Rectal endometriosis and prolactinoma

Sir,

With reference to the article by Novella-Maestre et al. (2009) on the experimental treatment of endometriosis with cabergoline (Cb2), the authors suggested that Cb2 manifests its anti-angiogenic effect by acting via VEGFR-2. A case which we recently encountered seems to support this hypothesis.

A 36-year-old woman presented in September 2008 with complaints of abdominal, lower back and pelvic pain of 5 months’ duration, as well as recent onset of bleeding per rectum. Irregular, edematous and fragile mucosa, between 14 and 17 cm, was reported on colonoscopic evaluation, and biopsy specimens were obtained with a preliminary diagnosis of colorectal cancer. However, histopathological examination of the obtained specimens did not reveal any signs of malignancy, just non-specific colitis. She was started on a 2-week course of metronidazole and ciprofloxacin. A repeat rectoscopy in November was normal.

Two months later, symptoms of inguinal pain and rectal bleeding recurred, and rectosigmoidoscopy performed in April 2009 revealed an irregular, lobulated and fragile mass-like appearance in the rectum (between 10 and 15 cm), occluding nearly half of the lumen. Findings observed on histopathological examination were consistent with a solitary rectal ulcer. A subsequent abdominal MR scan revealed thickening of the rectosigmoid wall to 1 cm with a 3-cm thick-walled cyst in the right ovary. The patient eventually underwent a total of 10 rectosigmoidoscopy procedures during a 1-year follow-up period up to October 2009. The most recent evaluation showed an irregular appearance in the rectum, at 15 cm, partially occluding the lumen. Biopsy specimens only revealed edematous colon mucosa. The patient was finally referred for surgery and low anterior resection was performed in December. The surgically resected specimen consisted of a rectal segment of 12 cm in length. At 4.5 cm from the distal edge of the specimen intramural endometriosis 4 × 4 × 0.8 cm in size, invading the submucosa, muscular layer and pericolic fat was observed. The lesion also had a 1-cm luminal protrusion. Three of the 11 dissected lymph nodes had endometrial glands.

Figure 1 Serum prolactin levels during and after cessation of dopaminergic agonist treatment in a 6-year follow-up.
Immunohistochemically, the endometrial glands were CK20 negative and CK7 positive, while the endometrial stroma was CD10 positive. Similarly the colon mucosa stained positive for CK20 and negative for CK7.

From her medical history, we learnt that in 2003, at 19 years of age, she had presented with galactorrhea and abdominal pain to an obstetrics and gynecology clinic. With the discovery of hyperprolactinemia [49 ng/ml (6–30)] a hypointense mid-adenohypophyseal lesion of 4 × 2 mm in size was detected on MRI. She was prescribed on a slow-release formulation of bromocriptine at a dose of 2.5 mg/day. By May 2005, she was switched to 0.25 mg cabergoline, twice a week. Follow-up prolactin levels are depicted in Fig. 1. A hypophyseal MRI in April 2007 did not reveal any lesion prompting discontinuation of treatment. However, despite normal findings on a repeat MRI in March 2009, her symptom of galactorrhea recurred.

Endometriosis is a rare cause of gastrointestinal bleeding that may be undetectable on endoscopic biopsy (Miller et al., 1994; Yantiss et al., 2001). The submucosal localization of the endometriosis in this case may have contributed to the negative histopathological findings on repeat biopsies. For colorectal endometriosis, MRI and rectal endoscopic sonography are both diagnostic modalities with comparable accuracy (Bazot et al., 2007). Surgical extirpation is recommended for advanced endometriosis (Bailey et al., 1994).

The recurrence of galactorrhea followed by rectal bleeding between April 2007 and March 2009, during which period the patient was not on Cab2 treatment seems to support the ideas proposed by Novella-Maestre et al. Apparently the patient had neglected her follow-up visits for her prolactinoma after receiving a premature diagnosis of rectal cancer.

### References


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### Reply: Rectal endometriosis and prolactinoma

We thank Dr Kurt and co-workers for providing a clinical example showing a possible link between hyperprolactinaemia and endometriosis, and the potential beneficial effect of dopamine agonists (DA) in the treatment of the disease.

Several previous reports have focused on the association between hyperprolactinaemia and endometriosis (Gregoriou et al., 1999; Cunha-Filho et al., 2002). It has been postulated that the hyperprolactinaemic state could explain infertility related to mild and moderate endometriosis, but perhaps this misses the main point: hyperprolactinaemia may increase angiogenesis and induce/maintain endometriotic lesions. Their letter describes a patient with rectosigmoid endometriosis and simultaneous galactorrhea and hyperprolactinaemia. She had recurrent rectal bleeding but, during the period of time that she was under DA treatment, bleeding stopped and appeared again when the medication was discontinued.

We know that active angiogenesis is a requisite for the endometriotic implants in order to be established and grow (Nisolle et al., 1993; Maas et al., 2001; Lasche and Menge, 2007). We employed DA to target angiogenesis and endometriosis experimental lesions for several reasons: (i) the demonstrated effect of DA as antiangiogenic in experimental oncologic models (Basu et al., 2001); (ii) Our own experience in ovarian hyperstimulation syndrome, both in animals (Gomez et al., 2006) and humans (Alvarez et al., 2007); and (iii) the safety of these drugs even in pregnant patients (Robert et al., 1996; Ricci et al., 2002). With this background we anticipated that DA can be an ideal drug to treat a chronic disease such as endometriosis. Our published work shows the effect of cabergoline on experimental endometriosis lesions through an inhibition of angiogenic process (Novella-Maestre et al., 2009). Moreover, we have finished a pilot study in humans that basically confirms the findings in rodents.

We have only focused so far in peritoneal endometriosis because we believe it is the first step of the disease and because it is easier to design studies with lesions in this stage. The case reported by Kurt et al. suggests that DA may be also useful to treat deep endometriosis, the most severe presentation of the disease. Several hormonal treatments have been shown to provide pain relief (Vercellini et al., 2009), but if the description of Kurt et al. is confirmed, we may have found a drug able to target more complicated symptoms, such as rectosigmoid bleeding. This would represent an important advancement in the treatment of the disease and deserves to be further explored.

### References
