Thrombosis of the superior mesenteric vein in association with hormonal contraceptive use.
A case report and review of the literature

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Thrombosis of the superior mesenteric vein in association with hormonal contraceptive use: a case report and review of the literature.

INTRODUCTION: *There are a number of reports in the literature which describe the association of venous thrombosis with oral contraceptives. Venous thrombosis is a rare form of mesenteric ischemia which may be lethal if not diagnosed and treated quickly. Although the non specificity of clinical signs do not always permit an early diagnosis.*
MATERIALS AND METHODS: *The patient, aged 52, with a case history characterized by alteration of the alvus with occasional emission of blood, and abdominal pain. She referred with metrorrhagia of about one year, and was being treated with Ethynylestradiol\Gestodene. A CAT scan with contrast showed the signs of thrombosis in the superior mesenteric vein. The patient underwent surgical laparotomy. On opening the peritoneum we found a large tumefaction formed of conglobate iliac loops together with intense inflammation. A resection of the tumefaction was performed "en bloc".*
DISCUSSION: *Pharmacological contraception remains in various cases as the only identified risk factor and there are reports which also censure a relationship of greater risk with increased hormonal doses and even reports of mesenteric venous thrombosis in patients taking triphasic drugs. Thus, we may state with near certainty, that a relationship between pharmacological contraceptives and mesenteric venous thrombosis exists and is probably more than a simple risk factor in contrast to that which exists for tobacco smoking and obesity.*
CONCLUSIONS: *Before the prescription of contraceptive therapy the examination of risk factors is necessary, compiled preferably by hematochemical screening to exclude haematological and/or coagulative pathologies, and not deriding the use of non-pharmalogical methods of contraception when possible. Considering the technological advancement of instrumentation (CAT scan, angiogram), even a diagnosis aimed at a suspected clinical history, starting from less invasive screening by ultrasonographic Doppler, might induce to a rapid intervention and thereby avoid sacrificing too much intestinal tissue if it is the case.*

KEY WORDS: Contraceptive therapy; Intestinal ischemia; Mesenteric venous thrombosis.

Introduction

Venous thrombosis is a condition in which a small quantity of blood clots inside a vein and adheres to its walls. As a consequence, the passage of blood through the vein is partially or completely blocked. Hypoxic phenomena attributable to various causes which compromise the blood flow may occur in the small intestine, colon, or both. Venous thrombosis is a rare form of mesenteric ischemia which may be lethal if not diagnosed and treated quickly [1] and properly . It is frequently associated with hemoglobinopathy, beta-thalassemia, antiphospholipid syndrome [2] and congenital coagulative deficits [3]. Technological progress in radiology has considerably improved physicians' ability to diagnose and treat this condition [4], although, due to the unspecific nature of the clinical signs and symptoms, it is not always possi-

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ble to formulate a diagnosis in time to avoid intestinal resection, and manage the patient with thrombololytic and anticoagulant therapy. The common symptoms of superior mesenteric vein thrombosis SMVT) are cramp-like epigastric pain, vomiting, anorexia and diarrhea [5], symptoms which do not always immediately lead to a more thorough investigation and a rapid diagnosis. Irreversible enteric damage may be prevented by early diagnosis, and less invasive techniques of direct thrombolysis (using transjugular, transfemoral, transradial and also transhepatic portal percutaneous access) [6,7]. There are a number of reports in the literature which describe the association of venous thrombosis with oral contraceptives [8-33]. Several authors maintain that interrupting the administration of contraceptives may prevent intestinal tissue damage and some even recommend suspension of the drug in the case of unknown causes of abdominal pain [9,10].

Case report

R.E., a 52-year-old female, was hospitalised in our Polyclinic with a history of diffusely radiating epigastric pain and altered bowel habits consisting of episodes of diarrhea occasionally mixed with blood and mucus . The patient had spent 10 days at another hospital where no diagnosis was reached, and, despite worsening of the symptoms, she had been discharged with antibiotic therapy. She had a family history of colon cancer. She had suffered from metrorrhagia for about one year, and was being treated with Ethynylestradiol\Gestodene (Milvane). She had smoked cigarettes (one pack for day) for about 30 years, but neither drank alcohol nor was obese. Clinical examination revealed a globular abdomen, tender in all quadrants to superficial palpation and with increased pain upon deeper palpation in the left iliac fossa. There was dullness on percussion in the left iliac fossa and left flank. The organs in the left and right hypochondrium were within normal limits and peristalsis was torpid. The patient appeared to be suffering from partial intestinal occlusion. She underwent blood tests and diagnostic imaging. The blood tests revealed hypochromatic microcytic anemia with neutrophilia and monocytosis. A standard abdominal X-ray showed air-fluid levels in all abdominal quadrants (Fig. 1).

A computed tomography (CT) scan with contrast medium showed, distended loops of small intestine with hyperemic mucosa, corresponding to a plane passing to the left of the median umbilical fold and the left paramedian umbilical fold. The venous phase images revealed a slight dishomogeneity of the perivisceral mesenteric soft tissue. Superior mesenteric vein thrombosis, extending from the origin of the vein to its confluence with the splenic vein, was diagnosed. There was a partial filling defect of the main branch of the portal vein which, however, was pervious at the hilum and in its intra-hepatic branches. The uterus was fibromatous and very much enlarged. Subsequent magnetic resonance angiogra-

Fig. 1: Standard abdominal x-ray.

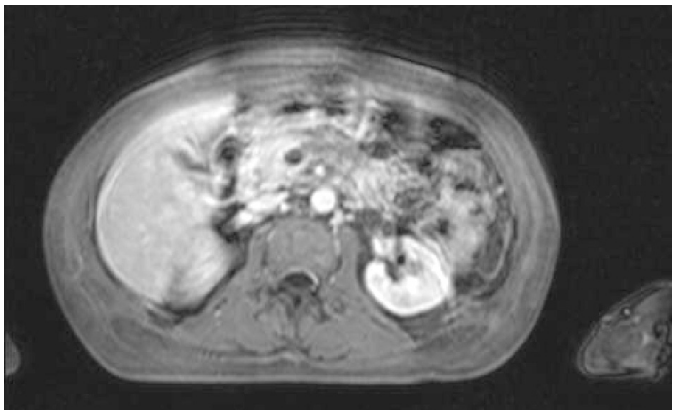

Fig. 2: MRA.

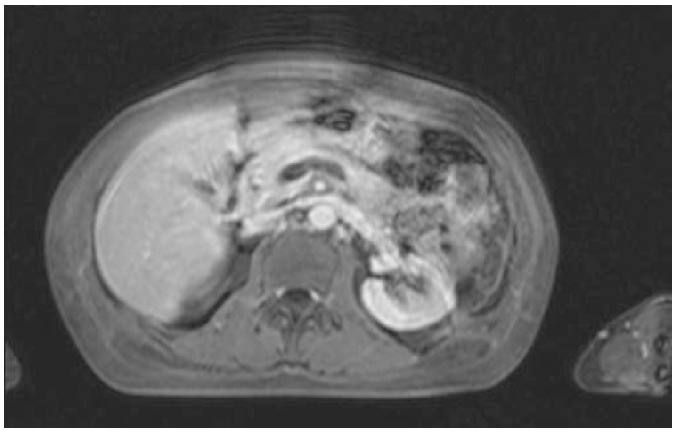

Fig. 3: MRA.

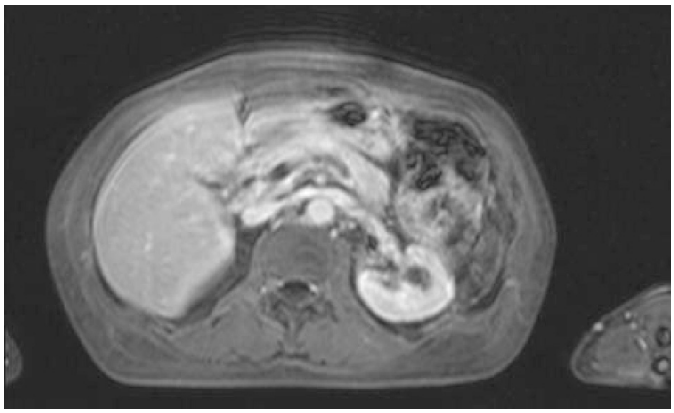

Fig. 4: MRA.

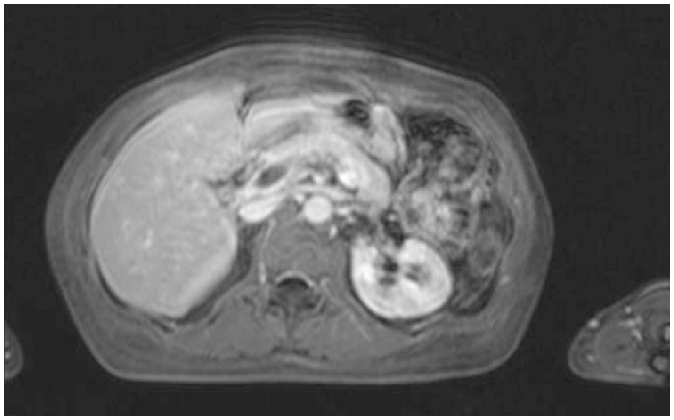

Fig. 5: MRA.

phy(MRA) revealed a regular opacification of the abdominal aorta, of the celiac trunk, of the superior mesenteric artery, of the renal arteries and of the inferior mesenteric artery. (Figgs. 2, 3, 4, 5).
This confirmed the CT scan results and showed a filling defect of the superior mesenteric vein which appeared of enlarged calibre up to the confluence with the splenic vein. There was partial thrombosis of the portal vein, which was, however, pervious at the hilum, as were the intrahepatic branches of the portal vein. The splenic vein showed regular opacification. Due to the case history and blood test results, the patient underwent surgical laparotomy. Upon opening the peritoneum more than 1000 ml of serous liquid was found, as well as a large tumefaction formed of iliac loops stuck together as a result of intense inflammation. One of the loops, hidden at the centre of the tumefaction, was perforated. An en bloc resection of the conglomerate of intestinal loops was performed, followed by isoperistaltic anastomosis with a proximate linear stapler,GIA75, (Autosuture, Hamburg, Germany), and apposition of the omentum to protect the anastomosis. The resection was performed using the LigaSure Atlas™ instrument (Tyco/Healthcare/Valleylab, Boulder, Colorado, USA), resulting in a shortened operative time with guaranteed vessel sealing (Fig. 6).

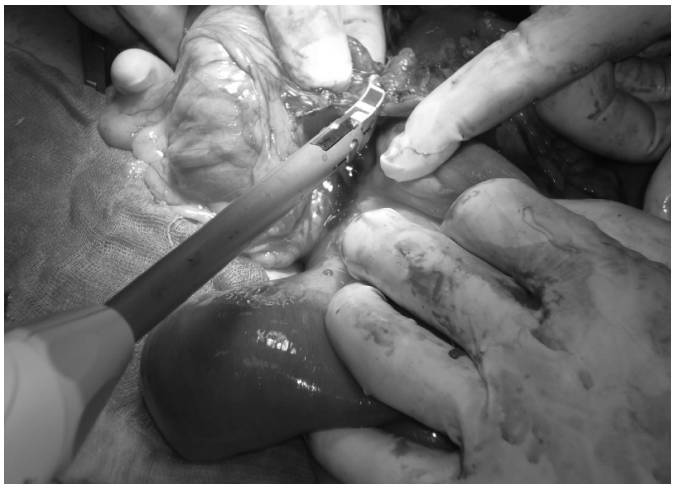

Fig. 6: Dissection by Ligasure Atlas Tyco™.

Fig. 7: Surgical specimen:resected small bowel.

The definitive histological exam showed hemorrhagic infarction with necrosis of the mucosa, and numerous areas of hemorrhagic steatonecrosis with areas of microabscesses in the perivisceral fat in which thrombosed venous trunks were also found (Fig. 7).
The patient had a smooth postoperative course. Therapy with low molecular weight heparin (LMWH), which was administered in the preoperative phase with 4000 U/I twice daily for the two days preceding surgery, was increased to 8000 U/I administered twice daily following surgery and was continued until discharge on postoperative day ten. Upon discharge the patient was prescribed LMWH, 6000 U/I twice daily, to be continued at home for two weeks. A Doppler ultrasound examination was performed 25 days after surgery and showed the total resolution of thrombosis. The patient was then sent to the gynaecology ward for a hysterectomy. Heparin therapy was continued at a lower dose.

Discussion

Superior mesenteric vein thrombosis is characterised in the preoperatively by signs and symptoms which are unspecific. As a result, diagnosis frequently takes a long time. The excellent results obtained with interventional radiology are therefore not always applicable to all cases and it is sometimes necessary, although fortunately not frequently, to resort to intestinal resection. According to some authors, mesenteric venous thrombosis should be suspected in the presence of:
1) inexplicable abdominal pain with abdominal distension, nausea, vomiting, and haematological alteration;
2) intractable ascites;
3) inexplicable hematic ascites;
4) inexplicable portal hypertension;
5) inexplicable bleeding of the superior gastrointestinal tract or progressive splenomegaly in the absence of splenic hyperfunction;
6) inexplicable paralitic intestinal occlusion, necrosis or peritonitis [35,36].
The first diagnostic step should be Doppler utrasonography. If the findings are positive, advanced imaging techniques such as a CT scan or MRA, which provide more specific detail, should be used. Whenever surgery is necessary, the administration of LMWH in the perioperative phase makes it possible to treat the cause of SMVT in safety, so that after removal of the causative stimulus, in the case reported here oral contraceptives, there is complete resolution of the thrombosis. In this particular case, the 52 year-old patient had been taking Ethynylestradiol\Gestodene (Milvane) for some time for severe uterine fibromatosis which probably should have been treated earlier with a hysterectomy. Numerous reports in the literature describe isolated cases of SMVT in association with OCP therapy, so that this association appears to be conclusive, especially due to the exclusion of other risk factors in various cases [8-34]. It must also be emphasised that use of OCPs, the most widespread contraceptive method in the world, is not the only form of contraception that increases the risk of mesenteric venous thrombosis. According to a case report published in 2003, intravaginal contraceptives were also found to be involved in the genesis of venous thrombosis [20]. Thus, we may state with near certainty, that a relationship between pharmacological contraceptives and mesenteric venous thrombosis exists and is probably more than a simple risk factor [37] in contrast to tobacco smoking and obesity. Factors which would influence the induction of thromboembolism [22] are related to:
1) modification of the state of coagulation: coagulation appears only to be modified by synthetic estrogens which would increase intravessel coagulation capacity and the number of anomalous forms of fibrinogen with slightly greater molecular weight [28, 32];
2) modifications of the vessel wall; venous walls become thinner and smooth muscle cells proliferate;

TABLE I - *Risk factors*

Hemoglobinopathy
μeta-thalassemia
Antiphospholipid Syndrome
Congenital Coagulative Deficit
Janus Kinase 2 Val617Phe mutation
Pharmacological contraceptives
Tobacco smoking
Obesity

3) an immunological role for contraceptives; from an immunological viewpoint it is possible that contraceptives lead to the production of anti-ethynylestradiol antibodies which appear as circulating immune complexes [28]. In various reports pharmacological contraception is the only identified risk factor [15,19]. There are reports which also point to an increased risk with increased hormonal doses [23] and even reports of mesenteric venous thrombosis in patients taking triphasic drugs [22,23]. It is interesting to note, that the risk of developing mesenteric venous thrombosis is reduced or disappears with the suspension of contraceptive therapy [28]. One of the risk factors which appear to be involved in the pathogenesis of mesenteric vein thrombosis, is a Val 617Phe mutation of Janus Kinase 2 (JAK2 V617F). In a study in 2008, it is noted that in patients who are carriers of essential thrombocythemia, with JAK2 V617F there is a higher incidence of venous thromboembolism than in patients without the mutation [16,17]. A review of the literature indicates that, as already mentioned, the common denominator in the majority of case reports analyzed was the use of contraceptives [8-34,37], even when taken intravaginally and not orally [20]. Table 1 shows the main risk factors involved in the pathogenesis of mesenteric vein thrombosis (Table I).
Of the cases considered in association with contraceptives, the majority required surgical intervention [8-1215,19,22,27,29-31]. Pregnancy, a harbinger of hypercoagulability and relaxation of the venous walls, is a factor that appears in several reports. In the majority of cases pregnant patients required surgery [2, 24,38]. As a consequence, we believe that physicians still have difficulties in providing an accurate diagnosis early enough for medical treatment or interventional radiolology to be useful. The case described above does not differ from the reports in the literature that we have analysed, since the patient had a thirty-year history of cigarette smoking and a one-year history of OCP therapy as risk factors. Considering that uterine fibromatosis with metrorrhagia was already present in an advanced stage, we conclude that a hysterectomy performed at the appropriate time would probably have prevented the need for the intestinal resection which the patient subsequently underwent.

Conclusions

From an analysis of the risk factors for SMVT based on appropriate diagnostic imaging examinations, these factors and the consequent diagnostic or therapeutic choices made, which represent the only form of prophylaxis possible, are purely gynaecological in nature. In addition, especially since OCP therapy is so widely used, closer examination of risk factors is necessary. Hematochemical screening should be performed to exclude coagulopathies and/or other disorders, and the use of non-pharmalogical methods of contraception whenever possible should not be derided. Considering the technological advances that have been made in diagnostic imaging (CT scan, MRA), even a diagnostic iter based on a suspicious clinical history, beginning with less invasive screening using Doppler ultrasonography, might lead to more rapid intervention and thereby avoid the loss of intestinal tissue.

Riassunto

Viene presentano un caso di ischemia intestinale da trombosi venosa mesenterica superiore, sottoposto ad intervento chirurgico di resezione di 70 cm di tenue, in una paziente in terapia ormonale estroprogestinica per fibromatosi uterina sintomatica; si espongono gli aspetti eziopatogenetici e fisiopatologici della sindrome, con revisione letteraria e le procedure diagnostiche e chirurgiche adottate nel caso. Gli Autori riconoscono l'estrema gravità dell'ischemia intestinale e del rilevante rischio di mortalità e sottolineano l'importanza di una corretta analisi dei fattori di rischio e di una diagnosi tempestiva al fine di procedere, nell'impossibilità di una risoluzione conservativa, ad un intervento chirurgico personalizzato, nella sua entità demolitiva e nel suo momento applicativo, per un pieno risultato clinico.

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