



# Metastatic Ovarian Granulosa Cell Tumor to the Clavicle Bone Twenty Years After Primary Diagnosis: A Case Report and Literature Review

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## Abstract

Ovarian granulosa cell tumor (GCT) is the most common malignant sex cord–stromal tumor, representing 2% to 3% of all ovarian cancers. It is generally considered to have a good prognosis with late recurrence typically occurring 5 to 20 years later. The majority of these tumors are locally aggressive and recur in the abdomen, pelvis, or lymph nodes. Distant metastases have been reported, particularly to the lung and liver, bone metastases are extremely rare and reflect hematogenous spreading. We present a case of a 60-year-old woman who was found to have an isolated lytic lesion in the right medial clavicle. The clavicle lesion proved to be a metastatic GCT with recurrence 20 years later. There are only a few GCTs with bone metastases reported in the literature and to the best of our knowledge this is the first reported metastasis to the clavicle bone.

**Keywords:** Ovarian Cancer; Granulosa Cell Tumor; Metastasis; Bone; Clavicle; Tumor Recurrence; Fine-Needle Aspiration; FOXL2

## Abbreviations

**GCT:** Granulosa Cell Tumor; **ACE:** Angiotensin Converting Enzyme; **FDG:** Fluorodeoxyglucose; **FNA:** Fine-Needle Aspiration; **CA125:** Cancer Antigen 125; **SMA:** Smooth Muscle Actin; **CD99:** Cluster of Differentiation 99; **CK7:** Cytokeratin 7; **WT1:** Wilms Tumor Protein1; **EMA:** Epithelial Membrane Antigen; **BMI:** Body Mass Index; **FIGO:** International Federation of Obstetrics and Gynecology; **FOXL2:** Forkhead Box L2; **GnRH:** Gonadotropin Releasing Hormone; **SMAD:** Drosophila mothers against decapentaplegic protein; **VEGF:** Vascular Endothelial Growth Factor; **AKT:** Serine/Threonine Kinase; **PI3K:** Phosphatidylinositol-3-kinase; **AMH:** Anti-Müllerian Hormone; **TGF-β:** Transforming growth factor beta

## Introduction

Granulosa-cell tumor (GCT) is the most common sex-cord stromal tumor of the ovary with an incidence of 0.47 to 1.6 per 100,000 [1]. GCTs account for 2–5% of malignant ovarian neoplasms and are considered to have a good prognosis [2]. The two classifications are juvenile GCT and adult GCT, with

the majority of the cases being the adult type [3]. The clinical presentation of GCT may include abdominal pain with or without a mass, vaginal bleeding, amenorrhea, menorrhagia, and irregular menstruation [4]. Slow growth, local invasion, and late recurrence characterize the progression of this tumor [5]. Many patients with GCT present with early-stage disease that is locally aggressive and curative with surgery alone, however insidious recurrence of GCT has been reported in the literature most commonly occurring in the peritoneum. Rare cases have been reported showing distant metastases [6]. We report a case of metastatic adult GCT to the bone diagnosed by cytopathology. Emphasizing the need for continued follow up and monitoring due to the propensity of late recurrence as illustrated by this case. The most critical factor contributing to mortality for GCT patients is high recurrence rate [7]. At present, early diagnosis and prevention of recurrence is the most important challenge to reduce mortality associated with GCT.

## Case Presentation

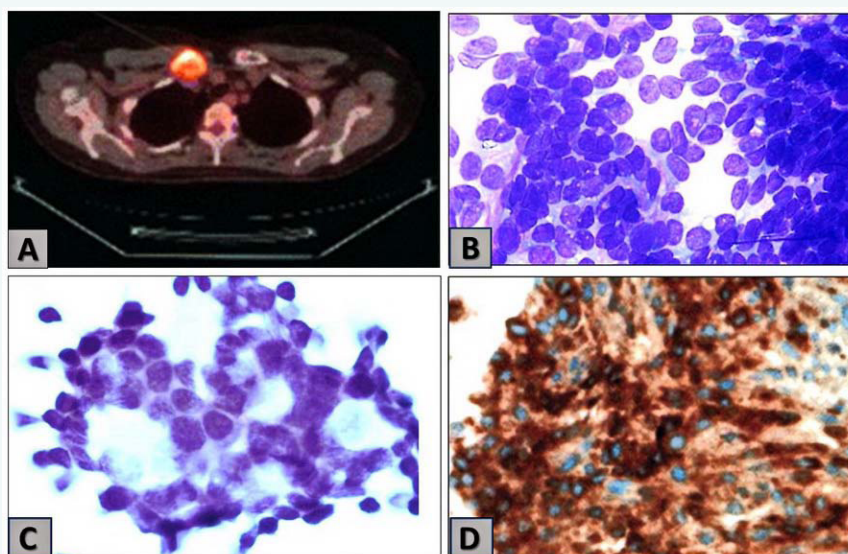
A 60-year-old woman presented with right lower neck pain lasting for three weeks. Physical examination revealed an ill-defined mass arising from the medial aspect of the right clavicle. She had history of hypertension controlled with ACE inhibitor, hypercholesterolemia controlled with Lipitor and a remote history of ovarian tumor 20 years ago. She reported history of oral contraceptives, and her mother died of advanced breast carcinoma at the age of 58. X-ray imaging of the right clavicle showed an isolated, irregular bony lesion arising from the medial clavicle. A PET/CT scan showed an FDG-avid, destructive lesion in the medial right clavicle (**Figure 1A**). A CT-guided fine-needle aspiration (FNA) was performed. Cytopathologic examination of the cytology smears and cell block revealed aggregates of neoplastic cells arranged singly and in large sheets, with overlapping round-oval nuclei, many with nuclear grooves, high nuclear to cytoplasmic ratio, and increased mitotic activity in a bloody background consistent with a metastatic malignant tumor (**Figure 1B**). Occasionally, tumor cells appeared to

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**Figure 1** Imaging studies and cytomorphologic analysis of the FNA of the clavicle mass

Figure 1A: PET/CT scan showed an FDG-avid, destructive lesion in the medial right clavicle

Figure 1B: neoplastic cells arranged singly and in large sheets, with overlapping round-oval nuclei, many with nuclear grooves, high nuclear to cytoplasmic ratio, consistent with a metastatic malignant Granulosa cell tumor. (Diff Quick stain X100)

Figure 1C: Occasionally, tumor cells appeared to surround eosinophilic hyaline globules resembling call-Exner bodies. (Papanicolaou stain X100)

Figure 1D: Tumor cells positive for inhibin (IHC X40)

surround eosinophilic hyaline globules resembling Call-Exner bodies (**Figure 1C**). The striking cytomorphologic characteristics prompted questioning and investigation of the prior remote ovarian tumor. Surgical pathology report of the prior tumor was retrieved, and it showed a GCT 20 years prior to current presentation treated with right ovarian cystectomy. At that time, patient declined further surgery or treatment due to fertility desires. The cytomorphologic features and the immune-profile of the current clavicle tumor were compared with the described histomorphology and immune-profile of the prior tumor. The tumor cells in the current clavicle tumor were positive for Inhibin (**Figure 1D**), CA125, Vimentin, SMA, CD99, S100, and synaptophysin, while negative for Cytokeratin AE1/AE3, CK7, CAM5.2, WT1, P40, EMA, CD56, Desmin, CD31, and Myogenin. The reported immuno-profile of the prior ovarian tumor was positive for Inhibin, CA125, CD99, and Vimentin, while negative for all cytokeratins, WT1, and Desmin. As both tumors showed similar pathological and immunohistochemical features, a diagnosis of metastatic GCT to the right medial clavicle bone was rendered. Full body survey revealed no other sites of metastasis. The clavicle tumor was surgically removed with safe margins and the patient received adjuvant chemotherapy. The patient was followed for four years with no evidence of tumor recurrence, after which she was lost to follow up.

## Discussion

The most common malignant sex-cord stromal tumor is GCT, which makes up approximately 2% to 3% of ovarian cancers [1]. Contrasting with epithelial ovarian cancers, this tumor is characterized by its relatively indolent course [8]. The

two classifications of GCTs are juvenile and adult. The juvenile type accounts for approximately 5% of GCTs, typically affecting teenagers younger than 20 years of age [1] and is associated with isosexual precocious puberty [5]. Due to the likelihood of long disease-free intervals and therefore the reasonable opportunity for reproduction, choosing fertility-sparing treatments in spite of the high risk of recurrence in the long term is important [3]. The adult type accounts for approximately 95% of GCTs, frequently affecting post-menopausal women with the highest incidence occurring between the ages of 50 and 54 [6]. The major risk factors of GCT include nulliparity, high BMI, oral contraceptives and family cancer history [7].

The clinical presentation of GCTs commonly present with nonspecific symptoms, including abdominal pain, distention, and bloating. Additionally, two-thirds of patients present with endocrine symptomatology related to tumor hormonal release, most commonly estrogen. In addition to nonspecific abdominal symptoms, these patients may also present with vaginal bleeding due to estrogen release. As might be expected, 50-60% of patients developed endometrial hyperplasia leading to 5-10% developing uterine cancer and 3.7-20% increase in incidence of breast cancer [5].

GCTs have a favorable prognosis with a slow progression, however reoccurrence demonstrates a less favorable clinical course leading to disease-related mortality [9]. Prognostic factors include stage, size of tumor, age of diagnosis, rupture of tumor, residual disease after initial surgery, and molecular markers. The most significant prognostic factors of recurrence are the stage at diagnosis and presence of residual disease



**Table 1:** Six selected cases of granulosa cell tumor metastasis to the bone and current case, listed chronologically.

Author	Year	Age at diagnosis	Location	Tumor Markers	Treatment of recurrence	Recurrence (years later)
Asher et al. [current case]	2020	40	Right Clavicle	Inhibin, CA125, Vimentin, SMA, CD99, S100, and synaptophysin	CR, chemo	20
Burns et al. [15]	2013	36	L1	-	RT	6
Huang et al. [16]	2010	35	T4, T7, S1, S2	-	Palliative decompressive laminectomy, RT	10
Dubuc-Lissoir et al. [2]	2001	25	T7	-	CR, RT, MA	39
Thirumala et al. [1]	1998	68	L1	-	-	16
Rose et al. [17]	1989	24.5 (median)	Not specified	-	-	-
Fox et al. [18]	1975	52.6 (mean)	Not specified	-	RT, Chemo	-

Abbreviations: **CR:** Complete resection **RT:** Radiotherapy; **Chemo:** chemotherapy; **MA:** Megestrol Acetate

[10]. GCT is staged based on the International Federation of Obstetrics and Gynecology (FIGO) classification system. Due to the symptomatic presentation secondary to hormone secretion, 85-90% of patients are diagnosed in stage I, thus resulting in a greater than 90% survival rate with treatment. Poor prognostic indicators are lymphatic invasion, tumor size, high mitotic index, and tumor rupture [5]. The rate of recurrence of GCTs is 31% [11] and increased recurrence is associated with residual tumor after initial surgery [2]. Although recurrence may appear as late as 20 years after initial diagnosis, the average time to recurrence is between 5 and 10 years [2].

The majority of recurrences occur locally in the peritoneum, while distant metastases are rare [13]. While a majority of recurrences are found in the abdominopelvic area, metastases to the liver, lung, kidney, heart, gastrointestinal tract, and bone have been reported in the literature, with the liver being the most common site of distant metastasis followed by the small intestine [2]. Bone metastases spreading hematogenously are extremely rare, and to our knowledge have only been reported six times in the literature.

Due to the anecdotal nature of GCT recurrence, long-term follow up with surveillance is undeniably vital for patient management [6]. Based on the rarity of GCT and the potential of late recurrence, acceptable guidelines for management and treatment have yet to be established. Despite the good prognosis of GCT, approximately 80% of patients with recurrence die due to the disease [9].

Grossly GCTs commonly present as a smooth, unilateral mass that is yellow or grey in color [13]. Microscopically GCTs comprise small round cells with a "coffee-bean" appearance showing a grooved-nuclei. These cells arrange in groups, forming Call-Exner bodies. Histology along is non-predictive of the clinical course of these tumors due to the variability in mitotic activity and nuclear atypia [3].

Fine-needle aspiration cytology has been identified as a reputable technique in diagnosing benign and malignant ovarian neoplasms with a 90% accuracy [1]. Tumor markers including estradiol, Inhibin, and Mullerian inhibiting substance have been identified as GCT tumor markers, with estradiol having the most value. However, diagnosis of GCT is noted to be difficult due to the absence of specific symptoms and specific tumor markers [6].

The differential diagnosis of GCT includes poorly differentiated ovarian carcinoma, lymphoma, carcinoid tumor, Brenner tumor, and small-cell carcinoma and can be differentiated based on cytology, immunohistochemical studies, and clinical presentation. Poorly differentiated carcinomas portray large atypical nuclei with mitotic figures and positively stain with antibodies to cytokeratin and epithelial membrane antigen. Lymphoma presents with cells that lack a nuclear groove and are not in groupings. In addition, lymphomas have positive immunoreactivity for leukocyte-common antigen, and in contrast are negative for cytokeratin and epithelial membrane antigen. Carcinoid tumors have cytoplasmic granules that stain positive for antibodies to chromogranin and appear as round, small cells with dense nuclei. Brenner tumors, another ovarian tumor with characteristic nuclear grooving, stain positive for antibodies to epithelial membrane antigen and cytokeratin, and their cellular morphology can be differentiated by their plentiful cytoplasm. Small-cell carcinomas stain positive for antibodies to both cytokeratin and neuron-specific enolase, have hyperchromatic nuclei and abundant mitotic figures, and typically present in younger patients [1].

The most important mutant gene in GCT formation is FOXL2. The presence of the FOXL2 mutation is found in 97% of adult GCT cases, while it is seldom detected in other ovarian cancers. FOXL2 is a transcription factor that plays a part in the regulation of granulosa cell proliferation and apoptosis, as well as ovarian response to GnRH and hormone production. While further studies are necessary, the FOXL2 mutation emerges as the first possible





pathognomonic finding for adult GCT. While FOXL2 remains the prominent mutant gene in GCT, it has been demonstrated that GATA4, SMAD, VEGF, PI3K/AKT, AMH and TGF- $\beta$  also contribute. In fact, a complex network of signaling pathways is involved in causative mechanisms, such as TGF- $\beta$ , NOTCH and PI3K/AKT, hence none are isolated and independently responsible [7].

The recent integration of cytology and radiology has allowed for minimally invasive, safe, accurate, and cost-effective diagnosis of suspicious masses; which was previously accessible only by surgical biopsy techniques. As a result, cytologists are increasingly called upon to diagnose disease in specimens procured under image guidance for different organs. Rather than causing delay, cytology facilitates timely diagnosis and management and is an integral part of a multimodal approach to various tumor diagnoses. On-site cytology interpretation increases the diagnostic yield of the procedure by allowing for additional needle passes as necessary [14].

While initial stage treatment for GCT is complete resection of the tumor, there are no standard guidelines for treatment of recurrence. Although several modalities including: surgery, chemotherapy, radiotherapy, and hormonal therapy have been outlined in the literature, establishing a treatment of recurrent tumors requires further investigation. It has been demonstrated that patients with GCT recurrence who underwent repetitive debulking surgery achieved longer survival [11]. Control of widespread disease can be managed with chemotherapy and or radiotherapy with a mortality benefit depending on degree of cytoreduction and whether confined to the pelvis or abdomen. The role of hormonal therapy is limited to refractory GCT. Important to note, fertility preserving surgery is possible for females at reproductive age due to the slow progression of GCT [6].

Only a few cases of metastatic GCT to the bone have been described in the literature, and to the best of our knowledge, this is the first reported case of clavicle metastasis. Due to the late manifestations of metastatic disease, the case described here emphasizes the need for close clinical-pathological cooperation in diagnosis and long-term follow up for patients with a known history of GCT of the ovary. To improve the patient outcome and efficacy of novel treatments, there is an imperative need for better insight into the pathology, molecular biology and genetics of metastasis from GCTs. Currently, there is no consensus treatment protocol for recurrent GCTs. It is our hope that this report raises awareness of what remains an unmet need in the definitive diagnosis and management of various ovarian malignancies. Furthermore, that the continued investigation drives further development of efficacious diagnosis and safe treatments for improving patient outcomes.

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