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Insights of Uterine Leiomyoma: a review

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Abstract : Uterine leiomyoma are benign mesenchymal solid tumors originating from smooth muscle cells during the fertile stage of life. There are various factors that are associated to underlie the development and incidence of these myomas. A number of chromosomal alterations and gene mutations are responsible for the leading cause of uterine leiomyoma: the most common of which include translocation on chromosome 7 and translocation on chromosome 12 targeting *HMGA* and *RAD51L1* mutation.

Key words: leiomyoma, menorrhagia, hysterectomy, polymorphism, myoma.

Introduction

Uterine leiomyoma (UL) are benign mesenchymal solid tumors which originate from smooth muscle cells exclusively during the fertile stage of life and are usually referred to as Fibroid[5]. Along with the smooth muscles leiomyoma are composed of extracellular matrix (i.e. collagen, proteoglycans, and fibronectin)[5]. UL are the most common uterine neoplasm with about approximately 25% of reproductive age women having clinically apparent tumors and exhibiting symptoms like menorrhagia, urinary dysfunction, constipation, abdominal discomfort and infertility[3].

The prevalence of UL is estimated as 77% based on systemic histological examination of hysterectomy specimen[9]. UL are usually monoclonal tumors of the smooth muscle cells of the myometrium[22].

Historically, UL were not considered as genetic disease, but since the year 2000, several gene array studies were done to examine differential gene expression between uterine fibroids and normal myometrium. Presently, studies are going on for the identification of DNA polymorphism which influence the leiomyoma risk[9]. The various genetic causes of UL reported are t(12;14)(q15;q24)[7], t(1;2)(p36;p24)[17], deletion in (7q11.23-q22-q32)[16]. The targeted genes of UL include *HMGA2* gene at 12q15[5], *HMGA1* gene at 6p21[11], *RAD51L1* gene at 14q23-24 [5], *MORF* gene at 10q22[5].

Based upon the location of leiomyoma in the uterus, they are classified into Subserosal leiomyoma in which the leiomyoma are situated just beneath the uterine serosa. These can be pedunculated which are attached to the corpus by a narrow stalk or they can be sessile with a broad base. Intramural leiomyoma are present within the thickness of myometrium and are capable to distort the uterine cavity or cause an irregular uterine contour. Submucous leiomyoma are situated beneath the uterine mucosa and they appear as pedunculated or sessile [20].

Risk Factors

Various risk factors are cited based upon the epidemiologic data women during their forties are more likely to be diagnosed with myoma. There is an increased chance of myomal growth with increases in progesterone concentration and the size of myoma decreases with the decrease in estrogen level[22]. The risk of developing myoma increases 2.5 times when the first degree relatives are effected and they are likely to have more than twice the strong expression of *VEGF-α (*a myoma related growth factor)[16].

Reports show that African-American women have a 2.9 times greater risk of having myoma than Caucasian women[13]. According to recent studies women with Val/Val genotype of an essential enzyme in estrogen metabolism, Catechol-O-Methyl Transferase (COMT), are more likely to develop myoma with a prevalence of 49% African-American women and 19% of white women[2]. A prospective study states that the risk of the myoma increases 21% with an increases of 10kg in body weight than the body mass index[6]. Increased intake of beef, red meat, ham, oral contraceptives and decreases in physical exercise, increase the risk of myoma development[15].

Symptoms

Uterine myoma cause morbidity and affect quality of life. Most common symptoms include abnormal uterine bleeding; menorrhagia. 46% women with myoma have reported 'gushing blood' during their menstrual cycle[14]. Women with myoma also experience pelvic pain, symptoms of dyspareunia, dysmenorrhea or non-pelvic pain[12]. Affected women are also likely to have decrease in uterine volume following decrease in urinary frequency, nocturiaor stress incontinence[12.]

Diagnosis

Ultrasonography can be done transvaginally or transabdominally to detect endometrial carcinoma. Saline Infusion Sonohysterography based imaging is used as a supplementary or adjunct imaging modality for characterization of focal uterine masses. Magnetic Resonance Imaging, is touted as the most sensitive modality for evaluating Uterine Myoma[1]

Hormones

Hormones like estrogen and progesterone plays a major role in the development of myoma which are frequently observed during the reproductive years. Increased level of aromatase, an enzyme that converts androgen to estrogen are involved in *de novo* production of estrogen within the myoma tissue. Low level of enzymes that convert estradiol to estrone are found in myoma cells which initiates the accumulation of estradiol, causing up-regulation of estrogen and progesterone receptors. Myoma show increased concentration of progesterone receptors A and B. Gonadotrophin Releasing Hormone (GnRH) acts as an agonist to decrease the size of myoma[22].

Transforming Growth Factor β (TGF β), basic fibroblast growth factor (B FGF), platelet derived growth factor (PDGF), insulin like growth factor (IGF), prolactin, epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF) are the various growth factors associated with myoma growth[6].

Cytogenetics

Karyotyping, comparative genome hybridization, whole genome hybridization studies are done to identify chromosomal alterations like deletion, duplication, inversion, translocation associated with Uterine Myoma. Nearly 40% of the UM have non random and tumor specific anomalies which include 7q deletion, trisomy 12, rearrangements like 12q15, 6p21, 10q22. Other abnormalities also include rearrangement of chromosome X, 1, 3 and 13 [8]. Rearrangements of 12q14 -15, typically t (12;14)(q14-15; q23-24) is the most common characterized transporation which occurs approximately in 7.5% of all Uterine Leiomyoma. This translocation is primarily associated with tumorigenesis and with larger sized UL. It also results in the elevated expression of high mobility group (HMGA) family member *HMGA2* located on 12q14.3 [9]. 12q15 is a part of t(12;14) in leiomyoma and a der (14)t(12;14)(q15;q23~q24) is also frequently observed in UL. Abnormalities of chromosome 7q represents approximately 15% of all UL and 20-35% of karyotypically abnormal UL. Deletion of 7q is the sole alteration in a non mosaic state, playing a primary role in UL pathobiology. Translocation in 7q22 results due to loss of heterozygosity between the markers D7S2453 and D7S501 in 7q22.2-7q22.3. UL

also occur due to repeated polymorphism in the X- linked androgen receptor and the phosphoglycerokinase gene[6].

HMGA Gene

The high mobility group (*HMGA*) non histone chromatin proteins are the ones that alter chromatin structure and thus regulate the transcription of genes by either enhancing or suppressing the transcription factors.

The *HMGA*2 gene spans approximately 160kb and have 327bp coding region, and 854bp 5' untranslated region (UTR) and a 2966bp 3'UTR which together encodes for 4.1kb Mrna. The *HMGA1* gene (10kb) consists of 8 exons; 1-4 exons are non coding, exons 5-7 contain the AT hooks corresponding to exons 1-3 of *HMGA2*, and exon 8 encodes the acidic C-terminus of the protein[20].

Rearrangements in *HMGA* genes results in benign human mesenchymal tumors and unarranged *HMGA* overexpression results in malignant tumors[19]. *HMGA2* is reported as the driver gene for tumors carrying 12q15 rearrangements. *HMGA2* located on 14q24 is the targeted translocation partner in leiomyoma. HMGA1 located at 6p21 is also involved in some cases[20].

RAD51L1 Gene

RAD51L1 is a member of recombination family mapped on 14q23-24 and designated as translocation partner for *HMGA2* in UL. This gene results in the loss of exon encoding the 3' end of predominant exon. Exon 8-11 of *RAD51L1* included in *HMGA2/RAD51L1* fusion is located either upstream *HMGA2* on der (14) or in the der (12) remote from *HMGA2*, based on the position of chromosome 14 breakpoint[20].

Conclusion

In current scenario, uterine Leiomyoma is one of the major health issue among the women of reproductive age whose adverse stage can lead to cancer. A number of genetic abnormalities along with hormonal imbalances are associated with the underlying condition. Approximately 40% of the UM have non random and tumor specific anomalies which include 7q deletion, trisomy 12, rearrangements like 12q15, 6p21, 10q22. Other abnormalities also include rearrangement of chromosome X, 1, 3 and 13 along with mutations in *HMGA* gene family and *RAD51L1*. Early detections along with advanced treatment can be a better option for reducing the prevalence of Uterine Leiomyoma and further replenishing the related cancers.

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