Systemic Thrombolysis for Isolated Splenic Vein Thrombosis Secondary to Oral Contraceptives: A Case Report

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Abstract: Isolated splenic vein thrombosis (ISVT) is a very rare venous thromboembolism in the absence of pancreatic diseases, which can cause acute abdominal pain and chronic left-side portal hypertension. Herein, we reported a 40-year-old female patient who developed ISVT after taking oral contraceptives. Anticoagulation with oral rivaroxaban was the first-line choice of therapy in this case. Since then, abdominal pain alleviated, but she did not achieve vessel recanalization. Thus, a 7-day systemic thrombolysis with urokinase was given. Abdominal pain disappeared, but ISVT was not significantly improved. During follow-up period, long-term anticoagulation with oral rivaroxaban was given. Collectively, this case indicates the possibility of oral contraceptives as a risk factor of ISVT as well as anticoagulation combined with systemic thrombolysis as a choice of treatment for ISVT. Certainly, long-term follow-up is necessary in this case.

Keywords: splenic vein thrombosis, oral contraceptives, anticoagulation, rivaroxaban, thrombolysis

Introduction

Portal vein system thrombosis, which refers to complete or partial thrombotic obstruction of the main portal vein and/or its branches with or without extension to splenic and superior mesenteric veins, has been increasingly recognized in clinical practice, due to its negative impact on the outcomes of patients. It is often associated with liver cirrhosis and abdominal malignancy. By comparison, isolated splenic vein thrombosis (ISVT) without involvement of portal vein and superior mesenteric vein is usually observed in patients with pancreatic diseases, especially pancreatitis and pancreatic cancer. This is because the splenic vein lies posterior to the pancreas and extends along the tail and neck. More than half of the patients with ISVT present with abdominal pain, followed by gastric variceal bleeding. Splenectomy is often performed in the majority of ISVT patients. Notably, ISVT in the absence of pancreatic diseases has been rarely reported yet. Herein, we report a case of ISVT secondary to oral contraceptives (OCs) without a history of pancreatic diseases who received anticoagulation combined with systemic thrombolysis.

Case Presentation

A 40-year-old female patient presented with left abdominal pain accompanied by diarrhea for one week at our department on August 9, 2023. She did not have hematochezia. She had no history of serious comorbidities or pancreatic diseases but took oral contraceptives (drospirenone 3mg and ethinylestradiol 0.03mg) daily during the past three months. She has no history of smoking. Contrast-enhanced computer tomography (CECT) scans showed unenhanced lesions in the splenic vein, suggesting a diagnosis of ISVT (Figure 1A). Laboratory tests showed that D-dimer level was 2.02mg/L (reference range: 0.00–0.55mg/L). She had consulted with a vascular interventionalist before our admission, and was given oral rivaroxaban. After our admission, antithrombin III, plasma protein C activity, plasma protein S activity, kappa
chain, lambda chain, antiphospholipid syndrome antibody, and thrombelastography (TEG) profile were within their reference ranges. Meanwhile, she continued to receive oral rivaroxaban. On August 11, 2023, she underwent upper gastrointestinal endoscopy showing superficial gastritis without gastroesophageal varices (Figure 2A and B). On

![Figure 1](https://example.com/image1) Contrast-enhanced CT images performed on August 7 (A), August 14 (B), August 22 (C), and September 26 (D) showing change of isolated splenic vein thrombosis (red arrow).

![Figure 2](https://example.com/image2) Upper gastrointestinal endoscopic images. There were no varices in the esophagus (A) or gastric fundus (B).
August 14, 2023, CECT scans were performed again, still showing low-density lesions in the proximal splenic vein (Figure 1B). Laboratory tests showed that D-dimer level was 1.06mg/L and R value was 4.6min (reference range: 5–10min). Plasminogen activator inhibitor type 1 gene test showed 4G/4G homozygous mutation. At this time, abdominal pain alleviated, but ISVT remained. Thus, she was informed about the efficacy and safety of thrombolysis. After that, she agreed to receive systemic thrombolysis with continuous intravenous injection of urokinase 500000u every 12 hours for a duration of 7 days. During the period of systemic thrombolysis, she did not develop any bleeding event. On August 22, 2023, abdominal pain disappeared, and CECT scans were repeated, showing a slight decrease in thrombus extension (Figure 1C). She was discharged with long-term use of oral rivaroxaban. On September 26, 2023, D-dimer level was 0.19mg/L, and CECT scans showed that the splenic vein became fibrotic cord (Figure 1D).

**Discussion**

At present, the data on ISVT are very scant. Thus, we have reviewed cases of ISVT or splenic vein occlusion in Table 1.5,7–44 Pancreatic diseases should be the most common risk factors associated with ISVT, followed by tumors, infections, and hematological diseases. A potential mechanism of ISVT is that inflammatory reaction and extravascular

### Table 1 Reported Cases of Isolated Splenic Vein Thrombosis or Occlusion: An Overview

<table>
<thead>
<tr>
<th>First Author (Country, Year)</th>
<th>Patient Age/Sex</th>
<th>Etiology</th>
<th>Symptoms</th>
<th>Diagnostic Method</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sutton (USA, 1970)7</td>
<td>40/M</td>
<td>Pancreatic pseudocyst, trauma</td>
<td>GIB</td>
<td>Splenic venogram</td>
<td>Splenectomy</td>
</tr>
<tr>
<td>Khan (USA, 1977)8</td>
<td>39/M</td>
<td>Chronic pancreatitis</td>
<td>GIB</td>
<td>Angiography</td>
<td>Splenectomy</td>
</tr>
<tr>
<td>Bunt (USA, 1983)9</td>
<td>45/M</td>
<td>Pancreatitis</td>
<td>GIB</td>
<td>Angiography</td>
<td>Splenectomy</td>
</tr>
<tr>
<td>Røder (NA, 1984)10</td>
<td>51/NA</td>
<td>Pancreatic pseudocyst</td>
<td>GIB</td>
<td>Angiography</td>
<td>Splenectomy</td>
</tr>
<tr>
<td>Madsen (NA, 1986)11</td>
<td>NA</td>
<td>NA</td>
<td>GIB</td>
<td>NA</td>
<td>Splenectomy</td>
</tr>
<tr>
<td>Singh (India, 1990)12</td>
<td>NA</td>
<td>Tuberculosis</td>
<td>NA</td>
<td>Splenectomy, jejural resection, antituberculous</td>
<td></td>
</tr>
<tr>
<td>Perisić-Savić (Yugoslavia, 1991)13</td>
<td>31/F</td>
<td>Pregnant</td>
<td>Asymptomatic</td>
<td>Ultrasonography</td>
<td>Splenectomy</td>
</tr>
<tr>
<td>Møller (Denmark, 1997)14</td>
<td>33/M</td>
<td>Pancreatic abscess</td>
<td>GIB</td>
<td>NA</td>
<td>Splenectomy</td>
</tr>
<tr>
<td>Tsuchida (Japan, 2003)15</td>
<td>46/F</td>
<td>Distal pancreatectomy</td>
<td>Asymptomatic</td>
<td>Ultrasonography, angiography</td>
<td>Splenectomy</td>
</tr>
<tr>
<td>Köklü (Turkey, 2004)16</td>
<td>26/F</td>
<td>Renal abscess</td>
<td>GIB, abdominal pain, fever, dyspnea</td>
<td>Ultrasonography, CECT</td>
<td>Splenectomy, nephrectomy</td>
</tr>
<tr>
<td>Joya Sejo (Spain, 2004)17</td>
<td>46/NA</td>
<td>Renal-cell carcinoma</td>
<td>GIB</td>
<td>CECT</td>
<td>Splenectomy</td>
</tr>
<tr>
<td>Biltki (Poland, 2004)18</td>
<td>61/F</td>
<td>Chronic pancreatitis</td>
<td>NA</td>
<td>NA</td>
<td>Splenectomy</td>
</tr>
<tr>
<td>Yamaguchi (Japan, 2005)19</td>
<td>53/M</td>
<td>Pancreatic neuroendocrine tumor</td>
<td>GIB</td>
<td>CECT</td>
<td>Splenectomy, distal pancreatectomy, partial resection of gastric fundus, lymph node dissection</td>
</tr>
<tr>
<td>Hiraiva (Japan, 2006)20</td>
<td>49/F</td>
<td>Colon cancer</td>
<td>Abdominal pain</td>
<td>CECT</td>
<td>Splenectomy, hemicolecotomy, distal pancreatectomy</td>
</tr>
<tr>
<td>Liu (China, 2006)21</td>
<td>42/M</td>
<td>Embolization of varices</td>
<td>Fever</td>
<td>Ultrasonography, CECT</td>
<td>Antibiotic</td>
</tr>
<tr>
<td>Hartharan (UK, 2006)22</td>
<td>64/M</td>
<td>Trauma</td>
<td>GIB</td>
<td>CECT</td>
<td>Refused any treatment</td>
</tr>
<tr>
<td>Allen (USA, 2007)23</td>
<td>49/F</td>
<td>Chronic pancreatitis</td>
<td>GIB</td>
<td>Angiography</td>
<td>Splenic artery embolization</td>
</tr>
<tr>
<td>Guler (Turkey, 2008)24</td>
<td>23/F</td>
<td>MTHFR C677T mutation</td>
<td>Abdominal pain</td>
<td>Ultrasonography</td>
<td>Low-molecular weight heparin, splenectomy, warfarin</td>
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</tbody>
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(Continued)
compression induce the injury of vascular endothelium, blood stasis, and hypercoagulability.4,42 Our case had no significant risk factors other than a history of OCs. OCs can produce von Willebrand factor, which plays an important role in platelet adhesion and activation through stimulation of endothelial cells. Besides, OCs also increase the levels of factors II, VII, VIII, and X and fibrinogen, and decrease the factor V level to influence the coagulation cascade. On the other hand, OCs decrease the levels of tissue factor pathway inhibitor, antithrombin, and total and free protein S.45,46

### Table 1 (Continued)

<table>
<thead>
<tr>
<th>First Author (Country, Year)</th>
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<th>Symptoms</th>
<th>Diagnostic Method</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tzur (Israel, 2008)25</td>
<td>46/M</td>
<td>Trauma, hyperhomocysteinemia</td>
<td>Chest pain</td>
<td>Magnetic resonance venography</td>
<td>Low-molecular weight heparin</td>
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<tr>
<td>Numura (Japan, 2009)26</td>
<td>39/F</td>
<td>Idiopathic</td>
<td>Abdominal pain</td>
<td>Autopsy</td>
<td>Transfusion without reporting other treatments</td>
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<tr>
<td>Karagkiozis (Greece, 2012)27</td>
<td>70/F</td>
<td>Autoimmune hemolytic anemia</td>
<td>Abdominal pain, vomiting, nausea, constipation</td>
<td>CECT</td>
<td>Splenectomy</td>
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<tr>
<td>Chen (China, 2013)28</td>
<td>77/F</td>
<td>Lymphoma</td>
<td>GIB</td>
<td>CECT</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Jain (India, 2014)29</td>
<td>16/F</td>
<td>Tuberculosis</td>
<td>Fever, dry cough, jaundice, vomiting</td>
<td>CECT</td>
<td>Low-molecular weight heparin, antituberculous</td>
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<tr>
<td>Käksal (Turkey, 2014)30</td>
<td>54/M</td>
<td>External compression</td>
<td>Fatigue, weight loss</td>
<td>CECT</td>
<td>Chemotherapy</td>
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<tr>
<td>Kiani (Iran, 2013)31</td>
<td>8/M</td>
<td>Idiopathic</td>
<td>GIB</td>
<td>CECT</td>
<td>Splenectomy</td>
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<tr>
<td>Parekh (USA, 2015)32</td>
<td>47/M</td>
<td>Lymphoma</td>
<td>GIB, lightheadedness, dyspnea, weakness</td>
<td>CECT</td>
<td>Splenectomy, chemotherapy</td>
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<tr>
<td>Lenhart (USA, 2016)33</td>
<td>73/M</td>
<td>Lymphoma</td>
<td>GIB</td>
<td>MRI</td>
<td>Splenic artery embolization</td>
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<tr>
<td>Franco-Avilés (Spain, 2017)34</td>
<td>31/M</td>
<td>Pancreatic pseudocyst</td>
<td>GIB</td>
<td>Angiography</td>
<td>Splenectomy</td>
</tr>
<tr>
<td>Lupascu-Ursulescu (Romania, 2017)35</td>
<td>37/F</td>
<td>Pancreatic cyst</td>
<td>GIB</td>
<td>Ultrasonography, CECT</td>
<td>Splenectomy, pancreatectomy</td>
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<tr>
<td>Salazar-Mejía (Mexico, 2017)36</td>
<td>26/M</td>
<td>Testicular cancer</td>
<td>GIB</td>
<td>CECT</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Patel (USA, 2019)37</td>
<td>65/M</td>
<td>Essential thrombocytosis</td>
<td>GIB</td>
<td>Splenic venogram</td>
<td>Splenic artery embolization</td>
</tr>
<tr>
<td>Hayashi (Japan, 2020)38</td>
<td>70/M</td>
<td>Idiopathic</td>
<td>Epigastric discomfort</td>
<td>CECT</td>
<td>Splenectomy</td>
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<tr>
<td>Park (Korea, 2021)39</td>
<td>23/F</td>
<td>Pancreatic desmoid type fibromatosis</td>
<td>Abdominal pain</td>
<td>CECT, MRI</td>
<td>Splenectomy, distal pancreatectomy</td>
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<tr>
<td>Zafar (UK, 2022)310</td>
<td>64/M</td>
<td>Chronic pancreatitis</td>
<td>Chest pain</td>
<td>CECT</td>
<td>Heparin, apixaban</td>
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<td>Sikana (Indonesia, 2022)40</td>
<td>28/M</td>
<td>Liver cirrhosis, chronic pancreatitis</td>
<td>GIB, Abdominal pain, Ascites</td>
<td>CECT</td>
<td>Proton pump inhibitors, diuretics, octreotide, antibiotic</td>
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<td>Capraro (USA, 2022)41</td>
<td>13/F</td>
<td>Acute pancreatitis</td>
<td>Abdominal pain</td>
<td>CECT</td>
<td>Low-molecular weight heparin, rivaroxaban</td>
</tr>
<tr>
<td>Füssel (Austria, 2023)42</td>
<td>45/F</td>
<td>Chronic pancreatitis</td>
<td>GIB</td>
<td>Angiography</td>
<td>Balloon dilatation and stenting</td>
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<tr>
<td>Pak (Korea, 2023)33</td>
<td>69/M</td>
<td>NA</td>
<td>GIB</td>
<td>CECT, angiography</td>
<td>Splenectomy</td>
</tr>
<tr>
<td>García Soria (Spain, 2023)44</td>
<td>42/M</td>
<td>Pancreatic neuroendocrine tumor</td>
<td>GIB</td>
<td>CECT, endoscopic ultrasonography</td>
<td>Anticoagulation, splenectomy</td>
</tr>
</tbody>
</table>

**Abbreviations:** GIB, gastrointestinal bleeding; CECT, contrast-enhanced computed tomography; MRI, magnetic resonance imaging; NA, not available.
risk of venous thrombosis with OCs is higher in women who are older than 40 years, and increased from the 4th month of administration, especially in those receiving OCs for the first time. Drosipirenone, a novel contraceptive pill, in combination with ethinylestradiol, leads to an increased risk of venous thrombosis. Like our case, Zhao et al also reported a young female treated with OCs at the same dosage who developed portal, superior mesenteric, and splenic vein thrombosis. However, the location of splanchic vein thrombosis in this case is completely different from ours.

Plasminogen activator inhibitor type 1 (PAI-1) gene mutation is theoretically associated with splanchic vein thrombosis, since the binding of 4G allele to transcription activator is associated with high levels of PAI-1, which can inhibit the efficacy of tissue-type and urokinase-type plasminogen activator, and promote the development of venous thrombosis. However, the clinical evidence regarding association of PAI-1 gene mutation with splanchic vein thrombosis is still insufficient and controversial. Notably, the thrombogenic effect of hypofibrinolysis status secondary to PAI-1 gene mutation can be synergistically amplified by the use of OCs. On the other hand, unfortunately, we did not screen JAK2V617F mutation which is a major risk factor of splanchic vein thrombosis, but it should be acknowledged that higher platelet count and splenomegaly, both of which are closely related to JAK2V617F mutation, were missing in our case.

Elevated D-dimer often indicates the probability of thrombosis. Certainly, imaging tests are needed to clarify the diagnosis and further identify the location of thrombosis. CECT and angiography are preferred for a definitive diagnosis of ISVT. Splanchnic vein thrombosis often presents as low-density defect in the vascular lumen on the portal vein phase of CECT scans. Ultrasound is a convenient diagnostic method for splanchnic vein thrombosis. Early stage of thrombosis may be echoless on ultrasound, and the echo gradually increases following fibrosis with or without blood flow. Both ultrasound and CECT seem to be equally reliable in assessing the presence and severity of ISVT. However, CECT is more helpful to further distinguish the nature of thrombosis, considering that ISVT is a marker of occult cancer.

A few patients with ISVT are asymptomatic, but most patients with chronic ISVT often present with gastroesophageal variceal bleeding. Left-side portal hypertension occurs due to complete splenic vein obstruction. Endoscopic and drug hemostasis are usually ineffective, and splenectomy has to be performed. By comparison, patients with acute ISVT often present with abdominal pain but without varices on endoscopy. Our case should be diagnosed with acute ISVT and treated with anticoagulation and thrombolysis to prevent from portal hypertension-related complications in a timely fashion. However, she did not achieve splenic vein recanalization at the last visit. Accordingly, screening for gastroesophageal varices by endoscopy is very necessary in our case during follow-up period.

Guidelines recommend low molecular weight heparin and vitamin K antagonists as traditional choices for early anticoagulation. Anticoagulation can promote vascular recanalization and prevent thrombotic progression in patients with splanchnic vein thrombosis. Recently, direct-acting oral anticoagulants (DOACs) are increasingly employed. Compared to traditional anticoagulants, patients’ adherence to DOACs was better, because the method of its administration was convenient and close monitoring and dosage adjustment were not required. Besides, Ageno et al demonstrated that oral rivaroxaban was effective in patients with splanchnic vein thrombosis with a complete recanalization rate of 47.3%. Naymagon et al also demonstrated that rivaroxaban, apixaban, and dabigatran had a higher rate of complete recanalization than warfarin in patients with portal vein thrombosis.

Anticoagulation seems to be promising for the treatment of ISVT but has been insufficiently explored. In our case, oral rivaroxaban did not contribute to complete vascular recanalization, but relieved abdominal discomfort to some extent.

Thrombolysis is recommended in the case of intestinal ischemia, especially if anticoagulation fails. Zhang et al demonstrated that thrombolysis had a higher rate of vascular recanalization and a shorter period of symptomatic improvement than anticoagulation in patients with splanchnic vein thrombosis. A systematic review and meta-analysis suggested that the rates of vascular recanalization and symptomatic improvement after thrombolysis in patients with portal vein thrombosis were 84% and 86%, respectively. To the best of our knowledge, our case should be the first one of ISVT receiving systemic thrombolysis. In our case, systemic thrombolysis relieved abdominal pain more significantly as compared to the use of anticoagulation alone. Unfortunately, vascular recanalization was not achieved, probably because we did not initiate thrombolysis as the first-line choice of treatment in this case. Additionally, we did not employ local thrombolysis via a catheter in the portal vein system or superior mesenteric artery, which might be more effective than systemic thrombolysis.

In conclusion, for patients who use OCs for the first time and need long-term maintenance, it should be appropriate to screen splanchnic vein thrombosis after the 3-month use of OCs. ISVT secondary to OCs is very rare in clinical practice, but this condition should be recognized. Its related chronic complications, such as left-side portal hypertension, should be closely screened.
during follow-up period. Thrombolysis may be a choice of treatment for acute ISVT, but its efficacy and safety should be further validated in a large group of patients with ISVT.

**Ethics Approval**

Institutional approval for publication of the case details was not required in accordance with local institutional requirements.

**Consent to Publish Statement**

Written informed consent for publication of the case details was obtained from the patient.

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**Author Contributions**

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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**Disclosure**

The authors report no conflicts of interest in this work.

**References**


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