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Castleman disease-associated diffuse parenchymal lung disease

A STROBE-compliant retrospective observational analysis of 22 cases in a tertiary Chinese hospital

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Abstract

Intrathoracic involvement is common in Castleman disease (CD), but CD-associated diffuse parenchymal lung disease (DPLD) is rare and not well-reported.

We conducted a retrospective analysis of 262 CD patients with a definite pathological diagnosis who were hospitalized between 1999 and 2015.

Twenty-two CD patients had DPLD based on chest computed tomography (CT) scans. Among them, 9 were male and 13 were female, with a mean age of 45.3 years. Coughing (72.7%), fever (68.2%), and dyspnea (59.1%) were the common clinical manifestations. In high-resolution CT, obvious lymphadenopathy (81.8%) was the most frequent, followed by multiple nodules of different sizes (72.7%), cysts (59.1%), and patches of ground-glass opacity (54.5%). Six patients had lymphocytic interstitial pneumonia (LIP)-like CT images. Superficial lymph node biopsies (63.6%), video-assisted thoracic surgery lung biopsies (27.3%), CT-guided percutaneous lung biopsies (9.1%), and endoscopic lymph node biopsies (9.1%) were performed to make final diagnoses. The hyaline vascular variant (27.3%), the plasma cell variant (63.6%), and the mixed variant (9.1%) were the pathological subtypes. All but 2 were prescribed chemotherapy, and none was administered anti-interleukin-6 therapy. Among them, 14 patients improved, 3 died, 2 were stable, 2 were refractory, and 1 was lost to follow-up.

Chinese CD-associated DPLD might be more prevalent in middle-aged female patients, with most cases being the plasma cell variant. Although a LIP-like pattern was reported, only one-quarter of the patients showed LIP-like CT images. Multiple nodules (especially solid nodules), cysts, and patchy areas were the common pulmonary radiological findings. More than half of the patients improved after chemotherapy. A well-designed prospective study should be performed to confirm these results.

Abbreviations: ANA = antinuclear antibody, BO = bronchiolitis obliterans, CD = Castleman disease, CHOP = cyclophosphamide, adriamycin, vincristine, and corticosteroid, CRP = C-reactive protein, CT = computed tomography, DPLD = diffuse parenchymal lung disease, ESR = erythrocyte sedimentation rate, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, GGO = ground-glass opacity, HHV-8 = human herpesvirus 8, HIV = human immunodeficiency virus, HRCT = high-resolution CT, HV = hyaline vascular, Ig = immunoglobulin, IgG4-RD = IgG4-related disease, LANA-1 = latency-associated nuclear antigen-1, LDH = lactate dehydrogenase, LIP = lymphocytic interstitial pneumonia, MCD = multicentric CD, PC = plasma cell, SAP = systolic pulmonary arterial pressure, UCD = unicentric CD, VATS = video-assisted thoracic surgery.

Keywords: Castleman disease, diffuse parenchymal lung disease, lung

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1. Introduction

Although approximately 70% of Castleman disease (CD) cases occur in the thorax, solitary mass (s) and/or mediastinal and/or hilar lymphadenopathy are the most common radiological manifestations for both unicentric CD (UCD) and multicentric CD (MCD).[1] Pulmonary parenchymal involvement is occasionally seen in MCD, and lymphocytic interstitial pneumonia (LIP)-like findings are the typically reported radiological imaging pattern.[2–5] However, in our previous analysis of Chinese CD patients, in addition the LIP-like findings, multiple nodules of different sizes and at different sites, and also areas of patchy, ground-glass opacity (GGO) and consolidation were also not rare. Here, we describe the detailed clinical and radiological characteristics of 22 patients with MCD-associated diffuse parenchymal lung disease (MCD-DPLD) from a single Chinese tertiary-referral hospital.

2. Materials and methods

2.1. Patients

Using a computer-assisted search for patients hospitalized at Peking Union Medical College Hospital from 1999 to 2015, 262 patients were pathologically diagnosed with CD. Fifty-three patients with polyneuropathy, organomegaly, endocrinopathy, M-protein, skin pigmentation syndrome were excluded even if they had a confirmed pathological diagnosis of CD. Finally, 22 patients with diffuse pulmonary disease were enrolled after reviewing their medical records, radiologic images, and pathological manifestations.

The following information was analyzed: age, sex, symptoms at presentation, physical examination and serological results, radiologic findings, pathological manifestations, treatments received, and outcomes. Two radiologists conducted a consensus reading of high-resolution CT (HRCT) chest scans, which were downloaded from our hospital's image bank. Two pathologists reviewed all biopsy sections. Pathological diagnoses of CD were made based on Flendrig and Keller's criteria in all enrolled patients.[6,7]

All patients and/or their relatives provided written informed consent, and the study was approved by the ethics committee of Peking Union Medical College Hospital (JS-1127, ZS-1058), in accordance with the Declaration of Helsinki.

2.2. Statistical analysis

Data were analyzed using the Statistical Analysis System (SAS) version 9.0 software package. Quantitative variables are presented as the mean ± standard deviation (SD), and categorical data, as the frequency and percentage in the text and figures.

3. Results

All 22 patients were found to be negative in human immunodeficiency virus (HIV) antibody screening tests and were diagnosed with MCD.

3.1. Demographic characteristics

The study group consisted of 9 male (40.9%) and 13 female (59.1%) patients, with a mean age of 44.8 years (range 23–67 years of age). Three patients (13.6%) were 20 to 29 years old and 3 were 60 to 69 years old, 6 patients (27.3%) were 30 to 39 years old and 6 were 50 to 59 years old, and 4 patients (18.2%) were 40 to 49 years old (Fig. 1). Eight patients were admitted from 2007 to 2010, and the other 14 were hospitalized after 2010 (Table 1).

3.2. Clinical manifestations

All patients suffered from at least 1 of the following symptoms: coughing (72.7%), fever (68.2%), dyspnea (59.1%), obvious body weight loss (more than 5 kg, 27.3%), fatigue (22.7%), abdominal distention (9.1%), and chest pain (4.5%). For those with a fever, only 2 showed a high-grade fever. Multiple superficial lymphadenopathies involving the neck, supraclavicular region, axillary fossa, supratrochlear zone, and inguinal region were found in 19 patients, and at least 2 lymph node zones were involved for them. Thirteen patients had hepatomegaly and/or splenomegaly.

3.3. Laboratory tests

All patients underwent a complete blood cell analysis and serum biochemical analysis. More than half of them (14/63.6%) had anemia, and the mean hemoglobin concentration was 96.4 ± 22.3 g/L. Eight (36.4%) had thrombocytosis, and 1 had thrombopenia. The mean platelet count was $315.0 \pm 155.4 \times 10^9$/L. Seventeen (77.3%) had hypoalbuminemia (serum albumin <35 g/L) and 19 (86.3%) had hyperglobulinemia (serum globulin>35 g/L). The mean serum albumin concentration was 27.7 ± 8.1 g/L, and the mean serum globulin concentration was 66.5 ± 34.8 g/L. The mean albumin/globulin ratio (A/G) was 0.6 ± 0.3. The results of serum protein electrophoresis showed polyclonal hypergammaglobulinemia, and the serum immunoglobulin (Ig) electrophoresis results were normal for all patients. Seventeen had serum A/G ratios less than 1. All but 2 patients did not undergo serum Ig analyses, and 16 (80%, n = 20) showed elevated serum IgG levels. The highest serum IgG level was 133 g/L, and the mean level was 41.7 ± 31.5 g/L. Among the 20 patients with serum Ig results, 8 showed elevated levels of IgM and IgA. Elevated serum IgA, IgM, and IgG levels were reported for 5 patients, and 4 only showed elevated serum IgG levels.

Among the 20 patients with erythrocyte sedimentation rate (ESR) results, 19 showed elevated ESRs (>30 mm/h). Serum C-reactive protein (CRP) tests were performed in 19 patients, and

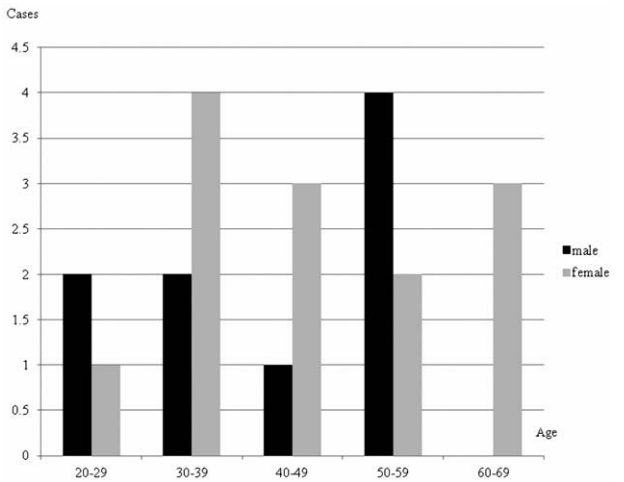

Figure 1. Age distribution of our enrolled MCD patients. MCD = multicentric Castleman disease.

Table 1

Demographic, clinical, and pathological features of the 22 patients.

No.	Sex/age	Year	Hb	IgG	Pathological pattern	Biopsy	Treatment	Outcome
1	F/38	2007	86	39.5	PC	Superficial LN biopsy	CHOP	Lose follow-up
2	F/47	2007	113	20.2	PC	VATS LN biopsy	CHOP	Died
3	F/64	2007	123	10	HV	Percutaneous and VATS lung biopsy	CHOP	Died
4	F/45	2009	97	24	PC	Percutaneous lung biopsy	E-CHOP	Recovered
5	M/54	2009	120	55.2	PC	Superficial LN biopsy	CHOP	Recovered
6	F/51	2009	138	26.8	PC	VATS lung biopsy	CHOP	Recovered
7	M/43	2009	80	38.2	PC	Superficial LN biopsy	CHOP	Recovered
8	M/34	2010	66	133	PC	Superficial LN biopsy	Without medication	Stable
9	F/36	2011	97	95.3	PC	VATS LN biopsy	CHOP	Died
10	M/39	2011	88	—	HV	Superficial LN biopsy	CHOP	Recovered
11	M/51	2011	121	15.6	PC	Superficial LN biopsy	R-CHOP	Refractory
12	M/23	2011	66	27.8	Mixed	Superficial LN biopsy	CHOP	Recovered
13	F/31	2011	120	19.1	PC	Superficial LN biopsy	CHOP	Recovered
14	F/62	2012	74	9.46	HV	VATS lung biopsy	CHOP	Recovered
15	F/67	2012	120	—	HV	Superficial LN biopsy	Without medication	Stable
16	F/37	2013	69	55.6	PC	Superficial LN biopsy	CHOP	Recovered
17	F/58	2014	92	42.7	PC	VATS lung biopsy	CHOP	Refractory
18	M/53	2014	57	87	PC	VATS lung and LN biopsy	CHOP	Recovered
19	M/56	2014	90	11	HV	Superficial LN biopsy	CHOP	Recovered
20	M/29	2015	123	62	PC	Superficial LN biopsy	TCP	Recovered
21	F/26	2015	94	23.3	HV	Superficial LN biopsy	TCP	Recovered
22	F/42	2015	87	37.4	Mixed	Superficial LN biopsy	TCP	Recovered

CHOP = cyclophosphamide, adriamycin, vincristine, and corticosteroid, E-CHOP = etoposide and CHOP, Hb = hemoglobin, HV = hyaline vascular, Ig = immunoglobulin, LN = lymph node, PC = plasma cell, R-CHOP = rituximab and CHOP, TCP = thalidomide plus corticosteroids and cyclophosphamide, VATS = video-assisted thoracic surgery.

17 showed elevated serum CRP levels (>8 mg/dL). Although serum lactate dehydrogenase (LDH) levels have been found to be elevated in patients with lymphoma and might be associated with their prognosis,[4] only 3 showed elevated serum LDH levels (>250 U/L).

Eight patients had serum interleukin (IL)-6 analysis results, and 7 underwent IgG subtype analyses. Serum IL-6 levels were elevated in all 8 of these patients (mean 24.9 pg/mL; range 11.6–49.8 pg/mL). Serum IgG4 levels were elevated for all 7 patients analyzed (mean 38842.8 mg/L; range 17,100–72,100 mg/L). Five patients underwent tests for total serum IgE, and all were found to have significantly elevated levels: more than 5000 KU/L in 2 patients, and 1776, 735, and 506 KU/L in the other 3. However, the percentage and count of eosinophil granulocytes were not elevated in these 5 patients. The antinuclear antibody (ANA) was screened for all patients, and 8 had positive results. Seven patients had low-grade positive titers for ANA, which ranged from 1:80 to 1:320. However, 1 showed a titer of 1:1280, with a speckled ANA pattern. All patients had negative double stranded DNA results. One patient had a titer of 1:10 for the antineutrophil cytoplasmic antibody.

3.4. Pulmonary function tests and echocardiography

Thirteen patients were examined pulmonary function tests, and only 4 had airflow obstruction with a forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) ratio <70% and no significant response to a bronchodilator test. The other 9 patients had normal FEV1/FVC, FVC, and total lung capacity values. Most (12, 92.3%) patients had impaired gas exchange, with a decreased diffusion capacity of the lung for carbon monoxide (DLco) (range 18%–67%). Only 1 patient whose chest CT scan showed multiple nodules had normal DLco.

Twenty-one patients underwent echocardiography. Systolic pulmonary arterial pressure (SAP) was estimated based on duplex echocardiography, and an SAP >50 mm Hg was defined as pulmonary hypertension. Among these 21 patients, 3 had pulmonary hypertension, with SAP values of 51, 56, and 70 mm Hg.

3.5. Radiological manifestations

All enrolled patients underwent HRCT scanning, and pulmonary parenchymal abnormalities were seen in all 22 patients. Eighteen had significant lymphadenopathy in the hilum and/or mediastinum. Multiple nodules of different size were the most common manifestation (72.7%), followed by cysts of different sizes and shapes (59.1%), GGO (54.5%), air trapping (40.9%), interlobular septal thickening (36.4%), the thickening of bronchovascular bundles (31.8%), and localized consolidation (22.7%). Seven had minimal pleural effusion, and none underwent thoracentesis. Although LIP-like patterns[2] have been reported in association with CD-DPLD,[5] this was only seen in 6 patients in our group. One patient, who had pemphigus-related complications, showed a typical diffuse bronchiolitis obliterans (BO)-like pattern.

3.6. Pathological features

Biopsies were performed in all enrolled patients, and some were performed during more than 1 biopsy surgery. Superficial lymph node biopsies were performed in 14 patients (63.6%), and 6 (27.3%) involved at least 2 biopsies. Medial lymph node biopsies were performed using video-assisted thoracic surgery (VATS) for 2 patients (9.1%). Two patients (9.1%) underwent CT-guided percutaneous lung biopsies, and 1 of them subsequently underwent a VATS lung biopsy 2 weeks later because of a nondiagnostic pathological manifestation firstly. Another 5 (22.7%) underwent VATS lung biopsies. After 2 pathologists reviewed the pathological manifestations, CD was definitively diagnosed in all enrolled patients. Based on Flendrig and Keller's criteria, 6 (27.3%) were diagnosed with the hyaline vascular

(HV) variant, 14 (63.6%) were diagnosed with the plasma cell (PC) variant, and the other 2 cases (9.1%) were diagnosed with the mixed variant. CD3, CD20, CD38, CD138, IgG, IgG1, and IgG4 staining was performed for all PC and mixed variant cases, and none met the diagnostic criteria for IgG4-related disease (IgG4-RD).[8] All our patients with a LIP-like pattern radiologically were diagnosed with the PC variant. Bone marrow aspiration and biopsy were arranged for those with obvious abnormalities complete blood count (CBC) analysis, and none of them showed malignancy.

3.7. Treatment and prognosis

Only 1 patient was lost during the follow-up. The mean follow-up period was 67.5 months. No patients underwent therapeutic surgery. Variable chemotherapy was arranged for 20 of the enrolled patients, with 15 being treated with CHOP (cyclophosphamide, adriamycin, vincristine, and corticosteroid), 1 with ECHOP (etoposide and CHOP), 1 with R-CHOP (rituximab and CHOP), and 3 with thalidomide plus corticosteroids and cyclophosphamide). The other 2 cases were only observed during regular clinic follow-ups and did not receive medication: 1 patient had complained of slight to moderate fatigue for at least 3 years, and the other, who had palpable multiple superficial lymphadenopathies for 11 years and LIP-like lung disease for 5 years, refused to accept chemotherapy.

Three patients died during the follow-up period: 1 had complications associated with pemphigus and BO, and she died of respiratory failure even after treatment with chemotherapy, macrolide antibiotics, and inhaled corticosteroids; 1 died of a severe pulmonary infection after the eighth chemotherapy treatment with CHOP; and 1 died from complications associated with severe pulmonary hypertension and heart failure. Two patients were stable, 2 were refractory and then responded to a new round of chemotherapy, and the other 14 improved after treatment.

4. Discussion

Either UCD or MCD develops more commonly in the thorax,[9–12] and a hilar/mediastinal mass is the most common for both intrathoracic UCD and MCD.[1,10] Although UCD has been shown to be more common in most studies,[11,12] approximately two-thirds of intrathoracic CD cases in our previous study were MCD.[1] After Barrie et al[13] reported on MCD-DPLDs, they have been discussed occasionally.[1,5,14–16] In the reported cases of non-HIV MCD-DPLDs, LIP-like patterns are the most commonly reported, either in radiological or pathological studies.[4,5,13,14] However, this same trend was not found in our enrolled CD patients.

In our cohort, all patients were negative for the HIV antibody. Therefore, we could focus on the characters of non-HIV MCD-associated diffuse lung disease. The disease was most prevalent in female patients, and most of them were 30 to 59 years old, with a mean age of 44.8 years and with a media age of 44 years. The demographic characteristics were similar to those of the patients in Johkoh et al's study[5] and Kawabata et al's study,[17] but were different from those in Robinson et al's[18] analysis and Liu

Table 2

Comparison of recent studies about MCD cases.

	References					
Characters	**Johkoh et al[5] (1998)**	**Zhu et al[20] (2013)**	**Kawabata et al[17] (2013)**	**Robinson et al[18] (2014)**	**Liu et al[19] (2016)**	**Ours**
Hospitalization period	1995–1997	2004–2012	2005–2012	2000–2009	1995–2015	1995–2015
Location	Japan	China (Shandong)	Japan	USA	Universal	China (Beijing)
Total cases	12	10	21	59	128	22
Age						
Range, y	23–58	31–75	13–70	18–≥65	2–80	23–67
Mean/median, y	42.9/–	47.4/44.5	–/46	53.4/55	–/50	44.8/44
Male sex (n/%)	5/41.7%	6/60%	12/57.1%	36/61%	74/57.8%	9/40.9%
Negative HIV (n/%)	NA	10/100%	13/100%[†]	35/62.5%	128/100%	22/100%
Clinical feature						
Fever (%)	—	—	35	39.4	52	68.2
Fatigue (%)	100	—	—	48.5	—	22.7
Blood test						
Hb (mean, g/L)	100	—	100	—		96.4
Anemia (%)	100	—	100	—	87[*]	63.6
IgG (mean, g/L)	41	—	49	—	—	41.7
IgG elevated	100%	—	—	—	77%[†]	80%[‡]
ESR (mean, mm/h)	107	—	—	—	—	>88.9[#]
ESR elevated	100%	90%	—	—	92%	95%
Chest CT						
LIP-like pattern	100%	—	—	—	—	27.3%
Pathological type (n/100%)						
Plasmacytic	2/16.7%	6/60%	18/94.7%[§]	25/49%[‖]	42/39%[¶]	14/63.6%
Hyaline vascular	0	2/20%	0	17/33.3%[‖]	23/21%[¶]	6/27.3%%
Mixed	10/83.3%	2/20%	1/5.3%[§]	9/17.6%[‖]	42/39%[¶]	2/9.1%

ESR = erythrocyte sedimentation rate, Hb = hemaglobin, HIV = human immunodeficiency virus, IgG = immunoglobin G, LIP = lymphocytic interstitial pneumonia, NA = not available.

[*] Ninety-one cases had analyzed hemoglobin in this study.

[†] Eight-two cases had analyzed γ-globulin, and in this study, serum IgG level had not been analyzed.

[‡] Twenty cases had undergone serum IgG analysis.

[§] Nineteen cases had detailed histopathological features.

[‖] Fifty-one cases had definite pathological subtype.

[¶] One hundred one cases had definite pathological information.

[#] The ESR was more than 140 mm/h for two cases.

et al's[19] meta-analysis of idiopathic MCD (iMCD). MCD cases in the 2 US MCD referral centers were more prevalent in males and in older patients than we found in our study[18] (Table 2).

Different from UCD, most MCD cases present with variable systemic clinical manifestations, for example, fever, night sweats, fatigue, body weight loss, diffuse lymphadenopathy, hepatosplenomegaly, and pleural effusion/effusion of serous cavities.[17,19,20] All of our enrolled patients were symptomatic, and most of them had obvious abnormal serum test results, including abnormal platelet counts, hemoglobin, serum globulin, albumin, and CRP levels and ESRs. Our enrolled patients had serum features similar to those reported previous studies.[17,19] Studies have shown that serum IL-6 is a pivotal cytokine in the pathogenesis, symptomatology, and histopathology of viral and/or iMCD.[21,22] In our hospital, serum IgG subtype analyses have been applied more commonly even after 2012, and the detection of serum IL-6 levels has been used universally since 2013. As our study was a retrospective analysis, not all enrolled patients had reported serum IgG4 and/or IL-6 levels. IgG4 data were available for 7 patients, and all showed significantly elevated serum IgG4 levels. However, 6 of the patients underwent serum IL-6 analyses, and their IL-6 levels were all significantly elevated. As listed in Table 2, the non-HV variant has been shown to be the major pathological type in reported MCD cases,[5,17–20] which is also the same as in thoracic CD cases.[1] Only about one-fifth of our enrolled MCD-DPLD patients had HV variants. Most of the cases were non-HV variants. Systemic IgG4-related lymphadenopathy could mimic the clinical signs of MCD.[23–25] Therefore, it is important to make a differential diagnosis between MCD and IgG4-RD. Although some patients with definite IgG4-RD show normal serum IgG4 concentrations, the elevation of serum IgG4 is more common in patients with IgG4-RD, and serum IgG4 levels ≥135 mg/dL is 1 of the major diagnostic criteria for IgG4-RD.[26–29] However, an elevated serum IgG4 level is not specific for IgG4-RD as it can also be associated with non-IgG4-RDs, for example, hematological malignancies and allergic diseases, especially MCD with the PC or mixed variant.[23–25] However, higher levels of serum IL-6 and IgG, along with increases in IgM and/or IgA, and differences in the $IgG4^+/IgG^+$ ratio and morphological manifestations in the involved tissue[23,24] have been seen in MCD cases. Patients with IgG4-RD have elevated serum IgG4 levels, but most of them have normal levels or lower increases in serum IL-6. We engaged in multidisciplinary discussions about cases of MCD that mimicked IgG4-RD and involved specialists in respiratory, rheumatological, hematological, pathological, and radiological departments. Then, we enrolled the patients with a final diagnosis of MCD in our study. Most of our enrolled patients showed elevated IgG levels, and most of these patients had concomitant elevations in IgA and/or IgM levels, which has been reported as a differential diagnostic feature of IgG4-RD.[30]

Johkoh et al's study described the characteristics of chest thin-section CT images for patients who had been pathologically diagnosed with LIP. The presence of areas of GGO, poorly defined centrilobular/subpleural nodules, the thickening of the interlobular septa, and randomly distributed thin-walled cysts were the main radiological features of LIP.[5,31] Pathological/radiological LIP-like patterns can be seen in a variety of diseases, including infectious and autoimmune diseases, and multiple lymphocytic-plasmatic diseases, such as HIV infections, Sjögren syndrome, various types of lymphoma, and MCD.[1,5,10,14,31] After Barrie et al[13] first reported on CD-associated diffuse interstitial lung disease, there were occasional reports of cases of MCD-DPLD, and the LIP-like pattern was the most frequently reported radiological pattern associated with MCD-DPLD

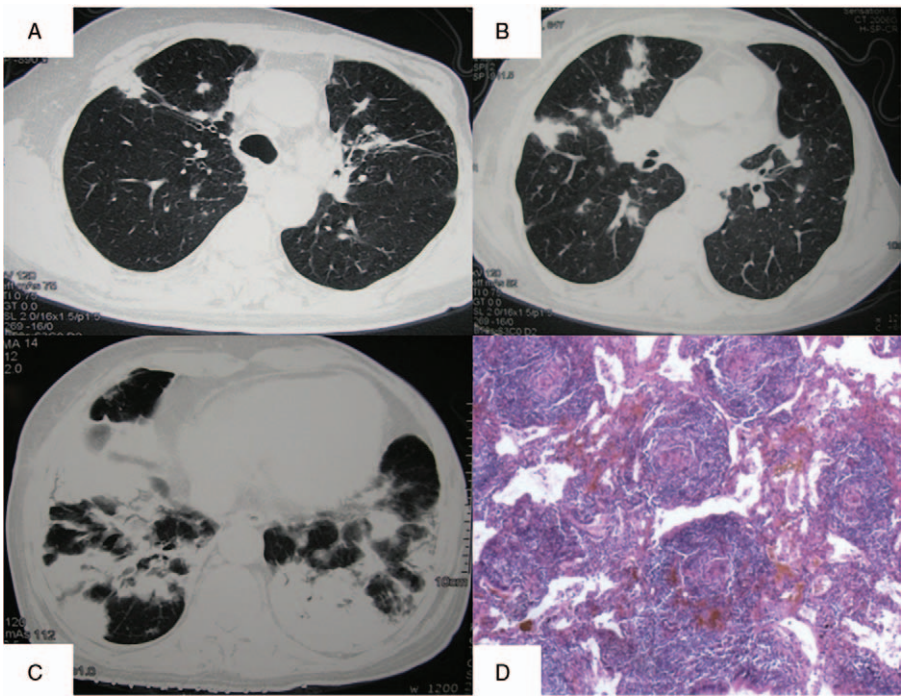

Figure 2. Chest CT showed multiple nodules of different size and consolidations in the bilateral lungs (A–C). Pulmonary biopsy showed hyperplasia of the lymphoid tissue with folliculus lymphaticus formation and atrophic germinal centers which were surrounded by expanded mantle zones of small lymphocytes forming concentric rings as "Onion-skinning" sign (D, HE stain, ×40). CT = computed tomography.

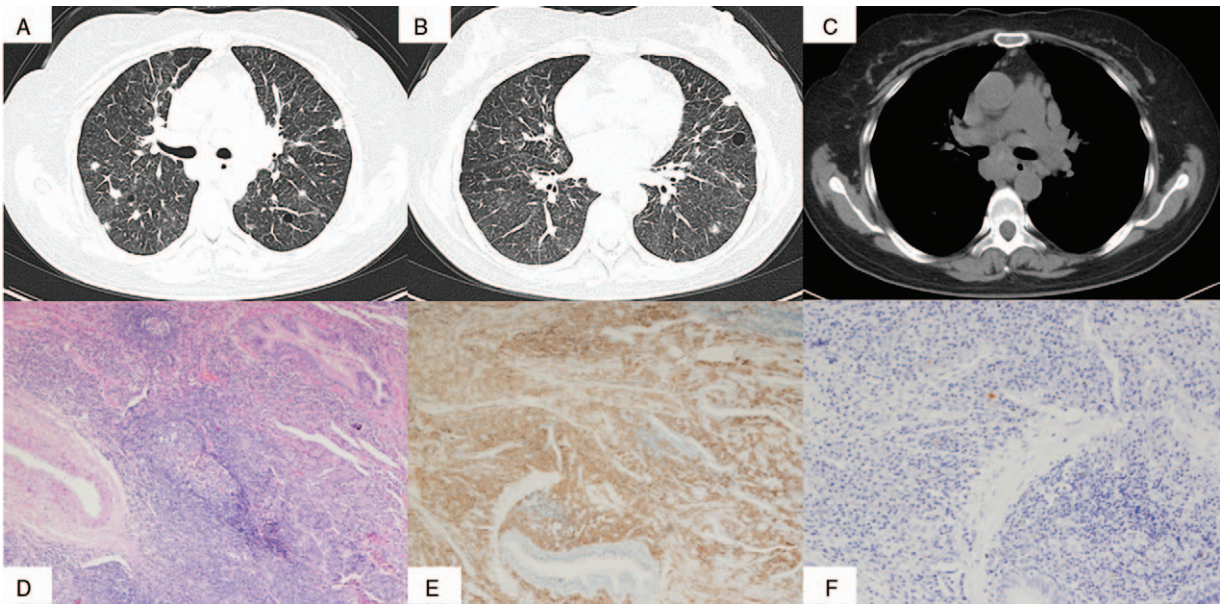

Figure 3. Chest HRCT showed multiple nodules and scattered cysts in both lungs (A and B), with significant lymphadenopathy in both hilum and mediastinum (C). There were a lot of plasma cells infiltrated in lung tissue, with lymphoid follicles formation (D, HE stain, ×40). (E, CD38 immunostaining, ×40). Also, there were scarce IgG4-positive cells in lung tissue, less than 5 cells per high power field (F, IgG4 immunostaining, ×100). HRCT = high-resolution computed tomography.

cases[5,10,14] and seemed as a minor diagnostic criteria for iMCD.[32] However, not all of our enrolled patients showed LIP-like patterns, neither pathologically nor radiologically (Figs. 2–4). Seven cases in our study underwent lung biopsies, and none of them showed LIP-like patterns, either in their chest HRCT scans or pulmonary biopsy manifestations, and all of these patients met the pathological diagnosis criteria for CD. The majority of these 7 patients showed multiple/diffuse nodules, and either solid or GGO-like nodular and patchy/consolidation areas in their lungs. Obvious mediastinal and/or hilar lymphadenopathies were not seen in 4 of these 7 patients. These characteristics have not been commonly reported in other studies. In the new consensus diagnostic criteria for iMCD, the pathological feature for the involved lymph node was well-described. But the pulmonary histopathological manifestations were not involved.[32]

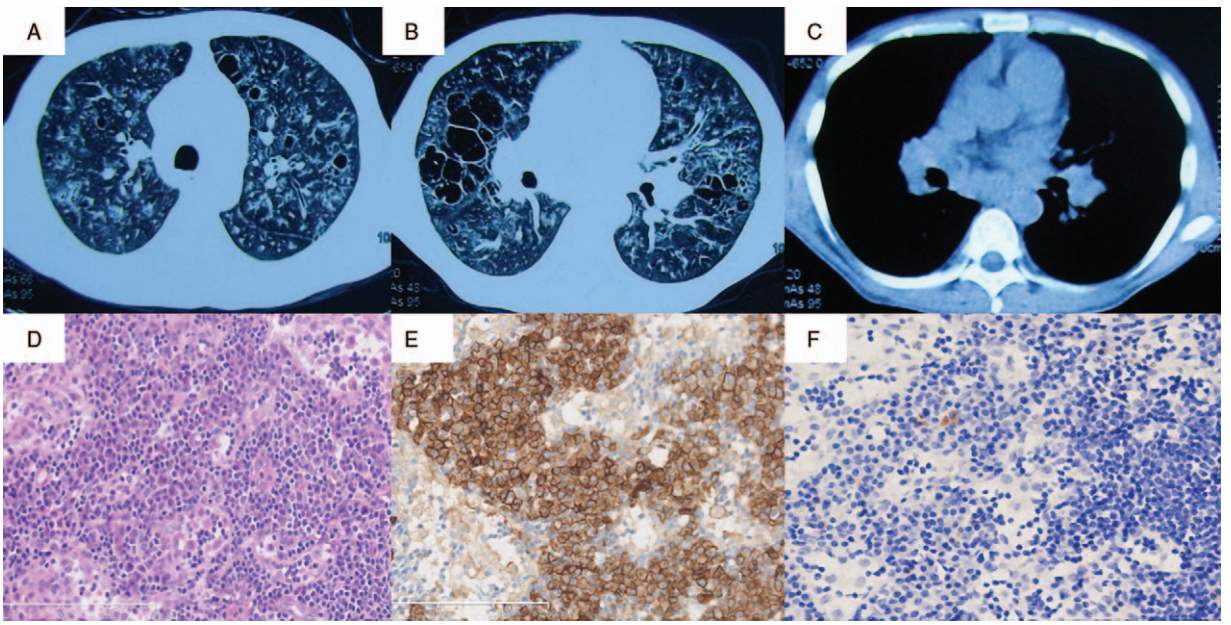

Figure 4. Chest HRCT showed poorly defined diffuse centrilobular GGO nodules, multiple cysts (A, B), and obvious hilar and mediastinal lymphadenopathy (C). Cervical lymph node biopsy showed confluent plasma cells infiltrated in the interfollicular region (D, HE stain, ×200; E, CD38 immunostaining, ×200), and scattered positive cells with IgG4 immunostaining, less than 5 cells per high power field (F, ×100). GGO = ground-glass opacity, HRCT = high-resolution computed tomography.

Unlike complete surgical resections for treating UCD, several systemic treatment strategies have been recommended for treating iMCD, including chemotherapy, targeted treatments with biologic agents directed against CD20 and IL-6, or the IL-6 receptor.[33] Traditional chemotherapy or anti-CD20 therapy combined with chemotherapy was performed for most of our enrolled patients. As anti-IL-6 or anti-IL-6 receptor biologics had not been clinically approved in China before 2016, none of these patients were treated with IL-6 or IL-6 receptor targeting agents. However, most of them improved or stabilized after treatment. Severe pulmonary infections, respiratory failure because of diffuse BO, or severe pulmonary hypertension were the main causes of death in our study.

There were several limitations in our study. Firstly, all enrolled patients had a definite diagnosis of MCD, which could cause a selection bias. Secondly, it was a retrospective study, and several serum tests were not performed for all patients, for example, IgG subtype analyses, IL-6 and IgE assays, eosinophil granulocyte counts, B-cell counts, and human herpesvirus 8 (HHV-8) tests. Serum IgE levels were not routinely checked in our hospital for patients with CD, and studies have rarely focused on examining serum IgE in patients with MCD. It was reported in Ujihara et al's[34] study that serum IgE levels were elevated in their patient with MCD. Five patients with non-HV variant MCD in our cohort underwent serum IgE analyses, and all of them had elevated levels. Unlike the patient in Ujihara et al's study, whose CBC showed eosinophilia, these 5 cases in our study showed normal peripheral eosinophil granulocyte counts. The characteristics of serum IL-6, IgG4, IgE, eosinophils, and B cells were not studied systemically in patients with CD or MCD. Therefore, a well-designed prospective study of iMCD should be performed. Thirdly, the absence of HHV-8 status in the lymph node pathological specimen, for example, the latency-associated nuclear antigen-1 (LANA-1) staining, was disappointing. It was well-known that HHV-8 infection was associated with all HIV-positive MCD cases and few HIV-negative MCD cases. The LANA-1 staining in the lymph node was nearly 100% positive for HHV-8-associated MCD cases.[21] As some of our patients were not under lymph node biopsy, and none of our enrolled patients was HIV-positive, LANA-1 staining was not performed during this retrospective study. The LANA-1 staining might be included in the further study. Fourthly, not all enrolled patients underwent lung biopsies. More than half of the patients were diagnosed with CD based on lymph node biopsies, without lung biopsies, even in those with diffuse pulmonary infiltrations. However, for these cases, the pathological manifestations and serum analyses were sufficient for the diagnosis of CD, and to avoid excessive damage, lung biopsies were not recommended.

5. Conclusions

Castleman disease-associated DPLD might be more prevalent in middle-aged female patients, with most cases being the PC variant. Coughing, fever, and dyspnea were the common clinical manifestations. Anemia, polyclonal hypergammaglobulinemia, and elevated ESRs and CRP levels were common. The elevation of serum IL-6, IgG4, and IgE levels was reported in all patients who were tested for these factors. Although a LIP-like pattern was reported, only one-quarter of the patients showed LIP-like CT images. Multiple nodules (especially solid nodules), cysts, and patchy areas were the common pulmonary radiological findings. More than half of the patients improved after chemotherapy. A well-designed prospective study should be performed to confirm these results.

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