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Early-Stage Mucinous Ovarian Adenocarcinoma with Extensive Clotting in a Previously Healthy Young Female Patient: An Uncommon Presentation of a Relatively Uncommon Disease

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Female, 24
Final Diagnosis: Mucinous ovarian adenocarcinoma
Symptoms: Nonproductive cough • shortness of breath with exertion
Medication: —
Clinical Procedure: —
Specialty: Oncology

Objective: Rare co-existance of disease or pathology

Background: Mucinous ovarian adenocarcinoma is one of the less common epithelial cancers of the ovaries, and typically does not occur in younger women. Nearly all mucinous ovarian adenocarcinomas present with early-stage disease without significant sequelae of cancer, such as clotting. Anchoring bias is a common problem in medicine that has been shown to significantly affect physician decision-making.

Case Report: We present the case of a 24-year-old healthy female Chinese immigrant with no significant past medical history, who presented with a subacute history of nonproductive cough and shortness of breath with exertion. Initial workup was directed towards diagnosis of tuberculosis and other infectious etiologies due to anchoring to patient's nationality and her positive family history for tuberculosis. She was eventually diagnosed with extensive bilateral pulmonary emboli and bilateral deep vein thromboses as well as a right ventricular thrombus. This extensive clot burden helped lead to the diagnosis of mucinous ovarian adenocarcinoma.

Conclusions: This case is significant not only because the diagnosis of mucinous ovarian adenocarcinoma is uncommon in healthy young females under the age of 25, but, more importantly, because such extensive pulmonary emboli and deep vein thromboses in a young female with local/early-stage ovarian cancer is very rare. This case is also significant because it serves as an important reminder of the risks of anchoring bias in skewing perceptions and delaying the correct diagnosis by physicians.

MeSH Keywords: Adenocarcinoma, Mucinous • Ovarian Neoplasms • Venous Thromboembolism

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/903214

Background

Ovarian cancer is the most common gynecological cause of death in the United States [1]. Most ovarian malignancies (95%) are epithelial. Serous carcinoma is by far the most common of the epithelial ovarian cancers, whereas mucinous carcinoma is much rarer [2] and accounts for less than 5% of all primary ovarian cancers [3]. It often presents in perimenopausal women in their late 40s to early 50s, although cases have been reported in women as young as in their mid-teens and women as old as in their mid-80s [4]. Nearly all mucinous ovarian adenocarcinomas present with early-stage disease without significant sequelae of cancer, such as clotting.

Case Report

A 24-year-old woman who recently immigrated from China, with no significant past medical history, presented to the hospital with a 5-day history of nonproductive cough and shortness of breath with exertion. She denied any chest pain, pleuritic pain, fever or chills, night sweats, weight loss, lymphadenopathy, joint pains or swelling, oral ulcers, or skin rashes. Review of systems was positive only for constipation and left ankle pain. She was on no medications, had no prior surgeries, and had no significant allergies. She did not smoke. She denied any bird, cat, or significant dust, gas, or chemical exposures. Of note, her mother had tuberculosis 7 years prior to admission, which had been treated, and was in remission.

Vital signs were temperature of 37.3°C, heart rate of 90 beats per minute, respiratory rate of 24 breaths per minute, and blood pressure of 134/80 millimeters of mercury. On examination, the patient was alert and oriented, and in no acute distress. Head, eyes, ears, nose, and throat exams were unremarkable. Neck and supraclavicular exams did not reveal lymphadenopathy. A lung exam revealed diminished breath sounds in the right base. A heart exam was unremarkable. Basic labs, including basic metabolic panel, liver function tests, and coagulation studies, were unremarkable. A chest x-ray showed a large right pleural effusion with collapse of the middle and lower lobes, which was later confirmed by computed tomography (CT) of the chest. CT of the chest also revealed left upper lobe airspace disease and rounded areas of left lower lobe consolidation extending into the pleural surface, with surrounding ground-glass opacity.

Diagnostic and simultaneously therapeutic thoracentesis of the right pleural effusion was performed. Based on the pleural fluid results (Table 1), the effusion was determined to be exudative. Notably, pleural fluid cytology was negative for malignant cells. Despite thoracentesis, her symptoms of dyspnea and cough persisted. Over the next 2 days, her cough became productive with streaks of blood in the sputum. Initially, it was thought that her diagnosis was likely an infectious process, either a community-acquired pneumonia or pulmonary tuberculosis given her positive family history and the fact that she had emigrated from a place where tuberculosis is endemic. All the effort initially was being directed towards this hypothesis. Blood cultures, serum acid-fast culture, and serum fungal cultures were obtained in the Emergency Department. Bacterial, fungal, and 3 acid-fast smears and cultures were also obtained from pleural fluid during the thoracentesis. Three acid-fast smears and an acid-fast culture were obtained from sputum, and a sputum bacterial culture was also obtained. All of the above infectious workup eventually came back negative. Serum Quantiferon Gold was obtained and came back indeterminate (QFT TB Ag minus Nil 0.00, Quantiferon Mitogen 0.06, Quantiferon Nil 0.04, Quantiferon TB Ag 0.03).

Table 1. Thoracentesis results, serum LDH, serum protein.

Pleural fluid	Serum	Concentrations	Units
Albumin		2.9	grams/deciLiter
Amylase		15	Units/Liter
Bilirubin		0.6	milligrams/deciLiter
Cholesterol		39	milligrams/deciLiter
Glucose		91	milligrams/deciLiter
LDH		332	Units/Liter
Lactate		1.2	millimoles/Liter
pH		7.46	No units
Protein		4.4	grams/deciLiter
	LDH	297	Units/Liter
	Protein	7.2	grams/deciLiter

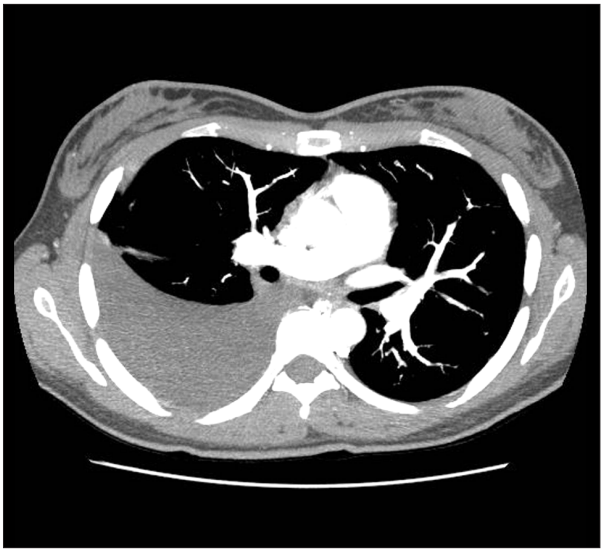

Figure 1. Computed tomography pulmonary angiography – Sample CT image slice depicting extensive pulmonary emboli.

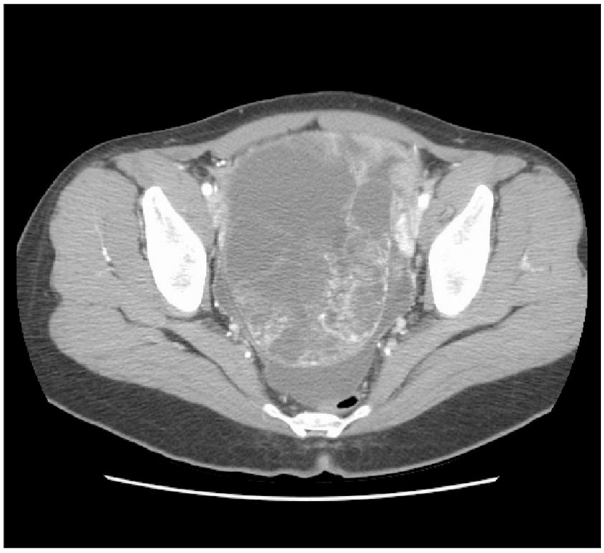

Figure 2. Computed tomography abdomen depicting the multicystic ovarian mass.

Regarding her ankle pain, the patient reported on admission that it had been bothering her for the past couple of weeks or so. She did not recall any trauma to the left foot, though she did mention that she ran regularly and may have inadvertently sprained her ankle. On examination, there was no edema, erythema, or warmth of the ankle. Homan's sign was negative. She could bear weight on it, so it was decided to treat this as a sprain and manage it conservatively. However, over the next few days, her ankle pain became worse and she started to develop trace edema in the left foot. An x-ray of her left ankle was initially obtained, which showed no evidence of fracture or dislocation. Though she had no obvious risk factors for deep venous thrombosis (DVT), given that her left lower-extremity pain and swelling was worsening with conservative measures, it was decided to obtain a venous Doppler of her left lower extremity, which showed acute DVTs of her left tibioperoneal trunk and popliteal, posterior tibial, peroneal, and soleal veins. Given such extensive DVTs, there was a concern that her shortness of breath and cough could be due to a pulmonary embolus. Computed tomographic pulmonary angiography was obtained and indeed showed acute pulmonary emboli within the right upper-lobe segmental and subsegmental pulmonary arteries, middle-lobe pulmonary artery, and lower-lobe pulmonary artery and several of its segmental and subsegmental branches. It also showed acute pulmonary emboli within the left upper-lobe anterior and apical segmental pulmonary arteries, and the lingular branches of the pulmonary artery, as well as within the lower-lobe segmental and subsegmental pulmonary arteries (Figure 1). Venous Doppler of her right lower extremity was obtained and showed acute DVTs in her right popliteal, gastrocnemius, posterior tibial, and peroneal veins.

The patient was started on enoxaparin (1 milligram/kilogram BID, subcutaneous route) and warfarin (5 milligrams daily, PO route). However, it was yet unclear what precipitated such extensive clots in this patient. Per the history obtained, she had no obvious risk factors: she had no recent long plane or car trips or other reasons for immobility, she had no history of trauma or surgery, she was not a smoker, she was not overweight or obese, she was not pregnant (urine pregnancy test on admission was negative), she was not on contraceptives of any kind, she had no personal or family history of clots, and she did not fit the typical age range. This left 2 other main etiologic categories: hypercoagulable disorders and malignancy. Hypercoagulable workup was obtained and showed no evidence of factor V Leiden or prothrombin 20210 gene mutations. Eventually, at different points in time in the outpatient setting, other hypercoagulable workup was done and was unremarkable: anticardiolipin antibodies, Beta-2-microglobulin antibodies, and lupus anticoagulant were obtained and were negative; antithrombin III, protein S, and protein C levels were all normal; and homocysteine levels were borderline low.

Further history was obtained regarding the constipation she had mentioned on admission. She described a "bloating" feeling with decreased frequency of bowel movements over the past several weeks. She described lower abdominal and pelvic pain when she coughed. On examination, there was no tenderness to palpation of her abdomen nor was there distention. Given that the suspicion for malignancy was higher with the findings of diffuse clots, a CT of the abdomen and pelvis was obtained, which showed a multicystic pelvic mass measuring 17 by 14 by 15 cm, suspected to be an ovarian mass (Figure 2). There was also mild-to-moderate ascites without

definite evidence of peritoneal carcinomatosis, and no evidence of distant metastasis. Cancer antigen 125 was found to be markedly elevated at 1318 units per milliliter (reference range: 5.5–35 units per mL).

Exploratory laparotomy was planned by the Gynecologic Oncology service. Pre-operative echocardiogram revealed a right ventricular thrombus, but after repeat imaging a week later showed stability of the right ventricular thrombus, the patient underwent a left salpingo-oophorectomy. Pathology revealed stage Ia, grade 2 moderately-differentiated mucinous adenocarcinoma of the ovary. The patient received 6 cycles of chemotherapy with Carboplatin and Paclitaxel in the outpatient setting. She tolerated the chemotherapy well, with minimal adverse effects. She has been following up regularly with a gynecologic oncologist, and has been disease-free for about 15 months. Her anticoagulation was stopped by her hematologist after over a year of therapy and after repeat echocardiograms showed no evidence of thrombus.

Discussion

Several factors involved in the immune response to neoplasia, such as the development of acute-phase reactants, abnormal protein metabolism, tumor necrosis, and hemodynamic rearrangements, can all contribute to the overall activation of blood coagulation in cancer patients. However, a prominent role is attributed to tumor-specific prothrombotic mechanisms, which include several tumor cell properties. Malignant cells can interact with the hemostatic system in multiple ways, but the 2 principal categories of interaction are: 1) the capacity to produce and release procoagulant and fibrinolytic activities, as well as inflammatory cytokines; and 2) direct interaction with other blood cells such as endothelial cells, platelets, and monocytes [5].

The presentation of epithelial ovarian carcinoma can be acute or subacute. Women who present in an acute fashion typically do so due to a condition that requires urgent care and evaluation, such as a malignant pleural effusion or bowel obstruction. Though our patient did present with a pleural effusion, pleural fluid cytology was negative for malignant cells, and the pleural effusion was more likely due to the extensive bilateral pulmonary emboli the patient was found to have.

Although imaging and tumor markers (CA 125, CEA for mucinous cancers) can be helpful in suggesting ovarian cancer, essentially it is a histologic diagnosis. Diagnosis and staging are surgical and typically involve total extrafascial hysterectomy and bilateral salpingo-oophorectomy with pelvic and paraaortic lymph node dissection [6]. Ovarian cancer is staged using either the 2014 International Federation of Gynecology and Obstetrics (FIGO) system or the Tumor, Nodes, Metastasis (TNM) classification system, with stage Ia (T1aN0M0 or FIGO stage IA, as seen in our patient), suggesting that the tumor is limited to 1 ovary or fallopian tube; no tumor on ovarian or fallopian tube surface; and no malignant cells in ascites or peritoneal washings [7]. Women with ovarian cancer should undergo adjuvant treatment, typically with a platinum-based regimen, with the exception of those with grade 1, stage Ia/Ib. Our patient received platinum-based chemotherapy, despite being stage Ia, because she was grade 2. Prognosis for patients with stage Ia ovarian cancer is very good: overall survival is 98%, 96%, and 90% at 1, 2, and 5 years, respectively. NCCN guidelines suggest that posttreatment surveillance include office visits every 3 to 6 months up to 5 years posttreatment, then annually, and CA-125 or other tumor markers should be assessed at every clinic visit if initially elevated, if indicated. Standard imaging techniques, including ultrasound, computed tomography, magnetic resonance imaging, and positron emission tomography, have limited sensitivity to detect recurrent ovarian cancer or to improve survival and thus are not a part of regular surveillance in asymptomatic women [8].

Among the histological subtypes of ovarian carcinoma, serous adenocarcinoma is by far the most commonly associated with VTEs, accounting for almost half of all cases with ovarian cancer and VTEs. Cancers of low malignant potential on histopathology are the next biggest group, making up about 20% of cases. Endometroid, high-grade undifferentiated tumor, and mixed epithelial cancers make up about 5–10% of cases each. Mucinous and transitional cell carcinoma have the least association with VTEs. These statistics are based on an in-depth study of a cohort of approximately 650 women who had a diagnosis of epithelial ovarian adenocarcinoma and were followed for VTEs over a 10-year period [9].

Patients diagnosed with early-stage ovarian cancer infrequently present with a venous thromboembolism (VTE). In a study that included 528 693 patients with 19 of the most common cancers in the United States, only 596 (0.11%) had a VTE diagnosed at the same time or in the year preceding the diagnosis of the cancer. Of these, only 229 (0.04%) had a pulmonary embolism, and the others had only a deep venous thrombosis. The mean age ±SD of the cohort was 66±17. It was noted by the authors of the study that most cases of VTE were confined to metastatic disease. Local disease, as was seen in our patient, was much less common. This cohort consisted of 12 051 patients with ovarian cancer, and only 27 (0.22%) were diagnosed with VTE. It is unclear from review of the study: (1) how many of these 27 cases were less than 25 years of age, (2) how many of these 27 cases had pulmonary emboli and how many only had deep vein thromboses without pulmonary emboli, (3) how many of these 27 cases had local disease instead of advanced or metastatic disease, and 4) how many

of these 27 cases had all 3 features (being less than 25 years of age, having pulmonary emboli, and having early-stage disease) [10]. Unfortunately for our patient, studies have shown that survival rates are significantly lower and prognosis poorer for patients who have cancer at the time of an episode of VTE compared to patients who have cancer without a history of VTE [11]. For now, our patient is doing well and has been in remission for over a year.

Conclusions

This is a case of an uncommon presentation of a relatively uncommon disease. As discussed, mucinous ovarian cancer is uncommon by itself in such a young healthy female, but even less common is such an extensive clotting in a young woman with only early-stage mucinous adenocarcinoma. This is not only because of the early stage, but also because, of all the epithelial ovarian cancers, mucinous ovarian cancers are among the least associated with VTEs.

This case also serves as a reminder that anchoring bias is a common problem in medicine, and one must be cognizant of it to prevent it from negatively affecting and interfering with medical decision-making. Anchoring bias was first described by Tversky and Kahneman in 1974 [12], and has been shown to be one of the many biases that seriously contributes to diagnostic errors and delays in medicine [13]. This bias dictated the initial infectious workup in this case, and recognizing and then avoiding this bias eventually led to the correct diagnoses of venous thromboembolism and mucinous ovarian adenocarcinoma.

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