Retroperitoneal Angiofollicular Lymph Node Hyperplasia (Castleman's Disease)

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1 Introduction (Epidemiology)

Angiofollicular lymph node hyperplasia, also known as giant lymph node hyperplasia or Castleman's disease (CD), is a chronic lymphoproliferative disorder. It was firstly reported and named by Castleman and Towne (1954), which is one of unexplained reactive lymphadenopathy characterized by painless enlargement of giant lymph nodes. Vascular follicular lymph node hyperplasia is rarely seen with an unclear incidence. It can occur at any age, more common in people aged 10–45 years. There is no significant difference in incidence between men and women. Medical history of the patients may range from several months to decades. Castleman's disease is mainly manifested as enlargement of lymph nodes in any part of the body, most commonly seen in mediastinal lymph nodes (70%) and spreading along the bronchial and tracheobronchial tree or hilar lymph node to the neck, shoulders, armpits, groin, and vulva (20%), while rarely arises from the retroperitoneum or mesentery (7%), demonstrating an extremely low incidence of retroperitoneal Castleman's disease.

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2 Etiology

The etiology and pathogenesis of Castleman's disease is unclear, which may be associated with abnormal immune function and chronic inflammation response. Some studies indicate a close relationship between Castleman's disease and infection of human herpesvirus-8 (HHV-8) (Bacon et al. 2004) and Epstein-Barr virus (EBV) (Al-Maghrabi et al. 2006). The presence of HHV-8 in lymph nodes, peripheral blood mononuclear cell, and bone marrow has been confirmed in patients of multicentric plasmacyte subtype. HHV-8 is detected in up to 100% of infected HIV patients with Castleman's disease.

Castleman's disease is often accompanied by increased production of abnormal B-cell growth factor, such as interleukin-6 (IL-6), which mainly stimulates differentiation of lymphocytes and plasmacyte. In the presence of IL-6 gene analogs in HHV-8 genome (Kawabata et al. 2007), lymph node B-cell proliferation is induced by HHV-8 to produce large amount of IL-6. IL-6 is proposed to be involved in the pathogenesis of Castleman's disease, because it promotes upregulation of vascular endothelial growth factor (VEGF) expression and induces vascularization of germinal center in lymph nodes. Thus, immune deficiency or dysregulation may be an important factor contributing to the onset of Castleman's disease (Beck et al. 1994). Furthermore, Schulz (2000) proposed that Kaposi's sarcoma and malignant lymphoma may be associated with immune

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deficiency of angiofollicular lymph node hyperplasia. In summary, the pathogenesis of Castleman's disease results from combined effects of multiple factors, and its etiology needs to be further investigated.

3 Pathogenesis and Pathobiology

The main pathological manifestation of Castleman's disease is tumorlike proliferation of lymphoid tissue and small blood vessels, which is specifically divided into three types:

a. Hyaline vascular type (HV type), accounting for about 80–90% of all types, manifested as hyperplasia of a large amount of follicular dendritic cells, with follicular hyperplasia of varying sizes, distributed throughout the parenchyma of lymph nodes, disappearance or fibrosis of lymph sinus, and smaller germinal center. Small neoarteries with swelling endothelial cells and hyaline degeneration penetrate through the center. The mantle zone that consists of small lymphocytes arranged in a concentric ring ("onion skin") pattern is thickened surrounding germinal centers. Moreover, proliferation of interfollicular capillaries and infiltration of lymphocytes, plasma cells, immunoblasts, and eosinophils are universally presented in hyaline vascular variant.
b. Plasma cell (PC) type, accounting for about 10% of all types, manifested by significant expansion of germinal centers in lymphoid follicles and thinning of surrounding mantle zone. There is massive interfollicular infiltration of mature plasma cells, small lymphocytes, and immunoblasts with Russell bodies, without obvious capillary proliferation.
c. Mixed type, which is rarely seen and characterized by the coexistence of the histopathologic features of both variants. It commonly occurs beyond the lymph nodes.

The positive expression of CD20, CD45RO, CD45RA, and κ- and λ-light chains has been demonstrated in the lymph nodes of Castleman's disease using immunohistochemical staining. Pathological specimen of retroperitoneal Castleman's disease presents as well-encapsulated lymph nodes in oval or circular shape with enlarged volume, varying sizes, and off-white uniform cross section (Fig. 22.1). Hyaline vascular type is the most common one in pathology.

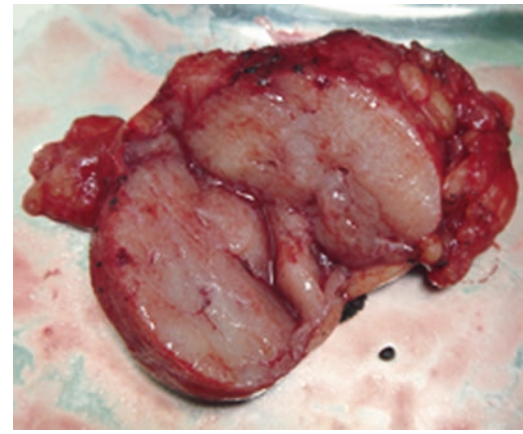

Fig. 22.1 Pathological specimen of retroperitoneal Castleman's disease

3.1 Clinical Manifestation

Castleman's disease can be divided into localized (LCD) and multicentric (MCD) types on the basis of lymph node involvement. LCD is mostly hyaline vascular type and commonly occurs in young people. It is manifested as locally enlarged painless lymph nodes without systemic symptoms in most patients. It frequently develops in the neck, followed by the mediastinum, armpit, and groin but rarely in the extranodal tissue. Compression symptom may be secondary to increased volume of the tumor or involvement of the surrounding tissue or organs.

MCD is plasma cell type dominant and commonly seen in the elderly. It is systemic diffuse lymphadenopathy, mainly manifested as multiple enlarged lymph nodes at different sites of the body, accompanied by systematic symptoms

such as chronic low-grade fever or high fever, fatigue, weight loss, accelerated erythrocyte sedimentation rate (ESR), liver and spleen enlargement, and anemia. It may be complicated by multiple system involvement, such as nephrotic syndrome, autoimmune cytopenias, Sjögren's syndrome, amyloidosis, bone marrow fibrosis, stomatitis, keratitis, paraneoplastic pemphigus (PNP), and POEMS syndrome (polyneuropathy, hepatosplenomegaly, endocrine disorders, elevated M protein levels, and skin pigmentation).

LCD is the major type of retroperitoneal Castleman's disease. It slowly grows along lymph chain in the retroperitoneum or at mesenteric roots and presents as solitary lymph node enlargement. Clinical manifestation includes waist and abdominal pain, loss of appetite, nausea, vomiting, abnormal defecation and urination, and other compression symptoms. In a few cases of retroperitoneal Castleman's disease complicated by PNP, oral mucosal erosion or pemphigoid is the first symptom. As symptoms of lung infection or bronchiolitis obliterans, such as chest tightness, suffocation, and cough, occur concurrently, these cases are easily misdiagnosed. Wang et al. (2005) reported that Castleman's disease is the most common tumor complicated with PNP in China.

3.2 Examination and Staging

Laboratory findings are often nonspecific for LCD patients. In contrast, increased ESR, thrombocytopenia, elevated γ-globulin and immune globulin, hypoalbuminemia, antinuclear antibodies, anti-double-stranded DNA antibodies, rheumatoid factor positive, and Coombs test positive are common in MCD patients.

Imaging findings of Castleman's disease are closely associated with histopathology of different types, corresponding to histopathological features of each type and varying greatly between different types. Color Doppler ultrasound, CT, MRI, and angiography are commonly applied, of which CT plays a major role in the diagnosis of Castleman's disease.

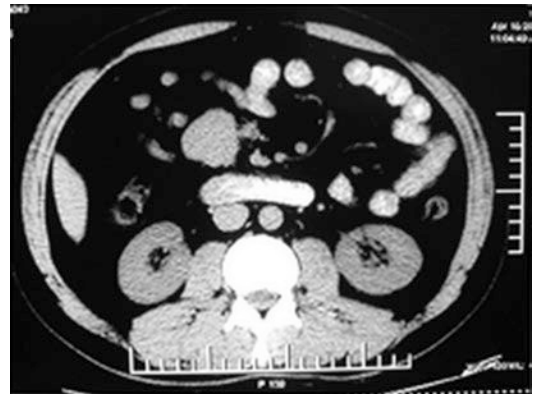

Fig. 22.2 Imaging of confined HV subtype Castleman's disease

Imaging findings of localized HV-type Castleman's disease (Figs. 22.2) include:

a. Lesions with well-defined margin, solitary soft tissue mass, round or oval in shape, uniform in density (a larger lesion with a center of relatively low density) .
b. After injection of contrast agent, the early- and mid-stage lesions exhibit enhancement to varying degrees. The early-stage significant enhancement and delayed clearance is manifested as cystic degeneration and necrosis. Dotted and striped vessels in the lesion are feeding arteries. The degree of enhancement may be affected by the number of proliferative capillaries in the lesion and the surrounding feeding arteries. In addition, injection method, dosage, and flow rate of contrast agent can also affect the degree of enhancement.
c. Dendritic calcification is the most representative feature in part of lesions and specific to HV type.

Color Doppler ultrasound mainly displays:

a. An intact capsule is clearly visible; nodular lesions and tumor margin present as clear contour, isolated hypoechoic, with normal internal structure and well-defined cortex and medulla; larger lesions are heterogeneous with hypoechoic foci.

b. Lesions with calcification exhibit high degree of echogenicity with acoustic shadowing.
c. Lesions with rich blood supply, surrounded by thickened veins and arteries.
d. Low impedance waveform is visible in diastolic phase, as one of the characteristics.

The imaging findings on PC-type angiofollicular lymph node hyperplasia are different from those on HV type and lack significant specificity. There are more enlarged lymph nodes in PC, which can be further divided into solitary and regional subtypes. Fusion of regional lymph nodes results in changes in appearance of mass-like lesions. Lesions exhibit ill-defined marginal profile and different densities in the region. Some lesions display infiltration of fat space and thickening of local fascia, with heterogeneous enhancement, accompanied by involvement of surrounding organs, such as pleural and peritoneal effusions and hepatosplenomegaly. Color Doppler ultrasound identifies multiple hypoechoic nodules with homogeneous echo pattern, normal and intact internal structure, well-defined cortex and medulla, and rare blood flow signals.

Imaging findings of mixed angiofollicular lymph node hyperplasia are more complex, as a mixture of both HV type and PC type. According to the clinical course, Castleman's disease can be classified into four categories: (a) stable, (b) chronic relapsing, (c) progressive, and (d) malignant. Stable and chronic relapsing are dominant types in LCD patients, while progressive is dominant type in MCD patients with a tendency toward lymphoma development. Four diagnostic criteria for MCD have been proposed by Frizzera (1988): (a) characteristically pathological changes of hyperplastic tissue, (b) significant lymphadenopathy and multiple peripheral lymph nodes, (c) obvious multi-system involvement, and (d) exclusion of possibly known causes.

As hyaline vascular type prevails in retroperitoneal Castleman's disease, CT has high diagnostic value. However, some retroperitoneal tumors, such as hemangioma, teratoma, and pheochromocytoma, may have similar CT findings, thus increasing the difficulty in preoperative diagnosis. Currently, the diagnosis of retroperitoneal Castleman's disease can only be established on the basis of a combination of clinical symptoms and pathological findings.

4 Treatment

As LCD is mostly benign, en bloc resection of lesions is preferred, with low recurrence rate. If there are contraindications to surgery or unresectable lesions, radiotherapy and/or glucocorticoid therapy can be effective. Chronowski et al. (2001) reported that 13/18 (72%) cases of Castleman's disease had complete or partial response to radiotherapy. For patients with retroperitoneal Castleman's disease accompanied by PNP, en bloc resection combined with postoperative adjuvant corticosteroids and anti-infection treatment would be preferred; however, most patients have poor prognosis due to complicated pulmonary damage.

MCD angiofollicular lymph node hyperplasia is potentially malignant, manifested by multiple lymph node involvement, polyserositis, and multi-organ involvement. Moreover, it is a systemic disease and should be treated with systemic regimen due to the lack of standard and specific therapy. Surgery combined with chemotherapy, radiotherapy, antiviral therapy, corticosteroids and immunomodulators, and comprehensive treatment may be considered for patients. En bloc resection is indicated for patients with small lesions; most patients with extensive disease have complete response to systemic chemotherapy with CVP (cyclophosphamide + vincristine + prednisone) or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) regimen but are predisposed to relapse. For younger patients with MCD, if conventional chemotherapy cannot effectively control the disease, autologous hematopoietic stem cell transplantation may be considered; alternatively, prednisone may be used as a single therapy. Interferon, ganciclovir, and other antiviral drugs are also effective in treatment of MCD. Targeted medicine such as anti-IL-6 antibody and anti-IL-6 receptor antibody (Nishimoto et al. 2005) (Akahane et al. 2006), anti-CD20 monoclonal antibody (rituximab) (Ide et al. 2006), and bortezomib (a protease inhibi-

tor) (Stary et al. 2008) has been developed based on the potential pathogenesis of the disease and proved effective in treating patients with MCD.

5 Efficacy and Prognostic Factors

Castleman's disease is a type of lymphoproliferative disorder that lies between benign and malignant diseases. Patients with LCD that is restricted to a particular area generally have a good prognosis after surgery; conversely, patients with MCD have relatively poor prognosis, especially those with plasma cell type. Those patients with viral infection history are particularly predisposed to severe infection and multiple organ failure due to immune dysfunction and bone marrow plasmacytosis. A small number of cases of MCD can develop into malignant lymphoma or Kaposi's sarcoma within several months to years, thus leading to a poor response to therapy.

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