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Original Article

A Rare Complication of Anticoagulant Therapy: Intramural Hematoma of the Small Bowel

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Abstract

Background: Non-traumatic intramural hematomas of the small bowel (IHSB) are rare conditions which occur due to anticoagulant therapy. In this study, we aimed to explain our clinical approach to non-traumatic IHSB due to anticoagulant overdose and to present the long-term outcomes of the cases who were hospitalized.

Methods: Sixteen patients with non-traumatic IHSB were included and their medical records were retrospectively reviewed.

Results: Our patients included ten women and six men, with a mean age of 77.5 ± 8.4 (range: 65–95) years. All patients had been using oral anticoagulants (OACs) due to various cardiovascular and cerebral comorbidities. Common complaints at the time of admission included abdominal pain, vomiting and weakness. Ten patients (62%) had anemia, fifteen (94%) had leukocytosis and all patients (100%) had high levels of C-reactive protein (CRP). Abdominal computed tomography (CT) established the final diagnosis of IHSB in all patients. Fourteen patients (87%) were followed up with conservative therapy. Since the clinical course did not improve in two patients (12%), surgery was mandated. The mean duration of hospitalization was 10.25 ± 3.6 days (range: 3–17 days). Mortality occurred in two patients (12%).

Conclusion: IHSB should be considered in patients presenting with abdominal complaints and increased levels on coagulation tests. The diagnosis should be confirmed by abdominal CT scan, if possible. Accurate and timely diagnosis allows patients to be successfully treated without need for surgery.

Keywords: Adverse effects, Anticoagulant, Intestines

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Introduction

Oral anticoagulants (OACs) are often used for treatment of cardiovascular system diseases or as prophylactic treatment in patients who have some risk factors. They can cause various complications, the most important of which is the bleeding.[1,2] Bleeding may occur in 5%–48% of patients, but only 2%-4% of them are seen in the gastrointestinal tract.[3]

Intramural hematoma of the small bowel (IHSB) occurs due to blunt trauma, especially in children, and the duodenum is usually affected.[4] It was first described by McLauchlan in 1883 following cadaveric examination of a male who had died from dehydration caused by duodenal tumor.[5] Non-traumatic IHSBs are very rare. They usually emerge as a serious complication of anticoagulation therapy, but may also occur due to pancreatitis, bleeding disorders, malignancies, vasculitis and upper gastrointestinal endoscopy. Jejunum is the most commonly affected part in non-traumatic IHSB, unlike the traumatic type.[6-9]

In this study, we aimed to explain our clinical approach to non-traumatic IHSB due to anticoagulant overdose, to present the long-term outcomes of the patients who were hospitalized and also to draw the clinicians' attention to this rare entity.

Materials and Methods

We retrospectively analyzed the medical records of patients who had been diagnosed with IHSB in Izmir Katip Celebi University, Ataturk Training and Research Hospital (Izmir-Turkey) General Surgery Department between 2000 and 2017.

Sixteen patients with spontaneous IHSB were evaluated within the scope of the study, after excluding 34 patients with history of trauma and 2 patients with no history of OAC therapy.

Demographics (sex, age), coexisting medical conditions, previous medications, presenting symptoms and signs, laboratory and radiological findings, management interventions, hospitalization course and the outcome of the patients were evaluated.

All patients but one (who underwent emergent diagnostic laparoscopy due to acute abdomen) were hospitalized for conservative treatment. Their OAC treatment and oral

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food intake were discontinued and parenteral nutrition was initiated. Intravenous antacid, antiemetic, analgesic and broad-spectrum antibiotic (in order to prevent bacterial translocation) were administered. All patients received fresh-frozen plasma (FFP) transfusion and vitamin K supplementation to neutralize the effect of OAC. Patients who had anemia additionally received red blood cell (RBC) transfusions. Hemoglobin and clotting parameters were checked on a daily basis. When international normalized ratio (INR) levels regressed to therapeutic levels, OAC therapy was started under control for all patients.

Surgical treatment was opted for in case of acute abdomen at the time of admission or due to development of acute abdomen during the conservative treatment. The patients were prepared on supine position under general anesthesia in the operating room after hemodynamic stability was established. Diagnostic laparoscopy was chosen as the first step approach. Drainage of hematoma and washout of abdominal cavity was performed. The bowel segment was resected in case of bowel necrosis or perforation. The patients were operated on by a surgical team including a senior general surgeon and two residents. The patients were followed up in the intensive care unit after the operation and transferred to the ward when hemodynamic stability was achieved. Oral intake was started after passage of gas and stool.

The patients were followed up by outpatient visits with 3-month intervals in the first year and then annually.

The patients or their relatives were informed about the study, advanced pathological investigations and data to be obtained from their records. Ethics committee approval was received for this study from the Ethics Committee of our institute.

Statistical Analysis

The statistical program SPPS 20 (IBM Corp. released 2011. IBM SPSS Statistics for Windows, version 20.0, Armonk, NY: IBM Corp.) was used for the evaluation of the data. Mean ± standard deviation and percentage and frequency values are reported for the variables.

Results

Out of the total 16 patients, 10 (62%) were women and 6 (37%) were men, with a mean age of 77.5 ± 8.4 (range: 65–95) years. Thirteen patients were admitted to the emergency department and three were admitted to the outpatient general surgery clinic.

All patients had a history of OAC therapy for various cardiologic and/or cerebrovascular disorders (Table 1). The most common indications for OAC were coronary arterial stent (CAS) and/or coronary bypass (CAB) surgery (14 patients, 87%).

The common complaint of all patients was abdominal pain with an average duration of 4 days (range: 3–7 days). In addition, there were other accompanying complaints such as vomiting (62%), weakness (50%), anorexia (37%), hematochezia (25%) and constipation (25%). Table 2 presents the patients' complaints and the findings of physical examination findings at the time of admission.

Table 1. Indications for Warfarin Sodium in All Patients (n = 16, 100%)

Indications	n; %
CAS	4; 25
CAB	4; 25
CAB + aortic valve replacement	2; 12
CVA	2; 12
CVA+ CAS	2; 12
CVA+ CAB	2; 12

CAS, coronary artery stent; CAB, Coronary bypass; CVA; Cerebrovascular accident.

Table 2. Complaints and Signs of Admission in All Patients (n =16, 100%)

Complaints	(n; %)	Signs	(n; %)
Abdominal pain	16; 100	Abdominal tenderness	16; 100
Vomiting	10; 62	Abdominal distension	12; 75
Weakness	8; 50	Ecchymosis	12; 75
Anorexia	6; 37	Dehydration	8; 50
Hematochezia	4; 25	Anemia	8; 50
Constipation	4; 25	Rebound tenderness	4; 25

Blood tests revealed that in all patients, the INR levels were higher than the intended range (normal range: 0.85–1.25) and the mean INR value was 15 ± 5.1 (range: 8.6– >25). Additionally, 10 patients (62%) had anemia (Anemia: hemoglobin level <12 for women, <13 for men), 15 (94%) had leukocytosis and all patients (100%) had elevated C-reactive protein (CRP) levels. The results of the blood count and clotting parameters of the patients are summarized in Table 3.

Plain abdominal radiography, abdominal ultrasonography (US) and abdominal computed tomography (CT) examinations were performed in all patients. Twelve patients (75%) had small bowel-type air-fluid levels and the remaining four patients (25%) had normal abdominal radiography. On ultrasonographic examination, seven patients (44%) had both segmental wall thickening and dilatation in the small bowels, while five patients (31%) were found to have intra-abdominal free fluid and the remaining four patients (25%) had normal US findings (Table 4). On US, intramural hematoma, mesenteric ischemia or inflammatory bowel syndrome were suspected.

All patients were found to have segmental or multiple IHSB on abdominal CT (Figure 1). Intra-abdominal free fluid was detected in three patients which was extensive in two of them. Mean eight units (range: 5-14) of FFP transfusion were administered until normal INR values were accomplished. INR levels decreased to the therapeutic range after a mean period of 5.7 days (range: 3–10 days).

During the hospital stay, 14 patients (87%) received

Table 3. Patients' Complete Blood Count and Clotting Parameters

Patient No.	Age	Sex	Hb	Htc	WBC	Platelet	INR	CRP
1	95	F	10	32.9	10.940	352.000	12.5	9.25
2	73	F	12.1	38.2	17.570	350.000	>25	5.24
3	65	M	15.3	47.3	14.570	271.000	18.8	3.03
4	76	M	14.2	46.6	15.680	375.000	11.2	11.6
5	81	F	7.3	23.3	12.320	292.000	16.7	16.8
6	68	F	9.2	31.6	14.752	356.000	9.4	2.3
7	79	M	12.7	42.5	18.900	274.000	8.6	7.85
8	85	F	7.6	25.1	21.100	180.000	>25	21.12
9	70	M	11.2	36.4	16.500	195.000	10.4	6.15
10	83	F	9.6	29.7	18.950	210.000	19.8	14.3
11	72	F	13.1	42.1	14.380	386.000	9.7	8.2
12	71	M	14.9	49.6	19.160	317.000	16	10.3
13	69	M	11.3	35.7	13.680	280.000	15.1	6.8
14	86	F	12	38.3	15.890	243.000	13.2	11.5
15	78	F	10.6	32.9	17.010	346.000	17.6	9.55
16	89	F	9.4	30.4	16.500	189.000	11.7	7.38

M, Male; F, Female; Hb, Hemoglobin (g/dL); Htc, Hematocrit (g/dL); WBC, white blood cell count (cells/mm^3); Platelet, Platelet count (cells/mm^3); INR, international normalized ratio; CRP, C-reactive protein (mg/L).

Table 4. Radiologic Findings, Treatment, Hospital Stay and Mortality in Patients with Spontaneous Intramural Hematoma on Admission (n = 16, 100%)

Patient No.	Radiological findings	Treatment	Hospital stay (day)	Mortality
1	X-ray: Air-fluid levels; US: Mural wall thickening of the small bowel? mesenteric ischemia? CT: Diffuse jejunal wall thickening	Conservative	16	+
2	X-ray: Air-fluid levels; US: Multisegmental jejunal wall thickening, İBS?; CT: Intramural hematoma of jejunum	Conservative	8	—
3	X-ray: Normal; US: Normal; CT: Proximal ileal and jejunal wall thickening	Conservative	3	—
4	X-ray: Air-fluid levels; US: Minimal intra-abdominal fluid; CT: Segmental jejunum wall thickening, intra-abdominal fluid	Conservative	10	—
5	X-ray: Air-fluid levels; US: Severe intra-abdominal fluid, mesenteric ischemia?; CT: Severe intra-abdominal fluid, all small bowel wall thickening, intramural hematoma? mesenteric ischemia?	Surgery (diagnostic laparoscopy + drainage)	12	—
6	X-ray: Normal; US: Normal; CT: Jejunal and proximal ileal wall thickening	Conservative	9	—
7	X-ray: Air-fluid levels; US: Jejunal wall thickening; CT: Segmental jejunal wall thickening and moderate intra-abdominal fluid	Conservative	7	—
8	X-ray: Air-fluid levels; US: Severe intra-abdominal fluid, mesenteric ischemia?; CT: Severe intra-abdominal fluid, all small bowel wall thickening, intramural hematoma? mesenteric ischemia? IBS?	Surgery (diagnostic laparoscopy + drainage)	17	+
9	X-ray: Air-fluid levels; US: Multisegmental jejunal wall thickening, İBS?; T: Segmental jejunal wall thickening and moderate intra-abdominal fluid	Conservative	10	—
10	X-ray: Air-fluid levels' US: Mural wall thickening of the small bowel? mesenteric ischemia?; CT: Diffuse jejunal wall thickening	Conservative	12	—
11	X-ray: Normal; US: Normal; CT: Segmental jejunal wall thickening	Conservative	8	—
12	X-ray: Air-fluid levels; US: Jejunal wall thickening; CT: Diffuse jejunal wall thickening	Conservative	7	—
13	X-ray: Air-fluid levels; US: Normal; CT: Intramural hematoma of jejunum	Conservative	10	—
14	X-ray: Normal; US: Minimal intra-abdominal fluid; CT: Segmental jejunal wall thickening and minimal intra-abdominal fluid	Conservative	11	—
15	X-ray: Air-fluid levels; US: Minimal intra-abdominal fluid; CT: Segmental jejunal wall thickening and moderate intra-abdominal fluid	Conservative	9	—
16	X-ray: Air-fluid levels; US: Mural wall thickening of the small bowel? mesenteric ischemia?; CT: Severe intra-abdominal fluid, all small bowel wall thickening, mesenteric ischemia?	Conservative	15	—

US, Ultrasonography; CT, Computed tomography; IBS, Inflammatory bowel syndrome.

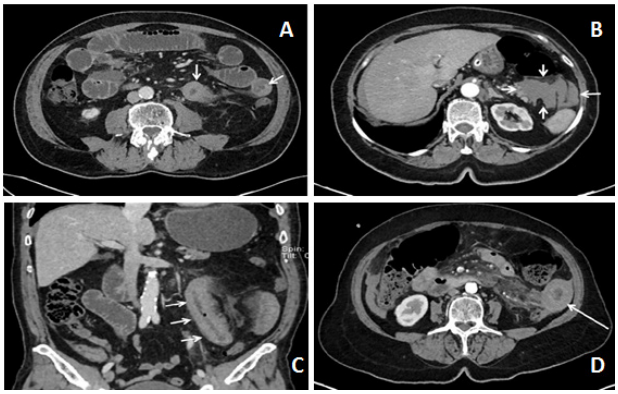

Figure 1. Diffuse Hyperdense Thickening in Jejunal Wall, Indicating Intramural Hemorrhage, Luminal Narrowing, Obstructive Dilatation in Proximal Bowel Loops in Axial (A-B) and Coronal (C) Planes (White Arrows). (D) Circumferential Hemoperitoneum (Arrows).

medical treatment and two patients (12%) underwent surgery. Surgical treatment was opted for due to the presence of the signs of acute abdomen at the time of the admission in one patient and due to the development of the signs of acute abdomen on the second day of medical treatment in another patient. In these cases, there was diffuse intra-abdominal hemorrhagic fluid. Therefore, the hematoma was drained and the peritoneal cavity was washed out. Resection of any bowel segment was not required in either case, since there was no necrosis or perforation in the small bowel (Figure 2).

During the hospitalization period, a total of two patients (12%), including one who underwent surgery and another who received medical treatment, died due to myocardial infarction. The mean duration of hospitalization was 10.25 ± 3.6 days (range: 3–17 days). Two patients died and two patients were lost to follow-up. During the mean 56 months (range: 4–72 months) of follow-up, out of the remaining 12 patients, two (17%) had a relapse of IHSB and another two (17%) died due to causes not related to IHSB.

Discussion

Intramural hematomas usually occur due to blunt trauma or hematological disorders, especially in children and the duodenum is usually affected.[4] Spontaneous intramural hematoma developing as a complication of anticoagulation therapy is very rare and it is directly related to an uncontrolled increase in INR levels.[10] The incidence of IHSB among patients receiving anticoagulation therapy has been reported at 1/2500.[11] Due to its lower incidence, the previous papers in the literature addressing this clinical entity are mostly case reports.

Recently, the incidence of IHSB seems to be increasing. The probable cause of this situation is assumed to be widespread use of advanced diagnostic methods such as CT and increased use of OAC therapy. The incidence is comparatively higher in males and in patients aged 69 to

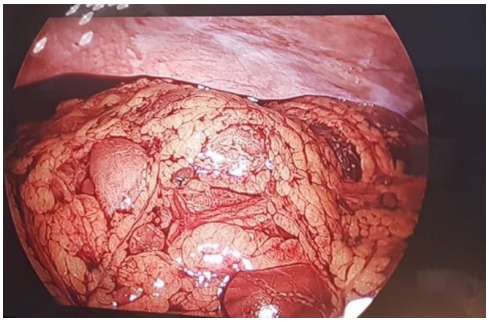

Figure 2. Diagnostic Laparoscopy. Hematoma in the intestinal wall and hemoperitoneum are seen.

76 years.[12] The majority of our patients were women (n = 10, 62%) and their mean age was 77.5 ± 8.4 years (range: 65–95 years). Eight patients (50%) were diagnosed in the last three years.

Totally, 85% of spontaneous intramural hematomas caused by anticoagulation therapy in the gastrointestinal tract are located in the small bowel. The jejunum is the most commonly affected part. These hematomas may progress to the colon or stomach. There are some hypotheses claiming that teniae coli prevent colonic progression.[13] All of our patients had intramural hematomas in the jejunum and five patients also had hematomas in the ileum. None of our patients had progression of hematoma to the colon or stomach.

The most common symptoms in patients who receive long-term anticoagulation therapy are mild or severe abdominal pain, vomiting and weakness, the severity of which may vary depending on conditions such as intestinal obstruction and acute abdomen.[13,14] Intra-abdominal/gastrointestinal bleeding, perforation or necrosis may accompany IHSB. In this case, the patient may develop peritonitis, hematemesis, melena, rectal bleeding and hemorrhagic shock due to massive blood loss.[15] The average time from the onset of symptoms to hospital admission is 2.5 days. The duration of receiving anticoagulation therapy at the time of admission has been reported at 25.4 months on average.[15]

All of our patients were on long-term anticoagulation therapy and suffering from abdominal pain at the time of hospital admission. In addition to the abdominal pain, other accompanying complaints including vomiting, weakness, anorexia, hematochezia and constipation were mentioned. Two patients (12%) also had peritonitis due to intra-abdominal hemorrhage in small quantities.

Laboratory tests usually reveal increased levels of prothrombin time (PT), activated partial thromboplastin time (aPTT), and INR due to anticoagulant therapy as well as decreased levels of hemoglobin due to bleeding.[16] Bleeding does not cause any significant deterioration in most patients, since hemorrhage is usually in small quantities. The INR value of all our patients were above

the normal range. Two of the patients (12%) had severe anemia. While all of the patients were detected to have increased CRP, 15 patients had leukocytosis (94%). Other blood parameters were within normal limits.

Abdominal radiographs may show air-fluid levels, but it is impossible to make a definitive diagnosis on this basis. In the past, barium X-ray was used for diagnosis but it was not reliable. Submucosal thickening of small bowel wall can be detected by US. However, this image is not specific to IHSB and can also be seen in some diseases such as inflammatory bowel disease and mesenteric ischemia.[17,18]

Computed tomography scan may be considered as the gold standard for the diagnosis of IHSB. Intramural hematomas may often be detected without contrast-enhanced CT scan or multidetector CT.[19,20] Some authors have claimed that contrast-enhanced CT alone may mask the presence of intramural hemorrhage.[15] In fact, the most reliable diagnosis is a combination of US and CT which can show the exact pathology in all patients.[16,19] Wall thickening on CT may also be found in other pathologies such as malignancy, inflammatory disease and ischemic bowel disease. However, complete normalization of the imaging findings usually occurs within two months after the onset of symptoms.

Endoscopy does not have any advantage over US or CT for diagnosis. Besides, it is an invasive procedure, so it is not commonly used as a diagnostic method. Still, it can be used for treatment of patients with duodenal hematomas.[21]

The patients with IHSB should be primarily followed up with medical treatment unless there are findings of peritonitis. First, anticoagulant treatments and oral food intake should be discontinued, stomach decompression should be maintained with a nasogastric tube, and FFP and vitamin K should be administered. RBC transfusion should be administered in patients with anemia. Symptomatic remission and recovery usually occurs within 4–6 days with conservative treatment.[16,19,22] Dissolution of hematoma generally takes two months at most.[13]

Surgical management should still be considered in cases where intestinal ischemia, perforation, peritonitis, intra-abdominal hemorrhage and refractory gastrointestinal blockages persist.[16,19,22] In our study, thirteen patients (81.2%) were successfully treated conservatively while one patient (6.2%) died during hospital stay. The other two patients (12.5%) underwent diagnostic laparoscopy and drainage procedure due to the exacerbating symptoms and signs of peritoneal irritation.

This study has some limitations such as small patient population and its retrospective nature. In addition, review period of our series is 17 years which is too long for establishing a standard approach to these cases. IHSB is a rare disease and the number of patients in published series in the literature is limited. Multi-center prospective studies with adequate sample size are required to determine the ideal approach to IHSB.

Anticoagulant therapy has been used very often and the incidence of IHSB is also increasing as a result. IHSB should be considered in every patient presenting with abdominal complaints and an increased INR value; the diagnosis should be confirmed by abdominal US and CT scan, if possible. Prompt diagnosis and appropriate medical treatment will preclude unnecessary surgical interventions.

Authors' Contribution
All authors contributed equally to this manuscript.

Conflict of Interest Disclosures
All of the authors declare that there are no conflicts of interest in connection with this paper.

Ethical Statement
Ethics committee approval was received for this study from the Ethics Committee of Izmir Katip Celebi University Ataturk Training and Research Hospital.

Informed Consent
Written informed consent was obtained from the patients / relatives of patients who participated in this study.

Financial Disclosure
All of the authors declare that there is no financial disclosure in connection with this paper.

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