Evaluation of Japanese and international diagnostic criteria for idiopathic multicentric Castleman disease

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Introduction

There are two recent major diagnostic criteria for idiopathic multicentric Castleman disease (iMCD). The Japanese diagnostic criteria (Modern Rheumatology 2018) and the international diagnostic criteria of the Castleman Disease Collaborative Network (Blood 2017). We compared these two diagnostic criteria and cross-examined their validity.

Patients and Methods

13 patients with histologically confirmed iMCD (male/female: 8/5, mean age: 47) were evaluated at a single center. All patients had at least a 1-year therapy period for iMCD. In addition, 3 patients (male/female: 2/1, mean age: 67, final diagnosis: tuberculosis lymphadenitis, 1 patient; Hodgkin disease, 1 patient; non-Hodgkin lymphoma, 1 patient) who were unable to be excluded after the first histological diagnosis were evaluated.

Conclusion

The diagnostic results of the Japanese and CDCN diagnostic criteria were almost identical. However, detailed exclusion criteria need to be considered for accurate diagnosis. If the histological diagnosis and exclusion diagnosis are incomplete, these diagnostic criteria will not be applicable.

Japanese Diagnostic Criteria for Castleman disease

Essential Diagnostic Criteria for Castleman Disease (both A and B must be met)

A. Both of the following conditions should be met:

1. Single or multiple swollen lymph node/s (the longest diameter > 1 cm) should be present.

2. Histopathological findings of the affected lymph node(s) or organ(s) should be consistent with one of the following histological types of Castleman disease*:
   1)Hyaline vascular type
   2)Plasma cell type
   3)Mixed type

B. The following diseases should be excluded as the cause of lymphadenopathy.

1.Malignant neoplasms:
Angioimmunoblastic T-cell lymphoma, Hodgkin lymphoma, follicular dendritic cell sarcoma, renal cell carcinoma, malignant mesothelioma, lung cancer, cervical cancer, etc.

2. Infectious diseases:
Nontuberculous mycobacterial infection, cat scratch disease, rickettsial disease, toxoplasmosis, fungal infection, infectious mononucleosis, chronic active Epstein-Barr (EB) virus infection, acute HIV infection, etc.

3. Autoimmune diseases:
Systemic lupus erythematosus, Sjögren's syndrome, etc.

4.Other diseases manifesting symptoms similar to Castleman disease:
IgG4-related diseases¶, histiocytic necrotizing lymphadenitis, sarcoidosis, idiopathic portal hypertension, etc.

Supplementary information for diagnosis

1. Castleman disease can present with various clinical symptoms of different degrees of severity. Frequent symptoms include low- to moderate-grade fever,general malaise, easy fatigability, weight loss, night sweats, and superficial lymphadenopathy. Some cases manifest with skin lesions (flat) or slightly elevated brown or dark red eruptions, pemphigoids, xanthoma, atopic dermatitis, or hemangiomas), abdominal distension, edema, shortness of breath, dyspnea, and hemorrhagic tendency. Castleman disease can be associated with vascular events, such as cerebral infarction or peripheral neuropathy.

2. In addition to lymphadenopathy, imaging examinations may reveal hepatosplenomegaly, ascites, pleural effusion, and pulmonary interstitial shadows.

3. Blood tests usually show a positive CRP and elevated serum IL-6. Microcytic anemia and thrombocytosis are frequently observed. Decreased serum LDH and albumin levels, and increased serum alkaline phosphatase, IgE, and VEGF levels are also frequently observed. Polyclonal hypergammaglobulinemia is another important feature of Castleman disease. Autoantibodies, such as anti-nuclear antibody, are occasionally detected.

4. In some cases, renal dysfunction, interstitial pulmonary lesions, pulmonary hypertension, dilated cardiomyopathy, autoimmune thrombocytopenia, autoimmune hemolytic anemia, endocrinopathy (such as hypothyroidism), and/or AA-amyloidosis accompany the disease.

5. Elevation of serum IgG4 levels or increased IgG4 positive cells in the lymph nodes can be observed, not only in IgG4-related disease, but also in Castleman disease. Presence of fever, microcytic anemia, thrombocytosis, and elevations of serum CRP, which are caused by overproduction of IL-6, are signs supporting the diagnosis of Castleman disease rather than IgG4-related disease.

6. HHV-8-associated multicentric Castleman disease can be diagnosed by the typical histopathological features and the presence of the HHV-8 genome in the blood or in the lymph nodes. Majority of patients with HHV-8-associated Castleman disease are HIV positive, and Kaposi's sarcoma occasionally develops simultaneously or subsequently.

7. POEMS syndrome is a disease entity with monoclonal gammopathy accompanied by polyneuropathy, organomegaly, and endocrinopathy. This entity is believed to be a relative of multiple myeloma, but a part of its pathological conditions overlaps with those of Castleman disease. POEMS syndrome is not excluded from Castleman disease in this classification.

8.TAFRO syndrome is a medical condition or disorder presenting with thrombocytopenia, anasarca, fever, bone marrow fibrosis, and organomegaly. Histology of lymph nodes from patients with this syndrome is indistinguishable from that of Castleman disease. In this classification, TAFRO syndrome is not excluded from Castleman disease.

Evaluation of Japanese diagnostic criteria for Castleman disease

All MCD patients met the Japanese diagnostic criteria. However, the three non-MCD patients also met the Japanese diagnostic criteria at first.

Results

Positive ratio in international criteria

			Major criteria		Minor criteria (Laboratory data)						Minor criteria(Symptoms)				
Age	Sex	Diagnosis	Histology	Enlarged lymph nodes	Elevated CRP/ESR	Anemia	Thrombocytopenia/thrombocytosis	Alb 3.5>	eGFR 60>	IgG >1700	Constitutional symptoms	Large spleen/liver	Fluid accumulation	Skin symptom	Lymphocytic interstitial pneumonia
61	M	MCD	○	○	×	×	×	○	NE	○	×	×	×	×	×
26	F	MCD	○	○	○	○	×	○	NE	○	○	○	○	×	×
53	M	MCD	○	○	○	○	×	○	NE	○	×	○	×	○	×
39	F	MCD	○	○	○	○	○	○	NE	○	○	○	×	×	×
34	M	MCD	×	○	○	○	×	○	×	○	○	○	×	×	○
45	F	MCD	○	○	○	○	○	○	×	○	NE	○	×	×	×
54	M	MCD	○	○	×	×	×	×	×	○	×	×	×	×	×
53	F	MCD	○	○	○	○	×	○	×	○	×	○	×	×	×
47	M	MCD	○	○	○	○	×	○	○	○	×	○	×	○	○
58	M	MCD	○	○	○	○	×	○	×	○	×	×	×	×	×
69	M	MCD	○	○	○	○	○	○	○	○	×	○	×	×	○
27	M	MCD	○	○	○	○	○	○	×	○	×	○	×	×	×
28	F	MCD	○	○	○	○	○	○	×	○	○	○	×	○	×

The international criteria of CDCN consist of two major criteria, eleven minor criteria, and exclusion criteria. Twelve of 13 iMCD patients were diagnosed by the international criteria of CDCN. Only one patient could not be diagnosed by the international diagnostic criteria of CDCN because of lung biopsy instead of lymph node biopsy.

			Major criteria		Minor criteria (Laboratory data)						Minor criteria (Symptoms)				
Age	Sex	Diagnosis	histology	enlarged lymph nodes	elevated CRP/ESR	anemia	thrombocytopenia/thrombocytosis	Alb3.5>	eGFR 60>	IgG >1700	constitutional symptoms	large spleen/liver	fluid accumulation	skin symptom	lymphocytic interstitial pneumonia
65	F	Tuberculosis lymphadenitis	○	○	○	○	○	○	×	×	×	×	×	×	×
67	M	Non−Hodgkin lymphoma	○	○	×	×	○	○	×	○	×	○	×	×	×
88	M	Hodgkin disease	○	○	○	○	×	○	×	○	○	○	×	×	×

Three non-MCD patients met the CDCN criteria at first, they were diagnosed with other diseases later.

Major criteria

Histopathologic lymph node feature;12 of 13patients (92.3%)
Enlarged lymph nodes 13 of 13 patients (100%)

Minor criteria

Elevated CRP: 11 of 13 patients (84.6%) (41%)
Anemia: 11 of 13 patients (84.6%) (32%)
Thrombocytopenia or thrombocytosis: 5 of 13 patients (38.5%)(20%)
Hypoalbuminemia: 12 of 13patients(92.3%) (57%)
Renal dysfunction: 2 of 13 patients(15.4%) (5%)
Polyclonal hyper gammmaglobulinemia: 13 of 13 patients(100.0%) (32%)
Constitutional symptoms: 4 of 13 patients(30.7%)(68%)
Large spleen/liver: 10 of 13patients(76.9%)(19%)
Fluid accumulation: 1 of 13 patients(7.6%)(34%)
Eruptive cherry hemangiomatosis/violaceous papules: 3 of 13 patients(23.0%)
Lymphocytic interstitial pneumonia: 3 of 13 patients(23.0%)

Red percentage denotes the positive ratio from Siltuximab trial