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Uterine Cellular Leiomyomata with Chromosome 1p Deletions Represent a Distinct Entity

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Abstract

OBJECTIVE—This study aims to determine whether 1p deletion defines a subset of cellular leiomyomata (CL), a hypercellular variant of uterine leiomyomata (UL) that may have delayed malignant potential, and correlate this genetic change with clinical and pathologic characteristics including those present in uterine sarcomas.

STUDY DESIGN—Available CL cases at Mayo Clinic (n=101) and variant cases reported by Giuntoli *et al.* (n=16) were identified. Each case with sufficient tissue that met histologic criteria for CL when reviewed by a single pathologist underwent interphase FISH to determine the presence of 1p deletion. Clinical characteristics of women with confirmed CL were compared on the basis of 1p deletion status using univariate analysis.

RESULTS—Of the Mayo cohort of histologically confirmed CL, 23% had deletion of 1p. Women with this subset of CL when compared to those without 1p deletion were more likely to be postmenopausal (P=0.049) and their uteri tended to be heavier (P=0.039) with a larger dominant leiomyoma (P=0.030). The pathological features associated with 1p deletion were high cellularity (P=0.036) and hyaline necrosis (P=0.047), which remained significant after inclusion of the CL cases from the Giuntoli *et al.* series.

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CONCLUSION—Deletion of 1p occurs in approximately one-quarter of CL. This genetic alteration is potentially associated with clinicopathologic features present in uterine sarcomas, suggesting a distinct clinical entity that may have malignant potential. Our findings are particularly pertinent considering the increased preference for uterine-sparing options in leiomyoma treatment, suggesting assessment of 1p deletion status in CL may influence clinical surveillance decisions.

Keywords

cellular leiomyomata; chromosome 1p; FISH; leiomyosarcoma; uterine leiomyomata

INTRODUCTION

Uterine leiomyomata (UL), commonly referred to as fibroids, represent a major concern in women's health due to their high prevalence, morbidity, and impact on the health care system. UL arise from the smooth muscle layer of the uterus known as the myometrium in up to 77% of women based on systematic review of hysterectomy specimens.¹ These benign tumors result in significant morbidity in many of the ~25% of reproductive-age women in whom they are clinically detected with symptoms including abdominal pain, heavy and prolonged menstrual bleeding, urinary incontinence, constipation, and fertility impairment.²⁻⁴ In the United States, such frequency and high morbidity result in UL accounting for one-third of hysterectomies and ever increasing expenditures, up to an estimated \$5.9 to \$34.4 billion annually.⁵⁻⁸

UL are typically comprised of whorled bundles of smooth muscle cells forming well-circumscribed nodules with abundant pink cytoplasm, uniform spindle-shaped nuclei and scant and normal mitoses.⁹ In contrast, cellular leiomyomata (CL) represent a variant that is significantly more cellular and occurs in <5% of cases.^{9,10}

Although historically CL have been clinically approached as being within the benign spectrum of typical UL, developing evidence suggests that CL may have long-term malignant potential. A recent case-control analysis of CL defined solely by pathologic review versus typical UL demonstrated that CL cases have a distinct clinical phenotype with a subset of characteristics overlapping those in leiomyosarcoma (LMS).¹¹ Three of 18 women with CL or atypical leiomyomata (AL) variants were also shown to have disease-related deaths (*i.e.* deaths directly connected to the variant tumors) occurring >6 years after diagnosis in contrast to the benign outcome of typical UL or the poorer prognosis of LMS.¹² In addition, chromosome and loss-of-heterozygosity analyses identified a limited number of CL with chromosome 1p deletion, and the expression profile of one such tumor segregated with LMS rather than the normal uterine tissue (myometrium) or typical UL in a hierarchical cluster analysis.¹³

The current study demonstrates that 1p deletion is a common genetic abnormality in CL and suggests a correlation between 1p deletion status with certain pathologic characteristics and the clinical phenotype of the women in whom these variant tumors arise.

MATERIALS AND METHODS

Study Design and Participants

Approval for this study was obtained from the Mayo Clinic Institutional Review Board. Formalin-fixed paraffin-embedded (FFPE) tissues of pathologist-designated CL were acquired from Mayo Clinic surgical specimens between 1/89 and 12/08, which represents the same cohort as our case-control analysis of women with a CL (n=94 as five blocks were not available)¹¹, as well as CL cases identified subsequent to that study (n=7). A single CL tumor was analyzed from each patient. In addition, FFPE tissues from the leiomyoma variant cases studied by Giuntoli *et al.* were included (n=16 as two blocks were not available).¹² A fresh hematoxylin and eosin (H&E) stained section from each case was reviewed by a single pathologist using accepted criteria by Bell *et al.*¹⁴, which includes the assessment of cytologic atypia (degree: mild, moderate or severe; and extent: focal or diffuse), mitotic index (mitotic figures per 10 high power fields), as well as the presence or absence and quality of necrosis (coagulative, degenerative/hyaline or hydropic). Additional histologic characteristics were recorded such as epithelioid features, myxoid change and cellularity (mild, moderate, high). CL was diagnosed when the specimen was highly cellular but lacked significant cytologic atypia or coagulative type necrosis. The diagnosis of CL was accepted in the presence of elevated mitotic index (up to 10 mitotic figures per 10 high power fields) if cytologic atypia or coagulative necrosis was not identified. A mitotic index of 4 mitotic figures per 10 high power fields in combination with moderate or severe atypia or any mitotic activity in the presence of coagulative necrosis was not classified as CL (*i.e.* diagnosed as LMS). The H&E slides were also used to delineate the region of interest for subsequent determination of 1p deletion status using interphase fluorescence *in situ* hybridization (FISH).

Retrospective review of Mayo Clinic patient medical records resulted in ascertainment of clinical, intraoperative and pathologic information. Premenopausal status was defined as the occurrence of at least one menstrual period in the 12 months prior to surgery. Leiomyoma recurrence is based on either radiographic or pathologic evidence of new tumors after the initial surgery. The mean clinical follow-up in the entire 67 cases of the Giuntoli *et al.* series was 3.7 years/44.4 months and the median follow-up for uterine disease-specific survivors was 15.6 years/187.2 months while the mean of the Mayo cohort was 4.85 years/58.2 months.

Probe Design

The enumeration probe set included a 1p21.1 target region probe, labeled in Spectrum Orange-dUTP (Abbott Molecular) which gives a red appearing signal, that consisted of RP11-729K11, RP11-701D1, CTD-2306N18, RP11-10C14, and CTD-2310O4 (572 kb total size). The control probe at 1q25.2, labeled in Spectrum Green-dUTP (Abbott Molecular), contains RP5-990P15, RP5-1098D14, RP11-18E13, and RP4-595C2 (470 kb total size with a 75 kb gap). The second control probe at 1q21.3, labeled in Spectrum Aqua-dUTP (Dyomics, Jena, Germany), contains RP11-48P22, CTD-2147N16, RP11-204K12, CTD-3011N3, RP11-936M7, and RP11-68O11 (572 kb total size).

FISH

All samples, including both those meeting criteria for CL and those given an alternate designation by a single pathologist, were randomly sorted and analyzed in a blinded manner (without knowledge of the pathologic diagnosis). Two technologists independently scanned the entire tissue section to assess tumor heterogeneity and then each scored 50 representative nuclei. Cases were considered to have “1p deletion” that had loss of the 1p signal in >15% of nuclei while cases were called “relative 1p deletion” that had fewer 1p signals compared to additional copies of the 1q control probes in >15% of nuclei. The data were subsequently decoded and compared to the pathologic and clinical findings. The conservative false-positive cut-off of 15% for 1p deletion was established by approximately doubling the positive rate found in typical UL.

Statistical Analyses

Data were coded and entered into an Excel database (Microsoft, Redmond, WA, USA). Statistical analyses were performed using JMP for Windows, 7.0.1 (SAS Institute, Cary, NC, USA). For non-normally distributed continuous variables, means and standard deviations are reported while differences between groups of women were assessed using Wilcoxon rank-sum tests. For nominal or categorical variables, frequency counts and percentages are reported while differences between groups of women were assessed using Pearson's χ^2 or Fisher's exact test, as appropriate. $P < 0.05$ was considered statistically significant in all analyses.

RESULTS

Frequency of 1p Deletions in Mayo Clinic Cohort of CL

UL arise from the uterine myometrium and are usually defined on H&E stain by fascicles of smooth muscle cells with abundant pink cytoplasm, uniform spindle-shaped nuclei and a low mitotic index (Figure 1A). In contrast, the pathologic variant CL is similar but significantly more cellular (Figure 1B). Of cases originally diagnosed as CL that had available tissue from the Mayo Clinic cohort (n=101), the majority were confirmed by a single pathologist as CL (n=85 which includes 17 with hyaline necrosis) while a subset of cases were classified with other designations (n=16); specifically, typical UL (n=4 for those with hyaline necrosis and n=7 for those without hyaline necrosis), AL (n=1), AL with low recurrence risk (n=1), smooth muscle tumor of unknown malignant potential or STUMP (n=2), and mixed endometrium stromal and smooth muscle neoplasm (n=1).

To identify 1p deletions, an enumeration FISH probe set was developed that targeted 1p21.1 (red) with control probes at 1q21.3 (aqua) and 1q25.2 (green) (Figure 2A). Interphase nuclei from tumors with the normal complement of two copies of chromosome 1 exhibit a 2R2G2A signal pattern (Figure 2B). A typical deletion of the 1p target region results in a 1R2G2A pattern (Figure 2C) while the presence of additional copies of the controls probes with relative loss of the 1p target probe presents with multiple patterns such as 2R4G4A (Figure 3D). The target region on 1p was selected as 1p21.1 based on the smallest region of

overlapping LOH in 10 cases of CL as defined by the polymorphic microsatellite markers employed in a recent study.¹³

Using this FISH strategy, 23% (18 out of 79) of the confirmed CL in the Mayo cohort was shown to have a 1p deletion, 6% (5 out of 79) had relative loss of 1p, and 71% (56 out of 79) were normal. FISH was not possible on a subset of confirmed CL cases due to failed hybridization (n=6). All cases with pathologic designations other than CL (n=16) were normal by FISH analysis.

Frequency of 1p Deletions in Giuntoli *et al.* Series of Leiomyoma and Uterine Tumor Variants

Sixteen of 18 leiomyoma variant cases presented in a series examining updated criteria for LMS diagnosis¹², which were originally reported as AL (n=4) and CL (n=12), were available for further study. Re-examination of these cases by a single pathologist in the current effort reclassified the AL tumors into CL (n=3) and LMS with epithelioid features (n=1) while the CL cases were described as CL (n=7 which includes 1 with hyaline necrosis and 1 with epithelioid features), AL (n=1), UL (n=1), LMS (n=1), mixed endometrial stromal/smooth muscle neoplasm (n=1), and adenofibroma (n=1).

FISH on the Giuntoli *et al.* series demonstrated a typical deletion of 1p in 47% (7 out of 15), relative loss of 1p in 6% (1 out of 15), and a normal result in 47% (7 out of 15). FISH was not possible on a single CL case due to failed hybridization. The 7 cases with a typical deletion of 1p were classified as CL (n=4 which includes 1 with epithelioid features), LMS (n=2 which includes 1 with epithelioid features), and UL (n=1). The single case with relative loss of 1p was a CL. The 7 cases with normal FISH results were categorized as CL (n=4 including 1 with hyaline necrosis), AL (n=1), mixed endometrial stromal/smooth muscle neoplasm (n=1), and adenofibroma (n=1).

Thus, in the combined Mayo cohort and Giuntoli *et al.* series of tumors confirmed to be CL by a single pathologist that were successfully evaluated by FISH, 25% of cases (22 of the 88 total CL) had 1p deletion.

Univariate Analysis

Univariate analysis was used to compare the clinical characteristics of women with CL based on 1p deletion status and confined to those with tumors confirmed by a pathologist using current criteria to be CL with successful FISH after removal of tumors with relative 1p deletion (n=18 CL with 1p deletion and n=56 CL without 1p deletion) (Table 1). The number of women included in the analysis of each clinical characteristic was based on data availability with a minimum of 16 from the 1p deletion group and 52 from the group without 1p deletion. In the Mayo cohort, women with a CL that had 1p deletion were more likely to be postmenopausal (27.8 vs 9.0 %; P=0.049) and had heavier uteri (1028.1±1385.0 vs 574.3±613.0 grams; P=0.039) with a larger dominant leiomyoma (10.6±4.9 vs 8.0±4.6 %; P=0.030). The pathological features associated with 1p deletion were high cellularity (38.9 vs 14.3 %; P=0.036) and hyaline necrosis (38.9 vs 17.9 %; P=0.047). It is of note that the

single CL case with a 1p deletion that had a recurrence in Table 1 has been clinically classified as a benign metastasizing leiomyoma (BML).

Using the same criteria for inclusion, cases from the Giuntoli *et al.* series were combined with the 74 CL cases from Table 1 and univariate analysis was applied (n=22 CL with 1p deletion and n=60 CL without 1p deletion) (Table 2). The pathological features of high cellularity (45.5 vs 18.3 %; P=0.022) and hyaline necrosis (41.0 vs 18.3 %; P=0.045) remained statistically significant.

COMMENT

Cellular leiomyomata represent a relatively rare subgroup of UL that are hypercellular. Recent evidence has brought into question the historical association of CL with a benign clinical course and suggested 1p deletions may be associated with malignant behavior. Such a question of clinical significance has been answered for another pathologically defined uterine tumor variant, plexiform leiomyomata, with molecular evidence supporting a benign classification.¹⁵ This inspired the present study to correlate the clinical characteristics and 1p deletion status in a large cohort of CL cases.

In 2007, a retrospective study of medical records from 1976 to 1999 of 67 “uterine LMS” was conducted in which the tumors were reclassified as 47 LMS, 13 CL, 5 AL, and 2 UL using contemporary pathologic criteria.¹² The median survival from the time of diagnosis (defined relative to the primary surgical procedure date) was 2.1 years for LMS and >25 years for the leiomyoma variants. However, there were 3 disease-specific deaths among the 18 leiomyoma variants (1 CL and 2 AL) that occurred 6 to 11 years after diagnosis, suggesting delayed malignant behavior or malignant evolution.

A concurrent study identified 6 leiomyoma variant cases (5 CL and 1 AL) with karyotypes that included 1p deletions while loss-of-heterozygosity analysis of an additional 10 leiomyoma variants (8 CL and 2 AL) demonstrated 1p deletions in 5 of the CL tumors. Transcriptional profiling of two such tumors (1 CL and 1 AL) showed their alignment with malignant LMS in a hierarchical cluster analysis, which was based on the expression of 146 genes previously shown to segregate myometrium, typical benign UL and malignant LMS.¹³ These results provided further evidence that CL may have malignant potential and suggested 1p deletion may be a frequent aberration in CL.

A case control analysis was also recently completed in which medical records from 99 women with a diagnosis of CL who had surgery at Mayo Clinic between 1989 and 2008 were compared to those of matched controls (*i.e.* women with UL that had the same surgical procedure performed by the same surgeon within 2 years of the CL case).¹¹ A multivariate analysis demonstrated that women with CL were significantly younger and had more surgery for leiomyoma-related symptoms. In addition, CL were similar to LMS as they were usually either the largest or only uterine mass. Therefore, CL have a clinical phenotype that is distinct from typical UL including some characteristics that overlap with those of LMS.

The current investigation expands this Mayo cohort and also includes leiomyoma variants from the Giuntoli *et al.* series to determine whether 1p deletion defines a subset of CL and is

associated with distinct clinical behaviors. The finding of 1p deletion in 23% of the Mayo cohort indicates that this genetic change is common in CL. Deletion of 1p also appears to be relatively specific for CL compared to typical UL or other leiomyoma/uterine tumor variants; only two LMS cases and one UL with borderline cellularity had 1p deletion while all other uterine tumor entities in both the Mayo cohort and the Giuntoli *et al.* series were normal.

The finding of 1p deletion in two LMS cases is consistent with the literature as a study using chromosomal microarray identified recurrent chromosome 1 imbalances in LMS.¹⁶ This is interesting considering leiomyomata may evolve into LMS despite the disparate population frequency of these two entities. It is therefore possible that a specific subset of leiomyomata such as CL with 1p deletion give rise to LMS. Alternatively, having 1p deletions in common could indicate this genetic change is a general marker of aggression in uterine neoplasms.

The expanded Mayo cohort was also interrogated using univariate analysis which demonstrated that having a CL with 1p deletion versus those without 1p deletion was associated with heavier uterine/compound weight, postmenopausal status, a larger dominant leiomyoma, and tumor hypercellularity and hyaline necrosis. Similar clinical characteristics were associated with CL in contrast to typical UL in the previous case control study¹¹; this suggests that tumors with 1p deletion could be the subset of CL that drive this leiomyoma variant to present as a distinct clinical entity. Importantly, such characteristics also occur in uterine sarcomas, suggesting that CL with 1p deletions may fall on the malignant side of the uterine mass spectrum rather than with typical benign UL.

The question of whether a subset of CL have malignant potential was initially raised in 2007 due to evidence of delayed disease-related death of leiomyoma variants.¹² We therefore included this case series in our analysis to assess whether 1p deletion is related to clinical outcome. Of the available cases that were confirmed by a single pathologist to be CL using current criteria, typical deletion of 1p occurred in 44% (4 out of 9), a percentage that is even higher than that observed in the Mayo cohort. However, the mean clinical follow-up in the entire 67 cases of the Giuntoli *et al.* series was 3.7 years/44.4 months and the median follow-up for uterine disease-specific survivors was 15.6 years/187.2 months, which is distinctly longer than that of the Mayo cohort (mean=4.85 years/58.2 months, median=3.0 years/36.0 months). In addition, only one of the three variant leiomyoma or uterine tumor cases in the Giuntoli *et al.* series associated with disease-related deaths was considered a CL and available for further study. Finally, of the Mayo cohort of women with confirmed CL excluding cases in which FISH failed or there was relative 1p deletion, 20% had uterine-sparing procedures (n=10 myomectomies and n=5 hysteroscopic resections out of 74 total) while 80% had hysterectomies (n=59 hysterectomies out of 74 total), which limits the cases that can be assessed for clinical recurrence. Longer-term prospective follow-up of the Mayo cohort is therefore needed to confirm a subset of CL have delayed malignant potential and to further explore whether the presence of 1p deletion predicts aggressive behavior.

Within the available follow-up time frame, a single case with leiomyoma recurrence was identified in the Mayo cohort from whom the primary CL had a 1p deletion. This 40-year old woman was diagnosed with pulmonary benign metastasizing leiomyoma (BML) that

became evident 120 months after vaginal hysterectomy for multiple CL.¹¹ Previous patients with BML similarly had antecedent CL.^{14,17-22} Thus, CL and BML may share a common pathogenic mechanism and may even be different manifestations of the same disease.¹¹

It is of note that, while cases originally classified as CL could be evaluated for inclusion in the present study, cases of CL originally designated as typical UL based on variable diagnostic criteria or pathologist sensitivity to the presence of this variant are not possible to ascertain. This limits the ability to identify the true population frequency of CL, although we did not find any correlation between 1p deletion status and year of diagnosis ($P=0.782$). In addition, expert pathologists can have diagnostic disagreement even using accepted criteria, as demonstrated by the findings of the Giuntoli *et al.* series. A molecular marker such as 1p deletion may therefore be particularly useful as an adjunct of histologic review to enhance diagnostic consistency and possibly identify the subset of leiomyoma cases that could have the potential for extended clinical aggressiveness.

In summary, this study demonstrates that 1p deletion is a recurrent abnormality in CL that is present in a significantly high proportion of tumors (~25%). Further, the difference in clinical characteristics of CL depending on the presence of 1p deletion suggests the presence of this molecular signature may define a distinct clinical entity and has the potential to help classify delayed malignant behavior, although longer term follow-up is needed. Considering the expansion of uterine-sparing treatment options, 1p deletion status may significantly influence clinical surveillance decisions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Pathologic characteristics of leiomyomata. Hematoxylin and Eosin stain at 100x and 400x magnification of a typical uterine leiomyoma (**A**) versus a cellular leiomyoma (**B**) demonstrates the significant contrast in hypercellularity that defines the pathologic variant.

Figure 2.

FISH probe design and signal pattern interpretation. (A) The chromosome 1 probe set is composed of clones for the target region at 1p21.1 (red) and the control regions at 1q21.3 (aqua) and 1q25.2 (green). (B) A normal signal pattern is 2R2G2A, which represents two copies each of the target and control probes. (C) Deletion of the 1p target region labeled in red results in the signal pattern 1R2G2A. (D) Relative deletion of the 1p target region, which is defined by fewer red signals on 1p compared to additional copies of the green and aqua control signals on 1q, presented as variable patterns including the example given of 2R4G4A.

Table 1

Clinical and pathologic characteristics of women with CL with 1p deletion versus no deletion excluding Guintoli *et al* case series¹

Variable	CL with typical 1p deletion n=18	CL with no deletion n=56	P
Clinical Features			
Age, years (mean, SD)	50.72 (14.60)	44.32 (10.08)	0.114
Uterine/Compound ² /Tissue ³ weight, g (mean, SD)	1028.06 (1384.96)	573.95 (612.97)	0.039
Number leiomyomata (mean, SD)	3.67 (3.40)	4.32 (5.66)	0.463
Number cellular myomas	1.11 (0.47)	1.36 (2.29)	0.978
Diameter of largest leiomyomata, cm	10.6 (4.86)	8.02 (4.56)	0.030
Postmenopausal, n (%)	5 (27.80)	5 (9.0)	0.049
Postmenopausal bleeding, n (%)	3 (16.67)	2 (3.60)	0.052
CL recurrence, n (%)	1 (5.56)	4 (7.14)	0.243
Surgery for CL recurrence, n (%)	1 (5.56)	4 (7.14)	0.243
Largest leiomyomata CL?, n (%)	18 (100)	51 (91.10)	0.416
Surgical indication enlarging CL, n (%)	5 (27.80)	11 (19.64)	0.803
Increasing abdominal girth	1 (5.56)	5 (9.0)	0.650
Pathologic Features			
High cellularity, n (%)	7 (38.89)	8 (14.29)	0.036
Hyaline necrosis, n (%)	7 (38.89)	10 (17.86)	0.047

¹ Cases from previously reported Mayo Clinic leiomyoma variants series (Guintoli *et al*., 2007).

² The weight of attached ovaries and/or fallopian tubes was included in a subset of cases.

³ The weight of only the available collected tissue was included in patients that underwent uterine sparing therapies.

Table 2
Clinical and pathologic characteristics of women with CL with 1p deletion versus no deletion including Giuntoli *et al* case series¹

Variable	CL with typical 1p deletion n=22	CL with no deletion n=60	P
Clinical Features	Age, years (mean, SD)	44.81 (10.25)	0.337
	Uterine/Compound ² /Tissue ³ weight, g (mean, SD)	580.66 (598.73)	0.078
	Diameter of largest leiomyomata, cm	8.02 (4.47)	0.083
	Postmenopausal, n (%)	6 (10.0)	0.151
Pathologic Features	High cellularity, n (%)	11 (18.34)	0.022
	Hyaline necrosis, n (%)	11 (18.34)	0.045

¹ Cases from previously reported Mayo Clinic leiomyoma variants series (Giuntoli *et al*., 2007).

² The weight of attached ovaries and/or fallopian tubes was included in a subset of cases.

³ The weight of only the available collected tissue was included in patients that underwent uterine sparing therapies.