

Thrombotic Storm in a Teenager With Previously Undiagnosed Ulcerative Colitis

AUTHORS: Umberto Maggi, MD, PhD,^{a,b} Giorgio Rossi, MD, PhD,^c Ettore Contessini Avesani, MD,^d Andrea Artoni, MD,^e Flavio Caprioli, MD,^f Luisa Napolitano, MD,^g and Ida Martinelli, MD, PhD^e

^aGeneral Surgery and Liver Transplantation Unit, ^aA Bianchi Bonomi Hemophilia and Thrombosis Center, Department of Internal Medicine and Medical Specialties, and ^gPediatric Emergency Unit, Fondazione IRCCS Ca'Granda, Ospedale Maggiore Policlinico, Milan, Italy; ^bDepartment of Digestive and Hepatobiliary Surgery, AP-HP, UFR de Médecine de l'Université Paris XII-Créteil, Créteil, France; ^cGeneral Surgery and Liver Transplantation Unit, Department of Surgical Sciences, ^dGeneral and Emergency Surgery Unit, and ^fGastroenterology Unit 2, Department of Medical, Surgical and Transplant Physiopathology, University of Milan, and Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy

KEY WORDS

thrombotic storm, venous thrombosis, inflammatory bowel disease, Budd-Chiari syndrome, Budd-Chiari syndrome/ complications, cerebral vein thrombosis, anticoagulant therapy, adolescent, ischemic/complications, ulcerative/complications, colitis, ulcerative/surgery, female, humans, proctocolectomy, treatment outcome

ABBREVIATION

CT—computed tomography

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Address correspondence to Umberto Maggi, MD, PhD, UO Chirurgia Generale e Trapianti di Fegato Fondazione IRCCS Ca'Granda, Ospedale Maggiore Policlinico, Via F. Sforza 35, 20122 Milan, Italy. E-mail: maggi.umberto@gmail.com

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abstract

Venous thrombosis can complicate inflammatory bowel diseases, both in adult and pediatric patients, and a few adult cases of thrombotic storm, ie, thrombosis at multiple sites occurring over a period of a few days to a few weeks, have been described. However, venous thrombosis as the first manifestation of an inflammatory bowel disease is extremely rare. We report the case of a 14-year-old girl presenting with ascites and marked hypertransaminasemia resulting from hepatic vein occlusion (Budd-Chiari syndrome). Despite anticoagulant therapy, in the following days she developed criteria suggestive of thrombotic storm to include cerebral vein, right atrial thrombosis, and bilateral pulmonary embolism. Thrombolytic treatment with recombinant-tissue plasminogen activator was started, with resolution of all venous thromboses and without bleeding complications. Additional examinations revealed a severely active ulcerative pancolitis, which did not respond to medical treatment and required surgery. No thrombophilia abnormality nor other risk factors for thrombosis were detected. We conclude that an underlying inflammatory state, such as ulcerative colitis, should be suspected in pediatric patients with venous thrombosis storm. *Pediatrics* 2013;131:e1–e4

The reported annual incidence of ulcerative colitis ranges from 3.4 to 10.5 per 100 000 individuals in Italy.¹ Twenty percent of patients with ulcerative colitis are younger than 20 years of age, and the incidence of the disease is increasing in the young. Hypercoagulability and thrombosis have been reported as extraintestinal complications of inflammatory bowel diseases, both in adult and pediatric patients.^{2–4} In particular, data on the relationship between hepatic vein thrombosis (Budd-Chiari syndrome) and ulcerative colitis in children are scarce, because only 5 cases have been reported so far.⁵ However, a thrombotic storm as the first manifestation of a previously unknown inflammatory bowel disease has never been reported to date.

PATIENT PRESENTATION

On May 6, 2011, a 14-year old, previously healthy girl was admitted in another hospital in our city because of the recent onset of diarrhea (7–8 bowel movements per day), vomiting, and lack of appetite resulting in a weight loss of 1.5 kg in the past 10 days. Biochemical results showed marked leukocytosis (white blood cells: 18 970 mm³), high C-reactive protein (41 mg/dL), and hypertransaminasemia (aspartate aminotransferase: 503 IU/L; alanine aminotransferase: 669 IU/L). Parenteral ampicillin was started, but 4 days later, because of the persistence of symptoms, the patient underwent an abdominal computed tomography (CT) scan that showed massive thrombosis of the inferior vena cava (up to the entrance in right atrium) and of the hepatic veins (Fig 1), with a patent portal vein, hepatosplenomegaly, mild ascites, and a collateral pleural effusion. She had never taken oral contraceptives and did not smoke. Anticoagulant treatment with intravenous unfractionated heparin was started with a target-activated partial

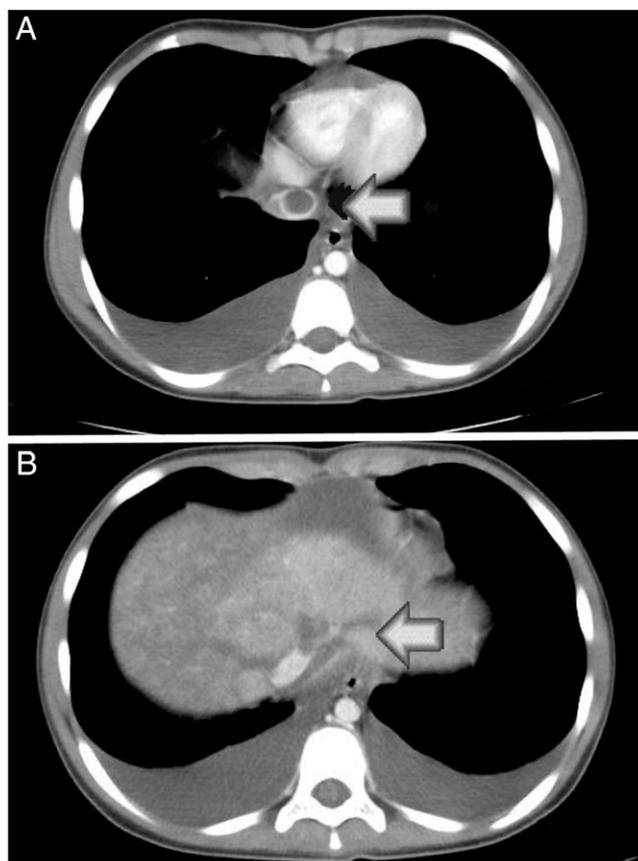


FIGURE 1

Abdominal CT scan showing massive thrombosis of the inferior vena cava up to the entrance in right atrium (arrow in A) and of the hepatic veins (arrow in B).

thromboplastin time ratio of 2.5, and the same day the patient was transferred to our liver transplantation unit. At admission, aspartate aminotransferase was 1125 UI/L and alanine aminotransferase was 994 UI/L. The patient's body weight was 42 kg (BMI: 16.4). She revealed that in the past few days diarrhea had sometimes streaks of blood. A blood count showed a hemoglobin concentration of 10.2 g/dL, a mean corpuscular volume of 78, a white blood cell count of 18 150 mm³, and a platelet count of 78 000 mm³. On May 11, 2011 she had an acute onset of paresthesia and partial motor deficit of the left lower limb. Cerebral angio-MRI showed venous thrombosis of the sagittal sinus. Ratios of the activated partial thromboplastin time and prothrombin time were 1.7 and 2.0, respectively, perhaps due to reduced

hepatic synthesis of vitamin K–dependent proteins. For the same reason, plasma levels of the natural anticoagulant proteins C and S were at the lower limit of normal ranges, whereas the remaining thrombophilia screening, including factor V Leiden, prothrombin G20210A mutation, antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies IgG and IgM, anti- β 2 glycoprotein I IgG and IgM), and fasting homocysteine, was normal. Paroxysmal nocturnal hemoglobinuria and myeloproliferative neoplasms were ruled out by means of biochemical examinations, bone marrow aspiration, and biopsy. Behçet syndrome and Hughes-Stovin syndrome, which may complicate with systemic thrombosis, were ruled out by means of testing HLA B27 and B51 (both negative) and the pattern of autoimmune

antibodies and serum complement levels (all normal). The patient had no arthralgia, uveitis, fever, aphthous stomatitis, or genital ulcers, nor had she declared them in the past. Stools were examined for bacteria, including *Clostridium difficile* and parasites, yielding negative results. On May 14, 2011, at nighttime, she had numerous bowel movements with bloody diarrhea and a decrease in hemoglobin to 7.4 g/dL. In the morning, flexible colonoscopy revealed severe inflammation in the rectum and sigmoid colon, with deep ulcerations and friability of the mucosal surface. Histologic examination of the rectal mucosa allowed the diagnosis of severely active ulcerative colitis, and treatment with oral corticosteroids (methylprednisolone 1.5 mg/kg once daily) was started. The same day in the evening she suffered from a rapidly worsening dyspnea and was transferred to the pediatric ICU where a lung angio-CT scan showed a large thrombus in the right atrium and a bilateral pulmonary embolism, together with a concomitant massive bilateral pleural effusion and lung collapse. Bilateral catheters for thoracentesis were placed, and thrombolytic treatment with recombinant-tissue plasminogen activator was started through a central venous catheter in the right subclavian vein at a dose of 0.3 mg/kg per hour for 6 hours. A CT scan showed complete resolution of atrial thrombus and partial resolution of pulmonary emboli, whereas the inferior vena cava and hepatic veins were still occluded. A second course of recombinant-tissue plasminogen activator at a dose of 0.4 mg/kg per hour for 6 hours was given, followed by intravenous unfractionated heparin. No hemorrhagic complications were observed. Her clinical conditions improved apart from bowel movements. Steroids were replaced by cyclosporine 4 mg/kg once daily, with no benefit. A plain abdominal radio-

graph showed signs of toxic megacolon, and a total colectomy was performed on May 30, 2011, with rectal preservation, rectostomy, and terminal ileostomy. Two weeks later, the rectal fistula was closed. A thoracic and abdominal CT scan performed on June 30, 2011, showed the complete resolution of thrombi in the heart, pulmonary circulation, inferior vena cava, and hepatic veins. In addition, the sagittal sinus was normally perfused on the angio-MRI on June 13, 2011. Transaminase re-entered within the normal ranges, as well as liver and spleen volumes. On July 23, 2011, the patient was discharged on oral anticoagulant treatment with a vitamin K antagonist (warfarin). Subsequent course was characterized by periodical activity of the rectal stump, treated with mesalamine and steroid enemas with partial success. Rectorrhagia required red blood cell transfusion on 2 different occasions. On July 24, 2012, the patient underwent proctectomy, and an ileo-pouch-anal anastomosis was constructed. She received postsurgery antithrombotic prophylaxis, and warfarin was withdrawn.

DISCUSSION

“Thrombotic storm” is defined as multiple acute or subacute thrombotic events occurring over a period from a few days to a few weeks and involving multiple sites, including the so-called unusual sites for thrombosis.⁶ Antiphospholipid antibodies are frequently encountered in patients with thrombotic storm, as recently reported in a review by the Thrombotic Storm Study Group⁷ that describes the clinical characteristics of these patients. Also, Behçet/Hughes Stovin syndrome may complicate with thrombosis, particularly of the inferior vena cava.^{8,9} Among the initiating conditions (“triggers”) for the development of thrombotic storm, there is an inflammatory

state. One of the 10 patients described in that review is a 20-year-old woman with multiple thrombosis and already overt Crohn disease. A second case series of thrombotic storm describes 8 children aged 2 to 18 years, none of whom who had inflammatory bowel diseases.¹⁰ On the other hand, mainly venous rather than arterial thrombosis is a frequent complication in children with overt inflammatory bowel diseases and is reported in >80% of these patients with active ulcerative colitis.⁵ In our patient, the diagnosis of ulcerative colitis was preceded by that of hepatic vein thrombosis. This is peculiar, because the 5 pediatric patients with ulcerative colitis and hepatic vein occlusion described to date had the thrombotic complication months or years after the onset of inflammatory bowel disease.⁵ The biochemical mechanisms by which inflammatory bowel diseases are associated with thrombosis are only in part elucidated and are likely to be multifactorial. Possibly, inflammatory cytokines activate coagulation proteins and disturb fibrinolysis, platelet, and endothelial functions.^{11–13} In our patient, the prothrombotic stimulus was so strong as to cause a life-threatening, multiorgan, venous thrombotic storm that required thrombolytic treatment, which may be potentially harmful because of the risk of worsening mucosal bleeding or of causing new hemorrhages. The efficacy and safety of thrombolysis in our patient were excellent. The possibility to use infliximab as a rescue therapy for severe steroid-refractory ulcerative colitis¹⁴ in our teenage patient was excluded because she developed megacolon that required a prompt colectomy. Moreover, current guidelines discourage the initiation of a third-line therapy in steroid-refractory ulcerative colitis after the failure of either infliximab or cyclosporine, due to the high risk of adverse events.¹⁵ Soon after surgery her clinical conditions

rapidly improved. Because a rectal trait of 20 cm was left, we decided to maintain oral anticoagulation with warfarin to prevent recurrent thrombosis, particularly because the inflammatory disease might reactivate in the rectum. After its removal, the underlying trigger of thrombosis was no longer present and, because no other permanent inherited or acquired risk factors for thrombosis have been recognized, anticoagulant therapy was withdrawn and only postoperative antithrombotic prophylaxis with low-

molecular-weight heparin was given. In the hypothesis that our patient may have a still unknown coagulation abnormality predisposing to venous thrombosis, she will receive antithrombotic prophylaxis in future high-risk situations.

CONCLUSIONS

This is the first case report of a pediatric patient with a thrombotic storm triggered by a previously unknown ulcerative colitis and with no other inherited or

acquired prothrombotic risk factors. Underlying inflammatory bowel diseases should therefore be considered when evaluating the spectrum of triggers of the thrombotic storm in pediatric patients.

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