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An atypical presentation of advanced-stage ovarian cancer: Is there value in routine screening?

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Abstract
As contemporary practice guidelines stand, the use of screening tools and confirmatory diagnostic testing for ovarian cancer is utterly reliant on clinical suspicion. Clinicians must consider symptomatology and risk factors in an effort to subjectively determine which of their patients requires ovarian cancer screening. Because disease risk factors are well-established, patients at elevated risk are routinely screened. However, in the case of a patient at average risk, clinical presentation becomes the key determinant in the decision to screen. Such symptoms, unfortunately, lack both sensitivity and specificity for ovarian cancer. The case elucidated in this manuscript provides an example of how clinical presentation alone is not a reliable predictor of ovarian cancer diagnosis, suggesting that there is value in routine screening. We present the case of a 43-year-old Female with diffuse abdominal pain, nausea, vomiting, and constipation. She did not present with weight loss, early satiety, abdominal bloating or any other symptoms proven to be independently associated with ovarian cancer. Had she been screened for disease at an earlier date, it is reasonable to assume that her tumor would have been caught early on, leaving her with a more favorable prognosis.

Keywords: Ovarian cancer, cancer antigen 125, symptom index, screening

Introduction
Ovarian cancer is the most lethal of all gynecological cancers with a five-year survival rate of 95% for stage I, 70% for stage II, 30% for stage III, and merely 15% for stage 4 [2]. In 2021, there were 20,032 total cases of ovarian cancer in the United States with an incidence rate of 10 new cases per 10,000 women [1]. Though these numbers place the disease burden just outside of the 10 most common forms of cancer in the United States, its prevalence is still daunting and warrants more keen clinical suspicion. Catching ovarian cancer in its early stages has always presented a challenge to clinicians. This can be attributed to the fact that its carcinogenesis is relatively poorly understood, placing a great deal of diagnostic responsibility on clinical suspicion. Therein lies the challenge, however, as the associated symptomatology is nonspecific and variable. Traditionally, suspicious symptoms include fatigue, weight loss, early satiety, abdominal distension, urinary frequency, pelvic pain, menorrhagia and dysmenorrhea [3].

In an effort to better translate clinical suspicion into diagnostic sensitivity, Goff *et al*. developed an ovarian cancer symptom index (SI) in 2007 based on a self-reported symptom survey of 488 women. The index was considered positive if a patient experienced either pelvic pain, abdominal pain, abdominal distension, bloating, difficulty eating, or early satiety for at least 12 days per month for less than 1 year. The index demonstrated a sensitivity of 56.7% for early-stage disease and 79.5% for advanced-stage disease [4]. Because it is so crucial to catch ovarian cancer in its early stages, this sensitivity is unsatisfactory. The SI has since been tested alongside molecular markers of ovarian cancer, such as human epididymis protein 4 (HE4) and cancer antigen 125 (CA-125) to bolster diagnostic predictability [5]. The US Preventive Service Task Force advises against screening for ovarian cancer in asymptomatic women [6]. However, the use of an SI alone to predict ovarian cancer has shown a sensitivity of 64% [5]. When used to select women for subsequent CA-125 and HE4 testing, it has demonstrated an even more concerning sensitivity of 58% [5].

It is clear that clinical suspicion alone is an unreliable prognosticator of ovarian cancer. As such, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial included bimanual palpation of the ovaries in its initial screening protocol.

This was discontinued 5 years into the study because no cases of ovarian cancer were detected solely from the physical exam technique [7]. All of this is to say, implementation of more accessible molecular testing represents our best hope to catch ovarian cancer in its early stages and decrease the disease's associated striking mortality rate.

In this manuscript, we present a case that further accentuates the need for objective screening measures in the world of ovarian cancer.

Case description

A 43-year-old Female, with a history of Generalized Anxiety Disorder and GERD, presented with crampy, diffuse abdominal pain onset 3 months ago. She reported that she had been unable to see a physician because she did not have health insurance and recently moved states. She endorsed constipation over the same timeframe and nausea with yellow vomit for the past 3 weeks. Patient denied fever, chills, abdominal distension, night sweats, weight loss, early satiety, and bladder/bowel incontinence. Pelvic physical exam was unremarkable, but the abdominal exam revealed moderate diffuse tenderness upon light palpation with localized severe tenderness to the RLQ and LLQ upon deep palpation. Patient's blood pressure was 180/100 mmHg, temperature was 98.8°F, respiratory rate was 14 bpm, and pulse was 85 bpm. Routine labs demonstrated a blood urea nitrogen of 34, creatinine of 4.08, GFR of 12, and a urinalysis with large blood. CT abd/pelv revealed a large complex left adnexal lesion with mass effect resulting in bilateral hydroureteronephrosis and compression of the distal colon. Prominent mesenteric, periaortic, and inguinal lymph nodes were also noted, concerning for neoplastic process [Figure 1]. As such, hematology/oncology was consulted. Subsequent US pelvis showed bilateral ovarian masses [Figure 2]. On the same day, the patient's cancer antigen 125 levels were elevated at 235 and 234 in the morning and evening, respectively. These studies were followed up with MRI pelvis which was interpreted as a cystadenoma/cystadenocarcinoma of the ovaries [Figure 3]. The following day, the facility's hematology/oncology surgeon performed an exploratory laparotomy with bilateral salpingo-oophorectomy and omentectomy.

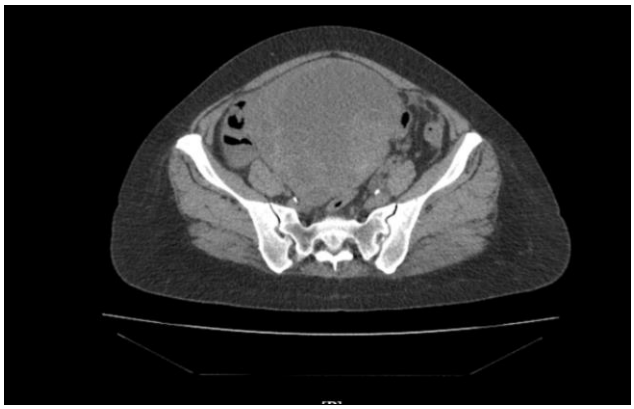

Fig 1: CT abd/pelv demonstrating a large complex left adnexal mass

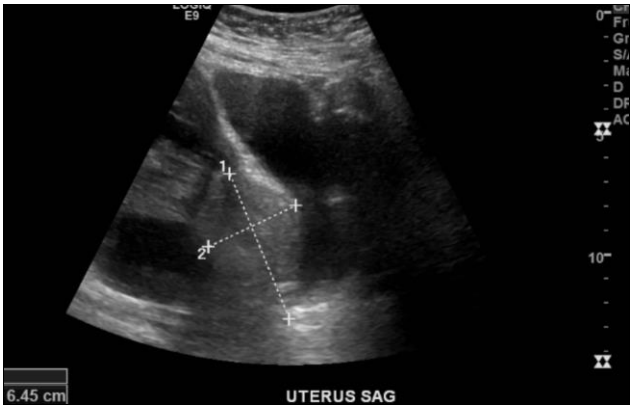

Fig 2: US of pelvis demonstrating bilateral ovarian masses

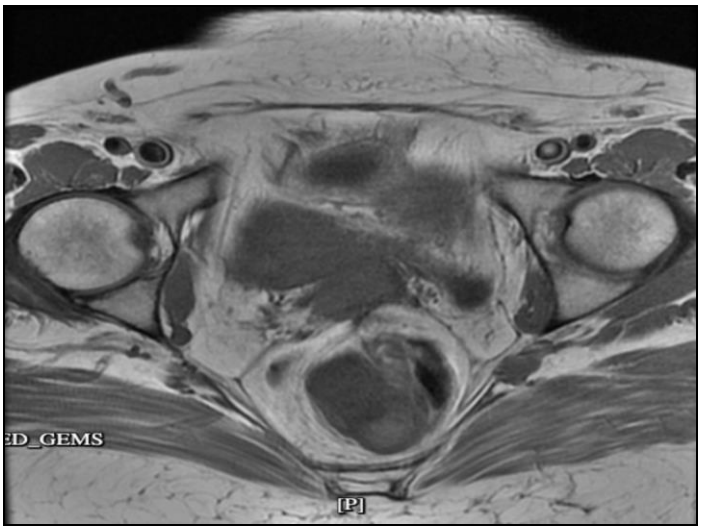

Fig 3: MRI of pelvis demonstrating cystadenoma/cystadenocarcinoma of ovaries

Discussion

Ovarian cancer is one of the leading causes of cancer deaths among women [8]. A woman's risk of getting ovarian cancer in her lifetime is about 1 in 87, while her lifetime chance of dying from ovarian cancer is about 1 in 130, or 7%. Perhaps these statistics are not immediately striking, but when juxtaposed with the risk of death from other common cancer diagnoses, ovarian cancer becomes far more menacing. It is the 6th most common cancer in women in the US behind cancer of the breast, colon/rectum, lung, endometrium, and cervix [8]. Among this list, the annual incidence of ovarian cancer, 19,000 [8], is most comparable to that of cervical cancer at 11,500 [9]. However, the lifetime risk of dying from cervical cancer is 2% [10] compared to the aforementioned 7% associated with ovarian cancer.

The increased risk of dying from ovarian cancer can be largely attributed to the current lack of universally accepted screening

measures for the disease. The algorithm for cervical cancer screening and diagnosis is well established: Cervical cytology by way of Pap smear should be performed every 3 years in women aged 21-65 [11]. An abnormal Pap is followed by colposcopy and potential biopsy to ascertain certainty of diagnosis. A 2019 retrospective epidemiologic study estimated that widespread Pap smear screening from 1976-2009 accounted for a decrease in the incidence of early-stage cervical cancer from 9.8 to 4.9 cases per 100,000 women and a decrease in late-stage disease incidence from 5.3 to 3.7 cases per 100,000 women [13]. In contrast, the USPSTF currently recommends against ovarian cancer screening for asymptomatic patients despite evidence that screening with serum CA-125 levels or transvaginal ultrasound can lead to earlier detection of ovarian cancer [11].

According to the American Cancer Society (2019), early detection of ovarian cancer at a localized stage (1A or 1B) results in far better disease prognosis. Specifically, the projected 5-year survival rate for these patients is about 92% compared to 32% in patients with advanced stage disease [14]. Most women, however, are not diagnosed until they have late-stage disease [15]. Intuitively, improved screening practices could vastly diminish mortality associated with an ovarian cancer diagnosis. This assertion begs the question: Have we already discovered sufficiently effective screening tools?

Nelson *et al*., a 2004 Randomized Control Trial, utilized CA-125 screening followed by transvaginal ultrasound for abnormally elevated levels. This multimodal approach demonstrated that 50% of patients with ovarian cancer in the screened group were in Stage I, while only 5% in the control group were in Stage I [16]. A larger cohort study screened exclusively with transvaginal ultrasound, reporting 59%-65% of ovarian cancers found in Stage I [17]. The USPSTF's contention with the use of CA-125 or ultrasound screening lies in the fact that a true determination of the tests' sensitivity is difficult. Previous studies that have attempted to assess the accuracy of such screening methods have utilized different thresholds to define biomarker elevation, they have generally included small numbers of patients, and they have involved different lengths of follow-up [11]. Regardless, in women at average risk of ovarian cancer, using thresholds of 30 U/mL or 35 U/mL, the 1-year follow-up sensitivity of CA-125 screening, followed by transvaginal ultrasound is reported to be about 80% with a specificity of nearly 100% [17, 18].

As contemporary practice guidelines stand, use of screening tools and confirmatory diagnostic testing for ovarian cancer is utterly reliant on clinical suspicion. Clinicians must consider clinical presentation and risk factors in an effort to subjectively determine which of their patients requires ovarian cancer screening. Disease risk factors are well established: nulliparity, postmenopausal state, estrogen therapy after menopause, and inheritance of BRCA1 or BRCA2 [19]. Consequently, a patient at elevated risk is routinely screened. However, in the case of a patient at average risk, clinical suspicion based on symptomatology becomes the key determinant in the decision to screen. Such symptoms, unfortunately, lack specificity for ovarian cancer. In 2007, Goff *et al*. developed an ovarian cancer symptom index based on self-reported experiences of 488 women. Per logistic regression analyses, pelvic/abdominal pain, increased abdominal size/bloating, and difficulty eating/early satiety were all independently associated with ovarian cancer. Thus, the group considered the symptom index positive if any of those symptoms occurred > 12 days per month but were present for less than a year. The sensitivity of this SI was 56.7% for early-stage disease and 79.5% for advanced-stage disease. Specificity was 90% for women age > 50 years and 86.7% for women age < 50 years [11].

It is clear that the use of CA-125 molecular screening with follow-up transvaginal ultrasound demonstrates superior sensitivity (80%) compared to the use of a symptoms index (56.7%). The case elucidated in this manuscript provides an example of how clinical presentation alone is not a reliable predictor of ovarian cancer diagnosis. Our patient presented with diffuse abdominal pain, nausea, vomiting, and constipation due to the mass effect of her late-stage tumor. She did not present with weight loss, early satiety, abdominal bloating or any other symptoms proven to be independently associated with ovarian cancer. Had she been screened for disease at an earlier date, it is reasonable to assume that her tumor would have been caught early on, leaving her with a more favorable prognosis.

Because the specificity of multimodal CA-125 and ultrasonographic screening is not 100%, implementation of routine screening would undoubtedly lead to false positive cases. A false positive case could result in unnecessary surgery in the form of ovarian biopsy, exposing the patient to risk of surgical complications as well as unwarranted anxiety. Despite this, the use of molecular biomarkers in ovarian cancer screening shows great potential, warranting further exploration.

Conclusion

This case highlights the limitations of current ovarian cancer diagnostic practices and underscores the need for improved screening methods. The patient's atypical presentation, coupled with her advanced-stage diagnosis, illustrates how reliance on clinical suspicion alone may delay detection, particularly in patients without traditional risk factors. While the implementation of molecular biomarkers such as CA-125 and transvaginal ultrasonography demonstrates promise, challenges related to sensitivity, specificity, and cost-effectiveness must be addressed.

The significant disparity in survival outcomes between early- and late-stage ovarian cancer diagnoses highlights the critical need for refining and integrating universal screening protocols to increase early detection. Enhanced screening practices, and consequently earlier detection, will significantly improve prognoses and reduce the disease burden. Future research should focus on optimizing multimodal screening strategies and standardizing use of molecular biomarkers and their associated thresholds. By prioritizing early detection through standardized screening, we can move toward mitigating the high mortality associated with ovarian cancer.

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