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Case study

Localized pulmonary crystal-storing histiocytosis complicating pulmonary mucosa-associated lymphoid tissue lymphoma presenting with multiple mass lesions☆,☆☆

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Crystal-storing histiocytosis (CSH) is an uncommon finding in lymphoplasmacytic disorders that presents histiocytes with abnormal intralysosomal accumulations of immunoglobulin light chains as crystals of unknown etiology. A 38-year-old woman with antiphospholipid syndrome had a surgical lung biopsy because of multiple lung mass lesions. In a right middle lobe lesion, lymphoplasmacytic cells had a monocytoid appearance, destructive lymphoepithelial lesions, and positive immunoglobulin heavy chain (*IGH*) gene rearrangements. A right upper lobe lesion manifested proliferating rounded histiocytes with abundant, deeply eosinophilic cytoplasm and negative *IGH* gene rearrangements. Electron microscopy and mass spectrometry revealed a case of pulmonary CSH: abnormal proliferation of the immunoglobulin κ chain of a variable region that may be crystallized within plasma cells and histiocytes. We report a rare case of localized pulmonary CSH complicating pulmonary mucosa-associated lymphoid tissue lymphoma with multiple mass lesions. We demonstrate advances in the understanding of the pathogenesis of CSH by various analyses of these lesions.

Abbreviations CT, computed tomography; CSH, crystal-storing histiocytosis; Ig, immunoglobulin; *IGH*, Ig heavy chain gene; LC/MS, liquid chromatography–tandem mass spectrometry; MALT, mucosa-associated lymphoid tissue; PCR, polymerase chain reaction; PET, positron-emission tomography; RA, rheumatoid arthritis

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1. Introduction

Crystal-storing histiocytosis (CSH) is a rare finding in plasma cell diseases and lymphoproliferative disorders; fewer than 90 case reports have been published so far. The condition has the characteristic feature of histiocytes with abnormal intralysosomal accumulation of immunoglobulin (Ig) in the form of crystals. In 2012, Dogan et al [1] reviewed information on 80 patients with CSH described in the English-language literature from 1950 to 2010 and divided the cases into 2 categories: (1) *localized CSH*, which they defined as a single deposit involving only 1 organ or site and accounting for 58% of the cases, and (2) *generalized CSH*, which they defined as deposits involving 2 or more organs or sites and accounting for 42% of the cases. As many as 90% of these patients had an underlying lymphoproliferative disorder or plasma cell disease, such as multiple myeloma (28.8%), lymphoplasmacytic lymphoma (21.3%), or paraproteinemia/monoclonal gammopathy of undetermined significance (18.8%). Of these 80 patients, 7.5% also had mucosa-associated lymphoid tissue (MALT) lymphoma. Some patients had various benign disorders that are associated with inflammatory disease such as rheumatoid arthritis (RA), pulmonary infections, and Crohn disease [1]. Generalized CSH almost always occurred in the bone marrow (97%), with lung lesions affecting 12% of the 34 patients reviewed. In contrast, as sites of localized CSH, the lung and pleura (24%) were the second most frequent locations, after the head and neck (35%), in 46 patients reviewed [1]. Only 6 case reports of localized pulmonary CSH complicating pulmonary MALT lymphoma have been published [2-6].

Because the precise pathogenesis of CSH remains unknown, we report here a rare case of pulmonary CSH complicating pulmonary MALT lymphoma with multiple mass lesions in both lungs, and we discuss the pathogenesis and mechanism of CSH development. To accomplish these goals, we used liquid chromatography–tandem mass spectrometry (LC/MS) and Ig heavy chain gene (*IGH*) rearrangement assessment to investigate the multiple mass lesions.

2. Pathological examination

2.1. Histopathology and immunochemistry

All surgical specimens were fixed in 10% buffered formalin, embedded in paraffin, cut into 4-μm sections, and stained with hematoxylin and eosin. Immunohistochemical analysis was performed using the following commercial antibodies: CD1a (Ventana Medical Systems, Tucson, AZ), CD3 (Ventana Medical Systems), CD20 (Ventana Medical Systems), CD68 (clone PGM-1) (Dako, Kyoto, Japan), CD138 (DakoCytomation, Kyoto, Japan), IgG (DakoCytomation), IgM (DakoCytomation), S100 (Ventana Medical Systems), TTF-1 (Ventana Medical Systems), CK7 (Dako), and Ig κ and λ light chains (Ventana Medical Systems).

2.2. Electron microscopy

Small pieces of tissue were subjected to electron microscopic evaluation. They were fixed in 2.5% glutaraldehyde, embedded in a few drops of epoxy resin (Epok 812; Oken, Tokyo, Japan), cut into 500-nm sections, and stained with uranyl acetate and lead citrate. The grids were examined with an H-7500 electron microscope (Hitachi, Tokyo, Japan) operating at 80 kV.

2.3. Laser-capture microdissection and LC/MS

The CSH and MALT lymphoma areas to be analyzed were selected via bright-field microscopy of fixed, paraffin-embedded tissue sections with laser-capture microdissection (LMD6000 Laser Microdissection System; Leica, Wetzlar, Germany). Each microdissection specimen contained an area of 50 000-80 000 μm^2, and 10-20 crystal-storing histiocytes or plasmacytoid cells in the MALT lymphoma lesion were microdissected and analyzed. Tissue samples were collected in 0.5-mL microcentrifuge tubes containing 30 μL of 10 mmol/L Tris/L mmol/L EDTA/0.002% Zwittergent 3-16 (Calbiochem, San Diego, CA). Samples were heated at 98°C for 90 minutes and sonicated in a water bath for 90 minutes, after which they were digested overnight with 3 μL of trypsin 0.1 mg/mL (Promega, Madison, WI) at 37°C. The raw MS data files were processed using 2 algorithms (MASCOT and X! TANDEM) to assign peptide and protein probability scores. The results were combined and assigned peptide and protein probability scores in SCAFFOLD (Proteome Software, Portland, OR) as a list of proteins based on the peptide spectra. Details of the methods are described elsewhere [7,8].

2.4. Polymerase chain reaction for detection of *IGH* rearrangement

The polymerase chain reaction (PCR) analyses were performed via the IGH Gene Clonality Assay (Invivoscribe Technologies, San Diego, CA) and the ABI Fluorescence Detection Kit (Thermo Fisher Scientific, Waltham, MA). Biopsy materials and formalin-fixed, paraffin-embedded tissue sections were used in these assays.

3. Case presentation

An asymptomatic 38-year-old woman who had never smoked was referred to our hospital after a chest radiograph performed during a health screening revealed multiple mass lesions in both lungs (Fig. 1A). Fluorodeoxyglucose positron-emission tomography (PET)–computed tomography (CT) showed multiple mass lesions (maximum diameter 42 mm),