are appropriate in patients with moderate (and severe) activity and in those with mild activity who do not respond to mesalazine.[31] For patients who relapse despite 5-ASA at optimal dose, or are intolerant to 5-ASA, or are steroid-dependent, immunosuppression with thiopurines is recommended for achieving and maintenance of remission.[31] Azathioprine is generally the first line and common complications are gastric intolerance, leukopenia and pancreatitis.[32] The occurrence of lymphoma remain a recognized risk, particularly in younger (under 30 years old) males and in patients with primary Epstein Barr virus infection[33]. A pre-immunosuppression assessment to exclude latent infections should always be performed. Patients with poor prognostic factors such as young age at disease onset, extensive colitis, deep ulcerations, those who require two or more courses of steroids in a year or develop steroid dependence, could also be treated with a combination of thiopurine and biologic therapy, mainly with the first line anti-Tumour Necrosis Factor (TNF), infliximab. [17]

A summary flowchart on the treatment approach in mild-moderate UC, taken from Gajendran M, Loganathan P, Jimenez G, *et al*.[17], is shown in figure 1.

Moderate to severe Disease

Patients with moderate to severe ulcerative colitis could be treated with oral corticosteroids[17], however the initial recommended treatment for severe active ulcerative colitis is intravenous steroids. All inpatients should receive low molecular weight Heparin (LMWH) for thromboprophylaxis.

The response to intravenous steroids is best assessed by the third day. If there is no response, then the next option includes immunosuppression[31] or biological therapy, like anti-TNF-α (such as infliximab). Maintenance of remission in this patients should be accomplished with immunosuppressive treatment and/or biologic therapy. [17]

A summary flowchart on the treatment approach in moderate-severe UC, taken from Gajendran M, Loganathan P, Jimenez G, *et al*.[17], is shown in figure 2.

Venous thromboembolism

DEFINITIONS

Venous thromboembolism (VTE) consists mainly of fibrin and red blood cells and occurs when stimulation of blood clotting exceeds the ability of normal anticoagulant mechanisms and the fibrinolytic system to prevent clot development.[34]

PHYSIOPATHOLOGY IN INFLAMMATORY BOWEL DISEASE

The basis of its etiopathogenesis is focused on inflammation. Inflammation affects the coagulation cascade, the fibrinolytic system, endothelial function, and the platelet system.

Coagulation Cascade

In IBD, regardless of disease activity, the cleavage of prothrombin into thrombin (enabled by the coagulation cascade) is continuously increased[35,36]. Besides that, some studies have shown that several coagulation factors (like V, VII, VIII, X, XI and XII) are elevated during an IBD flare.[37,38]

Fibrinolytic system

Normally, the fibrinolytic system allows the removal of fibrin clots by plasmin activity.[36] Plasmin is generated from the action of tissue plasminogen activator (tPA). CRP (an indicator of inflammation) has been shown to inhibit tPA and increase the expression of tissue plasminogen activator inhibitor (PAI-1)[5], which prevents plasmin formation.[36] Thus in IBD, in addition to a reduction in fibrinolysis activators (such as TPA), there is also an increase in their inhibitors.[38]

In addition, the thrombin activatable fibrinolysis inhibitor (TAFI), which is an enzyme activated by thrombin, is another inhibitor of the system that is also increased. An increase in thrombin production (as seen earlier) will condition a greater activation of TAFI, leading to additional protection of the fibrin clot.

Platelet system

Platelet activity reacts to inflammation on several levels. In terms of quantity, thrombocytosis relates to disease activity and severity[36]. Qualitatively, platelets in IBD circulate in a state of chronic activation and are more sensitive to activation[36], since high values of CD40 ligand (CD40L) are detected. Activated CD40L-positive platelets increase inflammation by interacting with CD40-positive endothelium in the intestinal mucosa[36]. Activation of this pathway is promoted by inflammation, more specifically by TNF-alpha.

Endothelial function

Endothelial dysfunction has been demonstrated in IBD and markers of its damage such as von Willebrand factor (vWF) and Endothelial protein C receptor are increased and correlate with disease activity. There appears to be an accumulation of vWF multimers that are more hemostatically active and favor platelet adhesion and aggregation.[36]

Medication

Corticosteroids, which are used to help induce remission in IBD patients, have some adverse side-effects including an increased risk of VTE. The mechanism is thought to be related to excess cortisol, as patients with Cushing's syndrome have an increased risk of VTE from an elevated production of procoagulation factors and an impaired fibrinolytic capacity. [39] And the same is true for patients on corticoids, since it increases plasma fibrinogen level, and decreases tPA activity and prostacyclin synthesis[3].

PREVENTION

Patients with IBD should be investigated for additional risk factors of thrombosis, as the presence of multiple factors might increase the risk even further. A set of risk factors for venous thromboembolism is shown in table IV.[40] When the VTE event is provoked by a temporary major risk factor (e.g. surgery), the risk of recurrent VTE is low after stopping therapy when the risk factor has disappeared, and long-time anticoagulation is not warranted in general. In case of a persistent major risk factor, such as active cancer, the risk of recurrence is high as long as the factor is present and, therefore, anticoagulation should be continued.[40] To prevent these events patient education is needed to control important factors such as long-term immobilization and smoking. Oral contraceptives and hormone replacement therapy should be avoided.[5]

The foundation of prophylactic treatment is heparin[4], and results indicate that the risk of thrombosis is reduced by 50% with its use[5]. Heparin provides its anticoagulant effect by inhibiting clotting factor X in the presence of antithrombin. There is little evidence that heparin (in therapeutic dose) is associated with increased bleeding, even in cases of IBD-related bleeding. Thus, all inpatients should have thromboprophylaxis[4]. In the consensus statements of the Canadian Association of Gastroenterology on prevention of VTE in IBD[8] pharmacological thromboprophylaxis is recommended in all hospitalized patients with IBD, regardless of the reason for admission. Only inpatients with severe (gastro-intestinal) bleeding who are hemodynamically instable, mechanical thromboprophylaxis is recommended, but after hemodynamic stability is obtained pharmacological prophylaxis should be initiated.

Although outpatient IBD flares increase the risk of thrombosis, the absolute risk is low and therefore the use of anticoagulant thromboprophylaxis is not recommended[8]. Furthermore, a decision analysis exploring the economic feasibility of pharmacologic VTE prophylaxis during ambulatory IBD flares also does not recommend it.[41] The baseline case analysis demonstrated that although this intervention could reduce the lifetime incidence of VTE, the cost of administering LMWH during each moderate-severe IBD flare over a lifetime was prohibitive relative to the marginal benefit obtained.[41] Pharmacological thromboprophylaxis in ambulatory patients is only recommended if there is a history of VTE. [8]

A summary flowchart of prevention of VTE in IBD is shown in figure 3.

TREATMENT

The management of VTE in patients with IBD follows the same protocols as for patients without IBD. Short term anticoagulant therapies with LMWH or unfractionated Heparin (UFH) in low dose or Fondaparinux are preferred. While in the long-term vitamin k antagonists (such as warfarin) or Novel Oral Anticoagulants (NOAC's) could be used.[4] Indefinite anticoagulant therapy can be discussed with IBD patients who present with a VTE episode while in clinical remission without another provoking factor. In the same way, if there is a reversible risk factor, the anticoagulation should be given for at least 3 months and the risk factor is resolved for at least 1 month[4]. For IBD patients who are diagnosed with their first episode of VTE in the presence of active disease, anticoagulant therapy is suggested until the IBD is in remission for 3 months or indefinite anticoagulant therapy.[8]

A summary flowchart of treatment of VTE in IBD is shown in figure 4.

Cerebral venous sinus thrombosis

CLINICAL PRESENTATION AND DIAGNOSIS

Diagnosis is frequently delayed because of the wide spectrum of symptoms and the frequently subacute onset. The presentation of CVST is variable and falls broadly into three categories: symptoms and signs of raised intracranial pressure (ICP), a focal brain lesion, or both a focal lesion and raised ICP.[42] Headache is the most frequent symptom of CVST and occurs in almost 90% of all cases. This headache can range from a common migraine to clear features of raised ICP where papilloedema might also be visualised with fundoscopy.[42] In patients with focal deficits, headache, seizures or an altered consciousness, CVST should always be considered.[43]

The European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis (endorsed by the European Academy of Neurology), suggests using magnetic resonance

or computed tomographic angiography for confirming the diagnosis of CVST.[44] CT has the advantage that a CT venography protocol can be easily added and reliably demonstrates occlusive disease in the major cerebral veins and sinuses. Magnetic resonance imaging and magnetic resonance venography are more sensitive tools for identifying CVST and excluding alternative pathologies and more-subtle brain lesions.[42]

TREATMENT

There are no specific guidelines available regarding treatment of CVST among IBD patients, most likely because of relatively small number of reported clinical cases so far.[6]

Nevertheless, both the American Heart Association and American Stroke Association (AHA/ASA) and the European Federation of Neurological Societies guidelines recommend that patients should be anticoagulated even in the presence of haemorrhage.[42] The rationale for anticoagulant therapy in CVST is to avoid thrombus extension and to favour spontaneous thrombus resolution. It is recommended anticoagulation in acute CVST, preferentially using LMWH in the acute phase.

The AHA/ASA guidelines recommend that, following the immediate management, anticoagulation with long-term vitamin K antagonists, such as warfarin, with a target international normalised ratio (INR) of 2–3 should be used for 3–6 months in provoked CVST. NOACs remain a potential treatment option in patients for whom warfarin is not suitable, but would not be recommended as a first-line therapy.[42] In this regard, the European Stroke Organization also does not recommend the use of NOAC's for the treatment of CVST, especially during the acute phase.[44] However, recent studies are beginning to emerge that support the use of NOAC's. [45,46] The efficacy of NOAC's may not be inferior to vitamin K antagonists and the risk of bleeding does not appear to be higher than that of Warfarin.[45,46]

Clinical Case Report

PATIENT IDENTIFICATION AND HISTORY

The case refers to a 27 years-old male, caucasian patient that is autonomous for activities of daily living. The patient has no family history of IBD, nor of colorectal cancer. He was diagnosed with ulcerative colitis in 2014, at age 20. Maintenance therapy was based on oral 5-ASA 3g/day, and he was in clinical remission until 2021. On 31/03/21 he presented with a clinical flare of mild severity, treated with oral 5-ASA 4g/day and topical optimization: 4g 5-ASA enema/day and 1g suppository/day. However, he did not respond and, 2 weeks later, remission induction with oral prednisolone 40mg/day was initiated - this exacerbation occurred 8 days before the presentation of the thrombotic event under analysis.

He has no surgical history. The patient has never smoked and denies IV drug use. He reports alcohol consumption only in social context (about 3-4 U standard drink/week). As for food, he has a Mediterranean diet, with no dietary restrictions. And as for physical activity, he refers gym exercises 2x a week.

PRESENTATION OF THE THROMBOTIC EVENT

The patient was referred to the Santo António Hospital (Centro Hospitalar Universitário do Porto) emergency room (ER) on 22/04/21 for intense, pulsatile, right frontotemporal headache with retrocular pain with 1 day of evolution. The pain was continuous throughout the day, unrelated to position, and did not worsen with valsalva maneuvers. He also reported nausea, frequent vomiting, lipothymia, slight somnolence, and photophobia. He had been taking oral 5-ASA 4g/day and 4g enema at night and 1g suppository in the morning for 20 days. The patient reported having been to the ER 8 days before due to an exacerbation of ulcerative colitis and has been taking Prednisolone 40mg since then.

INAUGURAL EPISODE AND EARLY HISTORY OF ULCERATIVE COLITIS

At the age of 20, in December 2013, he started episodes of abdominal pain and bloody diarrhoea (3 to 5 bowel movements per day). Colonoscopy in January 2014 revealed continuous pancolitis without ulcers and normal ileoscopy. Biopsies revealed decreased mucosecretion, focal atrophy, and abundant inflammation involving the submucosa. Therapy with sulfasalazine 1g/day was started and the clinical condition improved, particularly with resolution of pain and bloody diarrhoea.

The patient discarded the medication after 2 weeks due to complete resolution of complaints, however the same symptoms recurred one week later. After clinical revaluation he restarted sulfasalazine 1.5g/day and iron supplementation. Laboratory tests on february 2014 revealed mild ferropenic anaemia (12.7 g/dL), slightly increased sedimentation rate (20 mm/h), slightly increased CRP of 9 mg/L. About 6 weeks later sulfasalazine was replaced for mesalazine (5-ASA) 2g/day and iron was discontinued.

DIAGNOSIS OF ULCERATIVE COLITIS

In May 2014, he was referred to the gastroenterology outpatient clinic for follow-up with a main clinical hypothesis of ulcerative colitis. Following the medication he had 1 soft stool discharge per day, no episodes of abdominal pain, no blood or mucus in the stools. On physical examination, the abdomen was soft and compressible, without pain on palpation and without masses.

After consultation, mesalazine dose was increased to 3g/day and a fibrosigmoidoscopy with biopsies for histology was requested. Fibrosigmoidoscopy was performed up to the distal sigmoid, not progressing further due to the presence of abundant formed stools. Abolition of the normal vascular pattern in the distal rectum was reported, with an upper limit within 7cm of the anal margin, the findings are visible in figure 5. The examination was suggestive of inflammation (probable Ulcerative Colitis, Mayo endoscopic Score 1). The biopsies revealed glandular mucosa of slightly distorted glandular architecture with abundant polymorphous inflammatory infiltrate and focal permeation of the epithelium. Neither cryptic microabscesses nor epithelioid granulomas were observed. After considering all the results, the diagnosis of Ulcerative Colitis was established, and topical 5-ASA enemas were added 3x/week.

EVOLUTION OF ULCERATIVE COLITIS

The patient achieved clinical and endoscopic remission of disease activity. Maintenance therapy was kept at oral 5-ASA 3g/day, requiring only a few adjustments in topical 5-ASA therapy. The evolution of the disease during consultations is shown in Table V.

EXACERBATIONS OF ULCERATIVE COLITIS

Prior to the episode that motivated hospitalization, the patient was evaluated in 2 emergency episodes for bloody diarrhoea and abdominal pain. In the first acute episode he had a mild acute flare of ulcerative colitis, with apyrexy, mild discomfort in the left lower quadrant, slight thickening of the descending and sigmoid colon at abdominal ultrasound - findings visible in figure 6. Analytically, only an increase in Lactate Dehydrogenase (253 U/L) and CRP (23.11 mg/dL) is highlighted, the remaining analysis is shown in Table VI. He was discharged with optimized oral and topical 5-ASA therapy. Two weeks later, after a slight recovery, the symptoms recurred with abdominal pain and bloody diarrhoea (6-8 bowel movements/day) and, as in the last episode, he remained apyretic and hemodynamically stable. Upper abdominal ultrasound revealed thickening and parietal stratification of the rectum up to the proximal descending colon - findings are visible in figure 7. Analytically, only an increase in CRP (17.42 mg/dL) was highlighted, without anaemia,

leucocytosis, or hypoalbuminemia. The remaining analysis is shown in Table VII. The patient started induction of remission with oral corticosteroids (prednisolone 40mg/day) and was discharged.

APPROACH TO THE THROMBOTIC EVENT AND HOSPITALIZATION

In the current thrombotic episode under study (on 22/04/2021), that is, 8 days after the institution of corticotherapy, in addition to the described clinical condition, the patient had no changes on physical and neurological examination, except for signs of dehydration, such as dehydrated mucous membranes. Analytically, he presented leucocytosis with relative neutrophilia and increased CRP (40.22 mg/dL). The remaining results are shown in Table VIII.

A cranioencephalic CT and CT angiography of the cerebral vein showed a spontaneous hyperdensity of the right lateral sinus, extending inferiorly to the gulf of the jugular vein and the superior segment of the right internal jugular vein, suggesting thrombosis, as can be seen in figure 8, 9 and 10. In the angiographic study performed, there was no filling along the entire right lateral sinus and right jugular vein, as evidenced in figure 11. On the posterior aspect of the superior sagittal sinus, a small focal filling defect was identified on the left side of the sinus, corresponding to a small thrombus. There are also spontaneous linear hyperdensities in small veins adjacent to the cerebellum tent, which also did not fill in the angiographic study, suggesting thrombi in contiguity with the right lateral sinus thrombosis.

With the assumption of a cerebral thrombosis of the right lateral venous sinus and ipsilateral jugular vein, the patient was admitted to the Neurology department with gastroenterology consultation and started therapeutic UFH hypocoagulation. He also adjusted to oral prednisolone 50 mg /day and maintained 5-ASA therapy.

EVOLUTION DURING HOSPITALIZATION

On the first day of hospitalization, the patient reported only mild right temporal headache associated with otalgia, intensity 4/10, with food tolerance. Vital signs, objective and neurological examination were unaltered. Blood count revealed leucocytosis (12.90 x10^3/uL) with relative neutrophilia and ESR 54mm. Control of UFH with coagulation study showed an activated partial thromboplastin time of 33.2 s, a prothrombin time of 13.7s and INR 1.17. As there were no haemorrhagic complications, he switched from UFH to LMWH (Enoxaparin 70mg every 12h) while maintaining the rest of the medication. Table IX shows the patient's analytical evolution during hospitalization. During hospitalization, fibrosigmoidoscopy was performed that showed mild

inflammatory features such as hyperemia and abolition of the vascular pattern, without friability, erosions or ulcerations, compatible with endoscopic Mayo score 1. He was discharged on the 4th day of hospitalization reporting only residual headache that resolved with acetaminophen. He switched to Dabigatran (NOAC), 150mg 12h/12h, and was instructed to follow an 8-week corticosteroid withdrawal plan.

FOLLOW-UP

Besides follow-up in IBD consultation, the patient was referred to neurology and infectious diseases follow-up consultation, given that he was proposed to start immunosuppression for maintenance of remission of IDB with azathioprine. At these revaluations, he reported total resolution of intestinal and abdominal symptoms with oral mesalazine (4g) and enemas, prednisolone 30mg/day and dabigatran 150mg every 12h. The infectious screening was negative, including latent tuberculosis. The patient underwent Streptococcus pneumoniae PCV13 vaccination and empirical eradication of Strongyloides with ivermectin (16mg, 2 days).

After a multidisciplinary consultation for inflammatory bowel disease in June 2021, and completion of a pre-immunosuppression inventory, vaccination, and normal Thiopurine methyltransferase enzyme dosing results, the patient was prepared to start azathioprine therapy. Permission was also given by the Farmacy and Therapeutic Department for treatment with infliximab in case of acute flare or intolerance to azathioprine treatment.

The patient finished the last cycle of corticosterioids in june,2021 and was revaluated on july. A colonoscopy was performed showing discrete colonic scarring, erased vascular pattern in the rectum and a sessile polyp (6mm) in the transverse colon, histologically compatible with a low grade displasia adenoma. The described changes can be seen in figure 12. Thus, clinical and endoscopic remission was admitted at this evaluation. The benefits, risks, and alternatives of immunosuppressive therapy with azathioprine were explained and discussed with the patient, who agreed to start therapy on January 2, 2022, with a starting dose of 25mg/day. On 11/01/2022 in an external IBD consultation, patient presents with good condition after 1 week of treatment (Hemoglobin: 15.7 g/dL; Leukocytes: 7.1 x10^9/L; Platelets: 337 000/mm3) and Azathioprine dose is increased to 75mg/day. On 15/02/2022, the azathioprine dose is again increased to 100mg/day and oral and topical 5-ASA therapy is maintained.

In an outpatient neurology consultation on 04/01/2022 the patient was asymptomatic and had a cerebral CT angiography performed on 29/12/2021 that described heterogeneous uptake of the right sigmoid sinus reflecting partial repermeabilization. The internal jugular vein captures to the periphery, keeping part of the lumen thrombosed. In the transition from the sigmoid segment to the transverse segment, the uptake is peripheral, seeming to maintain segmental luminal occlusion. The transverse sinus fills in a filiform fashion (partially thrombosed). In summary, improvement in right lateral sinus permeability has occurred, but still without full restoration of normal flow. It is planned to maintain Dabigatran for another 6 months.

Clinical Case Discussion

Throughout the case, we were able to see that the patient during an exacerbation of his inflammatory disease, presented to the ER a second time with an indication to escalate therapy to corticosteroids, in this case orally. And here we analyse, that although corticosteroids are well established as first line therapy for inducing remission in moderate to severe cases[31], may have several adverse effects and increase the risk of thrombotic events, since they increase the level of plasma fibrinogen, and decrease tPA activity and prostacyclin synthesis[3]. So, in this case, we should think about the role of corticoids in the unfolding of this event. As we have seen in the literature review, active inflammation due to UC exacerbation is already in itself a thrombotic risk factor[8]. Possibly there was a synergistic effect of active inflammation with corticosteroids that increased the thrombotic risk and it may have been in this context that the patient developed this neurological manifestation.

Regarding the prevention of thrombotic events, on his second visit to the ER, according to the state of the art, this patient had no indication for thromboprophylaxis. The patient had no severity criteria for hospitalization and so the indication remained to treat the patient as an outpatient, and since he had no history of venous thromboembolism, no indication for thromboprophylaxis was warranted[8]. As seen above, the absolute risk of VTE in the outpatient setting is low, and the practice of thromboprophylaxis in the outpatient setting has proven to date not to be cost-effective[41].

Since the patient had active IBD at his first episode of thromboembolism, anticoagulant therapy is indicated until the IBD goes into remission for at least 3 months.[8] In this case, the patient has already gone into remission (as seen above), and it is estimated that the patient will take a total of 14 months of anticoagulant therapy since the thrombotic event has not yet fully recovered. It was decided to perform anticoagulation with a NOAC, as there are recent studies to support this, given that NOACs appear to have a good efficacy and safety profile.[45] The choice considered the clear

advantages of NOACs in young, professionally active patients, as they do not require continuous monitoring, nor do they have food interactions.

When checked against the literature review, we can see that the patient was treated as expected and his approach considered the most recent recommendations. Although this was a mild exacerbation, this severe extra-intestinal event, which is related to active inflammation and poor disease control, elevates the severity of the disease and should be taken into account in the subsequent management of the patient. This occurrence was one of the factors that led to the introduction of immunosuppressive therapy and a stricter clinical, analytical and imaging follow-up to ensure that the patient maintained remission of the inflammatory disease. Thus, and considering the good results in the follow-up appointments, it is expected that the patient will have a good prognosis.

Conclusions

In summary, a clinical case of cerebral thrombosis in a patient with active UC was presented. More research is needed to identify risks factors in this population (patient risk factors or related to the disease and to the inflammatory exacerbation) that increase the risk of thrombotic events. Moreover, there are no guidelines that clarify an approach in these circumstances, most likely due to the rarity of this thrombotic complication. Thus, more research is needed to assess the best management and treatment of CVST in ulcerative colitis, particularly robust research to understand whether some of the ambulatory patients with active disease might benefit from thromboprophylaxis. Controlling the disease and achieving clinical, endoscopic and imaging remission is the best strategy to prevent these events (as they are related to uncontrolled inflammation) and thus, properly treating UC remains of enormous importance, as well as updating approaches so that these patients can always have the best possible treatment and avoid all associated complications.

Attachments

Tables

Table I. Distribution of UC (adapted from Silverberg MS, Satsangi J, Ahmad T, *et al*.[26])

Term	Distribution	Description
E1	Proctitis	Involvement limited to the rectum
E2	Left-Sided	Involvement distal to the splenic flexure
E3	Extensive	Involvement extends proximal to the splenic flexure (including pancolitis).

Table II. Severity of UC (adapted from TrueLove and Witts[29])

Severity	Mild	Moderate	Severe
Bloody stools/day	<4	4-6	>6
Pulse	<90 bpm	≤90 bpm	>90 bpm
Temperature	<37.5ºC	≤37.8ºC	>37.8ºC
Haemoglobin	>11.5 g/dL	≥10.5 g/dL	<10.5 g/dL
ESR	<20 mm/h	≤30 mm/h	>30 mm/h
CRP	Normal	≤30 mg/L	>30 mg/L

Table III. The Mayo Score[30]

Mayo Score	0	1	2	3
Stool frequency	Normal	1-2/day > normal	3-4/day > normal	5/day > normal
Rectal bleeding	None	Streaks	Obvious	Mostly blood
Mucosa	Normal	Mild friability	Moderate friability	Spontaneous bleeding
Physician´s global assessment	Normal	Mild	Moderate	Severe

Table IV. Risk factors for VTE, from Olivera PA, Zuily S, Kotze PG, *et al*.[40]

Major Risk Factors	Minor Risk Factors
Active Malignancy	Recente (<3 months) surgery with general anaesthesia for < 30min
Recente (<3 months) surgery with general anaesthesia for > 30min	Venous catheter
Trauma of lower limbs	>65 years
High-risk thrombophilia	Pregnancy and post-partum period (2 months after delivery)
Immobilization	Oral contraceptives (with oestrogens)
	Hormone-replacement terapy
	Lower-Risk Thrombophilia
	History of VTE
	Hyperhomocysteinaemia
	Obesity
	Long-haul flights

Table V. Record of Ulcerative Colitis progression in the consultation

Consultations	Weight (IMC)	CPR	Fecal Calprotectin	Treatment	Remarks
10/12/2015	67 Kg (19,3 Kg/m2)	-	-	3g 5-ASA orally/day and 1g 5-ASA topical (enema)/day	Mayo Score: 1
23/03/2016	69 Kg (19,9 Kg/m2)	1,08 mg/L	-	No new adjustment	Remission of disease activity (Truelove and Witts). And Clinical remission (Montreal)
20/09/2016	68 Kg (19,65 Kg/m2)	2,01 mg/L	739 mg/Kg	Maintain 3g 5-ASA orally/day and 1g 5-ASA topical/day: 5x/week as enema and 2x/week as suppository	Remission is maintained
23/03/2017	70 Kg (20,02 Kg/m2)	1,63 mg/L	1769 mg/Kg	Maintain 3g oral 5-ASA/day and increase frequency of 1g 5-ASA Topical: 1 Enema/day and Suppository 2x/week	Remission is maintained
25/09/2018	70 Kg (20,02 Kg/m2)	1,78 mg/L	69 mg/Kg	Maintain 3g 5-ASA orally/day and reduce frequency 1g 5-ASA Topical: 3x/week Enema and 2x/week Suppository	Remission is maintained
08/10/2020	70 Kg (20,02 Kg/m2)	-	-	Maintains 3g oral 5-ASA/day and has abandoned therapy with topical 5-ASA	Remission is maintained

Table VI. Results of the analysis of the first exacerbation of Ulcerative Colitis from 31/03/2021

HEMOGRAM	
Leukocytes	13,54x10^3/uL
Neutrophils	6,43x10^3/uL / 47,5%
Lymphocytes	2,83x10^3/uL / 20,9%
Monocytes	1,30x10^3/uL / 9,6%
Eosinophils	2,79x10^3/uL / 20,6%
Basophils	0,14x10^3/uL / 1%
Immature Granulocytes	0,4%
Red blood cells	4,56 x10^6/uL
Hemoglobin	14,3 g/dL
Hematocrit	40,7%
MCV - Mean Globular Volume	89,3 fL
MCHG - Mean Globular Hemoglobin	31,4 pg
CHGM - Hemogl. Glob. Média	35,1 g/dL
RDW - Red Cell Distrib. Eritrocites	12,6%
Platelets	388x10^3/uL
VPM - Mean Platelet Volume	10,7 fL
PDW - Platelet Distri. Plaquetetas	13,2%
PCT - Thrombocyte count	0,42%
Erythroblasts per 100 leukocytes	0,0
GENERAL BIOCHEMISTRY	
Pancreatic alpha Amylase	33 U/L (37ºC)
Lipase	35 U/L (37ºC)
Glucose	84 mg/dL
Creatinine	1,12 mg/dL
Urea	23 mg/dL
Total Bilirubin	0,26 mg/dL
Aminot. Aspartate (ASAT/TGO)	16 U/L (37ºC)
Alkaline phosphatase	91 U/L (37ºC)
Gamma-Glutamyl Transferase	10 U/L (37ºC)
Lactate dehydrogenase (LDH)	**253 U/L (37ºC)**
C-reactive protein	**23,11 mg/dL**
Sodium	141 mmol/L
Potassium	4,00 mmol/L
Chlorides	104 mmol/L

Table VII. Results of the analysis of the second exacerbation of Ulcerative Colitis from 14/04/2021

HEMOGRAM	
Leukocytes	11,54x10^3/uL
Neutrophils	5,24x10^3/uL / 45,4%
Lymphocytes	2,43x10^3/uL / 21,1%
Monocytes	1,02x10^3/uL / 8,8%
Eosinophils	2,69x10^3/uL / 23,3%
Basophils	0,12x10^3/uL / 1%
Immature Granulocytes	0,4%
Red blood cells	4,30x10^6/uL
Hemoglobin	13,7 g/dL
Hematocrit	39,0%
MCV – Mean Globular Volume	90,7 fL
MCHG – Mean Globular Hemoglobin	31,9 pg
CHGM – Hemogl. Glob. Média	35,1 g/dL
RDW – Red Cell Distrib. Eritrocites	13,2%
Platelets	366x10^3/uL
VPM – Mean Platelet Volume	10,3 fL
PDW – Platelet Distri. Plaquetetas	11,7%
PCT – Thrombocyte count	0,38%
Erythroblasts per 100 leukocytes	0,0
GENERAL BIOCHEMISTRY	
Glucose	81 mg/dL
Creatinine	0,89 mg/dL
Urea	22 mg/dL
Lactate Dehydrogenase (LDH)	225 U/L (37ºC)
Total Creatine Kinase (CK)	125,6 U/L (37ºC)
C-reactive protein	**17,42 mg/dL**
Sodium	140 mmol/L
Potassium	4,57 mmol/L
Chlorides	107 mmol/L

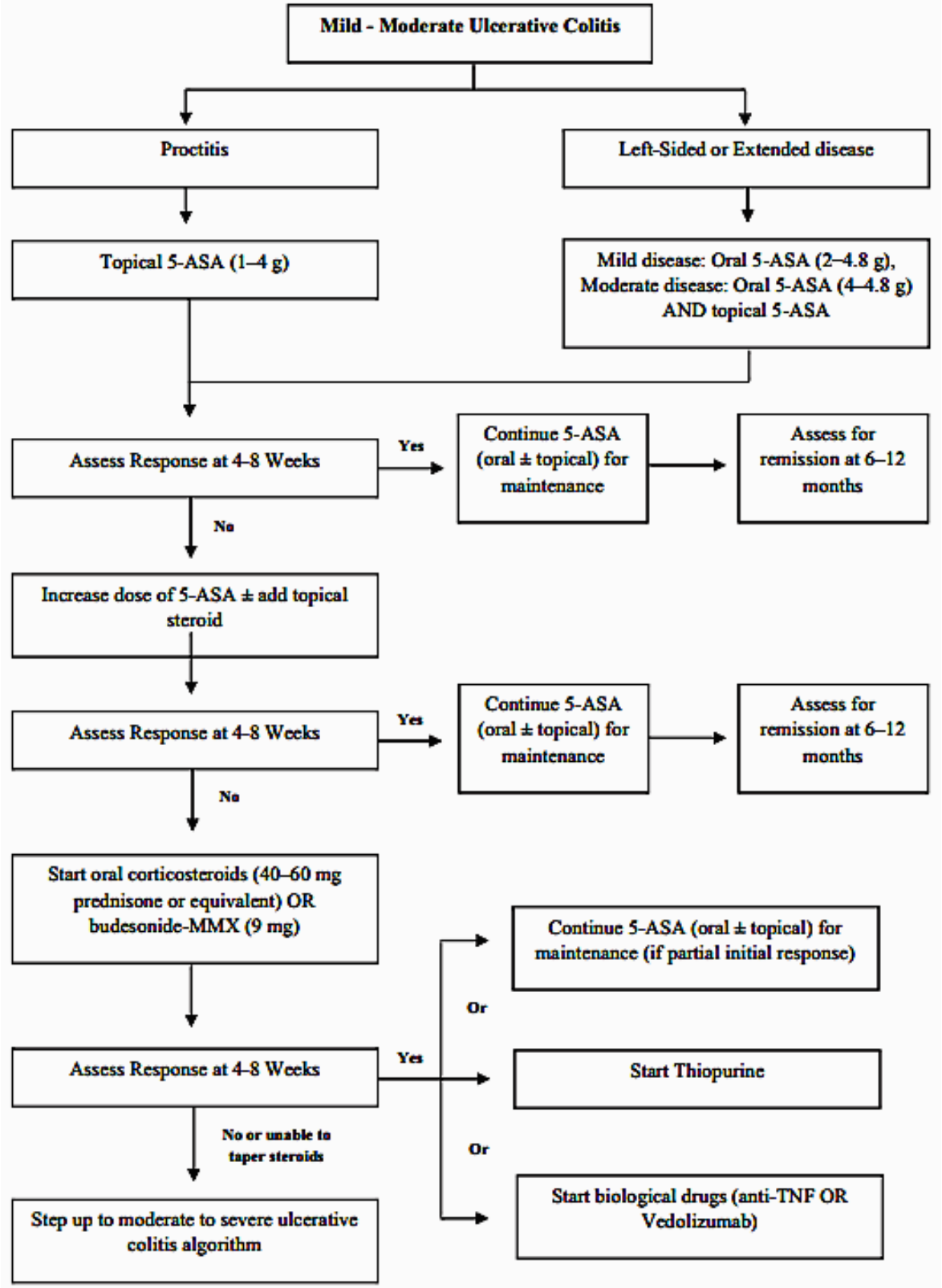
Table VIII. Results of the analysis of the thrombotic event presentation from 22/04/2021

HEMOGRAM	
Leukocytes	**12,56x10^3/uL**
Neutrophils	**9,17x10^3/uL / 73%**
Lymphocytes	2,24x10^3/uL / 17,8%
Monocytes	0,95 x10^3/uL / 7,6%
Eosinophils	0,09 x10^3/uL / 0,7%
Basophils	0,05 x10^3/uL / 0,4%
Immature Granulocytes	0,5%
Red blood cells	4,10 x10^6/uL
Hemoglobin	13,1 g/dL
Hematocrit	37,5%
MCV - Mean Globular Volume	91,5 fL
MCHG - Mean Globular Hemoglobin	32,0 pg
CHGM - Hemogl. Glob. Média	34,9 g/dL
RDW - Red Cell Distrib. Eritrocites	13,2%
Platelets	315 x10^3/uL
VPM - Mean Platelet Volume	10,3 fL
PDW - Platelet Distri. Plaquetetas	12,3%
PCT - Thrombocyte count	0,33%
Erythroblasts per 100 leukocytes	0,0
GENERAL BIOCHEMISTRY	
Glucose	102 mg/dL
Creatinine	0,88 mg/dL
Urea	23 mg/dL
C-reactive protein	**40,22 mg/dL**
Sodium	143 mmol/L
Potassium	3,65 mmol/L
Chloride	103 mmol/L

Table IX. Analytical evolution during hospitalization in the neurology service (D1, D2 and D4)

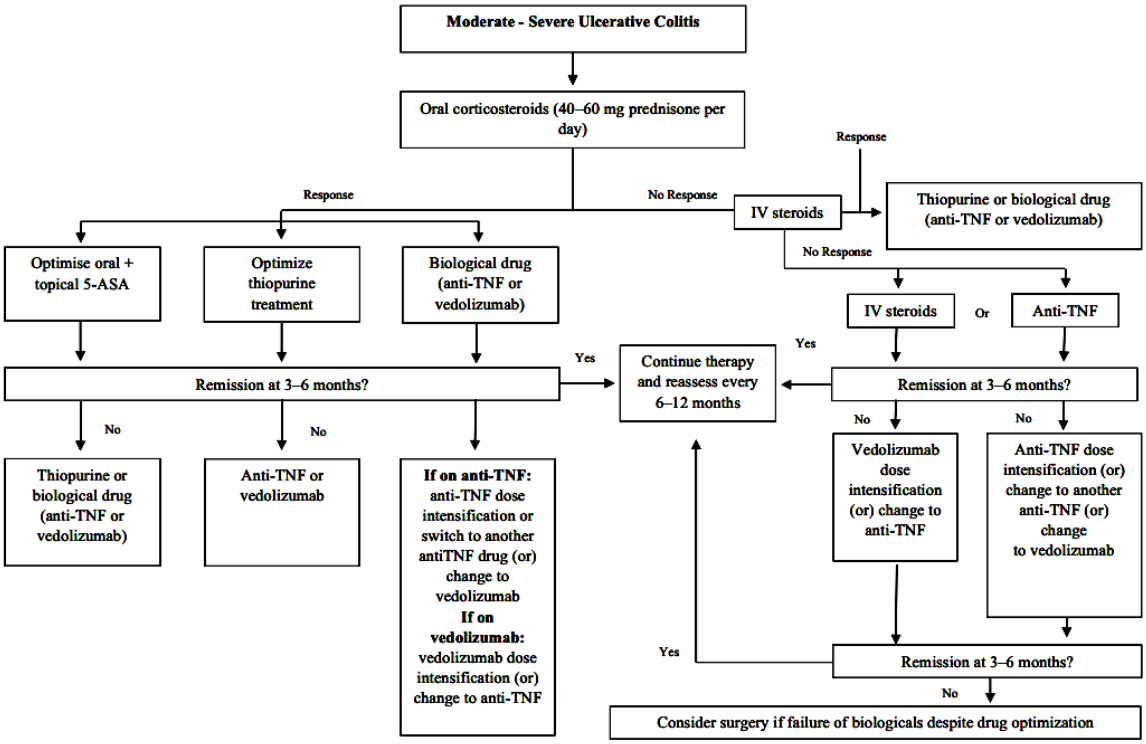
HEMOGRAM	D1	D2	D4
Leukocytes	**12,90x10^3/uL**	6,36x10^3/uL	10,06 x10^3/uL
Neutrophils	**11,57x10^3 /uL / 89,7%**	2,53x10^3/uL /39,8%	7,15 x10^3/uL /71,1%
Lymphocytes	0,97x10^3/uL /7,5%	2,55x10^3/uL /40,1%	2,12 x10^3/uL /21,1%
Monocytes	0,27x10^3/uL / 2,1%	0,41x10^3/uL /6,4%	0,61 x10^3/uL /6,1%
Eosinophils	0,0x10^3/uL / 0,0%	0,82x10^3/uL /12,9%	0,09 x10^3/uL /0,9%
Basophils	0,03x10^3/uL / 0,2%	0,04x10^3/uL /0,6%	0,04 x10^3/uL /0,4%
Immature Granulocytes	0,5%	0,2%	0,4%
Red blood cells	4,33x10^6/uL	4,87x10^6/uL	4,17x10^6/uL
Hemoglobin	13,4 g/dL	14,2 g/dL	13,1 g/dL
Hematocrit	38,5%	42,3%	37,5%
MCV - Mean Globular Volume	88,9 fL	86,9 fL	89,9 fL
MCHG - Mean Globular Hemoglobin	30,9 pg	29,2 pg	31,4 pg
CHGM - Hemogl. Glob. Média	34,8 g/dL	33,6 g/dL	34,9 g/dL
RDW - Red Cell Distrib. Eritrocites	12,8%	13,0%	12,9%
Platelets	312x10^3/uL	251x10^3/uL	332 x10^3/uL
VPM - Mean Platelet Volume	10,7 fL	12,3 fL	11,1 fL
PDW - Platelet Distri. Plaquetetas	13,1%	16,5%	13,8%
PCT - Thrombocyte count	0,33%	0,31%	0,37%
Erythroblasts per 100 leukocytes	0,0	-	0,0
Sedimentation Velocity (1stH)	**54mm**	4mm	-
CLINICAL HEMATOLOGY			
Activated partial thromboplastin time	**33,2 s**	-	-
Prothrombin time	**13,7s**	-	-
INR	**1,17**	-	-
GENERAL BIOCHEMISTRY			
Glucose	-	80 mg/dL	105 mg/dL
Creatinine	-	0,98 mg/dL	0,91 mg/dL
Urea	-	30 mg/dL	35 mg/dL
Aminot. Aspartate (ASAT/TGO)		17 U/L (37ºC)	13 U/L (37ºC)
Aminot Alanine (ALAT/TGP)		13 U/L (37ºC)	12 U/L (37ºC)
Alkaline Phosphatase		72 U/L (37ºC)	75 U/L (37ºC)
Gamma Glutamyl Transferase		6 U/L (37ºC)	12 U/L (37ºC)
C-reactive protein	-	1,23 mg/L	**29,47 mg/L**
Sodium	-	142 mmol/L	140 mmol/L
Potassium	-	4,44 mmol/L	3,46 mmol/L
Chlorides	-	99 mmol/L	104 mmol/L

Figures



Treatment approach for mild to moderate ulcerative colitis based on Toronto Consensus and European Crohn's and Colitis Organization guidelines (figure adapted from Ungaro et al.,[139] with permission from Elsevier).

Figure 1. Treatment approach for mild-moderate UC taken from Gajendran M, Loganathan P, Jimenez G, *et al*.[17]



Treatment approach for moderate to severe ulcerative colitis based on Toronto Consensus and European Crohn's and Colitis Organization guidelines (figure adapted from Ungaro et al.,[139] with permission from Elsevier).

Figure 2. Treatment approach for moderate-severe UC taken from Gajendran M, Loganathan P, Jimenez G, *et al*.[17]

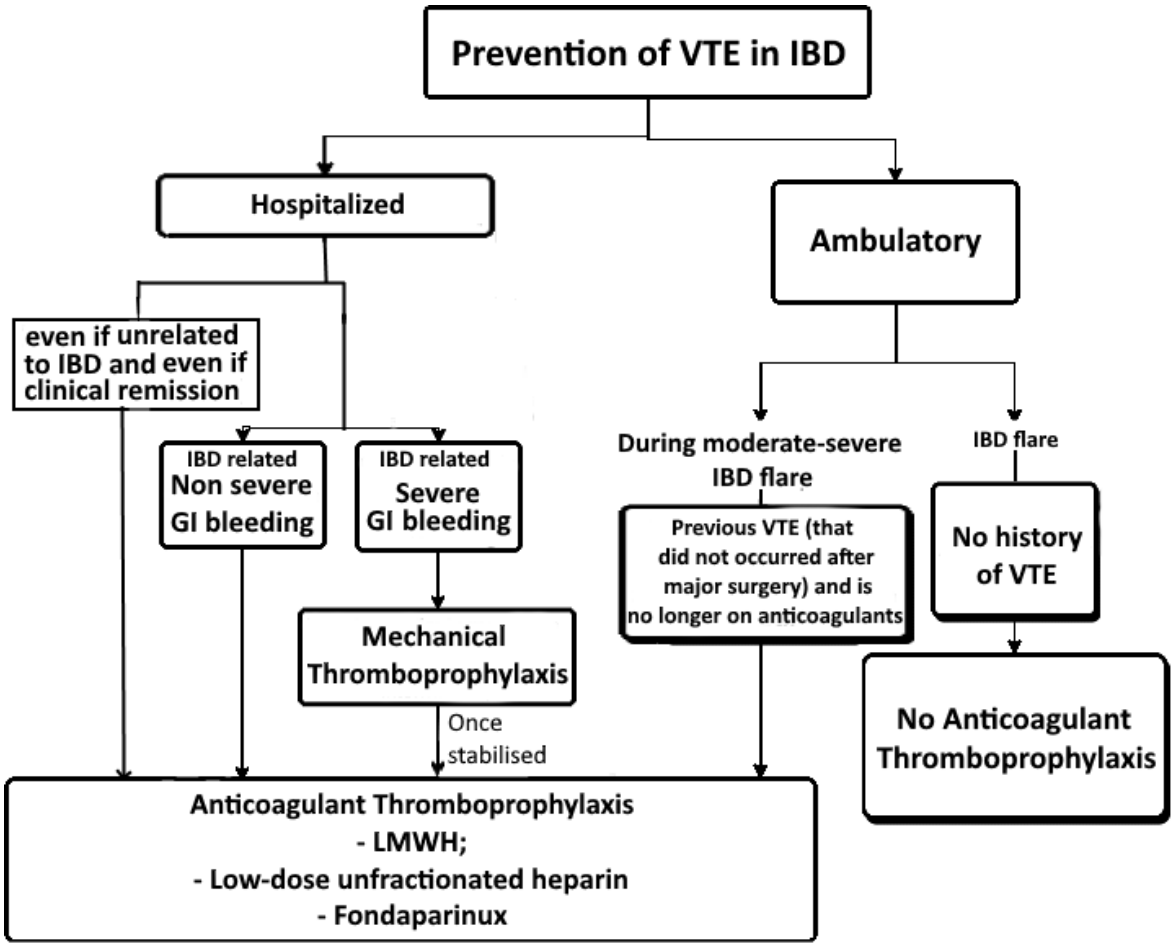


Figure 3. Adapted flowchart of Nguyen GC, Bernstein CN, Bitton A, *et al*. published consensus statements of the Canadian Association of Gastroenterology on prevention of VTE in IBD[8]

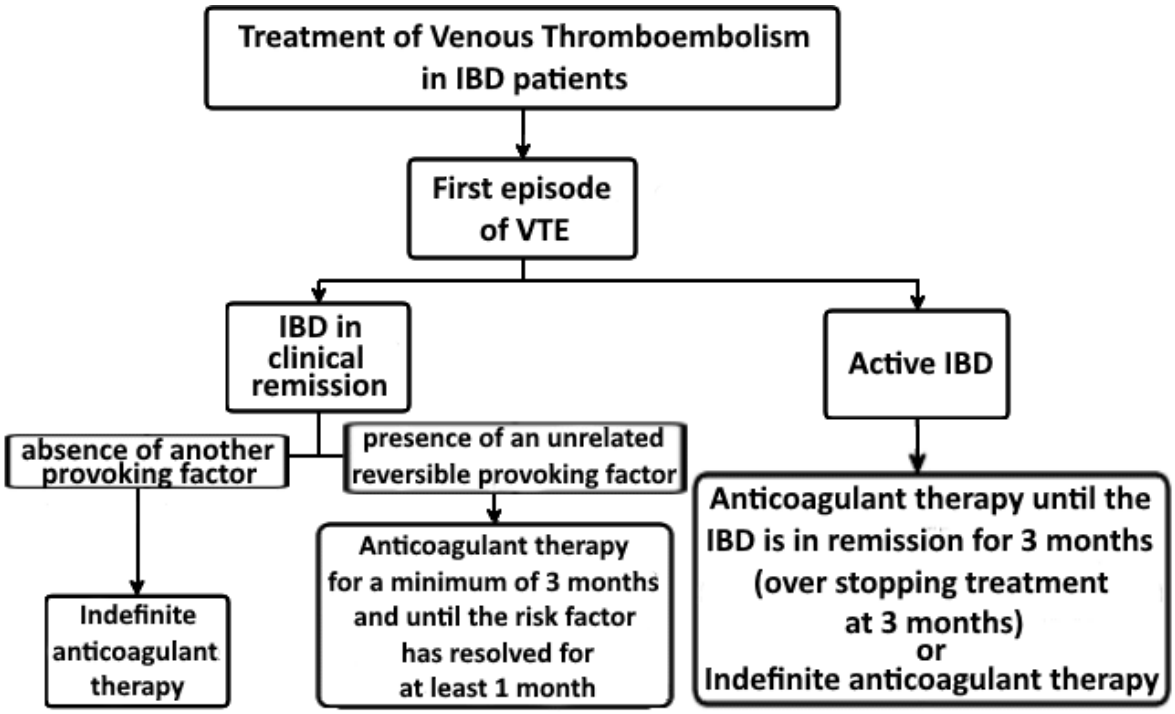


Figure 4. Adapted flowchart of Nguyen GC, Bernstein CN, Bitton A, *et al*. published consensus statements of the Canadian Association of Gastroenterology on treatment of VTE in IBD[8]

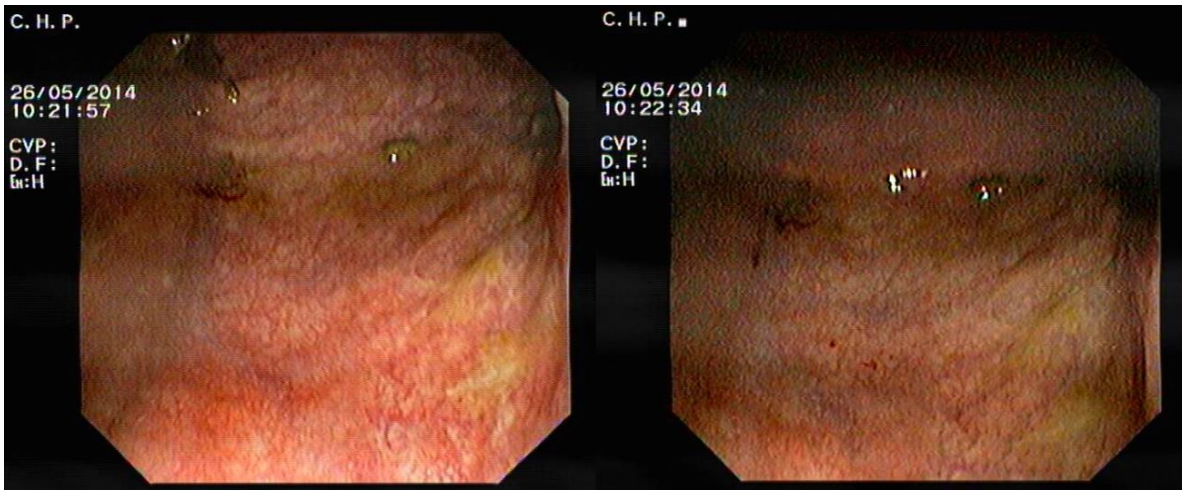


Figure 5. Fibrosigmoidoscopy from 21/05/2014 shows abolition of normal vascular pattern in the distal rectum. Suggestive of Ulcerative Colitis (Mayo 1).

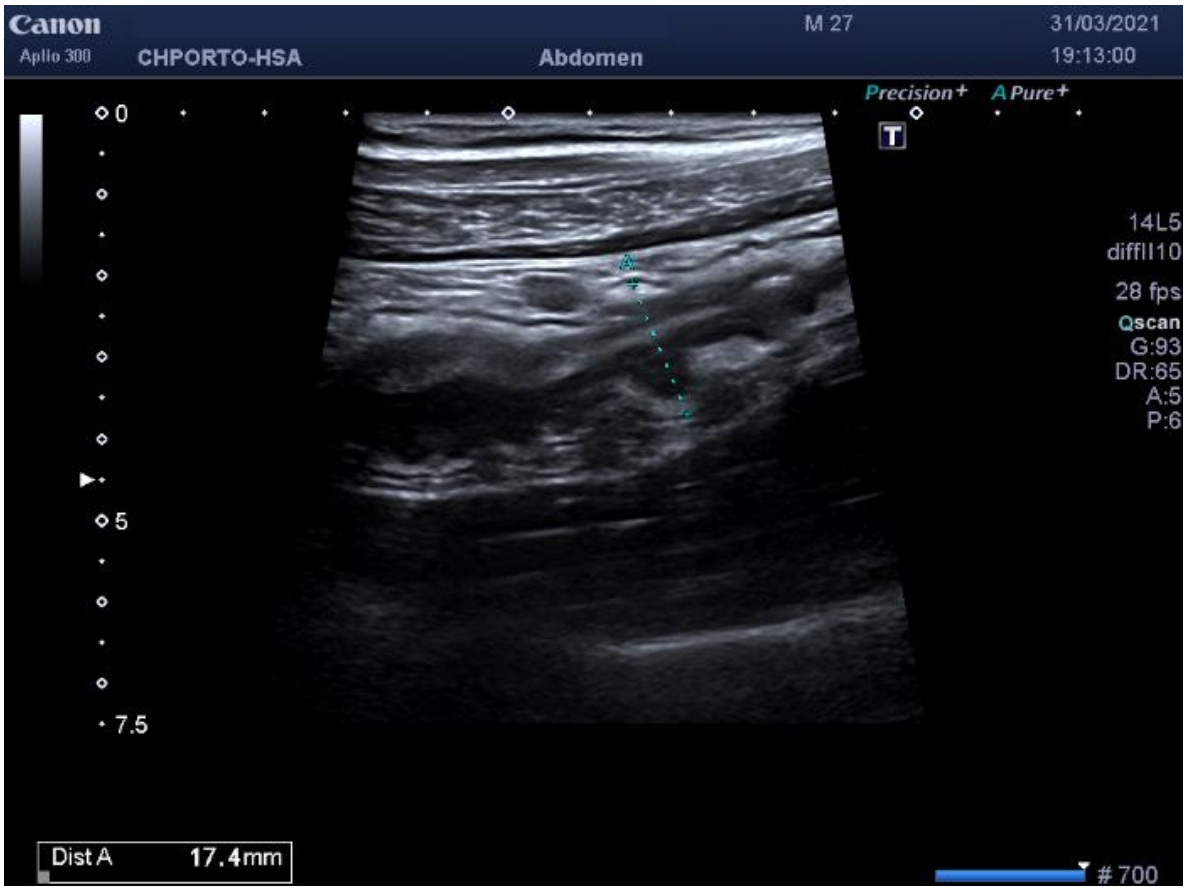


Figure 6. Abdominal ultrasound in the first exacerbation of Ulcerative Colitis from 31/03/2021

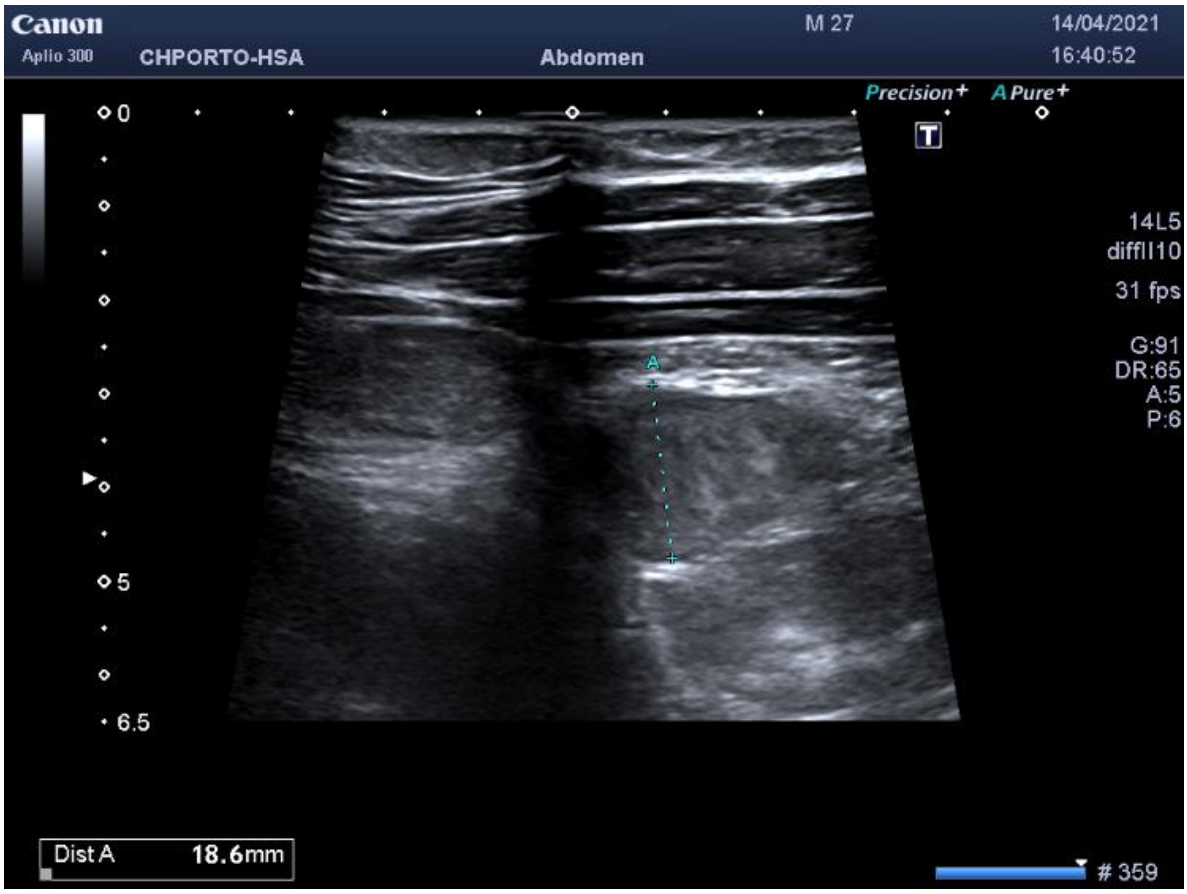


Figure 7. Abdominal ultrasound in the second exacerbation of Ulcerative Colitis from 14/04/2021

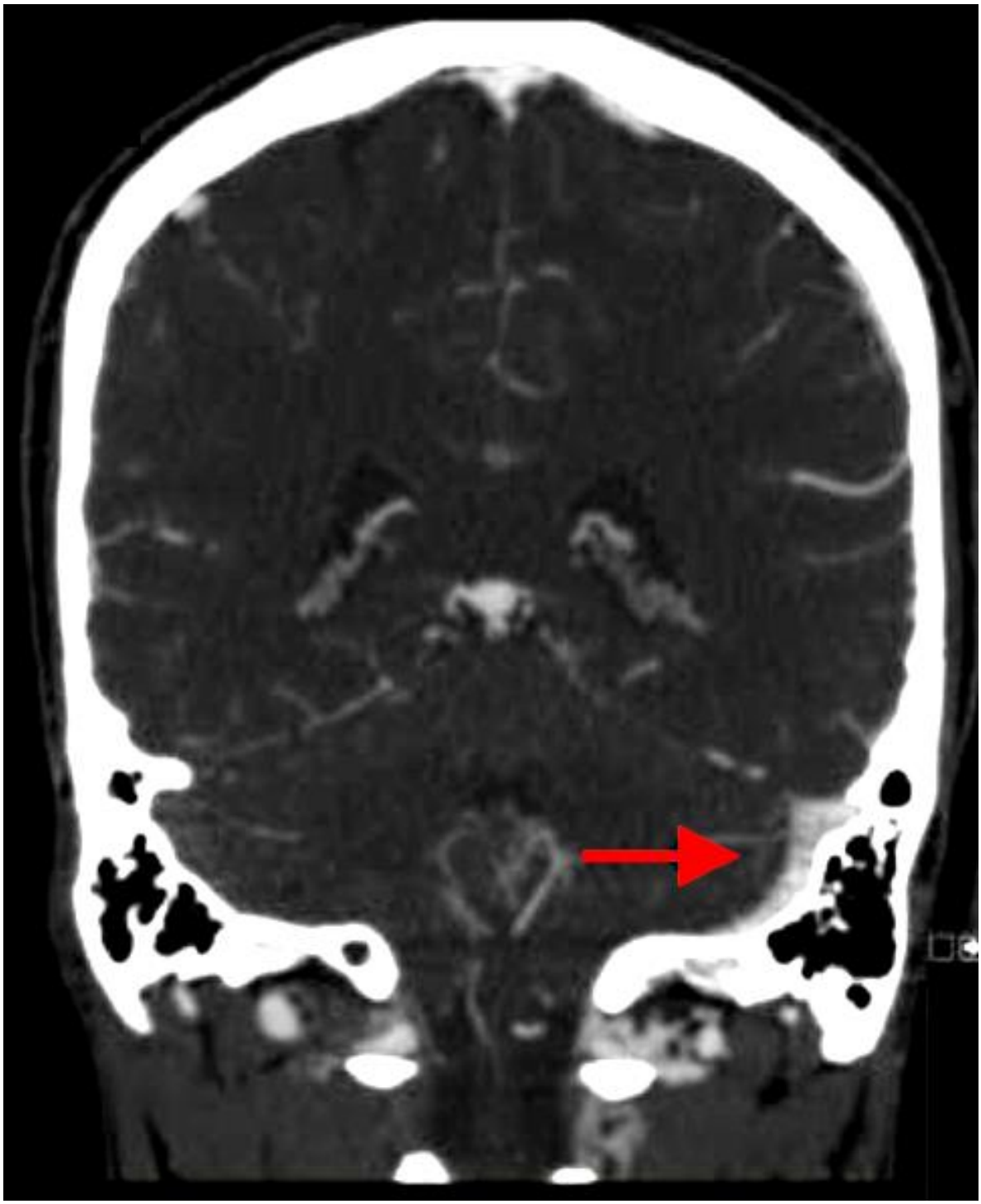


Figure 8. Coronal non-contrast CT image shows spontaneous hyperdensity in the right lateral sinus (arrow), extending interiorly to the jugular gulf and to the superior segment of the right internal jugular vein

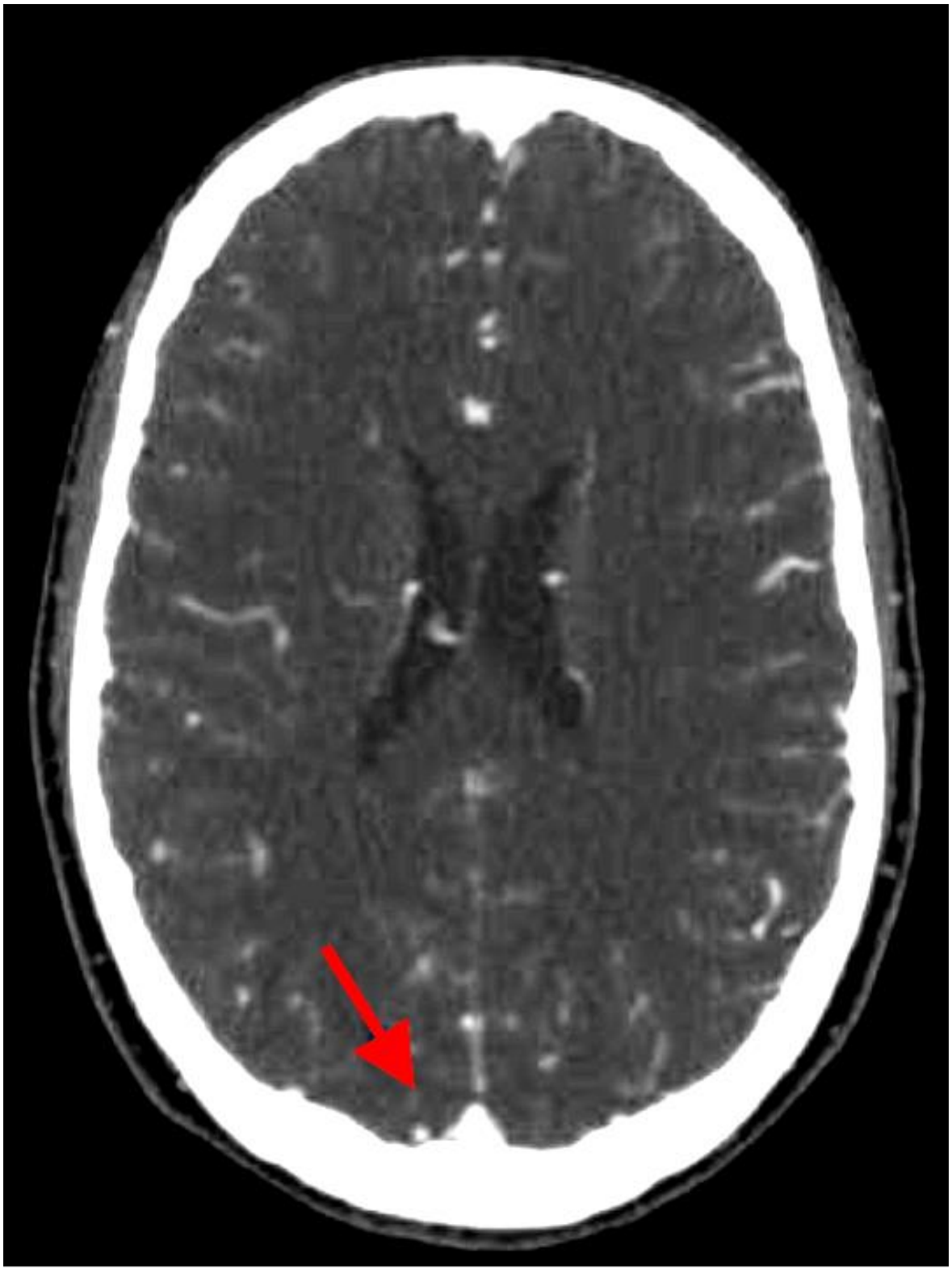


Figure 9. Axial non-contrast CT image shows a hyperdensity with a triangular shape in the posterior part of the superior sagittal sinus caused by the venous thrombus (the dense triangle sign - arrow)

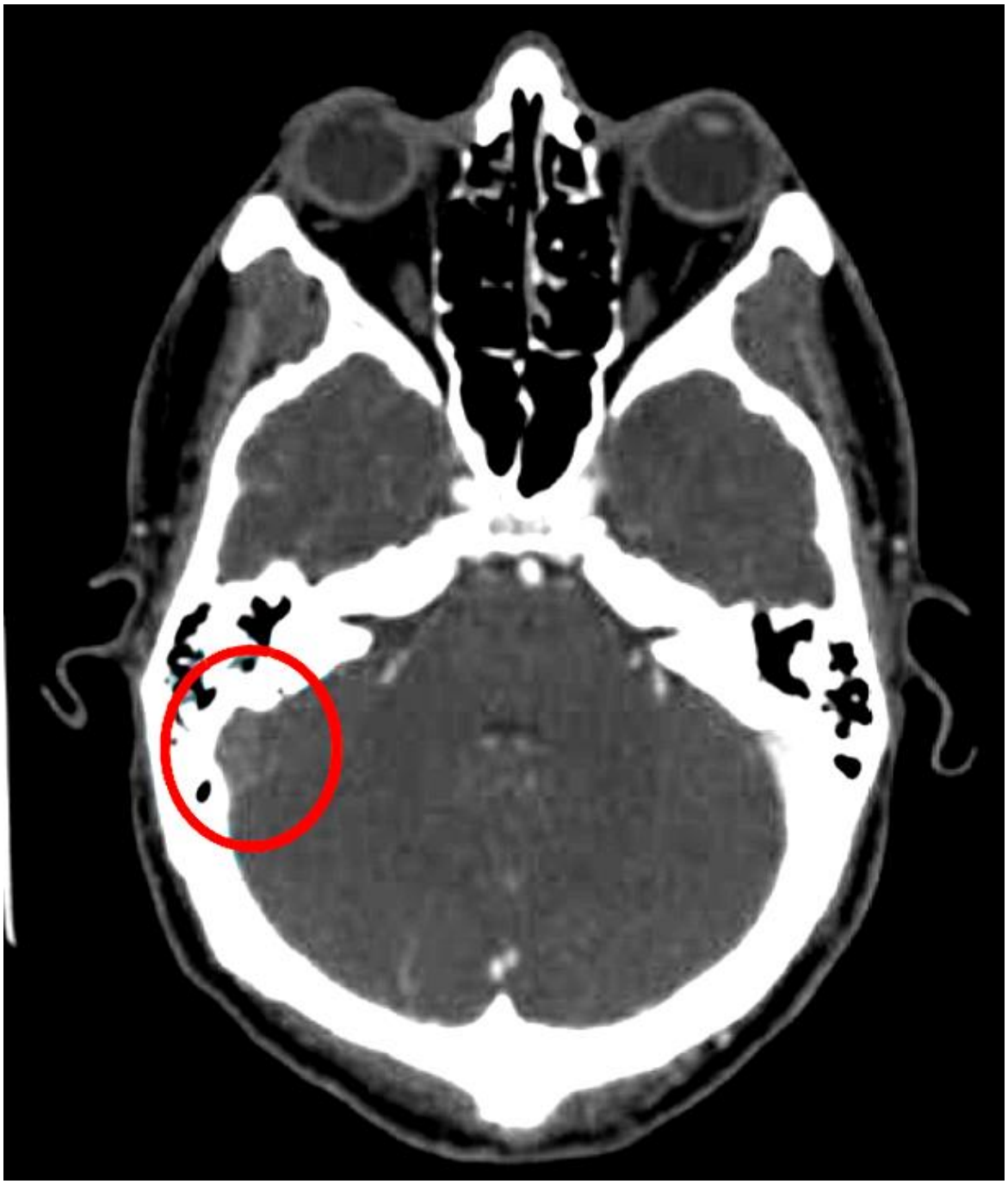


Figure 10. Axial contrast-enhanced CT image shows a filling defect in the right lateral sinus (circle)

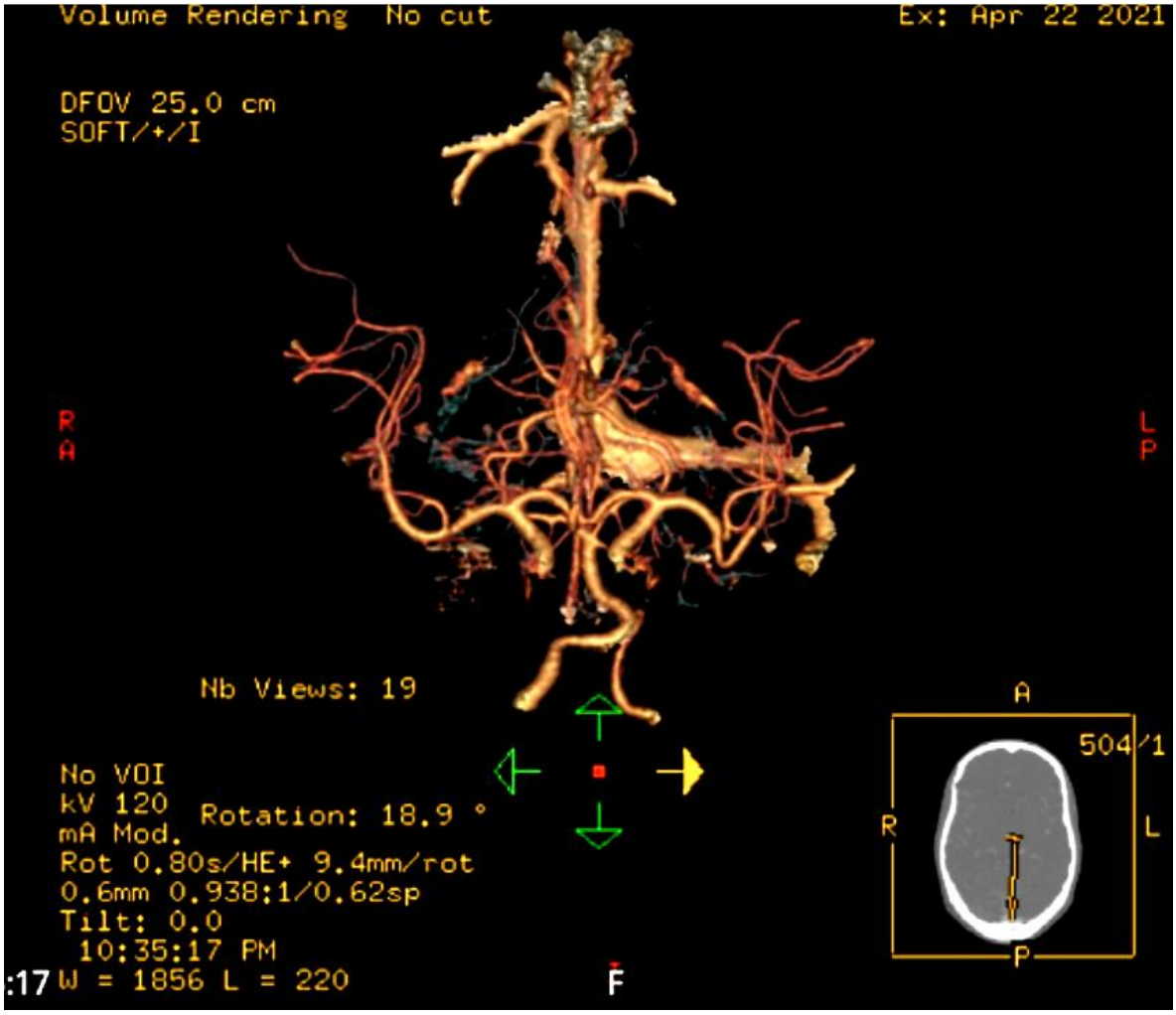


Figure 11. Angiographic study shows no filling along the entire right lateral sinus and right jugular vein

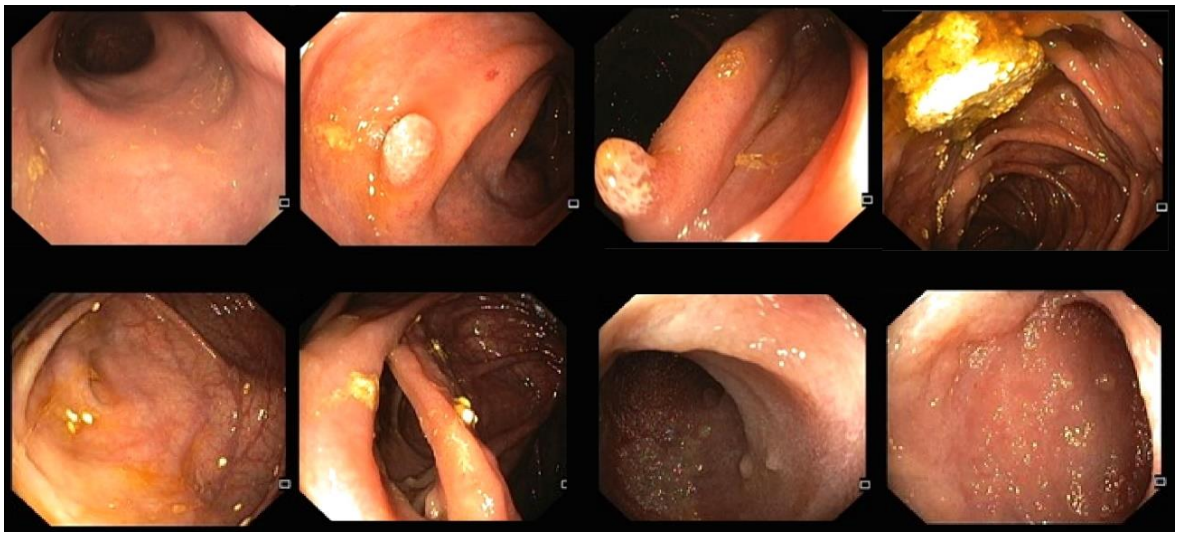


Figure 12. Follow-up Colonoscopy from 08/07/2021

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