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Case Report
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Is Epithelioid Hemangioendothelioma a Cold Tumor for Immune Check Point Inhibitors? A Case Report

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Abstract

Epithelioid Hemangioendothelioma (EHE) is a rare malignant vascular neoplasm. We herein report a rare pulmonary EHE case and consider the potential treatment target. A 55-year-old male patient with bilateral multiple pulmonary nodules underwent partial resection of the lung to obtain a definitive diagnosis, and the diagnosis of EHE was made. Since EHE is a chemotherapy-resistant tumor, we analyzed the molecular expression related to tumor immunity and hormone receptors by Immunohistochemistry (IHC). Major Histocompatibility Complex (MHC) class I and PD-L1 molecules in the tumor were significantly attenuated, and lymphocytes, CD8 T cells, and tumor-specific CD103-positive lymphocytes were scarcely observed in the tumor. Neither estrogen receptor nor progesterone receptor was expressed on tumor cells. The patient did not wish to be treated aggressively. Although our data revealed that neither immune checkpoint inhibitors nor hormonal therapy for pulmonary EHE could be expected to be effective, further analyses using more EHE cases are necessary to consider the potential treatment target for EHE.

Keywords: Epithelioid hemangioendothelioma; Surgery; Immunotherapy; PD-L1; CTL

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Abbreviations

EHE: Epithelioid Hemangioendothelioma; IVBAT: Intravascular Sclerosing Bronchoalveolar Tumor; WWTR1: WW domain-containing Transcription Regulator 1; CAMTA 1: Calmodulin-Binding Transcription Activator 1; CT: Computed Tomography; FDG: Fluorodeoxyglucose; PET: Positron Emission Tomography; VATS: Video-Assisted Thoracoscopic Surgery; IHC: Immunohistochemistry; MHC: Major Histocompatibility Complex; PD-L1: Programmed Cell Death Protein Ligand-1; ER: Estrogen Receptor; PGR: Progesterone Receptor; ICI: Immune Checkpoint Inhibitor; CTL: Cytotoxic T Lymphocyte

Introduction

Epithelioid Hemangioendothelioma (EHE) is a rare vascular neoplasm of low- or intermediate-grade malignancy. It was originally named as Intravascular Sclerosing Bronchoalveolar Tumor (IVBAT) in 1975 by Dail and Liebow [1]. It was then renamed as EHE, which has an endothelial cell deviation, in 1982 by Weiss and Enzinger [2]. The characteristics of EHE are associated with a translocation between chromosomes 1 and 3, resulting in a fusion protein of the WW domain-containing Transcription Regulator 1 (WWTR1) and the Calmodulin-Binding Transcription Activator 1 (CAMTA 1), leading to constitutive activation and malignant transformation [3]. However, there is no effective therapy for non-resectable EHE. We herein report a rare case of a patient with pulmonary EHE and consider the potential treatment target for EHE.

Case Presentation

The patient was a 55-year-old asymptomatic male who visited our hospital after abnormal shadows were detected on a chest X-ray. He had no history of malignant disease. Chest Computed Tomography (CT) revealed the presence of multiple well-demarcated solid nodules of from 0.5 cm to 2 cm in diameter in both lungs (Figure 1). A systemic CT examination revealed no tumors other than these pulmonary tumors. The abnormal accumulation of Fluorodeoxyglucose (FDG) could not be detected by Positron Emission Tomography (PET). We performed wedge resection

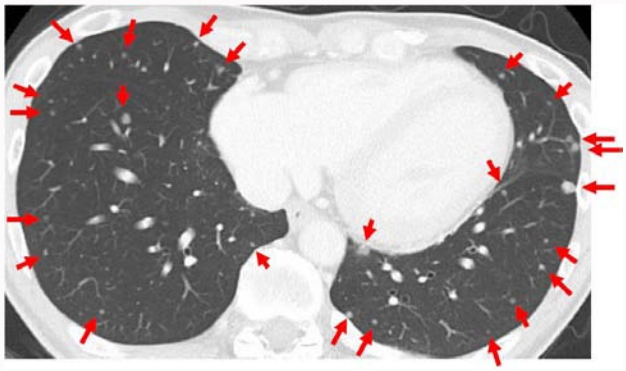

Figure 1: Chest Computed Tomography (CT) revealed the presence of multiple well-demarcated solid nodules of from 0.5 cm to 2 cm in diameter in both lungs.

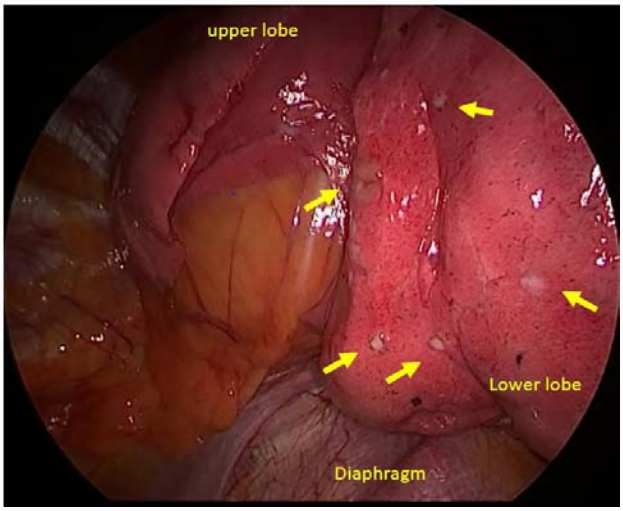

Figure 2: Surgical findings revealed a large number of well-defined yellowish-white nodules with pleural changes.

of the left lung by Video-Assisted Thoracoscopic Surgery (VATS). A large number of well-defined yellowish-white nodules with pleural changes were found (Figure 2). A linear stapling device was used to remove the lung nodules. The nodules were firm and solid. On the cut surface, these nodules appeared yellowish-white in color. A frozen section revealed cord-like or pseudopapillary proliferation of epithelioid tumor cells with enlarged nuclei, and eosinophilic cytoplasm was observed in the background of cartilage-like hyalinized stroma that was filled in the alveolar spaces. The center of the lesion showed strongly degenerated coagulative necrosis of the tumor cells. These findings were suggestive of EHE. The postoperative course was uncomplicated. The histopathological findings revealed a vitreous degeneration lesion with cholesterin cleft in the center, and the cord-like or individual cellular proliferation of atypical cells with enlarged nuclei and eosinophilic cytoplasm on a background of a myxohyalinous extracellular matrix resembling lobulated cartilage that filled the alveolar spaces in the periphery. Many tumor cells with intracytoplasmic vacuoles representing primitive vascular lumina were found. Mitotic figures were sometimes encountered (Figure 3A). Immunohistochemically, the tumor cells were positive for Factor VIII-related antigen, CD31 and CD34 (Figure 3B-3D) but were negative for cytokeratin (AE1/AE3), TTF-1, and D2-40. The MIB-1 index was 2% to 3%. The lesion was diagnosed as EHE based on these features. Since EHE is a chemotherapy-resistant tumor, we analyzed the molecular expression relating to tumor immunity and hormone receptors by Immunohistochemistry (IHC) to explore the possibilities of immunotherapy and hormonal therapy. Major Histocompatibility Complex (MHC) class I and Programmed cell Death protein Ligand-1 (PD-L1) molecules in the tumor were significantly attenuated, and lymphocytes, CD8 T cells, and tumor-specific CD103-positive lymphocytes were scarcely observed in the tumor (Figure 3E-3I). With its reduced MHC class I expression, the tumor cells appeared to be ignored by immune surveillance. In addition, microsatellite instability was confirmed to be negative (data not shown). Furthermore, neither Estrogen Receptor (ER) nor Progesterone Receptor (PGR) was expressed on tumor cells according to IHC (Figure 3I, 3J). Given these findings, neither Immune Checkpoint Inhibitors (ICIs) nor hormone therapy could be expected to be effective. The patient did not wish to be treated aggressively and is currently being followed up.

Discussion

There are no standard treatments or consensus guidelines for EHE because of its low incidence. Therefore, to examine the sensitivity to ICIs and hormonal therapy, the expression of immunological or hormonal molecules was analyzed by IHC in this study. Fusion genes, which are often observed in EHE cases, elicit powerful immunogenic tumor antigens that can induce strong immune responses [4]. In this analysis, the downregulation of MHC class I expression on the tumor cells was observed. Even if tumor cells have powerful immunogenic tumor antigens, such as fusion gene-derived antigens, they can theoretically escape from the tumor immune response by reducing the MHC class I expression. No infiltration of CD8 T cells or tumor-specific CD103 T cells into the tumor was observed, and expression of the PD-L1, which was mostly expressed after the immune response, was also weak. CD103 is a ligand of E-cadherin, an adhesion molecule, and lymphocytes expressing CD103 in breast cancer are cancer-specific lymphocytes. The prognosis is reportedly good if CD103-positive lymphocytes are present in the cancer [5]. In the present study, no immune response was observed to occur locally in the tumor. This phenomenon may have been due to a state which is called “immunological ignorance”, namely the tumor antigens were ignored by the tumor-specific lymphocytes. Loss of MHC class I is one of the mechanisms of escape from a Cytotoxic T Lymphocyte (CTL) attack. The hypothesis of immunoselection proposes that tumor cells remain genetically unstable in order to escape from immune surveillance; tumor cells sensitive to CTL attack are easily eliminated, while the refractory variant with deficiency of MHC class I expression may escape from immunosurveillance [6]. The upregulation of MHC class I is induced by proinflammatory cytokines, such as interferon α. Giacomini et al. [7] reported that interferon α-stimulated long-lasting MHC class I expression may amplify beta cell antigen presentation during the early phases of type 1 diabetes and that interferon α-inhibitors might need to be used at very early stages of the disease to be effective. Roudier-Pujol et al. [8] reported that partial remission was obtained after interferon α-2A treatment against EHE. Although a basic analysis was not performed, powerful immunogenic tumor antigens derived from fusion genes may have been forcibly expressed, possibly inducing an effective immune response, as interferon α-2A increases the MHC class I expression. Interferon α-2A may be an effective treatment for EHE and is worth investigating further. Ohori et al. [9] reported that the expression of ER and PGR, which can be targets of hormone therapy,

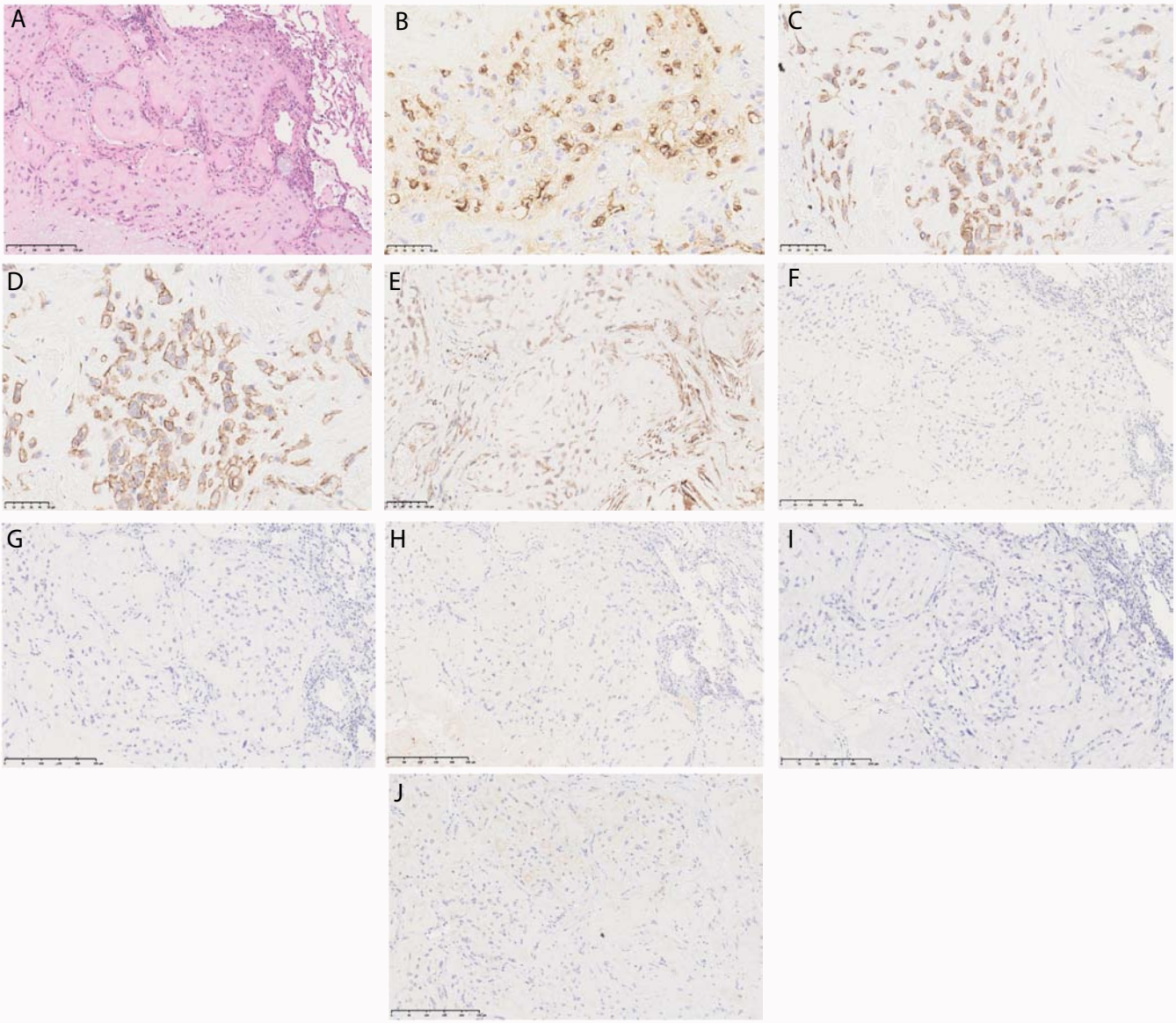

Figure 3: (A) The histopathological findings revealed a vitreous degeneration lesion with cholesterin cleft in the center, and the cord-like or individual cellular proliferation of atypical cells with enlarged nuclei and eosinophilic cytoplasm on a background of a myxohyalinous extracellular matrix resembling lobulated cartilage that filled the alveolar spaces in the periphery. (Hematoxylin and Eosin [HE] staining). HE staining showed no tumor-infiltrating lymphocytes. (B) Tumor cells were positive for Factor VIII-related antigen. (C) Tumor cells were positive for CD31. (D) Tumor cells were positive for CD34. (E) Tumor cells were weak for MHC class I (EMR8-5.1). (F) Tumor cells were almost negative for PD-L1 (SP263). (G) Immunostaining for CD8 (SP57) revealed no CD8 T cells among tumor cells. (H) Immunostaining for CD103 (EPR4166(2)) revealed no CD103 T cells among tumor cells. (I) Tumor cells were negative for estrogen receptor. (J) Tumor cells were negative for progesterone receptor.

in EHE was observed. However, in this case, neither ER nor PGR was expressed, so the efficacy of hormone therapy could not be expected. Although the 5-year overall survival rate among 80 pulmonary EHE patients undergoing surgery was approximately 60%, there is no single effective treatment for bilateral multiple pulmonary EHE. Lung transplantation should be considered for pulmonary EHE patients with pleural hemorrhagic effusion and anemia [10]. Thus far, there have been no reports on the immunological analysis of EHE, making this the first report. Although only one case was analyzed in the present study, our findings suggest that little efficacy of ICIs and hormonal therapy can be expected in cases of EHE. Further analyses will be necessary involving more cases to establish a new treatment for EHE.

Conclusion

We encountered a rare case of EHE, which is a chemotherapy-resistant tumor. Although we analyzed the molecular expression relating to tumor immunity and hormone receptors by IHC, our data suggested that neither ICIs nor hormonal therapy for EHE could be expected to be effective. However, studies with a larger sample size will be required in order to provide a more comprehensive understanding, which would help improve the clinical treatment and prognosis of patients with EHE.

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