

Case report

In pursuit of the primary

A 65-year-old, female nonsmoker presented to the emergency room of a hospital in southern India with history of worsening breathlessness for 1 week. She had no known comorbidities and denied a past history of tuberculosis. She had no history of fever, night sweats or weight loss, and denied any other systemic complaints. General examination revealed a respiratory rate of 32 breaths per min, a pulse rate of 115 beats per min, oxygen saturation of 84% on room air by pulse oximetry, blood pressure of 100/70 mmHg and a temperature of 37.6°C. There was no pallor, jaundice, clubbing, lymphadenopathy or pedal oedema. Examination of the respiratory system revealed deviation of the trachea to the left side with decreased breath sounds and dullness to percussion over the right hemithorax. The rest of the systemic examination, including abdominal, gynaecological and breast examination, was unrevealing. Her chest radiograph was suggestive of a massive, right-sided pleural effusion with a shift of the mediastinum to the left (figure 1). Her baseline blood investigations were as follows.

- White blood cell (WBC) count: 18800 per mm³ (reference range 4000–11000 per mm³)
- Differential WBC count: neutrophils, 85%; lymphocytes, 6.5%
- Serum creatinine: 3.2 mg·dL⁻¹ (reference range 0.6–1.3 mg·dL⁻¹)
- Serum urea: 78 mg·dL⁻¹ (reference range 16.6–48 mg·dL⁻¹)
- Serum total protein: 7.5 g·dL⁻¹ (reference range 6–8.3 g·dL⁻¹)

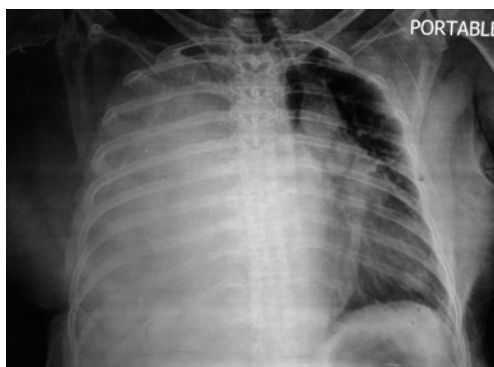


Figure 1 Portable chest radiograph showing a large, right-sided pleural effusion causing a shift of the mediastinum to the left side.

- Serum lactate dehydrogenase (LDH): 329 U·L⁻¹ (reference range 0–250 U·L⁻¹)

A diagnostic and therapeutic thoracentesis was performed. The pleural fluid analysis report was as follows.

- Protein: 5.6 g·dL⁻¹
- Glucose: 118 mg·dL⁻¹
- LDH: 1477 U·L⁻¹
- Total WBC count: 700 cells
- Differential WBC count: neutrophils, 48%; lymphocytes, 52%
- Adenosine deaminase (ADA): 14.7 U·L⁻¹
- Carcinoembryonic antigen (CEA): 1.10 ng·mL⁻¹

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Extraovarian primary peritoneal carcinoma (EOPPC) is a rare tumour of the peritoneum that shares many features with serous ovarian carcinoma because of a common embryological origin. We report a case of EOPPC presenting with a malignant pleural effusion. <https://bit.ly/3GMuKgL>



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Task 1

What are the Light criteria?

[Go to Answers >>](#)**Task 2**

How would you interpret these pleural fluid analysis reports?

[Go to Answers >>](#)**Task 3**

What are the main aetiologies of pleural effusion that you would consider for this patient?

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Microbiological analysis of the pleural fluid showed that both the Ziehl-Neelsen stain for acid-fast bacilli (AFB) and cartridge-based nucleic acid amplification test for *Mycobacterium tuberculosis* were negative. The AFB culture was ultimately found to be negative as well. The bacterial culture was sterile. Conventional cytological smears of the pleural fluid were positive for malignant cells, specifically adenocarcinoma (figure 2).

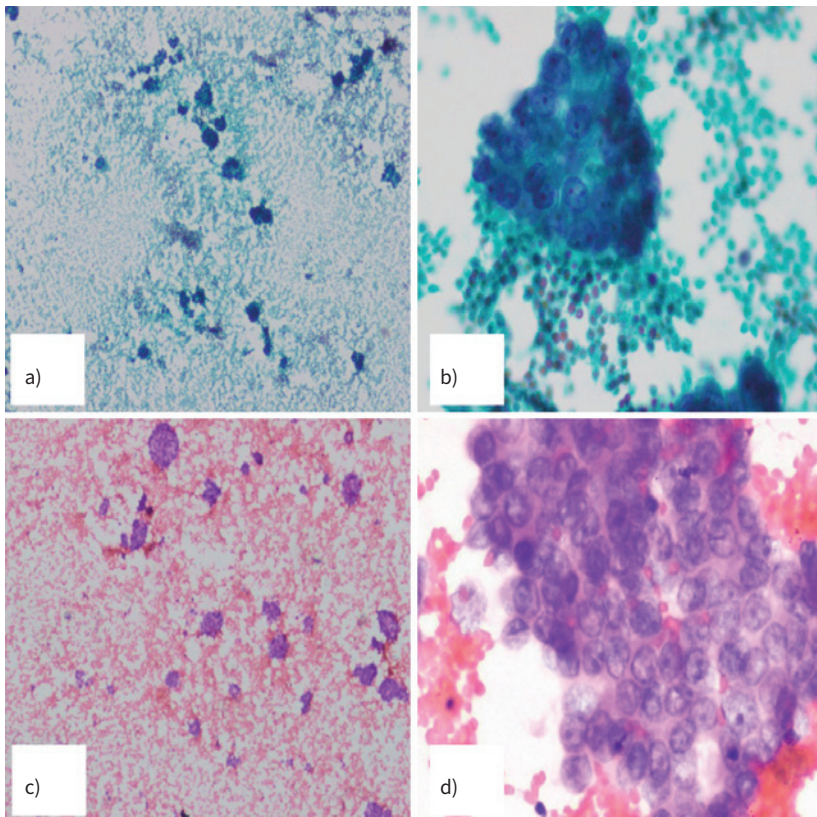


Figure 2 a) Cellular smear made up of three-dimensional clusters of atypical hyperchromatic cells (Papanicolaou stain, 4× magnification). b) Higher magnification revealed a papillary cell cluster with pleomorphic darkly stained nuclei (Papanicolaou stain, 20× magnification). c) Smear showing papillary clusters of neoplastic cells (May Grunwald-Giemsa stain, 10× magnification). d) Higher magnification revealed neoplastic cells with high nuclear/cytoplasmic ratio, irregular nuclear membrane and some of the nuclei with prominent nucleoli (May Grunwald-Giemsa stain, 40× magnification).

Task 4

What would the most appropriate next step of management be?

- a) Endoscopy of the upper and lower gastrointestinal tract
- b) Contrast computed tomography (CT) of the chest
- c) Contrast CT of the abdomen and pelvis
- d) Serum tumour marker measurement

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A noncontrast high-resolution CT of the thorax was performed instead due to the patient's worsening renal function, which showed only a minimal residual right hydrothorax without evidence of a lung/pleural-based mass lesion or thoracic lymphadenopathy. A tumour marker panel was subsequently performed and the cancer antigen (CA)-125 level was found to be elevated (2728 IU·mL⁻¹, reference range 0–35 IU·mL⁻¹). The serum CEA and α-fetoprotein levels were normal. An ultrasonogram of the abdomen and pelvis was normal, with no adnexal mass or ascites detected. A diagnosis of MPE with a clinically occult primary tumour was made.

Task 5

Which of the following condition(s) can lead to an elevated CA-125 level?

- a) Breast cancer
- b) Pelvic inflammatory disease
- c) Epithelial ovarian cancer
- d) Heart failure

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Due to rapid reaccumulation of the effusion, an intercostal chest tube drain was inserted and a cell block analysis was performed, which confirmed adenocarcinoma. The immunohistochemical analysis showed cytokeratin (CK)7, Wilms tumour 1 and paired box 8 positivity, and negative stains for CK20, thyroid transcription factor (TTF)-1 and napsin. The immunohistochemical profile favoured an epithelial ovarian carcinoma as the primary.

Task 6

What is a cell block?

[Go to Answers >>](#)**Task 7**

How does a pleural fluid cell block compare to a conventional cytological smear for the detection of malignant pleural effusion?

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The patient's acute kidney injury resolved with medical management, following which she underwent a contrast enhanced ^{18}F -fluorodeoxyglucose (FDG) whole-body positron emission tomography (PET)-CT. The scan revealed FDG-avid pelvic peritoneal thickening, and diffuse omental stranding and nodularity, along with increased uptake in the bilateral external iliac nodes, abdominal nodes (cardiophrenic, retrocrural and paracaval), mediastinal, right hilar and right supraclavicular nodes (figure 3). The uterus and bilateral adnexa did not demonstrate increased uptake and were reported to be normal.

Task 8

What differential diagnoses would you consider at this point?

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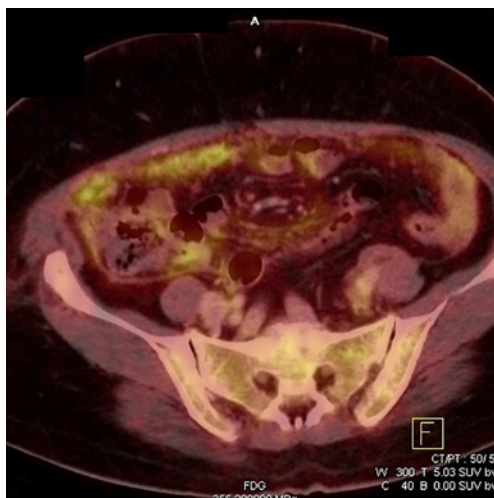


Figure 3 FDG PET-CT image showing increased uptake in the pelvic peritoneum and omentum.

With this diagnosis, the patient was given four cycles of neoadjuvant chemotherapy with paclitaxel and carboplatin, following which she underwent cytoreductive surgery. Intraoperatively, no ascites was detected. Deposits were noted on the diaphragm, small bowel mesentery and serosa, omentum, and over the surface of the left fallopian tube and uterine serosa. Histopathological examination of the resected pelvic peritoneum, greater omentum and small bowel mesentery showed tumour deposits consistent with a moderately differentiated serous adenocarcinoma (figure 4). The resected adnexa were reported to be free of the tumour on both sides. Post-operatively, the serum CA-125 levels had fallen to $18.6 \text{ IU}\cdot\text{mL}^{-1}$. The patient underwent successful pleurodesis with doxycycline prior to surgery and the chest tube was removed. She was diagnosed with metastatic extraovarian primary peritoneal carcinoma, and received two more cycles of adjuvant chemotherapy with paclitaxel and carboplatin. She is currently being followed up post-operatively.

The median survival following the detection of an MPE is 3–12 months, depending on the underlying malignancy, which in >80% of cases can be attributed to a lung, breast, gastrointestinal or genitourinary malignancy, or a lymphoma. ~11% of MPEs arise from an unknown primary tumour [8].

EOPPC is a rare tumour and an even rarer cause of MPE. Between 1995 to 2004, the tumour itself was reported to have an incidence of 6.78 per million in the USA and the worldwide incidence is unknown [9]. EOPPC commonly presents with gastrointestinal symptoms, abdominal distension and pain (secondary to malignant ascites), and respiratory complaints are uncommon at presentation [7]. Metastasis in EOPPC occurs mainly transperitoneally but may also occur by lymphatic and haematological routes; and metastases to cervical lymph nodes, the breast, the brain and the lungs have been reported in the literature [10–13].

To the best of our knowledge, there have been only four other case reports in the English-language literature documenting EOPPC presenting with a pleural effusion [14–17]. Two of these reported patients who presented with dyspnoea secondary to massive pleural effusions in the absence of ascites or with minimal ascites, which is unusual. In these cases, the localisation of the primary tumour was aided by the findings seen on contrast-enhanced

Discussion

MPE involves invasion of malignant cells into the pleural tissue and is diagnostic of advanced cancer.

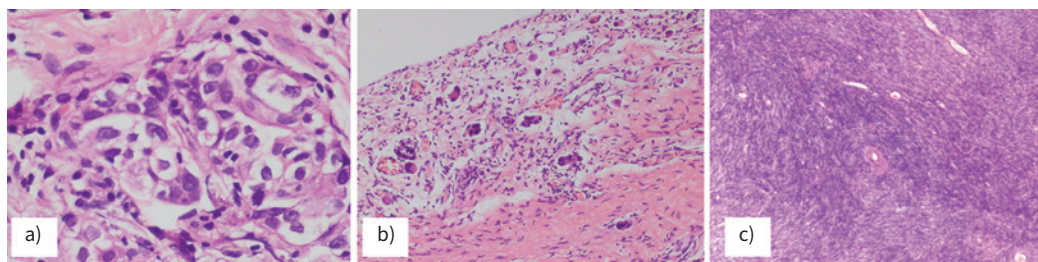


Figure 4 a) Section from small bowel mesentery showing tumour cells in an acinar pattern (May Grunwald-Giemsa stain, 40 \times magnification). b) Section from left paracolic gutter peritoneum showing tumour nodules in nests (May Grunwald-Giemsa stain, 40 \times magnification). c) Section from the left ovary showing normal ovarian stroma (May Grunwald-Giemsa stain, 10 \times magnification).

CT of the abdomen, and the diagnosis of EOPPC was established by a laparoscopic peritoneal biopsy and surgical pleural biopsy [14, 15]. DIETRICH *et al.* [16] also reported a case of EOPPC presenting with tension hydrothorax; however, their patient was found to have large ascites on further evaluation. Up to 81% of EOPPC cases are reported to have ascites at laparotomy; however, no ascites was detected in our patient pre-operatively on abdominal ultrasonogram or on PET-CT [7].

The National Institute for Health and Care Excellence has defined the entity “metastatic malignancy of undefined primary origin” as a “metastatic malignancy identified on the basis of a limited number of tests, without an obvious primary site, before comprehensive investigation” [18]. There is no universal consensus on the exact nature of these limited tests. The guidelines recommend standard histological examination of a biopsy specimen and basic immunohistochemistry (to establish if the malignancy is epithelial or nonepithelial in origin) in the initial line of investigations. In patients such as ours, who present with metastatic pleural involvement, the pleural fluid cell block can be used to perform this basic immunohistochemistry, as the sample can be obtained through a simple, inexpensive and less invasive procedure. Although the diagnostic yield

of a thoracoscopic pleural biopsy has been reported to be superior to that of the pleural fluid cell block (94.2% *versus* 71.4%), the cell block can serve as an ideal initial sample and as a useful adjunct in diagnosis [19]. In carcinoma of unknown primary syndromes, POMJANSKI *et al.* [20] reported correct identification of 85.5% of primary tumour sites by using a panel of six immunocytochemical markers (CK5/6, CK7, CK20, CA-125, TTF-1 and caudal-type homeobox 2) to evaluate metastatic effusions.

Conclusion

This case report highlights the rare occurrence of an EOPPC presenting as a massive pleural effusion in the absence of ascites. The diagnosis of a rare tumour like EOPPC can be challenging, since occult peritoneal disease can be difficult to detect on standard CT imaging. Furthermore, when the tumour presents solely with features of distant metastases, histopathological examination (including immunohistochemistry) becomes indispensable in identifying the source of the metastatic disease. Pleural fluid cell blocks can provide an inexpensive and less invasive method of obtaining a specimen for histopathological evaluation.

Key points

- EOPPC, a rare tumour can present with peritoneal deposits and MPE.
- CA-125 is an invaluable tumour marker and when elevated (even with normal ovaries on imaging) may indicate suspicion of EOPPC.
- Cell block of pleural fluid samples is an underutilised modality which when used judiciously can help in locating a clinically occult primary.

Answers

Answer 1

The Light criteria are used to distinguish between exudative and transudative pleural effusions [1]. An effusion is considered to be an exudate if at least one of the following criteria are met.

- Ratio of pleural fluid protein/serum protein >0.5
- Ratio of pleural fluid LDH/serum LDH >0.6
- Pleural fluid LDH greater than two-thirds of the upper limit of the reference range of the serum LDH

A transudative effusion must not fulfil any of these criteria.

[<< Go to Task 1](#)

Answer 2

This effusion is a lymphocyte-predominant exudate. It meets all three of the Light criteria for exudative effusions.

[<< Go to Task 2](#)

Answer 3

The main differential diagnoses to consider with a lymphocytic exudate would be tuberculous pleurisy (especially in countries like India that have a high tuberculosis burden), a malignant pleural effusion (MPE) and a parapneumonic effusion. ADA is a surrogate marker for tuberculosis and traditionally, a level $>40 \text{ U}\cdot\text{L}^{-1}$ is suggestive of tuberculous pleurisy [2]. However, ADA may also be elevated in empyema, rheumatoid pleural effusions and MPEs [1]. Falsely low levels may be seen in elderly or critically ill patients [3]. The low ADA level in this case makes tuberculous pleurisy unlikely. Although the pleural fluid CEA level is not elevated, this does not rule out a MPE since pleural fluid tumour marker levels have low sensitivity [1].

<< [Go to Task 3](#)

Answer 4

The next step would be to identify the primary malignancy by means of contrast-enhanced CT of the chest and/or abdomen and pelvis.

Endoscopies for gastrointestinal malignancies may be warranted in the presence of suggestive signs/symptoms, which were absent in this case.

<< [Go to Task 4](#)

Answer 5

All of these conditions can lead to elevated serum CA-125 levels.

Although most commonly associated with epithelial malignancy of the ovary, the causes of raised levels are diverse. CA-125 is a nonspecific marker and may also be elevated in other carcinomas of Mullerian origin (fallopian tube and peritoneal carcinomas), as well as in nongynaecological malignancies (breast cancer, lung cancer, pancreatic cancer, *etc.*) and benign conditions (endometriosis, pelvic inflammatory disease, benign ovarian neoplasms, ascites, heart failure, *etc.*) [4, 5].

<< [Go to Task 5](#)

Answer 6

A cell block is a sediment of tissue fragments obtained from a cytological specimen that can be processed, sectioned and stained like a histopathological specimen. Cell blocks can be prepared from various cytological specimens (fine-needle aspirates, effusion fluid, bronchial lavages, *etc.*) and by different methods. Commonly, a sediment of cells is extracted from the fluid sample either by centrifugation or by concentration along a membrane. A fixative is then added to bind together the cells and the resultant cell button is embedded in paraffin to form a cell block.

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Answer 7

When added to conventional cytology, pleural fluid cell block analysis has been shown to increase the diagnostic yield of pleural fluid samples for MPE. Some studies have also shown cell block by itself to be superior to conventional cytology for the diagnosis of MPE. The cell block has several advantages over conventional cytological smears, including higher cellularity, better preservation of cellular morphology and tissue architecture, and the ability to perform immunohistochemical staining/molecular analysis [1, 6].

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Answer 8

The lack of uptake in the adnexa suggests that extraovarian primary peritoneal carcinoma (EOPPC) would have to be considered along with an epithelial ovarian carcinoma (EOC) in the differential diagnosis. EOPPC can be differentiated from EOC using the diagnostic criteria put forth by the Gynaecologic Oncology Group [7]. A diagnosis of EOPPC requires histopathological examination of the ovaries and peritoneum.

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Conflict of interest

None declared.

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