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Specific Histology Type of Leiomyoma Related to Estrogen Receptor Expression

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Abstract

Uterine Leiomyoma or fibroid is the most common gynecologic benign neoplasm arising from the monoclonal proliferation of smooth muscle cells in the uterine wall. Some specific types of uterine leiomyoma, such as *cellular leiomyoma, atypical leiomyoma, mitotically active leiomyoma*, and *myxoid leiomyoma* have different histomorphology from the usual type leiomyoma. Additional non-invasive therapy that is predominantly used in leiomyoma includes many antagonist agents of the estrogenic receptor. So, important to determine estrogen receptor activity before that hormonal therapy. Histopathology parameter which could predict estrogen receptor activity in leiomyoma was not well understood. This cross-sectional study used 50 samples, which were divided into two sample groups including 25 samples collected from general-type leiomyoma patients and 25 samples from specific histologic-type leiomyoma patients. The proportion of both groups was analyzed by Pearson's chi-square test. There was a significant correlation between the specific histologic types of leiomyoma with estrogen receptor expression (p value=0.007; p<0.05)

Key Words: Leiomyoma, Estrogen Receptor

INTRODUCTION

Uterine leiomyoma or fibroid is the most common benign neoplasm in women that develops from the over-proliferation of smooth muscle cells of the uterine wall [1–3]. Based on predilection, uterine leiomyomas were most commonly located intramural (66.7%), followed by sub-serosal (22.2%), sub-mucosal (8.9%), and cervical (2.2%)[2]. The incidence of uterine leiomyoma worldwide is estimated to range from 217-3745 cases per 100,000 women with a prevalence of 4.5 -68.6% [2,4,5].

Several related risk factors including race (black), age at menopause, hypertension, and consumption of soy milk are said to increase the risk of uterine leiomyoma[5]. In Indonesia, it is estimated that the incidence of uterine leiomyoma is around 150,000 cases/per year. In Bali, the prevalence of uterine leiomyoma is about 40-60% of all hysterectomies performed, most of which are around 40% in women over 50 years of age with varying sizes [2,6,7].

Generally, uterine leiomyoma with a small size (<2 cm) is still asymptomatic, but the larger its size, the more likely cause clinical symptoms, including menorrhagia, bleeding outside the menstrual cycle, abdominal pain, and a palpable abdominal mass. Sometimes symptoms are related to the location of the tumor, submucosal leiomyoma tends to cause metrorrhagia because it can cause endometrial disruption, intramural leiomyoma causes menorrhagia because it interferes with myometrial contractions, whereas subserous leiomyoma rarely causes bleeding symptoms [8]. Vaginal bleeding with a volume of more than 1 liter/day has the potential to cause anemia and even hypovolemic shock, so symptomatic leiomyoma cases require immediate surgery. In addition, if leiomyoma occurs during pregnancy, it will interfere with fetal development and threaten a pregnancy [3–5].

There are various subtypes of leiomyoma according to WHO, which are commonly found, including leiomyoma with

hyaline degeneration (in 63% of cases), myxoid leiomyoma if myxoid degeneration is present (19%), cellular leiomyoma in tumors with increased cellularity, atypical leiomyoma if it contains atypical nuclei, and angioleiomyoma (vascular leiomyoma) [1,3,4]. Previous studies have linked the role of hormonal factors such as estrogen to the increase in tumor size. However, this contradicts the previous theory which stated that the pathobiology of leiomyoma is related to the age of menopause, at which time there is a decrease in estrogen activity. Other studies also mention the occurrence of tumor size regression after menopause. This certainly raises controversy, about whether estrogen plays a role in the pathobiology or progression of leiomyoma. Some literature guesses that the effect of a hormonal factor on leiomyoma depends on its subtype, but there have been no studies exploring the role of estrogen receptors in the progression of various uterine leiomyoma subtypes, recently [9,10]. Thereby, choosing hormonal therapeutic modalities such as gonadotropin-releasing hormone analog still need many consideration [4–6,8].

Until now, there are several biological markers used to assess the increase in myometrial proliferation, including EMA (Epithelial Marker), MSA (Smooth Muscle Actins), Desmin, and Caldesmon [8,9,11]. However, these biological markers have not yet been able to become parameters of targeting therapy. The development of therapeutic targets that act on the estrogen receptor (ER), indicates that there is a possible link between estrogen receptors in tumor progression and the histogenesis of uterine leiomyoma subtypes. ER is known as a nuclear transcription factor that is activated by the hormone estrogen [5,6,8,9]. It was previously known that ER has a major role in the pathobiology of carcinomas of several female organs such as breast, endometrial and ovarian carcinomas. This study will assess the relationship between leiomyoma subtypes with ER expression, to further explore the pathobiology and histogenesis of several leiomyoma subtypes.

METHOD

This study used a cross-sectional study design, which correlates uterine leiomyoma subtypes with the presence of ER expression. The sample is calculated based on the following formula:

$$n = \left(\frac{z\alpha/2 + z\beta\sqrt{PQ^2}}{(P - \frac{1}{2})} \right)$$

Based on this formula, the minimum total sample size is 45.92 rounded up to 46. In this study, the number of samples for each group was 25 samples, divided into two sample groups including 25 samples collected from general type leiomyoma patients and 25 samples of specific histologic type leiomyoma patients. The proportion of both groups was analyzed by Pearson's chi-square test. The significance test was determined at $p < 0.05$. Data precision is determined by a 95% Confident Interval (CI).

RESULT AND DISCUSSION

The study of uterine leiomyoma showed that the age range of patients was quite varied, ranging from 30–59 years of age, with a mean age of 44.50 ± 0.93. The highest number of patients was in the age range of 40-49 years (48%), with the highest accumulation of cases in the age range of 30-59 years (more than 75% of cases). The 3rd decade of reproductive life then grows to another 40% as it approaches 50 years of age. This is related to natural estrogen exposure at that age as well as the use of oral contraceptives containing estrogenic components [8,10,11].

The common type of leiomyoma has been more frequent in the 3rd decade of life, possibly associated with a single somatic mutation or lesser exposure to estrogen component than certain leiomyoma subtypes that frequent in the 4th decade of

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age. It might be related to more complex mutations or longer time exposure to exogenous estrogen from hormonal agents like contraceptive therapy [10,12].

Table 1. Sample Characteristic (n= 50)

Characteristic	Means ±Deviation	n(%)
Age (year)	44.50±0.93	
<30		4 (8%)
30-39		12 (24%)
40-49		24 (48%)
50-59		8 (16%)
>/=60		2 (4%)
Leiomyoma Group		
Leiomyoma (**Usual Type**)		25 (50%)
Leiomyoma (**Specific Subtype**)		25 (50%)

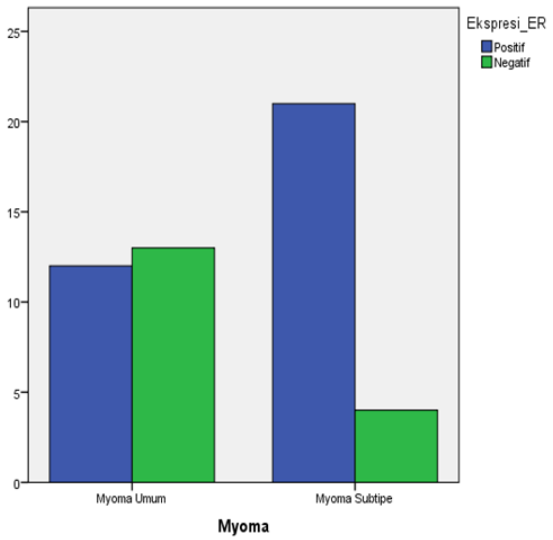

Figure 1. ER expression between two samples group (General leiomyoma/Myoma Umum and Specific Leiomyoma/Myoma Subtype)

Macroscopic description of 25 cases of generalized leiomyoma showed there were 16 (64%) cases that had tumors 2 cm in size. Meanwhile, in 25 cases of leiomyoma of certain subtypes, 7 (28%) tumors were 2 cm in size and 18 (72%) tumors were >/= 2 cm. The difference in tumor size between cases of general type leiomyoma vs. specific subtype leiomyoma was not significant p=0.544; p>0.05. Various literatures state that there is no association between leiomyoma subtype and tumor macroscopic size [11–14].

Based on this study result, 12 cases of general type leiomyoma showed positive ER expression and 22 cases of specific type leiomyoma had positive ER results. Pearson Chi-Square analysis was performed with the results of the significance analysis determined at p < 0.05 (CI=95%). This study showed the difference in ER expression between the generalized leiomyoma group and certain subtypes showed significant results, with a value of p=0.007 (p<0.05).

The results of the ER visualization in Figure 2 show that in the general type leiomyoma group the comparison between ER-expressing samples is almost comparable to those that do not express ER while in the leiomyoma group certain subtypes show significant differences in expression levels. This indicates that the morphological development and tumor progression in certain leiomyoma subtypes may be influenced by estrogen activity and the amount of estrogen receptor expression.

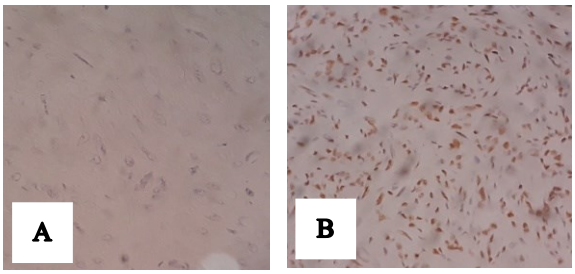

Figure 2. Negative ER expression of Usual type Leiomyoma (A) and Positive ER expression of Cellular type Leiomyoma (B)

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Several studies suggest that genetic changes in certain subtypes may give rise to more estrogen receptors in the nucleus of leiomyoma cells[14,16]. Some specific types of leiomyoma, such as atypical leiomyoma and cellular leiomyoma tend to have complex mutations like HMGA1 mutation and KAT6B-KANSL1fusion that activate more estrogen receptors which then activate by estrogenic component, in turn, developed more proliferation profiles of specific type leiomyoma [(14–16)].

CONCLUSIONS

There was a significant difference in ER expression between the generalized leiomyoma type versus certain subtype leiomyoma. Significant positive ER expression in certain subtype leiomyoma groups indicated a role for ER in the molecular progression of certain leiomyoma subtypes. So in histopathology reporting leiomyoma cases may be considered for inclusion of a leiomyoma subtype/variant because it has clinical implications as a marker for the progression of leiomyoma which will affect the decision to determine adequate therapy for the patient recurrence. The decision of hysterectomy is not only related to the patient's age and tumor size but further considers the leiomyoma subtype aspect.

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