

Case Report

Non-teratomatous ossification of the ovary, a rare entity: case report and review of the literature

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Abstract: Ossification in non-teratomatous ovaries is extremely rare. This phenomenon may occur in various non-neoplastic or neoplastic ovarian diseases. A 34-year-old woman presented with lower abdominal pain of about 3 months. Transvaginal ultrasonography and plain abdominal radiography revealed an ovoid, calcified mass in left adnexa. Computed tomography (CT) demonstrated a well-defined cystic lesion measuring 7.7 × 5.1 cm with internal hemorrhage and peripheral curvilinear calcifications. The patient underwent laparoscopic surgery. The cut surface revealed a hemorrhagic cyst with a hardened wall and a muddy, yellow surface. Histologic examination revealed an ovarian hemorrhagic cyst with ossification. The authors present an unusual case of ossification in the ovary associated with an old hemorrhagic cyst and include a review of the literature.

Keywords: Non-teratomatous, ossification, ovary

Introduction

Calcification of the ovary commonly occurs in mature teratoma and is usually focal and localized. On the other hand, ovarian ossification is extremely rare; only about 33 cases have been reported in the English literature (**Table 1**). Conditions associated with ovarian ossification include endometriotic cyst, ovarian stone, and benign and malignant tumors of the ovary [1]. Plain abdominal films, ultrasonography, and computed tomography can be used for the diagnosis of ovarian ossification [2]. The pathogenesis of ossification of the ovary remains unknown, but the condition may occur as an unusual reaction to tissue damage and repair [3]. Here, we report an unusual case of ossification in the ovary associated with an old hemorrhagic cyst and include a brief review of the literature.

Case presentation

A 34-year-old woman presented with lower abdominal pain of about 3 months' duration. Transvaginal ultrasonography revealed a homo-

geneous echogenic lesion with a hyperechoic rim of the left ovary measuring 7.2 × 4.6 cm (**Figure 1A**). Plain abdominal radiography disclosed an ovoid, 7.7 cm × 5.1 cm sized, calcified shadow in the left adnexa (**Figure 1B**). Further evaluation of the mass was performed by computed tomography (CT), and axial and coronal-reformatted contrast-enhanced CT scans demonstrated a well-defined cystic lesion with internal hemorrhage and peripheral curvilinear calcifications in the left ovary (**Figure 2**). The mass was first considered to be a mature cystic teratoma. The patient had no past medical, family, or surgical history (with exception of laparoscopic appendectomy), and no history of associated gynecologic problems. Preoperative serum CA125 level was within normal limits, and hematological and other laboratory parameters were normal.

The patient underwent laparoscopic left ovarian cystectomy. A well-encapsulated smooth mass with minimal periovarian adhesion was identified (**Figure 3**). The cut surface of the mass revealed a muddy, yellow hemorrhagic cyst with a hardened wall (**Figure 4A**). Micro-

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Table 1. Non-teratomatous ossification of the ovary reported in the literature

Author	Age (Yr)	Clinical presentation	Ovarian size (cm)	Ossification extent (cm)	Diagnosis	Other findings
Secondary						
Anteby et al. (1992)*	53	Fever, abdominal pain	4	small	Infected gallstones in dermoid cyst	all of 6 cases: prior laparoscopic cholecystectomy/GB stone
Tursi et al. (1993)*	70	Abdominal pain, adnexal mass	4	small	Gallstone adherent to ovary, pelvic peritoneum	
Pfeifer et al. (1996)*	39	Chronic pelvic pain	normal	small	Gallstone adherent to ovary	
Vadlamudi et al. (1997)*	30	Infertility	normal	small	Gallstone embedded in ovary	
Chand et al. (2001)*	45	Abnormal uterine bleeding	normal	small	Gallstone adherent to ovary	
Pantanowitz et al. (2007) [5]	53	Asymptomatic	normal	1	Gallstone embedded in ovary	
Non-neoplastic lesions						
Clement et al. (1992) [15]	50	Asymptomatic	normal	focal	Idiopathic	incidental
Su et al. (2002) [6]	42	Severe abdominal pain, dysmenorrhea	5	extensive	Ovarian stone, endometrioma	
Ding et al. (2002) [2]	30	Severe abdominal pain, dysmenorrhea	7	7	Ossification with dystrophic calcification	
Badawy et al. (2005) [16]	32	Secondary infertility, dysmenorrhea	5	focal	Endometrioma	
Sharma et al. (2007) [17]	NA	Asymptomatic	normal	0.8	Small follicular cyst	incidental
Lanzafame et al. (2007) [14]	65	Chronic pelvic pain	5.5	extensive	Endometrioma	
Campo et al. (2007) [18]	42	Abnormal uterine bleeding	normal	focal	Simultaneous ovarian & endometrial osseous metaplasia	
Shaco-Levy et al. (2007) [4]	46	Chronic pelvic pain	3	3	Endometrioma	
Rosa e Silva et al. (2010) [19]	31	Chronic anovulation	2.5	focal	Isolated osseous metaplasia, normal ovaries	
Singh et al. (2018) [3]	42	Lower abdominal pain	3.5	focal	Endometrioma	
Gabrilovich et al. (2019) [1]	35	Severe abdominal pain, dysmenorrhea	1.3	1.0	Endometrioma	
Our case (2020)	34	Lower abdominal pain	7.7	7.7	Hemorrhagic cyst	

*: cited in Reference 5.

Author	Age (Yr)	Clinical presentation	Ovarian size (cm)	Ossification extent (cm)	Diagnosis	Other findings
Neoplastic lesions						
Sotto et al. (1956) [20]	21	Asx. adnexal mass	7	7	Fibroma	
Shipton et al. (1965) [12]	63	Right thigh pain	5	5	Benign cyst	
Barua et al. (1982) [21]	60	Abdominal distension	20	focal	Serous cystadenocarcinoma	
	53	Urinary incontinence, Asx. both adnexal mass	8 and 7	3 and 4	Serous cystadenocarcinoma	
Bosscher et al. (1990) [7]	46	Vaginal bleeding, lower abdominal pain	20	focal	Serous cystadenocarcinoma	
Misselevich et al. (2000) [22]	75	Asx. adnexal mass	10	focal	Mucinous cystadenoma	
Mooney et al. (2000) [11]	20	Asx. adnexal mass	6	0.7	Sertoli-Leydig cell tumor	
Zahn et al. (2001) [23]	19	Asx. adnexal mass	6	1.3	Mucinous cystadenoma	
Morizane et al. (2003) [8]	51	Lumbar backache	NA	NA	Luteinized thecoma	
Mukonoweshuro et al. (2005) [13]	66	Recurred adnexal mass	5.4	NA	Endometrioid adenocarcinoma	
Godbole et al. (2005) [24]	16	Lower abdominal pain, dysmenorrhoea	Large	focal	Simple cyst	cloacal anomaly
Miliaras et al. (2007) [25]	37	Asx. adnexal mass	7	3	Serous cystadenoma	

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Kim et al. (2008) [26]	69	Torsion, lower abdominal pain	7.0	7.0	Cavernous hemangioma	
Pervatkar et al. (2009) [10]	66	Postmenopausal bleeding	10	10 (massive)	Luteinized thecoma	endometrial adenocarcinoma
Mardi et al. (2015) [27]	45	Lower abdominal pain	20	extensive	Endometrioid carcinoma	Sex cord-like variant
Kumar et al. (2018) [28]	57	Vault mass	NA	extensive	Fibroma	

*NA: not available, *Asx: asymptomatic; extensive: areas of ossification were extensive, but size was not mentioned.

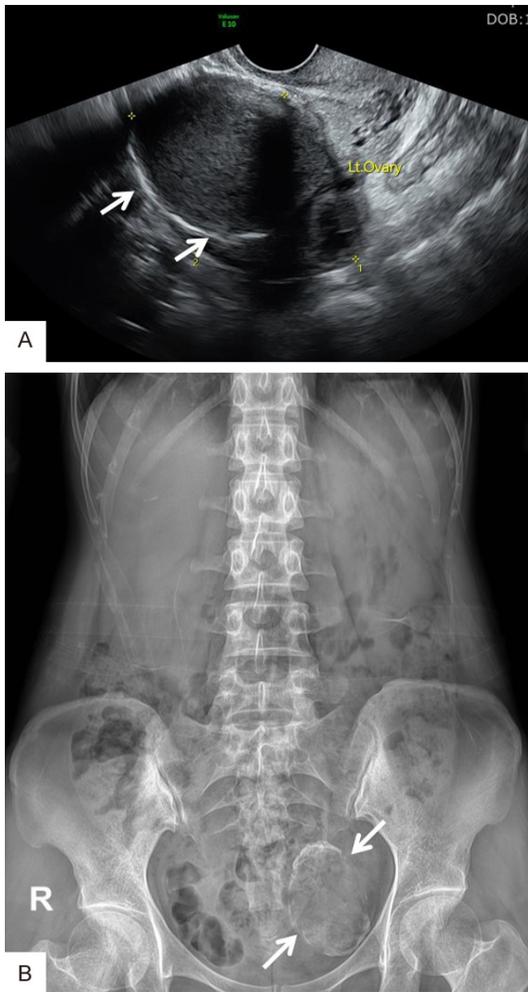


Figure 1. Ultrasonography and plain radiography findings. A. Transvaginal ultrasonography revealed a homogeneous echogenic lesion with a hyperechoic rim (arrows) of the left ovary. B. Plain radiograph of the abdomen showing an ossifying mass (arrow), measuring 7.7 cm × 5.1 cm, on the left side of the pelvis.

scopically, bone trabeculae and old hemorrhage were observed (**Figure 4B**). Involved corpora albicantia were also evident in ovarian stroma. No teratomatous elements were noted in the tumor, and the possibility of an underlying teratoma was excluded. Immunohistochemically, tumor tissues were CD10 negative. Her postoperative course was uneventful. At 6 months postoperatively, the patient became pregnant.

Discussion

Focal calcifications are frequently encountered in non-neoplastic and neoplastic diseases of

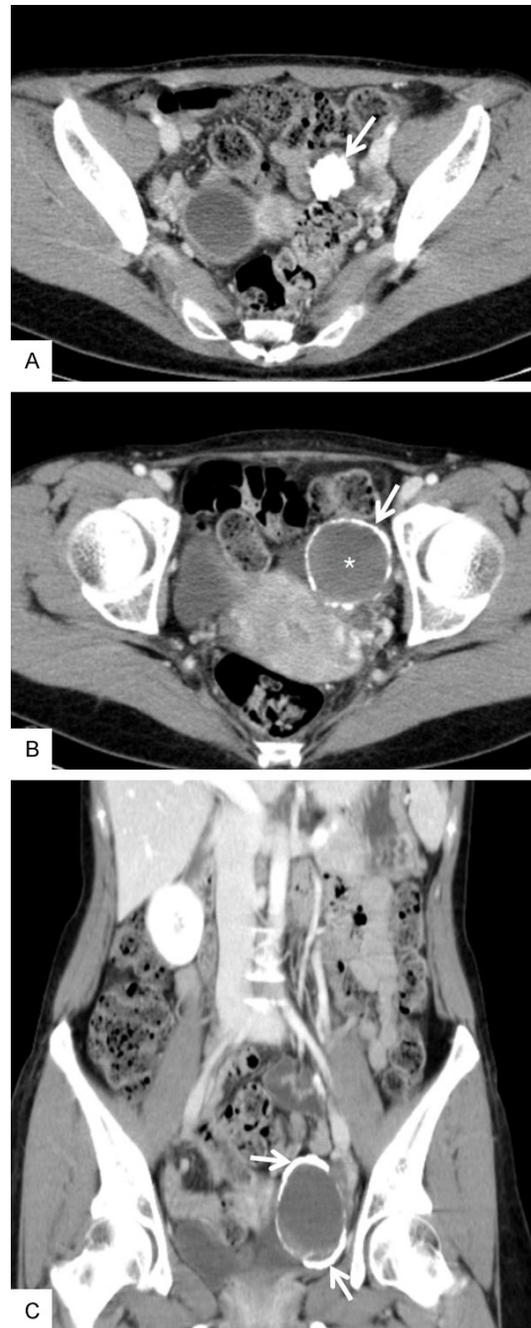


Figure 2. Computed tomographic findings of ossification of the ovary. Axial (A, B) and coronal-reformatted (C) contrast-enhanced CT images showing a well-defined cystic lesion with internal hemorrhage (*) and peripheral curvilinear calcifications (arrows) in the left ovary. A functional cyst was noted in the right ovary.

the ovary and are usually associated with mature teratoma. However, ossification in the ovary is an exceedingly rare condition [4]. Such a phenomenon may occur due to unusual reac-

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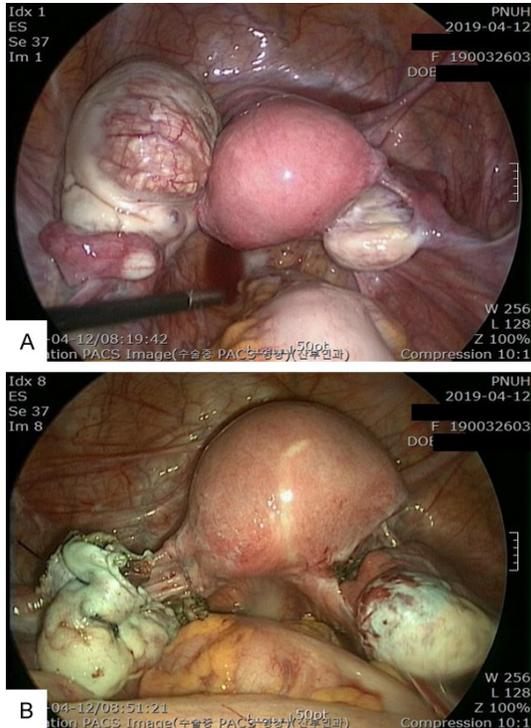


Figure 3. Intraoperative findings. A. The enlarged left ovary contained a cyst with ossification within the cyst wall; the right ovary was normal sized. B. Postoperative finding after left ovarian cystectomy.

tions to tissue damage and repair in a wide range of non-neoplastic or neoplastic conditions [3].

Previous reports have described ossification in the ovary using various terms. We conducted a search of online PubMed and Embase for articles on ossification of the ovary, published in English using the keywords “ossification, ossifying, osseous metaplasia, massive calcification, stone, or cholelithiasis” and “ovary” and identified a total of 33 patients (Table 1) which occurred in patients ranging from 16 to 75 years old. Extents of ossification were variable, and the largest ossification was 10 cm. Focal microscopic ossification was observed in large ovarian tumors, which were discovered incidentally or sometimes symptomatically due to mass effects. Clinical presentation mainly depended on ovarian disease and not on the presence of ossification (Table 1).

Mature teratoma is the most common ovarian tumor that exhibits bone formation. Teratomas usually show teeth-like calcifications, which are focally involved and localized, and frequently contain a lipid component. Other conditions

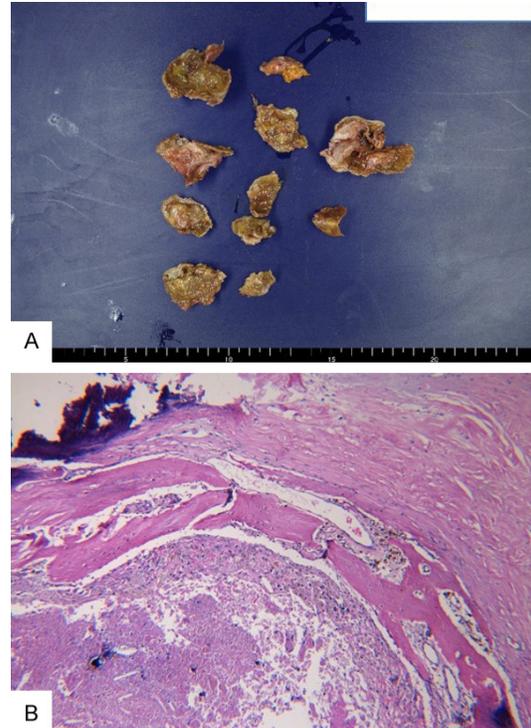


Figure 4. Histologic features of the mass. A. Gross specimen of the left ovarian cyst. Fragments of hard bony tissue were noted within the cyst wall. B. Bony trabeculae (middle) and old hemorrhage (left lower) were demonstrated (H&E, × 100).

associated with ovarian ossification include endometriotic cyst, ovarian stone, benign or malignant ovarian tumors, and idiopathic calcification. Based on the results of the review, we categorized lesions as secondary, non-neoplastic, or neoplastic (Table 1).

As regards secondary lesions, spillage and loss of gallstones into the peritoneal cavity during laparoscopic cholecystectomy may cause cholelithiasis of the ovary [5]. Hence, a search for a history of previous gallbladder surgery is important for pathologists and gynecologists. Dropped gallstones can adhere to or embed in the ovary. This condition tends to be asymptomatic and discovered incidentally at surgery. Choleliths may cause chronic pelvic pain, intra-abdominal inflammation and abscess formation, adhesion, ectopic pregnancy, or infertility [5]. Only 6 cases of gallstones adherent to or embedded in the ovary have been reported (Table 1).

Seven cases of osseous metaplasia, including our case, have been reported in association with endometriotic cyst (Table 1). Also, ossifica-

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tion occurs in normal ovaries incidentally or in hemorrhagic or functional cysts. Chronic inflammation has been suggested to contribute to bone formation in these lesions [1]. Inflammatory insults to ovarian tissues induce the formation of calcifications and subsequent osseous metaplasia of undifferentiated stem cells [4]. Furthermore, torsion causing infarction in normal ovaries or in endometriotic cysts may cause ossification [6]. In the present case, cyst contents consisted of old hemorrhage and a muddy yellow material. The ossification was probably caused by a hemorrhagic cyst or old endometriosis associated with chronic inflammation, although immunohistochemical staining for CD10 was negative.

Osseous metaplasia of both benign and malignant tumors of the ovary, such as ovarian cavernous hemangioma, mucinous and serous cystadenoma, serous and endometrioid adenocarcinoma, has been described [3]. Four cases of ovarian mucinous cystadenoma with bone formation have been reported; two of these cases reported in the old literature were not included in **Table 1** [7]. Ossification has rarely been reported in sex-cord stromal tumors, such as luteinized thecoma, fibroma, and Sertoli-Leydig cell tumor [8-11]. Morizane et al. reported the first case of luteinized thecoma with extensive stromal calcification and metaplastic ossification [8]. Four cases of thecomas with non-ossifying extensive stromal calcification and psammoma bodies have been reported [9]. Pervatkar et al. reported a case of bilateral luteinized thecomas of the ovary with massive ossification associated with endometrial adenocarcinoma [10].

The cause of ossification of the ovary is not known, though several hypotheses have been suggested. Heterotopic bone formation may be stimulated by blood clots, infections, or traumatic inflammation [12]. Overgrowth of coexisting coalesced psammomatous calcifications or spontaneous necrosis of the tips of papillae of papillary tumors are also possible explanations. Some authors have suggested that metaplastic processes of multipotential stromal cells in neoplastic lesions may result in bone formation and postulated that a tumor may produce bone forming factors like transforming growth factor (TGF) β and bone morphogenetic proteins (BMP) that cause the metaplastic transformation of undifferentiated mesenchy-

mal stromal stem cells into osteoblasts [1, 7]. Furthermore, ossification in malignant tumor may be possible when a carcinoma is preceded by a teratoma that has undergone malignant transformation [7, 13].

We summarize our review of the literature as follows: 1) a gynecologic history including prior laparoscopic cholecystectomy is required to detect a secondary cause (e.g., cholelithiasis of the ovary) of non-teratomatous ossification of the ovary; 2) this condition does not appear to have any prognostic significance; 3) the histogenesis of ossification of the ovary remains unclear and may involve interplay between multiple factors; 4) when a calcified or ossifying adnexal mass is observed by imaging, it may be misdiagnosed as mature ovarian teratoma or rarely as calcified leiomyoma [14], thus, the differential diagnosis includes various conditions of the ovary. We recommend calcified/ossifying thecomas be included in the differential diagnosis of extensively calcified ovarian tumors detected by radiologic or pathologic examination.

We report an unusual case of ossification of the ovary associated with hemorrhagic cyst, possibly old endometriosis. Various diseases including benign and malignant lesions should be considered in the differential diagnosis of an ossifying adnexal mass.

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Disclosure of conflict of interest

None.

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