Clinicopathological features and therapeutic advances in primary pulmonary lymphoepithelioma-like carcinoma (Review)

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Abstract. Primary pulmonary lymphoepithelioma-like carcinoma (PPLELC) is a rare subtype of non-small cell lung cancer, the clinicopathological features and molecular mechanisms of which are markedly different from those of other lung cancer subtypes. In recent years, with in-depth research in molecular pathology and immunology, notable progress has been achieved in the pathogenesis, diagnostic methods and therapeutic strategies of PPLELC. Epidemiological studies have shown that PPLELC is closely associated with Epstein-Barr virus (EBV) infection and the role of EBV in tumorigenesis has become a particular research focus. In addition, the unique immune microenvironment characteristics of PPLELC provide potential targets for immunotherapy. The present review systematically summarizes the epidemiology, pathological features, molecular biological mechanisms and diagnostic methods of PPLELC and focuses on discussing the association between EBV infection and tumorigenesis, the characteristics of immune microenvironment, as well as the latest advances in targeted therapy and immunotherapy. The aim was to provide a comprehensive diagnostic and therapeutic framework for clinicians and to prospect future research directions.

Contents

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1. Introduction

Primary pulmonary lymphoepithelioma-like carcinoma (PPLELC) is a rare subtype of primary epithelial malignant tumors of the lung, accounting for <1% of all types of lung cancer (1). Histologically, this tumor manifests as undifferentiated carcinoma with prominent lymphocytic infiltration and is associated with Epstein-Barr virus (EBV) infection, exhibiting a relatively higher incidence in Asian populations (2). A study indicated that the EBV infection rate in patients with PPLELC is ~81.08%, which is markedly higher compared with that in other types of lung cancer (3). These unique histological features and viral associations result in notable differences in biological behavior and clinical characteristics between PPLELC and other non-small cell lung cancer (NSCLC) subtypes (4). In previous years, with the rapid advances in molecular pathology and immunotherapy, the understanding of PPLELC has been continuously advanced. Genomic studies have revealed that PPLELC possesses distinct molecular characteristics, including low tumor mutation burden (TMB) and high programmed death-ligand 1 (PD-L1) expression (5). Single-cell transcriptome analysis has uncovered high expression of both AKT3 and fibroblast growth factor receptor 2 in PPLELC, which may serve as potential therapeutic targets (6,7). In addition, metabolomic studies have demonstrated that linoleic acid remodels the tumor microenvironment (TME) through the peroxisome proliferator-activated receptor-α/tissue factor axis to facilitate tumor progression (8,9). These findings provide novel insights into the in-depth comprehension of PPLELC pathogenesis.

Despite progress achieved in diagnosis and treatment, PPLELC still faces numerous challenges. Owing to its rarity and non-specific clinical manifestations, PPLELC is frequently misdiagnosed as squamous cell carcinoma or other types of lung cancer (1). With regard to treatment, although surgery is the standard therapeutic modality for early-stage disease, to the best of our knowledge, there is no unified treatment regimen for advanced patients (4). Immune checkpoint inhibitors (ICIs) have exhibited promising application prospects in the treatment of PPLELC. Numerous studies have demonstrated that PD-1/PD-L1 inhibitors combined with chemotherapy may markedly improve patient prognosis (10,11). Despite this, certain issues, such as how to screen the optimal beneficiary population and overcome immunotherapy resistance, still require further exploration (10). The present review aimed to comprehensively summarize the latest research progress of PPLELC, encompassing its epidemiological characteristics, molecular mechanisms, diagnostic criteria and therapeutic strategies, thereby providing a theoretical basis for clinical practice. By systematically collating existing evidence, the present review endeavored to promote an in-depth understanding of this rare tumor and offer references for future research directions.

2. Epidemiology and clinical features

Epidemiological characteristics. PPLELC is a rare subtype of lung cancer with distinct geographic and ethnic disparities in its epidemiological characteristics. It has been demonstrated that the incidence of this disease is notably higher in Asian populations compared with those of European and American countries (12). This geographic clustering is closely associated with regional variations in EBV infection, given that EBV-encoded RNA (EBER) can be detected in the tumor tissues of the majority of Asian cases, whereas the association of lymphoepithelioma-like carcinoma, including PPLELC, with EBV infection is relatively rare or uncommon in Western populations (13). Overall, patients with pulmonary LELC are generally younger compared with those that have other subtypes of NSCLC. A study involving 36 patients with PPLELC demonstrated a median age of 57 years (range, 37-76 years) (14) and another study reported a mean age of 57.6 years (15); both values were considerably lower compared with the age at onset of common types of lung cancer. With regard to sex distribution, no notable sex differences have been observed in previous studies. For example, among 36 patients included in one study, 16 were male and 20 were female (14). Notably, PPLELC exhibits a weak association with smoking history, in contrast to other lung cancer subtypes, in which tobacco smoking has been a well-recognized major etiological risk factor (16). An underlying reason may be that PPLELC is predominantly driven by EBV infection rather than cigarette smoke exposure.

Clinical manifestations. PPLELC presents with diverse and non-specific clinical manifestations, which poses certain challenges for early diagnosis. Furthermore, PPLELC is largely indistinguishable from metastatic nasopharyngeal carcinoma (NPC), both morphologically and by EBER *in situ* hybridization status. Therefore, secondary NPC must be rigorously excluded before diagnosing the latter, which is much rarer. Early symptoms of patients are often atypical, predominantly presenting as non-specific respiratory symptoms such as cough, chest pain and hemoptysis (17). In certain cases, the clinical manifestations resemble those of infectious diseases. For instance, it has been indicated that its radiological and pathological features may be misdiagnosed as pulmonary tuberculosis, leading to delayed correct diagnosis (17). In terms of disease progression, PPLELC exhibits a degree of invasiveness and ~20% of patients present with distant metastasis at diagnosis, with common metastatic sites including bone, liver and adrenal glands (13). A large-scale study on non-nasopharyngeal lymphoepithelial carcinoma noted that the lung was the most common primary site, accounting for 64.0% of all cases (18), highlighting the important role of PPLELC in this type of tumor. A number of patients may present with paraneoplastic syndromes, although detailed descriptions remain limited in the current literature. Due to its complex clinical manifestations, clinicians should maintain a high index of suspicion.

With regard to radiological features, PPLELC typically appears as a well-defined mass on CT scans, with moderate to marked enhancement on contrast-enhanced scans (15). A radiological study of primary tracheal lymphoepithelioma-like carcinoma also demonstrated that the majority of lesions present as solitary, broad-based, eccentric irregular nodules or tracheal wall mural thickening, which may cause notable luminal stenosis (19). In addition, studies have reported that advanced PPLELC cases with large tumor sizes frequently present as a central lesion, with visceral pleural invasion being observed in >50% of cases (24/43 cases; 55.8%) (20,21). These findings indicate that PPLELC is a rare pulmonary neoplasm with distinct clinical and radiological features that differ markedly from other types of NSCLC, which is key in improving early recognition and accurate diagnosis of PPLELC.

3. Pathological features and diagnosis

Histopathological characteristics. PPLELC exhibits distinct histopathological features. A key step in pathological diagnosis is to exclude metastatic NPC, as the undifferentiated morphology and EBER positivity cannot be distinguished from the latter. The typical histological appearance of PPLELC is characterized by nests or sheets of undifferentiated carcinoma cells accompanied by extensive lymphocyte infiltration (22). This distinctive histological structure morphologically differentiates it from other subtypes of NSCLC. The carcinoma cells are generally large, with vesicular nuclei and prominent nucleoli that often exhibit a syncytial growth pattern, which is further associated with EBV infection (4). In the tumor stroma, in addition to abundant lymphocyte infiltration, inflammatory cells including plasma cells and eosinophils are also commonly observed, contributing to marked immune TME interactions (5). This inflammatory background may be associated with the immune response induced by EBV infection and further provides a pathological basis for the favorable responsiveness of this tumor to immunotherapy (23). Notably, the borders of PPLELC tumor cells are often indistinct, with obvious intercellular bridges. These features help to distinguish it from other poorly differentiated carcinomas such as squamous cell carcinoma.

Immunohistochemical characteristics. PPLELC exhibits a characteristic immunophenotypic profile. Epithelial markers such as cytokeratin (CK) and epithelial membrane antigens exhibit strong positive expression, which help to determine its epithelial origin (24). In addition, lymphoid markers CD3 and CD20 clearly delineate the infiltrating lymphocyte populations in the stroma, consisting mainly of T cells and B cells that constitute an important component of the TME (4). The positive rate of EBER by *in situ* hybridization exceeds 90%, which serves as a key diagnostic criterion for PPLELC and an important indicator in distinguishing it from EBV-negative lung carcinomas (5). Furthermore, PPLELC frequently demonstrates high expression levels of PD-L1, which is associated with its lymphocyte-rich microenvironment and EBV infection, indicating the immunotherapeutic potential of this tumor (23). Other immunophenotypic markers, including p63 and CK5/6, are also positive in the majority of cases, whereas thyroid transcription factor-1 and napsin A are typically negative. These features facilitate the differential diagnosis from lung adenocarcinoma (25). Collectively, these immunohistochemical characteristics are not only valuable for diagnosis but also provide important evidence for the selection of therapeutic strategies.

4. Molecular biological characteristics

EBV-associated mechanisms. EBV serves a key role in the pathogenesis of PPLELC. EBV activates the NF-κB and janus kinase (JAK)/STAT signaling pathways of host cells through latent membrane proteins (LMP)-1 and 2A, thereby promoting cell proliferation and survival (26). LMP1 interacts with tumor necrosis factor receptor-associated factor family proteins through the three carboxy-terminal activating region (CTAR) subdomains (CTAR1, CTAR2 and CTAR3) of its C-terminal domain and then activates the downstream NF-κB and MAPK pathways (27). In addition, LMP2A activates the PI3K/Akt pathway by mimicking B cell receptor signals, further promoting cell survival and immune escape (28). The persistent activation of these pathways leads to cell cycle regulation disorders and apoptosis inhibition, providing favorable conditions for tumorigenesis and development. EBV-encoded microRNAs (miRNAs) also serve an important role in regulating the expression of host cell cycle and apoptosis-related genes.

EBV-miR-BART2-5p and miR-BART11-5p directly target retinoblastoma protein and cyclin-dependent kinase inhibitor p21 to inhibit their expression, thereby promoting cell proliferation and migration while inhibiting apoptosis (29). In addition, EBV-miR-BART7-3p impairs the host antiviral immune response by downregulating the expression of IFNL3, further promoting viral latent infection and tumor immune escape (30). These viral miRNAs not only regulate host gene expression, but also alter the chromatin structure through epigenetic modification, affecting the transcriptional activity of tumor-related genes (30). EBV-induced immune escape mechanisms also serve a key role in tumorigenesis. The virus reduces tumor antigen presentation by downregulating the expression of major histocompatibility complex (MHC) class I and II molecules, thereby evading immune system recognition (31). In addition, EBV-infected tumor cells express PD-L1 highly, which inhibits T cell activation and proliferation by binding to PD-1 on the surface of T cells, forming an immunosuppressive TME (32). EBV can also recruit regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSC) by secreting immunosuppressive cytokines such as IL-10 and TGF-β, further inhibiting the anti-tumor immune response (33,34). These immune escape mechanisms collectively provide an immunological basis for the progression of EBV-related tumors (Fig. 1). Despite having elucidated EBV-mediated PPLELC pathogenesis, key limitations remain. First, LMP1/LMP2A-related signaling studies rely on *in vitro* models or small samples, lacking *in vivo* validation; the role of individual LMP1 CTAR subdomains is also unclear. Second, EBV-encoded miRNAs are insufficiently characterized as their redundancy/synergy remains unstudied and the mechanism by which their epigenetic effects are associated with chromatin changes is unclear. Third, EBV-induced immune escape mechanisms have not been systematically studied, with their relative importance and crosstalk with MHC downregulation, PD-L1 overexpression and immunosuppressive cell recruitment still being unclear. Finally, the impact of EBV latent infection on pathogenesis is also understudied. Current studies appear mostly descriptive, lacking functional demonstration of causal associations and ignoring inter-individual heterogeneity.

Genomic characteristics. Whole-exome sequencing has shown that PPLELC has a relatively low mutation burden but possesses a characteristic mutation spectrum (35). Compared with other lung cancer subtypes, the TMB of PPLELC is usually low, which may be associated with its EBV-driven pathogenesis (36). However, there are a number of high-frequency mutated genes in PPLELC, such as TP53, PIK3CA and NOTCH family genes. TP53 mutations are relatively common in PPLELC, leading to the loss of cell cycle checkpoint function and increased genomic instability (37). Activating mutations of PIK3CA promote cell proliferation and survival by further activating the PI3K/AKT/mTOR pathway (38). Mutations in NOTCH family genes (such as NOTCH1, NOTCH2 and NOTCH3) have also been reported in PPLELC and these mutations may affect cell differentiation and tumor progression by disrupting the NOTCH signaling pathway (39). Amplification of chromosome 9p24.1 is an additional important genomic characteristic of PPLELC and this region contains PD-L1 (CD274) and PD-L2 (PDCD1LG2) genes (40). Amplification of 9p24.1 leads to the upregulation of PD-L1/PD-L2, further enhancing the immune escape ability of tumor cells. In addition, the amplification of this region is also associated with upregulation of the JAK2 gene, which promotes the proliferation and survival of tumor cells by activating the JAK/STAT pathway (41). Whole-genome analysis has also indicated that there are other copy number variations (CNVs) in PPLELC, such as amplification of 1q, 3q and 8q, as well as deletion of 9p and 17p, changes which may affect the invasiveness and metastatic potential of tumors (42).

The genomic characteristics of PPLELC also include the specificity of EBV integration sites. The EBV genome tends to integrate into specific proto-oncogene and tumor suppressor gene loci of host cells, including MYC, BCL2, BCL6, REL, BCL11A, CCND1 (proto-oncogenes) and TP53, p16/INK4a

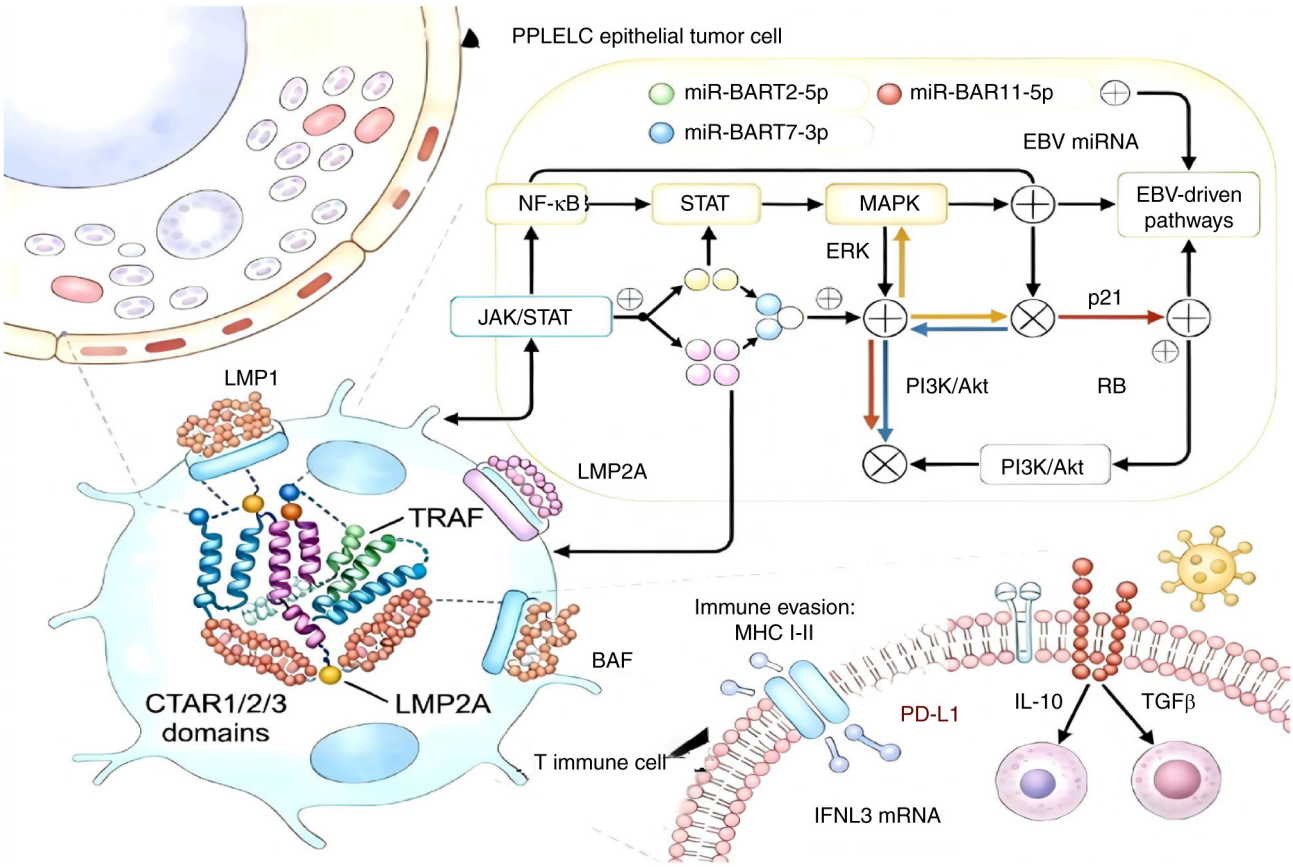

Figure 1. Core pathogenic mechanisms of PPLELC driven by EBV, involving EBV-encoded molecules, signaling cascades and immune escape: i) EBV-encoded LMPs and signaling activation: EBV-encoded LMP1 binds to TRAF through its CTARs (including CTAR1/2/3 domains), triggering the NF-kB/STAT/MAPK cascade. Another EBV-encoded protein, LMP2A, mimics B cell receptor signals to activate the JAK/STAT pathway. These cascades form EBV-driven signaling axes that promote tumor cell proliferation; ii) regulation by EBV-encoded miRNAs: EBV-derived BamHI-A rightward transcript miRNAs (miR-BART2-5p, 11-5p and 7-3p) modulate PPLELC progression as miR-BART2-5p/11-5p targets RB and cyclin-dependent kinase inhibitor p21 to release cell cycle checkpoints and miR-BART7-3p downregulates IFNL3 mRNA, impairing host antiviral immunity; iii) involvement of the PI3K/Akt pathway: The PI3K/Akt pathway is activated by upstream signals, synergizing with the RB/p21 axis to accelerate cell cycle progression; and iv) EBV-mediated immune escape: EBV-driven pathways induce immune escape through downregulating MHC I/II to reduce tumor antigen presentation, upregulating PD-L1 to inhibit T cell activation and secreting IL-10 and TGFβ to recruit inhibitory immune cells, forming an immunosuppressive tumor microenvironment that facilitates PPLELC progression. PPLELC, primary pulmonary lymphoepithelioma-like carcinoma; miRNA, microRNA; EBV, Epstein-Barr virus; JAK, janus kinase; RB, retinoblastoma protein; LMP, latent membrane protein; MHC, major histocompatibility complex; PD-L1, programmed death-ligand 1; CTAR, carboxy-terminal activating region; ERK, extracellular signal-regulated kinase; BAF, BRG1/BRM-associated factor.

(tumor suppressor genes) (43). In addition, the latent infection pattern of EBV (such as latent type I or II) can also affect the gene expression profile and epigenetic modification of host cells, further shaping the molecular characteristics of tumors (43,44). The identification of these genomic characteristics not only helps to understand the pathogenesis of PPLELC but also provides potential molecular options for the development of targeted therapeutic strategies (Fig. 2). Despite the identification of key PPLELC genomic features (low TMB, high-frequency mutations, specific CNVs and EBV integration patterns), notable limitations persist. First, the majority of studies rely on small, single-center cohorts, lacking large-scale multi-center validation to determine the universality of these genomic characteristics across ethnic or clinical subgroups. Second, the causal associations between genomic alterations and PPLELC pathogenesis remain undetermined. Associations (such as 9p24.1 amplification with PD-L1 upregulation, EBV integration with oncogene expression and low TMB with EBV infection) lack functional validation, with confounding factors rarely being controlled. Third, the clinical utility of these genomic features as biomarkers also remains understudied. To the best of our knowledge, no consensus exists regarding their association with treatment response or prognosis. Furthermore, actionable targets (including PIK3CA mutations) lack clinical validation; the predictive value of 9p24.1 amplification for ICI response has not yet been established. Fourth, the impact of EBV latent infection patterns on genomic features and outcomes has not been elucidated due to unclear regulatory mechanisms and insufficient characterization of EBV integration site heterogeneity. Finally, genomic studies lack integration with transcriptomics, proteomics or epigenomics, limiting comprehensive pathogenic understanding. Future research should aim to focus on large-scale validation, functional experiments and clinical utility to bridge these basic and clinical research gaps.

5. Differential diagnosis

Key points of differential diagnosis. PPLELC has a broad range of differential diagnoses. A common diagnostic pitfall

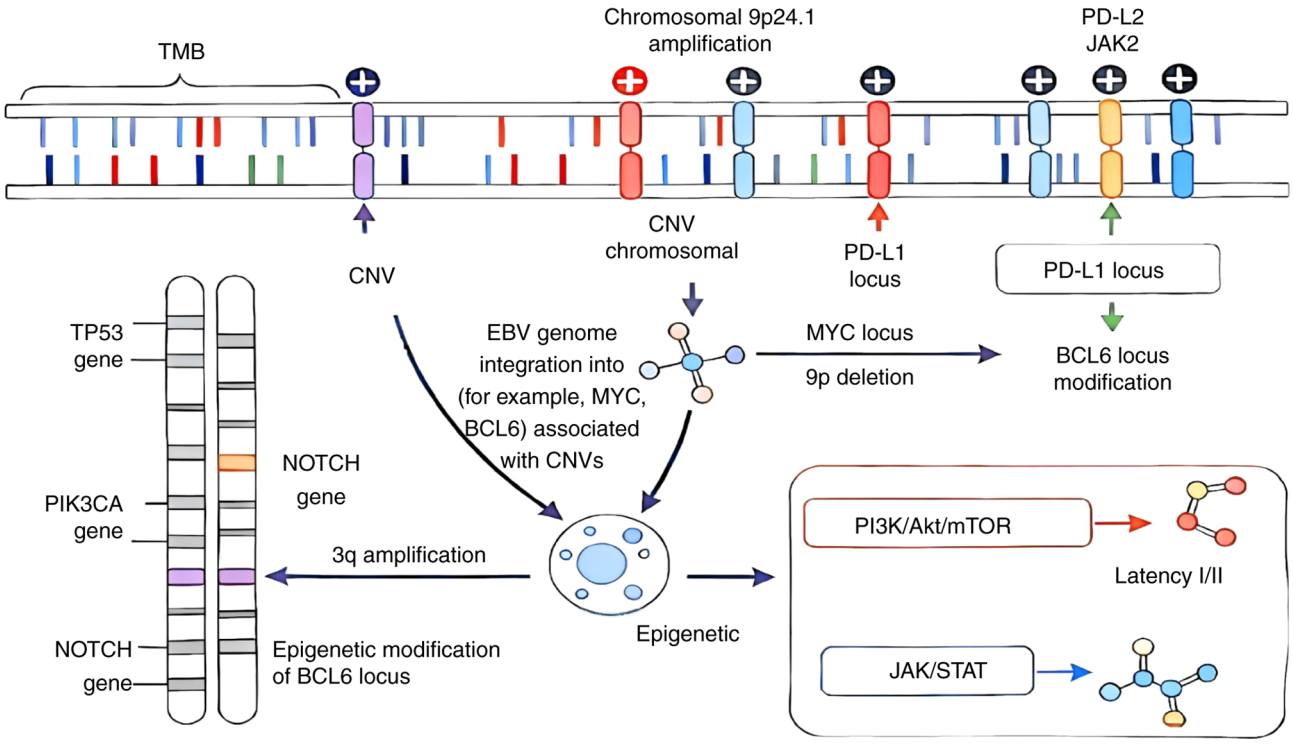

Figure 2. Established molecular features of PPLELC, an EBV-associated rare lung cancer subtype. Molecular features include: Genomic traits: A low TMB (a distinctive phenotype of PPLELC), chromosomal 9p24.1 amplification targets loci of PD-L1, PD-L2 and JAK2, driving their upregulation (a hallmark linked to immunotherapeutic sensitivity) and CNVs (such as 3q amplification and 9p/17p deletion) and driver mutations (including TP53, PIK3CA and NOTCH family genes) disrupt cell homeostasis to enable malignancy; ii) EBV-mediated regulation: EBV genome integrates into host chromosomal loci (such as MYC and BCL6) alongside CNVs and induces epigenetic modification of the BCL6 locus to dysregulate oncogenic transcription; and iii) activated signaling cascades: The PI3K/Akt/mTOR pathway promotes tumor cell proliferation and survival, the JAK/STAT pathway enhances tumor growth and EBV maintains latency I/II to synergize with these pathways and sustain the malignant phenotype of PPLELC. PPLELC, primary pulmonary lymphoepithelioma-like carcinoma; EBV, Epstein-Barr virus; JAK, janus kinase; PD-L, programmed death-ligand; JAK, janus kinase; CNV, copy number variation; BCL6, B cell lymphoma 6; TMB, tumor mutation burden.

is that metastatic NPC may be misclassified as PPLELC due to overlapping histological and molecular features. It should be emphasized that secondary NPC must always be excluded before diagnosing PPLELC, which is much rarer. Secondly, other differential diagnoses include lung squamous cell carcinoma, large cell carcinoma, pulmonary lymphoma and metastatic carcinoma (45). Since the histological manifestation of PPLELC is represented by undifferentiated or poorly differentiated tumor cells accompanied by marked lymphocytic infiltration, its morphology overlaps with that of lung squamous cell carcinoma or large cell carcinoma, especially large cell neuroendocrine carcinoma (46). Therefore, morphological observation alone may not be sufficient for diagnosis. *In situ* hybridization for EBER is a key indicator for differential diagnosis, as the majority of PPLELC cases are closely associated with EBV infection and EBER positivity in tumor cell nuclei is an important molecular pathological feature of PPLELC (4,5). In addition, before diagnosing PPLELC, it is necessary to rule out the possibility of lymphoepithelioma-like carcinoma metastasizing to the lung from other primary sites (such as the nasopharynx).

6. Treatment strategies

Surgical treatment. For patients with PPLELC, surgical resection is the preferred treatment modality for early-stage patients. It has been demonstrated that for resectable early-stage patients with PPLELC, radical surgery can promote good long-term survival benefits (4). A retrospective analysis of patients with PPLELC showed that those who underwent surgical resection exhibited an improved prognosis compared with other NSCLC subtypes and that their 5-year overall survival (OS) rate could reach a relatively high level. This was associated with the unique clinicopathological characteristics exhibited by these individuals, being of a relatively young age, non-smoking and showing a good tumor therapeutic response (4).

The surgical method typically used is a lobectomy, the standard procedure for radical lung cancer surgery that aims to completely resect the tumor and ensure sufficient surgical margins (47). In lobectomy, systematic lymph node dissection is a key component, as it helps to accurately stage, evaluate prognosis and guide subsequent treatment decisions. It has been shown that for clinical stage N0 patient with NSCLC, video-assisted thoracoscopic surgery lobectomy is the standard choice and systematic lymph node dissection must be performed during the operation, following oncological principles such as not touching the lymph nodes themselves and not damaging the lymph node capsule (47). However, the role of adjuvant chemotherapy after PPLELC surgery remains controversial. Although a number of studies have suggested adjuvant chemotherapy for certain high-risk patients (such

as those that are lymph node-positive), due to the rarity of PPLELC, there is a lack of evidence from large-scale randomized controlled trials to support this, and further research is therefore needed to clarify whether adjuvant chemotherapy is required and which chemotherapy regimen is the most effective for this special subtype of PPLELC (48). Therefore, for patients with PPLELC, the decision regarding adjuvant therapy after surgical resection should be based on individualized risk assessment, comprehensively considering factors such as tumor stage and pathological characteristics.

Chemotherapy and radiotherapy. For patients with advanced or unresectable PPLELC, platinum-based chemotherapy regimens are the main systemic therapeutic modality (6). Although driver gene mutations [such as EGFR and anaplastic lymphoma kinase (ALK)] are rare in PPLELC, chemotherapy remains the first-line foundational treatment. Platinum doublet chemotherapy (for example, cisplatin or carboplatin combined with other agents) is the standard first-line regimen for the advanced treatment of numerous solid tumors (49). Retrospective studies have also supported the application of chemotherapy for PPLELC. Radiotherapy serves an important role in the treatment of PPLELC, especially for patients with unresectable locally advanced disease, as it can effectively achieve local tumor control. Advances in radiotherapy techniques, such as intensity-modulated radiotherapy and stereotactic body radiotherapy, have improved treatment precision, enhancing local efficacy while protecting normal tissues (50,51).

Concurrent chemoradiotherapy may improve survival rates in patients with locally advanced PPLELC. Concurrent chemoradiotherapy refers to the combined administration of chemotherapy and radiotherapy during the same period, a modality proven to increase local control and OS rates in a number of locally advanced solid tumors (including esophageal cancer, cervical cancer and NSCLC) (52). Its mechanism lies in that chemotherapy not only exerts a radiosensitizing effect but also controls potential micrometastases simultaneously. A case report has shown that patients with advanced PPLELC respond well to platinum-based concurrent chemoradiotherapy regimens (4). However, concurrent chemoradiotherapy is accompanied by a relatively high risk of toxicity, such as myelosuppression, radiation esophagitis and pneumonitis (4). Therefore, it is necessary to balance efficacy and safety, with close monitoring and supportive care for patients. In summary, platinum-based chemotherapy combined with radiotherapy constitutes a core strategy for non-surgical treatment of advanced PPLELC.

7. Advances in targeted therapy and immunotherapy

ICIs. PPLELC is a distinct subtype of NSCLC, with the following core characteristics: i) A histology that is highly similar to that of undifferentiated NPC but lacking specific diagnostic markers in routine pathology (53); and ii) a strong etiological association with EBV infection, particularly prominent in Asian populations, with a study by Chen *et al* (3) showing an EBV positivity rate of 81.08% (54).

Notably, the immune escape induced by EBV infection provides a core basis for the application of ICIs and has become a central direction in current PPLELC treatment research. At the molecular level, EBV-encoded miRNAs, such as miR-BART11 and miR-BART17-3p, can downregulate FOXP1 and polybromo-1 gene expression, leading to PD-L1 upregulation (55,56) and the formation of a T cell exhaustion-type TME (57,58). This EBV-driven immune escape process is a key target for ICIs. By blocking the PD-1/PD-L1 pathway, ICIs can reverse EBV-mediated immune suppression and restore the anti-tumor immune function of the body, potentially explaining why an elevated EBV DNA load is associated with poor prognosis of PPLELC and why PD-1/PD-L1 inhibitors can improve this prognosis (59,60).

It has been demonstrated that PPLELC has a higher PD-L1 expression compared with other NSCLC subtypes, markedly enhancing its sensitivity to ICIs and further highlighting the dominant role of ICIs in PPLELC treatment (60). EBV infection can also inhibit the anti-tumor function of protective cytotoxic lymphocytes such as $CD8^+$ T cells by regulating the TME (61), with immune escape characteristics mainly manifesting as T cell exhaustion, upregulation of inhibitory checkpoints (such as PD-L1) and metabolic-epigenetic reprogramming (62,63).

Specifically, in the TME, EBV-associated antigens activate immune cells such as T cells and natural killer cells, while inducing the secretion of immunosuppressive cytokines including IL-10, thereby forming a contradictory microenvironment with coexistent anti-tumor immunity and immunosuppression (5). The TME of PLELC is characterized by high lymphocyte infiltration, mainly including $CD8^+$ T cells, $CD4^+$ T cells and B cells; a infiltration pattern similar to that of nasopharyngeal lymphoepithelioma-like carcinoma, suggesting that the immune system may attempt to control tumors through cytotoxicity (64). However, the coexistence of Tregs and MDSCs in the TME promotes tumor immune escape by inhibiting effector T cell function. In addition, PLELC exhibits high expression of PD-L1 (mostly diffuse strong positive expression) as its high expression on tumor cells and infiltrating immune cells mediates T cell exhaustion through the PD-1/PD-L1 pathway, thereby aiding tumors to evade immune surveillance. These features render PLELC a potentially sensitive subtype for ICIs (such as anti-PD-1 antibodies) (65).

Accordingly, the core function of ICIs is to reverse such immunosuppression, as targeting immune checkpoints such as PD-1/PD-L1 can alleviate T-cell exhaustion and restore their tumor-killing capacity. Notably, the prevalent high expression of PD-L1 in PPLELC provides both theoretical support and therapeutic rationale for the application of ICIs, rendering them one of the most promising treatment options for this malignancy. In clinical practice, ICIs (particularly PD-1/PD-L1 pathway inhibitors) have demonstrated good therapeutic potential and emerged as a core treatment strategy for PPLELC. A clinical study has determined that PD-1/PD-L1 inhibitors achieve an objective response rate of 30-40% in patients with PPLELC, which is markedly higher compared with conventional chemotherapy (66). This therapeutic advantage directly stems from EBV-induced high PD-L1 expression, as EBV-encoded latent membrane proteins (including LMP1) can upregulate PD-L1 by activating the NF-κB signaling pathway (67), while ICIs specifically block PD-1/PD-L1 binding, relieve immune

suppression and exert potent anti-tumor effects, a mechanism that demonstrates the specific advantage of ICIs in PPLELC treatment.

As an important biomarker for predicting ICI efficacy, TMB further optimizes the ICI-based treatment strategy for PPLELC. It has been shown that a small number of patients with PPLELC and a high TMB can produce more abundant tumor neoantigens, enhance T cell-mediated anti-tumor immune responses and thus improve sensitivity to ICIs (68). This finding provides a basis for the precise application of ICIs, helping screen patients most likely to benefit, optimize treatment regimens, improve therapeutic efficacy and promote the precision of PPLELC immunotherapy. Currently, ICI combination therapy has become an important development direction within PPLELC immunotherapy, with numerous exploratory clinical trials focusing on the synergistic effect of PD-1/PD-L1 inhibitors combined with chemotherapy to further improve ICI efficacy (59). For example, a phase II clinical study on advanced PPLELC showed that pembrolizumab (a PD-1 inhibitor) combined with platinum-based chemotherapy, prolonged the median progression-free survival (PFS) to 8.5 months with controllable safety (22), providing important support for the clinical application of ICI combination therapy.

Overall, ICIs have become a core strategy for the treatment of PPLELC and advances in their monotherapy and combination therapy may represent improved survival for patients. However, larger-scale prospective clinical trials are still needed to determine their long-term survival benefits and safety, as well as to further optimize ICI treatment regimens. Although accumulating evidence has established an association between EBV infection and PPLELC and suggested the potential advantages of ICIs in the treatment of PPLELC, the overall research field still has numerous limitations (22). First, the majority of basic research remains in the preliminary exploration stage, where the molecular mechanisms and immune regulatory networks have not yet been fully clarified, lacking support from in-depth mechanistic studies. Second, the majority of clinical studies are small-sample, retrospective studies with low evidence levels and large-sample, multi-center, randomized controlled phase III clinical trials are lacking, which cannot fully verify the long-term efficacy and safety of ICI treatment. Third, the application of biomarkers (such as PD-L1 and TMB) has limitations, with the absence of unified detection standards and efficacy prediction thresholds, making it very difficult to achieve precise screening for ICI treatment. Fourth, issues such as ICI resistance mechanisms, optimization of combination therapy regimens and cost-effectiveness ratio have not been effectively resolved, which limits the widespread application of ICIs in PPLELC management. Future research should therefore focus on these shortcomings. Through multi-center, large-sample basic and clinical studies, it is necessary to clarify the causal association between EBV and PPLELC, the molecular mechanisms of ICI action and drug resistance, establish a unified diagnostic standard and efficacy prediction system, optimize ICI monotherapy and combination regimens, consider cost-effectiveness and advance PPLELC immunotherapy towards precision, standardization and popularization.

Exploration of targeted therapy. EBV-associated proteins provide a unique entry point for the targeted therapy of PPLELC. EBV-encoded LMP1 and LMP2A proteins promote tumorigenesis by activating pathways such as NF-κB and PI3K/AKT, thus serving as potential drug targets (67). A preclinical study has shown that LMP1-targeting affibody molecules (for example, ZLMP2A-N110) can effectively inhibit the proliferation of EBV-positive tumor cells and block the activation of the AKT/GSK-3β/β-catenin signaling axis (69). In addition, the NOTCH signaling pathway is often abnormally activated [these viral proteins induce ligand-independent activation, stabilize the NOTCH intracellular domain (NICD), or mimic NICD function to sustain persistent pathway activation, independent of normal regulatory signals]. In PPLELC and its inhibitors (including γ-secretase inhibitors) have exhibited anti-tumor effects in preclinical models. It has been found that NOTCH1 inhibitors (such as brontictuzumab) can markedly reduce the invasiveness of PPLELC cells, but their clinical application is limited by dose-dependent gastrointestinal toxicity (70).

Therapeutic strategies targeting angiogenesis have also gained attention. Anti-VEGF drugs (including bevacizumab) combined with chemotherapy have demonstrated synergistic effects in a number of patients with PPLELC. A retrospective analysis showed that bevacizumab combined with paclitaxel/cisplatin increased the disease control rate of advanced PPLELC to 65%, but adverse reactions such as intestinal perforation should be noted (71). Future studies should aim to further optimize the selectivity and delivery efficiency of targeted drugs; for example, precise targeted delivery of EBV-specific proteins can be achieved through nanocarrier technology. Nanocarrier technology refers to the use of nanoscale materials as carriers to wrap, protect and deliver bioactive molecules such as proteins, genes or drugs to specific target tissues or cells in a precise and controlled manner (72). In addition, current targeted therapy regimens in lung cancer are mainly applicable to patients with EGFR and ALK gene mutations, while patients with PPLELC have a low probability of benefiting from these traditional targeted therapies (73). To date, only a limited number of small-scale retrospective studies have explored the mutation frequencies of EGFR and ALK in PPLELC. A study of 42 patients with PPLELC found no ALK rearrangement in any patient, with only 1 patient carrying the EGFR exon 21 L858R mutation (74). An additional study reported no mutations in either EGFR exon 19 or 21 in 32 patients with PPLELC (75). Furthermore, a study of 46 patients found an EGFR mutation rate of 17.4% (8/46) in PPLELC, but the vast majority (7/8) were non-classical EGFR mutations (60).

Current PPLELC targeted therapy research exhibits key limitations. First, LMP1/LMP2A-targeted strategies remain preclinical and therefore lack clinical validation. Second, NOTCH inhibitors are limited by toxicity and to the best of our knowledge, no mitigation strategies have been explored. Third, anti-VEGF combination data lack large-scale validation. Fourth, EGFR/ALK mutation studies are small and inconsistent, with the importance of non-classical mutations being unclear and no available data on tyrosine kinase inhibitor responses. Overall, PPLELC targeted therapy is underdeveloped, lacking validated actionable targets and standardized regimens.

8. Prognostic factors and follow-up

Prognosis-related factors. PPLELC prognosis is affected by a number of factors, among which clinical stage is considered to be the most important prognostic indicator. It has been demonstrated that the TNM stage of the tumor is closely associated with the survival outcome of patients. For example, in NSCLC, tumor stage (TNM classification) is the basis for evaluating recurrence risk and adjuvant therapy requirements (76). A retrospective cohort study on PPLELC also showed that TNM stage is an independent prognostic factor affecting the OS and PFS of patients (22). In addition, as an important component of T stage, tumor size measurement methods (such as axial, multi-planar or three-dimensional CT measurement) are in good agreement with pathological measurement results and the clinical T stage obtained by different measurement methods has no notable difference in prognostic prediction efficiency, which further supports the value of tumor size assessment based on imaging in prognostic judgment (77). Plasma EBV DNA load has been markedly associated with disease progression and prognosis of PPLELC. As a tumor closely associated with EBV, monitoring circulating EBV DNA levels is of clinical importance. It has been shown that elevated baseline plasma EBV DNA level before treatment is an independent predictor of poor prognosis in patients with PPLELC, which is associated with shorter distant metastasis-free survival and PFS (78). EBV DNA level after treatment also has prognostic value. Persistently detectable or elevated EBV DNA level after treatment often indicates a higher risk of recurrence and a worse survival outcome (79). In PPLELC, the dynamic changes of plasma EBV DNA load (such as high load before treatment, failure to turn negative after treatment or re-elevation during follow-up) are more valuable prognostic prediction tools compared with single-time point detection (80). In addition, the combined application of EBV DNA and other biomarkers has been explored. For example, in NPC, the baseline EBV DNA load has been shown to be positively associated with IL-6 and VEGF levels, with the combination of the three perhaps providing stronger prognostic information (81).

The degree of tumor-infiltrating lymphocytes (TILs) in the TME is an additional important factor affecting the prognosis of PPLELC. TILs reflect the immune response state of the body to the tumor. Often, a high level of TIL infiltration, especially $CD8^+$ T cells and $CD20^+$ B cells, is associated with an improved prognosis. For example, in early-stage oral squamous cell carcinoma, high infiltration of $CD57^+$ natural killer cells and $CD20^+$ B cells indicates a longer OS (82). In colorectal cancer, a high density of $CD3^+$ or $CD8^+$ TILs in the tumor center or invasive margin is an independent indicator of good prognosis (83). However, the prognostic importance of TILs is tumor-type-specific. For example, in invasive lobular breast cancer, the presence of TILs is associated with a worse prognosis (84). For PPLELC, its histological characteristics themselves are manifested as notable lymphocytic infiltration, but the association between the specific subtypes, spatial distribution and density of TILs and prognosis still needs further clarification. Evidence has shown that in tumors such as melanoma, the diffuse distribution and high density of TILs is associated with improved disease-specific survival (85). Therefore, evaluating the quality and quantity of TILs in PPLELC may have potential value in understanding its biological behavior and predicting the efficacy of immunotherapy.

Follow-up strategies. For patients with PPLELC who received radical treatment, the establishment of a systematic and standardized follow-up strategy is key in the early detection of recurrence or metastasis. Given the relatively high risk of recurrence in the initial years after treatment, intensive follow-up is recommended within the first 2 years following therapy completion. In general, comprehensive clinical assessments are suggested every 3-6 months, including history taking, physical examination, imaging studies such as chest CTs and necessary laboratory examinations (86). Such an intensive follow-up approach facilitates the timely detection of subclinical disease progression before the onset of overt clinical symptoms, thereby allowing sufficient time for subsequent interventions. For instance, in the follow-up of postoperative patients with NSCLC, site-specific recurrence models established based on 10-year follow-up data have provided a basis for formulating individualized follow-up endpoints and frequencies according to recurrence risk (87).

Dynamic monitoring of plasma EBV DNA levels should be regarded as a core components in the follow-up of PPLELC. EBV DNA represents a sensitive and specific molecular marker and changes in its levels often precede radiologically visible tumor progression. It has been demonstrated that in patients with PPLELC treated with ICIs, dynamic changes in plasma EBV DNA levels have been consistent with variations in tumor volume and an elevation in EBV DNA levels may indicate molecular disease progression numerous months earlier compared with CT imaging (88). Therefore, measurement of plasma EBV DNA at each follow-up visit is of great value for evaluating treatment response and providing early warning of recurrence. If EBV DNA converts from negative to positive or shows a continuous increase during follow-up, high suspicion should be maintained and further investigations or close monitoring should be considered, even in the absence of definite radiological progression.

9. Conclusions and future perspectives

In conclusion, PPLELC represents a rare and distinct subtype of lung cancer characterized by unique clinicopathological features and a strong association with EBV infection. This entity not only expands the molecular classification of lung cancer but also highlights the key contribution of viral oncogenesis to lung tumor development. A standardized diagnostic approach combining morphological features, immunohistochemistry and EBER *in situ* hybridization has been established, while the incorporation of PD-L1 testing enables a direct transition from diagnosis to therapeutic decision-making, embodying the principle of precision medicine.

Surgical resection remains an established treatment method for localized PPLELC, with favorable 5-year survival rates markedly higher compared with those of other NSCLC subtypes. For advanced disease, ICIs have changed the therapeutic landscape, achieving high objective response rates, particularly in patients with high PD-L1 expression. The distinctive immune microenvironment of EBV-associated tumors likely underlies the heightened sensitivity to immunotherapy observed in PPLELC, offering valuable insights into identifying predictive biomarkers of immunotherapy response.

Current challenges include the incomplete and inconsistent understanding of EBV-driven oncogenic mechanisms. Future investigations should therefore employ multi-omics integration, organoid models and single-cell sequencing to systematically delineate the dynamic interplay between EBV infection and lung epithelial malignant transformation. Clinical translation will require optimized strategies for combining surgery and immunotherapy, especially in locally advanced diseases.

Moving forward, research priorities should aim to focus on three key areas: i) Elucidating the regulatory networks between EBV-encoded miRNAs and host epigenetic modifications; ii) developing liquid biopsy-based assays for dynamic EBV-DNA monitoring; and iii) exploring novel therapeutic approaches including dual immune checkpoint blockade and EBV-specific T-cell therapy.

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Competing interests

The authors declare that they have no competing interests.

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