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【 CASE REPORT 】

# Diffuse Pulmonary Meningotheliomatosis Presenting with the Cheerios Sign Diagnosed by a Transbronchial Lung Cryobiopsy: A Case Report

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**Abstract:**

The "Cheerios sign" is a ring-shaped pulmonary nodule with central lucency, as observed on chest computed tomography. A 48-year-old woman with Turner syndrome presented with diffuse pulmonary nodules exhibiting the Cheerios sign. Although transbronchial lung biopsy is non-diagnostic, transbronchial lung cryobiopsy (TBLC) revealed nodules composed of meningothelial-like cells that were positive for epithelial membrane antigen, progesterone receptor, and CD56, thus leading to a diagnosis of diffuse pulmonary meningotheliomatosis. Estrogen and progesterone hormone therapy were discontinued, and the disease remained stable without treatment. This case highlights the diagnostic utility of TBLC for the evaluation of small pulmonary nodules that exhibit the Cheerios sign.

**Key words:** Cheerios sign, Diffuse pulmonary meningotheliomatosis, Multiple minute meningothelial-like nodule, Transbronchial lung cryobiopsy

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## Introduction

The "Cheerios sign" is a radiological term referring to a ring-shaped pulmonary nodule with central lucency observed on chest computed tomography (CT) (1). This distinctive finding has been observed in various pulmonary diseases, including pulmonary Langerhans cell histiocytosis, granulomatosis with polyangiitis, metastatic lung tumors, and diffuse pulmonary meningotheliomatosis (DPM). DPM is a rare benign disease characterized by multiple minute meningothelial-like nodules (MPMNs) that are histologically similar to meningiomas and are diffusely distributed throughout the lungs (2).

Although most previously reported patients with DPM were diagnosed using surgical lung biopsy (SLB), several recent reports have obtained successful diagnoses using bronchoscopic procedures (3). Given that DPM is a benign condition, a bronchoscopic diagnosis is preferable when feasible, owing to its lower invasiveness compared to SLB. However, the diagnostic yield of transbronchial lung biopsy (TBLB) for DPM is only approximately half, and in all previously reported patients for whom TBLB failed to provide a definitive diagnosis, subsequent SLB was required. In contrast, transbronchial lung cryobiopsy (TBLC) enables the collection of larger and less crushed specimens than TBLB while being less invasive than SLB. Therefore, for patients with suspected DPM, TBLC may be a less invasive alternative to SLB, even when TBLB is nondiagnostic.

We herein report a rare case of DPM presenting with multiple small pulmonary nodules exhibiting the Cheerios sign, in which TBLC successfully achieved a definitive diag-

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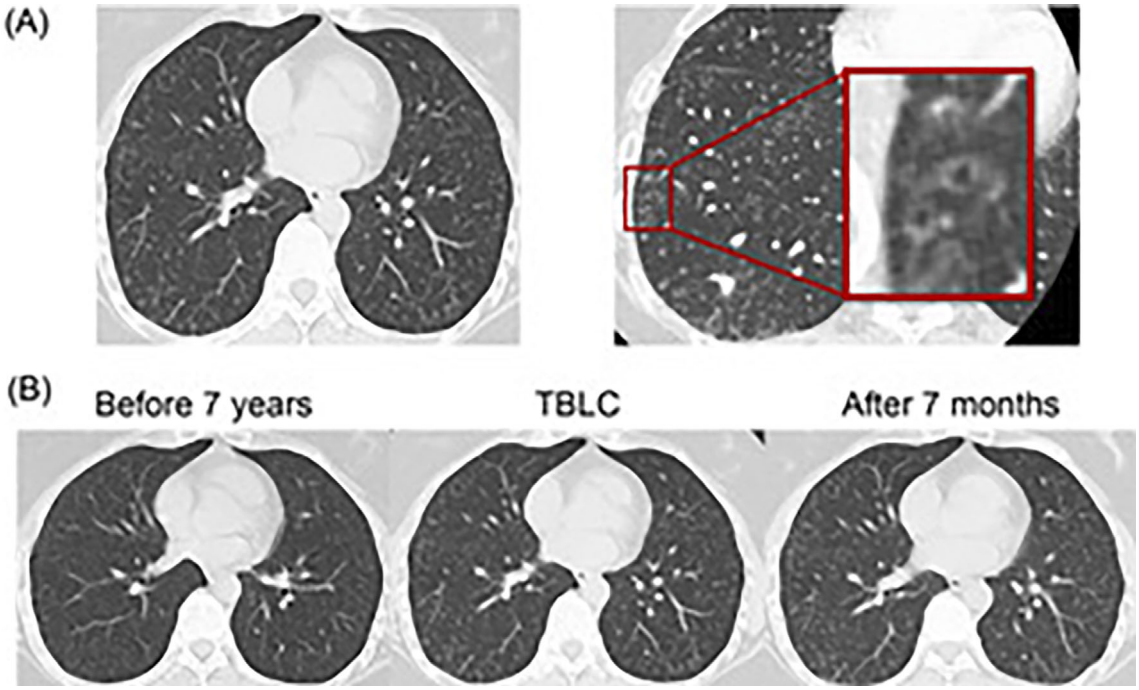


**Figure 1. Computed tomography (CT) of the chest showing diffuse pulmonary meningotheliomatosis. (A) CT of the chest at transbronchial lung cryobiopsy (TBLC) showing diffuse centrilobular granular opacities and nodular shadows in both lungs. Some nodules had central lucency with a surrounding thin wall, consistent with the "Cheerios sign". (B) Serial CT images demonstrating progression of the bilateral pulmonary nodular lesions compared to seven years earlier. No further disease progression was observed over a follow-up period of seven months without treatment.**

nosis after TBLB failed. To our knowledge, this is the first report to demonstrate the utility of TBLC for diagnosing DPM when TBLB is inconclusive. Based on our findings, we propose that TBLC should be considered the initial diagnostic approach for patients who present with the Cheerios sign and suspected DPM, as it may help to avoid both SLB and repeated bronchoscopic procedures.

## Case Report

A 48-year-old non-smoking woman presented with an abnormal shadow on chest radiography during routine health screening. The patient had a history of Turner syndrome and had been receiving hormone supplementation with estrogen and progesterone since childhood. Although the patient had few symptoms, she visited a local hospital because of the results of the routine health screening. Chest CT revealed diffuse centrilobular granular opacities and nodular shadows in both lungs, with some nodular shadows accompanied by central cavities (Fig. 1). Bronchoscopy revealed a mildly elevated lymphocyte fraction of 21 % in the bronchoalveolar lavage fluid (BALF). Although the TBLB sample included alveolar areas, the target lesion could not be captured; therefore, a definitive diagnosis could not be established. The patient was subsequently referred to our hospital for further examination, as chest CT demonstrated progression of the bilateral pulmonary nodular shadows that had been noted seven years earlier.

On arrival at the hospital, her vital signs were within the normal limits: respiratory rate, 16/min; blood pressure, 111/86 mmHg; heart rate, 89 beats/min; body temperature, 36.0 °C; and oxygen saturation, 98 % on ambient air. The auscultation findings were unremarkable. Laboratory tests, including those for angiotensin-converting enzyme, *Trichosporon asahii* antibody, bird-specific IgG antibody, β-D-glucan, *Cryptococcus* antigen, T-SPOT test, and tumor markers, showed no significant abnormalities (Table 1). Based on the characteristic CT findings of nodules with central cavitation, known as the Cheerios sign, differential diagnoses including pulmonary Langerhans cell histiocytosis, DPM, granulomatosis with polyangiitis, metastatic lung tumors, and infectious diseases, such as fungal or mycobacterial infections, were considered. Thus, a second bronchoscopy was performed.

Bronchoalveolar lavage was performed to exclude any infectious causes, and the cultures for bacteria, mycobacteria, and fungi in the BALF were all negative. Subsequently, TBLC was performed using a 1.9 mm cryoprobe with a 6-second freezing time and the blood-blocking balloon technique. One sample was obtained from each of the right $B^{8b}$ and $B^{9}$ segments where the Cheerios sign was clearly observed. Histopathological examinations of both specimens revealed multiple small nodules measuring approximately 2 mm in diameter in the interstitium (Fig. 2). The nodules consisted of low-grade, round to short spindle-shaped cells resembling meningeal epithelial cells, with uniform round

**Table 1. Laboratory Findings at Admission.**

| | | | |
|---|---|---|---|
| Hematology | | Serology | |
| WBC | 5,310 /μL | CRP | 0.08 mg/dL |
| Neu | 68.1 % | IgG | 1,123 mg/dL |
| Lym | 25.6 % | IgG4 | 21.8 mg/dL |
| Eo | 0.6 % | IgA | 251 mg/dL |
| Hb | 14.8 g/dL | IgM | 39 mg/dL |
| PLT | $24.5\times10^4$ /μL | IgE | <20.0 IU/mL |
| | | ACE | 11.1 U/L |
| Chemistry | | ANA | <×40 |
| TP | 7.4 g/dL | RF | <5.0 IU/mL |
| Alb | 4.2 g/dL | Anti-CCP Ab | <1.3 U/mL |
| BUN | 12.4 mg/dL | Anti-SS-A Ab | <1.0 U/mL |
| Cre | 0.61 mg/dL | Anti-Scl-70 Ab | <1.0 U/mL |
| Na | 139 mEq/L | Anti-ARS Ab | <5.0 |
| K | 3.8 mEq/L | PR3-ANCA | <1.0 U/mL |
| Cl | 108 mEq/L | MPO-ANCA | <1.0 U/mL |
| AST | 27 U/L | *Trichosporon asahii* Ab | (−) |
| ALT | 38 U/L | bird-specific IgG Ab | (−) |
| T-Bil | 0.8 mg/dL | β-D-gulcan | <6.00 pg/mL |
| LDH | 174 U/L | *Cryptococcus*Ag | (−) |
| ALP | 82 U/L | T-SPOT | (−) |
| γ-GTP | 102 U/L | CEA | 1.1 ng/mL |
| CK | 58 U/L | CA19-9 | 6.2 U/mL |
| HbA1c | 5.2 % | sIL-2R | 260 U/mL |
| KL-6 | 128 U/mL | | |

Ab: antibody, Ag: antigen, ACE: angiotensin-converting enzyme, Alb: albumin, ALP: alkaline phosphatase, ALT: alanine aminotransferase, ANA: antinuclear antibody, ARS: aminoacyl-tRNA synthetase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, Ca: calcium, CA19-9: carbohydrate antigen 19-9, CCP: cyclic citrullinated peptide, CEA: carcinoembryonic antigen, CK: creatine kinase, Cl: chloride, Cre: creatinine, CRP: c-reactive protein, Eo: eosinophils, γ-GTP: gamma-Glutamyl transpeptidase, Hb: hemoglobin, Ig: immunoglobulin, KL-6: Krebs von den Lungen-6, LDH: lactate dehydrogenase, Lym: lymphocytes, Neu: neutrophils, PLT: platelet count, RF: rheumatoid factor, Scl-70: Scleroderma 70, sIL-2R: soluble interleukin-2 receptor, SS-A: Sjögren's Syndrome A, T-Bil: total bilirubin, TP: total protein, WBC: white blood cells

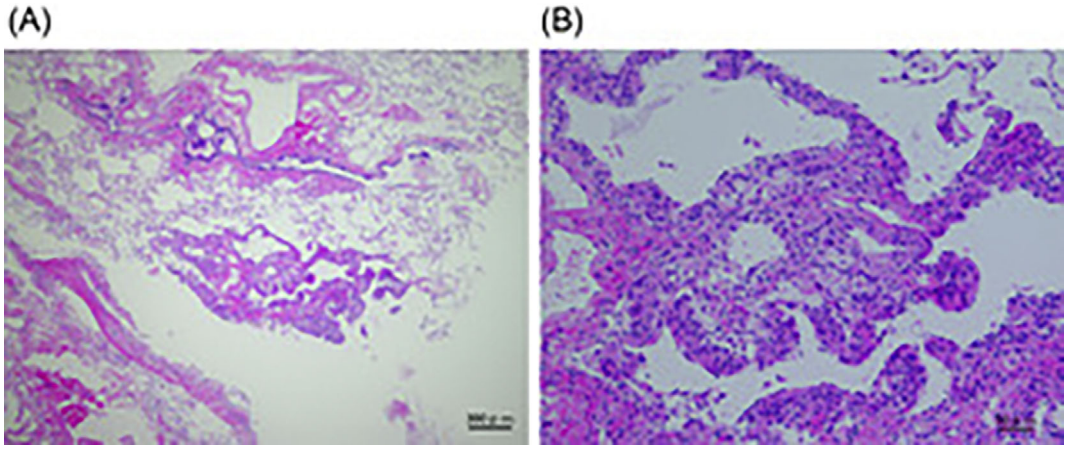


**Figure 2. Histopathological findings of transbronchial lung cryobiopsy samples from the right lower lobe. (A) Hematoxylin and eosin staining showing multiple small nodules, measuring approximately 2 mm in diameter, in the interstitium. (B) The nodules consist of low-grade, round to short spindle-shaped cells resembling meningeal epithelial cells, with uniform round nuclei and eosinophilic cytoplasm. No cellular atypia, necrosis, or significant inflammation is observed.**

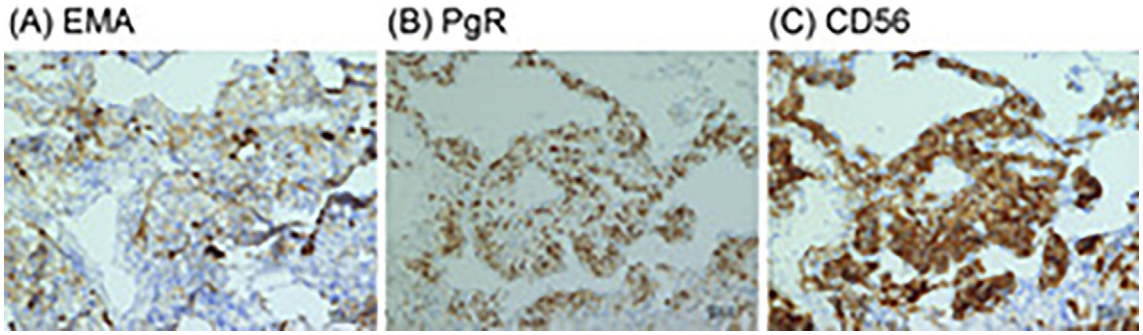


**Figure 3. Immunohistochemical findings of the nodular lesions. The cells are positive for epithelial membrane antigen (EMA) (A), progesterone receptor (PgR) (B), and CD56 (C).**

nuclei and eosinophilic cytoplasm. No cellular atypia, necrosis, or significant inflammation was observed. Immunohistochemically, these cells were positive for the epithelial membrane antigen (EMA), progesterone receptor (PgR), and CD 56 (Fig. 3). The histological and immunohistochemical findings were characteristic of MPMN. There were no complications associated with TBLC such as significant bleeding, infection, or pneumothorax. Magnetic resonance imaging of the brain revealed no evidence of meningioma, and the patient was diagnosed with DPM based on the radiological and histopathological findings.

At the time of the DPM diagnosis, the patient was diagnosed with a uterine polyp. Given the potential hormonal influence on both the DPM and uterine polyps, estrogen and progesterone supplementation was discontinued, with the expectation that hormone withdrawal might halt disease progression. This decision was also supported by the general recommendation that hormone replacement therapy be continued until the typical menopausal age. After discontinuation, the patient remained asymptomatic, with no significant issues related to Turner syndrome. Furthermore, the patient's pulmonary function did not decline, and both the clinical and radiological findings remained stable during the seven-month follow-up period without treatment.

## Discussion

DPM is a rare, benign disease, characterized by diffuse, multifocal MPMNs that are morphologically and histopathologically similar to meningiomas (4, 5). The nodules are typically subpleural or located within the pulmonary interstitium, and they are often distributed along the alveolar septa. Histologically, spindle-shaped or epithelioid cells resembling meningioma cells proliferate in nests or vortex shapes around small veins and have indistinct nucleoli and eosinophilic cytoplasm. Immunohistochemically, tumor cells are commonly positive for EMA and PgR and negative for neuroendocrine markers (6).

The radiological presentation of DPM is variable; however, the presence of ring-shaped nodules with central lucency, known as the Cheerios sign, is a distinctive feature (1). The Cheerios sign is observed on CT images and it is characterized by a central lucency surrounded by a thin rim, resembling the shape of a breakfast cereal. This radiological pattern is not specific to DPM, as it can also be observed in pulmonary Langerhans cell histiocytosis, granulomatosis with polyangiitis, metastatic lung tumors, and infectious diseases. Therefore, establishing a definitive diagnosis based solely on imaging findings remains challenging. Although the exact mechanism underlying cavitation in MPMNs is unknown, it has been suggested that destruction of the alveolar wall due to the expansion of meningioma cells along the alveolar septa may contribute to their formation (7).

In the present case, small cavitary nodules exhibiting the Cheerios sign were observed. Although TBLB was initially performed, it failed to provide a diagnostic sample, because the target lesion was not captured. Conversely, TBLC enables a definitive diagnosis of DPM. A recent literature review summarized 44 cases of DPM, in which SLB was selected as the initial diagnostic approach in 33 cases (75.0%) owing to its high diagnostic accuracy (3). However, because SLB is more invasive than bronchoscopy, its use should ideally be avoided when a reliable diagnosis can be achieved through a less invasive bronchoscopic procedure. To date, 15 cases have been reported in which bronchoscopy has been used for the diagnosis of DPM (Table 2). Among the cases in which TBLB was performed, six were successfully diagnosed. In contrast, six cases failed to yield a diagnosis, likely due to the small size and peripheral location of the lesions, which limited adequate sampling, and SLB was subsequently performed. On the other hand, in all reported cases in which TBLC was selected as the initial diagnostic procedure, a definitive diagnosis of DPM was successfully achieved. To our knowledge, this is the first report to show that TBLC can provide a definitive diagnosis of DPM after TBLB is nondiagnostic, thus highlighting the diagnostic utility of TBLC.

TBLC allows the collection of a larger tissue sample with less contusion than a forceps biopsy and it has been reported to improve the diagnostic yield for peripheral pulmonary lesions (21, 22). In particular, an adequate tissue sampling method is crucial for diagnosing multiple small nodular lesions, such as those presenting with the Cheerios sign,

**Table 2. Cases of Diffuse Pulmonary Meningotheliomatosis in which Bronchoscopy was Performed.**

| Reference | Sex | Age | Radiologic Findings | Sampling Procedure |
|---|---|---|---|---|
| Bernabeu Mora, et al.[8] | F | 59 | Diffuse bilateral, randomly-distributed micronodules, most poorly-defined with a cotton wool appearance and cavitation | TBLB |
| Gleason, et al.[9] | F | 63 | Diffuse bilateral micronodules up to 4 mm with a miliary pattern | TBLB |
| Jayaschandran, et al.[10] | F | 74 | Diffuse bilateral micronodules up to 5 mm with GGO and cavitation | TBLB |
| Karakas, et al.[11] | F | 59 | Diffuse bilateral small nodules up to 5 mm with a random pattern | TBLB |
| Melocchi, et al.[3] | M | 55 | Diffuse bilateral micronodules randomly distributed; some with cavitation | TBLB |
| Melocchi, et al.[3] | F | 56 | Diffuse bilateral micronodules randomly distributed | TBLB |
| Kumar, et al.[12] | F | 58 | Diffuse bilateral micronodules with ground-glass opacities | TBLB failed → SLB |
| Dzian, et al.[13] | M | 60 | Diffuse bilateral micronodules up to 5 mm | TBLB failed → SLB |
| Noguchi-Konaka, et al.[14] | F | 77 | Diffuse bilateral granular shadows | TBLB failed → SLB |
| Murata, et al.[15] | F | 54 | Diffuse bilateral micronodules with a peripheral zone predilection. Some nodules with central lucency and ring-shaped appearance | TBLB failed → SLB |
| Healy, et al.[16] | F | 50s | Diffuse bilateral nodules | TBLB failed → SLB |
| Sakano, et al.[17] | M | 64 | Diffuse bilateral ground-glass nodules up to 5 mm | TBLB failed → SLB |
| Morresi-Hauf, et al.[18] | F | 60 | Diffuse bilateral micronodules randomly distributed | TBLC |
| Fadl, et al.[19] | F | 63 | Diffuse bilateral small, subcentimeter, ground-glass nodules with a random pattern | TBLC |
| Swenson, et al.[20] | F | 61 | Innumerable small ground glass nodules, some with cavitation | TBLC |
| This case | F | 48 | Diffuse bilateral centrilobular granular opacities and nodular shadows, with some nodular shadows accompanied by central cavities | TBLB failed → TBLC |

F: female, M: male, SLB: surgical lung biopsy, TBLB: transbronchial lung biopsy, TBLC: transbronchial lung cryobiopsy

and TBLC may be a more suitable modality for such cases. Although the optimal number of TBLC specimens required for DPM diagnosis has not been established, previous studies have obtained up to three samples (18), thus suggesting that collecting at least two to three specimens may be advisable, as is commonly practiced in interstitial lung diseases, and that specimens should preferably be obtained from characteristic cavitary nodules.

Although TBLC of cavitary lesions may raise concerns regarding potential risks, such as bleeding, infection, and pneumothorax, no serious complications were observed in the present patient. In addition, previously reported patients who underwent TBLC for DPM did not report any severe complications. The cavitary nodules in patients with DPM were relatively small, which likely contributed to their lower risk. These findings suggest that TBLC can be safely performed for small cavitary nodules characteristic of the Cheerios sign, provided appropriate hemostatic measures and careful patient selection are performed. Given its superior diagnostic performance and minimally invasive nature, we propose that TBLC should be considered as the initial diagnostic approach in patients presenting with the Cheerios sign and suspected DPM.

In addition, BALF findings in DPM have generally been reported to be normal or show a predominance of macrophages (12). In the present patient, a mild increase in the number of lymphocytes was observed; however, this was not considered to be a characteristic feature of DPM, and it was likely nonspecific. Therefore, a BALF analysis may not provide meaningful diagnostic insights into DPM.

Although the pathogenesis of DPM remains unclear, hormonal factors have been postulated to play a role because DPM occurs more frequently in females and is frequently PgR-positive (6, 15). In our case, the patient had Turner syndrome and was undergoing long-term hormone replacement therapy with estrogen and progesterone. Based on the possible hormonal association, hormone therapy was discontinued after the diagnosis, and the patient remained asymptomatic, with stable radiological findings during the follow-up.

This case report highlights the importance of considering DPM in the differential diagnosis of cavitary pulmonary nodules that present with the Cheerios sign, and it reveals that TBLC can facilitate a definitive diagnosis even when TBLB is non-diagnostic. By enabling the collection of larger and less crushed specimens, TBLC may help avoid both SLB and repeated bronchoscopic procedures, thus supporting its consideration as an initial diagnostic approach in such patients.

**The authors state that they have no Conflict of Interest (COI).**

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**Ethics Approval and Consent to Participate**

Not applicable.

**Consent for publication**

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

**Availability of data and materials**

All the data generated during this study are included in this article. Further inquiries can be directed to the corresponding authors.

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**Authors' contributions**

TH analyzed and interpreted the clinical data and drafted the manuscript. KS conceptualized the study and critically revised the manuscript for important intellectual content. SSh contributed to patient data interpretation and manuscript revision. KY, SSa, YH, TM, TN, and HI contributed to the data acquisition and manuscript review. HH and NH supervised the study and revised the manuscript critically. All authors have read and approved the final manuscript.

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