ORIGINAL ARTICLES

The contribution of Magnetic Resonance Imaging in the differential diagnosis between leiomyoma typical, atypical and uterine sarcomas: Personal experience

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Abstract

Purpose: Evaluate the role of Magnetic Resonance Imaging (MRI) in the differential diagnosis between degenerated leiomyomas, cellular leiomyomas and uterine sarcomas.

Materials and methods: From February 2015 to August 2015, 42 patients were enrolled, aged between 18 and 75 years, suffering from uterine "mass" waiting for surgery and considered at risk and/or uncertain clinical and laboratory investigations and imaging. These patients were submitted to MRI exam of the pelvis that was performed by morphological study, DWI sequences and dynamic sequences post-contrastographic.

Results: The analysis of MRI images of the 42 patients made possible to do a diagnosis of uterine sarcomas in 8 patients with the aid of sequences weighted in diffusion and dynamic, proving a sensitivity of 100% and a specificity of 88%.

Conclusions: Based on our experience, we may consider that by morphological study with DWI sequences weighted in diffusion and dynamic post-contrastographic sequences, the MRI is a working aid in the differential diagnosis between degenerated leiomyomas and uterine sarcomas.

Keywords

Uterus, Uterine sarcomas, Degenerated leiomyoma, Cellular leiomyoma, Magnetic Resonance Imaging

1 Introduction

Leiomyomas are the most common benign uterine tumors and the most frequent benign gynecological tumors. They occur in more than 20% of women older than 30 years [1]. They are predominantly composed of smooth muscle cells separated by variable amount of fibrous connective tissue. Exuberant development of these formations, not supported by an adequate blood supply, implicates different types of degeneration: hyaline, myxoid, calcified, cystic and red. Leiomyomas are classified in submucosal, intramural and subserosal; these last ones can be pedunculate and in some cases simulate an ovarian malignancy. Although the leiomyomas are asymptomatic in most of cases, the presence of one or more submucosal fibroids can determine menometrorrhagia or be an obstacle to reproduction (greater rate of abortions); less

frequently the presence of very large leiomyomas may be linked to pressure symptoms on the surrounding structures or to abdominal pain [2, 3].

A particular subtype of leiomyomas is represented by cellular leiomyomas which are composed of compact smooth muscle cells and by a poor or absent connective component [4]. The uterine sarcomas are rare tumors representing approximately 1% of female genital neoplasms and 3%-7% of all uterine cancers [5]. Histologically, they are divided into carcinosarcomas, endometrial stromal sarcomas, leiomyosarcomas (LMS), undifferentiated stromal sarcomas and mullerianadenosarcomas [6]. The complete excision of the tumor is the only effective treatment modality of uterine sarcomas [7].

In April 2014, the *Food and Drug Administration* (FDA) in a *safety communication*, has discouraged the use of morcellator during routine laparoscopic myomectomy or hysterectomy. The warning follows the outcry provoked all around the world for some cases of secondary sarcoma localization occurred, due to the dissemination of cancer cells from uterine sarcomas mis-diagnosed and underwent to laparoscopic morcellation [8-11].

Since we are still lacking a sufficiently sensitive and specific strategy that enable to differentiate preoperatively a myoma from a sarcoma, and there are no signs or pathognomonic symptoms of sarcoma, in a 0.2%-1% of the patients, the diagnosis of uterine sarcoma is set retrospectively on the basis of a definitive histologic diagnosis in patients undergoing a surgery for a clinical suspicion of myoma. In these cases that are not preoperatively diagnosed, the use of electronic morcellator could increase the stage of the disease, encouraging the intra-abdominal dissemination of neoplastic cells, and worsen the prognosis. Thus it is clear the need for an accurate preoperative differential diagnosis between myoma and sarcomas [7].

Although ultrasound represents the first instance investigation in the study for imaging of the female pelvis, it has some limitations in revealing large tumors, due to a limited field of view, and in tissue characterization; moreover there is a significant overlap between the sonographic appearance of degenerated leiomyomas and that of the sarcomas [12-18].

Magnetic Resonance Imaging (MRI) is the most accurate imaging method for the detection and localization of leiomyomas. On T2 images typical leiomyomas appear as circumscribed hypointense masses compared to myometrium [2], while sarcomas appear as large iso-hyperintense masses. The same appearance is shown by cellular leiomyomas and some types of degenerated leiomyomas, which then may mime sarcomas. Therefore, the differential diagnosis between myoma and sarcoma can be difficult if it is just based on conventional sequences without administration of contrast agent [19-21].

Diffusion Weighted Imaging (DWI) in recent studies has shown promising results in the differential diagnosis between benign and malignant gynecological tumours [22-26]. Nevertheless, using DWI in the diagnosis of uterine sarcomas is still limited. Particularly significant are also the post-contrastographic sequences that showed how sarcomas present a quick and avid enhancement compared to benign lesions [27-28]. Recently, according to some authors, the use of post-contrastographic-sequences can provide a more accurate information rather than sequences weighted in diffusion and it is preferable to DWI [29].

Upon these considerations, the aim of our study is to confirm the value of MRI and, especially, of DWI and dynamic post-contrastographic-sequences in the differential diagnosis between degenerate myomas, cellular myomas and sarcomas.

2 Materials and methods

This is a prospective study carried out with the collaboration of the Division of Gynecology and Obstetrics of the University “Magna Graecia” of Catanzaro.

2.1 Population

From February 2015 to August 2015, 42 patients aged between 18 and 75 years have been enrolled. Clinical findings and symptoms are shown in Tables 1 and 2.

Table 1. Chief symptoms of the study patients

Chief symptoms	Leiomyomas (30 cases)	Sarcomas [8]	Adenomyosis and malformation of mullerian ducts [4]
Hypermenorrhea	20	5	5
Anemia	20	7	3
Abnormal genital bleeding	5	3	0
Dysmenorrhea	14	2	3
Prolonged menses	10	3	2
Sterility	10	4	2

Table 2. Clincal findings of the study patients

Variable	Leiomyomas (30 cases)	Sarcomas [8]	Adenomyosis and malformation of mullerian ducts [4]
high levels of total LDH, and/or isoforms (3, 4 and/or 5)	14	6	2
High levels of Ca125	12	5	3
Central vasculature at ECD examination	14	5	0

2.2 Inclusion criteria

Patients suffering from uterine “mass” waiting for surgery, that are considered at risk and/or of uncertain clinical laboratory investigations and imaging interpretation (US).

The risk is defined by:

- onset of uterine masses in postmenopausal women;
- rapid increase in size (> 6 weeks in 9-12 months) [30];
- failure of feedback to the treatment with GnRH analogues;
- high levels of total LDH, and / or isoforms (3, 4 and/or 5);
- high levels of Ca125;
- presence of central and peripheral vasculature, with a low flow resistance, high systolic peak at echo-color Doppler examination (ECD) [31].

All patients expressed informed consent.

2.3 Exclusion criteria

Uncooperative patients or with contraindications to MRI examination.

The same patients have later undergone surgery laparotomic or laparoscopic myomectomy or hysterectomy, so that the clinical, biochemical, and ultrasound data and the one of MRI preoperative could have been related to the final histology data.

Among the 42 patients:

- 14 have undergone laparoscopic myomectomy with protected morcellation;
- 4 have been subjected to laparoscopic hysterectomy;
- 8 have undergone staging surgery (laparotomy with peritoneal washing + bilateral hysteroannessiectomy + lymphadenectomy);
- 2 have been subjected to hysteroscopic biopsy;
- 2 have been subjected to hysteroscopic biopsy + resectoscopy with metroplasty;
- 12 have been subjected to laparoscopic hysterectomy.

These patients had more uterine lesions but we evaluated the most suspicious lesions.

2.4 MRI protocol

Before the MRI investigation, the patients were request to fast for at least 4-6 hours. Few minutes before the test, an antiperistaltic was administered (i.m.) in order to limit motion artefact of the small intestine and a moderate bladder distension. Patients were placed supine. The sequences were acquired through a magnet with high field strength (Philips InteraAchieva 1.5 T) and phased-array coils reaching an excellent anatomic detail of the structures under consideration.

The study protocol includes a morphological study by the acquisition of turbo spin-echo sequences (TSE) T1-weighted, T2-weighted, IR sequences and DWI using three factors of b-values (0, 400, 800 s/mm^2) then it is undertaken a dynamic study with 3D T1 FAT SAT sequences before and after the administration of paramagnetic contrast agent, Gd-BOPTA administered at a dose of 0.1 ml/kg via an automatic injector (Medrad) with a flow of 2 ml/sec, according to the sizes of the axial, sagittal and coronal space. The dynamic study consists of six stages: one using a pre-contrast medium and the others five post-contrastographics.

The sequences acquired at 20, 60, 120, 150 and 180 seconds after the administration of a.d.c. represent another criterion in the differential diagnosis between sarcomas and uterine leiomyomas, because it has been demonstrated that sarcomas show an intense and avid enhancement with respect to the benign formations [27-29]. In addition, in the post-processing it was possible to process the captured images through subtraction and calculation of time-intensity curves. The regions of interest (ROI) were positioned in the areas of identified enhancement, and we performed a “semi-quantitative” analysis, which consists of a numerical measurement of the signal intensity over a period of time, thus creating the time-intensity curves.

2.5 Image analysis

Through the morphological imaging, we’ve evaluated: the seat, the maximum size on three orthogonal planes, the contours (rounded, oval or lobulated), margins (regular or irregular), the components within the lesion (hemorrhagic, cystic, cellular, hyaline, mixoid areas); the presence of fluid effusion, enlarged lymph nodes, the relationship with the surrounding structures. We’ve also evaluated the signal growth to high values of b-value on DWI sequences. Finally, we’ve evaluated the contrastographic behaviour of lesions. In particular, after the injection of a.d.c., the level of enhancement of the lesion has been defined as follows:

- 1 mild enhancement (less than the myometrium); 2 moderate enhancement (as the myometrium); 3 intense enhancement (greater than the myometrium);
- Also time–signal intensity curves have been taken into account;
- One radiologist, blinded to the histological results independently, analyzed MRI datasets of each participant.

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3 Results

Of the 42 patients who underwent surgery, the histological examination gave the following results:

- 14 degenerated leiomyomas;
- 8 sarcomas (4 carcinosarcomas and 4 stromal sarcomas polymorphs of which one of high-grade);
- 16 cellular leiomyomas;
- 2 malformation of mullerian ducts (uterine septum) with associated adenomyosis;
- 2 adenomyosis.

4 MRI features

The different MRI features, DWI and enhancement pattern are shown in Table 3.

Table 3. Comparison of different MRI features, DWI and enhancement pattern

Variable	Leiomyomas (30 cases)	Sarcomas [8]
Tumor margins		
regular	30	0
irregular	0	8
Size (mm)	80 mm	100 mm
T2-weighted signal		
Low	4	0
Intermediate	26	8
T2-weighted signal heterogeneity	26	8
Intra-tumoral haemorrhage	1	0
High b 800 signal	16	8
Heterogeneous enhancement Dynamic contrast enhanced		
early	4	8
later	26	0

Four of the eight sarcomas were carcinosarcoma, all of voluminous dimensions of which one at the stage IV, all of voluminous dimensions. The largest new formation measured 12.6 cm ×3.8 cm ×5.2 cm (D.L × D.AP × DT); it had irregular borders, extended from the uterine fundus to the cervix with the commitment of the endometrial cavity and showed heterogeneous signal intensity due to the presence of fluid components hyperintense on T2 images and solid components hypointense on T1 and T2 images (see Figure 1). It also marked and displaced the bladder formerly-cranially and contracted relations of contiguity/continuity whit the rectosigmoid. Finally in the left iliac and bilateral inguinal regions, there were enlarged lymph nodes and discreet payment extended in the abdominal and pelvic regions. The other sarcomas had the edge not always well-defined, showed etherogeneous hypointense signal on T1 a hyperintense area on T2.

Of the four endometrial stromal sarcomas polymorphic, one was at stage IV. In this case the uterus was no longer identifiable and there was a voluminous formation of 11 cm × 12 cm × 12 cm (D.L × D.A.P × D.T) with irregular margins and heterogeneous structure for the presence of solid components, that were hypointense on T1 and T2, frankly liquid components, hypointense on T1 and hyperintense on T2 and serum/protein as hyperintense on T1. This formation displaced formerly the bladder and bowel loop and then contracted relations of contiguity/continuity with the rectosigmoid. Finally in the bilateral inguinal enlarged there were lymph nodes and a thin fluid collection in the left iliac fossa. The other

formations showed inhomogeneous hypointense signal on T1 images with hyperintense areas on T2/IR and impressed the endometrial cavity.

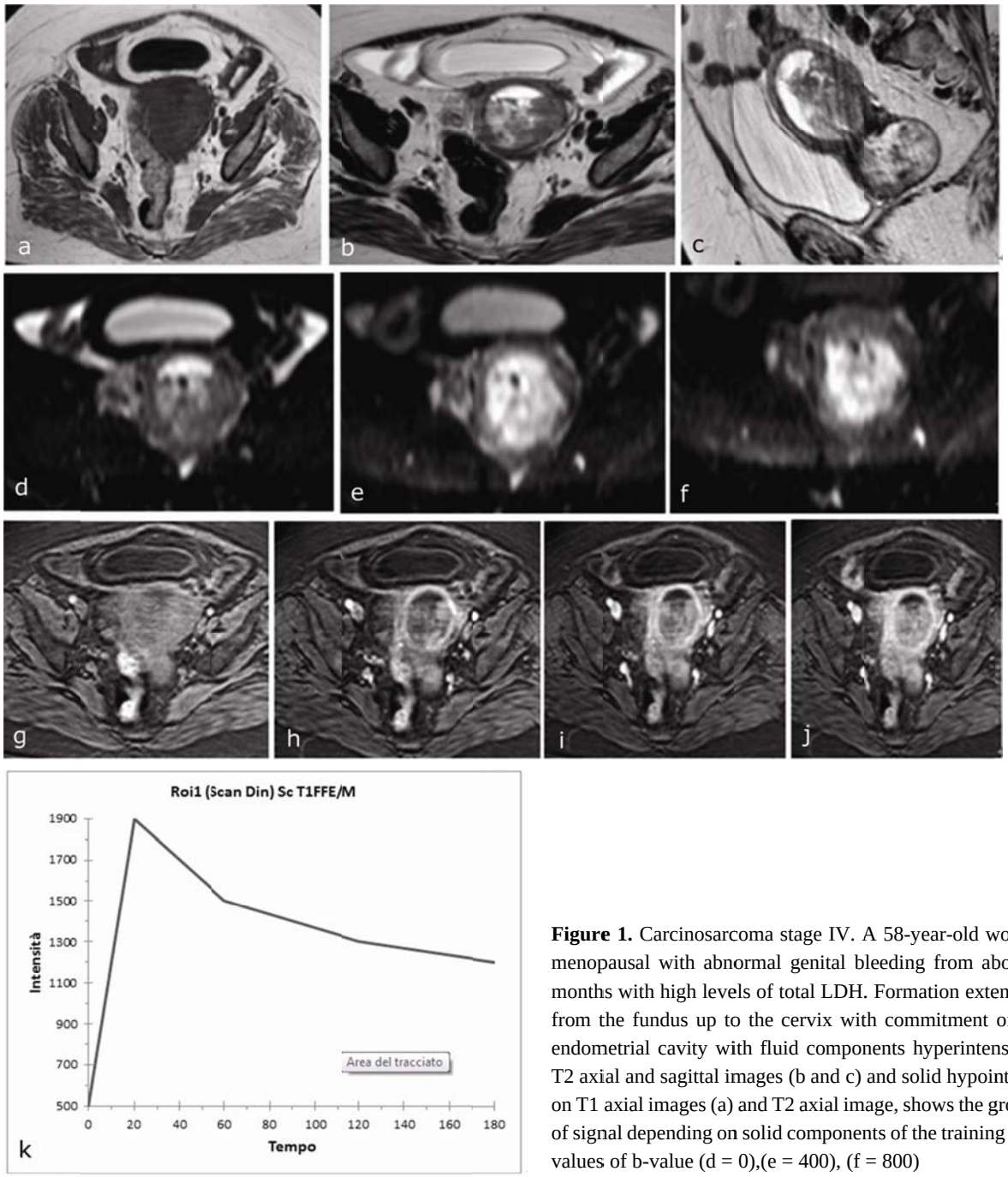

Figure 1. Carcinosarcoma stage IV. A 58-year-old woman menopausal with abnormal genital bleeding from about 3 months with high levels of total LDH. Formation extending from the fundus up to the cervix with commitment of the endometrial cavity with fluid components hyperintense on T2 axial and sagittal images (b and c) and solid hypointense on T1 axial images (a) and T2 axial image, shows the growth of signal depending on solid components of the training high values of b-value (d = 0),(e = 400), (f = 800)

Of the fourteen degenerated leiomyomas all presented themselves as massive formations (7 cm-11 cm) rounded, uneven, 13 of which appeared hypointense on T1 images and T2 images with striae and hyperintense areas on T2/IR images (see Figure 2), while only 1 case had no streaks and spots hyperintense on T1 images as content from serum/protein hemorrhagic. In 10 degenerated leiomyomas, margins appeared well defined, while in 4 cases they came out to be hazy. Enlarged lymph nodes were not present in any case, and in four cases there was a flap of payment in the pelvic.

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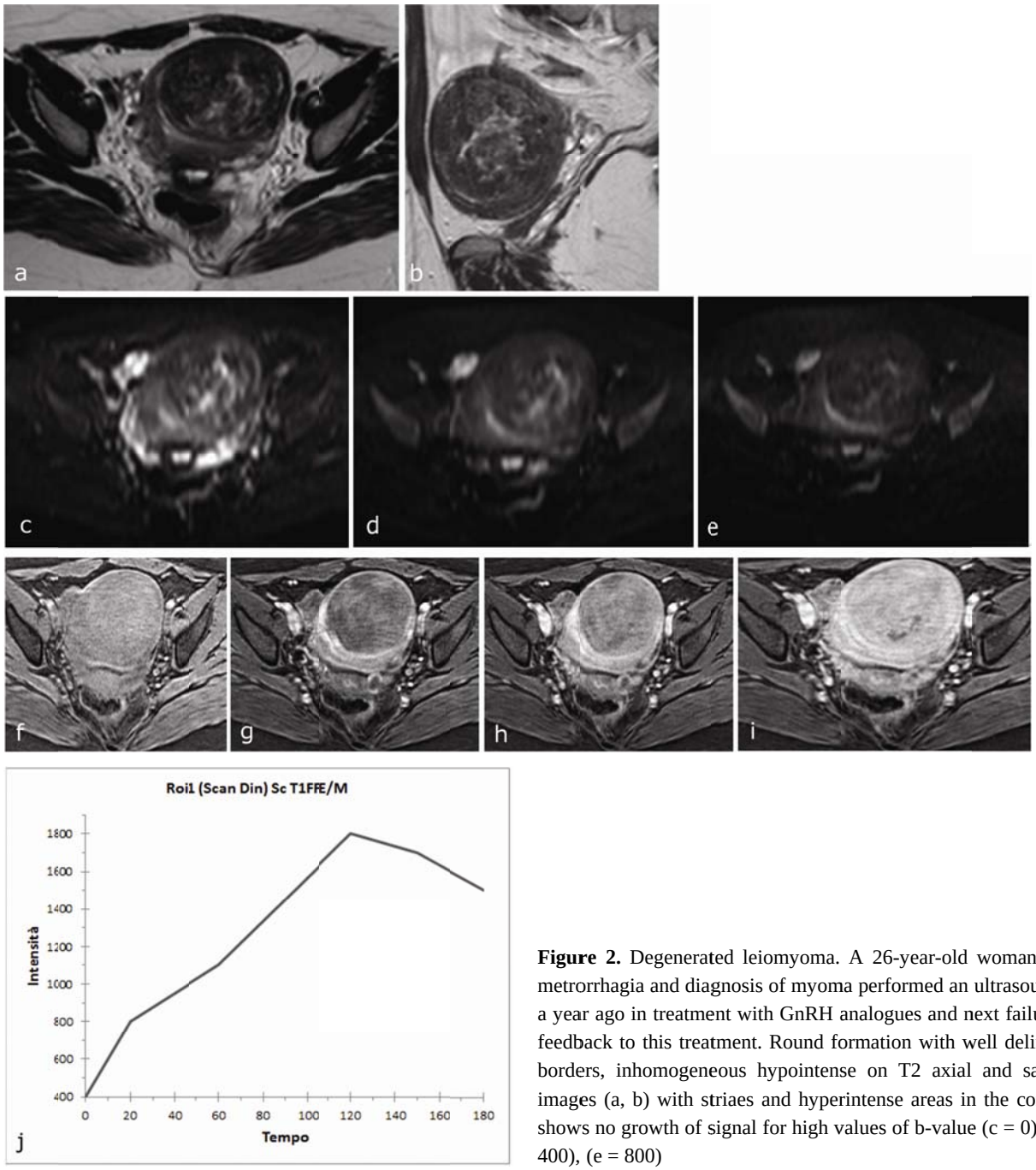

Figure 2. Degenerated leiomyoma. A 26-year-old woman with metrorrhagia and diagnosis of myoma performed an ultrasound to a year ago in treatment with GnRH analogues and next failure of feedback to this treatment. Round formation with well delimited borders, inhomogeneous hypointense on T2 axial and sagittal images (a, b) with striaes and hyperintense areas in the context, shows no growth of signal for high values of b-value (c = 0), (d = 400), (e = 800)

Of the sixteen cellular leiomyomas all the formations showed smooth margins; 15 had bulky size (5 cm-7 cm), while only one was centimeter (see Figures 3, 4). Twelve appeared hypointense on T1 images and T2 images with striaehyperintense on T2/IR images, while 4 were isointense to myometrium on T1 images and hypointense on T2/IR images. In no one case enlarged lymph nodes were present and in 4 cases there was a flap of payment in the pelvic.

Of the 4 patients of where MRI did not show the presence of neo-formations: two presented an anomaly of Muller's duct and a widely uneven appearance of the myometrium with thickening of the junctional zone of about 12 mm associated with cystic areolas, signal of adenomyosis; two cases had a negative outcome of the MRI exam was negative (uterus in AVF within the dimensional limits of the standard and good differentiation of the zonal anatomy without alterations of

focus in the context) and instead we performed biopsies draw blood during hysteroscopy and the outcome of histological analysis showed adenomyosis.

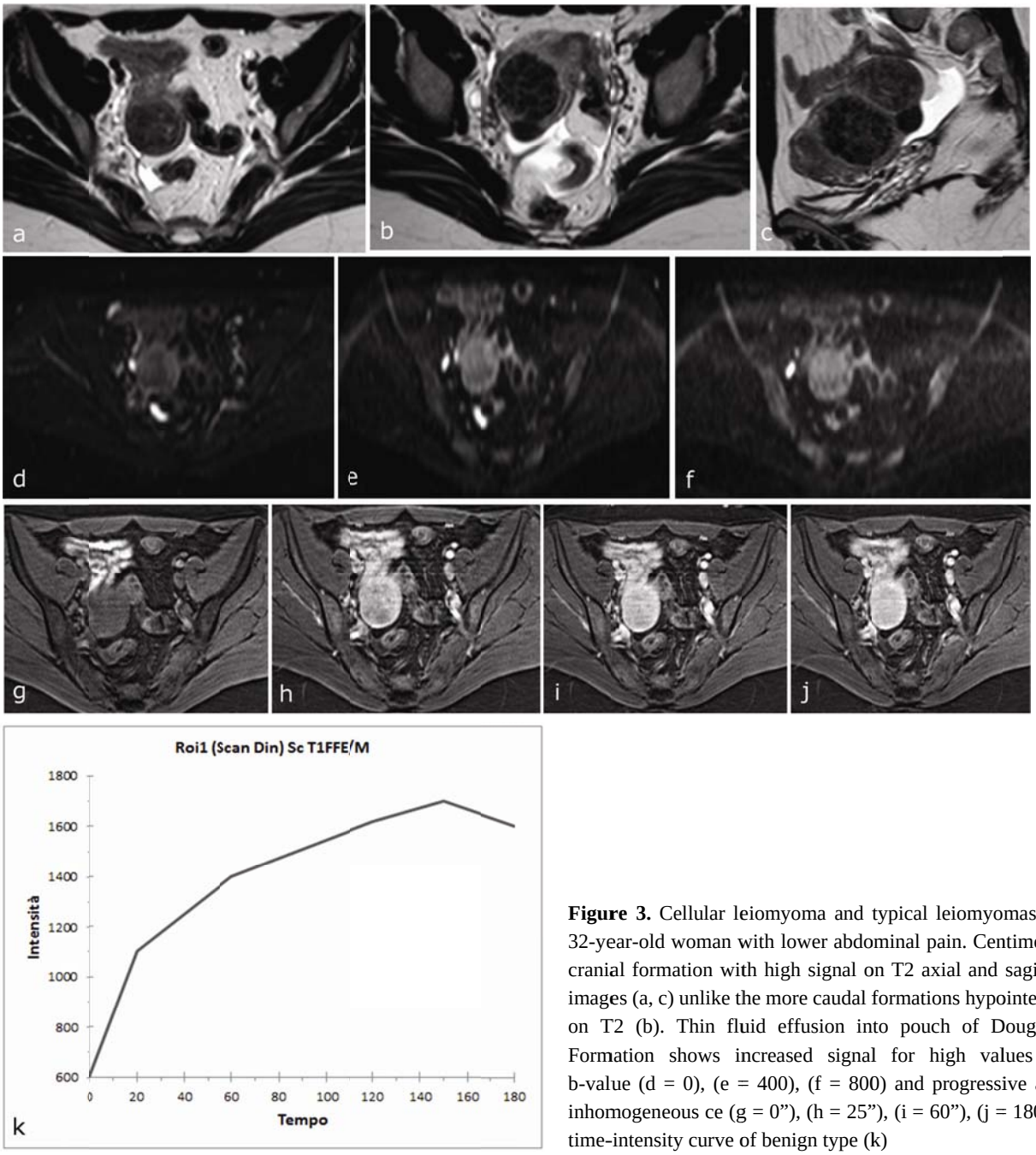

Figure 3. Cellular leiomyoma and typical leiomyomas. A 32-year-old woman with lower abdominal pain. Centimeter cranial formation with high signal on T2 axial and sagittal images (a, c) unlike the more caudal formations hypointense on T2 (b). Thin fluid effusion into pouch of Douglas. Formation shows increased signal for high values of b-value (d = 0), (e = 400), (f = 800) and progressive and inhomogeneous ce (g = 0”), (h = 25”), (i = 60”), (j = 180”), time-intensity curve of benign type (k)

The eight sarcomas showed hypersignal for high values of b-value in particular at the level of solid components (see Figure 1).

The 14 degenerated leiomyomas showed no hypersignal for high values of b-value (see Figure 2).

The sixteen cellular leiomyomas showed hypersignal for high values of b-value (see Figures 3, 4).

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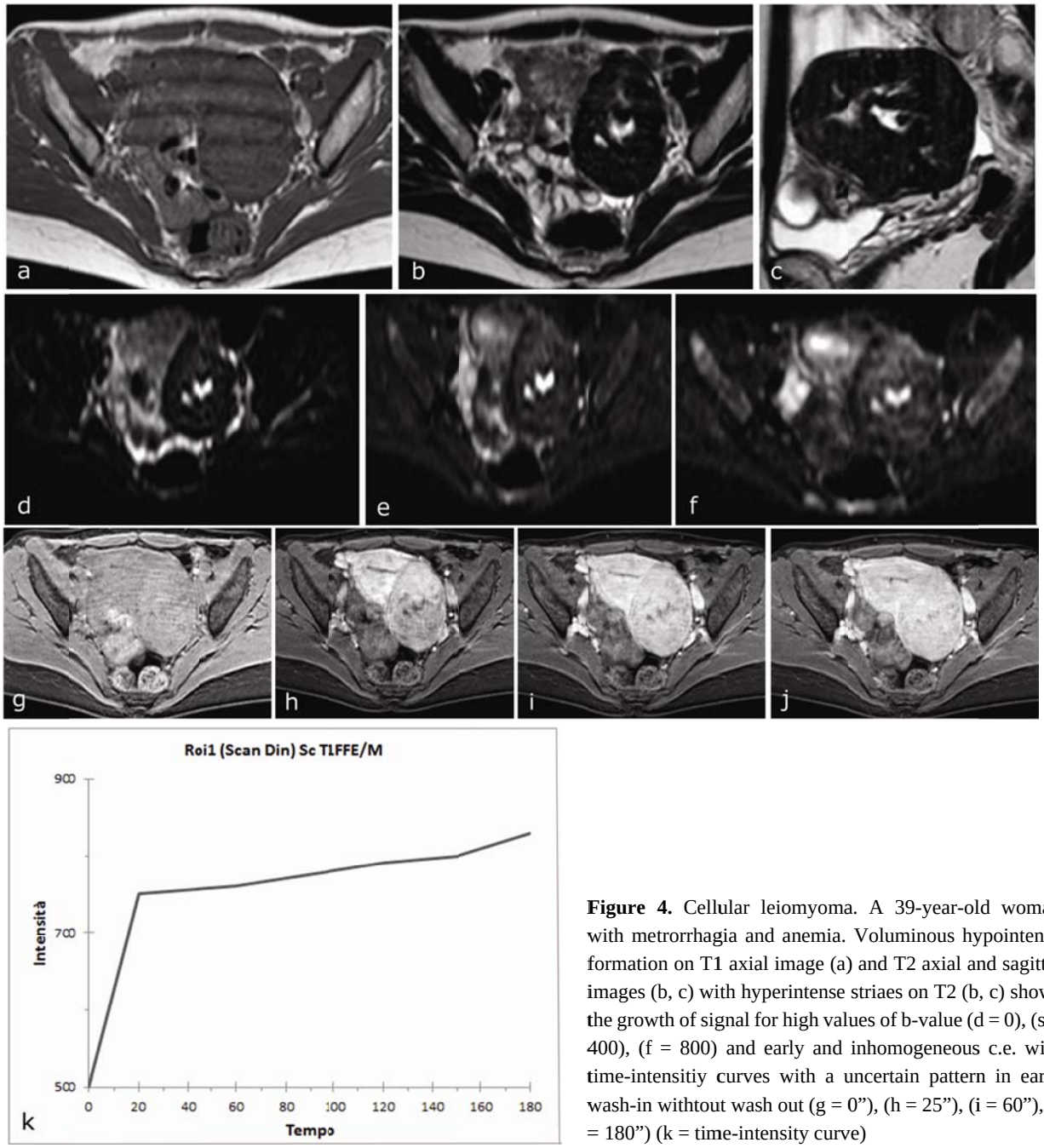

Figure 4. Cellular leiomyoma. A 39-year-old woman with metrorrhagia and anemia. Voluminous hypointense formation on T1 axial image (a) and T2 axial and sagittal images (b, c) with hyperintense striaes on T2 (b, c) shows the growth of signal for high values of b-value (d = 0), (s = 400), (f = 800) and early and inhomogeneous c.e. with time-intensitiy curves with a uncertain pattern in early wash-in withtout wash out (g = 0"), (h = 25"), (i = 60"), (j = 180") (k = time-intensity curve)

The eight sarcomas showed an early and intense c.e after i.v. infusion of a.d.c. (see Figure 1) with time-intensity curves with pattern of malignant type characterized by rapid wash-in and wash-out fast.

The 14 degenerated leiomyomas showed progressive tenuous and uneven c.e. after i.v. infusion of a.d.c. (see Figure 2), with time-intensity curves with pattern of benign type characterized by slow and progressive wash-in without a clear washout .

Of the sixteen cellular leiomyomas:

- 8 showed progressive and inhomogeneous c.e. (see Figure 3);

- 2 showed nuanced and progressive c.e.;
- 2 showed progressive and more evident in the late stages c.e.;

with time-intensity curves with pattern of benign type characterized by slow and progressive wash-in without a clear washout.

Only for four cellular leiomyomas whose morphology was correctly directed by-MRI, the post-contrast-MRI offered different possible interpretation: the formations, indeed, showed early and inhomogenous c.e. with time-intensity curves with type doubt pattern characterized by early wash-in without obvious wash-out (see Figure 4).

5 Discussion

Leiomyomas are the most common benign uterine tumors in young women. They occur in 20% of women over 30 years old.

Uterine sarcomas are rare tumors representing approximately 1% of cancers of the female genitalia and 3%-7% of all uterine cancers [5]. To date there is no sufficient and sensitive method to allow an accurate preoperative differential diagnosis between myoma and sarcoma yet.

However, recent studies suggest that MRI through diffusion and post-contrastographic sequences, represent emerging valuable technique for the differential diagnosis between degenerate leiomyoma and sarcomas [21, 22, 25-28].

According to some authors, high signal intensity in DWI in malignant tissue is attributed to his topathological characteristics, including hypercellularity, enlargement of nuclei, hyperchromatisms and angulation of the nuclear contour, that result in a reduction of diffusional displacement of water molecules [23].

Leiomyomas showed variable signal intensity on T2-weighted images, and may reflect a wide variety of histological features depending on degeneration or cellular content with abundant hyalinised collagen.

Tamai *et al.* [22, 23] demonstrated that cellular leiomyomas may not be distinguished from sarcomas based on DWI by increased cellularity. On the other hand, degenerated leiomyomas tended to exhibit low SI on DWI compared with sarcomas.These results mayreflect the presence of abundant water content within thelesions. A ccordingly, DWI can aid inthe differentiation between degenerated leiomyomas andsarcomas.

According to some authors, in our study the cellular leiomyomas and sarcomas showed hypersignal for high values of b-value. Instead, the degenerated leiomyomas showed no hypersignal for high values of b-value.

According to some authors, even post-contrastographic sequences allow to obtaine more precise data compared to DWI sequences [29].

Lin *et al.* demonstrated that CE-MRI yielded significantly higher diagnostic accuracy and specificity as compared with DWI, in differentiation between sarcomas and benign leiomyomas [29].

The sarcomas showed early and avid enhancement on contrast-enhanced images [24].

In our study, the sarcomas showed an early and intense enhancement on contrast-enhanced images with time-intensity curves with pattern of malignant type characterized by rapid wash-in and wash-out fast. The 26 leiomyomas showed progressive tenuous and uneven enhancement on contrast-enhanced images, with time-intensity curves with pattern of benign type characterized by slow and progressive wash-in without a clear washout.

Only four cellular leiomyomas showed early and in homogenous enhancement on contrast-enhanced images with time-intensity curves with type doubt pattern characterized by early wash-in without obvious wash-out.

The true positive, false positive, true negative and false negative results are shown in Table 4.

Table 4. True positive (TP), false positive (FP), true negative (TN) and false negative (FN) results

	M+	M-
T+	8 (TP)	4 (FP)
T-	0 (FN)	30 (TN)

Statistical analysis of our study shows an increased sensitivity of 100% in using diffusion-weighted and post-contrastographic sequences compared to morphological examination, a specificity of about 88%, a PPV of about 66%, a NPV of about 100% and a diagnostic accuracy of about 90%.

We cathegorized leiomyomas into histopathological subtypes. Our population study include patients with other benign myometrial conditions, such as adenomyosis.

Our results show that combined DWI and post-contrastographic sequences is better than DWI alone in the differentiation of uterine sarcomas from benign leiomyomas, especially from cellular leiomyomas.

However the limitations of this study are represented by the low number of reported uterine sarcomas and by the size of the sample. Thus, a larger study should be prospectively performed to verify our results.

6 Conclusions

In clinically uncertain cases, DWI and dynamic sequences allowed us to distinguish sarcomas from cellular and degenerate leiomyomas as sarcomas showed hypersignal in diffusion-weighted sequences and early and high c.e. in post-contrastographic sequences, with time-intensity curves of malignant type.

The DWI along with dynamic sequences could be a valuable tool to support radiologists in the differential diagnosis of atypical leiomyoma, cellular and uterine sarcomas. Such data may allow the gynecologists the most appropriate approach to a single patient.

Conflicts of interest disclosure

The authors have declared no conflicts of interest.

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