Colite ischémique chez une patiente sous traitement avec tamoxifene et exemestane

Ischemic Colitis in a Patient Treated with Tamoxifene and Exemestane for Breast Cancer

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Mots clés

- Ischémie mésentérique
- Colite ischémique
- Infarctus mésentérique
- Ischémie multifocale
- Tamoxifène
- Exémestane

Résumé

En novembre 2011 arriva au secours de nôtre hôpital une patiente de 64 ans, présentant un tableau clinique, laboratoire et d'imagerie d'infarctus intestinal, la symptomatologie étant débuté 18 heures avant.
La patiente ne souffrait d'aucune pathologie emboligène. Antécédents : *mastectomie pour carcinome ductal de premier stade, traitement avec tamoxifène puis exémestane, parathyroïdectomie pour iperparathyroïdisme primaire, diagnose endoscopique et bioptique de colite ischémique ou maladie inflammatoire intéstinale*.
La patiente fut opérée en urgence, l'exploration révélant multiples et délimitées zones nécrotiques du grêle distal et du côlon. À cause de la rapide et progressive aggravation hémodynamique, due au choc septique, on n'a pu réaliser qu'une iléostomie terminale décompressive. Après défonctionnalisation de l'intestin ischémique et nécrotique, rééquilibration hydroélectrolytique, antibiotiques, traitement de l'acidose métabolique, il était devenu possible réaliser un second look chirurgical pour exclure la progression de l'ischémie et faire une résection iléocolique jusqu'au côlon gauche, avec sigmoïde occlus et iléostomie terminale. Trois mois et demi après la continuité intestinale a été rétablie par anastomose iléosigmoïdienne non protégée, résultant en rapide guérison.
En considérant l'absence de maladie emboligène et la multifocalité des infarctus, la cause était vraisemblablement l'occlusion thrombotique de artères collatérales de petit et moyen diamètre de l'artère mésentérique supérieure. L'étiologie vasculitique avait été exclu par l'anatomopathologie et par l'absence de manifestations auto-immunes soit cliniques soit de laboratoire.
Nous avons donc formulé l'hypothèse étiologique de sténose artérielle thrombotique due au traitement avec tamoxifène (pendant 3.5 ans), déclenchée par le changement thérapeutique avec exémestane (8 mois avant). Il est bien connu que ces médicaments provoquent une augmentation du risque thromboembolique, mais référée uniquement à l'ischémie cérébrovasculaire et cardiaque. Il n'a été signalé en littérature jusqu'à présent aucun cas d'ischémie mésentérique liée à ces médicaments.

Keywords

- Ischemic colitis
- Mesenteric ischemia
- Mesenteric infarct
- Mesenteric infarction
- Multifocal ischemia
- Patchy ischemia
- Tamoxifene
- Exemestane

Abstract

In November 2011 a 64 years old woman came to our emergency room, presenting clinical, blood and consistent imaging features with intestinal infarction, the symptoms having started 18 hours before.
The patient did not show any emboligen disease. In her medical history: *mastectomy for an early stage breast cancer, treatment with tamoxifen then exemestane, right hip replacement, endoscopical and bioptic diagnosis of ischemic colitis or inflammatory bowel disease.*
The patient underwent an emergent laparotomy, which revealed multiple and confined necrotic patches in her terminal ileum and colon. Because of fast and progressive hemodynamic worsening, due to onset of septic shock, only a diverting ileostomy could be performed. After defunctioning ischemic and necrotic bowel, restoring intravascular volume, giving wide spectrum antibiotics, correcting metabolic acidosis and having reached a stable hemodynamic balance, it became possible to carry out the second surgical look. Extension of ischemia could be excluded and an ileocolic resection, including the descending colon, was performed, leaving the sutured sigmoid stump in the pelvis and the ileostomy previously done. Three and a half months later bowel transit has been restored by an ileum-sigmoid anastomosis, followed by a fast recovery.
Because of absence of emboligen diseases and considering the patchy necrotic lesions, the cause is likely to be a thromboembolic occlusion of medium and small arterial branches of the superior and inferior mesenteric arteries. The vasculitic etiology has been excluded by pathological findings, lack of clinical symptom and by blood immunological tests.
Hence we hypothesized a thrombotic stenosis, due to the long lasting treatment with tamoxifen (3.5 years), critically deteriorated by the therapeutical switch with exemestane (8 months before), as the etiologic factors.
It is well known indeed as those drugs can rise the thromboembolic risk, but it is referred only to cerebrovascular and cardiac ischemia. Until the date, there are no reports about mesenteric ischemia related to neither tamoxifen nor exemestane.

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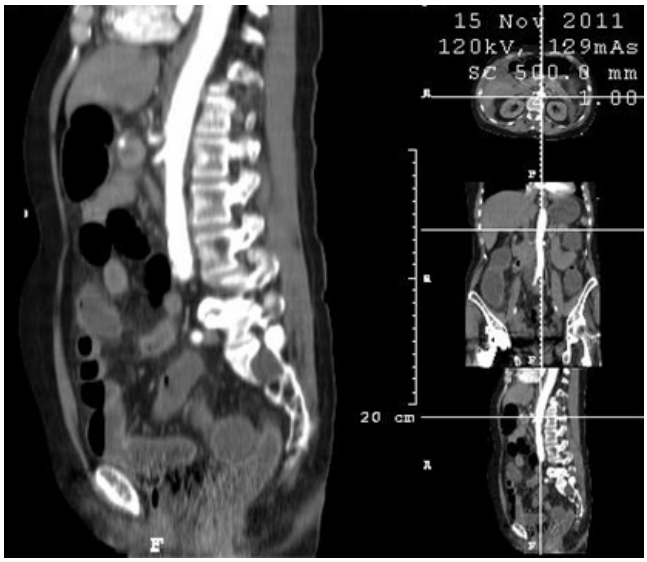

Figure 1 - CT scan: SMA with normal flow at sagittal view.

The acute abdomen due to bowel infarction often presents considerable diagnostic issues. Elderly, embolic diseases, such as atrial fibrillation, previous embolism even elsewhere (brain, lung, and lower limbs) may suggest the diagnosis, as well as systemic atherosclerotic disease, with previous thromboembolism, clinical suspicion of *volvolus*, and clinical history of *vasculitis*.
In a patient not that old, without any embolic cardiac disease, any previous embolic arterial obstruction, any atherosclerotic sign or symptom, any immune system disorder and presenting with a completely soft abdomen, this severe disease can represent a real diagnostic challenge.
Moreover the patchy aspect of the necrotic lesions was completely unexpected at the first surgical approach.
Possible causes of such a multifocal ileocolic necrosis are discussed, referring to anatomical extension of mesenteric ischemia and to multifocal ischemia related to *vasculitis*, and the medical, endovascular and surgical therapeutic options are presented, with particular mention to the opportunity to carry out a second surgical look.
Since the patient had been in adjuvant treatment with tamoxifen, then switched to exemestane, because of a breast cancer, the ischemic adverse effects of those drugs have been examined. Among them, however, the mesenteric ischemia had never been reported up to the date.

Observation

In November 2011 a 64 years old woman came to our observation in the emergency room, because of a severe and sudden 18 hours lasting pain to the whole abdomen, with bloody diarrhea and food vomiting.
In her clinical history: appendectomy at age 21, right hip replacement for traumatic fracture at age 57, transvaginal hysterectomy for myoma at age 60.
When she was 59, she underwent a left mastectomy for a ductal carcinoma in Ist stage, then she was given tamoxifen for 3 and half years as adjuvant hormonal treatment. At age 63, in march 2011, 8 months before she came to our emergency room, a switch of hormonal treatment to exemestane was carried out.
One month later, in April 2011, the patient referred to the emergency room of another hospital, because of abdominal pain and rectal bleeding. At the complete colonoscopy a stricture was observed in the colon 60 cm above the anal verge. Biopsies showed a pattern consistent with either ischemic colitis or inflammatory bowel disease (IBD). Since then she was on treatment with mesalazine and ciprofloxacine.
In June 2011 she referred to the emergency room of a different hospital for abdominal pain and the ongoing treatment was confirmed.
At home therapy: *she was on calcium 0.50 µg 1 tablet, exemestane 1 tablet, calcitriol 1 tablet every other day, sulfasalazine 800 mg 1 tablet thrice daily.*
When she arrived to our emergency room her hemodynamic conditions were stable, but her face looked really suffering with cool pale skin and marbling skin at the lower limbs.
The abdomen was distended, painful in all quadrants, without peritoneal rebound sign. Bowel movement was reduced but present.
Blood tests showed: *neutrophilic leucocytosis (WBC 25.610/µl, N 84%), early kidney failure (creatinine 2.2 mg/dl), bowel cytolysis (CK 237 U/l, LDH 531 U/l), clotting disorders (d-dimer 13 µg/ml), and metabolic acidosis (lactate 68.7 mg/dl, pCO2 22 mmHg, HCO3- 11.3 mmol/l, base excess -15.2 mmol/l).*
The plain X-rays of the abdomen reported marked bowel distension with air-fluid levels.
Waiting for the computed tomography (CT scan), her general conditions quickly worsened. *A severe hypotension (80/50 mmHg), peritoneal rebound sign and discharge of purple liquid stools, with dark spotting, onset at once.*
The abdomen CT scan showed thickened walls of coeliac trunk, such as atherosclerotic disease, and a normal superior mesenteric artery (SMA) (fig01), considerable hypodense free fluid in the whole abdomen, biliary sludge in the gallbladder, bowel loops distended and air-fluid levels in the pelvis.
Therefore the patient underwent an urgent surgery because of the clinical suspicion of bowel infarction, but at laparotomy the kind of ischemia encountered was a completely unexpected one: there were many and big necrotic patches from the terminal ileum to the left colon included (fig02).
Because of the extension and the amount of those necrotic lesions and due to her unstable hemodynamic, nothing else could be performed than an end ileostomy, to detend the bowel and divert the stools. Any further decision had to be postponed to a second surgical look.
The patient has been treated with amines since before the operation and then was transferred to the intensive care unit for the early postoperative period.
She was treated with wide spectrum antibiotics. After the metabolic acidosis and hypovolemia were corrected and the cardiac and renal function had improved, the patient could undergo the second surgical look.
The necrosis involved the same areas already detected in the first intervention, without further extension or confluence of

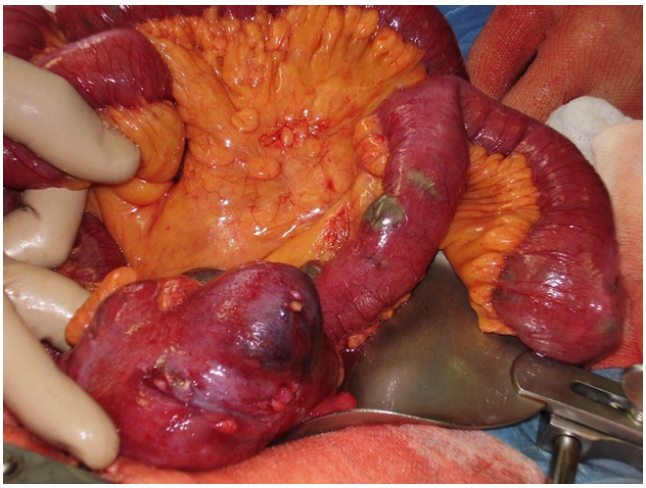
Figure 2 - Patchy necrotic lesions of ileocaecal region at first laparotomy.

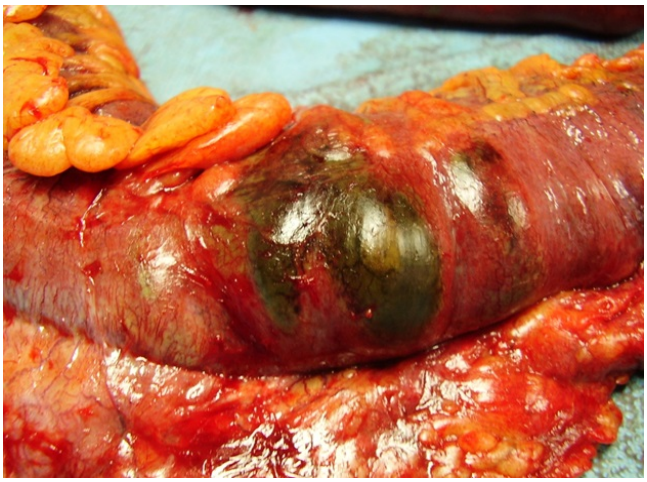
Figure 3 - Necrotic area in the colon at 2nd surgical look.

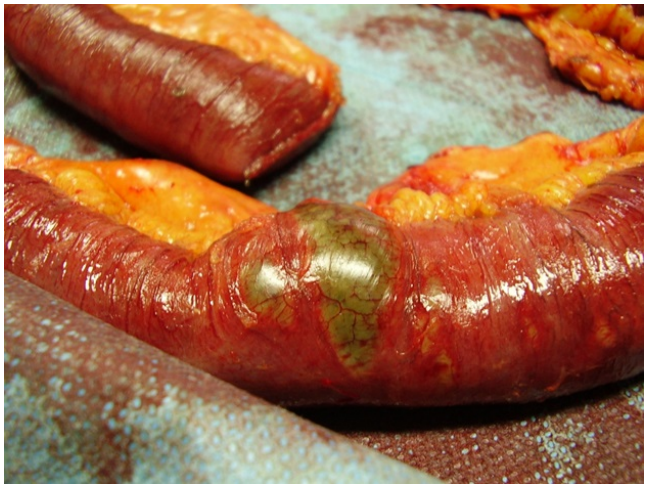
Figure 4 - Necrotic area in the terminal ileum at 2nd surgical look.

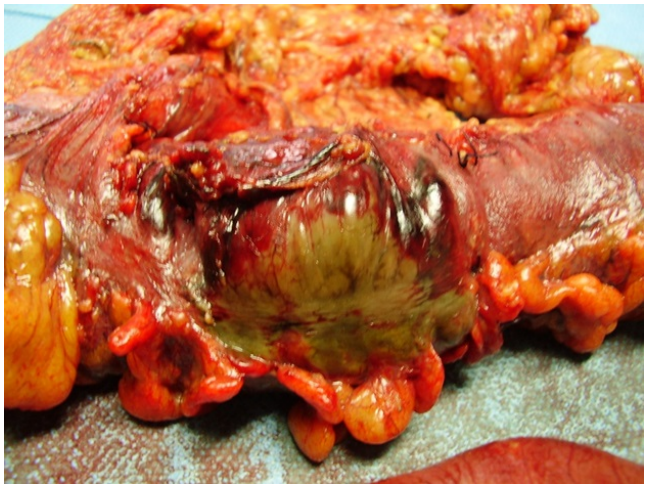
Figure 5 - Necrotic area in the transverse colon at 2nd surgical look.

the patchy lesions (fig03-05). Thus an ileocolic resection, from the terminal ileus up to the descending colon was performed (fig06). The sigmoid flexure, free of lesions, was sutured and left in the pelvis; the terminal ileostomy was left in the same place where it was previously performed.
The pathological result was: *acute ischemic ileocolitis with extended mucosal necrosis and marked congestion, reactive hyperplasia in the lymph nodes, omental tissue with hematic congestion.*


Figure 6 - Surgical specimen: terminal ileum + colon.

The following postoperative course was complicated by *hemoperitoneum*, because of an oozing bleeding in the left *hypocondrium* and because of a small laceration of the inferior splenic pole. On the postoperative day 7 the patient underwent a third surgery to achieve a complete hemostasis.
Then she suffered from a sepsis by Candida albicans, methicillin-resistent *Staphylococcus epidermidis* (MRSE), *Enterococcus faecalis* multiresistent, and she was treated with fluconazole and vancomicyne.
She was finally discharged in postoperative day 15, considering the last surgery, 34 days after she came to the emergency room.
The blood tests carried out to exclude autoimmune diseases, such as vasculitides *(ESR, CRP, CK, LDH, protein electrophoresis, urinary sediment, reuma test, cryoglobulins, ANCA, ANA, ENA, anti-ADN, C3, C4, LAC, anti-beta2 GPI IgG and IgM, anti-cardiolipine IgG e IgM, S and C coagulative proteins, APC resistance, hepatitis markers)* were all negative. Also blood coagulative tests excluded a thrombophilic disease.
After three and a half months, the patient underwent the stoma reversal, with ileo-sigmoid-anastomosis, cholecystectomy and she could be discharged on day 9 after surgery.
One and half year after the acute event, the patient is in good general status, she does not suffer from *claudicatio abdomins* nor from malabsorption syndrome *(body mass index = BMI 19.5)*.
During the first admission, treatment with exemestane had been suspended, and then she did not take any other hormonal nor chemotherapic agent. The breast cancer is in clinical and radiological remission.

Discussion

Causes of mesenteric ischemia can be etiologically classified as follows (1-7):
- Embolic 50 %
- Thrombotic 25 %
- Non-occlusive 18 %
- Mesenteric venous thrombosis 7 %

Our patient had never suffered from any emboligen disease (no arrhythmia nor cardiac valvulopathy), she had never presented in her clinical history any ischemic disease related to systemic arterial atherosclerosis (no acute myocardial infarction nor stroke nor chronic peripheral arterial occlusive disease). Seven months earlier she experienced rectal bleeding, with endoscopic diagnosis of ischemic colitis or IBD (Inflammatory Bowel Disease), but a real pattern of *claudicatio abdominis* had never been described. In the following months she went only once to the emergency room complaining about abdominal pain. She did not show hypovolemia or

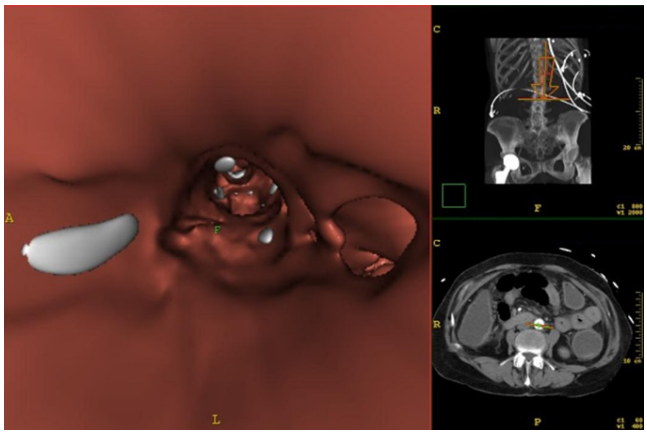

Figure 7 - CT scan, 3D reconstruction: aortic tract between AMS and AMI. Possible presence of thromboembolic fragments.

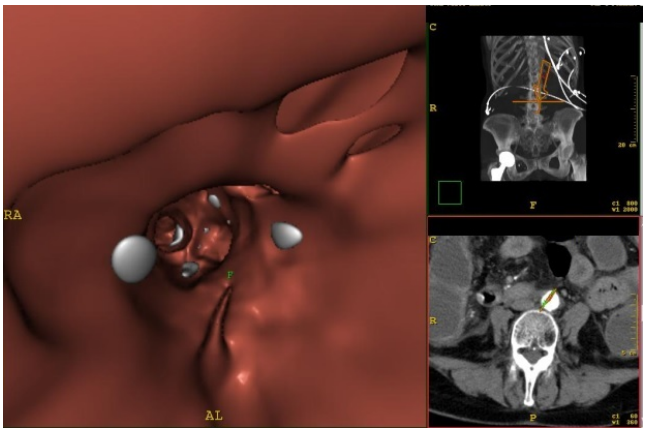

Figure 8 - CT scan, 3D reconstruction: distal aortic tract before iliac arteries. Possible presence of thromboembolic fragments.

hypotension, such as to represent the unobstructive cause of mesenteric ischemia. Last, at laparotomy small bowel and colon affected by the necrosis were far different in morphology from the bowel affected by venous obstruction infarction. Even if a mild form of chronical ischemia was present, however the acute ischemia onset quickly, probably as a result of the shortage of collateral arterial supply.

At laparotomy patchy necrosis from the distal ileum to the left colon was present. Only proximal and medial ileum, sigmoid colon and rectum were spared. This discontinuous but extended ischemia suggests that the obstruction affected the small arteries in the territory of distal SMA (ileocolic tract), right and medial colic artery and IMA. As the CT scan showed a thrombotic thickening of the celiac trunk, with a normal SMA, we then hypothesized that multiple small emboli could have been disrupted and brought to small branches of ileocolic, right colic, medial colic arteries and of IMA (fig07,08). Proximal and medial ileum can have been supplied by the patent proximal SMA, sigmoid colon and rectum could receive blood from the internal iliac artery through the rectal arterial anastomoses.

Because of the particular patchy presentation of the ischemia and the probable involvement of small arteries, we wanted to exclude a vasculitic disease as a main pathogenetic factor. It is well known indeed that many inflammatory and/or immune arterites lead to mesenteric ischemia by means of atheroma formation and promoting thromboembolic disease.

The *vasculitis* is responsible for less than 2% of cases of mesenteric ischemia (3). Among these inflammatory diseases of blood vessels, the ones acting through a thromboembolic mechanism are: systemic lupus erytematosus (LES), Wegener's granulomatosis, Behçet disease, anti-neutrophil cytoplasmic antibody (ANCA) negative systemic vasculitis (8).

Last but not least, the thromboangiitis obliterans (Büerger's disease), a not vasculitic inflammatory occlusive disease, involving medium sized or smaller vessels of extremities, rarely can be responsible for acute mesenteric ischemia. Occlusion of coeliac trunk and IMA (Inferior Mesenteric Artery) with stenosis of 70% of SMA has been reported (9).

Considering that diagnosis of vasculitis relies on clinical correlation, blood investigations and pathology, we must point out that our patient had never showed symptoms of any immunological or inflammatory disorder. The pathological findings on the resected bowel could exclude phlogistic cells, immune system cells and immune complexes or complement deposits around the vessels. Blood tests about inflammation and immune system, carried out after the patient completely recovered, resulted negative. Moreover she never smoked and arterial flow in her extremities had always been normal.

Once excluded the most frequent causes of mesenteric ischemia/infarction, the rare *vasculitic* causes and the thromboangeitis, we hypothesized that the adjuvant hormonal treatment with tamoxifen over 3 years and a half and with exemestane over the following 8 months was responsible for the atherosclerosis of medium-sized arteries in the celiac and mesenteric territory, that complicated with thromboembolic peripheral acute occlusion.

This etiopathogenetic hypothesis is substantiated by several reports in the literature about the thromboembolic toxicity of tamoxifen (10). This medication is reported to cause thromboembolic events, such as ischemic stroke more frequently than raloxifene (11,12) and then letrozole (13). This happens in spite of its beneficial effects on several cardiovascular risk factors, such as CRP, fibrinogen, LDL, thickeness of the intimal layer in the common carotid artery (14). Furthermore a rare case of myocardial infarction during the treatment with tamoxifen, due to coronary embolism in a patient with artial fibrillation, is reported (15). As patients in treatment with tamoxifen present a relative risk of 1.9 for deep venous thrombosis and a relative risk of 3 for pulmonary thromboembolism, some authors hypothesize that tamoxifen has a procoagulant effect, enhancing the formation of atrial thrombi.

Concerning the exemestane, no prospective randomized or observational study about its eventual ischemic toxicity is reported in literature. The only available data are those listed in the prescribing information: a higher incidence of cardiac ischemia versus tamoxifen (1.6% vs 0.6% respectively) and a greater number of deaths due to ischemic stroke (with ratio 6:2) are reported. The adverse effects related to the digestive tract (nausea, vomiting, abdominal pain, constipation, diarrhea) occur with a comparable frequency with exemestane and with tamoxifen. Anyway, neither mesenteric ischemia nor *infarctus* are reported for any of them (16).

Finally, surgical treatment is based on three pillars (1-4,6-7,17-19):

- Revascularization (embolectomy or thromboendarteriectomy with or without patch or bypass) if a reversible ischemia is found.
- Resection of necrotic bowel ± anastomosis ± stoma in presence of necrotic lesions.
- Second look within 24-48 hours.

Most authors agree in suggesting a surgical second look within 24-48 hours, when possibly reversible ischemia is present or, on the other hand, when a worsening is suspected (1-4,6-7,18-22).

In our patient, owing to the evidence of multiple patchy ischemic and necrotic areas, extended to a long tract of colon, a second surgical look would however have been planned in any case, in order to decide the length of the resection. At the second look indeed the absence of new necrotic lesions was verified.

The surgical revascularization did not appear indicated, being already present multiple necrotic areas and mostly because the arterial obstructions were really distally located.

Conclusions

At the time being, as no similar clinical cases have been reported in literature, ours remains an etiopathogenetic hypothesis difficult to prove, formulated excluding other causes. The diffusion of hormonal treatment with tamoxifen and exemestane in breast cancer, since they are effective not only in adjuvant treatment but also as prevention, is widely spreading everywhere.
If their atherosclerotic and thromboembolic impact on the small and medium mesenteric arteries are confirmed, they first will have to be given with special awareness to patients presenting other atherosclerotic, thrombotic or embolic risk factors, on the other hand any abdominal pain, evocative of *claudicatio abdominis* or acute bowel ischemia, will have to be taken in serious account.

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