Castleman's Disease
**DIAGNOSIS**

**ESSENTIAL:**
- Hematopathology review of all slides with at least one paraffin block representative of the lymphoproliferative disorder. Rebiopsy if consult material is nondiagnostic.
- An FNA or core needle biopsy alone is not generally suitable for initial diagnosis of Castleman’s disease. Excisional or incisional biopsy are preferable.
- Adequate immunophenotyping to establish diagnosis.
  - IHC panel: kappa/lambda, CD20, CD3, CD5, CD138, HHV-8 LANA-1
  - EBER-ISH

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Molecular analysis (PCR) to detect immunoglobulin and TCR gene rearrangements
- IHC: Ki-67 index; Ig heavy chains, CD10, BCL2, BCL6, cyclin D1, CD21, or CD23, CD38, MUM1, PAX-5
- Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10

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**WORKUP**

**ESSENTIAL:**
- Physical exam: attention to node-bearing areas, including Waldeyer’s ring, and to size of liver and spleen
- Performance status
- Assess for criteria for active disease
- CBC, differential, platelets
- Comprehensive metabolic panel
- LDH, CRP, ESR
- Beta-2-microglobulin, serum light chains, quantitative immunoglobulins
- HIV ELISA, HHV-8 DNA titer by PCR, Hepatitis B testing, EBV DNA titer by PCR
- sIL-6, sIL10, VEGF, uric acid, ferritin
- PET-CT scan (preferred) or chest/abdominal/pelvic CT with contrast of diagnostic quality
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)
- Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NKT-Cell Neoplasms (NHODG-A).

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**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
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Unicentric CD

**PRIMARY TREATMENT**

- **Surgically resectable**
  - Complete resection → Observation → Recurrence
  - Partial resection
    - Asymptomatic → Observation → Recurrence
    - Symptomatic → See Surgically unresectable below

- **Surgically unresectable**
  - Observation
  - Recurrence
  - Recurrence
    - Surgically resectable
      - Complete resection → Observation
    - Partial resection
      - Asymptomatic → Observation → Recurrence
      - Symptomatic → See Surgically unresectable below

**SECOND-LINE THERAPY**

- **Symptomatic**
  - Consider local therapy with surgery or RT or embolization if amenable or Systemic therapy with Rituximab ± prednisone ± cyclophosphamide or Siltuximab/tocilizumab

- **Recurrence**
  - Surgically resectable
    - Complete resection → Observation
  - Partial resection
    - Asymptomatic → Observation → Recurrence
    - Symptomatic → See Surgically unresectable below

- **Surgically unresectable**
  - Observation
  - Recurrence
  - Recurrence
    - Surgically resectable
      - Complete resection → Observation
    - Partial resection
      - Asymptomatic → Observation → Recurrence
      - Symptomatic → See Surgically unresectable below

- **Relapsed/refractory disease**
  - Consider local therapy with surgery or RT or embolization if amenable or Systemic therapy with Rituximab ± prednisone ± cyclophosphamide or Siltuximab/tocilizumab applies to HIV(-)HHV-8(-) patients

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[^1]: Patients with non-bulky disease may be observed after RT.
[^k]: Encourage biopsy to rule out transformation to DLBCL or concomitant development of other malignancies or opportunistic infections.
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**Discussion**

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**PRIMARY TREATMENT**

- **HIV-1(-) or HHV-8 (-)**
  - **MCD** (Criteria for active disease present but no organ failure)
    - **Siltuximab** or **Rituximab ± prednisone**
      - **Response**
      - **No response**

- **HIV-1(+) or HHV-8(+)**
  - **Rituximab** (preferred) ± **liposomal doxorubicin** ± **prednisone** or **Zidovudine + ganciclovir/valganciclovir**
    - **Response** → **Observation** → **Relapsed disease**
    - **No response**

- **MCD (Fulminant HHV(+) ± organ failure)**
  - **Combination therapy** ± **rituximab**
    - **CHOP**
    - **CVAD**
    - **CVP**
    - **Liposomal doxorubicin**
      - **Response** → **Observation** → **Relapsed disease**
      - **No response**

**RELAPSED DISEASE**

- **If siltuximab, continue until progression**
  - **If rituximab, observe and retreat at progression**

- **Relapsed disease**
  - **Treat with alternate primary treatment before moving onto treatment for refractory disease**

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**CD-3**

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**See Criteria for Active Disease (CD-A).**

**Encourage biopsy to rule out transformation to DLBCL or concomitant development of other malignancies or opportunistic infections.**

**All HIV+ patients should be on combination antiretroviral therapy (cART).**

**Concurrent Kaposi sarcoma therapy is required when rituximab or prednisone is given for primary treatment.**

**Combination of rituximab and liposomal doxorubicin is strongly recommended for patients with Kaposi sarcoma to avoid flare-up.**

**Rituximab ± prednisone may repeat without limit if progression ≥6 months of completion of rituximab.**
Refractory or progressive disease

**Single-agent therapy**
- Etoposide [oral or IV]
- Vinblastine
- Liposomal doxorubicin

**Combination therapy**
- CHOP
- CVAD
- CVP
- Liposomal doxorubicin
  
- **Observation or Maintenance valganciclovir if HHV-8(+)**

- **Response**

- **No response**
  - Treat with alternate combination therapy ± rituximab not previously given

- **Relapsed/refractory disease**

**Consider alternative single-agent or combination therapy**
- Bortezomib ± rituximab
- Tocilizumab
- Anakinra
- Thalidomide ± rituximab
- Lenalidomide
- High-dose zidovudine + valganciclovir
- Autologous hematopoietic stem cell transplant

### Relapsed/Refractory Disease

- **Autologous hematopoietic stem cell transplant**

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*CD-4*
CRITERIA FOR ACTIVE DISEASE

- Fever
- Increased serum C-reactive protein level >20 mg/L in the absence of any other etiology
- At least three of the following other MCD-related symptoms
  - Peripheral lymphadenopathy
  - Enlarged spleen
  - Edema
  - Pleural effusion
  - Ascitis
  - Cough
  - Nasal obstruction
  - Xerostomia
  - Rash
  - Central neurologic symptoms
  - Jaundice
  - Autoimmune hemolytic anemia