Primary Pulmonary Lymphoepithelioma-like Carcinoma on FDG PET/CT

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Abstract A 69-year-old male smoker was referred to ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET/CT) with the indication of a suspicious solitary pulmonary nodule. FDG PET/CT determined a 2.5 × 2-cm soft-tissue lesion (SUVmax, 16.2) with spiculated margins in the hilum of the right lung. A 1-cm diameter lymphadenopathy on the right hilum with an SUVmax of 3.2 was also determined. Transbronchial biopsy of the right hilar lymphadenopathy did not reveal any malignant features in histopathologic examination, and it was determined to be reactive. The patient underwent a right upper lobe segmentectomy, and the histopathologic evaluation revealed that the tumor was a primary lymphoepithelioma-like carcinoma (LELC) of the lung with negative Epstein-Barr virus (EBV) on in situ hybridization studies. In this case report, we mainly focus on the FDG avidity of this very rare kind of tumor comparatively with previous reports and possible explanations of discordancy in FDG avidity in relation to histopathologic characteristics.

Keywords Lymphoepithelioma-like carcinoma · Lung cancer · SUV · FDG · PET/CT

Introduction

Lymphoepithelioma-like carcinomas (LELCs) are extremely rare, accounting for approximately 0.92 % of lung cancers [1]. Although they are categorized as non-small cell lung tumors, LELCs have been reported to have a better prognosis than other types of non-small cell lung cancers.

Lymphoepithelioma was first described in the 1920s by Regaud and Schmincke [2] in the head and neck region of Asian individuals. They have morphologic features identical to undifferentiated nasopharyngeal carcinomas (NPC) but occur outside the nasopharyngeal region. They are histologically characterized by undifferentiated carcinoma with prominent lymphoid stroma [3].

LELCs have been described in many regions subsequently: the nasopharynx, salivary glands, thymus, lung, and stomach [3–8]. Most of these tumors are also concomitant with Epstein-Barr virus (EBV) infection [3]. Primary LELC of the liver has recently been reported as well, although it is extremely rare [9].

Latent EBV infection has been implicated in the pathogenesis of both NPC and LELC. However, the carcinogenesis of LELC is still debated and EBV-induced tumorigenesis is uncertain, because of increasingly reported cases with the absence of association with the EBV genome in the Caucasian LELC lung population, like in our case [10]. To the best of our knowledge, there are only a limited number of reports about the characteristics of LELCs on FDG PET/CT.

Case Report

A 69-year-old male smoker underwent a computed tomography (CT) scan of his thorax due to coughing and shortness of breath. The CT scan revealed a 2-cm soft-tissue mass with

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spiculated corners and with air broncograms inside it, in the right hilar region, spreading toward the apex, throughout the right upper lobe bronchus. In addition, a few mediastinal lymph nodes, the largest of which had a 1-cm diameter and a subcentimetric non-specific nodule in the lower segment of the right lung, were also identified.

The patient was referred to FDG PET/CT with the indication of a suspicious solitary pulmonary nodule. FDG PET/CT determined a 2.5×2 -cm soft-tissue lesion with spiculated margins in the hilum of the right lung, spreading to apex throughout the right bronchus, with an SUVmax of 16.2 (Fig. 1a–d). A 1-cm diameter lymphadenopathy on the right hilum with an SUVmax of 3.2 was also determined. The subcentimetric nodular lesion in the lower segment of the right lung did not show pathologic FDG uptake (SUVmax, 0.9). The primary mass in the hilum of the right lung was reported as a malign lesion and the 1-cm diameter lymphadenopathy on the right hilum with an SUVmax of 3.2 was reported to be a possible malign or reactive lymphadenopathy. The PET/CT survey showed no other pathologic lesions (on the CT) and no pathologic level of FDG uptake elsewhere in the body. The nasopharyngeal region was also clean on the PET/CT. A further detailed review of the scans did not show any significant lymphadenopathy elsewhere in the whole body. Transbronchial biopsy of

the right hilar lymphadenopathy did not reveal any malignant features in histopathologic examination, and it was determined to be reactive.

The patient underwent a right upper lobe segmentectomy, and the histopathologic evaluation revealed that the tumor was an LELC of the lung with negative EBV on in situ hybridization studies. There were small amount of epithelial tumor cells with abundant lymphoplasmacytic cell infiltration (Fig. 2). CD68 (not shown), CD4, CD20 were heterogeneously positive and the pattern of CD8-positive lymphoid areas was determined (Fig. 3). The tumor was staged as pT1bN0M0 together with the whole-body FDG PET/CT survey and postoperative histopathologic evaluation.

As the tumor was determined as early stage LELC no other intervention, like chemotherapy, was considered. The patient has received follow-ups for 3 years with conventional radiology and whole-body FDG PET/CT surveys and has remained disease-free thus far.

Discussion

LELC of the lung is a rarely seen tumor and its frequency has been reported to be 0.92 % among other lung malignancies [1]. It mostly affects Asians in comparison to Caucasians. No gender tendency has been found to be associated with LELC

Fig. 1 F-18 FDG PET/CT shows a 2.5×2 -cm soft-tissue lesion with spiculated margins in the hilum of the right lung, spreading to apex throughout the right bronchus with an SUVmax of 16.2, on (a) MIP, (b) transaxial PET image, (c) transaxial CT and (d) transaxial fusion PET/CT images

Fig. 2 Histological view of the mass consisting small amount of epithelial cells surrounded by a significant lymphocytic infiltration consistent with LELC. Since the lymphocytic infiltration was so significant, neoplastic epithelial cells were inconspicuous (**a** and **b** H & E, $\times 200$), and proliferative activity of lymphocytic component with Ki-67 was very high (**c** immunohistochemistry, $\times 200$)

[2]. Latent EBV infection has been implicated in the pathogenesis of both NPC and LELC. However, the carcinogenesis of LELC is still debated and the association with EBV is variable [11]. Most of the literature is published on the Asian population. According to the immunohistochemical and molecular findings, EBV-induced hyperplasia and premalignant lesions result from epithelial proliferation occurring due to the interaction between the virus and CD receptors of B lymphocytes [12]. The association of the LELC with EBV infection is especially related to Asian Chinese population but not the Caucasian population. Also, LELCs of the bladder, skin, vagina, and cervix have no EBV association [3]. There

is an increasing number of cases reported with the absence of association with the EBV genome in the Caucasian LELC lung population, like the one presented in our case.

Early stage LELCs are observed on CT mostly as poorly circumscribed, peripherally placed <3.5 cm nodules and are not associated with lymphadenopathy [13, 14]. On the other hand, determination of advanced stage disease is made by detection of large, well circumscribed, centrally located lesions with evidence of vascular encasement and peribronchovascular lymphadenopathy. In our reported case of early LELC, CT imaging revealed an intermediate (2 cm) dimensional, but centrally located lesion with spiculated

Fig. 3 Immunohistochemistry results ($\times 200$): *CD3* CD3-positive T cells; *CD20* a few CD20-positive B cells; *CD4* lower numbers of T-helper (CD4-positive) cells; *CD8* CD8-positive cytotoxic T cells

margins and peribronchovascular lymphadenopathy. The final diagnosis was determined as early stage LELC. The prediction of the stage of LELCs depending on the CT characteristics can be insufficient.

On PET/CT, the SUVmax of the lesion was considerably high (16.2), but the 1-cm hilar lymphadenopathy had a non-specific SUVmax for defining it as malignant and differentiating it from reactive and/or inflammatory lymphadenopathies. In this case, the contribution of the PET/CT survey in identifying the status of the lymphadenopathy was limited to guiding the bronchoscopic biopsy. As a whole, however, the PET/CT survey showed no other pathologic lesions (on the CT) and no pathologic level of FDG uptake elsewhere in the body. The nasopharyngeal region was also clean on the PET/CT. A further detailed review of the scans did not show significant lymphadenopathy, and the possibility of lymphoma was excluded as a differential diagnosis. In light of the foregoing, a right upper lobe segmentectomy was planned and the tumor was diagnosed as primary LELC in the pT1bN0M0 stage that was negative for EBV. In those cases diagnosed as primary LELC of the lung: if there is no suspected lesion in the nasopharyngeal region, or a lesion cannot be visualized on CT, conducting a biopsy on this region is not recommended [15].

FDG PET/CT findings of pulmonary LELCs have been rarely reported. The FDG avidity of this very rare kind of tumor is controversial. A case of EBV-positive pulmonary LELC displaying conversion from FDG-negative to FDG-positive avidity during a 2-year follow-up period was reported by Shen et al. [16] They suggested that the observation of such altered FDG uptake in the tumor could be related to the accelerated progression of EBV infected cells after viral latency. In the report of Dong et al. [7], the tumor had a very high affinity for FDG with an SUVmax of 34.5. FDG avid mediastinal lymph nodes were also metastatic. Very high FDG avidity of the tumor in their report was associated with high Ki-67 of the neoplastic epithelial cells. In our case, the early stage tumor without any metastatic lymph nodes also showed a strong FDG uptake (SUVmax, 16.2), similar to the one in Dong et al.'s report. This may be explained by the high proliferation index of substantially lymphoplasmacytic cells in the stroma of the tumor rather than the small amount of neoplastic epithelial tumor proportion. Increased FDG uptake through increased glucose transporters is not tumor specific. Inflammatory cells can also show increased FDG accumulation when they are activated [17]. This type of pulmonary carcinoma has distinct morphological features such as heavy lymphocytic infiltration. In this case, lymphocytic infiltration was composed of prominent T cells (CD3 positive), especially cytotoxic (CD8 positive) T cells, and also lower numbers of T-helper (CD4 positive) cells (Fig. 3). Histocytes expressing CD68 (Not shown) and plasma cells were also present. The histopathologic evaluation revealed that the tumor consisted of a small amount of epithelial cells surrounded by a

significant lymphocytic infiltration. Since the lymphocytic infiltration was so significant, neoplastic epithelial cells were inconspicuous (Fig. 2a, b). The Ki-67 proliferation marker of the lymphocytic component was also very high (Fig. 2c), consistent with the degree of FDG accumulation of the tumor.

The prognosis of primary pulmonary LELC is a divisive issue: a high incidence of systemic metastases is suggested in cases with LELC of the lung. These metastases are reported to be prominently more chemosensitive compared to other non-small cell lung cancers [15]. Han et al. [18] reported that the recurrence of tumors and the histopathologic presence of 5 % or greater necrosis in the tumor tissue were associated with a poor prognosis, rather than metastasis. They also stated that the prognosis of LELC cases was better than that of other lung cancer cases. In our case, the patient has been receiving follow-ups for 3 years with conventional radiology and whole-body FDG PET/CT surveys and is still disease-free after the operation without chemotherapy. This outcome sustains the suggestion that the FDG avidity of primary pulmonary LELCs can reflect the histologic nature of the tumor stroma rather than its malignancy or poor prognosis, unlike most other malignant tumors. Long-term follow-up data about the rarely seen LELC of the lung are quite limited. Very recently Chan et al. [19] reported the utility of FDG PET/CT in assessment of pulmonary LELC via seven cases. They determined that pulmonary LELCs are FDG avid and can be assessed with FDG PET/CT in initial staging and followed-up to determine the response to treatment and also for diagnosis of recurrence. In our case FDG PET/CT was useful in determining the metabolic active primary lesion, in guiding the biopsy of the hilar lymphadenopathy, also in assessing the true stage of the disease via whole-body survey. Unfortunately, there was not any determination about the meaning of different SUVs of the primary tumors in relation to prognosis in any other previous reports and in the recent report of Chan et al. The cases in the latter report were mostly late-stage pulmonary LELCs. The one in our report was an early stage LELC, but had an SUVmax (16.2) higher than the upper limit of the SUVmax range (7.6–14.5) determined on their series. We suggest that the SUVmax of the LELCs can reflect the high proliferative lymphocytic infiltration surrounding the tumor cell nests instead of the higher stage, higher malignancy potential or the poor prognosis.

Taken as a whole, primary LELC of the lung is very rare, and EBV-induced tumorigenesis and FDG avidity of the reported tumors are controversial. Both high proliferative malignant tumor cells and the lymphoplasmacytic cells in the tumor stroma can accumulate high FDG: SUVmax of the primary tumor may be discordant between the reported cases and also incongruous with its prognosis. The prognostic information about this rare tumor type can be found in histopathologic evaluation together with the spread of primary tumor determined on whole-body PET/CT evaluation. The

significance of different SUVmax in initial diagnosis and prognostic prediction via FDG avidity is still debated and is a likely topic for investigation.

Compliance with Ethical Standards

Conflict of Interest Gul Ege Aktas, Nuray Can, Selin Soyluoğlu Demir and Ali Sankaya declare that they have no conflict of interest.

Ethical Statement All procedures performed were in accordance with the ethical standards of the institutional review board and with the 1964 Helsinki declaration and its later amendments. All subjects in the study gave written informed consent or the institutional review board waived the need to obtain informed consent.

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