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## Case Report

# Ovarian clear cell carcinoma arising in a large endometrioma — A case report with pathological correlation and literature review<sup>☆</sup>

Eduardo Negrão, MD<sup>a,b,\*</sup>, Beatriz Flor-de-Lima, MD<sup>a,b</sup>, Ana Luísa Duarte, MD<sup>a</sup>, Ana Costa Braga, MD<sup>b,c</sup>, Raquel Portugal, MD<sup>b,c</sup>, António J. Madureira, MD<sup>a,b</sup>

<sup>a</sup> Department of Radiology, Centro Hospitalar Universitário de São João, Porto, Portugal

<sup>b</sup> Faculdade de Medicina da Universidade do Porto, Porto, Portugal

<sup>c</sup> Department of Pathology, Centro Hospitalar Universitário de São João, Porto, Portugal

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## ABSTRACT

Endometriosis-associated ovarian cancer represents the most common form of malignancy associated with this benign disease. It has a better prognosis than most types of ovarian cancer, with endometrioid adenocarcinoma and clear cell carcinoma as the main histological types. Clinical presentation is usually nonspecific and tumor biomarkers can be misleading, since they can also be elevated in the presence of benign ovarian endometriosis. We report a case of a 52-year-old woman with known ovarian and deep pelvic endometriosis, who developed ovarian clear cell carcinoma within a large endometrioma. The imaging findings highlight the key role of magnetic resonance imaging in detecting suspicious features such as loss of the “T2 shading” sign, loss of high T1 signal of an endometrioma, or the presence of mural nodules. Early detection of these malignancies is fundamental for adequate surgical treatment and overall outcome.

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## Introduction

Endometriosis, a benign gynecological condition, is characterized by the growth of endometrial tissue outside of the uterus, affecting 10%–15% of women in reproductive age, and its main symptoms include pelvic pain and infertility [1–5].

Endometriosis-associated ovarian cancer (EAOC) was first reported by Sampson et al. [6], who recognized malignant transformation of ovarian endometriosis (OE), which occurs in 1% of women with this disease [3]. It represents the disease’s most common form of associated malignancy, with endometrioid adenocarcinoma (EC) and clear cell carcinoma (CCC) as the main histological types [2,3,5–8]. EAOC has an overall better outcome and prognosis than other types of ovar-

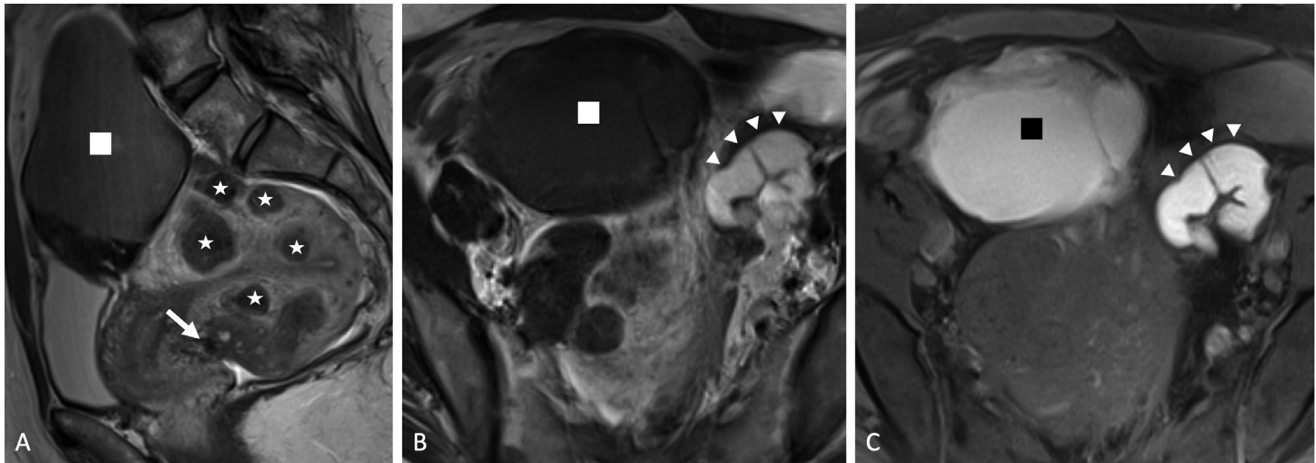
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\* Corresponding author.

E-mail address: [eduardo.negrão@gmail.com](mailto:eduardo.negrão@gmail.com) (E. Negrão).

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**Fig. 1 – MRI (2017).** (A) T2W sagittal image – an enlarged retroflexed uterus, with multiple leiomyomas (stars), a large right endometrioma with the “T2 shading” sign (square), and a spiculated nodule of deep pelvic endometriosis adjacent to the uterine torus, with myometrial invasion (arrow); (B) T2W axial image – dilated “C shaped” left Fallopian tube (arrowheads), showing high signal on T2-weighted axial image, indicating hydrosalpinx; (C) T1W FS axial image—the same left Fallopian tube exhibiting high T1 signal, indicating hematosalpinx (arrowheads).

ian cancer, and it typically presents in women 10 to 20 years younger [3,8].

Ultrasound is usually the first line imaging modality for the assessment of OE, but magnetic resonance imaging (MRI) is the recommended imaging technique when EAOC is suspected, allowing a thorough assessment of ovarian endometriotic cysts with suspicious features, such as solid components, mural nodules or papillary projections, which usually represent malignancy [2].

Early diagnosis is of the utmost importance for oncologic work-up and surgical treatment, since EAOC is less sensitive to conventional platinum-based chemotherapy, particularly CCC [3,8].

## Case report

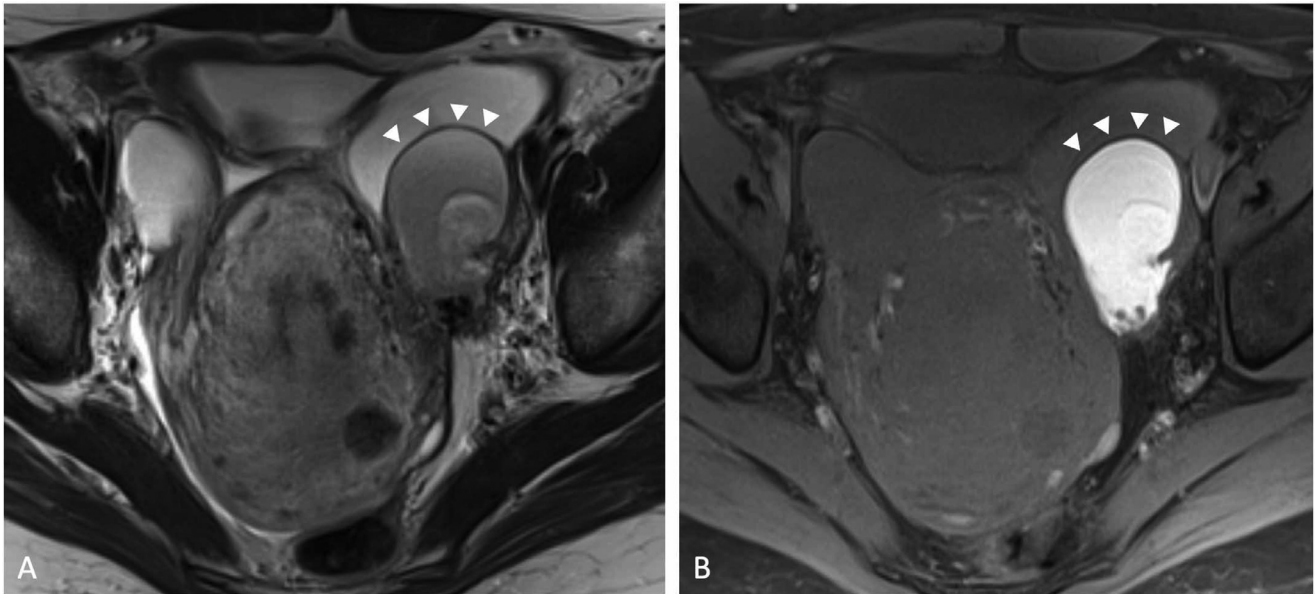
A 52-year-old nulliparous woman was followed at our hospital's Gynecology department due to ovarian endometriosis diagnosed at young age, as well as multiple uterine leiomyomas. She experienced occasional mild pelvic pain, controlled with nonsteroidal anti-inflammatory drugs. The patient had a history of appendectomy due to symptomatic appendiceal endometriosis at 18 years of age, but no other endometriosis-related pelvic surgeries. Menarche was at 12 years of age. No other remarkable medical or surgical history was present, as well as no family history of malignancy.

MRI and transvaginal ultrasound were routinely performed as follow-up, but paramagnetic intravenous contrast was never administered because of patient's refusal. In 2017, an MRI performed on a 3-Tesla magnet – using T1- (T1W) and T2-weighted sequences (T2W), with and without fat suppression, and also diffusion-weighted imaging (DWI) and ADC map sequences – showed a markedly enlarged retroflexed uterus, with multiple intramural leiomyomas (Fig. 1), as well as several manifestations of pelvic endometriosis: 2 large en-

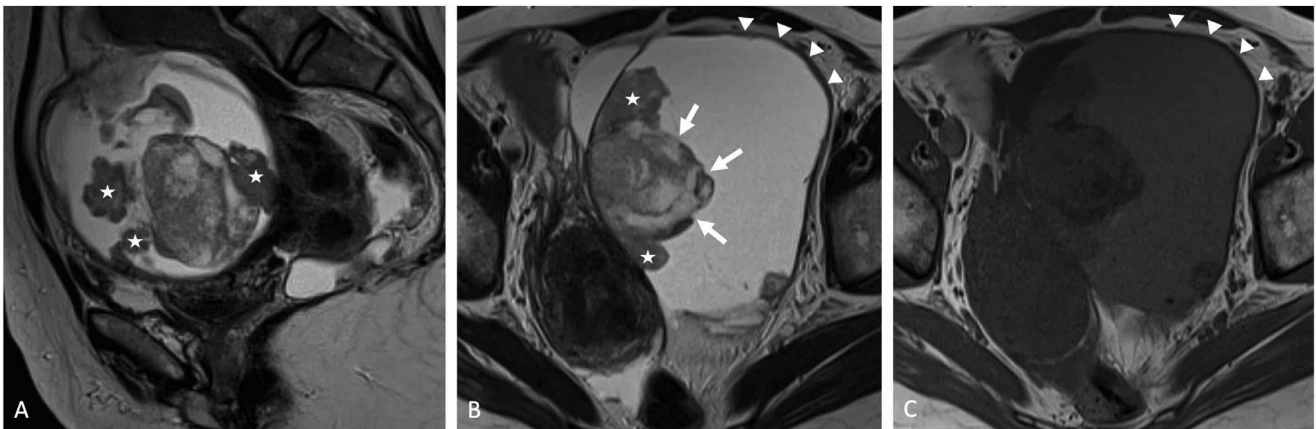
dometriomas (around 11 cm on the right side and 4 cm on the left side), both presenting high signal on T1-weighted sequences and the “T2 shading” sign, suggesting the presence of blood products (methemoglobin), with no solid components, mural nodules or papillary projections (Fig. 2); left-sided fluid-distended Fallopian tube with high signal on T1 and T2-weighted sequences, indicating hematosalpinx (Fig. 1); a spiculated nodule of deep pelvic endometriosis adjacent to the uterine torus, infiltrating the posterior myometrium (Fig. 1). At this time, tumor biomarkers, including cancer antigen 19-9 (CA19-9) and cancer antigen 125 (CA125), were negative.

In 2020, symptoms of bloating in the lower abdomen worsened and a new MRI was performed, again without paramagnetic intravenous contrast. It showed a marked increase in size of the left endometrioma, now measuring around 15 cm (vs 4 cm in 2017), with loss of the “T2 shading” sign and loss of high signal on T1-weighted sequences (Fig. 3). Also, several heterogeneous solid mural nodules and a prominent 5 cm papillary projection were now present along its medial wall, with low signal on T1-weighted sequences and heterogeneous signal on T2-weighted sequences (Fig. 3). These solid components presented restricted diffusion, while the cystic content of the endometrioma did not (Fig. 4). Unfortunately, dynamic contrast-enhanced sequences were again not performed due to patient's refusal. These imaging findings were regarded as highly suspicious for malignant degeneration of the left endometrioma. Concurrently, tumor biomarkers CA19-9 and CA125 were elevated. Subsequent computed tomography (CT) of the thorax and upper abdomen showed no signs of distant metastases.

The patient underwent hysterectomy with bilateral salpingo-oophorectomy, omentectomy, as well as radical pelvic and para-aortic lymphadenectomy. The postoperative recovery was uneventful. Pathology examination reported diffuse foci of deep pelvic endometriosis, with involvement of the posterior uterus, as well as multiple leiomyomas, adenomyosis, a large endometrioma on the right ovary, and



**Fig. 2 – MRI (2017).** (A) T2W axial image – cystic lesion on the left ovary (arrowheads) with the “T2 shading” sign, compatible with endometrioma, with no mural nodules or papillary projections; (B) T1W FS axial image – the same endometrioma (arrowheads) with high T1 signal, confirming hematic cystic content.



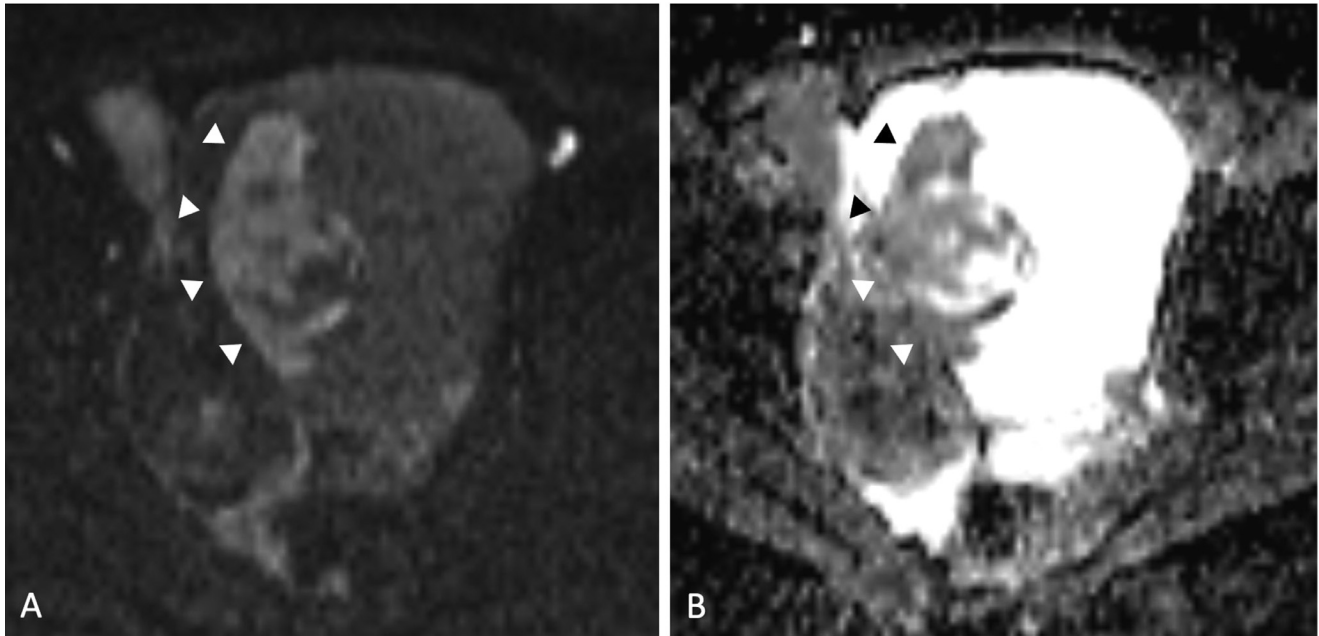
**Fig. 3 – MRI (2020).** (A and B) T2W sagittal and axial images – marked enlargement of the left ovarian endometrioma (arrowheads), showing high T2 signal and absence of the “T2 shading” sign, with several solid mural nodules (stars) along its medial wall and a prominent 5 cm solid papillary projection (arrows); (C) T1W axial image – absence of high T1 signal on the cystic component of the endometrioma (arrowheads).

xantogranulomatous salpingitis on the left side. No signs of disease were detected on peritoneal tissue or resected lymph nodes. Regarding the left ovarian mass, the macroscopical assessment showed a left ovary replaced by a nodular, cystic and solid lacerated neoplasm, showing irregular outer and inner surfaces, with a yellowish lobulated external surface. Microscopical analysis revealed an endometriosis lesion associated with ovarian carcinoma (Fig. 5). Further analysis of the neoplasm revealed histological features compatible with CCC, showing tubulocystic, solid and papillary patterns, with clarified and sometimes eosinophilic cytoplasm. Strong and diffuse Napsin A immunoreactivity was also observed in the neoplastic cells (Fig. 6).

After surgery and pathological diagnosis, the patient underwent 6 cycles of adjuvant chemotherapy with a combination of paclitaxel and carboplatin. Follow-up imaging exams – abdominal and pelvic MRI, and thoracic CT – have been negative for signs of disease recurrence ever since.

## Discussion

Endometriosis-associated ovarian cancer (EAO) is rare, occurring approximately in 1% of women with ovarian endometriosis. The main histological types are endometrioid



**Fig. 4 – MRI (2020).** (A) DWI b1000 s/mm<sup>2</sup> axial image – hyperintensity of the papillary projection and mural nodules of the endometrioma (arrowheads); (B) ADC map axial image – low signal of the papillary projection and mural nodules (arrowheads). These findings indicate restricted diffusion of the papillary projection and mural nodules. Note that the cystic component of the endometrioma does not have restricted diffusion.

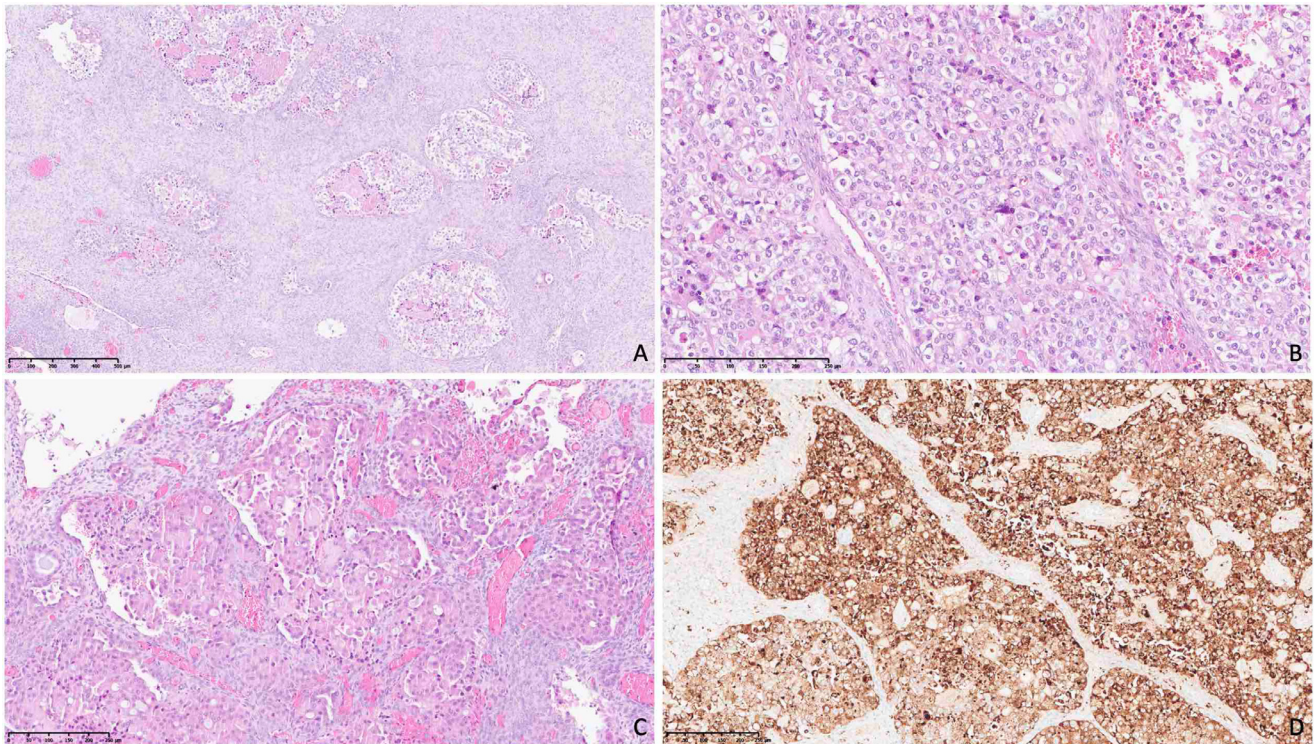


**Fig. 5 – (A)** Macroscopic image showing left ovary totally replaced by nodular, cystic and solid lacerated neoplasm; the outer and inner surfaces are partially irregular and hemorrhagic, and partially bumpy and yellowish; **(B)** Macroscopic image of detached fragment of ovarian neoplasm, yellowish, with lobulated external surface and fleshy and solid section surface; **(C)** Low magnification histological section of endometriosis (\*) associated with ovarian carcinoma (#) (hematoxylin and eosin [H&E]).

adenocarcinoma (EC) and clear cell carcinoma (CCC), with the latter being the least common [2–8]. EAO has a better prognosis for curative surgery than most other types of ovarian cancer and it typically presents in women 10 to 20 years younger [3,4,8]. Nevertheless, CCC should be regarded with special caution, having worse prognosis in most cases, due to its chemoresistant phenotype [3,4,8]. EAO is defined by the presence of ovarian cancer in the setting of ipsilateral or contralateral ovarian endometriosis, pelvic endometriosis or histopatho-

logical demonstration of transition from benign to malignant endometriosis [6,8].

Although endometriosis itself is a risk factor for EAO, with some studies even considering endometriosis as a precursor of EAO, other risk factors include hyperestrogenic states, such as obesity and hormonal replacement therapy [3–5,8,9]. Somatic mutations responsible for malignant transformation of endometriomas have been described, including activation of oncogenic KRAS and PI3K pathways, as well as inactivation



**Fig. 6 – Histological images showing clear cell carcinoma with tubulocystic (A), solid (B) and papillary (C) patterns. The neoplasm consists of polyhedral cells, with clarified (A and B) and sometimes eosinophilic (C) cytoplasm. Occasional colloid/hyaline content is observed (A) [H&E]. Strong and diffuse Napsin A immunoreactivity was observed in neoplastic cells (D).**

of tumor suppressor genes PTEN and ARID1A [5,9]. Regarding CCC, studies have also shown that upregulation of HNF-1 $\beta$  is responsible for malignant progression of endometriotic cells [7].

Malignant transformation of OE is clinically non-specific and vague, with overlapping symptoms with benign endometriosis. However, worsening of dysmenorrhea and dyspareunia or new onset of lower abdominal bloating can occur [2,9]. EAO tumor biomarkers, such CA125, should be looked at with caution, since they can also be elevated in benign endometriomas [9].

The mainstay treatment for EAO confined to the ovary is surgical (hysterectomy and salpingo-oophorectomy), with or without adjuvant chemotherapy or radiotherapy.

Ultrasound is predominantly used as the first line of imaging for assessment of EAO. However, while very sensitive for the detection of mural nodules, it cannot differentiate tumoral from non-tumoral nodules or papillary projections [2]. MRI has become the recommended imaging modality not only for diagnosing OE, but also for differentiating OE and EAO, since it has better tissue contrast, allows for better depiction of blood products and can adequately characterize solid components and papillary projections within endometriotic cysts [3–5], especially when intravenous contrast is administered.

An endometrioma, or endometriotic cyst, represents the benign form of OE. It presents as a cystic ovarian lesion, lined with functional endometrial epithelium, typically with high T1 signal and intermediate to low signal on T2-weighted se-

quences (“T2 shading” sign), due to the presence of degraded blood products (methemoglobin). These lesions can measure up to 15 cm, and are also often bilateral [2,3,7,9].

Several MRI features of endometriomas should raise suspicion of malignant transformation. A new enhancing solid mural nodule within an endometrioma is the most sensitive and valuable MR imaging feature suggestive of malignancy [3,4]. These nodules homogeneously enhance on T1-weighted post-gadolinium sequences, and are best visualized after subtraction imaging, since the internal hemorrhagic cystic content has spontaneous high T1 signal [3,7,9]. Morioka et al. [7] also concluded that mural nodules with CCC were more commonly focal, eccentric and polypoid. Concerning nodule size, Tanase et al. [2] stated that larger nodules were commonly malignant, and that the “height” of the nodule (maximum vertical length from the bottom of the cyst to the top of the nodule) was also an indicator of malignancy. Tanaka et al. [4] concluded that mural nodules larger than 3 cm in maximum diameter were a strong indicator of malignancy. Furthermore, the presence of internal nodular septations should be considered suspicious, whereas linear smooth septations are typically benign [9].

Loss or absence of the “T2 shading” sign, along with absence of high T1 signal and new onset of high T2 signal within an endometrioma is worrisome, since it most likely represents dilution of hematic content by tumor-secreted fluid [2,9]. This feature, when accompanied by sudden marked enlargement of the endometrioma size, is even more suspicious, especially

for CCC [3,4,7,9]. Tanaka et al. [4] also stated that large cyst size per se constitutes a risk factor for malignancy.

Diffusion restriction is non-specific, since it can also occur in benign endometriomas and hemorrhagic cysts. Nevertheless, new onset of diffusion restriction on mural nodules, with its absence on the background cystic component, should also be regarded as suspicious [9].

Our case presents several suspicious findings for EAO in the left endometrioma. It shows significant increase in size (from 4 to 15 cm), causing symptoms of bloated lower abdomen. The cystic component of the endometrioma lost the “T2 shading” sign, indicating dilution of blood products due to fluid secretion from the tumor. Multiple de novo solid mural nodules and a large papillary projection showing restricted diffusion, along with loss of the usual restricted diffusion of the endometrioma’s cystic component, are also highly suspicious. Unfortunately, administration of paramagnetic intravenous contrast was not possible due to patient’s refusal, which would probably show enhancement of the solid components described.

## Conclusion

Endometriosis-associated ovarian cancer is an important subtype of ovarian cancer, with specific clinical presentation, demographics, prognosis, imaging features and histopathology.

The radiologist plays an important role in recognizing malignant transformation of endometriotic cysts, either into endometrioid or clear cell carcinoma. MRI features such as loss or absence of the “T2 shading” sign, significant increase of cyst volume, solid enhancing mural nodules or papillary projections, or restricted diffusion of solid components, should all be taken into account as suspicious when considering this type of malignancy, particularly when they appear concomitantly.

Since this type of neoplasms has better prognosis than most types of ovarian cancer, suspicious imaging features may allow a prompt and early diagnosis, with consequent better surgical outcome and overall survival.

## Patient consent statement

The authors obtained written informed from the patient for publication of this case report.

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## REFERENCES

- [1] Kong MK, Jung HJ, Kim YH, Kim J, Kim S. Clear cell carcinoma arising from endometriosis at the cesarean scar site: a case report. *Arch Clin Med Case Rep* 2019;03(06):494–9. doi:10.26502/acmcr.96550126.
- [2] Tanase Y, Kawaguchi R, Takahama J, Kobayashi H. Factors that differentiate between endometriosis-associated ovarian cancer and benign ovarian endometriosis with mural nodules. *Magn Reson Med Sci* 2018;17(3):231–7. doi:10.2463/mrms.mp.2016-0149.
- [3] McDermott S, Oei TN, Iyer VR, Lee SI. MR imaging of malignancies arising in endometriomas and extraovarian endometriosis. *Radiographics* 2012;32(3):845–63. doi:10.1148/rg.323115736.
- [4] Tanaka YO, Okada S, Yagi T, et al. MRI of endometriotic cysts in association with ovarian carcinoma. *Am J Roentgenol* 2010;194(2):355–61. doi:10.2214/AJR.09.2985.
- [5] Tanaka YO, Yoshizako T, Nishida M, Yamaguchi M, Sugimura K, Itai Y. Ovarian carcinoma in patients with endometriosis: MR imaging findings. *Am J Roentgenol* 2000;175(5):1423–30. doi:10.2214/ajr.175.5.1751423.
- [6] Sampson JA. Endometrial carcinoma of the ovary arising in endometrial tissue in that organ. *Am J Obstet Gynecol* 1925;9(1):111–14. doi:10.1016/S0002-9378(25)90949-0.
- [7] Morioka S, Kawaguchi R, Yamada Y, Iwai K, Yoshimoto C, Kobayashi H. Magnetic resonance imaging findings for discriminating clear cell carcinoma and endometrioid carcinoma of the ovary. *J Ovarian Res* 2019;12(1):1–3. doi:10.1186/s13048-019-0497-1.
- [8] Robinson KA, Menias CO, Chen L, et al. Understanding malignant transformation of endometriosis: imaging features with pathologic correlation. *Abdom Radiol* 2020;45(6):1762–75. doi:10.1007/s00261-019-01914-7.
- [9] Colarossi C, Picardo MC, Colarossi L, et al. Clear cell carcinoma arising in an abdominal wall cesarean section scar: a case report with description of pathological and molecular features. *Front Surg* 2021;8(September):8–11. doi:10.3389/fsurg.2021.735381.