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Systemic Plasmacytosis
– A Case Report with a Review of the Literature –

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Systemic plasmacytosis is an uncommon disorder characterized by widely disseminated macular skin eruptions composed of polyclonal lymphoplasmacytic infiltrates associated with variable extracutaneous involvement. An aggressive clinical course has been observed in a small number of patients, but most cases have followed chronic and benign clinical course without spontaneous remission. Previously reported cases of this entity have been described almost exclusively in Japanese patients. We recently experienced a case of systemic plasmacytosis in a 48-year-old Korean female patient. Initial skin biopsy specimen revealed patchy perivascular and periadnexal infiltrates of mature plasma cells. Serum immunoelectrophoresis revealed polyclonal hypergammaglobulinemia, and polyclonal plasmacytosis was noted on the subsequent biopsy specimens of left supraclavicular and axillary lymph nodes. Multiple tiny pulmonary nodules appeared six years after the initial cutaneous presentation and were found to be of the same histologic appearance. We herein report a rare case of systemic plasmacytosis with a review of the literature.

Key Words: Plasmacytosis; Giant lymph node hyperplasia; Interleukin-6

Cutaneous and systemic plasmacytosis is a rare disease arising primarily in the Asian population. After its first recognition as a distinctive cutaneous lesion in 1976, since then approximately 60 cases have been reported worldwide, the vast majority of them being from Japan.[1,2] Previously termed as "cutaneous plasmacytosis," the condition has been subsequently named as "cutaneous and systemic plasmacytosis" to reflect the high frequency of lymphoplasmacytic infiltration of extracutaneous sites.[1] The term cutaneous plasmacytosis is mainly used for a disorder, which accompanies dark brown skin eruption but lacks systemic involvement. Cutaneous and systemic plasmacytosis is characterized by a cutaneous polyclonal plasma cell infiltration accompanied by lymphadenopathy, and polyclonal hypergammaglobulinemia. The most common manifestation of extracutaneous involvement is superficial lymphadenopathy. Involvement of lung is presented as lymphoid interstitial pneumonia or as multiple tiny nodules.[3] Involvement of the liver, spleen, and kidney is of less common occurrence.[1,4] In our present study, we describe a case of Korean patient, who was initially diagnosed to be suffering from cutaneous plasmacytosis, which later involved systemic involvement when the patient underwent lymph node biopsies on the left axilla and supraclavicular area. To the best of our knowledge, this is the third case to be reported in Korean literature.[5,6]

CASE REPORT

A 48-year-old Korean woman presented with a 3-year history of diffuse, asymptomatic brownish red macules on the chest and back. Examination of a punch biopsy specimen revealed the occurrence of nodular mixed cell infiltrate of lymphocytes with a predominance of plasma cells characterized by the small, uniform sized nuclei (Fig. 1). Physical examination revealed no superficial lymphadenopathy. On laboratory evaluation, the complete blood cell count with differential was notable only for normocytic anemia with a hematocrit of 30.3%. The level of lactate dehydrogenase was 249 U/L. Serologic tests for human immunodeficiency virus and syphilis produced negative findings, and anti-DNA antibody activity was negative. Serum proteins level was elevated to 10.4 g/dL (reference range, 6.4 to 8.3 g/dL). Serum protein electrophoresis revealed polyclonal hyper-

gammaglobulinemia with levels of IgG as 4,058 mg/dL (reference range, 880 to 1,800 mg/dL), IgA as 576 mg/dL (reference range, 126 to 517 mg/dL), IgM as 466 mg/dL (reference range, 52 to 270 mg/dL), and IgE as 2,701 mg/dL (reference range, 0 to 450 mg/dL). A bone marrow biopsy specimen revealed a normocellular marrow, with a normal myeloid to erythroid ratio, and slight plasmacytosis representing 5% of marrow cellularity. From based on histopathologic and immunoelectrophoretic evaluation, the diagnosis of cutaneous plasmacytosis was made. Initially, the patient underwent melphalan and prednisone combination chemotherapy with mild improvement, and is under constant observation from the past four years without any further treatment.

Follow-up computed tomography scan of the neck revealed multiple enlarged lymph nodes along the bilateral parotid space, posterior neck, submental, submandibular, supraclavicular region, and level II, III, IV, and V areas. Enlargement of upper mediastinal and both axillary lymph nodes were also observed. Lymph node biopsies on the left axilla and supraclavicular area showed reactive germinal centers with marked interfollicular plasma cell infiltrates (Fig. 2). Immunohistochemical staining revealed polyclonal reactivity for kappa and lambda immunoglobulin light chains with clusters of plasma cells reactive for CD138 (Fig. 3). The patient was diagnosed to be suffering from systemic plasmacytosis.

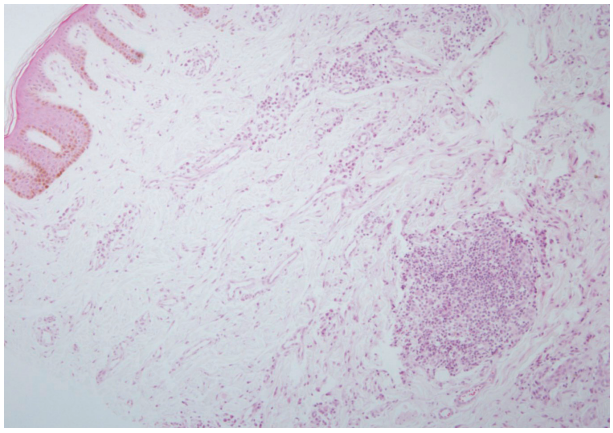

Fig. 1. Low-power view of cutaneous plasmacytosis showing nodular infiltrates of lymphocytes and plasma cells in the mid dermis.

Two years later, the patient presented with cough and sputum lasted for several months. A chest computed tomography scan showed diffuse bronchial wall thickening and multifocal ill-defined nodular opacities with interstitial thickening in both lungs. Multiple enlarged mediastinal and both axillary lymph nodes were still prominent. Radiologic findings suggested lymphoproliferative disorders, including lymphoma and lymphocytic interstitial pneumonia (LIP), or multifocal bronchopneumonia with mainly peribronchiolar inflammation. Subsequently, the patient underwent video-assisted wedge resection of the right lower lobe. Microscopically, the lung parenchyma revealed nodular and septal plasma cell infiltrates with lymphoid follicles and interstitial infiltrates of lymphocytes and histiocytes (Fig. 4). Based on this pathologic finding, differential diagnosis included LIP, follicular bronchiolitis, nodular lymphoid hyperplalsia, low-grade lymphoma of bronchus-associated lymphoid tissue, and pulmonary involvement by systemic plasmacytosis. Immunohistochemical studies for kappa and lambda showed polyclonal staining and clusters of reactive small lymphocytes reacted for CD20. There were also small numbers of CD3-positive cells. Given the patient's previous history of cutaneous plasmacytosis, the final diagnosis of pulmonary manifestation of

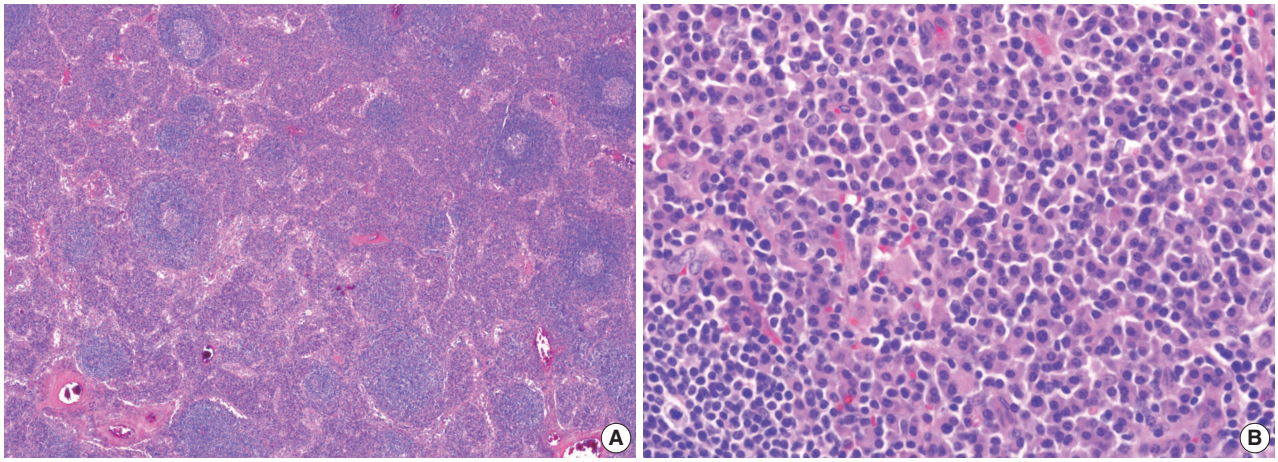

Fig. 2. (A) Lymph nodes revealing reactive germinal centers and an interfollicular infiltrate of plasma cells. (B) High-power view revealing a monomorphous population of plasma cells.

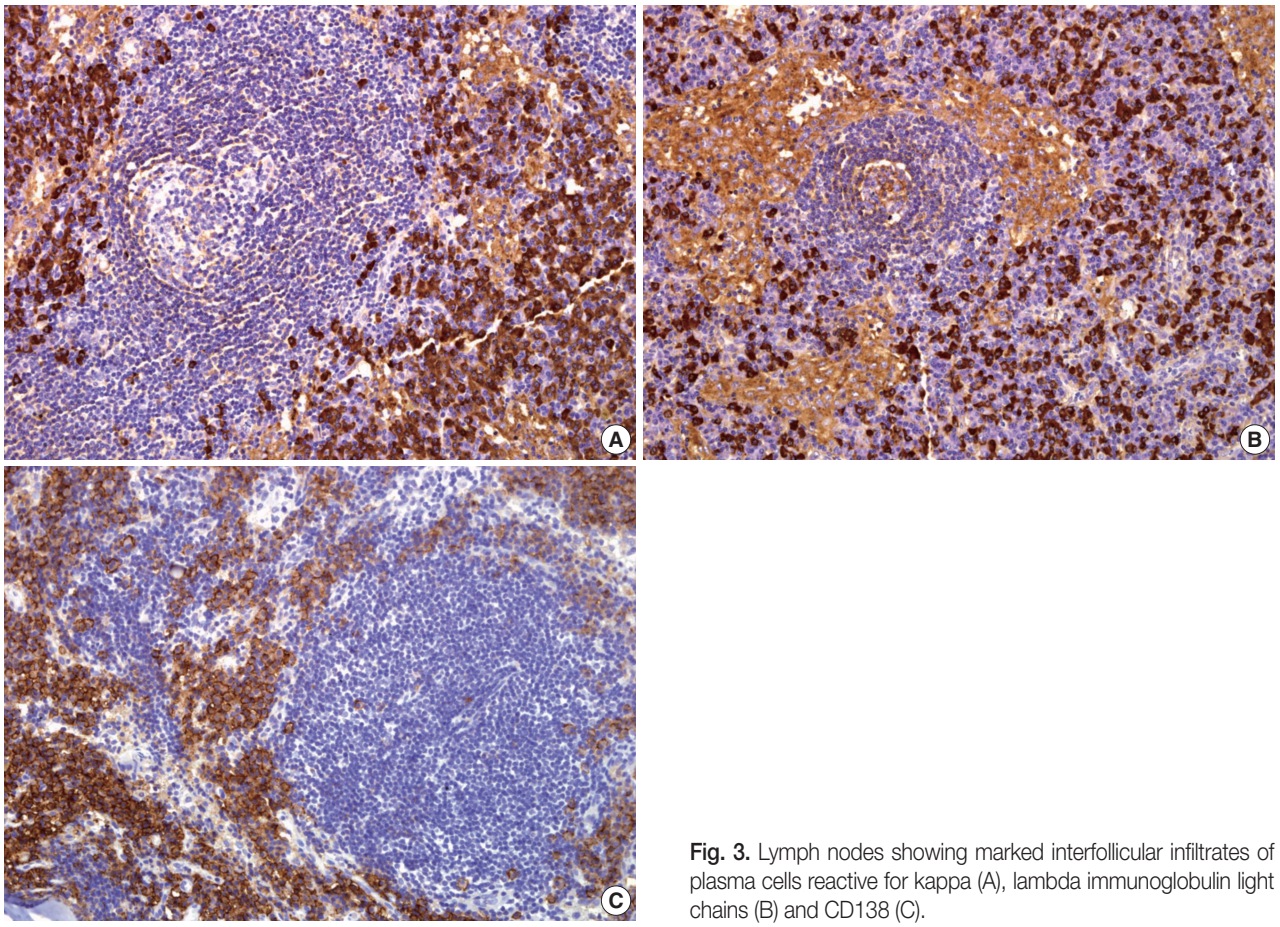

Fig. 3. Lymph nodes showing marked interfollicular infiltrates of plasma cells reactive for kappa (A), lambda immunoglobulin light chains (B) and CD138 (C).

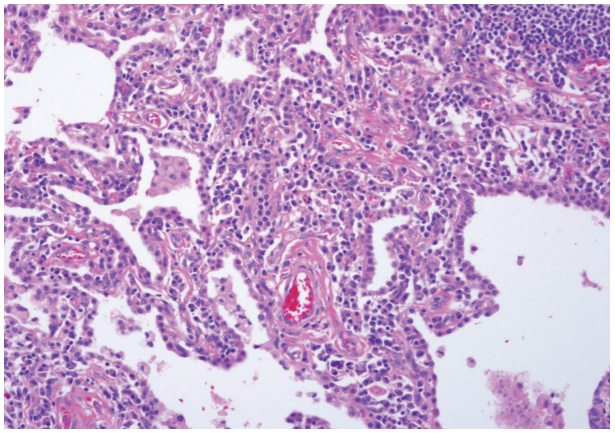

Fig. 4. Histologic findings of lung wedge resection specimen from the right lower lobe. Thickened alveolar septa due to dense infiltrates of mononuclear cells with numerous plasma cells are noted.

systemic plasmacytosis was made. Ever since, the patient has been on 100 mg of prednisone with resultant effective reduction in pulmonary symptoms.

DISCUSSION

Cutaneous and systemic plasmacytosis is a rare reactive lymphoplasmacytic disorder that typically affects middle-aged to elderly individuals. It is characterized by asymptomatic, disseminated, reddish-brown macules composed of mature, polyclonal plasma cell infiltrates with no atypia, polyclonal hypergammaglobulinemia and extracutaneous involvement.[7]

We reviewed relevant English and Korean literatures, and identified twenty cases of cutaneous and systemic plasmacytosis for which the data were available.[1-3,8-17] The characteristics of the cases are summarized in Table 1. Totally, there were eighteen men and two women. The age of the subjects ranged from 7-78 years (mean age, 49.5 years). The median follow-up period was 4.4 years (range, 0.8 to 7 years). Cutaneous plasmacytosis without systemic involvement was noted in six cases (30%). Of 14 patients with systemic involvement, seven had simultaneous extracutaneous involvement at the presentation, and the other seven initially had cutaneous and later systemic manifestations. The duration between initial cutaneous presentation and extra-

Table 1. Summary of the reported cases

Reference	Sex/ Age (yr)	Cutaneous or systemic disease	Duration between cutaneous and systemic disease (yr)	Organ involved	Treatment	Follow up after initial presentation (yr)
Miyagawa-Hayashino *et al.*[3]	M/54	S	5	Lymphadenopathy, interstitial lung disease	Prednisolone, 15 mg	6.5
	M/55	S	3	Lymphadenopathy	Tacrolimus ointment	3.3
	M/61	S	1.5	Lymphadenopathy, bone marrow plasmacytosis	Prednisolone, 15 mg	4.5
Leonard *et al.*[1]	M/67	S	Simultaneous	Lymphadenopathy, nodular infiltrates, and calcified granulomas of lung	N/A	N/A
Carey *et al.*[8]	M/78	S	1.8	Lymphadenopathy, hepatosplenomegaly, hemolytic anemia, and thrombocytopenia	Cyclophosphamide/prednisone, 60 mg	3
Gilliam *et al.*[9]	F/15	C	N/A	Skin	N/A	N/A
	M/7	C	N/A	Skin	N/A	N/A
Amin *et al.*[10]	M/49	S	N/A	Lymphadenopathy, innumerable tiny perivascular nodules of lung	Cyclophosphamide, doxorubicin, vincristine, and prednisone	7
Nitta[11]	M/59	S	5	Lymphadenopathy, splenomegaly	Cyclophosphamide, vincristine sulfate, prednisolone, and bleomycin	Died of T-cell lymphoma of diffuse mixed type
Tada *et al.*[12]	M/73	S	3	Lymphadenopathy	Conservative	4
Yamamoto *et al.*[13]	M/30	C	N/A	Skin	Intralesional triamcinolone injection	N/A
	M/47	C	N/A	Skin	Intralesional triamcinolone injection	N/A
	M/43	C	N/A	Skin	Intralesional triamcinolone injection	N/A
Kodama *et al.*[14]	M/54	S	Simultaneous	Lymphadenopathy, multiple masses around the ureters	Prednisolone, 30 mg/ cyclophosphamide	N/A
	M/56	C	N/A	Skin	Conservative	N/A
Ma *et al.*[2]	M/49	S	Simultaneous	Lymphadenopathy	Tacrolimus ointment	6.2
Kayasut *et al.*[15]	M/71	S	Simultaneous	Lymphadenopathy	Prednisolone	0.8
Shadel *et al.*[16]	M/36	S	Simultaneous	Lymphadenopathy	Conservative	N/A
Higashi *et al.*[17]	F/39	S	Simultaneous	Lymphadenopathy, diffuse nodular shadow of lung	N/A	N/A
	M/46	S	Simultaneous	Lymphadenopathy	N/A	N/A
Present case	F/48	S	4	Lymphadenopathy, multifocal ill-defined nodular opacities with interstitial thickening	Melphalan and prednisone combination chemotherapy and prednisone, 100 mg	6

M, male; N/A, not available; F, female; S, systemic; C, cutaneous.

cutaneous manifestations was 3.3 years in average (range, 1.5 to 5 years). In our case, the duration was 6 years. According to Tada *et al.*,[12] the prognosis of systemic plasmacytosis is less favorable than that of cutaneous plasmacytosis, due to systemic complications such as, renal dysfunction and malignant lymphoma. In our review, there was one case of systemic plasmacytosis with an incidence of malignant lymphoma (T-cell lymphoma of diffuse mixed type), but the rest showed no remarkable complications. The most common manifestation of extracutaneous involvement was superficial lymphadenopathy, occurring in approximately 70% of the patients. Lung involvement was also noted in four cases, and presented as lymphoid interstitial pneumonia, nodular infiltrates and calcified granulomas or as multiple tiny nodules. The splenic involvement was revealed in two cases, and the hepatic and peri-ureteral involvement was noted in one case, each. On the other hand, there was no involvement of the liver, spleen and kidney diseases in our patient.

Cutaneous plasmacytosis should be differentiated from other conditions, which result in plasma cell proliferation (Table 2).[1,9] In the case of primary cutaneous marginal zone B-cell lymphoma, the condition is usually presented as an erythmatous papule, plaque or nodule localized preferentially on the trunk and extremities and has a tendency to recur on skin despite treatment, but extracutaneous dissemination is of rare occurrence.[18] Systemic lupus erythematosus (SLE) is a disease that has a varied presentation with possible involvement of every organ system including mucocutaneous lesion. Malar rash, characteristic

Table 2. Differential diagnosis for plasma cell infiltrates in the skin

Category/Disease	Histologic findings
Malignant condition	
Cutaneous plasmacytoma	Large collection of monoclonal plasma cells
Marginal zone B-cell lymphoma, follicle center B-cell lymphoma	Plasma cells sprinkled around periphery of germinal center formations
Skin cancers	Plasma cell infiltrates in association with epithelial malignant conditions
Autoimmune disease	
Lupus erythematosus and scleroderma	Sprinkling of plasma cells in predominantly lymphohistiocytic infiltrates
Infection	
Bacterial, fungal, mycobacterial, and treponemal	Plasma cells and neutrophils, clues to cutaneous infection
Others	
Plasmacellularis vulvitis	Sheets of polyclonal plasma cells in band-like infiltrates under epithelium
Primary cutaneous plasmacytosis	Collections of polyclonal plasma cells in the upper dermis
Nodular amyloidosis	Nodules of cellular material and plasma cells around fat lobules, adnexa, and vessels
Cutaneous Rosai-Dorfman disease	Sheets of plasma cells in dense nodular infiltrates with emperipolesis
Inflammatory conditions	Plasma cells in infiltrates in the scalp and mucosa

of SLE, is seen only in 30% of children at presentation, and in 70% during the course of the illness, thus many of the cutaneous manifestations can be non-specific in nature.[19] Nodular amyloidosis can occur in various sites, most commonly the legs, followed by the head, trunk, arms and genitalia as a single or multiple nodules, or plaques, and is characterized by diffuse infiltration of the dermis, subcutis and blood vessel walls with amyloid.[20] Cutaneous plasmacytosis is differentiated from malignant lymphoproliferative disorders by the absence of clonality in the infiltrate and by its unusual clinical presentation with numerous slow growing cutaneous lesions. Compared to Rosai-Dorfman disease, cutaneous plasmacytosis shows more prominence of plasma cells and lacks emperipolesis.

The histological features are identical to those of plasma cell variant of Castleman's disease except for the skin lesions.[17] Therefore, Higashi *et al.*[17] suggested that systemic plasmacytosis is a disease entity close to the multicentric variant of Castleman's disease and proposed the descriptive term, "multicentric variant of Castleman's disease with cutaneous manifestations" for patients presenting with cutaneous and systemic plasmacytosis. However, the multicentric variant of Castleman's disease clinically behaves in a highly aggressive manner and is restricted to elderly or immunosuppressed individuals with frequent association with other human herpesvirus 8 (HHV-8) associated tumors, including Kaposi sarcoma or primary effusion lymphoma. In contrast, there was no evidence of HHV-8 in cutaneous and systemic plasmacytosis.[10] Thus, cutaneous and systemic plasmacytosis is distinct from the multicentric variant of Castleman's disease and immunostaining or polymerase chain reaction (PCR) analysis for HHV-8 provides a readily available method to distinguish these two entities. In our case, lung specimens were negative for HHV-8 based on PCR analysis, with a confirmed diagnosis of systemic plasmacytosis (Fig. 5).

In the present and Amin's case,[10] extracutaneous lesions developed after four and seven years of the cutaneous manifestation, respectively. It is important to diagnose systemic plasmacytosis at an early stage to start effective therapy such as systemic steroids, cyclophosphamide and other chemotherapies.[12]

According to Tada *et al.*,[12] out of 68 reported cases with cutaneous plasmacytosis, 30 cases (44%) had no palpable lymph nodes and four of the 30 cases were subjected to blind lymph node biopsy. They all exhibited prominent invasion of plasma cells in the lymph nodes, suggesting that there may be more cases of systemic plasmacytosis, which have been incorrectly diagnosed as cutaneous plasmacytosis because of the lack of palpable lymph nodes. Thus, blind biopsy of superficial lymph nodes would help in detecting systemic involvement in all the cases of cutaneous plasmacytosis.

The etiology of systemic plasmacytosis is unknown. Although the proliferation of plasma cells is believed to be reactive, the inciting event leading to increased proliferation has not yet been identified.[1] The predominance of cases in Asia has led to the suggestion that a primary infectious cause is responsible for the proliferation. Kodama *et al.*[14] detected an increase in serum interleukin (IL)-6 levels with systemic plasmacytosis and speculated similar roles of IL-6 as in Castleman's disease. IL-6, which induces proliferation and the terminal differentiation of activated B cells to plasma cells, may be important in the pathogenesis of systemic plasmacytosis. A reduction in the levels of IL-6 and improvement in a few individuals with plasmacytosis has been observed due to therapy with intra-lesional corticosteroids.[13] Our patient was treated with prednisone, with resultant reduction in pulmonary symptoms.

Recent studies have shown the projection of IgG4-related

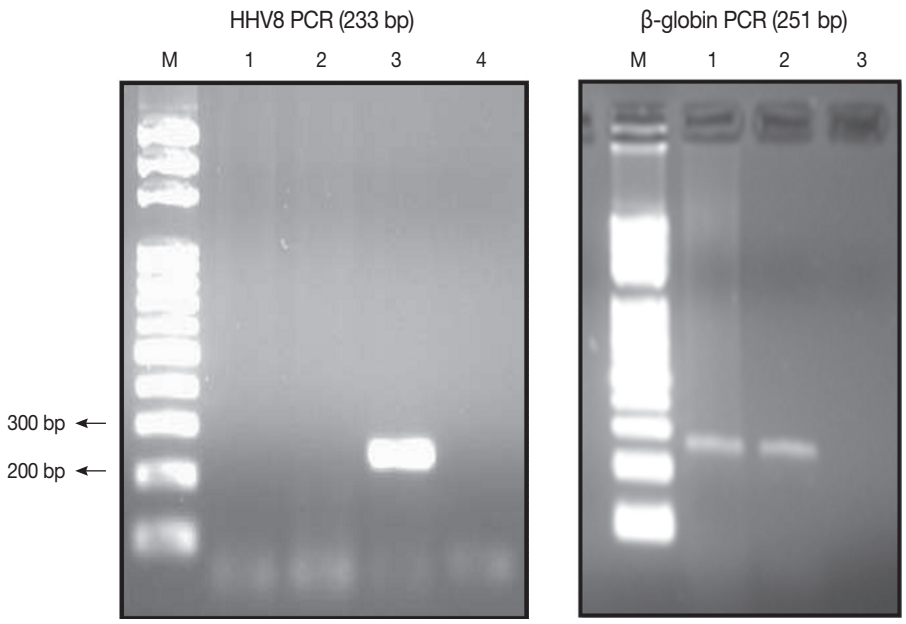

Fig. 5. Polymerase chain reaction (PCR) detection of human herpesvirus 8 (HHV-8) DNA. DNA is amplified, and electrophoresis is performed on 2% agarose gel. A region of the beta-globin gene is amplified to assess the integrity of DNA extraction and PCR procedures. M, molecular weight marker; lane 1, 1 μL of lung sample from patients with systemic plasmacytosis; lane 2, 3 μL of lung sample from patients with systemic plasmacytosis; lane 3, specimen for HHV-8 and β-globulin positive control; lane 4, specimen for HHV-8 and β-globulin negative control.

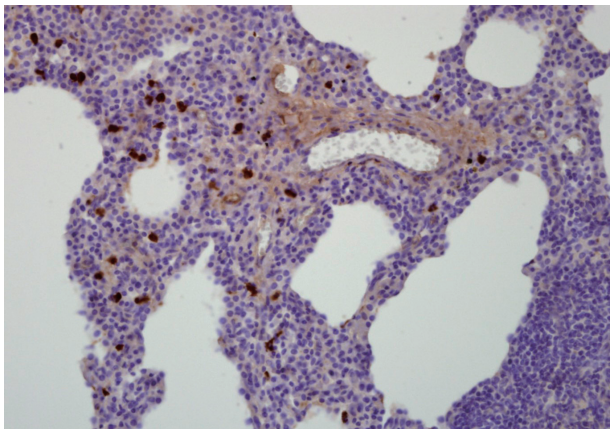

Fig. 6. Immunostaining for IgG4. Focal IgG4 positive plasma cell infiltration is seen in the lung.

sclerosing disease as a distinct disease entity.[3] IgG4-related sclerosing disease sometimes involves regional and/or systemic lymph nodes, and is often clinically and/or histologically suspected to be systemic plasmacytosis. The clinicopathologic similarities between systemic plasmacytosis and IgG4-related sclerosing disease indicate a relationship with systemic plasmacytosis as a manifestation of IgG4-related sclerosing disease, but further studies are needed to determine the role of IgG4 in the pathogenesis of this disease. Our case showed focal IgG4-positive plasma cell infiltration in the lung (Fig. 6).

Uhara *et al.*[7] reported that serum immunoglobulin level greater than 5,000 mg/dL and plasma cell counts in the bone marrow greater than 6.9% are the respective parameters associated with a more severe clinical course. In the present case, serum IgG level was 4,058 mg/dL and the bone marrow biopsy specimen represented 5% of plasma cell counts. Therefore, our patient had a favorable clinical course.

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