

***Case report***

# Right colonic ischemia due to factor V leiden mutation: Report of a case

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## SUMMARY

The protein C anticoagulant pathway is an important down-regulating mechanism of the blood coagulation cascade. Resistance to activated protein C (APCR) due to factor V Leiden mutation is now recognized as the single most common cause of hereditary thrombophilia. We report a 73-yr-old male with right colonic ischemia probably from occlusion of small branches of the superior mesenteric artery. Hemostasis laboratory analysis was normal except for the resistance to activated protein C. Genetic testing revealed that the patient was heterozygous for the factor V Leiden mutation. APCR caused by factor V Leiden mutation should be considered a possible etiological factor of ischemic colitis. In a review of the associated literature, we found only one case of ischemic colitis and two cases of ischemia of the small intestine attributed to factor V Leiden mutation.

## INTRODUCTION

Intestinal vasculopathy is not rare, comprising about 1 per 1000 hospital admissions.<sup>1</sup>

Despite phenomenal progress during the past quarter century in understanding the pathophysiology, natural history and therapy of mesenteric ischemia, acute mesenteric ischemia still has a high mortality, which is

directly related to diagnostic delay. The diagnosis is frequently delayed because mesenteric ischemia typically produces subtle and nonspecific early clinical findings and develops overt and specific clinical findings only when advanced. Acute intestinal ischemia can be the consequence of either intrinsic vascular disease, systemic disease, drugs or surgical procedures.<sup>2</sup> Activated protein C is a main inhibitor of the coagulation process.

Recently, in an attempt to find other factors that might contribute to the development of thrombosis, an important thrombophilic marker, the resistance to activated protein C (APCR) due to the factor V Leiden mutation has been under investigation.<sup>3</sup> Its cause has proven to be the mutation of factor V molecule (substitution of Glu for Arg at amino acid 506). We report a case of acute right colonic ischemia in a 73 years-old male patient which was finally attributed to factor V Leiden mutation.

## *Case report*

A 73 year-old male patient was brought to the emergency department with dizziness, sweating, weakness, decreased mentation and confusion. His clinical signs were hypotension, tachycardia and paleness. He had a history of hypertension treated with angiotensin-converting enzyme inhibitors and he had also been receiving 100mg of aspirin, daily, for many years. Laboratory data on admission were: Ht: 32.3%, WBC: 16400/ $\mu$ l, (neutrophils 78%, lymphocytes 20%), glucose: 207mg/dl, urea: 70mg/dl, creatinine: 1mg/dl, total protein: 4.9g/dl, albumin: 2.9g/dl, calcium: 7mg/dl, potassium: 5mEq/dl, sodium: 142mEq/dl, partial thromboplastin time: 44.8sec, prothrombin time: 12.7sec, pH 7.30, plasma bicarbonate: 22.2 mmol/L, PO<sub>2</sub>: 76, PCO<sub>2</sub>: 42, and oxygen saturation 94%. During clinical examination he suffered an episode of acute gastrointestinal bleeding, consisting of a large

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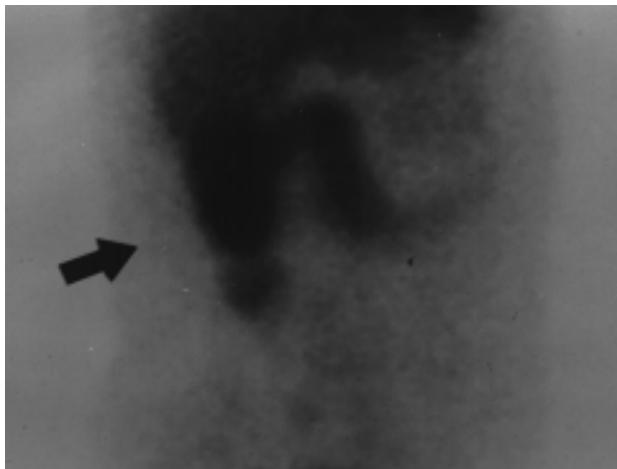
amount of fresh blood. He was submitted to emergency esophagogastroduodenoscopy, but the cause of hemorrhage was not identified in the upper gastrointestinal tract.

The patient was managed with blood and plasma transfusions together with intravenous administration of fluids and remained hemodynamically stable. He was then submitted to colonoscopy. The large intestine was examined up to the hepatic flexure revealing a mucosa uniformly covered by a mixture of blood clots and stools that obstructed its thorough inspection. No possible cause of hemorrhage was identified and passage of the instrument into the ascending colon was technically impossible.

$^{99m}$ Tc-labeled red blood cell scan was performed on the next day which revealed extravasation of autologous radio-labeled red blood cells beginning from the region between the middle of the ascending colon and the hepatic flexure and extending up to the sigmoid colon, at a smaller rate (**Figure 1**). At the same time the patient had another episode of hematochezia with signs of shock and required immediate surgical intervention.

A right semicolectomy with an end-to-end anastomosis was performed based exclusively on the  $^{99m}$ Tc-labeled red blood cell results. The resected bowel consisted of the last 10 cm of the terminal ileum, the ileocaecal valve, the whole ascending colon and half of the transverse colon. Eventually, the patient achieved an uneventful recovery.

Gross examination of the resected bowel specimen revealed an extensive and segmental distribution of red-



**Figure 1.** Extravasation of radioactive material in the middle of the ascending colon and at the hepatic flexure.

dish flat areas from the caecum up to the distal surgical margins (**Figure 2**). Microscopic findings included ulceration of the covering bowel epithelium with dilatation of the vessels in the lamina propria and the submucosa. There was also a patchy distribution of hemosiderin in the lamina propria. The above findings were consistent with segmental ischemic bowel disease starting from the caecum and extending up to the proximal transverse colon.

After diagnosis was established, a sample of venous blood was collected for determination of plasma levels of fibrinogen, protein C, protein S, antithrombin III (AT-III), and activated protein C resistance (APCR). The results were as follows: fibrinogen 275 mg/dl (normal range 200-400), protein C 71% (normal range 58-148%), protein S 97% (normal range 58-148%), antithrombin III 101% (normal range 80-120%) and APCR 1.2 sec (normal range 1.8-5 sec). APCR was measured by determining the activated partial thromboplastin time (APTT) in the absence and presence of APC (Coatest activated protein C resistance kit, Chromogenix, Moendal, Sweden).

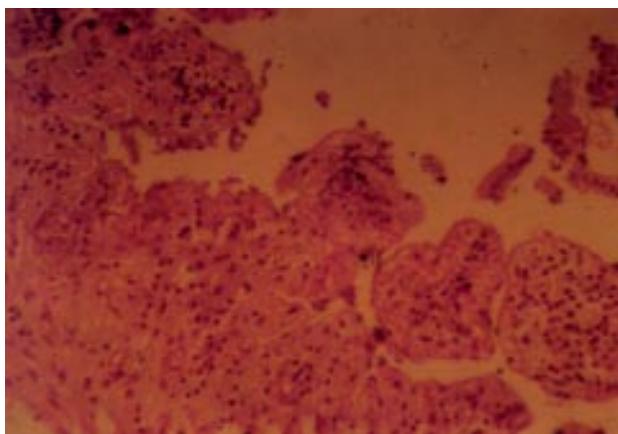
Genetic testing was then performed: genomic DNA isolation from EDTA blood, polymerase chain reaction, and detection of the factor V Leiden mutation were performed using the Factor V Gene Mutation Assay (Vienna Lab, Vienna, Austria). The patient was found to be heterozygous for the factor V Leiden mutation.

## DISCUSSION

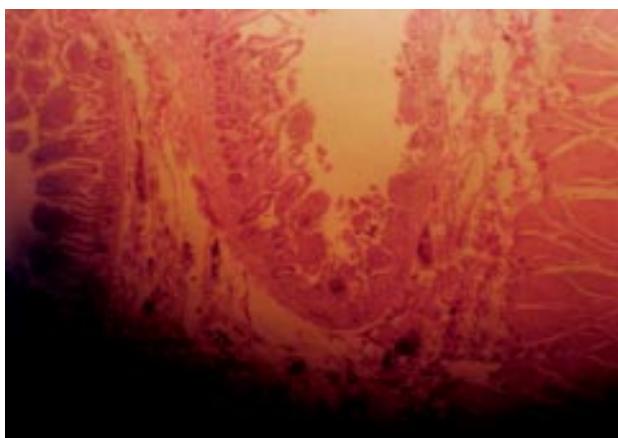
Ischemic colitis represents the most common form of intestinal ischemia and most commonly involves elderly patients with a variety of underlying conditions.<sup>4</sup> The typical clinical picture is that of acute abdominal pain followed by hematochezia.



**Figure 2.** Patchy distribution of reddish flat areas from the caecum up to the distal surgical margins.



**Figure 3.** Ulceration of the covering bowel epithelium (hematoxyline-eosin stain, magnification x 900).



**Figure 4.** Dilatation and congestion of blood vessels in the mucosa and submucosa (hematoxyline-eosin stain, magnification x 54).

However, a variety of symptoms and signs exists depending on the severity of the condition, including hypotension, vomit or melena.<sup>1</sup> Our patient had no pain at all, but presented with symptoms and signs of shock. The severity of ischemic colitis may range from mild to life-threatening. There have been few studies analyzing the factors associated with poor prognosis in ischemic colitis,<sup>5-9</sup> and most factors studied have proved to be unrelated to severity. Only right colonic involvement has been implicated, and only in one study.<sup>5</sup> This finding is in total agreement with our case of life-threatening right colonic ischemia.

The cause of ischemic colitis often remains obscure. A variety of associations have been described. These include alterations in the mesenteric vasculature that oc-

cur with old age,<sup>10</sup> 1-2% of subjects after aortic aneurysm repair,<sup>11</sup> cholesterol embolization<sup>12</sup> and colonic neoplasia.<sup>13</sup> The association with the antiphospholipid syndrome has been documented in a number of case reports<sup>14</sup> both in the presence<sup>15</sup> and in the absence<sup>16</sup> of rheumatological disease, although the association with small bowel disease is stronger than that with colonic disease.<sup>17-19</sup>

Ischemic colitis has also been associated with other clotting factor abnormalities such as antithrombin III deficiency<sup>20</sup> and other factors of possible etiological significance such as mitochondrial cytopathy<sup>21</sup> and long-distance running.<sup>22</sup>

The diagnostic evaluation of a patient with suspected intestinal ischemia should include the performance of plain abdominal roentgenogram mainly to exclude other abdominal disorders, <sup>99m</sup>Tc-labeled red blood cell scan, computed tomography of the abdomen (CT scan) and selective angiography.<sup>1</sup> Nuclear medicine scintigraphy has been reported to detect bleeding at a rate as low as 0.1 ml/min, but its sensitivity in detecting the precise location of hemorrhage is low.<sup>23</sup> Abdominal CT is only sometimes useful in diagnosing mesenteric arteriopathy but is useful in excluding mesenteric venopathy and other abdominal disorders in the differential diagnosis.<sup>24</sup> Selective mesenteric angiography is currently the mainstay of diagnosis and initial treatment of both occlusive and non-occlusive forms of mesenteric ischemia and should be performed early when mesenteric arteriopathy is suspected. Other diagnostic tests include colonoscopy, abdominal ultrasound and barium radiography. Colonoscopy is very helpful in diagnosing colonic ischemia, since it permits direct view of the mucosa and provides the opportunity to obtain mucosal biopsy specimens to exclude other pathologic entities.<sup>25</sup> However, it is rarely used to diagnose acute mesenteric arteriopathy because the area of intestine affected by the superior mesenteric artery occlusion is usually beyond the reach of the colonoscope. The sensitivity of barium enema is lower than that of colonoscopy and abdominal ultrasound with Doppler is useful in diagnosing mainly chronic mesenteric arteriopathy and venopathy.<sup>1</sup>

Activated protein C resistance (APCR) was first recognized by Dahlback et al in 1993 as a new mechanism for familial thrombophilia.<sup>26</sup> It is characterized by in vitro resistance to the anticoagulant effects of activated protein C and its cause was proved to be the replacement of Arg by Glu at residue 506 in the factor V molecule (factor V Leiden mutation).<sup>27</sup> Recent studies have shown that 11-20% of acute venous thrombotic events are caused by APCR.<sup>28</sup>

Factor V Leiden mutation and its subsequent APCR have been associated with cases of stroke,<sup>29</sup> pulmonary artery thrombosis,<sup>30</sup> retinal vein thrombosis,<sup>31</sup> artery thromboses in neonates,<sup>32</sup> placental lesions,<sup>33</sup> Budd-Chiari syndrome<sup>34</sup> and many other thrombotic conditions. However, in a review of the associated international literature we found only two cases of ischemia of the small intestine<sup>35,36</sup> and just one report of ischemic colitis caused by factor V Leiden mutation.

Our patient did not have all the typical symptoms of mesenteric ischemia. His presenting symptom was hematochezia and he did not mention any pain at all. Guided by that, we initially performed esophagogastroduodenoscopy and colonoscopy, which led to no significant results, instead of performing selective angiography. Therefore, the correct diagnosis of mesenteric ischemia was delayed. Due to the severity of the patient's clinical status, emergency surgery was performed before diagnostic evaluation had been completed, according to the findings of the <sup>99m</sup>Tc-labeled red blood cell scan. The diagnosis was finally established by pathologic examination of the resected bowel.

From the distribution of the ischemic lesions, we assumed that mesenteric ischemia was caused by the occlusion of small branches of the right colic artery and perhaps of the ileocolic artery. Venous thrombosis was excluded by the fact that the clinical course was extremely rapid. The patient had neither an obvious cause of thrombosis, like arteriosclerosis, nor any other uncommon causes of intestinal ischemia. This is why a hemostatic mechanism evaluation was finally performed, which revealed an abnormal activated protein C resistance. Genetic testing confirmed that the patient was heterozygous for the factor V Leiden mutation. Since no other cause of intestinal ischemia was identified, we assume that the former mutation was probably responsible for the ischemia.

In conclusion, factor V Leiden mutation is an uncommon cause of colonic ischemia. Our case was also rare because the mutation was not evident until the seventh decade of the patient's life, the location of the ischemia was uncommon and the typical symptom of pain was not observed. It is important to bear in mind this rare cause of colonic ischemia and to search for it in cases where no obvious cause is evident. Furthermore, genetic testing of the family members of the affected person will be useful in identifying those who are at increased risk for developing arterial or venous thromboses in the future.

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