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Full length article

Value of the ^{68}Ga-DOTATATE PET-CT in the diagnosis of endometriosis. A pilot study

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ABSTRACT

Objective: The non-invasive diagnosis of endometriosis remains challenging. Recent data suggested that somatostatin might be involved in its pathogenesis. High sensitive visualization of somatostatin receptors expression is possible using PET-CT imaging after the administration of a ^{68}Ga-labeled somatostatin analog (DOTATATE) that will bind to the somatostatin receptor sub-types 2 and 5. The aim of the present study was to assess the usefulness of ^{68}Ga-DOTATATE PET-CT in the diagnosis of endometriosis.

Study design: This is a prospective, single center pilot study. A pre operative ^{68}Ga-DOTATATE PET-CT was performed in all of the patients who presented with suspected endometriosis and who were scheduled for a laparoscopy. Surgical endometriosis staging and histopathological analysis, including somatostatin receptors SST1, 2 and 5 immunohistochemistry (IHC) of removed specimens, were confronted to the results of the ^{68}Ga-DOTATATE PET-CT.

Results: 12 patients were included in this study. ^{68}Ga-DOTATATE PET-CT performed pre operatively showed increased pathologic uptake in four patients with a deep infiltrating endometriosis (DIE) recto-vaginal lesion and in another patient with an adenomyoma. Expression of SST1, 2 and 5 receptors in surgical specimens was confirmed by IHC in these five lesions. Neither superficial peritoneal endometriosis, nor ovarian endometrioma were found to show an increased pathologic uptake on ^{68}Ga-DOTATATE PET-CT. IHC analysis confirmed that SST1, 2, and 5 receptors were not present in these lesions.

Conclusion: The results observed in this small size series of patients seem to confirm expression of somatostatin receptors only in recto-vaginal DIE and focal adenomyosis lesions. The usefulness of ^{68}Ga-DOTATATE PET-CT in the diagnosis of this entity is uncertain. Future research should concentrate on studying the role of somatostatin in the pathogenesis of DIE.

Introduction

Endometriosis is a very common disease characterised by the presence of ectopic endometrial tissue. Its prevalence is estimated to 10% of fertile women [1]. Endometriosis causes pelvic inflammation, which leads to pelvic pain, including dysmenorrhoea, and infertility. The prevalence of endometriosis is higher, ranging from 25 to 38.3%, in women suffering from chronic pelvic pain [2]. Similarly, it has been reported in 25–50% of infertile women [3].

Non-invasive techniques, such as transvaginal sonography (TVS), magnetic resonance imaging (MRI) and serum CA – 125 measurements, have shown a low sensitivity and specificity for the diagnosis of endometriosis [4–6]. The use of TVS and MRI is limited to the diagnosis of ovarian endometrioma and deep infiltrating endometriosis (DIE) but these techniques have no value in diagnosing peritoneal endometriosis [4,6,7]. Currently, the definitive diagnosis of endometriosis relies upon laparoscopic findings. Laparoscopy remains the “gold standard” of investigation, unless the disease is visible in the vagina or elsewhere [4]. Difficulties in diagnosing endometriosis partially explain the large ranges of reported prevalence.

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Differentiating ovarian endometrioma from suspected malignant ovarian masses may be difficult using imaging techniques, including PET [8]. Furthermore, pre-existing endometriosis favours the development of some epithelial ovarian cancers such as endometrioid and clear cell carcinoma [9].

Hyper metabolic activity of endometriosis has been reported in some "case – reports" using fluorodeoxyglucose (^{18}F-FDG) PET, when performed for other indications [10–13].

We prospectively investigated, in a previous study, the value of ^{18}F FDG PET-CT in diagnosing endometriosis. In this study, we observed no hypermetabolic anomaly related to endometriosis [14].

Recent data suggested that somatostatin receptors (SST 1, 2 and 5) are expressed in human endometrial tissue, as well as in its ectopic location [15]. Somatostatin analogs have been reported to reduce platelet-derived growth factor (PDGF)-induced endometrial cell proliferation and motility, which is one of the mechanisms leading to the development of endometriosis [16].

High sensitive visualization of somatostatin receptors expression is possible using PET-CT imaging after administration of a ^{68}Ga-labeled somatostatin analog (DOTATATE) that will bind to somatostatin receptor sub-types 2 and 5 (^{68}Ga-DOTATATE PET-CT). This technique is already clinically available for molecular imaging of neuro-endocrine tumors [17].

The present feasibility study assesses the value of ^{68}Ga-DOTATATE PET-CT in the diagnosis of endometriosis through a direct correlation with the pre-operative MRI results, the laparoscopic findings and somatostatin receptor (SST 1, 2 and 5) immunohistochemistry (IHC) on surgically removed specimens.

Materials and methods

Patients

Patients aged 18 years or more with suspected severe endometriosis (based on chronic pelvic pain and/or dysmenorrhoea resistant to medical therapy and/or infertility), for whom a laparoscopy was indicated, were eligible to enter this study. Exclusion criteria were: pregnancy or possible pregnancy. All patients underwent a preoperative standardised symptoms and signs assessment, a transvaginal ultrasound and/or MRI and CA 125 seric dosage. Eligible patients were invited to have a pre-operative ^{68}Ga-DOTATATE PET-CT during the follicular phase of the menstrual cycle that preceded surgery in order to avoid any risk of pregnancy.

In view of the negative results of a preliminary study using ^{18}F FDG PET-CT in diagnosing endometriosis [14] and in order not to expose our patients to unnecessary irradiation, we discussed all clinical, imaging and pathology results at a multidisciplinary meeting before inclusion of the next patient. We had decided to stop the study in the event of negative results. We observed, after the first six patients, an increased expression of somatostatin receptors on ^{68}Ga-DOTATATE PET-CT and at immunohistochemistry analysis only in patients with DIE lesions. We thereafter decided to only include patients with suspected DIE lesions.

The institutional review board, under reference AK/14-05-50/4379, approved the study. All included patients signed an informed consent.

^{68}Ga-DOTATATE PET-CT

The radiotracer ^{68}Ga-DOTATATE was produced in the radio pharmacy unit of the Jules Bordet Institute. The radio labeling of the precursor peptide DOTATATE was performed in-house, on an automated GMP-compatible synthesis module coupled to a GMP ^{68}Ge/^{68}Ga-generator. PET-CT images were acquired 60 min after the injection of 2 MBq/kg ^{68}Ga-DOTATATE, with the patients in a supine position, using a low dose CT without an intravenous contrast agent. The total duration of the PET-CT imaging procedure lasted less than 30 min.

PET data analysis

All PET-CT images were analysed by the same experienced nuclear medicine physician uninformed of the patients' clinical data. Any focal or diffuse ^{68}Ga-DOTATATE uptake above background in locations incompatible with normal anatomy and/or physiology was considered to be pathological and the SUV_{max} value was measured. Before surgery, PET-CT images were correlated with the MRI findings at a joint meeting involving the nuclear medicine physician, the surgeon and the radiologist.

Laparoscopy

Patients underwent bowel preparation consisting of a five-day fiber – free diet and two complete intestinal enemas the day before the procedure. A conventional laparoscopic investigation was carried out. The peritoneal cavity was inspected and the endometriosis lesions were described, using the ASRM classification [18].

Biopsies of the suspected lesions of endometriosis were performed. Removed tissues were sent for histopathological examination to confirm the diagnosis and to assess the expression of somatostatin receptors. Even in cases where endometriosis was not confirmed by histology, the patient was considered to have endometriosis if typical endometriosis lesions were observed through visual inspection during the laparoscopy.

Immunohistochemistry

After surgery, tissue samples were fixed in neutral-buffered formalin, embedded in paraffin, sectioned (4 μm thick) and processed for IHC. Sections were incubated with polyclonal rabbit antibodies: SST1 (Abcam Inc., ab2366, 1/33), SST2 (Abcam Inc., ab9550, 1/250) and SST5 (Abcam Inc., ab28618, 1/1000). Receptor positivity was assessed in ectopic endometrial tissue. Receptor status was considered as positive when more than 50% of the cells showed immunostaining.

Endpoint

The primary endpoint was to correlate data collected from ^{68}Ga-DOTATATE PET-CT with pre-operative MRI and intra-operative, laparoscopic findings. The second goal was to correlate ^{68}Ga-DOTATATE PET-CT results with the histopathological findings.

Statistical analysis

Descriptive statistics were used. We also calculated sensitivity, specificity, positive and negative predictive value of the pre-operative ^{68}Ga-DOTATATE PET-CT diagnosing DIE recto-vaginal lesions, as an exploratory analysis.

Results

Twelve patients were prospectively enrolled in this study between November 2014 and January 2016. Their main demographic characteristics are presented in Table 1. Their median age was 31 years [24–38]. Laparoscopy was indicated for infertility and/or pelvic pain (including dysmenorrhoea), or colic obstructive syndrome associated with menstruation or dysuria (with macroscopic hematuria) associated with menstruation. Four out of the