

Case report

Primary B-Cell lymphoma of the uterine cervix presenting with right ureter hydronephrosis: A case report

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ABSTRACT

Primary lymphoma of the uterine cervix is a very infrequent disease, usually affecting perimenopausal women. Symptoms are very similar to other gynecological malignancies, but treatment and prognosis completely differ, as most of these patients have a better survival. This condition has to be suspected in women with recent normal Pap smear test, rapidly growing tumor and initially non-contributory biopsies.

We report a case of primary diffuse large-B-cell lymphoma of the uterine cervix mimicking a locally advanced cervical cancer with right ureter hydronephrosis at diagnosis. She was medically managed with a combination of rituximab and chemotherapy with cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone, associated to methotrexate for central nervous system prophylaxis. We will discuss about the role of combined treatments with surgery and radiotherapy, and the fertility sparing management in young women.

1. Introduction

Primary lymphoma of female genital tract is an extremely rare entity, representing 0.2–1.1% of extra-nodal non-Hodgkin's lymphomas (Lagoo and Robboy, 2006), and less than 0.5% of gynecological cancers (Ferlay et al., 2013). The most common site of involvement in the female genital tract is the ovary, being the cervix the second most frequent location. Uterine corpus, vagina and vulva are less usual primary locations (Nasioudis et al., 2017; Wang et al., 2019). Diffuse large-B-cell lymphoma not otherwise specified (DLBCL NOS) is the most common histological subtype (Nasioudis et al., 2017). Most women are diagnosed at a perimenopausal age, around 50 years (Nasioudis et al., 2017; Slonimsky et al., 2018). Pelvic lymphomas are classified according to Ann Arbor staging system; in early stages, women are often asymptomatic, and common symptoms of more advanced stages are vaginal bleeding or discharge, abdominal distension, bloating, and pelvic discomfort depending on tumor location. Constitutional 'B-cell' symptoms such as fever, asthenia, night sweats and weight loss are not usually

seen in extra-nodal lymphomas (Nasioudis et al., 2017; Parnis et al., 2012).

Unfortunately, female genital tract lymphomas are often misdiagnosed and considered as primary genital malignancies, which delays the diagnosis. Although there are no standardized guidelines, most series describe a multimodal management combining chemotherapy with cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone (CHOP) -which is the mainstay of the treatment- along with surgery and radiotherapy (Nasioudis et al., 2017; Novotny et al., 2011; Coiffier et al., 2002; Evans and Hancock, 2003). Since both prognosis and treatment completely differ from other gynecological malignancies, it is crucial to establish the histological diagnosis as soon as possible.

We report a case of a young patient presenting a uterine cervical DLBCL NOS, mimicking a locally advanced cervical cancer with unilateral hydronephrosis.

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2. Case report

We present the case of a 36-year-old multiparous and non-smoker woman with overweight (body mass index of 29.1 kg/m²) and medical history of high blood pressure without medical treatment. Her surgical history included appendectomy and tonsillectomy. During the course of her first pregnancy, she developed a gestational diabetes and mild preeclampsia. The second pregnancy was complicated by a severe preeclampsia and a left adrenal vein thrombosis. Regarding gynecological history, she had a copper intrauterine device as contraceptive method and a normal Pap smear one year ago.

She attended the gynecological emergency department presenting vaginal bleeding, pelvic pain, dysuria and asthenia without fever, for the last two weeks. Gynecological examination revealed a firm and fixed cervical mass of 7 cm invading the right parametrium and the anterior vaginal wall. Rectal examination found a bulging fixed mass without invasion of the mucosa. There were no abnormalities in the blood test. Pelvic transvaginal ultrasound performed at the emergency department showed a 6-cm cervical mass including the intrauterine device. Abdomino-pelvic computed tomography evidenced a pelvic mass compressing the right ureter and causing a unilateral hydronephrosis (Fig. 1.A). After a failure of double-pigtail ureteral stent placement, a right nephrostomy was performed. The magnetic resonance imaging (MRI) confirmed an 8-cm cervical mass extending to the lower third of the uterus, the superior third of the anterior vaginal wall, the posterior wall of the bladder and the right parametrium (Fig. 1.B and C). Our first suspicion was a locally advanced cervical carcinoma. However, initial biopsies were non-contributory, showing a non-specific mixed inflammatory infiltrate with admixed scattered atypical epithelial cells (data not shown). Therefore, an evaluation under general anesthesia was scheduled and allowed to obtain larger and deeper cervical biopsies (Fig. 2) revealed sheets of medium to large size mononuclear cells with pleomorphic nucleus. Immunohistochemistry showed the tumor cells were positive for CD45, CD20 (B-cell marker), Bcl6, Bcl2, and MYC, and negative for CD3 (T-cell marker), CD10, MUM1, CD5 and cyclin D1, with a high Ki67 proliferation index (60%), consistent with a diagnosis of germinal center B-cell like DLBCL NOS. The positron emission tomography/computed tomography (PET/CT) revealed a cervical hypermetabolism (SUVmax 34.9) with a local uterine and vaginal extension. Left ovary hyperfixation was also evidenced (Fig. 3.A, D and G). Fig. 1.D and E shows PET/CT and MRI fusion imaging at diagnosis. According to Ann Arbor classification, it was considered a stage IV.

After discussion at tumor board, she was treated with 6 cycles of R-CHOP (Rituximab 375 mg/m² at day 1 plus Cyclophosphamide 750 mg/m² at day 1, Hydroxydaunorubicin 50 mg/m² at day 1, Vincristine 1.4 mg/m² at day 1, and Prednisone 40 mg/m² from day 1 to day 5) in a 14-day cycle, and 2 cycles of high-dose methotrexate were delivered for central nervous system prophylaxis. She presented a good tolerance to the treatment with a quick decrease of pelvic pain. The right nephrostomy was replaced by a double-pigtail ureteral stent after the first cycle of chemotherapy. Treatment response evaluation was performed after two cycles of R-CHOP with a PET/CT (Fig. 3.B, E and H), showing a complete response (cervical SUVmax 1.9, Deauville 5 points scale = 1, Delta SUVmax > 90%). The PET/CT performed after four cycles of chemotherapy showed a maintained complete metabolic response (Deauville 5 points scale = 1, Delta SUVmax > 90%) with neither residual cervical tumor nor left ovarian hyperfixation (Fig. 3.C, F and I). Fig. 4 shows the evolution of whole body maximum intensity projection at diagnosis -with cervical and ovarian uptake- and after starting chemotherapy (complete metabolic response). Before the fourth cycle of chemotherapy, the double-pigtail ureteral stent was removed. At the end of chemotherapy, physical examination revealed a complete clinical response with no residual cervical lesion. After a follow-up of 15 months, she was disease-free and she had returned to

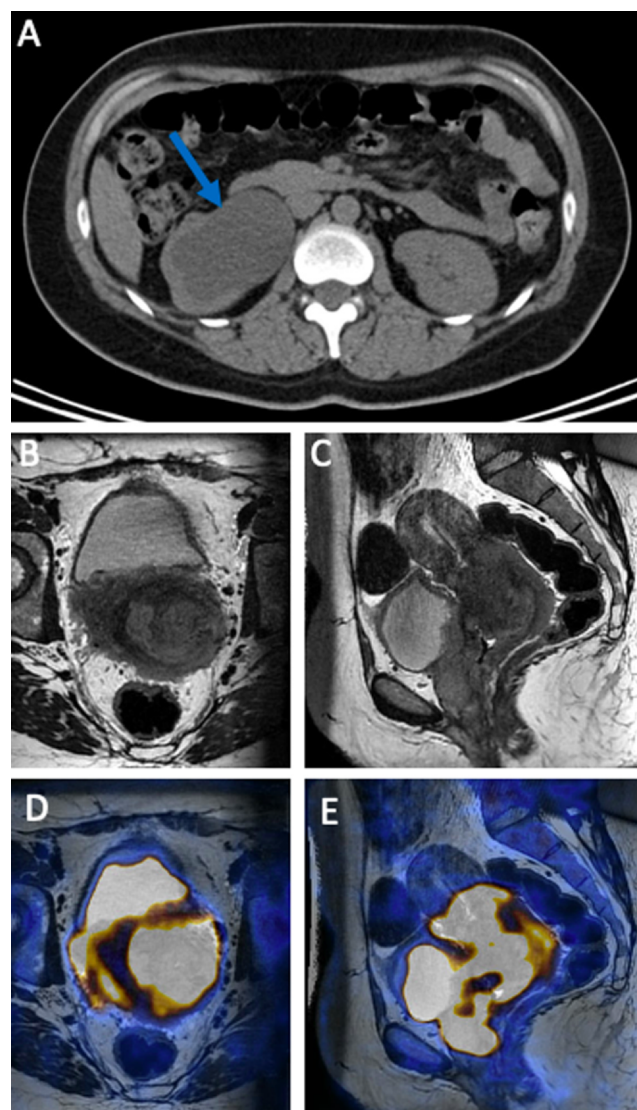


Fig. 1. Imaging at diagnosis. A Axial section of computed tomography showing right hydronephrosis (blue arrow). B Axial and C sagittal sections of magnetic resonance imaging (MRI) T2 sequences. The cervical mass infiltrates the right parametrium, posterior bladder wall and anterior vaginal wall. D Axial and E sagittal sections of positron emission tomography and MRI T2 fusion imaging with high and diffuse tumoral fluorodeoxyglucose uptake.

her professional activity.

3. Discussion

Primary DLBCL NOS of the uterine cervix is a very rare disease. Main symptoms -including abnormal uterine bleeding, vaginal discharge, and pelvic pain- are similar to gynecological diseases and, for this reason, they are often misdiagnosed (Nasioudis et al., 2017). In some cases, the definitive diagnosis is established after the histological analysis of the surgical specimen of a primary surgery. According to a very large series, most cases are diagnosed at an early stage (I or II) according to Ann Arbor classification (Nasioudis et al., 2017). However, other reports show that almost two third of the cases correspond to stage III or IV (Wang et al., 2019). Unlike other gynecological malignancies, primary lymphoma of the genital tract have a good prognosis, even when diagnosed at an advanced stage (Nasioudis et al., 2017; Wang et al., 2019). Nevertheless, their treatments completely differ, making it is essential to establish an accurate and quick diagnosis.

There is not a gold standard among imaging techniques to diagnose

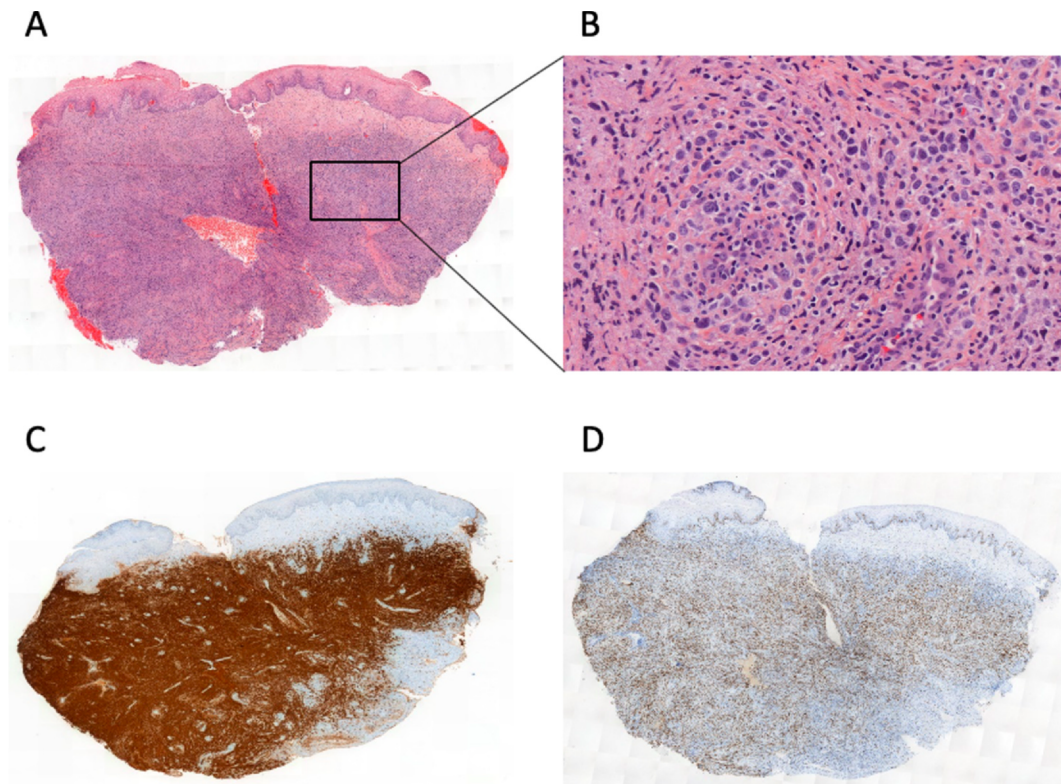


Fig. 2. Histological examination of the deep and large cervical biopsy. A (H&E, x200) and B (H&E, x400). Morphological analysis revealed deep infiltration by sheets of large to medium size cells with oval or round pleomorphic nuclei and scanty cytoplasm. C (anti-CD20 stain, x200) and D (Ki-67 stain, x200). Immunohistochemistry showed diffuse positivity for CD20 with a high Ki67 proliferative index.

pelvic lymphomas. Usually, ultrasound, MRI and PET/CT can be performed on the pretherapeutic assessment (Korivi et al., 2014). There are some features which can help in the differential diagnosis. On ultrasound, cervical lymphomas appear like a solid mass usually lobulated, expansive and well vascularized (Korivi et al., 2014; Groszmann and Benacerraf). On MRI, T2 sequences are useful to identify cervical lymphomatous involvement, which appears homogeneous and hyperintense. On T1-weighted sequences, cervical lymphomas are homogeneous and hypointense, with a strong uniform enhancement pattern on postcontrast imaging, which helps for the differential diagnosis with squamous cervical or endometrial carcinomas. Cervical and endometrial epithelium is usually intact, unlike cervical stroma which is often involved. In contrast, in cervical cancer, there is commonly a distortion of the mucosa with an heterogeneous enhancement and parametrial invasion (Thyagarajan et al., 2004). PET/CT is useful to identify distant metastases and it can also be performed during follow-up to detect disease recurrences. In large B-cell lymphomas, the fluorodeoxyglucose uptake is usually high, as in squamous carcinomas, while in adenocarcinomas the uptake is typically lower.

The definitive diagnosis is established with histological analysis. In case of vulvar, vaginal or cervical masses, diagnosis can be done with a biopsy performed during gynecological examination, while in ovarian and uterine masses, histological diagnosis is usually done in the surgical specimen (Nasioudis et al., 2017). Cervical lymphomas typically originate from cervical stroma and the superficial squamous epithelium is usually preserved. Some cases present with subepithelial masses without an evident ulceration or epithelial abnormality (Chan et al., 2005). For this reason, superficial biopsies may not be contributory as it happened for the first biopsies performed in our patient. Usually, superficial biopsies contain atypical epithelial cells coexisting with lymphoid infiltrates (Chan et al., 2005). It is recommended to perform deep incisional or excisional cervical biopsies to establish a definitive diagnosis when initial biopsies are non-contributory (Chan et al., 2005). We

believe that multiple surgical biopsies should be done with scalpel to avoid burn artifacts due to electrosurgical devices. Alternatively, a diagnostic conization would allow to obtain sufficient material for histological analysis. It is essential, whenever possible, to establish a histological diagnosis before starting any treatment. Regarding Pap smear test, some authors have reported that it can show atypical cells (Chan et al., 2005); however, our patient had a recent negative test.

Analogously to nodal DLBCL NOS, a regimen with R-CHOP is usually employed (Coiffier et al., 2002; Chan et al., 2005). In our patient methotrexate was associated to decrease the risk of central nervous system relapse, as some authors have reported a preferential dissemination in this localization, which has poor prognosis due to early mortality (Wang et al., 2019). Nasioudis et al. reported that in most cases the management also includes surgery and/or radiation therapy. Even though, combination of surgery and radiation therapy did not confer any survival benefit (Nasioudis et al., 2017). On the contrary, Wang et al. found that patients treated without surgery had a slightly better survival than patients in whom surgery was included in their management (Wang et al., 2019). Patients presenting residual disease after first line treatment may need a second line of systemic treatment. However, completion hysterectomy may be an option in case of partial response to chemotherapy with residual tumor. Some authors have advocated surgery or radiotherapy in addition to chemotherapy to decrease the risk of local recurrence (Chan et al., 2005).

A non-negligible number of cases of pelvic lymphomas occur in premenopausal women and, for this reason, fertility sparing management is an issue that must be addressed. Chemotherapy and, more specifically, cyclophosphamide has been associated with significant gonadotoxicity. GnRH agonists to temporary suppress the ovarian function and to reduce the risk of premature ovarian failure may be recommended. Moreover, oocyte and embryo cryopreservation should also be considered in selected patients before starting the treatment. As well, ovarian transposition before pelvic radiotherapy could be offered

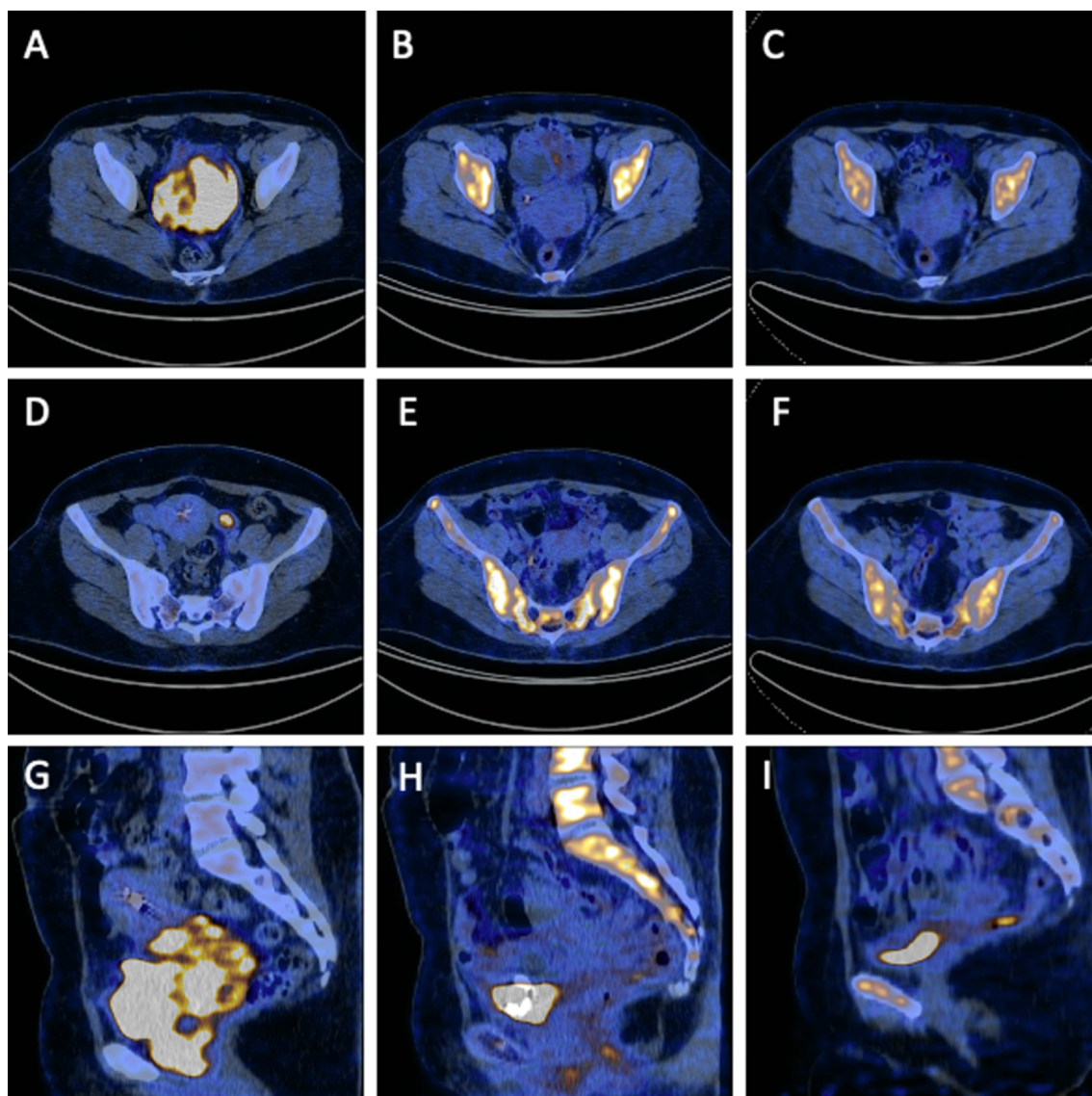


Fig. 3. Positron emission tomography (PET)/computed tomography (CT) imaging. A, B and C Axial sections showing the cervical mass at diagnosis, after 2 cycles of chemotherapy and after 4 cycles, respectively. D, E and F Axial sections showing the left ovary at diagnosis, after 2 cycles of chemotherapy and after 4 cycles. G, H and I Sagittal sections showing the cervical tumor at diagnosis, after 2 cycles of chemotherapy and after 4 cycles. At diagnosis PET/CT revealed a cervical hypermetabolism with local uterine and vaginal involvement, and left ovarian hyperfixation. After 2 cycles of chemotherapy, there was a complete metabolic response (Deauville 5 points scale = 1, Delta SUVmax > 90%), which was maintained after 4 cycles.

to preserve ovarian function (Nasioudis et al., 2017).

In conclusion, cervical uterine lymphomas may be one of the differential diagnosis in case of a cervical mass, particularly in women with previous normal Pap smear, rapidly growing tumor and initially non-contributory biopsies. Specific features of imaging can help orientating the diagnosis. However, histological evaluation is crucial to establish the definitive diagnosis. Treatment should be R-CHOP based chemotherapy to avoid increased morbidity of combined treatments with surgery or radiotherapy. Methotrexate should be considered for neuromeningeal prophylaxis and fertility-sparing management should be offered to young patients.

Patient Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

CRedit authorship contribution statement

Mathilde Del: Conceptualization, Data curation, Methodology,

Writing - original draft. **Martina Aida Angeles:** Conceptualization, Data curation, Methodology, Writing - original draft. **Charlotte Syrykh:** Conceptualization, Data curation, Methodology. **Carlos Martínez-Gómez:** Conceptualization, Data curation, Methodology. **Alejandra Martínez:** Conceptualization, Data curation, Methodology. **Gwénaél Ferron:** Conceptualization, Data curation, Methodology. **Erwan Gabiache:** Conceptualization, Data curation, Methodology. **Lucie Oberic:** Conceptualization, Data curation, Methodology.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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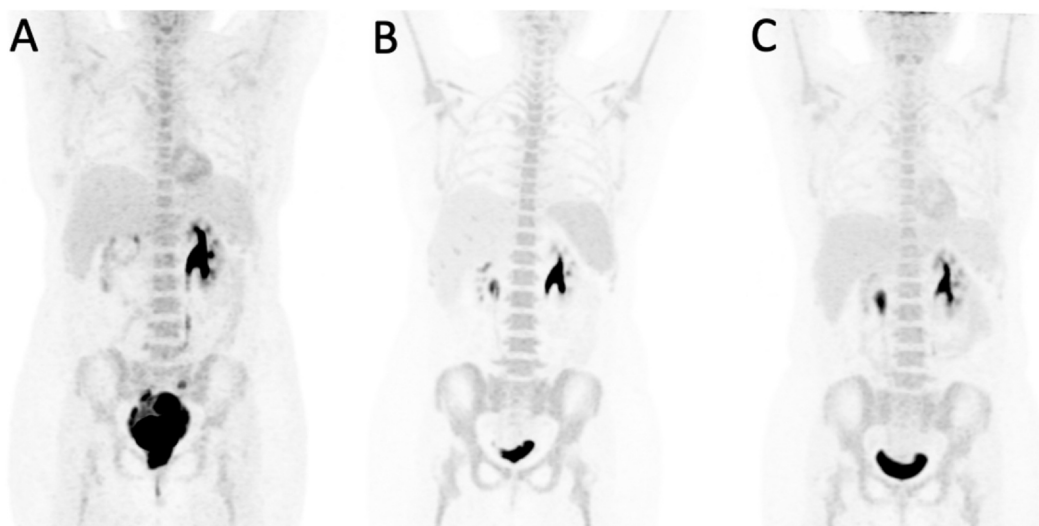


Fig. 4. Whole body maximum intensity projection. A Imaging at diagnosis showing a centro-pelvic tumoral uptake. B After 2 cycles of treatment, we can appreciate a complete metabolic response and C after 4 cycles of chemotherapy, the complete response was maintained.

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