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CASE REPORT

MINIMALLY INVASIVE LUNG ADENOCARCINOMA, MYCOBACTERIUM AVIUM INTRACELLULARE AND LANGERHANS HISTIOCYTOSIS

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Abstract. *Adenocarcinoma of the lung is the most common lung tumor, accounting for about 40% of the cases. Minimally invasive adenocarcinoma may be a part of a continuum of morphological changes, leading to the development of invasive adenocarcinoma of the lung. It is defined as a predominantly lepidic lesion measuring ≤3.0 cm with only small foci of invasion, the largest of which should be less than 0.5 cm. An association between lung cancer, Mycobacterium avium infection and Langerhans cell histiocytosis has already been described in past studies. We present a case of a 59-year-old patient with PET/CT data for metabolically active tumor (28 mm), which had increased in size and activity compared to the previous scan. On admission to our hospital, he had undergone 14 courses of chemotherapy at another institution for diffuse large B-cell lymphoma (DLBCL). After the left upper lobectomy, minimally invasive lung adenocarcinoma, Mycobacterium avium intracellulare and accompanying Langerhans cell histiocytosis were histologically verified.*

Key words: *lung adenocarcinoma, minimally invasive, Mycobacterium avium, Langerhans cell histiocytosis, case report*

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INTRODUCTION

Minimally invasive adenocarcinoma (MIA) has been introduced by the International Association for the Study of Lung Cancer (IASLC)/ American Thoracic Society (ATS)/European Respiratory Society (ERS) classification. It represents the link between adenocarcinoma in situ (AIS) and invasive adenocarcinoma (IAL) and is presumed to result from genetic changes occurring in the multi-step process of the development of IAL. This process starts with the atypical adenomatous hyperplasia (AAH), which progresses to AIS and MIA, resulting in the formation of IAL [1].

Mycobacterium avium complex (MAC) consists of multiple non-tuberculosis mycobacterial (NTM) species (including M. avium and Mycobacterium intracellulare), which can be distinguished with genetic testing. MAC is the most common cause of NTM species infections in humans, with respiratory system being the typical site of infection. Chronic lung diseases and immune-suppression are often predisposing risk factors [2].

Langerhans cell histiocytosis (LCH) is a rare interstitial lung disease. Co-existence of LCH with other malignancies, lymphoproliferative diseases, mainly Hodgkin's lymphoma, mantle cell lymphoma and angio-immunoblastic T-cell lymphoma have been described in the literature [3]. We will present a patient with a history of chemotherapy due to diffuse large B-cell lymphoma (DLBCL), who underwent surgery in our hospital. He was diagnosed with MIA. The infection with Mycobacterium avium intracellulare and LCH were incidental findings.

CASE REPORT

A 59-year-old patient with hemoptysis and fatigue was admitted to the hospital for the first time. The patient had a history of 14 courses of chemotherapy as part of therapy for Diffuse Large B-cell Lymphoma (DLBCL). Physical examination and laboratory tests showed no abnormalities. Chest computed tomography (CT) demonstrated that a previously known lung lesion had enlarged since the patient's previous scan (Figure1). Positron emission tomography/CT (PET/CT) showed tumor formation in the lingula of the left lung, approximately 28 mm in diameter, with extremely high metabolic activity and SUV (Standardized Uptake Values) measuring up to 23.6, on the background of a subsegmental atelectasis. The lesion has been enlarged both in diameter and activity in comparison to the previously performed PET/CT. An old echinococcosis cyst was found in the spleen with a size of 50 mm, as well as a partly consolidated fracture of the 11th rib on the left. No metabolically active lymph nodes suspicious of a lympho-proliferative process were found.

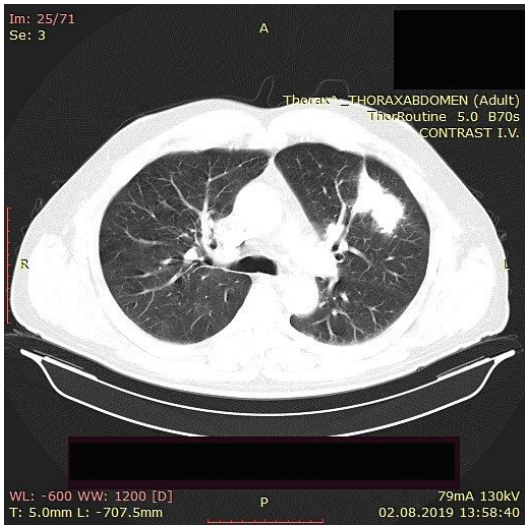

Fig. 1. Chest computed tomography (CT) demonstrating that a previously known lung lesion had enlarged since the patient's previous scan

Via lateral thoracotomy a densely-elastic lesion was found in the 3rd-4th segment, with a measure of 70/60 mm. There was a puckering of the visceral pleura. The lesion was fully resected via left upper lobectomy. There was some difficulty in the detachment of the upper lobe arteries, probably due to the previously performed chemotherapy. Seven mediastinal lymph nodes were also removed, all showing anthracotic-fibroblastic changes.

Histological examination showed a solitary lesion with the characteristics of MIA and a diameter of around 2 cm. A dominant lepidic growth pattern and an invasive component with a diameter less than 5 mm was detected. The lesion was surrounded by a dense peribronchiolar inflammatory infiltrate, composed of pigmented histiocytes, eosinophils, lymphocytes, fibrosis, focal necrosis and some giant cells. This structure formed a mass of around 7 cm, obliterating the lung parenchyma and resembling LCH. There was a reactive pneumocytic hyperplasia and granulomatous inflammation with fibroblastic focuses in the periphery of these changes, resembling an organizing pneumonia. There were also some recanalized thrombi. The lymph nodes showed no metastases. A sarcoid-like granulomatous reaction was observed in part of them (probably a reaction from the chemotherapy); in the remaining lymph nodes – chronic sinus lymphadenitis was present. There was no evidence of a lympho-proliferative process. Immunohistochemical examination was performed – positive expression for S-100 and CD1a and negative expression for CD45 was present. The LCH diagnosis was given (Figure 2). A molecular test was applied by the PCR method (AmoyDx BRAF V600/E/K/R/D kit) and the presence of a BRAF mutation was not established. Structures, resembling Mycobacterium avium intracellulare were proved by Ziehl-Nielsen staining and molecular testing, keeping to the official American Thoracic Society (ATS)/ Infectious Diseases Society of America (IDSA) statement [4]. After surgical treatment, the patient received rifampicin, ethambutol and clarithromycin, in accordance to the recommendations for the treatment of NTM pulmonary disease (NTM-PD) [5].

Two years later, the patient has relapsed DLBCL and has undergone chemotherapy.

DISCUSSION

MIA is characterized as a predominantly lepidic lesion measuring ≤3.0 cm with only small foci of invasion, the largest of which being ≤0.5 cm. A lepidic pattern of growth is defined as tumor cells proliferating along the surface of intact alveolar walls without stromal or vas-

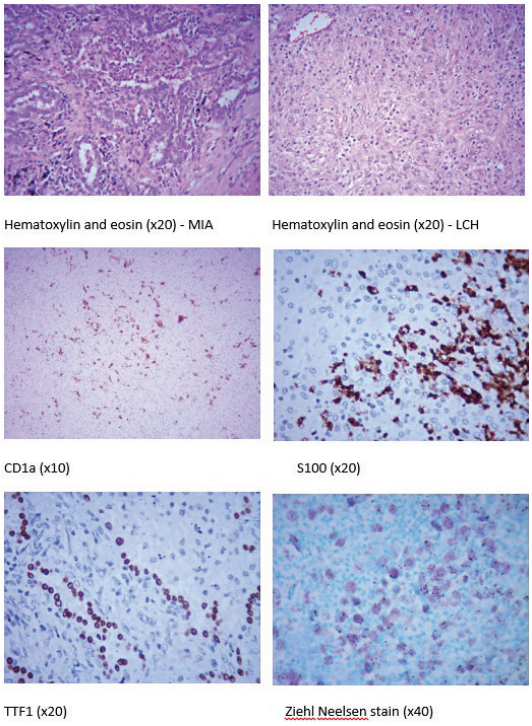

Fig. 2. Positive expression for S-100 and CD1a and negative expression for CD45 was present – Langerhans histiocytosis

cular invasion. The invasive component of MIA, has to be of histological type, other than lepidic – acinar, papillary, micropapillary and/or solid; or there have to be tumor cells invading the myofibroblastic stroma [6]. Studies have shown that a higher percentage of the lepidic component within the MIA and IAL correlates with a better five-year survival rate [7, 8].

Beside the various growth patterns there are three histologic types of MIA – non-mucinous, mucinous, and mixed. The non-mucinous shares the same positivity for immune-histochemical markers as the IAL – Thyroid transcription factor 1 (TTF1) and Napsin A, and the mucinous subtype is positive for Cytokeratin 20 (CK20) and Hepatocyte Nuclear Factor 4 Alpha (HNF4A), and negative for pneumocyte markers, sharing these characteristics with the mucinous IAL. The diagnosis of MIA is less common than that of the already invasive adenocarcinoma. This is due to the smaller size of MIA compared to IAL and the fewer symptoms, if any, compared to those in IAL [9].

Although the definition of MIA is a lesion of under 3 cm, a study by the Departments of Thoracic Surgery and Pathology and Clinical Laboratories, National Cancer Center Hospital, Tokyo; and Division of Respiratory Surgery, Nihon University School of Medicine, Tokyo, Japan has assumed that even a lesion with a diameter larger than 3 cm, but with an invasive component of less than 5 mm can be classified as MIA, since the invasive component is the most important prognostic criteria in these tumors. This broadens the better prognosis carrying MIA group of lesions [10]. Additionally, Yoshizawa et al., showed 100% disease free survival (DFS) for MIA with 100% overall survival [11]. In a study by Tsuta et al, 100% 5- and 10-year disease-specific survival rates for AIS and MIA were reported [12]. The possible transition from AIS to MIA and eventually IAL is a multi-step process involving various gene alterations like repression of Transforming Growth Factor β Receptor 2 (TGFBR2), amplification of Programmed Cell Death 6 (PDCD6) and Telomerase Reverse Transcriptase (TERT) genes, Epidermal Growth Factor Receptor (EGFR) mutation and amplification. The expression of two particular transcriptional factors is worth noting – Notch2 and Six1. Takahiro Mimae and colleagues concluded that paired upregulation of these transcriptional factors in invasive cancer cells in MIAs contributes to the transition from preinvasive to invasive adenocarcinoma with a more malignant phenotype in the long term [13].

LCH is a rare interstitial disease of the lung and is due to clonal proliferation of cells that display a BRAF (BRAF V600 E) mutation in around 57% of cases [14]. An increasing number of secondary malignant and non-malignant diseases associated with LCH have been reported in the literature, including pulmonary carcinoma, carcinoid, Hodgkin's and non-Hodgkin's lymphoma, and mediastinal ganglioneuroma [15]. Egeler et al, demonstrated the association between LCH with malignant neoplasms – lymphoma, leukaemia lung cancer and other solid tumors. It was revealed that in 75% (9 out of 12) of the patients with lung cancer, both cancer and LCH were concurrent which suggested that it may be due to specific dendritic cell proliferation and LCH is most likely a localized reactive process [16].

Pina-Oviedo et al, describe lymphoma-associated LCH without BRAF or MAP2K1 mutations and suggest that the RAS/RAF/MAPK pathway might be activated by non-mutational mechanisms such as cytokines or other products of the associated neoplasm. They conclude that in this case LCH might be considered benign [3].

In recent years, the incidence of MAC infections has increased worldwide. MAC infection is predominantly found in immune-suppressed patients. Symptoms in immunocompetent patients are non-specific, with chronic cough being the most frequent symptom [2]. It is possible that chemotherapy in this particular case, along with the co-morbidity of the patient, has created a predisposition for the development of MAC infection. The possible connection between the NTM and the development of the MIA deserves attention. A study conducted by Atsuhisa Tamura and colleagues, showed that in 2% of reported lung cancer cases between 2003 and 2011, the bronchial washings were positive for MAC or

other NTM-negative infections [17]. Similar results had also been published in previous studies [18]. Fujita et al. reported 3 cases of acute development of MAC lung disease in patients with lung cancer without X-ray fibrocavitary or reticulo-nodular changes that could indicate NTM infection at the initial diagnosis of lung cancer [19].

However, it is unclear whether the persistent chronic infection with MAC may be able to create a predisposing environment for the development of cancer or if the opposite is true. It is also important that these studies have not been conducted with the idea of unveiling a pathophysiological connection between an existing MAC infection and the development of a tumor lesion. It is still unclear whether such a connection exists, but an association between the two diseases is reasonable to be assumed.

In our case, the antecedent disease was DLBCL and the patient underwent 14 courses of chemotherapy. Even then, a minimal lung lesion was noted and was followed up by imaging. The patient was not sent for a surgical intervention, which we believe was mandatory. When an increase in the PET/CT lesion was detected, the patient was referred to the Thoracic Surgery Department for operative treatment. LCH remained unrecognized on all previous imaging scans and on the most recent PET/CT.

CONCLUSION

It is debatable whether the detected LCH is a reactive lesion, as a response to MIA, or vice versa – LCH contributed to the development of MIA. It may have been present at the time the DLBCL was diagnosed and may have been a reactive process due to the lymphoma or the chemotherapy. Some studies have noted an association between MAC infections, LCH, lymphomas and concomitant lung tumors, and although no clear pathophysiological connection has been established, the pathophysiological link between them deserves further research.

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Consent for publication: *Consent form for publication was signed by the patient and collected.*

Ethical statement: *This study has been performed in accordance with the ethical standards as laid down in the Declaration of Helsinki.*

REFERENCES

1. Hu X, Fujimoto J, Ying L, et al. Multi-region exome sequencing reveals genomic evolution from preneoplasia to lung adenocarcinoma. Nat Commun. 2019:5;10(1):2978. doi: 10.1038/s41467-019-10877-8. Erratum in: Nat Commun. 2021;12;12(1):2888.
2. Sami M, Fibi N. Mycobacterium avium Complex. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024; Feb 25.
3. Pina-Oviedo S, Medeiros LJ, Li S, et al. Langerhans cell histiocytosis associated with lymphoma: an incidental finding that is not associated with BRAF or MAP2K1 mutations. Mod Pathol. 2017;30(5):734-744. doi: 10.1038/modpathol.2016.235.
4. Griffith DE, Aksamit T, Brown-Elliott BA et al. An official ATS/IDSA statement: Diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007;175:367-416.
5. Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. Eur Respir J 2020; 56: 2000535, https://doi.org/10.1183/13993003.00535-2020.
6. WHO Classification of Tumours Editorial Board. Thoracic tumours. Lyon (France): International Agency for Research on Cancer; 2021. (WHO classification of tumours series, 5th ed.; vol. 5).
7. Kadata K, Villena-Vargas J, Yoshizawa A, et al. Prognostic Significance of Adenocarcinoma in situ, Minimally Invasive Adenocarcinoma, and Nonmucinous Lepidic Predominant Invasive Adenocarcinoma of the Lung in Patients with Stage I Disease. Am J Surg Pathol. 2014; 38(4): 448–460.
8. Strand T, Rostad H, Strøm E, Hasleton Ph. The percentage of lepidic growth is an independent prognostic factor in invasive adenocarcinoma of the lung. Diagn Pathol. 2015; 10: 94.
9. Chakraborty RK, Sharma S. Bronchoalveolar Cancer. StatPearls Treasure Island: StatPearls Publishing; 2024. //www.ncbi.nlm.nih.gov/books/NBK513281/
10. Suzuki S, Sakurai H, Masai K, et al. Departments of Thoracic Surgery and Pathology and Clinical Laboratories, National Cancer Center Hospital, Tokyo; and Division of Respiratory Surgery, Nihon University School of Medicine, Tokyo, Japan. A Proposal for Definition of Minimally Invasive Adenocarcinoma of the Lung Regardless of Tumor Size. J Thorac Oncol.2017 Dec;12(12):1788-1797. doi: 10.1016/j.jtho.2017.08.015.
11. Yoshizawa A, Motoi N, Riely GJ, et al. Impact of proposed IASLC/ATS/ERS classification of lung adenocarcinoma: prognostic subgroups and implications for further revision of staging based on analysis of 514 stage I cases. Mod Pathol. 2011;24(5):653-64. doi: 10.1038/modpathol.2010.232.
12. Tsuta K, Kawago M, Inoue E, et al. The utility of the proposed IASLC/ATS/ERS lung adenocarcinoma subtypes for disease prognosis and correlation of driver gene alterations. Lung Cancer. 2013;81(3):371-376. doi: 10.1016/j.lungcan.2013.06.012.
13. Takahiro M, Morihito O, Man H, et al. Upregulation of Notch2 and Six1 Is Associated with Progression of Early-Stage Lung Adenocarcinoma and a More Aggressive Phenotype at Advanced Stages. doi: 10.1158/1078-0432.CCR-11-1946
14. Badalian-Very G, Vergilio JA, Degar BA, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. Blood. 201016; 116(11):1919-23. doi: 10.1182/blood-2010-04-279083.
15. Tomashefski JF, Khiyami A, Kleinerman J. Neoplasms associated with pulmonary eosinophilic granuloma. Arch Pathol Lab Med. 1991;115(5):499-506.
16. Egeler RM, Neglia JP, Puccetti DM, et al. Association of Langerhans cell histiocytosis with malignant neoplasms. Cancer. 1993:1;71(3):865-73.doi:10.1002/1097-0142(19930201)71:3<865::aid-cncr2820710334>3.0.co;2-0.
17. Atsuhisa T, Akira H, Kei K, et al. Relationship Between Lung Cancer and Mycobacterium Avium Complex Isolated Using Bronchoscopy. Open Respir Med J. 2016; 10: 20–28.
18. Lande L, Peterson DD, Gogoi R, et al. Association between pulmonary mycobacterium avium complex infection and lung cancer. J Thorac Oncol 2012; 7:1345-51.
19. Fujita K, Yamamoto Y, Kanai O, et al.Development of Mycobacterium avium complex lung disease in patients with lung cancer on immune checkpoint inhibitors.Open Forum Infect Dis, 2020;7:ofaa067.