

Original Article

Diagnosis and Treatment of HHV-8-Associated Multicentric Castleman Disease: a Clinical Case From the National Scientific Oncology Center

Shalkarbekova Aidana Meirkhanovna¹, Karabekov Azat Baglanovich¹, Kemaikin Vadim Matveevich¹, Yusupova Meiramgul Muratovna¹

¹National Research Oncology Center, Astana, Republic of Kazakhstan

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Corresponding author's email:
shalkarbekova.aid@gmail.com



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Abstract:

Castleman disease (CD) is a rare lymphoproliferative disorder with heterogeneous clinical manifestations. This article presents a clinical case of HHV-8-associated multicentric Castleman disease (MCD) in an HIV-negative patient treated at the National Scientific Oncology Center. Diagnostic methods included histological and immunohistochemical evaluation, laboratory investigations, and imaging studies. The choice of therapy is discussed. The patient demonstrated resistance to rituximab monotherapy but achieved a favorable response to R-CHOP chemotherapy. This case highlights the importance of early assessment of HHV-8 status and an individualized approach to treatment selection.

Keywords: Castleman's Disease; Classification; Diagnosis; Treatment

Introduction

Castleman disease was first described by B. Castleman in 1954. Its morphological basis includes hyperplasia of lymphoid follicles with involution and hyalinization of germinal centers, along with prominent capillary proliferation in interfollicular zones featuring hyalinized vessel walls. Some vessels penetrate the hyperplastic follicles, producing the characteristic “lollipop” appearance.[2]

Variants of Castleman Disease

1. **Unicentric CD (UCD)** — affects a single lymph node or a single group. Symptoms may be absent or include lymphadenopathy, fatigue, fever, night sweats, and weight loss. Treatment typically involves surgical excision.
2. **Multicentric CD (MCD)** — involves multiple lymph node regions throughout the body and is associated with systemic symptoms such as fever, night sweats, weight loss, fatigue, anemia, and splenomegaly.

MCD may be associated with human herpesvirus-8 (HHV-8), particularly in immunocompromised and HIV-positive patients.[3]

Histological Types

- **Hyaline-vascular type** — characterized by hyalinized germinal centers and vascular proliferation.
- **Plasma cell type** — prominent plasma cell infiltration, more common in MCD.
- **Mixed type.**

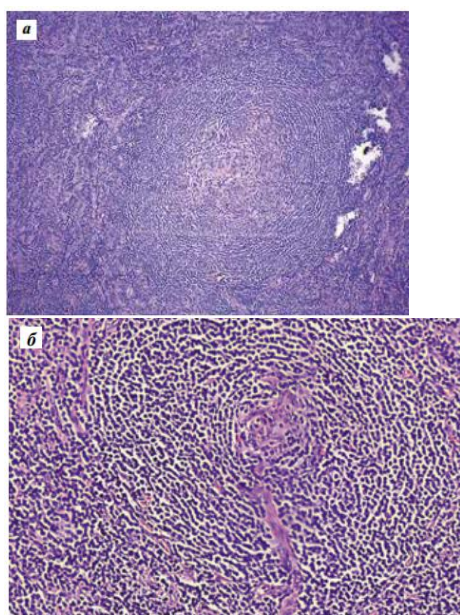


Fig. 1. Lymph node, hyaline-vascular variant:
a – regressed follicle with concentric mantle zones (“onion skin” appearance);

b – regressed follicle with hyalinized vessel penetrating the germinal center (“lollipop” sign). H&E ×100. [11]

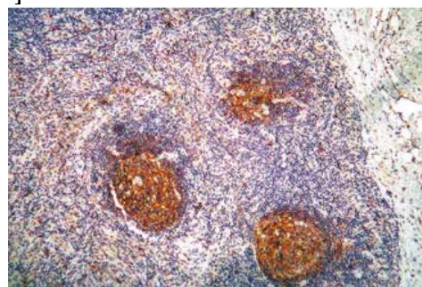


Fig. 2. Lymph node, plasma-cell variant. CD20 expression in hyperplastic follicles. IHC ×100. [11]

Clinical Features

- CD may mimic lymphoproliferative disorders such as lymphoma.
- Diagnosis relies on excisional biopsy, revealing characteristic features (follicular hyperplasia, angiogenesis, fibrosis).

According to NCCN guidelines, diagnosis requires differentiation of CD subtypes and exclusion of lymphoma and autoimmune diseases. Key steps include clinical assessment, laboratory testing, and lymph node biopsy.[7]

Essential Diagnostic Components

- Immunoglobulins: hypergammaglobulinemia (especially in MCD).
- IL-6: frequently elevated in CD, particularly in MCD.
- Viral testing:
- HHV-8 (strongly associated with MCD),
- HIV (HIV-positive individuals have higher risk).
- CT scan: evaluates lymphadenopathy and organ involvement.
- PET-CT: assesses active nodal disease and excludes malignancy.
- Ultrasound: evaluation of spleen, liver, large lymph nodes.
- Excisional lymph node biopsy — the diagnostic gold standard.

Histological Features

- UCD: follicular hyperplasia, vascular proliferation, hyalinization.
- MCD: more prominent vascularity, plasma cell infiltration.

Castleman disease is rare, with an estimated incidence of 21–25 cases per million per year.[5] It can occur at any age but is more common between ages 30–60. MCD is more prevalent in older adults; UCD can occur at any age. Some studies show a higher

incidence in males, particularly HHV-8-associated MCD.[5]

Epidemiology

- UCD: 70–80% of all CD cases
- MCD: 20–30% of cases, characterized by more severe systemic features.[6]

Etiology and Pathogenesis

Key factors include:

- Immune dysregulation: activation of T-cells and cytokine overproduction (notably IL-6).

- Viral infection: HHV-8 plays a major role in many MCD cases, particularly in immunocompromised hosts.[3]
- Genetic predisposition: reported in some cases.

Pathogenesis involves lymph node hyperplasia with abnormal follicular growth driven by IL-6, resulting in systemic manifestations such as fever and night sweats.[4]

Clinical Case

Patient O., 52 years old

Clinical Presentation and History

In April 2022, the patient developed paroxysmal dry cough, often accompanied by vomiting, marked weakness, dizziness, night sweats, and intensely pruritic skin eruptions. Periodic exacerbations lasted ~10 days with remissions of ~20 days. Pulmonary and infectious evaluations ruled out helminthiasis. Cetirizine partially relieved pruritus.

In 2023, the patient noted symmetrical enlargement of peripheral lymph nodes (cervical, axillary, inguinal), prompting further diagnostic workup.

Diagnostics

- Ultrasound and CT (2023): generalized lymphadenopathy; suspected lymphoproliferative disease.
- Fine needle aspiration / initial histology: suspicion of small B-cell lymphoma.
- Bone marrow exam: no evidence of lymphoma.
- Myelogram (Jan 2024): blasts 2.2%; hematopoiesis preserved; normal maturation.
- Bone marrow histology: reticulin fibrosis 0, no osteosclerosis, CD34+ ~3%,

predominance of CD3/CD5+ T-cells, fewer CD20+ B-cells, no lymphoma.

Cervical lymph node excisional biopsy (April 2023)

- **Histology:** features typical of hyaline-vascular CD — hyalinized germinal centers, penetrating vessels, “onion-skin” mantle zones, marked vascular proliferation, increased plasma cells, compressed sinuses.
- **IHC:** normal expression of CD20, CD3, CD5, CD7; CD23+ follicular dendritic cells; weak CD10; Bcl-2 negative in germinal centers; Cyclin D1 negative; HHV-8—positive cells identified.

Conclusion: Castleman disease, hyaline-vascular type, HHV-8-associated, consistent with multicentric clinical presentation.

Clinical data at admission (April 2024)

Moderate anemia (Hb 108 g/L), elevated CRP (29.6 mg/L), generalized lymphadenopathy on CT.

HHV-8 PCR — negative (does not exclude local tissue infection).

HIV ELISA — negative.

Serum and urine immunofixation — no pathological findings.

Treatment

1. Rituximab monotherapy

After four infusions, disease progression was documented based on:

- persistent B-symptoms,
- PET-CT (15 July 2024): metabolically active cervical, supraclavicular, thoracic, axillary, retroperitoneal, pelvic, and inguinal lymph nodes; metabolic activity in Waldeyer’s ring; enlarged hypermetabolic spleen; inflammatory activity in prostate; left-sided sinusitis.

According to NCCN Guidelines Version 1.2024 (Castleman Disease), treatment with siltuximab is

recommended; however, due to unavailability, a decision was made to initiate R-CHOP chemotherapy.

2. Transition to R-CHOP (siltuximab unavailable)

- Cycle 1 (July 2024): improvement of B-symptoms.
- Cycle 2 (August 2024): well tolerated.

Response Evaluation

PET-CT (04 September 2024):

- SUVmax reduced from 3–9 to 0.7–2.6
- Reduction in lymph node size
- Normalization of spleen metabolism
- No abnormal uptake in internal organs

Conclusion: Complete metabolic response (Lugano).

Discussion

This case highlights the importance of comprehensive diagnostic evaluation, including viral studies, histopathology, and advanced imaging.

Features of HHV-8-associated MCD

- robust IL-6-mediated inflammation,
- potential resistance to rituximab,
- need for timely treatment escalation.

Current Therapeutic Approaches

- Rituximab — first-line therapy, but less effective in HHV-8-positive MCD.

- R-CHOP — effective in resistant or aggressive disease.
- Anti-IL-6 therapy (siltuximab) — mainly used in idiopathic MCD.
- Antiviral therapy — investigational.

Limitations of This Case

- Follow-up <24 months.
- Inability to administer anti-IL-6 therapy due to resource limitations.

Conclusion

This clinical case demonstrates key aspects of diagnosing and managing HHV-8-associated multicentric Castleman disease. Rituximab resistance and marked systemic inflammation required escalation to R-CHOP therapy, which resulted in a pronounced

clinical and metabolic response. Comprehensive diagnosis, including HHV-8 tissue testing, is critical for appropriate treatment selection. Further research is needed to optimize management strategies for virus-associated forms of MCD.

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