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Case Study

Successful Surgical Treatment for Pulmonary Crystal-Storing Histiocytosis Following the Onset of Gastric Non-Hodgkin Lymphoma

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Crystal-storing histiocytosis is a rare clinical entity characterized by an increase in the number of abnormal histiocytes accompanied by accumulation of crystallized immunoglobulins. We describe the case of an 80-year-old man who presented with crystal-storing histiocytosis of the lung 13 years after receiving a diagnosis of gastric non-Hodgkin lymphoma (NHL ; clinical stage, Lugano IA). After wedge resection of the left upper lobe, the histological findings showed crystal-storing histiocytosis with $CD68^+$, some small to medium lymphoid cells with $CD79a^+$ with $\kappa^{+(weekly)}$ and λ^-, and some plasma cells with $CD138^+$, and rearrangement of the immunoglobulin heavy chain. Based on the nonrecurrent gastric NHL, small B-cell population, and failure to detect the same clone by polymerase chain reaction analysis, our case was classified as pulmonary localized crystal-storing histiocytosis without underlying lymphoproliferative or plasma cell disorder. The findings of minor B-cell populations harboring a heavy chain rearrangement with slight light-chain restriction ($\kappa > \lambda$) may be related to the pathogenesis of crystallogenesis and crystal-storing histiocytosis. Moreover, surgical treatment may be an effective therapeutic option for solitary crystal-storing histiocytosis. 〔*J Clin Exp Hematop 53(3) : 241-245, 2013*〕

Keywords: gastric non-Hodgkin lymphoma, pulmonary crystal-storing histiocytosis, surgical treatment

INTRODUCTION

Crystal-storing histiocytosis is a rare clinical entity characterized by an abnormal increase in the number of histiocytes accompanied by a massive accumulation of crystallized immunoglobulins.[1-3] The clinical features, treatment, and prognosis of crystal-storing histiocytosis remain unclear because of the rare incidence of the condition.[1-3] Although reported in various organs such as the bone, bone marrow, head and neck, skin, kidney, stomach, and liver,[1-2] crystal-storing histiocytosis of the lung has been rarely reported.[3-9]

Although the etiology of crystal-storing histiocytosis has not been fully clarified, lymphoproliferative disorders such as low-grade lymphoma and multiple myeloma were assumed to be closely associated with the development of this disease.[4-9]

Here, we report the case of an 80-year-old man who presented with crystal-storing histiocytosis of the left upper lobe 13 years after receiving a diagnosis of gastric non-Hodgkin lymphoma (NHL).

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PATIENTS AND METHODS

Histopathology and immunohistochemistry

Pathological analyses were performed by H&E and immunohistochemical stainings of sections from excised tissues fixed with 10% formalin and embedded in paraffin.

Polymerase chain reaction analysis (PCR) of immunoglobulin heavy chain (IgH) *rearrangements*

For genomic analysis of crystal-storing histiocytosis, we performed a PCR analysis of immunoglobulin rearrangements as follows : DNA preparation was performed in part from

sections of paraffin-embedded tissues. DNA samples were extracted using a commercial kit (KAPA Express Extract, Kapa Biosystems, Boston, MA, USA) following the manufacturer's recommendations. The variable region (FR2B and CFW1) and variable diversity-joining region (SJHb) of a rearranged *IgH* gene were amplified by seminested PCR, using the sense primer FR2B along with antisense primers CFW1 (for first-round PCR) and SJHb (for second-round PCR). PCR amplification was performed with KAPA2G Robust Hotstart ReadyMix (Kapa Biosystems) for the first-round PCR and AmpliTaq Gold PCR Master Mix (Applied Biosystems, Foster City, CA, USA) for the second-round PCR. The first-round PCR conditions were as follows : an initial denaturation at 95℃ for 3 min was followed by 40 cycles (95℃ for 15 sec, 60℃ for 5 sec, and 72℃ for 30 sec) with a final extension at 72℃ for 10 min. The second-round PCR analysis consisted of 40 cycles of 95 sec for 30 sec, 63 sec for 30 sec, and 72℃ for 30 sec.

The primers had the following sequences : consensus V region primer : FR2B,[10] TGCAGGC (C/T) (C/T) CCGG (A/G) AA (A/G) (A/G) GTCTGG AGTGG-3′ ; consensus J region primers : CFW1,[11] 5′-ACCTGAGGAGACGGTGACCAGGGT-3′, and SJHb,[12] 5′-ACCAGGGTCCCTTGGCCCCA-3′. The amplified PCR products were evaluated in 3% agarose gels and visualized by ethidium bromide staining under ultraviolet light. PCR products of approximately 250 bp were expected. The genomic locus of β-actin was used as an internal control. The expected size of the genomic β-actin for the nested PCR was 148 bp. The results were determined to indicate which samples were polyclonal or monoclonal.

CASE REPORT

An 80-year-old man presenting with a solitary mass lesion on the left upper lobe of the lung was referred to a regional hospital on April 26, 2011. He had a history of gastric NHL [diffuse large B-cell lymphoma (DLBCL) ; clinical stage, Lugano IA] diagnosed on June 10, 1997. His gastric NHL was treated with a combination of surgery and 3 courses of standard CHOP chemotherapy regimen consisting of 50 mg/m^2 intravenous (i.v.) doxorubicin, 1.4 mg/m^2 i.v. vincristine, and 750 mg/m^2 i.v. cyclophosphamide on day 1, and 60 mg/m^2 i.v. prednisolone for 5 days every 4 weeks. After the treatment, he attained complete remission (CR) and remained disease-free for 13 years.

On admission, the patient was normotensive (116/66 mmHg), with a heart rate of 66 beats/min. Physical examination revealed that he had no signs of systemic lymphadenopathy. The Brinkman index was 1,180 (20 cigarettes smoked per day × 59 years of smoking). Laboratory findings showed a hemoglobin concentration of 11.4 g/dL, platelet count of 410 × 10^9/L, and white blood cell count of 3.1 × 10^9/L, with 56% neutrophils, 32% lymphocytes, 9% monocytes, and 3% eosinophils. The serum lactate dehydrogenase level was 194 mg/dL ; soluble interleukin-2 receptor level was 272 IU/L ; and tumor markers of lung cancer such as carcinoembryonic antigen, cytokeratin 19 fragments, squamous cell carcinoma, progastrin-releasing peptide, and neuron-specific enolase were all negative. In addition, the serum protein analysis results were normal, with the following values : total protein, 7.6 mg/dL ; albumin, 4.6 mg/dL ; immunoglobulin G, 1,591 mg/dL ; immunoglobulin A, 286 mg/dL ; and immunoglobulin M, 61 mg/dL. Moreover, the flow cytometric analysis of peripheral blood did not reveal abnormal B-cell and plasma cell phenotypes but revealed normal B- and T-cell populations. Based on the negative findings of lymphoproliferative disorder or plasma cell, bone marrow examination was not performed at this setting.

Furthermore, analysis of bronchoscopic specimens gave negative findings on bacterial culture and cytological analysis. Fluorodeoxyglucose-positron emission tomography/computed tomography scan showed a solitary mass lesion (19 × 29 × 52 mm) with spicula formation and a pleural indentation on the left upper lobe of the lung (Fig. 1). Taking these findings together, we made a preoperative diagnosis of lung cancer. We performed wedge resection of the solitary mass lesion on the left upper lobe of the lung. After the surgery, he developed fever of unknown etiology, which gradually resolved

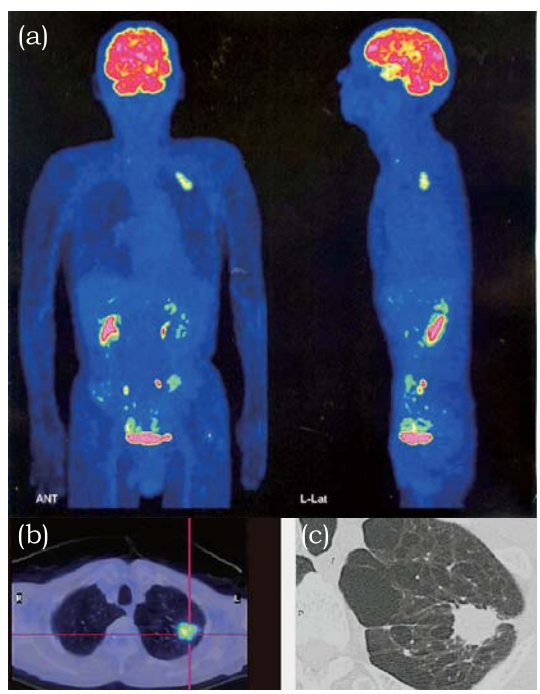

Fig. 1. Fluorodeoxyglucose-positron emission tomography/computed tomography scan showing a solitary mass lesion (19 × 29 × 52 mm) with spicula formation and a pleural indentation on the left upper lobe of the lung (*1a-1c*).

with treatment with nonsteroidal anti-inflammatory drugs and antibiotics.

After the surgery, a macroimage of the resection specimen showed the solitary soft mass lesion (19 × 29 × 52 mm) within the white lesion (Fig. 2A). Histological findings with H&E staining showed crystal-storing histiocytes proliferating diffusely in the pulmonary tissue (Fig. 2b, 2c). Crystallized immunoglobulin was massively accumulated (Fig. 2b, 2c). Some small to medium lymphoid cells and plasma cells proliferated in a nodular pattern in the pulmonary tissue (Fig. 2b, 2c). Furthermore, to clarify the components of crystal-storing histiocytosis, we additionally performed immunohistochemical staining for CD68 (histiocyte marker), CD79a (B-cell marker), and CD138 (plasma cell marker). Immunostaining of the pulmonary tissue revealed that the crystal-storing histiocytes were $CD68^{+}$ (Fig. 2d). Some small to medium lymphoid cells were $CD79a^{+}$ (Fig. 2e) with $\kappa^{+(weekly)}$ (Fig. 2g) and λ^{-} (Fig. 2h). Some plasma cells were $CD138^{+}$ (Fig. 2f). Consequently, based on the histological findings, the criteria of B-lymphoproliferative disorder was not fulfilled because of the minor B-cell population with $CD79a^{+}$ with $\kappa^{+(weekly)}$ and λ^{-}. Moreover, genotypic analysis by PCR demonstrated the rearrangement of the *IgH* in the lung tissue (Fig. 3). However, the genomic PCR analysis with stomach and lung tissues did not reveal the same clone. Taking these histological findings together, we finally made a diagnosis of pulmonary crystal-storing histiocytosis with unknown etiology after the onset of gastric NHL at the CR state.

The patient was assessed to have attained a complete response. The treatments performed in this case were effective, with the resolution of the solitary pulmonary crystal-storing histiocytosis. Thus, 23 months after the diagnosis of pulmonary crystal-storing histiocytosis, he remained disease-free without any treatment.

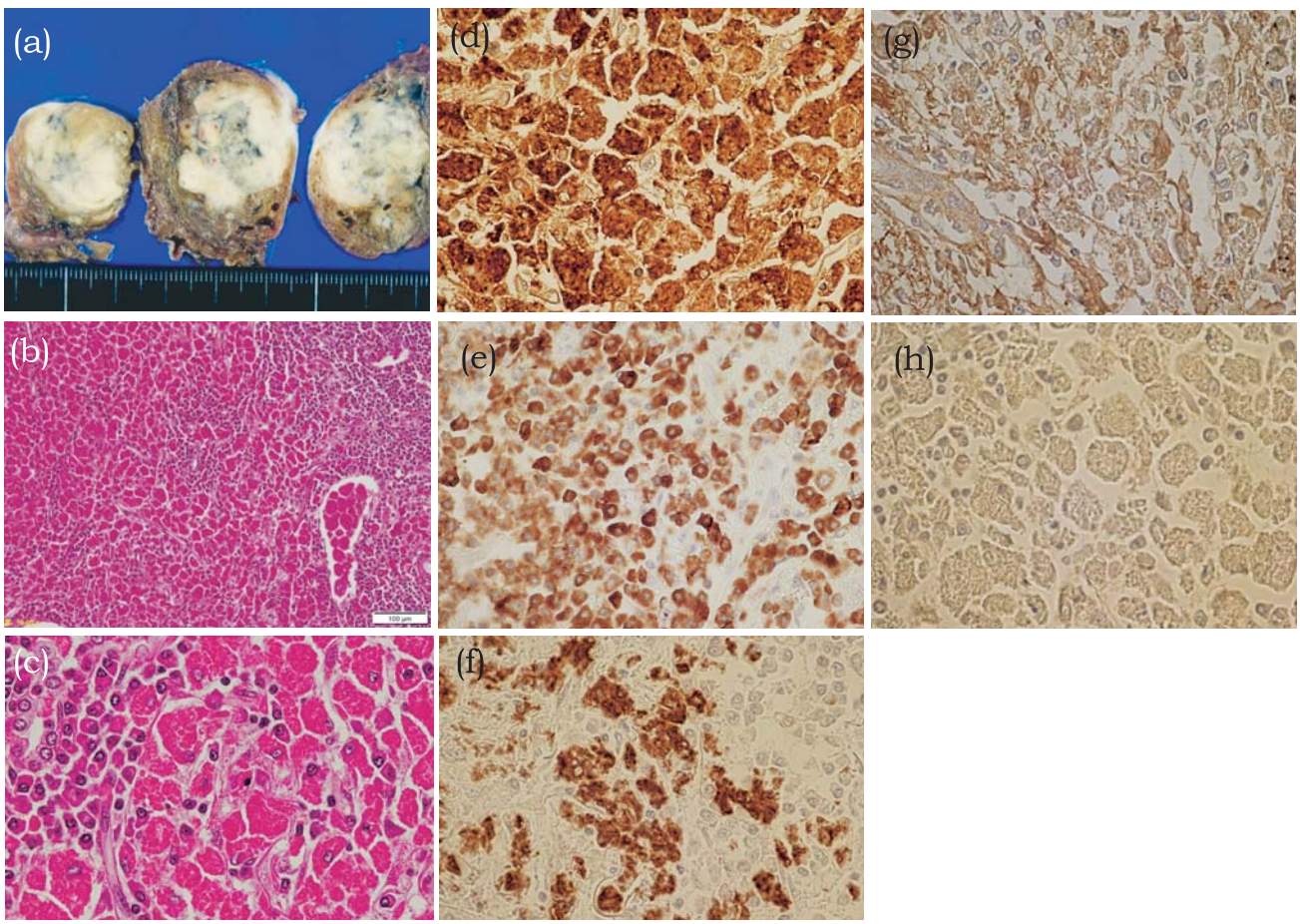

Fig. 2. Macroimage of the resection specimen showing the solitary soft mass lesion (20 mm) within the white lesion (*2a*). The findings from the histological examination with H&E staining showed that crystal-storing histiocytes proliferate diffusely in the pulmonary tissue (*2b*, *2c*). Crystallized immunoglobulin is massively accumulated. Some small to medium lymphoid and plasma cells proliferate in a nodular pattern in the pulmonary tissue. Immunostaining of the pulmonary tissue revealed that the crystal-storing histiocytes were $CD68^{+}$ (*2d*). Some small to medium lymphoid cells were $CD79a^{+}$ (*2e*) with $\kappa^{+(weekly)}$ (*2g*) and λ^{-} (*2h*). Some plasma cells were $CD138^{+}$ (*2f*).

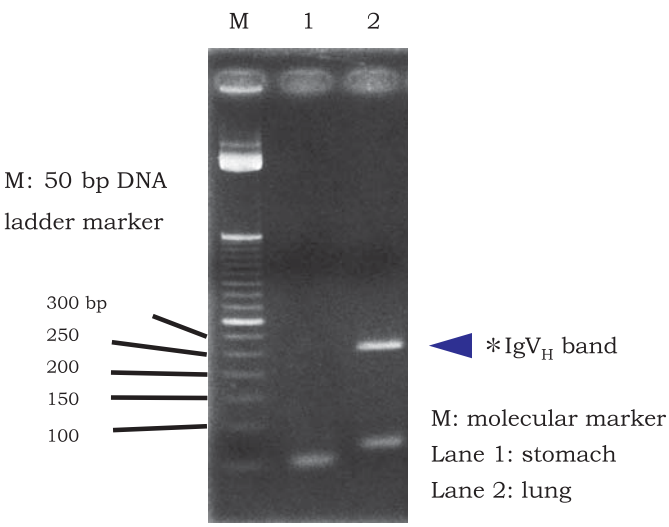

Fig. 3. Polymerase chain reaction (PCR) genotypic analysis demonstrating the rearrangement of the immunoglobulin heavy chain in the lung tissue. PCR genotypic analysis demonstrating no rearrangement of the immunoglobulin heavy chain in the stomach tissue because of the old and inappropriate samples.

DISCUSSION

Pulmonary crystal-storing histiocytosis with lymphoproliferative disorders is rarely reported, and its clinical features, treatment, and prognosis remain unclear.[4-9,13,14] Recently, Dogan *et al*.[13] reported a case of crystal-storing histiocytosis, with a review of the literature (80 cases) and a proposed classification, treatment, and prognosis.

Compared with those in previous reports, our case was classified as pulmonary localized crystal-storing histiocytosis without underlying lymphoproliferative or plasma cell disorder (LP-PCD). The findings of minor B-cell populations harboring a heavy chain rearrangement with slight light chain restriction ($\kappa > \lambda$) may be related to the pathogenesis of crystallogenesis and crystal-storing histiocytosis. Moreover, pulmonary wedge resection may be an effective treatment option for solitary pulmonary crystal-storing histiocytosis. However, the surgery triggered an immunological reaction in our patient, causing a fever of unknown etiology during the postoperative period.

Of the 80 cases of crystal-storing histiocytosis, 90% had an etiology related to multiple myeloma, lymphoproplasmacytic lymphoma, monoclonal gammopathy of undetermined significance, and mucosa-associated lymphoid tissue.[13] However, crystal-storing histiocytosis without underlying LP-PCD was found in a few cases (7 cases).[13] Surprisingly, among the 7 cases, the organs involved in crystal-storing histiocytosis primarily consisted of the lung (3/7). According to the distribution of lesions with crystal-storing histiocytosis, crystal-storing histiocytosis may be subdivided into 2 categories, namely localized (46/80) and generalized crystal-storing histiocytoses (34/80).[13] Among the cases of localized crystal-storing histiocytosis, 35% (16/47) were in the head and neck. The second most common site for localized crystal-storing histiocytosis was the lung and pleura (11/26 or 24%).

Our case was classified as pulmonary localized crystal-storing histiocytosis without underlying LP-PCD. Owing to the gastrectomy and rituximab plus CHOP therapy, the gastric NHL (DLBCL) in our case retained CR without evidence of recurrence during the 13-year period, although crystal-storing histiocytosis developed after gastric NHL (DLBCL). In terms of histological findings, the criteria for B-lymphoproliferative disorder was not fulfilled because of the minor B-cell population with CD79a$^+$ with kappa$^{+(weekly)}$ and lambda$^-$. Moreover, the genomic PCR analysis by stomach and lung tissues did not also reveal the same clone. Finally, according to previous reports, the etiology of LP-PCD was reported to be multiple myeloma, lymphoproplasmacytic lymphoma, monoclonal gammopathy of undetermined significance, and mucosa-associated lymphoid tissue. Thus, DLBCL was not previously reported. Considering these findings, we conclude that our case was classified as crystal-storing histiocytosis without underlying LP-PCD. However, crystal-storing histiocytosis may precede the development of a LP-PCD. Therefore, in our case, careful follow-up including a bone marrow examination was essential for monitoring the development of a LP-PCD.

In this report, the exact pathogenesis of the crystal-storing histiocytosis remains to be fully understood and may involve multiple factors ranging from simple overproduction to abnormal secretion to impaired immunoglobulin excretions.[13] The type of light chain was reported to have a more significant relationship with crystallogenesis than a specific heavy chain. In another mechanism of crystal-storing histiocytosis, the conformational alteration induced by the abnormal amino acid sequences may be related to the promotion of crystallization of the protein or may be adversely affecting its intralysosomal degradation or both.[13]

In our case, the findings of minor B-cell populations harboring a heavy chain rearrangement with slight light chain restriction ($\kappa > \lambda$) may be related to the pathogenesis of crystallogenesis and crystal storing histiocytosis. In the future, the accumulation of case reports may clarify the pathogenesis of crystal-storing histiocytosis.

Finally, the treatment and prognosis of patients with crystal-storing histiocytosis may vary according to the underlying disease.[13] Very little information is available regarding treatment such as simple excision or chemotherapy. However, according to the number or distribution of crystal-storing histiocytosis, patients with localized crystal-storing histiocytosis tend to have a better prognosis than patients with generalized crystal-storing histiocytosis.[13]

In our case, pulmonary wedge resection could have been

an effective treatment option for solitary pulmonary crystal-storing histiocytosis. However, the surgery triggered an immunological reaction in our patient, causing a fever of unknown etiology during the postoperative period. Further accumulation of cases may be essential to establish the treatment of crystal-storing histiocytosis and clarify the prognosis of crystal-storing histiocytosis.

In conclusion, our case was classified as pulmonary localized crystal-storing histiocytosis without underlying LP-PCD. Moreover, pulmonary wedge resection may be an effective treatment option for solitary pulmonary crystal-storing histiocytosis. However, crystal-storing histiocytosis may precede the development of a LP-PCD. Therefore, careful follow-up including bone marrow examination is essential for monitoring the development of a LP-PCD. Because of the rare incidence of pulmonary crystal-storing histiocytosis, the accumulation of cases is required to further understand the incidence, histological features, indications for treatment, and therapeutic strategies for pulmonary crystal-storing histiocytosis.

CONFLICT OF INTEREST

Noriaki Kawano and coauthors have no conflict of interest.

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