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Case report

A diagnostic dilemma of a pulmonary nodule of a patient who suffered advanced ovarian cancer: A case report and a hypothesis

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ABSTRACT

Introduction: This report presents a case of lung cancer which can be easily misdiagnosed as distant metastasis. Along with a literature review on the morphological, pathological and prognostic characteristics of lung cancer associated with cystic airspaces (LCCA), it would help to improve our understanding of the dynamic evolution of LCCA, to avoid its delayed diagnosis and treatment. We also propose here a hypothesis on the etiology of LCCA.
Case presentation: A patient with advanced ovarian cancer who presented with elevated serum CA125 at time of admission and had undergone TAHBSO at first, and second operation of sigmoid colon resection was performed due to her locoregional recurrence of ovarian cancer. After her second operation, patient showed further increment of serum CA125 and CECT scan indicated an airspace-related pulmonary nodule in the right middle lobe of her lungs. It was suspected that distant metastases of ovarian cancer had reoccurred postoperatively.
Clinical discussion: After comparing the characteristic of metastatic ovarian cancer with LCCA, we diagnosed the pulmonary nodule as primary lung cancer. Surgery eventually confirmed the pulmonary nodule as second primary lung cancer associated with cystic airspaces.
Conclusion: The rare occurrence of LCCA should merit special attention from clinicians and radiologists so as to avoid missed or delayed diagnosis. We propose here a hypothesis that LCCA is related to spreading of tumour cells during surgical procedures in lung cancer surgery. Should our hypothesis be substantiated in further studies, this would affect the operation procedures for surgeons in the future.

1. Introduction

This work has been reported in line with the SCARE 2020 criteria [1].

Ovarian cancer is known to be one of the most fatal female reproductive cancers. Patients at advanced stage usually present as pelvic metastasis and distant metastasis such as lung and liver. Kui Deng et al. discovered that lung metastasis ranked third among a litany of metastatic sites [2]. Along with the investigation of the prognostic factors for ovarian cancer, his analysis concluded that serum CA125 was a good indicator for postoperative monitoring in gynaecological cancers. In this report, we present a 52-year-old woman with underlying surgical history of TAHBSO for ovarian cancer. She developed progressive elevation of serum CA125 and lung nodules were revealed on her chest computed tomography (CT) scan. After multidisciplinary team (MDT) discussion, surgery was performed. Final histopathology report confirmed lung cancer associated with cystic airspaces (LCCA) rather than secondary distant lung metastasis.

2. Case

In June 2018, a 49-year-old postmenopausal married Chinese Han woman (G5P2A3) was admitted to our hospital due to a one month history of pelvic mass. She presented with amenorrhea for eight months and denied postmenopausal hormone replacement therapy. She had no smoking history and denied any cancer history run in her family. The patient was in general good condition, but a mass anterior to the uterus was palpated on physical examination, while other clinical signs were insignificant. Pre-operative serum CA125 was elevated at 562.9 U/ml. MRI of pelvis and abdomen revealed a cystic solid mass in the left adnexal area, about 7.5 × 4.1 cm in size. TAHBSO, resection of distal sigmoid mesangial and greater omentectomy was subsequently

Abbreviations: TAHBSO, Transabdominal total hysterectomy with bilateral salpingo-oophrectomy; TC, Paclitaxel and Carboplatin; TP, Paclitaxel and Cisplatin; FDG, fluorine 18 fluorode-oxyglucose.

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performed. The pathology report documented high-grade ovarian serous adenocarcinoma, grade 3 (FIGO) with no peritumoural lymphovascular permeation and perineural invasion. Postoperative diagnosis was stage IIIC serous adenocarcinoma of the left ovary. The patient there afer underwent 8 cycles of chemotherapy with paclitaxel and carboplatin and subsequently received regular follow up on CT and serum CA125.

In December 2018, her first follow up chest and abdomen CECT (contrast-enhanced CT) scan suggested an airspace-related lesion, size of 13 × 12 mm, in the right middle lobe of her lung. Regular follow up was suggested. There were no significant signs of locoregional recurrence of her pelvic mass till her next CECT in September 2019. She then be operated on transabdominal sigmoid colon resection in November 2019, which confirmed a metastatic ovarian cancer by pathology. The patient received 3 cycles of chemotherapy with TC regimen ensuingly, but TP regimen was administered afterwards due to intolerance to the previous regimen. Regular review after chemotherapy was conducted and two repeated CECT taken in October 2019 and March 2020 showed no significant changes in the size of the cystic airspace at right middle lobe. Her serum CA125 increased from 64 U/ml in November 2021 to 127 U/ml in January 2022. The CECT scan taken in January 2022 revealed nodular high-density shadow at the edge of the cystic cavity with clear boundary and lobulated shape, ranged 19 × 18 mm over the right middle lobe where the cystic airspace had enlarged to 22 × 16 mm, and two small ground glass opacity were also shown in the left lower lobe (Fig. 1). Positron emission tomography-computed tomography (PET/CT) was employed to further determine the malignancy of the nodule and showed absence of uterus and adnexal area, focal FDG hypermetabolism over lower sigmoid colon (colonoscopy diagnosed as inflammatory polyps) and nodules with thick-walled cavities in the right middle lobe. MDT discussion was held to determine the malignancy extent and operability of the nodule, and whether pre-operative biopsy was required for this patient. Surgical treatment was recommended, but patient herself and her relatives refused preoperative biopsy. Right middle lung lobectomy with lymphatic clearance was performed by a senior thoracic surgical consultant and his surgical team *via* video assisted thoracoscopic surgery (VATS) in January 2022. Final pathology report revealed invasive adenocarcinoma with solid growth predominant (75%) and lymphovascular permeation, and diagnosed as Stage Ic (T1cN0M0) (Fig. 2). The patient had an uneventful recovery and was discharged 5 days postoperatively. For long term prognosis, follow up

Fig. 1. Comparison of CT findings showed the changes of cystic airspace in 2018 (A), 2019 (B), 2020 (C) and 2022 (D) respectively. (A), (B), and (C) showed no significant changes in the size of the cystic airspace at medial segment right middle lobe of the lung, whereas (D) showed nodular high-density shadow at the edge of the cystic cavity with clear boundary and lobulated shape.

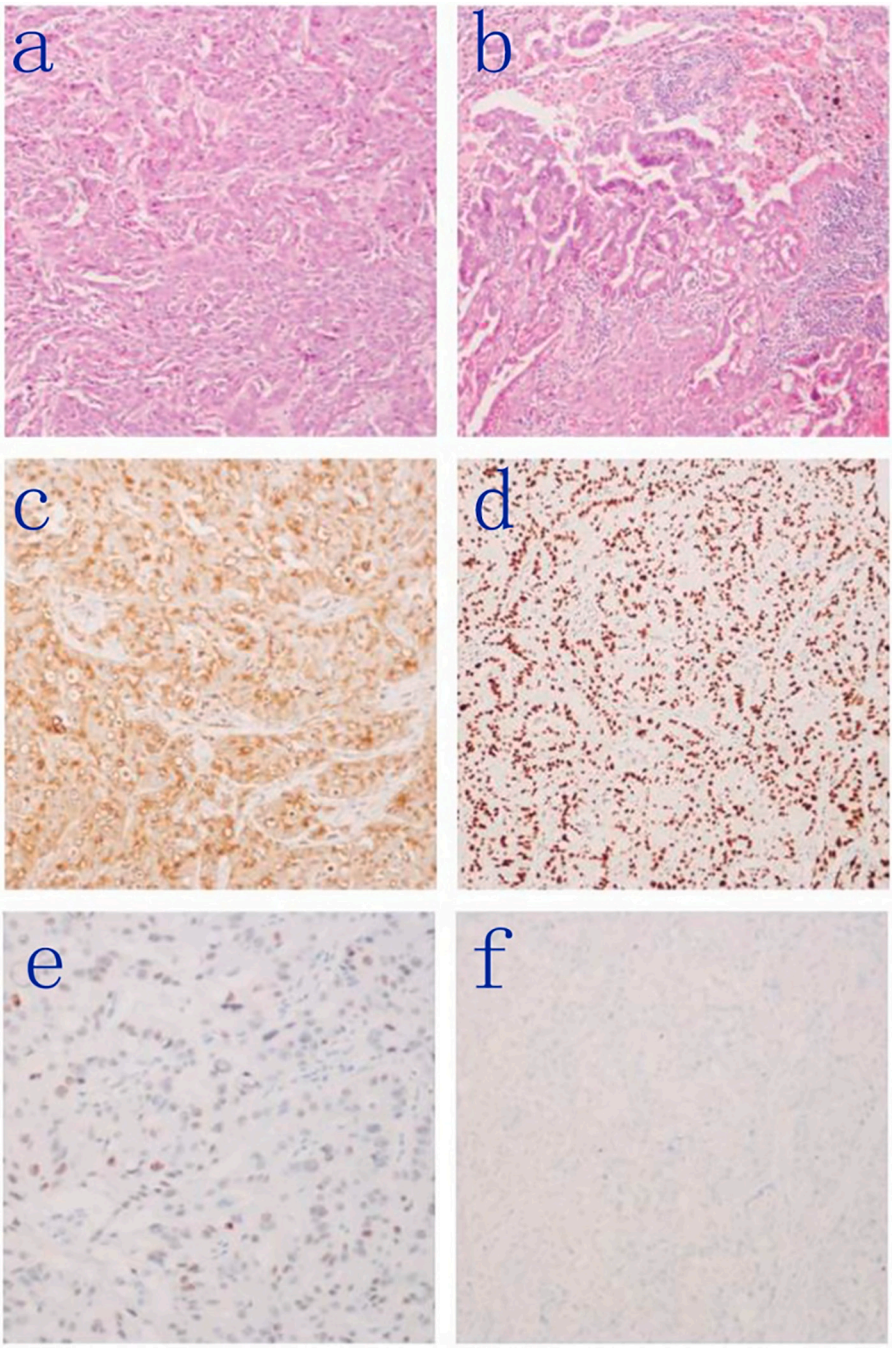
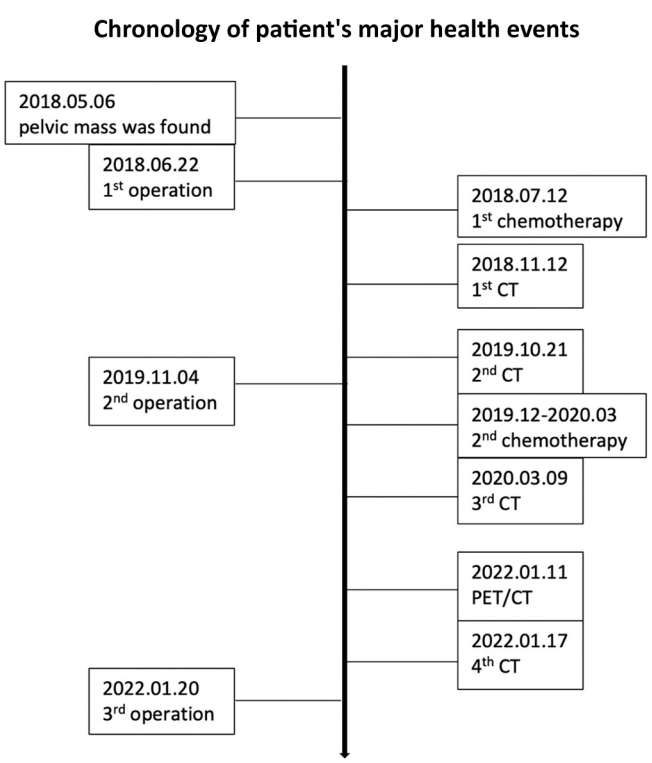


Fig. 2. (a) Adenocarcinoma displayed solitary predominant growth.
(b) Tumour cells showed glandular, cribriform with slit-like spaces and few micropapillary structures. (H and E, ×100).
(c) Tumour cells comprised of Napsin A antibodies (H and E, ×100) and TTF-1 antibodies (d) which confirmed primary lung carcinoma.
(e) Higher power histological image showed wild type p53 was expressed in this tumour which did not support high grade ovarian serous adenocarcinoma. (×200).
(f) Lower power histological image showed Pax-8 expression was negative, which did not support the tumour origin as gynaecological cause. (×100).

would be warranted.

3. Timeline



Chronology of patient's major health events

4. Discussion

Ovarian cancer is one of the most common gynaecological malignancies. Ovarian cancer remains to be the 7th most common form of cancer and the 8th leading cause of cancer-related death in women worldwide, with a 5 year survival rates below 45% [3]. To monitor the progression of ovarian cancer, serum CA125 is often used. Zhang Li *et al* demonstrated that the serum CA125 and TRIM24 were closely correlated with distant metastasis and FIGO grade of ovarian cancer [4]. Two different studies by PHILIP M and Gardner AB had reported a high rate of lung metastasis observed in ovarian cancer, accounting for 49% and 38% respectively [5,6]. The morphology of the lesion in this case resembles metastatic tumour. An image of intrapulmonary metastasis of a lung tumour is demonstrated below, in which the mass was located near the hilum as was in our patient, yet without cystic spaces (Fig. 3).

Lung cancer associated with cystic airspaces (LCCA) was first reported in 1940, and more cases had been published since then. LCCA is an uncommon presentation, with an incidence rate <5% [7], it is often missed due to its vague definition and benign manifestations of cystic lesions as emphysematous bullae or fibrotic cysts. A retrospective study discovered 14 cases out of 37,500 lung cancer patients were missed, of which 2 cases were initially presented as cystic airspaces. Thus, LCCA contributed to only 0.005% of lung cancer cases [8]. With the widespread use of chest CT in lung cancer screening, LCCA is becoming more frequently diagnosed. Yingran Shen et al. reported an incidence of 1.14% LCCA out of 10,835 lung cancer cases [9]. Overall, the incidence of LCCA is low and the classification of cystic airspaces-related lung cancer is not well established. The morphological appearances of cystic airspaces are hard to classify comprehensively. There are three main classification systems at present.

Mascalchi et al. and Florian et al. proposed LCCA classification schemes in 2015 and 2017 respectively [9]. In 2019, Shen et al. developed another classification scheme based on previous work and categorise LCCA into four types: Type I/II having a thin/thick wall around the air spaces, Type III showing an exophytic/endophytic nodule abutting the cyst wall, and Type IV corresponding to multicystic lesions with soft tissues interspersed with cystic airspaces [9]. The case in this report was classified as Type III. Patients with Type III LCCA tend to have a worse prognosis than other types. Studies have shown that the proportion of moderately/poorly differentiated subtypes was high in Type III

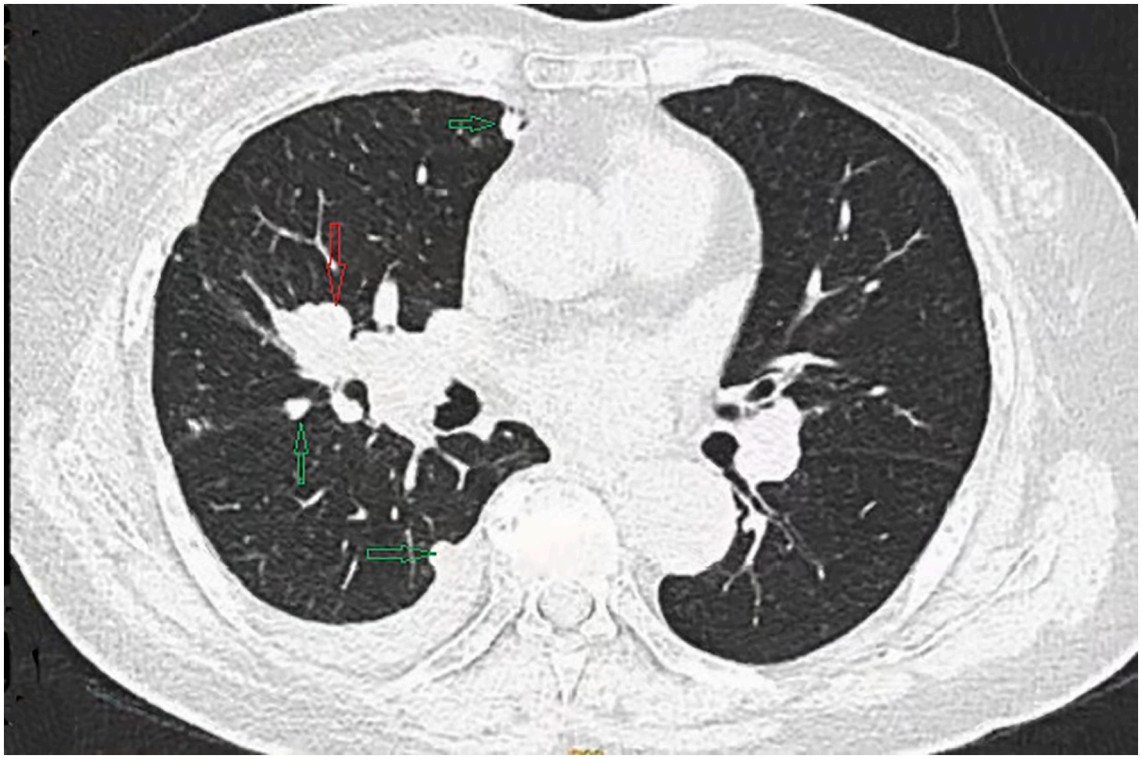


Fig. 3. Intrapulmonary metastasis in a patient with squamous cell carcinoma of the lung. The red arrow indicated nodular lesions near hilum while the green arrow indicated small scattered metastases. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and LCCA with part solid/solid component in wall shows significantly poor prognosis [9]. Jung et al. explored a stepwise progression of morphological changes of LCCA and concluded that there were 4 phases in LCCA evolution [10]. As time progressed, solid components appeared and increased in phase III and IV, with increasing proportion of moderate/poorly differentiated solid and micropapillary subtype and decreasing proportion of lepidic subtype. The increased frequency of moderate/poorly differentiated solid and micropapillary subtype observed by Jung et al. provided a very different viewpoint from previous study that solid or micropapillary growth of LCCA was relatively rare [10].

While the pathogenesis of LCCA remains unclear, there are two more widely accepted theories in explaining its underlying mechanisms. One theory assigned the cause of LCCA to a pre-existing cystic abnormal component. The other theory suggests that cystic airspaces have resulted from a check-valve mechanism due to microscopically small malignancy lesion that only becomes visible after increase in sizes of cystic airspaces. Florian J. et al. investigated and evaluated long term histological changes of cystic airspaces in 30 cases of LCCA patients. Among these 30 cases observed histologically, 6 of them were due to emphysema, 2 were due to bullae, and check-valve mechanism due to airway obstruction was seen in 8 patients [11].

Numerous literatures have reported that majority of patients had a past surgical history of lung cancer prior LCCA formation. In our opinion, these patients are more prone to diagnosed as LCCA (Table 1). Here we make a bold hypothesis that carcinogenic mechanism of LCCA is partly caused by tumour cells spreading through the airways during the surgical procedure, in which the bronchus is usually the last to be managed. Based on this hypothesis, surgeons may need to obstruct the corresponding bronchus in order to minimize the occurrences of LCCA. Large-scale clinical trials are essential to substantiate this hypothesis.

Ovarian cancer occurs as lung metastasis is common, especially in those patients with elevated serum CA125. Nevertheless, some studies have shown that such patients with history of ovarian cancer have a high risk of developing a second primary lung cancer, especially in American Indian and Asian Pacific women [13]. In our present case report, the patient had postoperative locoregional recurrence after her resection of ovarian cancer with elevated serum CA125, and taking the PET/CT results also into consideration, diagnosis of primary lung cancer was agreed by the MDT. According to the NCCN guidelines, the risk of preoperative biopsy outweighs the benefits for the patients. A surgical procedure without preoperative biopsy was hence adopted with patient consent. The diagnosis of LCCA in our patient was finally confirmed with pathology.

In view of severe intraoperative bleeding, the patient refused to undergo biopsy before or during surgery. PET/CT has a relatively poor ability to distinguish tubercle from tumour. If lobectomy is performed directly and resulted as tubercle under postoperative pathology, doctors may take sole responsibility and risk medical disputes. Therefore, biopsy should be performed prior pulmonary lobectomy only if conditions permit.

5. Conclusion

Advanced ovarian cancer is likely to metastasize to the lung, a site where the patients are more prone to develop second primary cancer. Chest CT examination should be routinely performed for patients with advanced ovarian cancer at initial diagnosis. Furthermore, chest CT findings of lung cystic airspaces-related lesion, especially in patients with previous lung cancer history, should raise suspicion of LCCA and requires follow up closely. If there is thickening of the lumen wall or exophytic/endophytic nodule exist around the lumen, the possibility of LCCA should be considered to be highly likely, thus prompt diagnosis and surgical operation are crucial to improve patients' prognosis.

Table 1
Studies included in analysis of LCCA patients who have cancer history.

	Total number of LCCA cases	Lung cancer history	Other cancer history
Mascalchi M [9]	24	6	3[a]
Florian J [11]	30	14	N/A
SnoechxA [10]	13	N/A	N/A
HaiderE [12]	11	4	N/A

N/A: not provided.
[a] Including 2 cases of bladder cancer and 1 case of laryngocarcinoma.

Patient perspective

The patient has no interest in sharing her cancer experience any further.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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Ethical approval

The ethics committee of the University of Hong Kong-Shenzhen Hospital approved this study.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Shengchun Xiong: Conceptualization, Validation, Writing: original draft preparation, Supervision.
Keiyui Tang: Writing: Review & Editing, Visualization.

Research registration

N/A.

Guarantor

Shengchun Xiong.

Declaration of competing interest

All authors declare that there is no conflict of interest in this work.

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