Postmenopausal osseous metaplasia of the endometrium: An uncommon histopathological entity: A case report

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Abstract. Endometrial osseous metaplasia is a rare histopathological condition characterized by the presence of ectopic bone tissue within the endometrium. Although most commonly reported in women of reproductive age presenting with secondary infertility and menstrual abnormalities, it may occasionally occur in asymptomatic postmenopausal women. A 55-year-old postmenopausal woman with a history of invasive ductal breast carcinoma treated with surgery, radiotherapy, chemotherapy and 10 years of tamoxifen therapy was referred for evaluation of incidentally detected endometrial thickening (12 mm) on routine ultrasonography. Transvaginal ultrasound demonstrated a suspected endometrial polyp with posterior acoustic shadowing. Diagnostic hysteroscopy revealed osseous tissue and bone marrow within the endometrial cavity, raising concern for carcinosarcoma or another mesenchymal malignancy. Following multidisciplinary tumour board discussion, operative hysteroscopy with resectoscopy was performed, confirming the presence of osseous tissue; however, malignancy could not be definitively excluded. The patient subsequently underwent total hysterectomy with bilateral salpingo-oophorectomy. Final histopathological examination demonstrated atrophic endometrium containing two microscopic foci of bony tissue with degenerative and necrotic changes, confirming endometrial osseous metaplasia without evidence of malignancy. Notably, the patient had undergone pharmacologically induced abortion followed by dilation and curettage 35 years before diagnosis, suggesting that retained foetal bone fragments or trauma-induced metaplastic transformation may persist for decades and remain clinically silent before being detected incidentally. The present case highlights the importance of considering endometrial osseous metaplasia in the differential diagnosis of hyperechoic endometrial lesions, particularly in women with a history of pregnancy termination or uterine instrumentation. Transvaginal ultrasonography is a useful initial diagnostic modality, whereas hysteroscopy remains the gold standard for both diagnosis and treatment. Integration of clinical history, imaging findings and histopathological examination is essential to exclude malignancy and guide appropriate management.

Introduction

According to the literature, endometrial osseous metaplasia is a rare condition characterized by the presence of immature or mature bone tissue within the endometrium, with an estimated prevalence of ~3 per 10,000 women and <100 cases reported to date (1). Heterotopic ossification may also occur in other pelvic structures, including the ovary, vagina, cervix and mesosalpinx (2-4). Ectopic bone formation within the endometrium and other Müllerian-derived tissues may be explained by the inherent capacity of the Müllerian system for heterotopic differentiation or metaplastic transformation in response to pathological stimuli, whereby resident mesenchymal cells differentiate into osteoblast-like cells.

Endometrial osseous metaplasia most commonly occurs in women of reproductive age, although sporadic cases have also been reported in postmenopausal women (5). The condition is frequently associated with secondary infertility, but may also present with abnormal uterine bleeding, vaginal discharge and dyspareunia. Importantly, a proportion of affected women remain asymptomatic, with the diagnosis established incidentally during imaging or histopathological evaluation. The aetiology and pathogenesis of endometrial osseous metaplasia remain incompletely understood and continue to be the subject of debate; however, current evidence suggests a strong association with retained foetal bony fragments following incomplete separation during miscarriage, pregnancy termination, or curettage, where osseous material persists as a foreign body within the uterine cavity. Early recognition and appropriate treatment are crucial for preventing long-term fertility

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complications. Although ultrasonographic findings may raise suspicion of the diagnosis, hysteroscopy remains the gold standard for both definitive diagnosis through direct visualization and treatment via hysteroscopic resection and removal of osseous material (6).

The present report describes a case of endometrial osseous metaplasia in a 55-year-old female who presented with asymptomatic endometrial thickening and a history of breast cancer. In addition, a brief review of the current literature regarding its histogenesis, diagnosis, management and prognosis is provided.

Case report

A 55-year-old female was referred to our department for further evaluation and management of asymptomatic endometrial thickening measuring 12 mm, identified on abdominal ultrasonography. The obstetric history of the patient included two vaginal deliveries and one induced abortion performed 35 years previously. The medical history of the patient was significant for invasive ductal breast carcinoma (Luminal B subtype), diagnosed 15 years earlier, and treated with breast-conserving surgery and axillary lymph node dissection. Adjuvant treatment included radiotherapy, chemotherapy and hormonal therapy with tamoxifen for 10 years.

Transvaginal ultrasonography confirmed the presence of endometrial thickening and additionally demonstrated a suspected endometrial polyp with posterior acoustic shadowing, findings that warranted further investigation using diagnostic hysteroscopy (Fig. 1).

Histopathological examination of the hysteroscopic biopsy revealed the presence of bone tissue and bone marrow within the endometrium, raising a differential diagnostic dilemma between carcinosarcoma, despite the absence of features suggestive of a malignant epithelial neoplasm, and a mesenchymal malignancy. As the Department of Gynaecologic Oncology is accredited by the European Society of Gynaecological Oncology, all oncological cases are routinely reviewed in a multidisciplinary tumour board (MTB). The present case was discussed by a team comprising gynaecologic oncologists, radiation oncologists, medical oncologists, pathologists and radiologists. Following multidisciplinary review, further evaluation with operative hysteroscopy using a resectoscope was recommended.

Preoperative ultrasonography again demonstrated a hyperechoic endometrial lesion with posterior acoustic shadowing. Histopathological examination and immunohistochemistry on the operative hysteroscopy specimen confirmed the presence of bone tissue and bone marrow within the endometrium, and additionally identified groups of endometrial epithelial cells showing nuclear atypia and an altered nuclear-to-cytoplasmic ratio (Fig. 2A). Although these findings alone were insufficient to establish a definitive diagnosis, they raised high suspicion of malignancy. While nuclear atypia can represent reactive changes secondary to chronic foreign body irritation from the osseous tissue, the combination of these morphologic findings, the patient's oncologic history, postmenopausal status, and imaging abnormalities necessitated definitive histopathologic evaluation to confidently exclude malignancy. The case was re-evaluated by the MTB, and total hysterectomy with bilateral salpingo-oophorectomy was recommended to establish a definitive diagnosis. After comprehensive counselling regarding the potential risks and benefits of surgery, written informed consent was obtained from the patient.

Final histopathological examination demonstrated an atrophic endometrium containing two microscopic foci of bony tissue fragments with degenerative and necrotic changes of the overlying epithelium. The entire endometrium was extensively examined, and no evidence of a neoplastic process was identified (Fig. 2B and C). Additional findings included an endometrial polyp, adenomyosis within the myometrium and features of non-specific chronic cervicitis. Based on the clinical, hysteroscopic and histopathological findings, a final diagnosis of endometrial osseous metaplasia was established.

Following postoperative multidisciplinary review, close clinical surveillance was recommended. The postoperative course was uneventful, with no surgical complications observed. At the time of writing this report, the patient remained disease-free and under follow-up, with an overall survival of 6 months.

Discussion

The present case describes a female patient who was referred for evaluation of asymptomatic endometrial thickening identified on routine ultrasonography. The patient's medical history was notable for breast cancer treated with surgery, chemotherapy, radiotherapy and prolonged tamoxifen therapy. Endometrial osseous metaplasia is a rare condition, and its etiopathogenesis remains incompletely understood. Two principal hypotheses have been proposed. The first suggests that the condition results from retained foetal osseous tissue following a previous abortion (7). The second, and more widely accepted, hypothesis proposes metaplastic transformation of pluripotent endometrial stromal cells, particularly fibroblasts, into osteoblasts in response to chronic inflammation secondary to local trauma, intrauterine infection or neoplastic processes, such as cervical intraepithelial neoplasia (8,9). This theory implicates persistent inflammation as the principal driver of ectopic osteogenesis.

Within the inflammatory microenvironment, a complex network of cytokines regulates bone formation and remodelling. Cytokines such as interleukin (IL)-12, IL-18, IL-33 and interferons have been shown to inhibit osteoclast differentiation, thereby reducing bone resorption (10). In addition, transforming growth factor-β (TGF-β) and bone morphogenetic proteins (BMPs) may play a central role in osseous metaplasia via promoting osteogenic differentiation of local mesenchymal stromal cells. Under conditions of chronic inflammation, tissue injury and repeated repair, TGF-β contributes to fibroblast and mesenchymal cell activation, creating a permissive environment for metaplastic transformation. BMPs, particularly BMP-2 and BMP-4, are potent osteogenic factors that further facilitate ectopic bone formation (11).

Several additional factors have been implicated in the development of osseous metaplasia, including prolonged estrogenic stimulation and metabolic disturbances, such as hypervitaminosis D, hypercalcaemia and hyperphosphataemia, which may promote differentiation of mesenchymal cells into

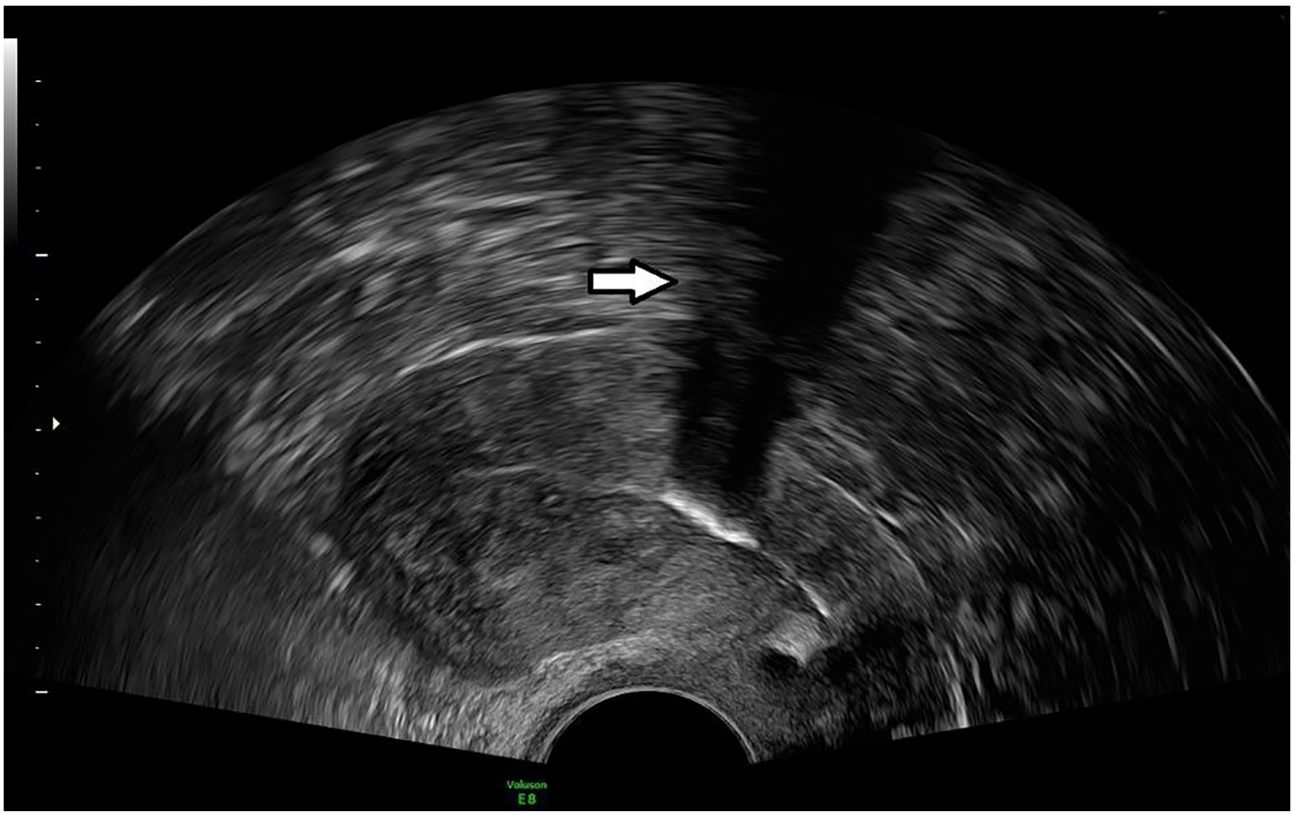

Figure 1. Transvaginal ultrasound image. The white arrow indicates the hyperechoic linear area with posterior acoustic shadowing.

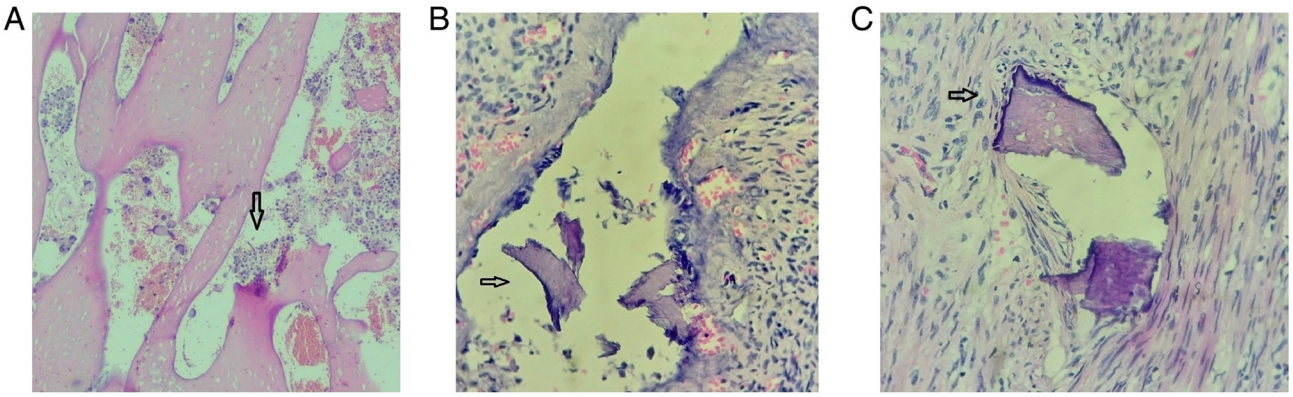

Figure 2. Histopathological and immunohistochemical features. (A) Photomicrograph of diagnostic hysteroscopy. The arrow indicates the presence of the bone tissue and bone marrow inside the endometrial tissue (magnification, x400). (B) Photomicrograph of the uterus specimen showing atrophic endometrium. The arrow indicates the presence of one microscopic focus of fragments of bony tissue with areas of degenerative changes and necrotic transformation of the overlying epithelial layer (magnification, x100). (C) Second photomicrograph of the uterus specimen showing a separate area of atrophic endometrium. The arrow indicates the presence of a second microscopic focus of fragments of bony tissue with areas of degenerative changes and necrotic transformation of the overlying epithelial layer (magnification, x100).

chondroblasts and osteoblasts (12,13). Dystrophic calcification should also be considered in the differential diagnosis. This process is characterized by calcium deposition within necrotic or devitalized tissue, and is commonly observed following tissue injury. Histologically, dystrophic calcification differs from osseous metaplasia by the absence of osteoblasts and the presence of amorphous calcium deposits, rather than mature bone formation (14). Soft tissue calcification has similarly been associated with tissue necrosis, chronic inflammation and local metabolic disturbances affecting calcium-phosphate homeostasis.

The patient described in the present report underwent a pharmacologically induced abortion followed by dilation and curettage ~35 years before diagnosis. However, there was no documented history of menstrual abnormalities, chronic endometritis or recurrent intrauterine infection. Furthermore, final histopathological examination demonstrated an atrophic endometrium without evidence of retained foetal tissue, findings that support a metaplastic rather than retained foetal bone origin. An additional factor of potential relevance is the patient's prolonged exposure to tamoxifen. Tamoxifen is known to induce endometrial stimulation and has been associated

Table I. Differential diagnosis of sonographic finding of hyperechoic, linear or irregular areas within the endometrium with posterior acoustic shadowing.

Entity	Sonographic features	Clinical features
IUCD	Linear echogenic structure with posterior shadowing	History of device use
Calcified endometrial polyp	Echogenic intracavitary lesion with calcification	Abnormal uterine bleeding
Calcified submucosal leiomyoma	Well-defined hypoechoic mass with calcified foci and shadowing	Menorrhagia, pelvic pressure, infertility
Mature teratoma	Complex mass with mixed echogenicity and calcifications	Pelvic mass, pain
Retained foreign body	Echogenic intrauterine material with shadowing	Prior uterine instrumentation
Endometrial tuberculosis	Endometrial irregularity, cavity distortion, adhesions	Infertility, menstrual disturbance, TB history
Asherman's syndrome	Intrauterine bands/synechiae, reduced cavity distensibility	Amenorrhea, infertility, recurrent pregnancy loss
Heterotopic bone formation	Highly echogenic foci with posterior shadowing	Prior pregnancy loss, curettage, chronic inflammation
Malignant mixed Müllerian tumour	Heterogeneous endometrial mass with irregular margins	Postmenopausal bleeding, pelvic pain

IUCD, intrauterine copper device; TB, tuberculosis.

with endometrial thickening, polyp formation and other proliferative changes. Chronic local stimulation may therefore have contributed to mesenchymal stromal cell differentiation and subsequent osseous metaplasia.

The clinical presentation of endometrial osseous metaplasia is often non-specific and commonly includes infertility, abnormal uterine bleeding, pelvic pain or dysmenorrhoea. Nevertheless, a proportion of patients remain asymptomatic, with diagnosis established incidentally during investigations performed for unrelated indications, as occurred in the present case. A retrospective study of 63 women with hysteroscopically confirmed endometrial osseous metaplasia reported dysmenorrhoea in 34.9% of patients, abnormal uterine bleeding in 27.0%, infertility in 23.8% and a history of at least one miscarriage in 65.1% (15).

The mechanism underlying infertility is considered multifactorial. Osseous fragments may act as a foreign body within the uterine cavity, mechanically impairing embryo implantation in a manner analogous to an intrauterine contraceptive device (16). Furthermore, the associated inflammatory response may generate a cytokine-rich uterine microenvironment that is unfavourable for implantation and maintenance of pregnancy (17).

Transvaginal ultrasonography represents the first-line imaging modality for evaluation of suspected endometrial osseous metaplasia. Typical sonographic findings include linear or irregular hyperechoic lesions within the endometrial cavity, accompanied by posterior acoustic shadowing. Similar findings were observed in the present case, although they were not sufficiently specific to establish a definitive diagnosis. Three-dimensional ultrasonography, particularly when a coronal view is obtained, may improve lesion characterization and assist in distinguishing osseous metaplasia from retained intrauterine contraceptive devices or other foreign bodies (1). In diagnostically challenging cases, magnetic resonance imaging may provide additional information through superior soft-tissue characterization and evaluation of coexisting pathology (18). In postmenopausal women, hyperechoic endometrial lesions with posterior acoustic shadowing warrant consideration of a broad differential diagnosis that includes endometrial polyps, calcified lesions and endometrial malignancy.

Management of endometrial osseous metaplasia is primarily based on hysteroscopic removal of osseous fragments. Hysteroscopy is both diagnostically and therapeutically advantageous, as it permits direct visualization of the uterine cavity and facilitates exclusion of coexisting abnormalities, such as intrauterine adhesions, chronic endometritis or malignancy. Hysteroscopic resection has demonstrated optimal outcomes with respect to symptom resolution and restoration of fertility (18).

The differential diagnosis of hyperechoic endometrial lesions with posterior acoustic shadowing is extensive and includes retained intrauterine contraceptive devices, calcified endometrial polyps, calcified submucosal leiomyomas, mature teratomas, retained foreign bodies, endometrial tuberculosis, Asherman syndrome, heterotopic bone formation and malignant mixed Müllerian tumours (1,19). As ultrasonographic findings are not pathognomonic, hysteroscopy remains the diagnostic gold standard, allowing direct visualization and targeted biopsy for histopathological confirmation. The differential diagnosis of these sonographic findings is summarized in Table I.

Treatment should be individualized according to the patient's symptoms, reproductive goals and the extent of disease. Although hysteroscopic resection is considered the preferred treatment approach, complete removal may not be feasible in cases characterized by extensive disease, multifocal lesions or deep myometrial involvement. In such circumstances, hysterectomy may represent the most appropriate definitive

treatment option (20). In the present case, hysterectomy was performed because malignancy could not be confidently excluded based on repeated hysteroscopic assessments and histopathological findings.

The prognosis following complete surgical excision of endometrial osseous metaplasia is considered optimal. The majority of patients experience complete resolution of symptoms, and restoration of fertility has been reported within one year in females seeking pregnancy. Although recurrence appears to be uncommon, long-term follow-up is advisable given the rarity of the condition and the limited data regarding its natural history (1).

Although endometrial osseous metaplasia is an uncommon diagnosis, it should be considered in the differential diagnosis of hyperechoic endometrial lesions, particularly when accompanied by posterior acoustic shadowing and a history of pregnancy termination or uterine instrumentation. Transvaginal ultrasonography remains the preferred initial imaging modality, whereas hysteroscopy is regarded as the gold standard for both diagnosis and treatment. Accurate diagnosis requires integration of clinical history, imaging findings and histopathological examination to exclude alternative benign and malignant conditions. Further research is required to clarify the precise molecular mechanisms and etiological factors involved in the development of this rare entity.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

EAA contributed to the writing of the manuscript. EAA, AA and NDS were responsible for the collection of relevant literature for inclusion in the present review, and contributed to the conception and design of the case report. EAA, AA, NDS, CMS and SP contributed to the analysis and interpretation of the clinical data. EAA and AA confirmed the authenticity of all the raw data. EAA, CMS, AA and SP revised the manuscript critically for important intellectual content. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for publication, authorizing the use of their imaging, pathological and clinical data for publication.

Competing interests

The authors declare that they have no competing interests.

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