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Annals of Oncology Case Reports

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Mitotically Active Cellular Fibroma in an Adolescent Patient: A Rare Case Report

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Received: Oct 25, 2023

Accepted: Nov 21, 2023

Published Online: Nov 28, 2023

Journal: Annals of Oncology Case Reports

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Abstract

Ovarian fibromas, the most common stromal tumor, exhibit a diverse spectrum that includes conventional fibromas, cellular fibromas, and mitotically active cellular fibromas. Fibromas are usually benign with an excellent prognosis. However, cellular fibromas, in particular mitotically active cellular fibromas, are considered tumors with uncertain malignant potential that require long-term follow up. We report a case of an adolescent patient with mitotically active cellular fibromas on her right ovary. The patient was a 16-year-old girl with intermittent abdominal pain. Ultrasound study detected a 9.7 cm right adnexal mass, which was confirmed by CT and MRI. Patient was subjected right salpingo-oophorectomy with intraoperative evaluation. Histological evaluation revealed conventional fibroma intermixed with cellular spindle cell nodules featured with markedly increased mitotic activity (24 mitosis / 10 high power field) and high proliferative rate (Ki-67 = 90%). No significant cytological atypia, necrosis, or lymphovascular invasion was identified. Next generation sequencing was performed with no detection of significant mutations or gene fusions. The final diagnosis was mitotically active cellular fibroma. Considering the morphological features, phonotypical profile, and molecular study findings, the patient was managed conservatively with closed observation.

Introduction

Ovarian fibroma is a benign stromal tumor composed of spinal or ovoid neoplastic cells with variably amounts collagenous stroma. It represents 4 % of ovarian tumors, and frequently occurs in postmenopausal women [1]. Surgical excision is sufficient for treatment in most cases. Cellular fibroma, an variant of fibroma, accounting for approximately 10 % of total fibromas, demonstrates dense growth of bland spindle cells without cytological atypia [1]. Mitosis is usually increased, up to 3 mitotic figures per 10 X high power field (3 MFs/10 HPF). Different from conventional fibroma, cellular fibroma may recur after a long interval of surgical removal, warranting a close follow up [2-3]. Once this stromal tumor demonstrates mitotic activity higher than 4 MFs/10 HPF, two differential diagnoses should be included. Tumors with significant cytological atypia, with or without necrosis and herringbone pattern, favor fibrosarcoma [2]. While tumors with absence of cytological atypia, markedly increased

Cite this article: Fan Y, Buchanan KN, Nolan L, Kothari R, Ying S, et al. Mitotically Active Cellular Fibroma in an Adolescent Patient: A Rare Case Report. Ann Oncol Case Rep. 2023; 2(2): 1013.

cellularity and mitotic activity, are categorized as mitotically active cellular fibroma that are associated with a relatively favorable prognosis. These cases, however, are extremely rare and are not well recognized, which should be carefully evaluated to avoid the misdiagnosis of fibrosarcoma.

Case

Patient was a 16-year-old girl with a chief complaint of intermittent abdominal pain. Physical examination revealed a right adnexal mass that was confirmed on the ultrasound study, measuring 9.7 x 7.6 x 7.6 cm. The follow up CT and MRI redemonstrated a heterogenous enhancing solid ovarian mass that was stable in size over the time. The patient was then referred to the Obstetrics and Gynecology services for further clinical management. Five months later, the patient underwent an uncomplicated right salpingo-oophorectomy. A 11.0 x 9.0 x 6.0 cm ovarian mass was excised and sent for pathology review. Grossly, the mass demonstrated tan fleshy cutting surface, with no detectable hemorrhagic or necrotic areas. The representative sections on intraoperative evaluation showed homogenous spindle cell proliferation with no evidenced mitosis, cytological atypia, or tissue necrosis. A diagnosis of conventional ovarian fibroma was made, and the patient was discharged after recovery. Further histopathology examination revealed spindle cell proliferation with varying morphologies. The predominant area of the lesion was comprised of bland spindle cells in dense collagenous stroma, with scattered thin-walled ectatic blood vessels. Mitotic figures in these areas were not identified. Among these bland fibromatous areas are “pseudo lobular” cellular nodules with numerous mitotic figures (up to 24 MFs/ 10 HPF). Intermixed between the cellular spindle cell components were round epithelioid cells with scant vacuolated cytoplasm, arranged in small clusters and distributed throughout the nodules. Immunohistochemical studies were performed. The spindle cells were positive for Caldesmon, Smooth Muscle Actin, Progesterone receptor, and Estrogen receptor, and they were negative for EMA, CD34, Desmin, Inhibin, Calretinin, and DOG1. CD117 showed heterogeneous positivity (negative to weak positive). Special stain of reticulin demonstrated the presence of reticulin fibers around individual cells, with occasional fibers around the clusters of epithelioid cells. The immunohistochemical stain of Ki-67 showed an extremely high proliferation rate (greater than 90%) at the periphery of the cellular nodules, while demonstrating a very low activity (less than 1%) at areas with conventional fibromatous morphology. Based on the morphological and phenotypic findings, the differential diagnosis included mitotically active cellular fibroma versus low-grade fibrosarcoma.

To assist with a more definitive diagnosis and identify characteristic mutations and gene fusions, the specimen was submitted for solid tumor next generation sequencing panel and gene fusion panel (performed at Northwestern Memorial Hospital). The result showed that no significant mutations or gene fusions were detected, favoring a diagnosis of mitotically active cellular fibroma.

Discussion

Epidemiologically, ovarian fibromas represent approximately 4-6% of all ovarian neoplasms. Their occurrence spans a wide age range, often peaking in postmenopausal women aged 40-60. Clinically, patients with ovarian fibromas may present with pelvic pain, abdominal discomfort, and pressure symptoms. However, due to the gradual growth of the tumor, many cases are asymptomatic. In 2003, WHO categorized ovarian cellular

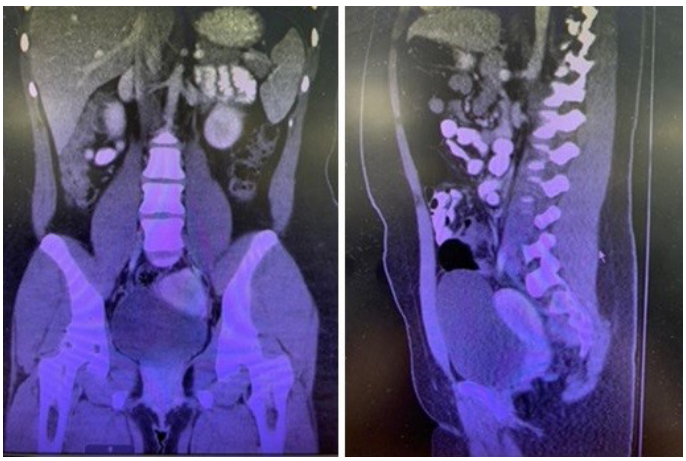

Figure 1: Computed Tomography (CT) of the abdomen detected right lower quadrant/pelvic homogeneous solid mass, suspected for right ovarian origin. Mass measures approximately 8.5 x 6.1 x 7.4 cm.

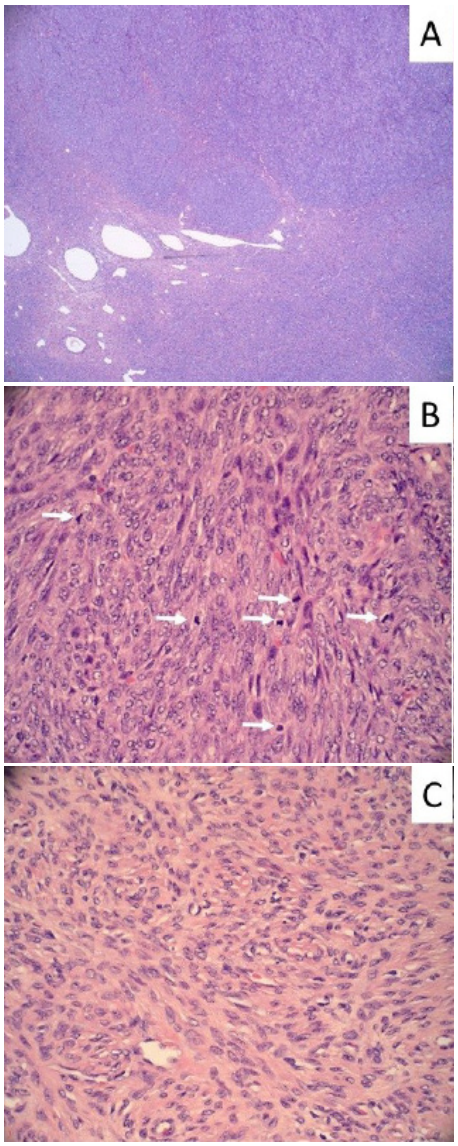

Figure 2: Photomicrograph of the ovarian mass. Lesion is composed of bland spindle cell proliferation in collagenous stroma, intermixed with cellular nodules with increased mitosis. **A:** Representation of the interface of conventional fibroma and the mitotically active cellular fibroma (HE-100x). **B-C:** Hypercellularity with markedly elevated mitosis (arrows) in the mitotically active cellular fibroma (B), compared with its adjacent conventional fibroma region (C) (HE-400x).

fibroma with a low malignant potential. These tumors featured with less than 4 MFs/10 HPF without significant cytological atypia [2-3]. Compared with cellular fibroma, ovarian fibrosarcoma was a malignant counterpart, located at the other end of this fibrous tumor spectrum with very poor clinical prognosis. It was defined as more than 4 MFs/10 HPF with severe cytologic atypia and frequently has underlying molecular alterations [4]. There was no consensus on how to classify the tumors with no nuclear atypia but showing markedly increased mitotic activity (> 4 MFs/10 HPF). In 2006, Irving et al. first advocated a new entity "mitotically active cellular fibromas" to fill the gap [5]. Till now, limited case reports have been published, which suggest an excellent prognosis after the surgical excision [2,3,5-7]. Since these tumors are extremely rare with histopathological similarity to fibrosarcoma, a correct diagnosis is the key for clinical management.

This case report is unique for several reasons. First, the occurrence of ovarian fibromas, in particular mitotically active cellular fibromas, in the adolescent population is very uncommon. Based on our knowledge, only one adolescent patient, aged 13- years old, was previously reported in 2012 [6]. A continuous collection and analysis of these cases is essential for establishing an appropriate clinical management strategy. Secondly, although the criteria of increased mitosis of more than 4 MFs/10 HPF is needed to satisfy the diagnosis of mitotic active cellular fibroma, an extremely high proliferation rate in the current case (24 MFs/10 HPF, Ki-67 90%) has never been observed in all the published literatures. Theoretically, if there is no severe cytologic atypia, and / or any classic features of sarcoma (such as herringbone pattern, necrosis, hemorrhage), an increase in mitosis by itself is not enough to justify a more worrisome diagnosis (i.e. fibrosarcoma), but it raises the concern. To assist with the differential diagnosis the next generation sequencing has been done, by which provides further supportive evidence of making the possibility of a low-grade fibrosarcoma less likely. Nevertheless, the distinction between low-grade fibrosarcoma and mitotically active cellular fibroma is very subjective, and it is impossible to provide rigid criteria with the current literature [2,3,5-7]. In this case, given the morphologic features, immunohistochemical profile, and negative findings in molecular studies, we recommend that this patient should be managed conservatively with careful close observation.

Conclusion

Mitotically active cell fibroma is an extremely rare ovarian fibromatous tumor that needs more comprehensive workup to satisfy its diagnostic criteria and rule out the differential diagnosis of fibrosarcoma. At present, conservative surgical excision and close follow up are appropriate in younger patients. Further observation and evaluation of these categorized cases is of great importance, and a revised classification may be necessary to establish a standard therapeutic strategy.

Author contributions: Kristen Nicole Buchanan, Yiyi Fan, Haoliang Xu: Involved in manuscript drafting and revision.

Liam Nolan, Rajul Kothari, Shanching Ying, Russell Fiorella: Involved in manuscript revision and intellectual discussion.

Acknowledgement: We would like to acknowledge the Departments of Pathology, Radiology, and Obstetrics-Gynecology, Sinai Healthcare System.

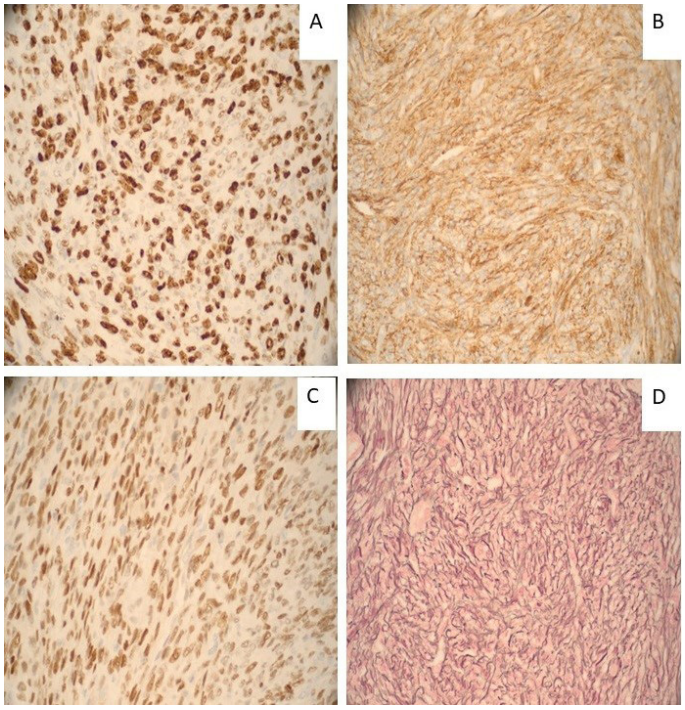

Figure 3: Immunohistochemical and special stains performed on the ovarian mass. The lesion demonstrated markedly elevated proliferation rate, with Ki-67>90% **(A)**, and it was phenotypically positive for Caldesmon **(B)** and PR **(C)**. Reticulin special stain showed reticulin fibers around individual cells **(D)**. (HE-400x).

Conflicts of interest: All authors declare that they have no potential conflict of interest.

Funding: Funding information is not applicable.

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