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Leiomyomatosis peritonealis disseminata in association with multiple congenital malformations: a new feature of Currrano syndrome?

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Abstract

Background

Leiomyomatosis peritonealis disseminate (LPD), is a rare disease in which multiple smooth muscles or smooth muscle-like nodules develop in a subperitoneal location in any part of the abdominal cavity. No reports of multiple congenital malformations associated with LPD have been found in English literature.

Case presentation

We report such a case of a 27 yr-old patient referred to our Gynaecology Unit for pelvic pain, amenorrhea, stress incontinence, chronic constipation and recurrent intestinal and urinary infections. Multiple congenital malformations had been previously diagnosed mostly of whom had required surgical treatment in the first years of her life: ectopic right ureteral orifice, megadolicouretere, ectopic vulvar anal orifice and sacral-coccygeal agenesis.

An ultrasound performed in our Department showed a complex 20 cm-size mass originating from the right pelvis that reached the right hypochondrium and the epigastrium. The patient underwent laparotomy. A great irregular complex mass was found in the abdominal cavity and was progressively resected. The histological diagnosis was of LPD.

Conclusions

The case we report has the peculiarity of the coexistence of this rare condition with multiple congenital malformations reminding Currarino’s syndrome. The Currarino’s syndrome belongs to the group of persistent neuroenteric malformations and consists of anorectal malformation, sacral bone deformity and presacral mass. Our report suggests that if two components of the triad are identified, the possibility of the third one (presacral tumor) should be always considered. Pelvic ultrasound, CT and MR should be performed to quickly recognize and opportunely treat the tumor.
KEY-WORDS: Currarino’s syndrome/ leiomyomatosis peritonealis disseminate/malformations.
Background

Leiomyomatosis peritonealis disseminate (LPD), also known as diffuse peritoneal leiomyomatosis, is a rare disease in which multiple smooth muscles or smooth muscle-like nodules develop in a subperitoneal location in any part of the abdominal cavity [1]. These nodules, while histologically benign, cannot be distinguished macroscopically from peritoneal carcinomatosis.

The aetiology is thought to be smooth muscle metaplasia of the subperitoneal mesenchyme [2]. The number of documented cases in the English–language-literature totalled approximately 100; patients with LPD are mainly female in their reproductive age [3], being only rare case affecting men reported in the literature [4, 5].

An association with high levels of exogenous and endogenous female gonadal steroids (i.e. pregnancy, prolonged exposure to oral contraceptives and/or combined hormonal replacement therapy, granulosa cell tumors of the ovary) has been found [6, 4], indicating that estrogens and progestins do play an important role in the pathogenesis of LPD such as for leiomyomata uteri.

Most LPD cases behave in a clinically benign fashion, and in some instances, the lesions may partially or completely regress [7, 5]. Alternatively, LPD may progress, recur or rarely undergo malignant transformation [8].

We report a case of a patient affected by LPD in which multiple congenital malformations reminding Currarino’s syndrome have been previously diagnosed.

Currarino’s triad is a rare form of caudal regression syndrome, consisting in anorectal malformation, sacral bone deformity and presacral mass.
Case presentation

A 27 yr-old Caucasian nulliparous female was referred to our Gynaecology Unit for pelvic pain and amenorrhea for the last seven months. She also complained of stress incontinence, chronic constipation and recurrent intestinal and urinary infections.

Her past history was characterized by several congenital malformations mostly of whom had required surgical treatment.

In the neonatal age, she had an anoplasty because an imperforate anus with an ectopic vulvar anal orifice.

Two month after the birth, the patient had undergone a laparotomy that showed an hydronephrosis due to the obstruction of the ectopic right ureteral orifice which had also caused megadolicouretere and recurrent urinary sepsis. A cutaneous ureterostomy was performed to improve the renal function.

However two months later, she had undergone a new laparotomy following an urography showing a decreased renal function. Right nefrectomy was performed. The histological diagnosis was chronic pielonephrite.

Furthermore she had been diagnosed a right hand’s thumb torsion of the articulation metacarpus-phalanx with an hypotrophy of eminenza tenar, valgus condition, and sacral-coccygeal agenesis with bladder dysfunction treated by pharmacological therapy.

An ultrasound performed in our Department showed a complex mass originating from the right pelvis that reached the right hypochondrium and the epigastrium. The trasversal extension was more than 20 cm. Fluid was noted in the Douglas pouch.

Computed tomography (CT) of the abdomen and pelvis confirmed a suspicious irregular polilobate complex mass of 24 x 19,5 x 13,5 cm.

Chest X-ray and CT were negative for pleural effusion or lung metastasis.

The patient underwent laparotomy. A great irregular complex mass was found in the abdominal cavity and was progressively resected (figure 1). The first (17 x 12 x 9 cm) and the
second (11 x 5 x 5 cm) samples were capsulated solid cystic mass containing clear fluid. The third sample, with the same macroscopic features, was composed by multiple tumour nodules, the biggest one measuring 14 cm x 13 cm. These samples were sent for frozen section assessment. A total hysterectomy was performed. The frozen section of mass showed a benign hypocellular tumor with mixomatous and oedematous stroma, with rare spindle cells arranged in a storiform pattern. No histological features of malignancy were found.

Histological examination of the pelvic mass exhibited multiple smooth muscle-like nodules with low cellularity, without any cytological atypia and few mitoses (figure 2). The immunohistochemical evaluation showed strong positivity for desmin and actin (figure 3), negativity for cytokeratin and EMA (Epithelial Membrane Antigen). All lymph node resulted seat of an reactive aspecific hyperplasia. Cytology examination of peritoneal liquid revealed only reactive mesothelial cells and foamy histiocytes.

The final diagnosis was of disseminated leiomyomatosis, that had to be considered aggressive for its unusual macroscopic presentation.
Conclusions

The aetiology of LPD is unknown, but it is thought to originate from metaplasia of submesothelial, multi-potential mesenchymal cells. The developing leiomyomatous nodules probably arise from Mueller’s epithelium which is distributed throughout the subperitoneal mesenchyme. In case of individual predisposition and hormonal stimulation, Muellerian derivates proliferate along lines of myofibrous differentiation [9, 6].

LPD is most common in women in their reproductive years. More than half of the reported patients are pregnant or under oral contraceptives at the time of diagnosis [10].

Quade et al proved that LPD has molecular genetic and cytogenetic features suggesting that individual tumorlets are monoclonal, with a pathogenesis similar to leiomyomata uteri. The smooth muscle cells of LPD are influenced by estrogens [11, 7] and sex steroids receptors have been identified in nearly all cases [12].

LPD can be associated with other estrogen-dependent diseases as endometriosis, ovarian clear cell carcinoma, endometrial carcinoma [13] and ovarian fibrothecoma [2]. Recently two cases of development of LPD and ovarian Brenner tumor during tamoxifen therapy have been reported [14-18].

The majority of LPD regards premenopausal women, even if some cases were found in postmenopausal women using [19] or not hormone replacement therapy [9, 20,21].

The identification of luteinizing hormone (LH) receptors in LPD nodules of a postmenopausal woman suggests that the typical postmenopausal increase of LH levels might affect its pathogenesis [18].

Recently, a familial occurrence of LPD has been described, showing an autosomal dominant model with varying degrees of penetrance [22].

Most patients with LPD present without specific symptoms and many of the documented cases of LPD have been discovered incidentally during surgery (caesarean section, laparotomy or laparoscopy). Sometimes patients may present with mostly non-specific symptoms, such as
irregular, heavy uterine bleeding and pain or a mass in the lower abdomen [23], discomfort, urinary frequency (due to the mass effect on the bladder), gastrointestinal bleeding and peritonitis (following the erosion of the LPD implant into the bowel wall) [7, 9, 14, 24]. Sometimes patients experienced symptoms directly related to LPD: urosepsis secondary to obstruction of the ureters and an acute abdomen due to ovarian torsion [25].

Sonographic and CT findings reported in literature include non-specific, solid, and complex soft tissue masses that are often large and mimic a leiomyomatous uterus. In some cases, the masses enhance in a fashion similar to that of normal uterine parenchyma, whereas others demonstrate heterogeneous enhancement. There may be confusion with peritoneal carcinomatosis if the masses are present diffusely throughout the abdomen and pelvis. Peritoneal carcinomatosis, however, is often associated with tumor cake, ascites, and liver metastases, which have not reported with LPD [25].

MR findings include masses similar in signal intensity to skeletal muscle or uterine parenchyma and when sarcomatous transformation occurs do not differ significantly from the features of benign implants. If the masses are located in the pelvis adjacent to the iliac vessels, they may be confused with lymphadenopathy [5, 10, 26-29]. Moreover some multiple, pedunculated leiomyomas arising from the uterus may mimic LPD implants.

However, the final diagnosis may be performed only with the histological examination and immunohistochemical evaluation.

Sometimes LPD may recur in patients taking HRT [9, 20, 21] even after hysterectomy and bilateral salpingo-oophorectomy [19], or in patients undergone in vitro fertilization [30]. In elder study Mathews and Speers reported a patient who died after fourth recurrence of LPD and distant metastases 10 years after hysterectomy. Each recurrence seems to be more like to morphological evidence of sarcoma [19].

Malignant change of LPD is an uncommon event and only ten cases have been documented in English literature [8, 25]. Of these only three occurred in postmenopausal women [25, 31]. The
interval between the initial detection of LPD and the development of sarcoma varies from synchronous diagnosis to up to 8 years. In most reports of malignant LPD no history of estrogen exposure was found. Bekkers hypnotized that LPD without exogenous or increased endogenous estrogen exposure and without expression of ER /PR by tumor cells may in fact represent a different entity carrying a higher risk of malignant transformation [3].

On the basis of these observations we can affirm that no established guidelines exist regarding the management of LPD. However therapy needs to be individualised according to patient's age, hormonal and reproductive status and symptomatology.

Medical treatment with different drugs (gonadotropin realising hormone agonist, megestrol acetate, danazol) has been considered in some cases but with poor results.

If intestinal and bladder mass effect symptoms are preminent, a surgical approach is indicated [32].

We report a case of LPD diagnosed in a young lady who has never used oral contraceptives and who was referred to our Department because of pelvic pain, amenorrhea, stress incontinence and chronic constipation.

The case we report has the peculiarity of the coexistence of this rare condition with multiple congenital malformations who had been diagnosed in our patient during the first years of her life.

According to a MEDLINE search of the English language literature we did not find any report of association of multiple malformations with LPD.

The congenital malformations diagnosed in our patient remind the Currarino’s syndrome.

The Currarino’s syndrome belongs to the group of persistent neuroenteric malformations and is associated with chronic constipation, bone sacral defect, presacral mass and anorectal stenosis or agenesis. It was defined using the initials ASP: anorectal malformation, sacral bone deformity, and presacral tumor [33].
The association of ASP is autosomal dominant with incomplete penetrance and variable expressivity. A gene responsible for the Currarino syndrome recently has been mapped at the terminal portion of the long arm of the chromosome 7 (7q36) [34].

Girls are more commonly affected, in more of 80% of cases, and ASP was commonly diagnosed in the first decade of life, whereas incomplete Currarino syndrome was diagnosed predominantly in adults [35-37].

The presacral tumor may be an anterior meningocele (68%), a benign teratomas (18%), an enteric cyst, a dermoid cyst, a lipoma, hamartoma, or, rarely a leimyosarcoma [33].

In our patient the presacral tumor was LPD; no cases of LPD associated with ASP has been previously reported according a MEDLINE search of the English language literature.

In our patient, chronic constipation has been caused primary by vulvar anus and sacral agenesis then probably increased by the extrinsic compression of the presacral mass.

In our patient the sacral bone defect was represented by total sacral-coccygeal agenesis.

Other associated anomalies in the ASP include tethering of the cord, hydrocephalus, duplex ureter, vescicoureteric reflux, hydronephrosis, neurogenic bladder, bicornuate uterus, rectovaginal fistula, hereditary spherocytosis, etc [38].

In the present case we found right hydroureterenephrosis due to the obstruction of the ureteral orifice.

However a definitive diagnosis of Currarino syndrome has not been done in our patient for the lack of reports regarding her relatives and the impossibility to perform any genetic test.

The aim of this report is to suggest an early diagnosis for Currarino syndrome to decrease the future morbidity and mortality. Furthermore evaluation of constipation, especially if it is intractable, represents the first step when Currarino triad is suspected. If two components of the triad are identified, the possibility of the third one (presacral tumor) should be considered. Pelvic ultrasound, CT and MR should be performed to quickly recognize and opportunely treat the tumor.
Competing interests

In the past five years we have not received reimbursements, fees, funding, or salary from an organization that may in any way gain or lose financially from the publication of this manuscript. There is no organization financing this manuscript.

We do not hold any patents relating to the content of the manuscript. We have not received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript.

We have not any other financial competing interests. There are not any non-financial competing interests (political, personal, religious, academic, intellectual, commercial or any other) to declare in relation to this manuscript.

Authors’ contributions

C. N. performed the removal of LPD and wrote the manuscript.
A. D. S. performed the removal of LPD, reviewed the literature and wrote the manuscript.
V. D. M. performed the removal of LPD and wrote the manuscript.
A. S. performed the pediatric surgical procedures and wrote the manuscript.
G.B. performed the surgical procedures and reviewed the literature.
C. M. performed the histological and immunohistochemical evaluations.
M. G. performed the removal of LPD and reviewed THE literature.

All authors read and approved the final manuscript.
References


Legends of figures:

Figure 1: Part of the great irregular complex mass found in the abdominal cavity.

Figure 2: Microscopic appearance of the mass showing low cellularity, without any cytological atypia and few mitoses. Hematoxylin and eosin, 25X.

Figure 3: The immunohistochemical evaluation shows strong positivity for actin, 25 X.