Supplemental data：Case presentation

Case 1.

A 67-year-old male with no smoking history or familial oncologic predisposition was referred for evaluation of a right upper lobe mass demonstrating interval growth over 24 months of surveillance. Contrast-enhanced chest CT revealed a lobulated soft-tissue attenuation mass measuring 3.5×2.2 cm in its largest cross-section, with well-defined margins, peripheral ground-glass opacity, and focal cystic changes (Fig. 5A). Preoperative PET-CT showed no evidence of distant metastasis, and a biopsy of the mass revealed lung adenocarcinoma. Endobronchial ultrasound-guided transbronchial needle aspiration confirmed the absence of lymph node involvement. The patient subsequently underwent video-assisted thoracoscopic surgery (VATS) for right upper lobectomy with systematic lymph node dissection. The postoperative histopathological evaluation confirmed a moderately differentiated invasive adenocarcinoma (WHO/IASLC Grade 2) characterized by predominant acinar subtype (80% acinar, 10% lepidic, 10% papillary), with absence of pleural invasion, perineural invasion, or vascular emboli (Fig. 5B, Supplemental Figure S1, and Supplemental Table S1). Lymph node stations II, IV, VII, IX, X, and XI showed no evidence of metastasis. The final pathologic staging was pT1cN0M0 (Stage IA3). Postoperative surveillance protocol included routine follow-up with chest CT every six months.

Fifteen months after surgery, a follow-up chest CT revealed the development of multiple new GGOs in the right lower lobe, which progressively enlarged over the next 10 months, showing solid components and characteristic cystic features (Fig. 5C, 5E,

and 5G). Multidisciplinary team (MDT) evaluation strongly suggested the possibility of malignant lesions, with a differential diagnosis favoring MPLC. The patient underwent resection of three right lower lung nodules. Histopathological examination revealed moderately differentiated adenocarcinomas (acinar, lepidic, and papillary subtypes) with spread through airspaces (STAS) but had no pleural invasion (Fig 5D, 5F, 5H, Supplemental Figure S1, and Supplemental Table S1). Further genomic profiling showed that the three right lower lung lesions shared 18 driver gene mutations with the previously resected right upper lung adenocarcinoma (Fig. 5I), supporting the diagnosis of IPM. The patient was subsequently started on adjuvant EGFR-TKI therapy based on the identified genetic mutations.

Case 2.

A 54-year-old male with a 40-pack-year smoking history presented with a right upper lung mass discovered one month prior. The patient had no personal or family history of cancer. CT imaging revealed a 4×4.5×3 cm cystic mass in the right upper lobe, with irregular shape, uneven thin walls, spiculated margins, adjacent pleural thickening, and bronchial distortion (Fig. 5J). The solid component showed mild enhancement on contrast scans. Preoperative PET-CT revealed no distant metastases. The patient underwent VATS for right upper lobectomy with systematic lymphadenectomy. Histopathological examination revealed moderately to poorly differentiated squamous cell carcinoma, with no perineural invasion or vascular emboli but with visceral pleural invasion. Lymph nodes from stations II, III, IV, VII, X, XI, and XII were negative for metastatic involvement. The final pathologic staging was pT2bN0M0 (Stage IIA), with

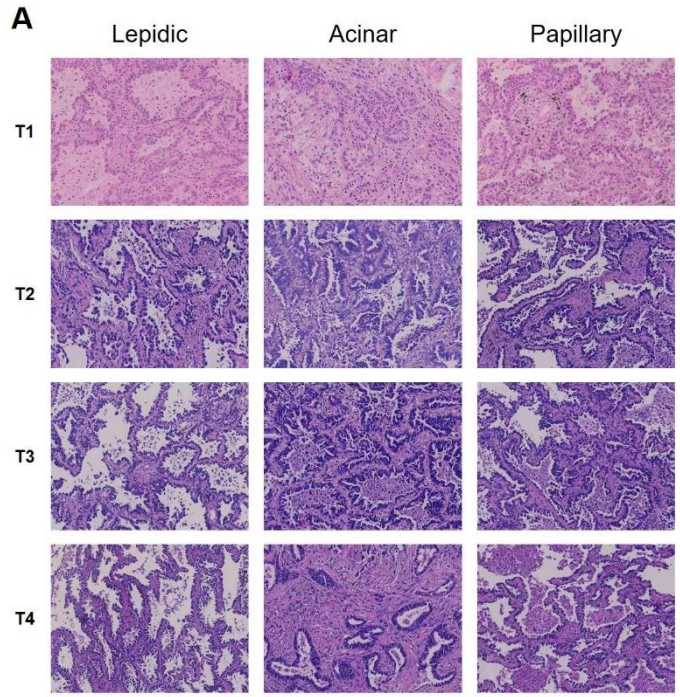
PD-L1 TPS score of 0. The patient subsequently received three cycles of adjuvant chemotherapy (paclitaxel + carboplatin).

At 24 months postoperatively, follow-up CT revealed a thin-walled cystic lesion in the right middle lobe near the mediastinum (1.5 × 1.3 cm) and a 0.7 cm GGO nodule in the posterior basal segment of the right lower lung (Fig. 5J). MDT review suggested that both the cystic nodule in the right middle lung and the GGO nodule in the right lower lung were likely malignant, with a strong suspicion for cancer, but not fitting the typical pattern of IPM, prompting a recommendation for surgical resection. The patient underwent right middle lobectomy and wedge resection of the right lower lung. Pathology showed moderately to poorly differentiated squamous cell carcinoma in the right middle lung with pleural invasion and MIA in the right lower lung (Fig 5K and Supplemental Table S1). Genomic profiling showed that the squamous cell carcinoma lesions in the right upper and right middle lungs had nearly identical mutation profiles. In contrast, the MIA in the right lower lung displayed a distinct genetic profile (Fig. 5L). Based on a comprehensive evaluation of imaging, histopathological, and genomic findings, the MDT concluded that the lesion in the right middle lobe was highly suggestive of recurrence or metastasis from the previously resected squamous cell carcinoma in the right upper lobe.

These findings challenge the prevailing clinical presumption that multifocal GGO-predominant lung malignancies universally represent MPLC. Rather, our observations underscore that IPM must be rigorously investigated when lesions display both morphologic congruity (notably cystic features) and clonal genomic signatures. A

tripartite diagnostic framework incorporating radiologic, histologic, and molecular profiling is advocated to refine classification accuracy and guide precision management strategies.

Supplemental Figure S1



Supplemental Figure S1. Histopathological characterization of Case 1.

T1: Invasive adenocarcinoma, acinar-predominant subtype (80% acinar, 10% lepidic, 10% papillary; WHO/IASLC Grade 2) with STAS. **T2:** Invasive adenocarcinoma, acinar-predominant subtype (70% acinar, 20% lepidic, 10% papillary; Grade 2) demonstrating STAS. **T3:** Invasive adenocarcinoma, acinar-predominant subtype (80% acinar, 15% lepidic, 5% papillary; Grade 2) exhibiting STAS. **T4:** Invasive adenocarcinoma, acinar-predominant subtype (80% acinar, 10% lepidic, 10% papillary; Grade 2) with STAS. None of the four nodules showed pleural invasion.

Supplemental Table S1. Clinical, radiological and histopathological characteristics of the two patients.

Case	Sex	Age	Presentation	Location	Size (cm)	CT feature	Histology	Subtype				
								Lepidic (%)	Acinar (%)	Papillary (%)	Micro-papillary (%)	Solid (%)
1	M	67	primary	RUL	3.5	pGGO+ cystic	IAC	10	80	10	0	0
			subsequent	RLL	1.5	pGGO+ cystic	IAC	20	70	10	0	0
			subsequent	RLL	1.2	pGGO+ cystic	IAC	15	80	5	0	0
			subsequent	RLL	1.3	pGGO+ cystic	IAC	10	80	10	0	0
2	M	54	primary	RUL	4.5	cystic+ pGGO	Squamous					
			subsequent	RML	1.4	cystic	Squamous					
			subsequent	RLL	0.7	GGO	MIA					

RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; GGO, ground-glass opacities; pGGO, partial-solid GGO; IAC, invasive adenocarcinoma; MIA, minimally invasive adenocarcinoma; Squamous, squamous cell carcinoma.