Am J Transl Res 2026;18(2):1584-1588
www.ajtr.org /ISSN:1943-8141/AJTR0166829

Case Report

Diagnosis of malignant pleural effusion using thoracoscopy combined with confocal endomicroscopy: a case report

Shenglan Ye[1*], Yu Feng[2*], Shan Zhu[1], Mingli Yuan[1], Cheng Song[1], Zhen Yang[1], Yi Hu[1], Jixiang Ni[1]

[1]Department of Respiratory and Critical Care Medicine, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, No. 26 Shengli Street, Jianghan District, Wuhan 430014, Hubei, China; [2]Department of Biomedical Engineering, Tsinghua University, Beijing 100084, China. [*]Equal contributors.

Received June 16, 2025; Accepted December 26, 2025; Epub February 15, 2026; Published February 28, 2026

Abstract: Thoracoscopy is widely used for the diagnosis and management of pleural diseases. This technique is valuable because it enables direct visualization of the pleural cavity surface and pathologic biopsy sampling of lesions. However, it is limited in detecting early-stage pleural lesions, carrying a considerable risk of misdiagnosis or missed diagnosis, which may delay treatment and ultimately compromise patient poutcome. Confocal laser endomicroscopy (CLE) is an emerging *in vivo* microscopy technique that can be integrated with traditional thoracoscopy platforms, providing real-time *in vivo* observation of pleural cellular and histologic features. This technology helps identify early microscopic lesions and guide thoracoscopic pleural biopsies, thereby reducing the risk of misdiagnosis and missed dignosis associated with conventional thoracoscopic biopsies. In this case report, we present a patient with unexplained pleural effusion and elevated tumor markers, for whom conventional thoracoscopy revealed no significant pleural abnormalities. Subsequently, under thoracoscopic guidance, we performed a CLE-based microscopic scan of the pleura, which revealed clusters of darkly pigmented cells with significant atypia. Targeted biopsy of this area under thoracoscopy confirmed a final pathologic diagnosis of right upper lung adenocarcinoma.

Keywords: Confocal laser endomicroscopy, thoracoscopy, pleural effusion, lung adenocarcinoma

Case report

A 77-year-old female patient had a history of pleural effusion and was admitted to our department 1 month prior with a diagnosis of "pulmonary infection". At that time, chest computed tomography (CT) revealed a moderate right pleural effusion. She underwent thoracoscopic pleural examination and biopsy: intraoperative findings showed extensive adhesions in the pleural cavity, and several pleural tissue samples were randomly collected. Pathologic results indicated granulomatous inflammation, and she was discharged after anti-inflammatory and anti-infective treatment.

She presented to our hospital again due to recurrent pleural effusion. A repeat chest CT scan (August 31, 2024) showed: 1. A new mass lesion in the right upper lobe, suggesting enhanced CT for further evaluation; 2. Bilateral interstitial pneumonia with localized bronchiectasis, which was more progressive compared to the previous scan; 3. Calcification in the left lower lobe and scattered bullae in both lungs; 4. Irregular thickening of the bilateral pleura; 5. New small right pleural effusion.

On admission, the patient reported a 1-month history of cough with white sputum (more severe in the morning), accompanied by right precordial pain aggravated by coughing and respiration. She denied fever, nausea, vomiting, abdominal pain, diarrhea, headache, blurred vision, or limb movement disorders. Serum tumor marker assays performed on August 30, 2024 revealed elevated levels of neuron-specific enolase (24.880 ng/ml) and carcinoembryonic antigen (3.19 ng/ml), both exceeding the respective reference ranges.

https://doi.org/10.62347/GVPD2984

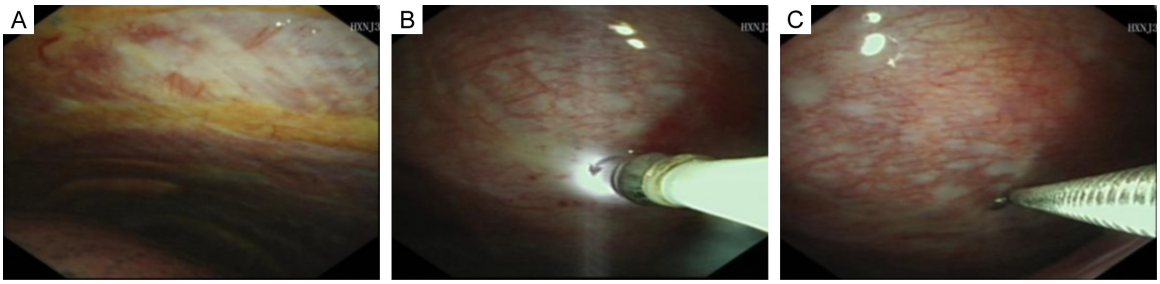

Figure 1. Direct visualization of pleural surface under thoracoscopy, CLE examination, and targeted biopsy. A. Direct visualization of the pleural cavity under thoracoscopy (no obvious lesions found). B. CLE scanning of the pleura under thoracoscopy guidance. C. Pleural biopsy of the abnormal areas identified by CLE under thoracoscopy.

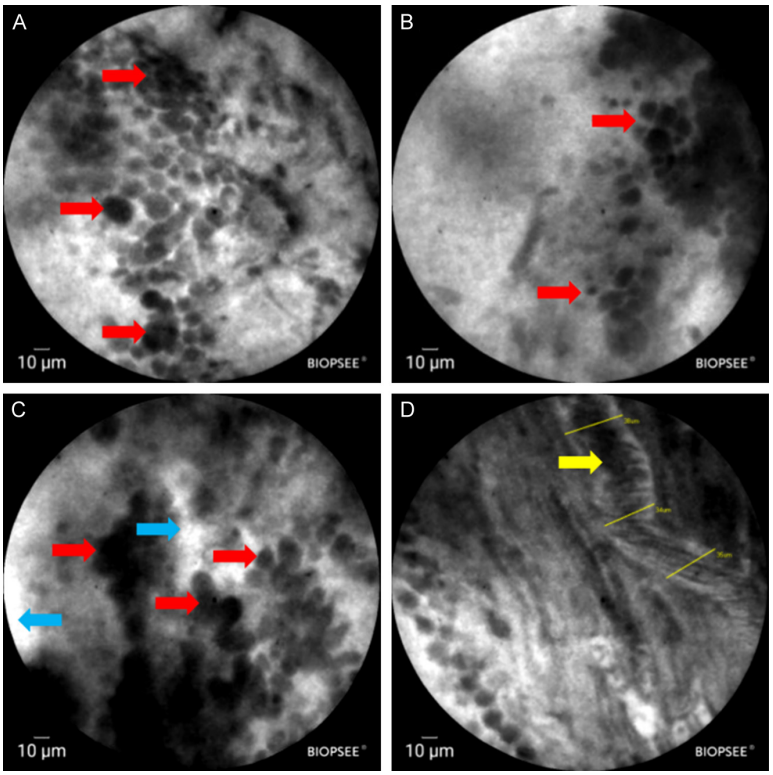

Figure 2. pCLE images of abnormal pleural lesions in the patient's pleural cavity. A. Numerous deeply black abnormal cells are densely clustered on the pleura, with significant cellular atypia (red arrow). B. Deeply black cells are clustered in a mass-like distribution, with significant cellular atypia (red arrow). C. Deeply black cells are clustered with significant atypia (red arrow), and fluorescein sodium leakage is noted in the background (blue arrow). D. Abnormally thickened and tortuous blood vessels are observed on the pleural surface (yellow arrow). Bar = 10 μm.

On September 2, 2024, the patient underwent video-assisted thoracoscopic surgery (VATS) with pleural biopsy. Given the patient's history of recurrent pleural effusion (following previous thoracoscopic random biopsy with a diagnosis of granulomatous inflammation) and newly elevated tumor markers combined with a new lung mass on CT, the underlying etiology remained unclear. Conventional thoracoscopic random biopsy had failed to clarify the diagnosis during the prior admission, and there was a high risk of missed or misdiagnosis for early or subtle lesions. To address this diagnostic dilemma, we integrated probe-based confocal laser endomicroscopy (pCLE) into the thoracoscopic procedure. Intraoperative thoracoscopic findings included pleural congestion with minor hemorrhage, mild adhesions, and a large volume of yellowish pleural effusion, without other significant abnormalities. A pCLE device (BIOPSEE® Viestar Medical Technology Co., Ltd., Suzhou, China) was introduced into the pleural cavity through the thoracoscopic port, and confocal imaging was performed through direct contact with the pleura, followed by thoracoscopic biopsy of suspicious areas (**Figure 1**). During pCLE examination at the margin of a slightly whitish pleural region, clusters of darkly pigmented atypical cells were identified, suggestive of pathologic changes (**Figure 2**). Rapid On-Site Evaluation (ROSE) of the thoracoscopic biopsy specimens revealed numerous deeply stained, pleomorphic nuclei, and based on these morphologic features, a high suspicion for pulmonary adenocarcinoma was raised (**Figure 3**).

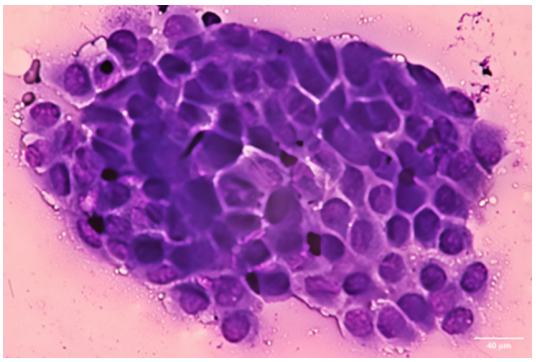

Figure 3. Rapid On-Site Evaluation (ROSE) view of thoracoscopic tissue biopsy. ROSE shows a large number of deeply stained heterogeneous nuclei. Bar = 40 μm.

Routine cytologic examination of the pleural fluid, conducted on September 2, 2024, confirmed the presence of malignant cells. Histologic analysis of the biopsy specimens on September 4, 2024 identified a malignant epithelial neoplasm, and the diagnosis of adenocarcinoma of the right upper lobe was established based on immunohistochemical findings (**Figure 4**).

Discussion

During thoracoscopy, patients with advanced pleural tumors typically present with marked pleural thickening, pleural effusion, pleural nodules and masses, as well as pleural congestion, edema, and adhesions [1-3]. In contrast, early-stage pleural tumors observed by thoracoscopy are mainly characterized by focal or diffuse pleural proliferation and thickening, accompanied by the formation of a few pleural surface nodules [4, 5]. For even earlier pleural tumor lesions, direct visualization using thoracoscopy may be inadequate for detection, since these lesions lack distinctiveness [6]. Although modern thoracoscopy enables comprehensive examination of the entire thoracic cavity [7, 8], identifying subtle lesional changes and accurately localizing biopsy sites remains challenging due to the inconspicuous nature of early lesions. This renders the diagnosis of early-stage pleural tumors rather challenging [9, 10].

In clinical practice, the diagnosis of pleural effusion-related diseases often relies on thoracoscopic random biopsy, which has inherent limitations. For patients with early or atypical lesions (such as the current case), random sampling may fail to obtain positive tissue, leading to misdiagnosis or delayed diagnosis. Many patients are confirmed to have malignant pleural effusion only when their condition deteriorates or metastases become evident, resulting in reduced efficacy of subsequent antitumor treatment. This case highlights the inadequacy of conventional thoracoscopic biopsy: the patient's first thoracoscopic random biopsy yielded granulomatous inflammation, but recurrent pleural effusion and new imaging findings indicated an underlying malignant process that was missed. This reflects a problem in clinical practice whereby conventional methods are insufficient to capture early microscopic lesions, leading to diagnostic delays.

Probe-based confocal laser endomicroscopy (pCLE) facilitates real-time *in vivo* histologic and cytologic visualization and enables targeted biopsy guidance, thus it is used for the diagnosis and management of digestive and respiratory disorders. Such conditions encompass Barrett's esophagus, esophageal adenocarcinoma, gastric cancer, lung cancer, *Helicobacter pylori* (HP) infection, ulcerative colitis, intraepithelial neoplasia, colorectal cancer, and chronic liver diseases, among others. pCLE is far superior for differentiating benign from malignant lesions, since it is not constrained by factors such as *ex vivo* specimen staining, thereby substantially enhancing the accuracy of differential diagnosis for benign and malignant lesions [11, 12]. Research has demonstrated that pCLE can function as a biopsy guidance technique to distinguish benign from malignant pleural lesions and effectively differentiate tumor deposits from pleural fibrosis in malignant pleural mesothelioma [13, 14]. This suggests that pCLE is an effective biopsy guidance tool, capable of guiding precise biopsy by identifying *in vivo* malignant cell regions and reducing the need for numerous repeated biopsy procedures [15].

The notable feature of the case reported herein is that, under conventional thoracoscopy, the pleura exhibited non-specific manifestations including congestion, adhesions, and pleural effusion, with no obvious signs of pleural thickening or nodular changes that are characteristic of malignant pleural disease. When pCLE was employed to scan the pleura at these non-specific congested and adherent sites, numer-

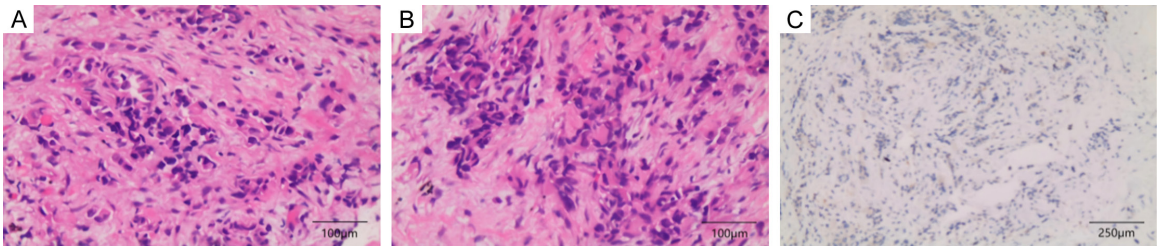

Figure 4. Pathologic images of pleural biopsies from CLE-identified abnormal sites. A and B. Cancer cells form glandular formations showing irregular size and shape, disordered arrangement, increased cell layers, and loss of polarity; nuclei are large, deeply stained, and round/oval/irregular in shape, with evident mitotic figures. C. Immunohistochemical findings: CK7, TTF-1, Napsin A (+); P40, CD56 (-); D2-40, CK5/6, calretinin (mesothelial +); Ki-67 index is approximately 15%. A: Bar = 100 μm; B, C: Bar = 250 μm.

ous dark black, highly atypical cells with a clustered distribution were detected at the edge of a slightly whitish pleural area (as observed under thoracoscopy), consistent with tumor. Subsequent to this exploration, under pCLE guidance, biopsy forceps were used to collect tissue samples from the abnormal areas for pathologic examination. The histopathologic results of the biopsy confirmed a malignant epithelial tumor, and in conjunction with immunohistochemical findings, the diagnosis was determined to be lung adenocarcinoma-consistent with the preliminary diagnosis based on pCLE observations. By providing real-time, high-quality cytologic microscopic images of tissues and enabling the identification of abnormal atypical cells, pCLE facilitated precise biopsy procedures during thoracoscopy, thereby enhancing the success rate and accuracy of tissue sampling in biopsies.

This case has several limitations worth noting. First, the interval between the patient's two admissions was 1 month, and cancer progression may have contributed to the detectability of tumor lesions by pCLE. Notably, even at the time of the second admission, no obvious macroscopic abnormalities (e.g., nodules, thickening) were observed on conventional thoracoscopy, indicating that random biopsy would still have had a high risk of missed diagnosis. Second, this is a single case report, and the clinical value of pCLE in guiding targeted biopsy for early pleural effusion requires validation in larger sample sizes. Future studies should focus on applying pCLE to patients with primary or early-stage pleural effusion to explore its microscopic features and optimize its role in clinical guidance for targeted biopsy.

In summary, pCLE can accurately identify early tiny lesions that are difficult to detect by thoracoscopy and guide precise pleural biopsies during thoracoscopy through the thoracoscope's working channel. This technology offers robust technical support for the early diagnosis of pleural diseases, aiding in improving the detection rate of malignant lesions, accurately assessing lesion severity, optimizing treatment plan selection, and enhancing prognosis. However, the widespread applicability of this technology remains to be validated through large-scale sample studies. We are confident that the integration of pCLE with medical thoracoscopy will prove useful for early diagnosis of pleural diseases.

Disclosure of conflict of interest

None.

Address correspondence to: Yi Hu and Jixiang Ni, Department of Respiratory and Critical Care Medicine, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, No. 26 Shengli Street, Jianghan District, Wuhan 430014, Hubei, China. E-mail: huyi@zxhospital.com (YH); Neejx77@163.com (JXN)

References

[1] Kho SS, Chan SK, Yong MC and Tie ST. Diagnostic yield of medical thoracoscopy in exudative pleural effusions in a region with high tuberculosis burden. Med J Malaysia 2020; 75: 254-259.

[2] Wang Z, Xu LL, Wu YB, Wang XJ, Yang Y, Zhang J, Tong ZH and Shi HZ. Diagnostic value and safety of medical thoracoscopy in tuberculous pleural effusion. Respir Med 2015; 109: 1188-1192.

[3] Aujayeb A and Astoul P. Use of medical thoracoscopy in managing pleural malignancy. Breathe (Sheffield) 2024; 20: 230174.
[4] Wang F, Wang Z, Tong Z, Xu L, Wang X and Wu Y. A pilot study of autofluorescence in the diagnosis of pleural disease. Chest 2015; 147: 1395-1400.
[5] Liu XT, Dong XL, Zhang Y, Fang P, Shi HY and Ming ZJ. Diagnostic value and safety of medical thoracoscopy for pleural effusion of different causes. World J Clin Cases 2022; 10: 3088-3100.
[6] Yu YX, Yang Y, Wu YB, Wang XJ, Xu LL, Wang Z, Wang F, Tong ZH and Shi HZ. An update of the long-term outcome of patients with nonspecific pleurisy at medical thoracoscopy. BMC Pulm Med 2021; 21: 226.
[7] So M, Chaddha U, Shojaee S and Lee P. Medical thoracoscopy for pleural diseases. Curr Opin Pulm Med 2024; 30: 84-91.
[8] Fantin A, Castaldo N, Palou MS, Viterale G, Crisafulli E, Sartori G, Patrucco F, Vailati P, Morana G, Mei F, Zuccatosta L and Patruno V. Beyond diagnosis: a narrative review of the evolving therapeutic role of medical thoracoscopy in the management of pleural diseases. J Thorac Dis 2024; 16: 2177-2195.
[9] Davies HE, Nicholson JE, Rahman NM, Wilkinson EM, Davies RJ and Lee YC. Outcome of patients with nonspecific pleuritis/fibrosis on thoracoscopic pleural biopsies. Eur J Cardiothorac Surg 2010; 38: 472-477.
[10] Mouchantaf FG and Villanueva AG. The long-term prognosis of patients with the diagnosis of nonmalignant pleural effusions after pleuroscopy. J Bronchology Interv Pulmonol 2009; 16: 25-27.
[11] Wallace MB and Fockens P. Probe-based confocal laser endomicroscopy. Gastroenterology 2009; 136: 1509-1513.
[12] Kramer T, Wijmans L, de Bruin M, van Leeuwen T, Radonic T, Bonta P and Annema JT. Bronchoscopic needle-based confocal laser endomicroscopy (nCLE) as a real-time detection tool for peripheral lung cancer. Thorax 2022; 77: 370-377.
[13] Bonhomme O, Heinen V, Louis R, Corhay JL and Duysinx B. Probe based confocal laser endomicroscopy in thoracic endoscopy. Rev Mal Respir 2024; 41: 145-155.
[14] Bonhomme O, Heinen V, Detrembleur N, Corhay JL, Louis R and Duysinx B. Probe-based confocal laser endomicroscopy for pleural malignancies diagnosis. Respirology 2021; 26: 188-195.
[15] Tian S, Huang H, Zhang Y, Shi H, Dong Y, Zhang W and Bai C. The role of confocal laser endomicroscopy in pulmonary medicine. Eur Respir Rev 2023; 32: 220185.