Discussion

Nicorandil is a nicotinamide ester marketed in France since the beginning of the 1990s under the trade names of Adancor® and Ikorel®. Oral mucosal ulceration related to the use of this product has been described since 1997 [6]. The first cases of anal lesions were reported in 2002 [2]. The largest series of anal lesions (24 patients) dates from 2005 [3] and, at the present time, more than 60 cases have already been published. Other digestive lesions have been described, particularly in the colon [7] and ileum [5]. The incidence today of ulceration induced by nicorandil, in any location, is estimated to be approximately 1 for 1500 prescriptions [3].

This iatrogenic anal ulceration appears in the months following the start of treatment in patients who, in general, have no particular history of digestive problems. It may occur in the anal canal, the anal margin or the peri-anal skin, and become apparent above all through pain. There may be a single or multiple instances of ulceration of varying sizes, extending and excavating progressively, even destructively. Analysis of their pathological anatomy is not specific. Other concomitant lesions, particularly in the mouth, are possible. Surgical treatment, without interrupting nicorandil administration, is ineffective. On the other hand, healing occurs within a few months of discontinuing administration [2—5].

The physiopathological mechanism of these ulcerations has not been elucidated. The hypotheses have been suggested of a vascular steal phenomenon and/or a toxic type of reaction. The effect seems to be dose-dependent since the ulcerations can sometimes heal simply by reducing the dose. It is probably the result of systemic passage since faecal excretion of nicorandil is slight, purely cutaneous lesions have been described and anal ulceration recurring after reintroducing the product in a patient who, in the meantime, had had a diverting colostomy. Whatever the mechanism, no factor encouraging the occurrence of this undesirable effect has been identified [3—5].

Conflict of interest statement

None.

References


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Chronic anemia resistant to erythropoietin in a patient treated with gemcitabine showing a hemolytic uremic syndrome (HUS)

Anémie chronique résistante à l’érythropoïétine chez un patient traité par gemcitabine révélant un syndrome hémolytique et urémique (SHU)

Hemolytic uremic syndrome (HUS) has been described for the first time by Gasser et al. in 1955 [1]. It involves several etiologies [2] with infections, connective tissue disease, some treatment (quinine, interferon, clopidogrel, etc.) and cancers. The first cases with cancer chemotherapy have been reported about 30 years ago with mitomycin C and 5-fluorouracil [1,2]. The use of gemcitabine nucleotide analog derivative from cytarabine [2,3] is rarely complicated by HUS. HUS typically results in thrombocytopenia, hemolytic anemia and renal failure [1—4]. The appearance of hypertension or worsening of figures in a patient treated with gemcitabine experienced hypertension are among the warning signs [4]. We report a case of HUS...
occurred in a hypertensive patient treated with gemcitabine for metastatic pancreatic cancer revealed an exacerbation of hypertension, anemia does not respond to erythropoietin, and renal failure.

**Observation**

A cancer of the tail of the pancreas metastatic to the liver had been found in the review of acute pancreatitis in December 2006 in a patient of 68 years. His medical history revealed an arterial hypertension known for several years, although controlled by the valsartan-hydrochlorothiazide (Cotareg®) and acebutolol (Acebutolol®) and Graves’ disease supplemented with levothyroxine (Levothyrox®).

Chemotherapy with gemcitabine (Gemzar®) was established. Cures September 1000 mg/m² weekly induction followed by 15 maintenance cycles were performed and well tolerated by the patient between December 2006 and March 2008. Each cycle consisted of three weekly treatments (j1 to j8, j15 1000 mg/m²) followed by a week of rest.

At j15 of the 15th cycle, the preoperative treatment showed a hypertensive to 170/100 mmHg and the onset of anemia in 8 g/dL normocytic clinically well tolerated. Platelets, leukocytes and renal function were normal. The haptoglobin and LDH were not measured. Erythropoietin therapy was instituted in the event of myelotoxicity of gemcitabine, and increased the dose of acebutolol. Evaluation before 16th cycle showed tumor progression with persistence of hypertension in 160/100 mmHg. The blood test before treatment was as follows: hemoglobin 6.5 g/dL, MCV 107 fl, creatinine 166 μmol/L (creatinine clearance 47 ml/mm), urea 9.7 mmol/L, haptoglobin ≤0.07 g/L, LDH 1600 IU/L, presence of 3% of schistocytes blood smear. The Coombs test was negative. White blood cells, platelets, prothrombin time, activated partial thromboplastin time, fibrinogen, folate and vitamin B12 were normal and there was no iron deficiency. There was proteinuria and hematuria low quality (a cross in urine dipstick Multistix®) urine sample. Three red blood cells were administered combined with a stop cotareg and adding a loop diuretic. The evolution was marked by a normalization of hemoglobin and blood pressure. The platelet count remained normal always. Association Xelox® had stopped after two treatments for gastrointestinal intolerance. A substitution of capecitabine for the SLV5FU2, generally better tolerated, was attempted. The hemolytic anemia syndrome does not recur with a decrease in 4 months. If the patient has been reported to the pharmacovigilance department of the University Hospital of Dijon.

**Discussion**

Gemcitabine is the standard medical treatment of pancreatic cancer [3]. It is usually well tolerated [2]. Its main side effects were hematologic, pulmonary and gastrointestinal [4]. HUS is a rare complication [1,2]. The incidence of this syndrome is estimated between 0.015 and 2.2% in different studies [1,4]. Thrombocytopenia, kidney failure and anemia are the major signs [1—3]. The hemolytic anemia is type as evidenced by the collapse of haptoglobin and elevation of LDH [4]. Renal failure, variable degrees [4] is the reflection of a micro-angiopathy thrombotic histological diagnosis [2,4] although renal biopsy is not essential for diagnosis [4]. The Gemzar is not nephrotoxic but the whole kidney in a patient with gemcitabine should be investigated in the HUS [4]. An inaugural hypertensive or exacerbation of preexisting hypertension may be of warning signs [1,4]. The diagnosis was suspected in our patient faced with worsening of anemia treated by erythropoietin, in the absence of iron deficiency, and exacerbation of arterial hypertension. The mechanism of onset of HUS is poorly understood [2,4]. The origin of HUS does not appear to be linked to the stage nor progression of the disease, nor to the duration of exposure or cumulative dose received [1,4,5]: indeed some patients had localized lesions, while others were in progress at the onset of the syndrome. The dose effect is unclear [4]. The relationship with duration of treatment varies depending on the study: 5-8 months depending Saif et al. [2] 3.8 to 13.1 months according to Man et al. [1]. The cumulative doses were also highly variable across studies: 2000-4000 mg/m² by Fung et al. [1]; 2890–5900 mg according Desramé et al. [4]. The time of occurrence compared to the last infusion from 1 to 2 months [1,4]. A pre-existing renal failure and chemotherapy could be confounding factors [1]. Angiotensin-converting enzyme and angiogenesis are available to treat hypertension induced HUS [4]. The treatment is based on the decision of gemcitabine and symptomatic management of HUS. It consists of a blood transfusion if anemia is not tolerated. It may require treatment with steroids, plasmapheresis or renal dialysis according to the degree of renal damage [1]. Mortality ranges from 10 to 70% in different studies [2]. These rates are to be taken with caution given the fact that the proportion of HUS itself and that of the underlying disease for which the chemotherapy was not specified in these studies. The immediate prognosis is related to early diagnosis therefore follow after each cycle of biological constants creatinine but especially haemoglobin (and especially if it falls therefore follow after each cycle of biological constants creatinine but especially haemoglobin (and especially if it falls after chemotherapy and blood transfusion).

**Conclusion**

The diagnosis should be considered not only when faced with anemia, thrombocytopenia, renal failure but also to all cases of hypertension in patients with normal tension or previously well balanced in terms of blood pressure. The support involves symptomatic treatment and permanent discontinuation of gemcitabine.

**Conflict of interest statement**

The authors have no conflict of interest.
Endometriosis of the appendix presenting as acute appendicitis: Report of a case

Endométriose appendiculaire revélée par un tableau d’appendicite aiguë

Introduction

Endometriosis is defined as the presence of ectopic endometrial tissue outside the lining of the uterine cavity [1]. Isolated endometriosis of the appendix is rare and presentation as acute appendicitis is even more uncommon [2].

We report a case of appendiceal endometriosis clinically presenting as acute appendicitis.

Case report

A 19-year-old woman was admitted with a 1-day history of right lower-quadrant pain, nausea and fever. On physical examination, there was a localized tenderness at McBurney’s point, with a present Rovsing’s sign. No abdominal mass was palpable. We did not perform a vaginal examination because patient was not yet married. Temperature was 38.2 °C. White blood cell count was 21,000/mm³ and C-reactive protein was 16.6 mg/dl. Urine analysis was normal, with no evidence of infection or haematuria. An ultrasonog-

Figure 1 Histological examination showing ectopic endometrial glands with stroma in the thickened muscular propria and subserosa. Haematoxylin and eosin, × 200.

Figure 2 Histological examination showing ectopic endometrial glands with stroma in the thickened muscular propria and subserosa. Haematoxylin and eosin, × 40.


Endometriosis is a common gynecological condition affecting 10 to 15% of the female population. Involvement of