Coagulation Disorders: Manifestations in the Gastrointestinal Tract

Wolfgang Fischbach^a Thomas Germer^b Florian Langer^c Joachim Mössner^d

^aInnere Medizin und Gastroenterologie Aschaffenburg, Aschaffenburg, Germany; ^bKlinik für Allgemein-, Viszeral-, Transplantations-, Gefäß- und Kinderchirurgie, Universitätsklinikum Würzburg, Würzburg, Germany;

^cII. Medizinische Klinik und Poliklinik, Zentrum für Onkologie, Universitäres Cancer Center Hamburg (UCCH), Hamburg, Germany; ^dMedizinische Fakultät, Universität Leipzig, Leipzig, Germany

Question 1: Acute mesenteric ischemia (AMI) is considered an acute life-threatening event with the need of emergency treatment. What are the main clinical signs of AMI, and which diagnostics do you need to establish the diagnosis?

Germer: Most patients usually present with abdominal pain of sudden onset. The acute abdominal pain can be accompanied by further clinical symptoms such as nausea and forced bowel emptying (vomiting and diarrhea). The location of pain can vary, but when ischemia progresses to infarction, pain becomes diffuse. In this stage of disease, fever, bloody diarrhea, and shock symptoms can occur. The early phase of acute mesenteric ischemia is often characterized by a discrepancy between the severity of abdominal pain and minimal findings on physical examination. The initial acute phase is followed by mild improvement before abdominal pain gets again worse due to the complication of AMI (infarction, perforation, peritonitis, etc.).

The most sensitive and specific test for the detection of AMI is computed tomography angiogram, also known as biphasic multidetector computed tomography, with a sensitivity of 85–98% and a specificity of 91–100%. There is no sensitive and specific laboratory test for early detection of AMI that has yet entered routine clinical practice. However, even if abdominal CT scan cannot detect radiological signs of AMI, surgical exploration should be

strongly considered if a patient's history and pre-existing health conditions still make AMI likely and other differential diagnostics can be excluded or cannot explain acute abdominal pain [1–3].

Langer: In cases of AMI not related to atrial fibrillation, overt malignancy or other evident causes, rare types of thrombophilia should be considered. These include the antiphospholipid syndrome, JAK2^{V617F}-positive myeloproliferative neoplasias and paroxysmal nocturnal hemoglobinuria. For some of these disorders, specific treatments are available, and their diagnosis is thus likely to change the long-term management of the patient.

Mössner: Patients present in the emergency department with so called “acute abdomen.” They may have had acute abdominal pain followed by a short period of less pain, which increases continuously in intensity. Unfortunately, there are no reliable laboratory parameters, such as lactate or fatty acid-binding protein, to enable an early diagnosis and to exclude other causes of acute abdomen. Thus, most patients with acute abdomen receive contrast-enhanced abdominal computer tomography. Due to the easy availability, the indication for an angio-CT of the abdomen in patients with abdominal pain is often made too uncritically. Unnecessary exposure to radiation with the secondary risk of cancer is a rising problem. On the other hand, the diagnosis of AMI is often made too late.

Question 2: Which other mesenteric vascular disease has to be differentiated from AMI, and how can you do that?

Germer: Embolism is mainly responsible for acute mesenteric ischemia (approx. 50%); however, mesenteric ischemia can also be caused by thrombosis and stenosis that are associated with systemic atherosclerosis. Further reasons for mesenteric ischemia are mesenteric venous thrombosis (approx. 5–10%) and non-occlusive mesenteric ischemia. Mesenteric venous thrombosis is usually seen in patients with hypercoagulability resulting from either inherited disorders (factor V Leiden, etc.) or acquired thrombophilia due to malignancies, inflammation, or hematologic disorders. Non-occlusive mesenteric ischemia (approx. 20%) occurs mainly in severely ill patients due to circulatory failure and vasoconstriction of the mesenteric vessels.

A rarity is the median arcuate ligament syndrome, where the median arcuate ligament is located slightly inferior to its normal location. This congenital abnormality results in compression of the celiac artery against the crux of the diaphragm with limitation of the blood flow during expiration. During inspiration, the ligament moves cranially, and the blood flow improves [2].

Patients' history as well as computed tomography angiogram are helpful to distinguish the different disease entities.

Mössner: Some patients complain about pain during and after eating due to mesenteric ischemia, so-called abdominal angina. In these cases, patients do not develop ischemic necrosis of the gut. An aneurysm of the abdominal aorta may cause abdominal pain and back pain. Rupture of an aneurysm of the splenic artery due to chronic pancreatitis may be life-threatening. Bleeding may be stopped by angiographic interventional coiling. Portal hypertension; e.g., due to liver cirrhosis, may cause a retention of the blood flow in the mesenteric veins and dilation of the mesenteric arteries. This maldistribution of the circulation is the cause of hepatorenal syndrome.

Question 3: Platelet inhibitors and anticoagulants are widely used drugs offering clear cardiovascular benefits in a group of patients who are candidates for colorectal cancer screening due to their age. How do you advise a patient on antiaggregation and/or anticoagulation asking for colorectal cancer screening?

Germer: Depending on the individual risk factors of the patient and kind of intervention (screening colonoscopy, colonoscopy with intervention), medication should be interrupted. Here, it is helpful to follow international guidelines and recommendations [4].

Mössner: Colorectal cancer screening is offered to individuals at an age >50 years. There are two options: fecal immunological stool test or screening colonoscopy (starting at the age of 50 and 55 years for males and females, respectively). This is, indeed, at an age where cardiovascular diseases and their therapy or medical prevention become more and more frequent. Thus, doctors often face the clinical situation of a colorectal screening procedure in individuals taking antiplatelets or anticoagulants. Several options have to be considered in this context. If colonoscopy is the preferred screening tool and dual platelet inhibition or anticoagulation is temporally restricted, the procedure can be postponed for a certain period; i.e., 6 months. In case of colonoscopy after a positive stool test, an individual approach is needed as shown in the article by Fischbach [5] in this issue. Those who favor fecal immunological stool test stool testing as a screening method can directly proceed to do so irrespective of antiplatelet therapy or anticoagulation.

In routine screening colonoscopy in patients without family history of colon cancer, one will find pathologies in about 10% of the cases. Thus, in 90%, colonoscopy does not lead to therapeutic consequences and can be safely performed even in patients treated by anticoagulants such as warfarin or phenprocoumon. In therapeutic consequences, which do not allow antiplatelets or anticoagulation, the patient has to tolerate the discomfort of a repeated bowel cleansing.

Question 4: Which therapeutic options can be offered to a patient in case of major gastrointestinal bleeding under antiaggregation and/or anticoagulation?

Germer: Therapeutic options depend on the severity and location of bleeding. Furthermore, the indication for platelet inhibition and/or anticoagulation therapy has to be reconsidered and may be stopped, or the type of medication has to be changed, respectively. Today, endoscopic approaches are the first step for the treatment of gastrointestinal bleeding. However, surgery should be involved early to ensure adequate surgical therapy if the endoscopic approach fails.

Langer: In cases of direct oral anticoagulants (DOACs), interruption of oral anticoagulation is of utmost importance, because the half-life of DOACs is comparatively short. If bleeding persists or if the severity of bleeding requires immediate reversal of the anticoagulant activity, a specific antidote (idarucizumab) is available for the direct oral thrombin inhibitor dabigatran. In addition, andexanet alfa has been approved for the treatment of acute life-threatening or uncontrollable bleeding in patients taking rivaroxaban or apixaban. In cases of couma-

rin derivatives, such as warfarin or phenprocoumon, substitution of vitamin K and prothrombin complex concentrate is the treatment of choice. Prothrombin complex concentrate might also be an option in DOAC-related bleeding, if no specific antidote is available. Protamine can be used to reverse the anticoagulant activity of unfractionated heparin, but its efficacy in patients receiving low-molecular-weight heparin (LMWH) is less clear. Antifibrinolytics such as tranexamic acid should be considered as an adjunct hemostypticum, especially in cases of diffuse mucosal hemorrhage. Transfusion of platelet concentrates is the “ultima ratio” in severely bleeding patients taking antiplatelet agents in whom administration of desmopressin (DDAVP) is either ineffective or not a therapeutic option because of contraindications.

Mössner: The wide range of therapeutic options in patients with upper or lower gastrointestinal bleeding does not really differ, whether the patient receives anticoagulants or not. A bleeding artery of a gastroduodenal ulcer will be treated endoscopically by clipping and injection of epinephrine followed by intravenous infusion of a proton pump inhibitor (PPI). The main challenge remains prevention of rebleeding. Thus, whenever possible, one will stop therapy with antiplatelets until the lesion has healed. In patients who need antiplatelet drugs again; i.e., for secondary prevention of cardiac infarction, one will prescribe a continuous therapy with PPIs after an event of upper gastrointestinal bleeding. In cases of lower gastrointestinal bleeding, the situation may be more differentiated; the risk of rebleeding is depending on its primary cause. There are no drugs available for “protection” of the lower gastrointestinal tract.

Question 5: Are there any preventive strategies avoiding gastrointestinal bleeding under platelet inhibition or anticoagulation?

Germer: The evidence about prevention strategies avoiding gastrointestinal bleeding under platelet inhibition and anticoagulation is weak. However, some international guidelines recommend adding a proton-pump inhibitor if acetylsalicylic acid is used [6].

Langer: Concomitant antiplatelet and anticoagulant therapy should be avoided whenever possible because the bleeding risk is significantly increased in cases of dual or triple antithrombotic therapy. For instance, in most patients with atrial fibrillation and chronic coronary syndrome receiving effective oral anticoagulation, platelet inhibitors can be omitted. Strictly adhering to DOAC dose adjustments according to the summaries of product characteristics is another important issue. Non-steroidal anti-inflammatory drugs increase the risk for gastrointestinal bleeding and should thus be avoided in patients on oral anticoagulation.

Mössner: The majority of gastrointestinal bleedings arise from gastroduodenal ulcers. Comedication of a PPI can effectively decrease the bleeding risk. Over and beyond this, testing for *Helicobacter pylori* infection and consequent eradication therapy may be an option. We do know that antiaggregation/anticoagulation and *H. pylori* infection are co-risk factors. By eliminating one factor, the bleeding risk can be reduced.

There are studies from Hongkong showing that *H. pylori* eradication may be sufficient when gastroduodenal bleeding happened under therapy with ASS 100 mg/day. Substitution of ASS by clopidogrel does not decrease the risk of rebleeding. In gastroduodenal bleeding due to non-steroidal anti-inflammatory drugs, *H. pylori* eradication alone does not decrease the risk of rebleeding. Thus, the indication for a continuous therapy with PPIs is usually made very generously.

Question 6: Is paraneoplastic thromboembolism a common problem in oncology? Which patients should receive medical prophylaxis of cancer-associated venous thromboembolism (VTE), and how do you realize that?

Germer: Several studies have shown that cancer patients have an increased risk for thromboembolism. Since surgical procedures are a further risk factor for thromboembolism, oncologic patients undergoing operation should receive medication for the prevention of thromboembolism. Medical and physical thrombosis prophylaxis should be adapted to individual risk factors of each patient [7, 8].

Langer: Thromboembolic complications, including venous and arterial vascular events, are the second leading cause of death in cancer outpatients and have a significant impact on the quality of life of affected patients. In certain tumor entities, such as pancreatic or stomach cancer, the incidence of VTE may be as high as 20 %, with locally advanced or metastatic tumor stages conferring a significantly higher risk than localized tumor stages. While pharmacological VTE prophylaxis with LMWH is the standard of care in all surgical cancer patients and immobile cancer patients hospitalized for an acute medical illness, the net clinical benefit in cancer patients receiving ambulatory chemotherapy is less clear. In this setting, guidelines recommend an individualized approach based on shared decision-making and validated risk assessment tools, such as the Khorana score. Pharmacological VTE prophylaxis should be considered in patients at intermediate to high risk of VTE, which includes all patients with locally advanced or metastatic pancreatic or stomach cancer, taking into account the bleeding risk. Based on two randomized controlled trials, prophylactic dosages of

rivaroxaban (CASSINI) or apixaban (AVERT) might be an alternative to LMWH in cancer outpatients, but neither of the two drugs is currently approved by the EMA for this specific indication.

Mössner: Paraneoplastic thromboembolism in oncology is not so rare. Especially in patients with small cell lung cancer and pancreatic cancer, thromboembolism may happen. The scientific evidence for routinely application of, e.g., LMWH is contradictory. Despite heparin, lethal thromboembolisms have been reported.

Conflict of Interest Statement

Wolfgang Fischbach: no conflict of interest.

Thomas Germer: no conflict of interest.

Florian Langer: has received personal fees for lectures or consultancy and/or research support from Aspen, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Chugai, CSL Behring, Daiichi Sankyo, LEO Pharma, Pfizer, Roche, Sanofi, SOBI, and Takeda.

Joachim Mössner: no conflict of interest.

Participants

Prof. Dr. med. Thomas Germer
Direktor der Klinik für Allgemein-, Viszeral-,
Transplantations-, Gefäß- und Kinderchirurgie
Universitätsklinikum Würzburg
Zentrum Operative Medizin (ZOM)
Oberdürrbacher Str. 6
97080 Würzburg, Germany
germer_c@ukw.de

Prof. Dr. med. Florian Langer
II. Medizinische Klinik und Poliklinik
Zentrum für Onkologie
Hubertus Wald Tumorzentrum –
Universitäres Cancer Center Hamburg (UCCH)
Universitätsklinikum Eppendorf
Martinistr. 52
20246 Hamburg, Germany
langer@uke.de

Prof. em. Dr. med. Joachim Mössner
Medizinische Fakultät
Universität Leipzig
Liebigstraße 27
04103 Leipzig, Germany
Joachim.Moessner@medizin.uni-leipzig.de

References

- 1 Tilsed JV, Casamassima A, Kurihara H, Mariani D, Martinez I, Pereira J, et al. ESTES guidelines: acute mesenteric ischaemia. *Eur J Trauma Emerg Surg*. 2016 Apr;42(2):253–70.
- 2 Gnanapandithan K, Feuerstadt P. Review article: mesenteric ischemia. *Curr Gastroenterol Rep*. 2020 Mar;22(4):17.
- 3 Erben Y, Oderich GS, Debus ES. Akute mesenteriale Ischämie. In: Debus ES, Gross-Fengels W, editors. *Operative und interventionelle Gefäßmedizin*. Berlin, Heidelberg: Springer Berlin Heidelberg; 2019. pp. 1–10.
- 4 Lynen Jansen P, Götz M, Trebicka J. S2k-Leitlinie Gastrointestinale Blutung. *Z Gastroenterol*. 2017 Sep;55(9):937–46.
- 5 Fischbach W. Platelet inhibition and anticoagulation in visceral interventions. *Visc Med*. DOI: 10.1159/000508580.
- 6 Gutermann IK, Niggemeier V, Zimmerli LU, Holzer BM, Battagay E, Scharl M. Gastrointestinal bleeding and anticoagulant or antiplatelet drugs: systematic search for clinical practice guidelines. *Medicine (Baltimore)*. 2015 Jan;94(1):e377.
- 7 Encke A, Haas S, Kopp I. The Prophylaxis of Venous Thromboembolism. *Dtsch Arztebl Int*. 2016 Aug;113(31-32):532–8.
- 8 Kraaijpoel N, Carrier M. How I treat cancer-associated venous thromboembolism. *Blood*. 2019 Jan;133(4):291–8.