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Case Report

Metastatic Leiomyosarcoma of the Thyroid Gland from a Prior Uterine Leiomyosarcoma. Case report of a Rare Clinical Presentation and Review of the Literature

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Abstract

Uterine leiomyosarcoma is an uncommon malignancy that develops from uterine smooth muscle and occurs more commonly in perimenopausal women. Because of its aggressive nature, high recurrence potential, and high ability to metastasize, it needs careful clinical post treatment long-term monitoring. This report intends to provide more insight to uterine leiomyosarcoma and its potential metastasis and unusual sites of metastasis. We report a case of a 49-year-old female, presented with a thyroid mass, which metastasized from a large uterine leiomyosarcoma, confirmed by cytology sampling examination utilizing ultrasound fine-needle aspiration. We review the differential diagnosis, clinical presentation, molecular basis, immunochemistry, prognosis, and treatment of metastatic uterine leiomyosarcoma.

Keywods: Uterine leiomyosarcoma; Uterine leiomyoma; Cytopathology; Malignant; Recurrence; Metastasis; Smooth muscle

Abbreviation

uLMS: Uterine leiomyosarcoma; **uLM:** uterine leiomyoma; **STUMP:** smooth muscle tumors of uncertain malignant potential. **IHC**: Immunohistochemistry

Introduction

Uterine leiomyosarcoma (uLMS) is an uncommon aggressive malignant tumor that originates from uterine smooth muscles [1]. It can also arise from any organ containing smooth muscles including rare sites such as the epididymis [15]. Once it reaches stage 4, it has the metastatic potential to reach other organs via hematogenous spread, where the lung is the most common site [2]. In rare cases, it has the potential to spread to the thyroid gland. Currently, there is no definite therapy for uMLS. Despite complete resection, the risk of recurrence is 50-70% [3]. Consequently, patients with uLMS have poor 5 years survival rate for stage 1, 2, 3 and 4 of 55.4%, 32.6%, 24.6% and 13.1% respectively [3].

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Typically, the patient presenting with uLMS is a perimenopausal woman with a median age of 50 years old. 70-80% of the uterine leiomyosarcoma cases are observed in perimenopausal women and 20-40% in women of reproductive age [4]. Although most patients remain asymptomatic, some patients with large pelvic masses can present with vaginal hemorrhage. Many uLMS are accidentally discovered during post-operation removal of the uterus for other conditions [5]. We present a case of metastatic leiomyosarcoma to thyroid gland originating from uterine leiomyosarcoma excised 14 months earlier.

Case Presentation

A 49-year-old woman presented with a thyroid mass. She noticed the mass four weeks prior to current presentation but was recently enlarging in size. Physical examination showed a firm thyroid mass measuring approximately 3.5 cm. Fine needle aspiration was performed and the diagnosis was "highly atypical cells present suspicious for malignancy with possible anaplastic features". Fourteen months earlier, patient underwent total hysterectomy with bilateral salpingo-oophorectomy for a large 13cm high grade pleomorphic and spindle cell uterine leiomyosarcoma. Post- operative treatment of the uterine tumor included combination chemotherapy gemcitabine plus docetaxel and followed by doxorubicin. No evidence of metastasis was present at the time.

A multidisciplinary tumor board meeting recommended treatment of current thyroid tumor with total thyroidectomy. Surgical removal showed a 3.5 tumor mass infiltrating right and left thyroid lobes. Histopathologic examination displayed cellular tumor comprised of spindled and fascicular cells with severe pleomorphism and no identified architectural pattern. Scattered bizarre cells and malignant multinucleated cells were identified. Abnormal mitosis exceeded 15 mitosis/10 HPF and prominent necrosis were easily seen (**Figure 1 A-B**). The

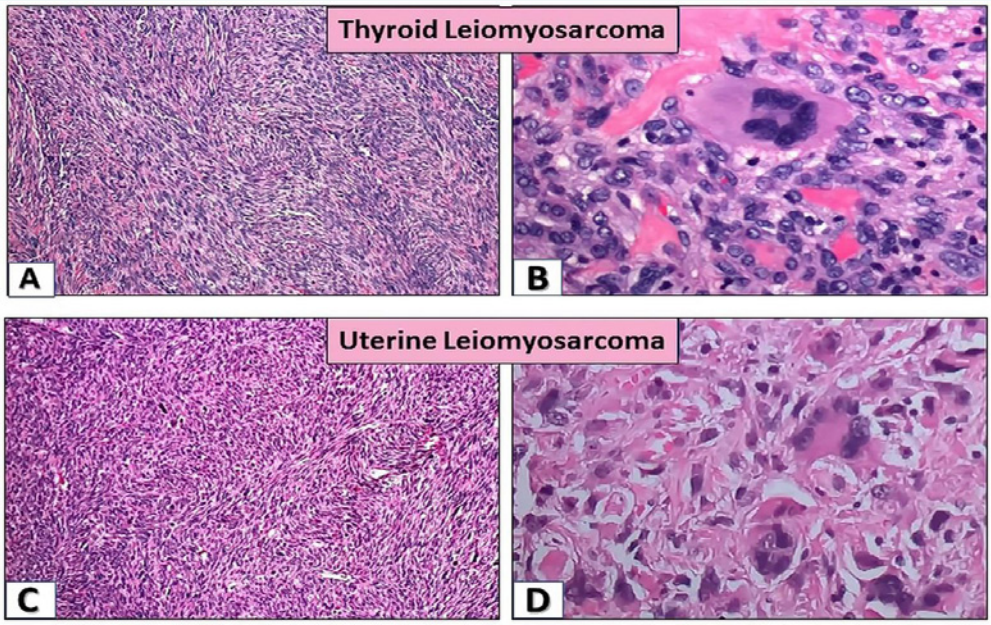

Figure 1 Microscopic examination comparing metastatic thyroid leiomyosarcoma and primary uterine leiomyosarcoma.
1A : Low power of metastatic leiomyosarcoma to the thyroid gland. cellular tumor comprised of spindled and fascicular cells with severe pleomorphism (H&E stain X20)
1B: High power of metastatic leiomyosarcoma to the thyroid gland. Scattered bizarre cells and malignant multinucleated cells (H&E stain X60)
1C: Low power of original primary uterine leiomyosarcoma similar to the thyroid metastatic tumor (H&E stain X20)
1D: High power of original primary uterine leiomyosarcoma showing scattered bizarre cells and malignant multinucleated cells similar to thyroid tumor (H&E stain X60)

histomorphologic features were suggestive of primary thyroid gland anaplastic carcinoma, versus metastatic malignancy, likely sarcoma. Immunohistochemistry (IHC) studies were utilized to determine the line of differentiation. Tumor cells showed strong immunoreaction to Vimentin, Smooth Muscle Actin (SMA), Desmin, CD10 and Estrogen receptors (ER), and focal reaction to H-Caldesmon. The tumor cells were negative for TTF-1, HMB45, CD34, and calcitonin (**Figure 2 A-B-C**). Scattered few cells showed immunoreaction with Pan Cytokeratin. Prior uterine tumor was reviewed and compared with the thyroid tumor. Both tumors showed similar features (**Figure 1 C-D**). The similar histomorphology as well as the immunohistochemistry profile were consistent with metastatic Leiomyosarcoma from the uterine Leiomyosarcoma. Post thyroidectomy treatment included adjuvant chemotherapy. Patient expired seven months later due to wide metastasis to the lung, liver and bone leading to multiple organ failure.

Discussion

Uterine leiomyosarcoma (uLMS) and its benign counterpart uterine leiomyoma (uLM) are usually presenting with similar symptoms. These symptoms include profuse menstrual bleeding, pelvic discomfort, infertility, increasing urinary frequency or incontinence, constipation, and dyspareunia. Thus, it is challenging for physicians to diagnose uLMS based on clinical presentation [4]. The main criteria to distinguish uLMS are postmenopausal status, postmenopausal bleeding, abnormal premenopausal bleeding, suspicious imaging finding, rapid tumor growth, age greater than 45 years, and tumor size greater than 8cm [5]. Histologically, uLMS is characterized by hypercellularity, multiple nuclear atypia, and high mitotic rate. uLMS also has characteristics of cell-rich spindle cell areas with severe cellular atypia. Most importantly, the differing criteria present in uLMS is the large area of tumor cell necrosis [5]. In contrast, uLM's histology is presented with benign monoclonal tumors with large collagen type 1 to 3 in disorganized fibril arrangements [4]. In smooth muscle tumors of uncertain malignant potential (STUMP), histology will show muscle cell proliferation with high-grade nuclear atypia and mitotic rate, but no cell necrosis [5]. In general, it appears that uterine sarcomas do not arise from benign leiomyomas, with rare exceptions.

Currently, staging uLMS is based on the Federation of Gynecology and Obstetrics. Stage 1 is where the tumor is limited to the uterus [2]. Stage 1 can be expanded into Stage 1A and 1B where stage 1A is a tumor less than 5cm and stage 1B is a tumor more than 5cm. Stage 2 is a tumor extended beyond the uterus but is within the pelvis. Further in stage 2, stage 2A is adnexal involvement and stage 2B is the involvement of other pelvic tissues. Stage 3 is tumor invaded abdominal tissues. Within stage 3, stage 3A is the tumor at one site in the abdominal area. Stage 3B is the tumor is located in more than one site, and stage 3C is tumor metastasis to pelvic and/or para-aortic lymph nodes. Stage 4A is tumor invaded the bladder and/or rectum, and stage 4B is the tumor has spread to distant organs [2].

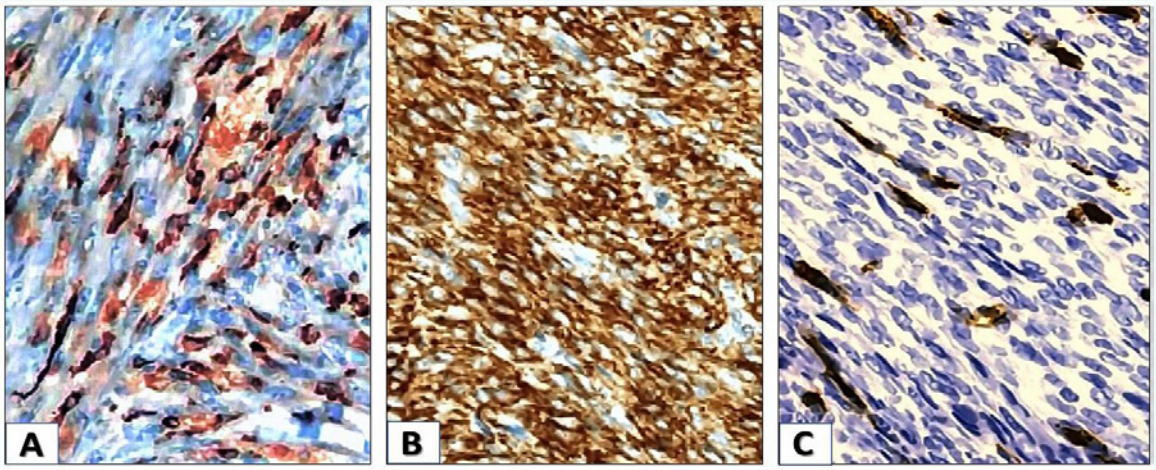

Figure 2 Immunohistochemistry studies of Leiomyosarcoma (Both thyroid and uterine tumors).
2A : Tumor cells positive for Desmin
2B: Tumor cells positive foe Smooth Muscle Actin (SMA)
2C: Tumor cells negative for CD34. Blood vessels are outlined by CD34

The study from Hayashi et al demonstrated the recurrence of uterine leiomyosarcoma and its hematogenous metastasis from a molecular standpoint. The study pointed out uLMS that comes from tumor stem-like cells has a significant recurrence in patients and plays a role in hematogenous metastasis. The studies further investigated and measured the level of vascular endothelial growth factors (VEGFs). Tumors that express high-level VEGF can promote the growth of new blood vessels and help tumor stem-like cells differentiate into endothelial cell progenitors. This allows tumor cells to spread through hematogenous spread [6].

A recent study shows that Dynamic Contrast-Enhanced magnetic resonance imaging (MRI) can help identify uLMS and discriminate between benign and malignant tumors. MRI shows uLMS as solitary heterogeneous and poor demarcated masses. It also presents high intensity on T1 weighted images, which indicates hemorrhage or necrosis. In contrast, uLM's MRI shows well-delineated masses with a variable size that can be solitary or multifocal with low intensities of T1 and T2 weight images due to increased concentration of smooth muscle [4].

Immunohistochemistry has been a great diagnostic tool because different tumors express different immunohistochemical profiles, which allows accurate and specific diagnosis. However, there is still a fallback on immunohistochemical staining due to cross reaction phenomenon leading to different tumors expressing the same immunohistochemical profile. For example, both uLMS and uLM expressed desmin, h-caldesmon, sm-actin, and histone deacetylase (HDCA8). However, uLMS also expressed CD 10, and epithelial markers such as keratin and EMA. 30-40 % of uLMS also showed positive estrogen, progesterone, and androgen receptors [5].

Uterine leiomyosarcoma has proved to be an aggressive tumor with local recurrence rates ranging from 45% to 73% and high metastatic potential. The most common locations of metastasis of uLMS are the lung and liver with 70-80% rate. The lymphatic metastases of uLMS is less prominent which account for 6-10% [6]. Some investigators also reported renal spread [7]. Metastatic tumors to the thyroid gland are unusual, with reported incidences as low as 0.1% in various clinical series [8]. This low rate of metastasis is due to the high vasculature of thyroid gland. The high blood flow prevents tumor cells from adhesion to the thyroid gland [9].

There is a challenge to distinguish primary thyroid neoplasm from secondary thyroid malignancies because both can present with spindle cell morphology and similar clinical presentation [10]. Patients usually present with compressive symptoms due to the thyroid mass [9]. Other similar characteristics of primary and secondary thyroid tumors are hoarseness of voice, dysphagia, weight loss, and dyspnea [9]. The difference of secondary thyroid tumor is that patient do not present with obstructive symptoms observed in anaplastic thyroid carcinoma [9]. Histologically, uMLS with metastasis to the thyroid is hypercellular spindle cell tumor with pleomorphic cells "arranged in interlacing fascicles with eosinophilic cytoplasm and hyperchromatic nuclei" [9]. The area also presents with coagulative necrosis and hemorrhage [11]. Immunohistochemistry can also aid in differentiating secondary thyroid carcinoma from primary thyroid carcinoma. uLMS metastasis to the thyroid is positive for desmin, smooth muscle actin and caldesmon and negative for myogenin, S100, calcitonin, synaptophysin, chromogranin, EMA, and TTF1 [9]. uLMS is also negative for cytokeratin, and thyroglobulin [12]. In contrast, primary thyroid carcinoma such as anaplastic thyroid carcinoma is positive for cytokeratin, p53, and vimentin, and negative for desmin, smooth muscle actin and caldesmon [12].

Radiological examination is another tool to help detect thyroid tumors, but it is poor in defining carcinoma type [12]. uLMS in Ultrasound presents with well or ill-defined hypoechogenic mass, cystic nodule, or calcified nodule. CT scan also shows large mass with necrotic areas and calcification [12]. A more definite

radiological tool is MRI. MRI displays intensified mass on T1 weighted images and intermediate signal mass on T2 weighted images, as well as a moderate enhancement on gadolinium enhanced T1 weight images [12].

Factors that determine the overall 5-year survival rate for uLMS are the tumor's stage, the tumor's size, and the patient's age [13]. In regard to tumor staging, stage 1 has the greatest 5-year survival rate of 51% compared to stage 2 which is 25% [5]. When looking at the tumor's size independently, the 5-year survival rate is greatest when the tumor is under 5 cm with the 5-year survival rate of 76.6%. Once the tumor size progresses to 5-10cm, the 5-year survival rate decreases to 52.9%, and subsequently further decreases to 41.9% when tumor size surpasses 10 cm. Most cases of uLMS have shown that women over the age of 40 years are risked of uLMS, and the incidence increased during perimenopausal years [13]. In a study using 52 years of age as a cutting-off point, patients aged less than 52 years had a 73.5% 5-year survival rate whereas patients aged greater than 52 years had a 56.1% 5-year survival rate [13].

Early treatment of uterine leiomyosarcoma is imperative because in 40-70% of the cases, the tumor metastasizes [14]. Once the tumor has metastasized, the median survival time is approximately 1 year [14]. Due to the rapid decline in survival rate, once the tumor has metastasized, there should be a crucial emphasis on finding well-defined universal treatments for uLMS [5]. Currently, due to an overall increase in cure and survival rates, surgery has been the preferred treatment for local relapse uLMS cases and/or metastasis because surgery has overall survival rate of 69% and 3- and 5-year cancer specific survival of 78% [13]. Once uMLS metastasizes, whether surgical or palliative care depends on patient's condition and comorbidity [9]. In a well fit patients, thyroidectomy with or without adjuvant therapy is the treatment of choice because the mean survival rate is higher compared to non-surgical [9]. Patients who received thyroidectomy has 34 months of mean survival compared to the patient without surgical treatment which was 25 months [9]. However, the majority of cases are palliative care.

In the past several years, chemotherapy has been used to treat patients with uLMS. Monotherapy or combination therapy is used depending on the toxicity that may cause harmful effects on the patients [14]. In monotherapy, doxorubicin or gemcitabine are used to treat uLMS. Gynecologic oncologists found that doxorubicin levels greater than 60 mg/m2 per 3-week cycle have proved optimal results and set a standard dose at 75 mg/m2 per cycle. Gemcitabine has shown a response rate as high as 21%. Trabectedin has also been used as a single agent to manage uLMS. Trabectedin significantly improved patient progression-free survival, which is 4.2 months compared to dacarbazine which has a progression-free survival of 1.5 months [14].

Combination chemotherapy has also been utilized in uLMS management. Combination chemotherapy includes gemcitabine plus docetaxel and followed by doxorubicin after the patients have completed uterus resection. The result showed 78% of patients were progression-free at 2 years and 57% of patients were progression-free at 3 years [14].

The immunotherapeutic approach is also being introduced in uLMS clinical trials. Olaratumab with doxorubicin showed a response rate of 18.8% compared to doxorubicin alone, which showed a response rate of 12.3% [14]. However, there is still room for exploring the immunotherapeutic approach because there could be a correlation between the efficacy of immunotherapy with specific biomarkers such as PI3K pathway activation and loss of PTEN [14]. We hope that this report raises awareness of what remains an unmet need in metastatic leiomyosarcoma diagnosis and management and that continued investigation drives further development of efficacious and safe treatments for improving patient outcomes.

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