# Castleman's disease

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**Abstract**
*Castleman's disease or angiofollicular lymphoid hyperplasia is a rare disease with two identified forms. The localized form, often pauci-symptomatic, is characterized by an isolated enlarged lymph node that regresses without sequelae after surgical excision. The multicentric form frequently presents general signs, polyadenopathy, organomegaly and sometimes a POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin) syndrome. The prognosis of the latter form is much less favorable and treatment often requires chemotherapy. The etiology of Castleman's disease remains unknown but recent reports have indicated a role of human herpesvirus 8 (HHV-8), especially in certain multicentric forms.*

**Keywords**
Castleman's disease, angiofollicular hyperplasia, angiofollicular lymphoid hyperplasia, human herpesvirus 8, POEMS syndrome.

## Name of the disease and synonyms

Castleman's disease is also called:

- angiofollicular lymph-node hyperplasia,
- angiofollicular lymphoid hyperplasia,
- giant lymph-node hyperplasia,
- lymphoid hamartoma,
- benign lymphoma or follicular lymphoreticuloma.

## Names of excluded diseases

Castleman's disease must be distinguished from reactive lymph-node hyperplasia, and malignant lymph-node hyperplasia, especially malignant lymphoma, even though the latter can be associated with it.

## Diagnostic criteria/Definition

Castleman's disease constitutes a clinicopathological entity, represented by lymph-node hypertrophy and histologically characterized by angiofollicular lymph-node hypertrophy.
Two forms are known: a localized form, in which the disease is restricted to one lymph node, and a multicentric or systemic form, in which several sites are involved.

**Comments on the differential diagnosis**

Clinically, Castleman's disease often presents with adenopathies and general signs suggestive of a lymphomatous pathology. In contrast, histological features of Castleman's disease are not those of a lymphoma. Indeed, Castleman's disease usually entails a polyclonal lymphocytic proliferation. Nevertheless, some cases can be associated with a monoclonal lymphomatous proliferation.

The histological aspect of angiofollicular lymphoid hyperplasia can also be observed in various dysimmune disorders, like rheumatoid arthritis or Sjögren's syndrome. It can also occur in association with congenital immune deficiencies, human immunodeficiency virus (HIV) infection, Kaposi's sarcoma, reactions to cancers and hemopathies, vaccinations, skin disorders or membranous glomerulonephritis.

A complete clinical, histological and immunohistochemical analysis is essential to obtain a definitive and differential diagnosis [8].

**Incidence**

Castleman's disease is a rare pathology whose precise incidence is not known.

The localized form, described for the first time by Castleman *et al*. [2] in 1956, is the most common. More than 400 cases have already been reported in the international literature. The largest series of 81 patients was published by Keller *et al*. [6] in 1972. The multicentric or systemic form, described for the first time by Gaba *et al*. [4] in 1978, is less common. Since then, numerous isolated cases have been reported. In 1985, Weisenburger *et al*. [13] described their series of 16 patients and, in 1996, Oksenhendler *et al*. [7] reported their study on 20 patients.

To improve our understanding of the evolutionary profile of Castleman's disease, we conducted a prospective study under the aegis of the Société Nationale Française de Médecine Interne [10]. Between 1995 and 2001, we identified 85 cases of Castleman's disease seen by 41 French internal medicine specialists in 33 hospital centers. Among the 85 cases, 49 (58%) had the multicentric form. This preponderance does not indicate a higher incidence of this form but merely reflects a recruitment bias, as internists more frequently treat the systemic form. As reported in the literature, we never observed the transformation of a localized form into a multicentric one.

**Clinical description**

Castleman's disease can occur at any age, even during childhood, with a peak frequency during adulthood. In our series, the mean age at the time of diagnosis was 43 years with a range of 10-87 years. The time to diagnosis is often long (mean: 18 months), attributable to the clinical polymorphism and the poor awareness of the disease.

Localized forms [5, 10] are asymptomatic in 51% of the patients and are often discovered fortuitously at the time of a routine physical examination, chest X-ray or abdominal ultrasonography. Sometimes, they can present as thoracic or abdominal pain, when the lesion is large and causes local compression. The size of the lesion varies widely, with a mean diameter of 6 cm (range: 1-12 cm). It is, by definition, localized in one site. The sites preferentially involved are, in decreasing order of frequency, the abdomen, peripheral lymph-node zones and the mediastinum. However, the most diverse sites can be affected. General signs, which are rare but can be observed in 31% of the patients, include: asthenia (20%), fever (20%) and weight loss (11%). The histological diagnosis requires lymph-node excision for peripheral adenopathy or lymph node biopsy by mediastinoscopy, thoracotomy or laparotomy for a deep central localization.

Multicentric forms, on the other hand, are always symptomatic [1, 5, 10]. The symptoms are, for the most part, a consequence of the elevated production of interleukin-6 (IL-6). General signs are quasi-constant, characterized by asthenia (65%), weight loss (67%) and fever (69%). Peripheral polyadenopathy is very common (84%) with a mean of 4 sites involved and is often associated with hepatomegaly and/or splenomegaly (74%). A POEMS (peripheral polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy (M-protein), and skin signs) syndrome [9] is observed in 24% of the patients. Finally, some multicentric forms of Castleman's disease are associated with Kaposi's sarcoma. The histological diagnosis is generally made upon examination of an excised peripheral lymph node.

**Management/Treatments**

The best treatment for localized forms of Castleman's disease is complete surgical excision. This treatment allows full recovery without relapse in almost all cases. Further follow-up does not seem necessary.

No therapeutic consensus exists at present for the multicentric forms of Castleman's disease. Indeed, the rarity and heterogeneity of the disease have prevented the undertaking of randomized therapeutic trials in this context. In practice, diverse treatments are used, often in combination, *e.g.*, surgery (35%), corticotherapy (53%) and chemotherapy (63%).

Cyclophosphamide (750 mg/m$^2$) is given in monthly pulses, although Castleman's disease is not recognized as an authorized indication for this drug. Vinblastine (6 mg/m$^2$/week) is administered intravenously, as authorized, in the context of associated Kaposi's sarcoma. However, the treatment of choice is monthly polychemotherapy. In this context, the most effective combinations seem to be regimens like CHOP (cyclophosphamide, vincristine, doxorubicin, prednisone) or AVBD (etoposide, ifosfamide and cisplatin alternating with doxorubicin, vinblastine, bleomycin and dacarbazine). Overall, the diverse therapies used induce a partial remission in 65% of the patients and a cure in 21%. But the prognosis of the multicentric forms remains poor, with a 5-year mortality rate of 18% in our study. However, the more systematic use of polychemotherapy should, in the future, lead to a significant lowering of the mortality rate. Other therapies, like interferon-alpha [15], retinoic acid [16] or anti-IL-6 antibodies [17] have been tried and gave punctually promising results.

**Etiology**

The etiology of Castleman's disease is still poorly understood. No genetic or toxic factor had been identified. The hypothesis of a viral infection has been raised. Indeed, the authors of several studies [1, 12] have suggested the role of human herpesvirus 8 (HHV-8), already implicated in Kaposi's sarcoma and which could be sexually transmitted. In multicentric forms of Castleman's disease, HHV-8 sequences have been detected in 60% [11] to 100% [12] of the patients infected with HIV and in 20% [11] to 41% [12] of those who were not. The percentages vary according to whether the authors searched for the virus in peripheral blood [11] or lymph node tissue [12]. In a small series of eight patients, two HIV-seronegative patients with the localized form of Castleman's disease were also found to be HHV-8 positive [11]. These findings suggest two possibilities concerning the genesis of Castleman's disease:
1) the opportunistic presence of HHV-8, favored by immune perturbations;
2) the direct pathogenic role of HHV-8, in association with a dysregulation of cytokines.
Recent studies seem to support the latter hypothesis because it was demonstrated that HHV-8 was able to produce an IL-6 homologue, vIL-6 [14].

**Biological diagnostic methods**

No specific biological anomalies of Castleman's disease have been identified. However, one can observe, especially in multicentric forms, an elevated erythrocyte sedimentation rate (77%), anemia (61%), thrombopenia (22%) and elevated polyclonal gammaglobulins (73% in our series). IL-6, synthesized in large quantities in the germinal centers of the involved lymph nodes, is responsible for the plasmacytosis and hypergammaglobulinemia often seen.
HIV serology should be systematically undertaken, with the patient's consent, but Castleman's disease rarely reveals this infection. Rather, it usually occurs in patients already being followed for HIV infection and afflicted with Kaposi's sarcoma. HHV-8 serology and search for HHV-8 DNA in peripheral blood by polymerase chain reaction (PCR) can be performed. In a cohort of 28 patients with Castleman's disease [11], including 71% of multicentric forms and 5 patients infected with HIV, we detected HHV-8 infection in 28.6%.
The diagnosis of Castleman's disease is based on histological examination of the lesion with immunohistochemical labeling. Castleman's disease is defined as angiofollicular lymphoid hyperplasia, which can present in different ways. The hyaline-vascular form, the most common, is often observed in the localized forms. The plasmacytic form, the rarest, is mostly seen in multicentric forms. Finally, an intermediary or mixed form has also been described. The lymphocyte proliferation is usually polyclonal. However, monoclonal proliferation and rearrangement of immunoglobulin and/or T-cell receptor genes have been reported in certain patients with multicentric Castleman's disease [3].

**Unresolved questions and comments**

Because of the rarity of Castleman's disease and its polymorphic character, few prospective cohort studies have been conducted. Thus, many questions remain unanswered, that is to say the etiology of the disease and the role of HHV-8, the relationships between Castleman's disease and lymphomatous pathologies, or the optimal treatment of the multicentric forms. However, analysis of the data available in the literature enables a clear-cut distinction to be drawn between the localized forms, often pauci-symptomatic and with excellent prognoses after lesion excision, and multicentric forms, with systemic involvement and often difficult to treat. Indeed, the angiofollicular lymphoid hyperplasia that defines Castleman's disease constitutes a non-specific histological lesion. It can thus be seen in diverse etiological settings. In light of the different clinical, virological and evolutionary profiles, localized and multicentric forms of Castleman's disease might be two distinct

entities that merely share a common histological aspect.

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