

CASE PRESENTATION

A 47 year old woman presents for a routine physical exam. She has no complaints other than a bit of weight gain (11#) over the past year.

She is 5-2 and weight 243#. Her vital signs were normal. She appeared in no acute distress. Her skin color was normal.

The health questionnaire she filled out did not reveal any complaints.

On physical examination she was noted to have a fullness in the lower abdomen.

- What additional history do you want ?
- What additional examination ?
- What laboratory tests ?

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Uterus sketch

Leiomyomata

- Commonly known as fibroids or myomas
- Well-circumscribed
- Benign tumors
- Arising from the smooth muscle of the myometrium
- Composed of
 - smooth muscle
 - extracellular matrix
 - collagen
 - proteoglycan
 - fibronectin)

Incidence and Etiology

- Most common solid pelvic tumors in women
- Clinically apparent in 20% to 25% of women during the reproductive years
- Pathologic inspection of the uterus - present in more than 80%
- Leiomyomas are clonal in origin
- Classic paradigm
 - Estrogen
 - Progesterone
- Now clear
 - transforming growth factor- β
 - basic fibroblast growth factor
 - somatic mutations of genes such as HMGI-C

Incidence and Etiology

- Characterized by their location in the uterus
- Subserosal leiomyomas
- Intramural leiomyomas
- Submucous leiomyomas
- Few leiomyomas are actually of a single "pure" type
- Most leiomyomas are hybrids that span more than one anatomic location
- Increased incidence of leiomyomas in women of color
- Risk is increased in women with greater body mass index
- Decreased in women who smoke or who have given birth
- Good epidemiological evidence to suggest that use of oral contraceptive pills decreases the risk for leiomyomas

Submucous Fibroid

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Benign Fibroid - Microscopic

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Micro of benign fibroid

Leiomyoma - microscopic

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leiomyoma

Benign Fibroid - Micro

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Benign fibroid

Epidemiology

- Studies on fibroids obscured by
 - Late onset symptoms
 - Method of diagnosis
 - Hysterectomy
 - Myomectomy
 - Imaging
 - Surgically managed patients may suggest that the initial non-surgical management is actually a risk factor (i.e. OC)

Demographics

- Highest prevalence in 5th decade
- 25% incidence in Caucasian women
- 50% incidence in Black women
- Women who smoke have lower incidence (2^o to decrease estrogen levels ???)

Epidemiology

- Age adjusted rates for blacks 2-3x whites
- Higher rates evident at all ages
- Rates peak earlier in blacks
- Randomly recruited women for TV U/S
 - Blacks 73%
 - Whites 48%
- Asian and Hispanic rates similar to whites

Overweight and Cigarettes

- Overweight is a Mixed bag
 - Increased BMI raised risk of fibroids
 - Heaviest are at greatest risk
 - Other studies show no difference
 - Perhaps heavy women have more symptoms needing surgical correction
- Smoking
 - Reduced risk of fibroids
 - Independent if BMI
 - Level of smoking or recency of smoking unclear

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Epidemiology

- Limited data from other countries
- Two major studies in the USA
- Incidence
 - 12.8/1000 person years - all methods of detection
 - 2.0/1000 person years - hysterectomy
- Rates increase through the reproductive years
- Decrease in post menopausal years (Dx by hyst)
- Age adjusted rates for blacks 2-3x whites
 - One case control study showed 9 fold increased risk

Relationship to Menses

- Risk increases as menarche decreases
- 2-3 fold risk difference between those with early and those with late menarche
- Postmenopausal: 70-90% reduced risk
 - Size and number are less in hysterectomy specimens

Childbearing

- At least one live born - 20-50% reduced risk
- Reduction in risk increases with number of children
 - 4 or 5 births are at 70-8% lower risk than nullipara
- No relation to miscarriage or abortion
- Risk increase with time since last baby
 - No added risk for age at first baby
- History of infertility
 - Recent study showed that nulliparity or infertility related only to submucous fibroids

Imaging

- U/S
- Sonohystography
- Office hysteroscopy
- HSG
- MRI
- CT

Differential Diagnosis

- Pregnancy
- Neoplasm - ovarian
- Neoplasm - uterine
- Adenomyosis
- Endometriosis

Multiple Fibroids

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Small Submucous Fibroid

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submucous fibroid

Symptoms

- 20% and 50% of women with leiomyomas have tumor-related symptoms
- Abnormal uterine bleeding
 - Prolonged menstrual flow (menorrhagia)
 - Submucous leiomyomas appear to be particularly prone
- Pelvic pressure.
 - Increase in uterine size
 - Pressure of particular myomas on adjacent structures
 - Colon
 - constipation
 - Bladder
 - urinary frequency.
 - Ureters
 - hydronephrosis

Fibroid – Red Degeneration

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degen fibroid - red

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RED DEGENERATION OF FIBROID- necrosis in intramural fibroid - generally one artery supplies each fibroid

Symptoms

- Recurrent miscarriage,
- Infertility
- Premature labor
- Fetal malpresentation
- Complications of labor
- Assessment of the uterine cavity before attempting pregnancy
- Sarcomatous transformation thought not to occur.
- Clinical teaching
 - Rapidly enlarging fibroid may be a sign of sarcoma
 - No support for this in the literature.

Diagnosis

- Easily determined by bimanual examination
 - Uterus is enlarged
 - Mobile
 - Irregular
 - Palpated abdominally above the symphysis
- Ultrasonography most common method
- Magnetic resonance imaging (MRI)
 - proton spin characteristics can often distinguish
 - Leiomyomas
 - Adenomyomas
 - Leiomyosarcomas
- Menorrhagia or recurrent pregnancy loss
- Examine after it is distended
 - Submucous fibroid can be missed on traditional ultrasonography

Submucous Fibroid

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MRI of Fibroid

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Treatment

- Primary therapy for patients with large or symptomatic leiomyomas is surgery
- Hysterectomy is the most often
- United States more than 175,000 hysterectomies are performed yearly for leiomyomas
- Diagnosis of leiomyoma the most common indication for this procedure
- Hysterectomy, the only true "cure" for leiomyoma, is a surgical option when women are no longer interested in future pregnancies

Treatment

- Preserve childbearing potential
 - Myomectomy may be performed
 - 18,000 myomectomies are performed yearly
 - Myomectomy diminishes menorrhagia in roughly 80%
 - Significant risk for recurrence of leiomyomas
 - Ultrasonographic evidence of recurrence in 25% to 51% of patients
 - 10% require a second major operative procedure

Treatment

- GnRH agonists (Lupron, Naferelin, Goserelin)
- Induce a hypoestrogenic pseudomenopausal state
- Fibroids are dependent on estrogen for their development and growth
- Hypoestrogenic state causes shrinkage
- Uterine volume has been shown to decrease 40% to 60% after 3 months of GnRH agonist therapy
- Induces amenorrhea
 - increase iron stores and hemoglobin concentrations
- Cessation of GnRH agonist treatment results in rapid regrowth
- GnRH agonist treatment is useful as a presurgical treatment
- Not as a long-term treatment option

Treatment

- Androgenic agents
 - Danazol
 - Gestrinone
- Progestins
 - Medroxyprogesterone acetate (Provera)
 - Depomedroxyprogesterone acetate (Depo-provera)
 - Norethindrone
- Do not consistently decrease uterine or fibroid volume
- Mechanism of action is thought to be the induction of endometrial atrophy
- Often not successful in controlling significant menorrhagia.

Embolization

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Subtraction Angiography

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Leiomyosarcoma protruding from myometrium

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Microscopic appearance of a leiomyosarcoma

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Leiomyosarcomas have spindle cells

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Leiomyosarcoma - microscopic

Images removed due to copyright reasons.

Somatic Mutation

- Somatic mutation is the **initial event** in most tumorigenesis
- Somatic mutations include a variety of chromosomal aberrations
 - **point mutations**
 - **chromosomal loss or gain.**
- Large chromosomal abnormalities such as **translocations and deletions** are often detected with standard cytogenetic karyotypes

Somatic Mutation

- Independent **monoclonal origin** of individual myomas
 - Suggests somatic mutations offer a **selective growth advantage** to the mutated myocyte
 - **Variety of chromosomal rearrangements** are associated with myomas
 - Most common chromosome aberrations involve chromosome bands **12q14-15 and 7q22**.
 - The **heterogeneity of the cytogenetic abnormalities** suggests that a number of different somatic mutations may be involved in myoma tumorigenesis.
 - Unique somatic mutations in individual myomas may be the biologic basis for the **differential responsiveness of individual myomas** to a variety of growth-promoting agents.

Genetics of Fibroids

- 40% have non-random chromosomal abnormalities
- Six main cytogenetic subgroups
 - Translocations between chromosomes 12 and 14
 - Trisomy 12
 - Rearrangements of short arm of chromosome 6
 - Rearrangements of long arm of chromosome 10
 - Deletions of chromosome 3
 - Deletions of chromosome 7
- Majority (60%) of fibroids are chromosomally normal

Genetics of Fibroids

- To be determined
 - GnRh responsiveness
 - Ethnicity
 - Recurrence
 - Malignant potential
 - Infertility

Genetics of Fibroids

- Multiple chromosomal derangements suggest Multiple genetic mechanisms
 - Translocations
 - Up regulate or down regulate
 - Juxtaposition of entire gene sequence next to ectopic regulatory element
 - Interruption of gene sequence → fusion genes
 - » Abolish protein synthesis entirely
 - » Functional novel chimeric proteins
 - Trisomies
 - Increase gene expression through increase gene dosage
 - Deletions
 - Loss of gene function

Genetics of Fibroids

t(12;14) Subgroup (20%) and 6p21 Subgroup (10%)

- HMGIC and HMGIY (High mobility group proteins)
 - Non-histone DNA binding proteins Regulate many activities such as transcription
 - Cellular proliferation and differentiation
 - Architectural role ?
 - Angiomyxoma
 - Breast fibroadenoma
 - Endometrial polyps
 - Hemangiopericytoma, lipoma, salivary gland adenomas

Genetics of Fibroids

Deletion on chromosome 7

- 17% of karyotypically abnormal fibroids
- More commonly detected in fibroids than any other solid tumor
 - Endometrial polyps
 - Lipomas
 - Some acute leukemias
- May be present alone or in combinations
- Bad prognosis in leukemia but no effect on prognosis with fibroids
- Cell cultures with with del 7 and t(12;14) are more stable than Del(7q) alone

Genetics of Fibroids

Clonality

- Long considered to be independent monoclonal lesions
- Multiple fibroids in the same uterus have differing rearrangements
- Current thought is that the chromosomal rearrangements are **SECONDARY** changes in tumorigenesis

Genetics of Fibroids

Heritability

- African American – 3-9 fold higher prevalence of fibroids
- Nurses Health Study – three-fold increase (controlled for risk factors, SES, access to care, etc)
 - Hysterectomy data on Twins
 - monozygotic twice as high as dizygotic
 - Familial clustering of fibroids
 - Twice as high in families
 - 6 times as high in early onset (<age 45) families
- Reed Syndrome
 - Familial leiomyomatosis cutis and uteri
 - Autosomal dominant with reduced penetrance

Somatic Mutation

- **Clonal proliferation** precedes the development of cytogenetic rearrangements
- Suggesting that somatic mutations which **cannot be detected cytogenetically** with the light microscope are the initial events in myoma tumorigenesis.
- Explains the **absence of cytogenetic abnormalities** in a large proportion of myoma specimens.
- Major goal is to **identify initiators** of somatic mutations.

Estrogen Receptors in Myometrium

- Both type of estrogens receptors (ER alpha and ER beta) mRNA are expressed in leiomyoma and normal myometrium.
- The expression of ER alpha is higher than that of ER beta in both leiomyoma and myometrium
- ER alpha expression is increased in leiomyoma compared to that the adjacent normal myometrium
- ER beta expression is the same or even lower in leiomyoma than in the adjacent normal myometrium
- Sixty-one percent of patients showed an increased ratio of ER alpha/ER beta in leiomyoma

Comparative Expression of Estrogen Receptors a and b in Human Uterine Leiomyoma and Adjacent Myometrium

T. Chiang, G. R Davis, R. M Williams, J.A McLachlan and S. Li

Annual meeting of American Association of Cancer Research April 2000, San Francisco

Role of Estrogen

- Estrogen considered the **major promoter of myoma growth**
- The long-term administration of a gonadotropin--releasing hormone (**GnRH**) agonist is associated with both **hypoestrogenemia** and a reduction in myoma volume
- Concentration of **estradiol found to be significantly higher in myomas** than in normal myometrium.
- Significantly **lower conversion of estradiol to estrone in myomas** compared with myometrium.
- Significantly **increased concentration of estrogen receptors in myomas** compared with autologous myometrium

Role of Estrogen

- Observations suggest that the intramyoma hormonal milieu is **hyperestrogenic**
- No evidence that estrogen directly stimulates myoma growth
- Mitogenic effects of estrogen are likely **mediated by other factors** and their receptors.
- Several estrogen-regulated genes have been confirmed in uterine myomas
- Evidence to suggest that estrogen stimulates
 - Progesterone receptor
 - Epidermal growth factor
 - Insulin-like growth factor-I

Role of Estrogen

- Involved in regulation of myoma **extracellular matrix**
- Estrogen directly stimulates **collagen types I and III m-RNA**
- Stimulates expression of gap junction protein **connexin-43**
- Stimulates local production of the **parathyroid hormone related peptide**
- Expression of these estrogen-regulated genes appears to be **greater in uterine myomas** than in the adjacent myometrium.
- **Hypersensitivity** to estrogen may be important in the pathogenesis of myomas.

Biochemical Evidence

- There are ultrastructural features of cultured smooth muscle cells that differ in uterine myomas and normal myometrium
- Myoma and myometrial cells in estrogen and progesterone containing medium appeared more active under the electron microscope than cells in estrogen only-containing or control medium.
- Myoma cells exposed to estrogen and progesterone revealed an increased number of myofilaments with dense bodies, suggesting that progesterone is involved in myoma differentiation.

Clinical evidence supporting critical role for progesterone in pathogenesis of myomas

- 1961 - Mixson and Hammond
 - 16 patients
 - Synthetic progestin norethynodrel
 - Maintain amenorrhea
- Fifteen of 16 patients demonstrated significant enlargement of the uterus
- Some decrease in uterine size in all patients 12 weeks after discontinuation of progestin therapy
- Return to pretreatment size was noted in 70% of the patients during the follow-up period.
- Norethynodrel causes rapid but reversible enlargement of uterine myomas.

Rein. *Am J Obstet Gynecol* 172, no. 1 (January, 1995): 14-18.

Clinical evidence supporting critical role for progesterone in pathogenesis of myomas

- Friedman - 16 patients with uterine myomas
 - randomized - daily subcutaneous leuprolide acetate
 - Daily medroxyprogesterone acetate
 - Daily placebo
 - No significant reduction in uterine volume compared with the 50% reduction noted among patients treated with leuprolide plus placebo.
- Carr - 16 women with large myomas
 - randomized - subcutaneous leuprolide acetate
 - Daily medroxyprogesterone acetate
 - Daily placebo
 - Uterine and myoma volume were assessed with magnetic resonance imaging studies.
 - No significant change in uterine or myoma volume

Rein. *Am J Obstet Gynecol* 172, no. 1 (January, 1995): 14-18.

Clinical evidence supporting critical role for progesterone in pathogenesis of myomas

- Uterine myomas regress in response to the antiprogestosterone agent RU-486
 - Murphy - daily RU-486 for 3 months
 - 10 patients with uterine myomas
 - Amenorrhea was induced in all patients
 - Myoma volume - 49% reduction after 12 weeks
 - Serum estradiol, estrone, and progesterone levels remained unchanged
 - Immunohistochemical examination - significant reduction in progesterone receptor but not estrogen receptor,
- Progestins inhibit and/or reverse the effectiveness of GnRH agonist - induced hypoestrogenism

Rein. *Am J Obstet Gynecol* 172, no. 1 (January, 1995): 14-18.