



## Tumor necrosis factor- and interleukin-6-producing high-grade B-cell lymphoma, not otherwise specified in the pleura



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### ABSTRACT

A 65-year-old man was admitted to our hospital with left-sided chest and back pain and dyspnea. Computed tomography demonstrated a marked circumferential left pleural thickening. A thoracoscopic pleural biopsy led to a diagnosis of high-grade B-cell lymphoma, not otherwise specified (HGBL, NOS). Lymphoma cells were positive for tumor necrosis factor (TNF) and interleukin-6. This is the first case report of TNF- and IL-6-producing aggressive HGBL, NOS in the pleura, in which radiological findings mimicked pleural mesothelioma. The aggressive tumor progression in the present case may have been caused by abnormal cytokine production from lymphoma cells.

### 1. Introduction

The differential diagnosis of pleural tumors includes pleural mesothelioma which is associated with asbestos exposure, pleural metastatic tumor, and lymphoma. Pleural lymphoma is extremely rare in whole malignant lymphoma and accounts for 2.4% of cases involving primary chest wall tumor [1]. Most cases are pyothorax-associated lymphoma, which is closely associated with persistent chronic tuberculosis pyothorax or artificial pneumothorax for long tuberculosis.

Here, we report the first case of TNF- and IL-6-producing high-grade B-cell lymphoma, not otherwise specified (HGBL, NOS) in the pleura, in which radiological findings mimicked pleural mesothelioma.

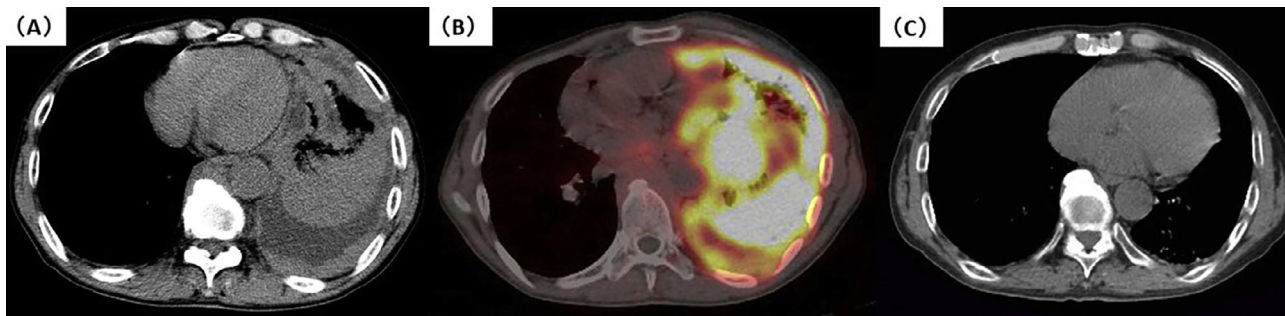
### 2. Case report

A 62-year-old man was admitted to our hospital with left-sided chest and back pain and dyspnea. He had a history of asbestos exposure when he worked as a pipe fitter and wrecker for more than 30 years without a history of tuberculosis. Results of blood analysis were as follows: white blood cell count,  $8.30 \times 10^9/L$  (66.3% neutrophils, 17.5% lymphocytes); hemoglobin, 105 g/L; platelet count,  $683 \times 10^9/L$ ; lactate dehydrogenase, 411 IU/L; and C-reactive protein, 3.80 mg/dL. Whole body computed tomography (CT) showed the marked circumferential left pleural thickening, and pleural effusion in the left

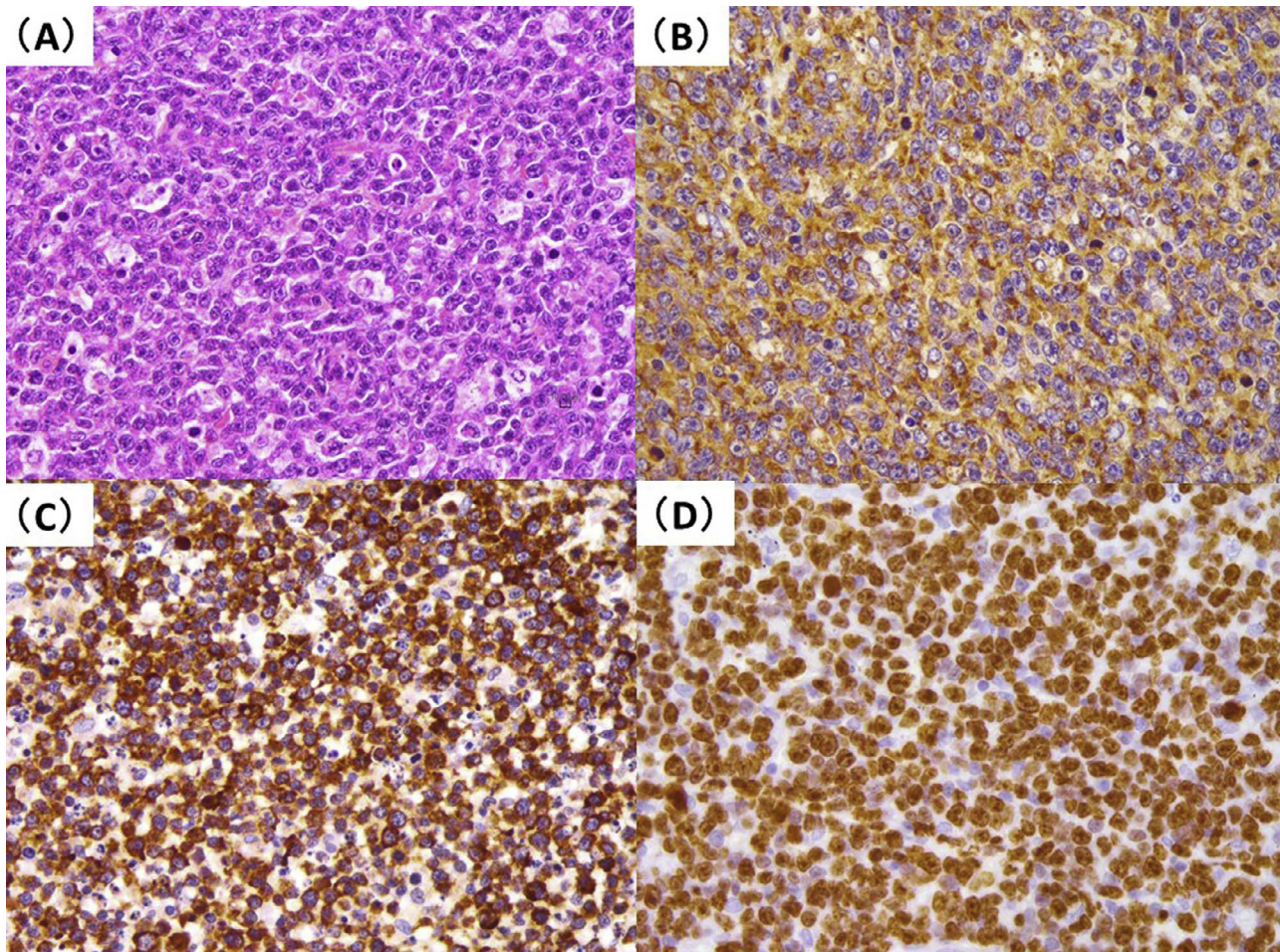
chest (Fig. 1(A)). Fluorodeoxyglucose positron emission tomography (FDG-PET)/CT, performed after 10 days, revealed the progressively increased pleural thickening with an intense FDG uptake (Fig. 1(B)). A thoracoscopic pleural biopsy showed the dense proliferation of lymphoblastoid cells, which were medium- to large-sized with conspicuous nucleoli. Tingible body macrophages were scattered among them, representing a “starry sky” appearance (Fig. 2(A)). Immunohistochemical analysis revealed that the lymphoblastoid cells were positive for CD20, CD79a, BCL2, and BCL6, but negative for CD3, CD5, CD10, MUM1, cyclin D1, and TdT. The lymphoblastoid cells were also positive for tumor necrosis factor (TNF) (52B83; Santa Cruz Biotechnology, Santa Cruz, CA) (Fig. 2(B)) and interleukin-6 (IL-6) (10C12; Novocastra, Newcastle Upon Tyne, UK) (Fig. 2(C)). *In situ* hybridization for Epstein–Barr-encoded RNA was negative. The proliferation index, as assessed by Ki67 (30-9; Ventana Medical Systems, Tucson, AZ) (Fig. 2(D)), was approximately 90%. Fluorescence *in situ* hybridization analysis did not detect *MYC* rearrangement. Southern blotting revealed clonal rearrangement of the immunoglobulin heavy chain gene (Fig. 3). The patient was eventually diagnosed with HGBL, NOS, according to the 2017 WHO classification [2]. Following treatment with 2 courses of R-CHOP therapy (a regimen of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone), the pleural thickening reduced. But after 3 courses of R-CHOP therapy, the tumor enlarged again. Following salvage chemotherapy with 3 courses of R-Hyper CVAD/MA

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**Fig. 1.** Radiological findings of CT. (A) CT scan on admission, demonstrating marked circumferential left pleural thickening, and pleural effusion in the left chest. (B) FDG-PET demonstrating intense FDG uptake by the left pleura. (C) CT scan after the chemotherapy, demonstrating disappearance of the tumor.



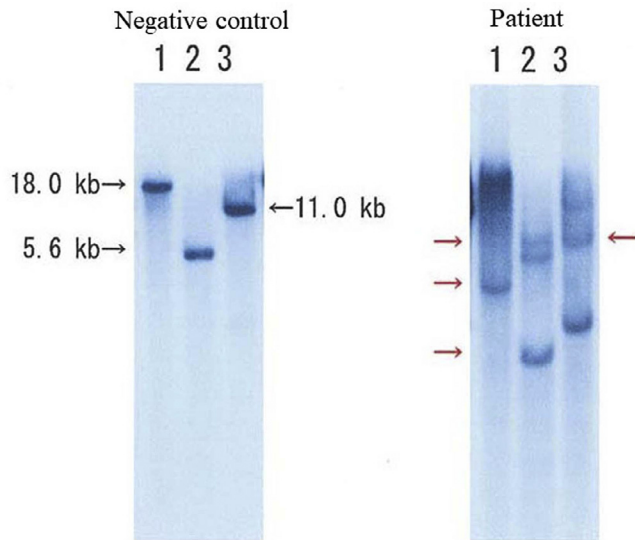
**Fig. 2.** Histological findings of the pleural biopsy. (A) The proliferative lymphoid cells were medium- to large-sized with conspicuous nucleoli. Macrophages were scattered among the lymphoid cells, representing a “starry sky” appearance. (hematoxylin–eosin staining; objective magnification, 40 $\times$ ). (B) The lymphoid cells were positive for TNF. (objective magnification, 40 $\times$ ). (C) The lymphoid cells were positive for IL-6. (objective magnification, 40 $\times$ ). (D) Approximately 90% of the lymphoid cells were positive for Ki67. (objective magnification, 40 $\times$ ).

therapy (a regimen of rituximab, hyper-fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with rituximab, methotrexate and cytarabine), the tumor disappeared (Fig. 1(C)).

### 3. Discussion

HGBL, NOS is a heterogeneous category of clinically aggressive mature B-cell lymphoma that lack *MYC* plus *BCL2* and/or *BCL6* rearrangements and do not fall into the category of diffuse large B-cell lymphoma, not otherwise specified, or Burkitt lymphoma [2]. In the present case, lymphoma cells were positive for TNF and IL-6. TNF is a

monocyte/macrophage-derived cytokine that is known to have a broad range of activities. TNF typically acts as a tumor-promoting factor and is linked to all steps of tumorigenesis, including transformation, proliferation, angiogenesis, invasion, and metastasis, primarily by the nuclear factor- $\kappa$ B pathway, in many tumors [3]. TNF directly facilitates tumor development by regulating the proliferation and survival of neoplastic cells. In addition, it indirectly facilitates tumor development via endothelial cells and inflammatory cells present in the tumor microenvironment [3]. In patients with non-Hodgkin lymphoma (NHL), higher plasma TNF levels are associated with poorer disease outcomes [4]. We previously reported that patients with diffuse large B-cell



**Fig. 3.** Southern blot analysis of the immunoglobulin heavy chain gene. Lane 1: EcoR I digestion. Lane 2: BamH I and Hind III digestion. Lane 3: Hind III digestion. The red arrows indicate clonal rearranged bands. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

lymphoma (DLBCL) who were immunohistochemically positive for TNF had a poorer prognosis than those who were negative for TNF [5]. However, the detailed mechanism for this phenomenon remains unclear.

IL-6 is a multifunctional cytokine that regulates immune responses, hematopoiesis, and acute-phase reactions, thus suggesting that it plays a vital role in host defense mechanisms [6]. In addition, studies have described IL-6-induced proliferation in certain tumors, including lymphoma and multiple myeloma [6,7]. IL-6 induces the activation of signal transducer and activator of transcription 3 (STAT3) transcription factor. STAT3, which is crucial for regulating genes that are important for tumor cell proliferation and survival, is constitutively active in several tumors, including lymphoma, multiple myeloma, leukemia, and solid tumors [8]. Reportedly, an elevated serum IL-6 level is a negative prognostic parameter in aggressive NHL [9]. However, it remains unclear whether IL-6 is produced by lymphoma cells themselves or by reactive cells present among lymphoma cells via other mechanisms. Previously, we reported a case of DLBCL immunostained for IL-6 exhibiting poor prognosis [10]. The aggressive tumor progression in the present case might be associated with abnormal cytokine production from lymphoma cells.

In the present case, because CT demonstrated the marked

circumferential pleural thickening, and because the patient had a history of asbestos exposure, pleural mesothelioma was initially suspected. Unexpectedly, a thorascopic pleural biopsy showed HGBL, NOS. The progression of HGBL is fast; hence, early therapy is required to rescue such patients. Therefore, physicians need to consider the possibility of lymphoma in patients who present with a history of asbestos exposure, and pleural thickening. Radiologically, this can be confused with more common malignancies, such as pleural mesothelioma; hence, biopsy is required for an immediate and accurate diagnosis, which can then lead to appropriate therapy.

#### Declarations of interest

None.

#### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lrr.2018.06.001.

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