



Malignant Pleural Mesothelioma with Tumor-Associated Blood/Tissue Eosinophilia and Increased Blood TARC/CCL17 Level: A Case Report

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Abstract

Malignant pleural mesothelioma (MPM) is a cancer of the pleura. There is an established correlation between asbestos exposure and MPM. Despite the ban of asbestos, MPM incidence is still expected to rise because of the very long lag-times between exposure and diagnosis. However, MPM remains a universally fatal cancer with median survival from diagnosis being only 9-12 months. We described a 60-year-old male with MPM presenting with various clinical manifestations, including tumor-associated blood eosinophilia, tumor-associated tissue eosinophilia, increased platelet number, hypercoagulable state and increased blood thymus and activation-regulated chemokine (TARC)/CCL17 level. TARC/CCL17 might be a biomarker and therapeutic target for a subpopulation of patients with MPM.

Introduction

Malignant pleural mesothelioma (MPM) is the most common primary tumor of the pleura and is related to asbestos exposure in more than 80% of cases [1]. Tumor-associated blood eosinophilia (TABE) has been detected in 0.5% to 1.7% of patients with malignancy [2], while TABE is a rare finding in MPM [3]. Tumor-associated tissue eosinophilia (TATE) is defined as "eosinophilic stromal infiltration of a tumor not associated with tumor necrosis or ulceration" [4]. Multiple studies have demonstrated that TATE is detected in various types of solid tumors [5]. However, in MPM specimens, macrophage, natural killer cell and T cell infiltrations are always detected, but dendritic cells, eosinophils, mast cells and neutrophils are rarely detected [6]. Thymus and activation-regulated chemokine (TARC/CCL17) functions as a selective chemoattractant for T cells that express a receptor binding TARC/CCL17 with high affinity and specificity, CC chemokine receptor 4 (CCR4) [7]. Here we report a case of MPM with TABE/TATE and an increased blood TARC/CCL17 level.

Case Presentation

A 60-year-old Japanese male was admitted to the Pulmonary Medicine Ward for a right-sided pleural effusion with unremitting productive cough, progressive weight loss, fever and fatigue. He had a smoking history of one pack per day for 35 years and no history of allergic diseases and previously worked in the coating industry for 40 years, which was suggestive of asbestos exposure. Radiographic findings revealed right-sided pleural effusion and contralateral pleural thickenings, some of which invaded the mediastinum massively (Figure 1a and 1b).

A blood test indicated an increased number of total white blood cells ($9.2 \times 10^3/\mu\text{l}$), eosinophils ($984/\mu\text{l}$) and platelets ($50.1 \times 10^4/\mu\text{l}$), and elevated levels of C-reactive protein (19.14 mg/dl), D-dimer (1.5 $\mu\text{g/ml}$, normal range $<1.0 \mu\text{g/ml}$), carcinoembryonic antigen (CEA) (7.4 ng/ml; normal range $<5.0 \text{ ng/ml}$), tissue polypeptide antigen (150 U/L; normal range $<70 \text{ U/L}$), soluble mesothelin related protein (5.4 nmol/L; normal range $<1.5 \text{ nmol/L}$), eosinophil cationic protein ($>200 \mu\text{g/L}$) and TARC/CCL17 (1777 pg/ml; normal range $<450 \text{ pg/ml}$). Drained pleural fluid also revealed an increased number of total white blood cells ($23.4 \times 10^3/\mu\text{l}$) and eosinophils ($11.7 \times 10^3/\mu\text{l}$). Fluid cultures for tuberculosis and other microbes were negative. A right parietal pleural biopsy revealed sheets infiltrated by malignant epithelioid cells with infiltration of eosinophils (Figure 2a). Immune staining was positive for calretinin (Figure 2b) and podoplanin (D2-40) (Figure 2c), and negative for thyroid transcription factor 1 (TTF-1), epithelial cell adhesion molecule (EpCAM: MOC-31 and Ber-EP4), CEA and Napsin A. The final diagnosis was malignant mesothelioma of epithelial type (stage IV: cT4NXM0).

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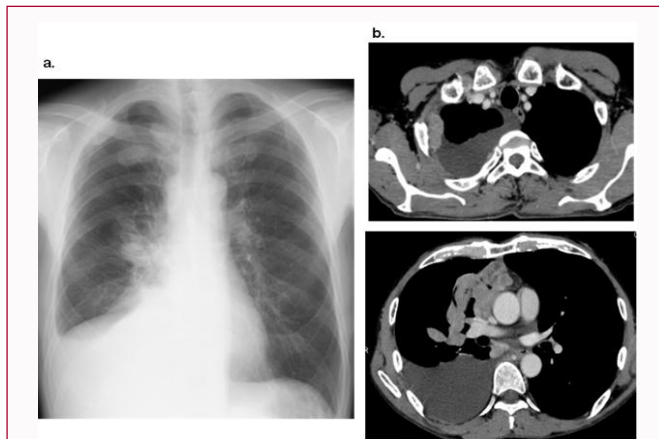


Figure 1: Chest X-ray a) and contrasted computed tomography scan b) on the first admission.

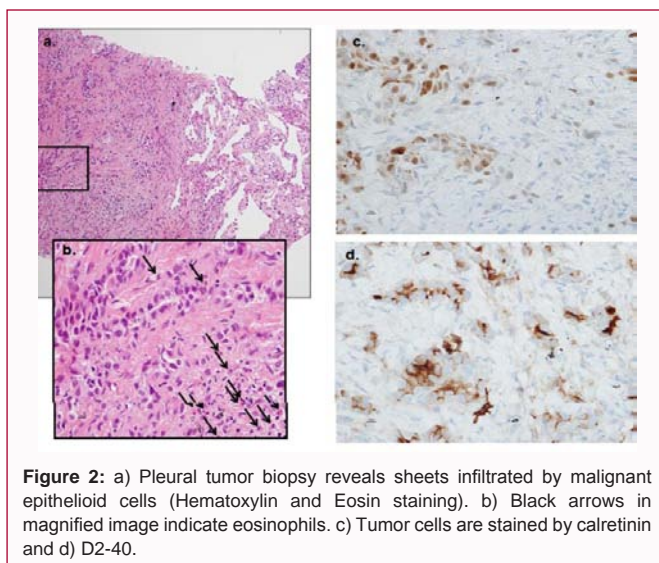


Figure 2: a) Pleural tumor biopsy reveals sheets infiltrated by malignant epithelioid cells (Hematoxylin and Eosin staining). b) Black arrows in magnified image indicate eosinophils. c) Tumor cells are stained by calretinin and d) D2-40.

After diagnosis, two courses of carboplatin + pemetrexed were administered until progressive disease, four courses of cisplatin + gemcitabine were continued until progressive disease, and third line chemotherapy was performed. Until before the fourth chemotherapy (the second cycle of cisplatin + gemcitabine), blood tests revealed mild to severe eosinophilia (Figure 3). However, blood eosinophilia disappeared after initiating continuous low dose steroid treatment for palliative care (for appetite loss and fatigue) at the time of the fourth chemotherapy. He died of progressive respiratory failure 12 months after the diagnosis.

Discussion

TATE was first described by Przewoski in 1896 in carcinoma of the cervix [8]. Multiple studies have demonstrated TATE in various types of solid tumors, including colon tumors, oral squamous cell carcinoma, esophageal squamous cell carcinoma, nasopharyngeal carcinoma, penile cancer, laryngeal carcinoma, pulmonary adenocarcinoma, bladder carcinoma, prostate cancer and Hodgkin lymphoma [5]. Hegmans et al. [6] examined the inflammatory component in MPM tumor tissue by immunohistochemistry and revealed that macrophages (CD68) and natural killer cells (CD16) constitute the majority of the inflammatory cell infiltration, and that interactions between cancer cells and host immune T-cells

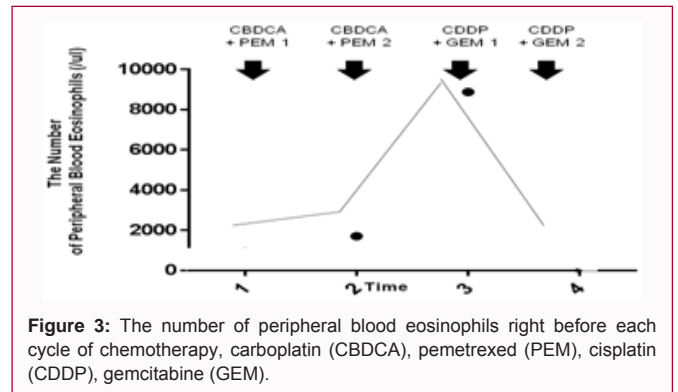


Figure 3: The number of peripheral blood eosinophils right before each cycle of chemotherapy, carboplatin (CBDCA), pemetrexed (PEM), cisplatin (CDDP), gemcitabine (GEM).

(pan-T (CD3), T helper/inducer (CD4) and T-suppressor/cytotoxic lymphocytes (CD8)) were visualized inside, at the rim and in the stroma of mesothelioma specimens. However, the authors rarely detected dendritic cells, eosinophils, mast cells, B-cells or neutrophils in MPM [6]. To our knowledge, this is the first case report of MPM with TATE.

Some tumor cells produce Interleukin-3 (IL-3), IL-5, eotaxin-1 and TARC/CCL17, which can collectively act on the differentiation and/or migration of eosinophils [5]. Hegmans et al. [6] also examined cytokine expression profiles in the supernatant of mesothelioma cell lines derived from patients with MPM and detected high levels of growth-related oncogene and RANTES but not eotaxin or TARC (IL-5 and IL-3 were not examined). In our case, a blood test revealed increased levels of TARC/CCL17 (1777 pg/ml; normal range <450 pg/ml) and eosinophil cationic protein (>200 µg/L; normal range <14.9 µg/L) at the time of diagnosis but no detection of IL-3 or IL-5 (eotaxin1 was not measured).

TARC/CCL17 is a ligand of CCR4 that specifically binds to and induces chemotaxis of Th2 and regulatory T (Treg) cells. Thielen et al. [9] reported that IL-5 and TARC/CCL17 expression highly correlated with eosinophilia in T-cell lymphomas, suggesting that these chemokines are involved in the recruitment of eosinophils into the tumors. As the tumor tissue in our case was not stained by immunohistochemistry with anti-TARC/CCL17 antibody, we could not determine whether TARC/CCL17 was produced directly or indirectly by tumor cells. However, we speculate that increased blood TARC/CCL17 levels are involved in TATE and TATE in this case.

Treg cells are prevalent within murine and human mesotheliomas, with their removal shown to result in tumor growth inhibition and the release of anti-tumor effector T cells from immunosuppression [10]. TARC/CCL17 is also highly expressed in the serum of patients with lymphoma [11] and gastric cancer [12] and potentially predicts and acts as a potent stimulator of colon [13] and lung cancer cell proliferation [14]. Furthermore, targeting immune checkpoints as treatments for various solid tumors has recently shown promise in clinical settings. We did not examine Treg cells in tumor tissue of our case. However, our patient displayed an increased serum TARC/CCL17 level. Thus, TARC/CCL17 might be a therapeutic target for a subpopulation of patients with MPM.

Additionally, TARC/CCL17 is known to induce platelet aggregation through CCR4, a receptor for TARC/CCL17 that is expressed on platelets [15]. Indeed, platelet and eosinophil counts in the peripheral blood of patients with active tuberculosis were significantly increased, and the platelet counts were positively

correlated with serum TARC levels [16]. Our case also displayed increased platelet number and hypercoagulable state in addition to eosinophilia (TABE and TATE). Therefore, these clinical manifestations might be related to an elevated serum TARC/CCL17 level. However, a hypercoagulable state is also known to be induced directly by eosinophilia [3].

In summary, we have described a case of MPM with various clinical presentations, including TABE, TATE, increased platelet number, hypercoagulable state and increased blood TARC/CCL17 level. TARC/CCL17 may be a biomarker and a therapeutic target for a subpopulation of patients with MPM.

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