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NEWS

The "popcorn" sign: the first early ultrasound sign of serous intra-parenchymal ovarian cancer in *BRCA* mutation carriers

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Introduction

High-grade serous ovarian cancer (OC) is the most aggressive ovarian histotype and, unfortunately, the most common epithelial OC type; it is responsible for about 70–80% of OC-related deaths [1]. In most cases, the diagnosis of high-grade serious OC is late (stage ≥ 3) [2] and there is often a genetic basis, as more of 25% of women diagnosed with OC carry a *BRCA1* or *BRCA2* mutation [3].

Since 2017, the "Preventive Hereditary Gynaecologic Oncology Clinic" of the University of Modena and Reggio Emilia in Italy has offered a specific surveillance program for women who carry *BRCA* mutations; our cohort includes more than 500 women. While risk-reducing bilateral salpingo-oophorectomy (RRSO) is the only intervention that can effectively reduce the mortality related to OC in these women [4], our Clinic provides the opportunity to monitor high-risk patients younger than 35 years old or who refuse RRSO by performing a transvaginal ultrasound (TV-US) and by measuring serum level of cancer antigen 125 (CA125) every 6 months [4, 5].

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In this paper, we report four cases of high-grade serous intra-parenchymal OC diagnosed since 2019 during the course of this surveillance program, all diagnosed at a very early stage (Stage I post-definitive surgery, Table 2). We have identified a common US sign that has never been described: the "popcorn" sign. The cases are ordered based on the actual size of the US sign (from the smallest to the largest) (Tables 1, 2). Different OC cases from the same cohort were previously reported in a published paper that also included other OC histotypes, tubal findings (and not only INTRA-PARENCHYMAL findings), and higher stages at diagnosis [4].

Cases

Case 1

This 49-year-old multiparous woman carries a *BRCA1* mutation, duringher perimenopause. In 2012, she had been diagnosed with breast cancer, for which she underwent neoadjuvant chemotherapy followed by mastectomy. She had no history of gynecological surgery. In June 2019, she came to our outpatient clinic with an initial finding of elevated CA125 (40.8 U/mL) associated with an unusual ultrasound pattern. Specifically, she presented a hyperechoic lesion with a mean diameter of 10.5 mm in the right ovary ("popcorn" sign) (Fig. 1a). Of note, the right ovary appeared slightly larger in dimensions, whereas the left ovary seemed normal. Twenty-eight days later, she underwent surgery. Histology confirmed the presence of a high-grade serous OC involving the ovarian capsule of the right ovary (a lesion 17 mm in mean diameter) with a normal tube. For this smallest US case, we have reported also the histopathological specimen, surrounded in blue line (Fig. 2). The carcinoma was also present on the other adnexa and involved the ovary as well

Table 1 Cases detailed features

Patient ID	Age at diagnosis	Genetic mutation	CA125 levels at the diagnosis (U/mL)	Ovary affected by pop-corn sign	Ultrasound lesion size (mean diameter) (mm)
Patient n.1	49	*BRCA1*	40.8	Right	10.5
Patient n.2	56	*BRCA2*	71.8	Right	11.0
Patient n.3	50	*BRCA1*	8.3	Left	11.5
Patient n.4	45	*BRCA1*	20.4	Right	27.5

Table 2 Histological definitive findings (after definitive surgery)

Patient ID	Time interval between diagnosis and surgery (days)	Histological intra-parenchymal lesion size (mean diameter) (mm)	Ovarian/tubal cancer final stage (FIGO stage 2021 update) [6]
Patient n. 1	28	17	I B
Patient n. 2	35	10	I C3
Patient n. 3	186	20	I C3
Patient n. 4	48	33	I C3

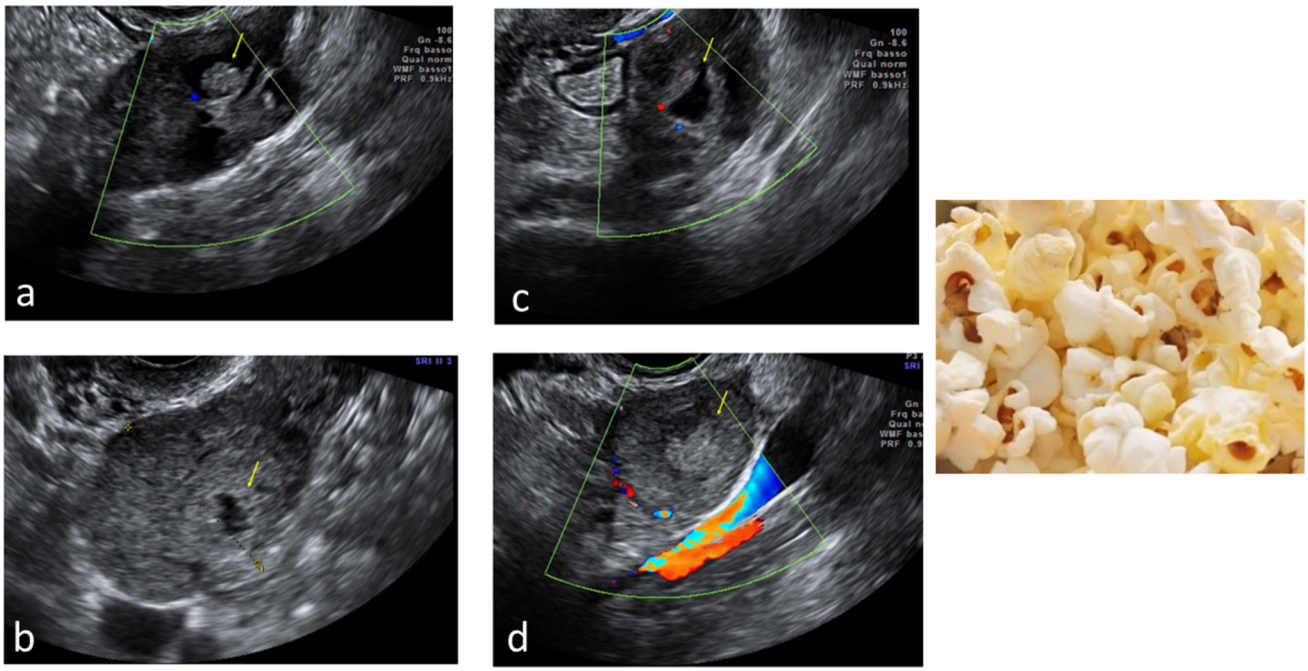

Fig. 1 **a**–**d** The pop-corn sign in case 1 (**a**), 2 (**b**), 3 (**c**) and 4 (**d**): see the text for the full details. The pop corn is signed with yellow arrow

as the fallopian tube. Her definitive cancer stage (post-definitive surgery) was IB [6].

Case 2

This 56-year-old nulliparous woman carried a *BRCA2* mutation and has been postmenopausal for 3 years. She had never undergone breast or gynecological surgery. Her routine 6-month ultrasound performed in February 2024 was the first time her CA125 serum level was outside the normal range (71.8 U/L). It was associated with the presence of an US-detected lesion affecting the right ovary. It measured 11 mm in average diameter, appeared hyperechoic, and showed no vascularity ("popcorn" sign; Fig. 1b). Thirty-five days after the diagnosis, the patient underwent surgery. The diagnosis was high-grade serous OC involving the right ovary and fallopian tube as well as the left ovary. Histology indicated a mean lesion size of

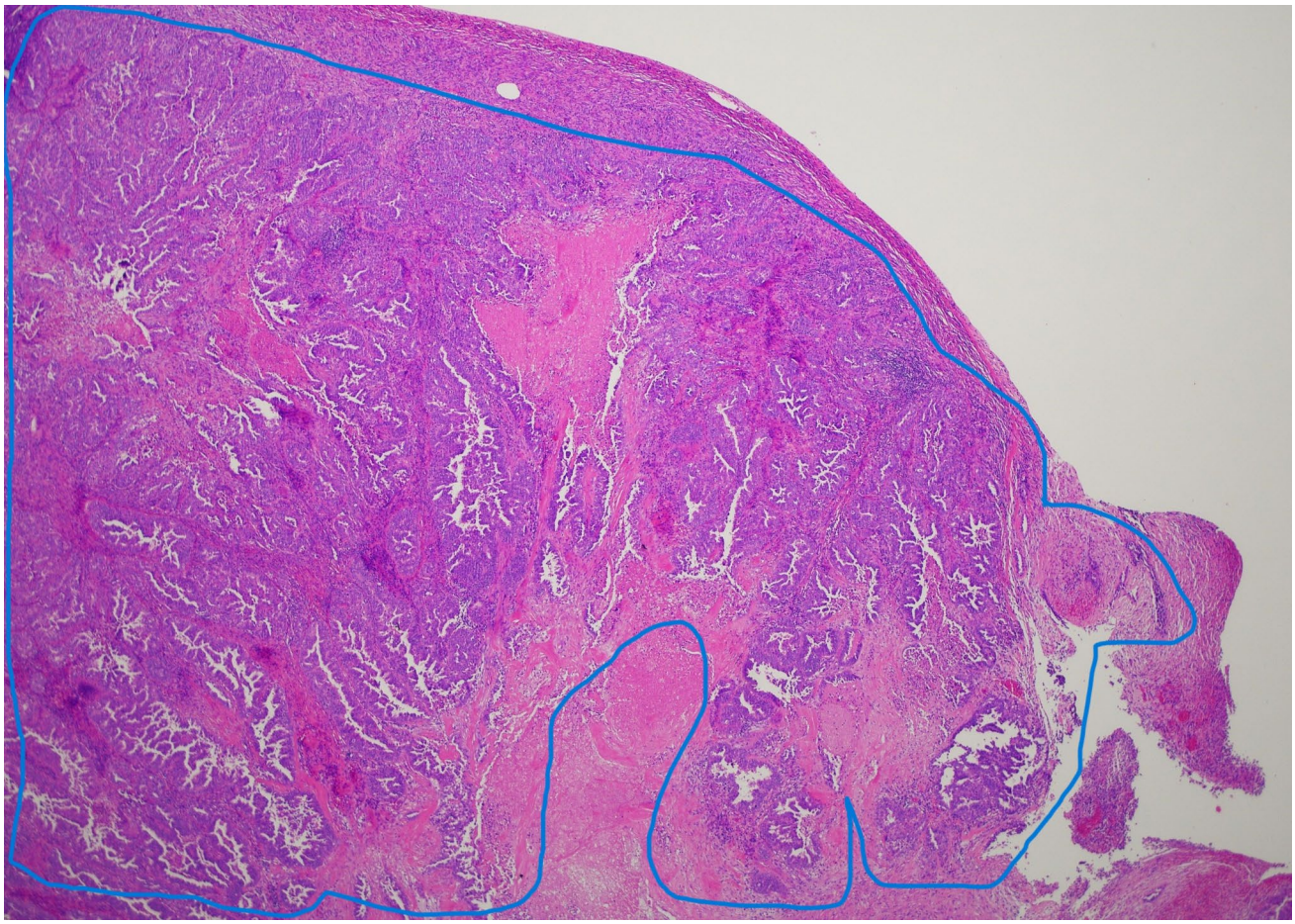

Fig. 2 Histological specimens of case 1 (2X hematoxylin–eosin). The ovarian parenchyma containing serous cancer is surrounded in blue line (corresponding to Fig. 1a)

10 mm. Her definitive cancer stage (post-definitive surgery) was IC3 [6].

Case 3

This 50-year-old nulliparous woman carries a *BRCA1* mutation was in perimenopause. She had no history of breast or gynecological surgery. In May 2022, an US examination revealed the presence of multiple pseudofollicular cysts on the left ovary with thin walls, non-vascularized, with an average diameter of 11.5 mm and another intra-parenchymal hyperechoic lesion of 12 mm ("popcorn" sign; Fig. 1c). Due to the uncertainty surrounding the described formations and considering that her CA125 serum level was within the normal range (8.3 U/mL), the woman was advised to undergo a follow-up examination after 1 month. However, she did not attend the scheduled appointment. After several months, the patient contacted us to inform that in November 2022 (186 days after her first US findings), she had undergone surgery at another hospital, where she was diagnosed with high-grade serous OC of the right fallopian tube and left ovary (lesion size 20 mm). The right ovary and left fallopian tube were free from neoplastic involvement. Her definitive cancer stage (post-definitive surgery) was IC3 [6].

Case 4

This 45-year-old primiparous woman carries a *BRCA1* mutation. In 2019, she received a diagnosis of breast cancer, for which she underwent bilateral mastectomy followed by chemotherapy. Cesarean section was the only gynecologic surgery in her medical history. In 2020, at her routine 6-month follow-up US examination, we noticed in the right ovary the presence of a solid formation with mixed echogenicity, poorly vascularized (CS2), without shadow cones, measuring 27.5 mm ("popcorn" sign; Fig. 1d). Forty-eight days later, the patient underwent surgery. The histological examination revealed high-grade serous OC of the right ovary and fallopian tube (with a mean lesion diameter of 33 mm), along with the presence of intraparenchymal

carcinoma that also involved the left ovary. Of note, her CA125 serum levels were always within the normal range (at the US diagnosis, it was 20.4 U/mL). Her definitive cancer stage (post-definitive surgery) was IC3 [6].

Discussion

This in-depth and careful description of four cases of OC detected with US screening in *BRCA* mutation carriers has revealed a novel, early intra-parenchymal sign of high-grade serous OC. This discovery was possible due to the very-high-risk population studied (all *BRCA* mutation carriers) and the detailed screening program that we have carried out for more than 5 years, always involving the same expert sonographer (G.G.). This new US sign (the "popcorn" sign) will be helpful and can be replicated in larger cohorts, especially in high-risk women.

Based on the detailed description of our small but unique sample, only one of our patients carries a *BRCA2* mutation; the other three women carries a *BRCA1* mutation. This finding is in line with the different OC risk related to the two genes: the lifetime risk of OC by the age of 70 years is approximately 44% for *BRCA1* mutation carriers and 17% for *BRCA2* mutation carriers [7].

At diagnosis, the CA125 serum levels were within the normal range (2/4) or slightly elevated (2/4). All of the patients had a small unilateral hyperechoic US lesion, associated with anechoic areas, with no (1/4) or limited vascularization (Color Score 2) (3/4), resembling a piece of popcorn (Tables 1, 2, Fig. 1). We think that this "popcorn" sign is the first indication of OC, signaling the flow of neoplastic serous cells into the ovarian parenchyma (Fig. 1).

Based on the histological findings, the carcinoma always involved the ovary with the US-detected lesion, but it may already affect one fallopian tube and/or the contralateral ovary. Moreover, the lesion size based on histological examination was similar to the size based on US (Tables 1, 2).

The International Ovarian Tumor Analysis (IOTA) introduced an international language that is useful for describing ovarian masses to better characterize them [8]. It uses several models to stratify the risks of malignancy related to adnexal maxes. Among them, Simple Rules (SR) was introduced to predict whether a mass is more likely to be malignant or benign; however, sometimes a specific lesion in our women cannot be characterized by applying this model. This model was not applicable for our cases because we did not have adnexal masses, only early intra-parenchymal signs. The greater difficulty encountered in applying the aforementioned models to our patients is likely linked to the fact that the IOTA was designed to describe adnexal masses in the general population setting, while the "popcorn" sign we found is a millimetric lesion that is difficult to characterize using the IOTA. In our minds, the "popcorn" sign can be considered a microscopic lesion that precedes the macroscopic lesions that are more easily classifiable with the IOTA. This sign is completely different in comparison to hemorrhagic corpus luteum that is a web-like cyst with an evolutive pattern of natural disappearance in 2–3 weeks [4] but also to a small endometrioma (ground glass echogenicity) or mature teratoma (mixed echogenicity and acoustic shadows) [8].

Many screening trials have revealed that measuring CA125 serum levels and performing an ultrasound do not reduce mortality in the context of OC [9]. The same topic is a matter of debate in women at high risk of developing OC due to genetic predisposition. We offer a screening every 6 months in young women or in those who refused RRSO [4, 5, 10] because, even if there is no evidence that it reduces OC mortality, careful surveillance can be the starting point for detailed descriptions like what we have presented in this article. Indeed, we have found an US sign that made it possible to diagnose OC early (even in cases where the CA125 serum levels were normal): all of our patients were diagnosed with a stage I tumor. This is very important because the survival rates of these patients depend on the stage of disease at the time of diagnosis [11]. This intraparenchymal finding could be ideally suited also for the use of intraoperative US [12] or for artificial intelligence in the near future.

Therefore, there is the urgent need for further investigation regarding early OC diagnosis and women with genetic mutations predisposing to OC (*BRCA* mutation carriers). We believe that our findings can be a starting point to discover hidden signs of OC and provide new insights in order to try to fill the diagnostic delay gap of this challenging disease.

Author contributions G.G.: study execution, scientific original idea, manuscript draft, manuscript revision, and final approval. A.S.: manuscript draft, manuscript revision, and final approval. L.C.: manuscript revision and final approval. A.T.: manuscript revision and final approval. M.D.: manuscript revision and final approval. V.G.: manuscript revision and final approval V.P.: manuscript revision and final approval. L.B.: study execution, manuscript draft, and final approval. A.LM.: scientific idea revision, manuscript revision and final approval.

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Data availability No datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical statement The authors certify that they have obtained all appropriate patient consent forms. The patients have given their written consent for their images and clinical information to be reported in the journal, apart patient 4 who had passed away in 2022. For this woman the consent was asked to the husband AG who gave a specific

written consent. The patients were also ensured that their names and initials will not be published, to ensure anonymity.

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