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HHV8-POSITIVE MULTICENTRIC CASTLEMAN'S DISEASE AND THROMBOTIC THROMBOCYTOPENIC PURPURA AMONG HIV-POSITIVE PATIENTS

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ABSTRACT

Castleman's disease (CD) and thrombotic thrombocytopenic purpura (TTP) are rare diseases that can affect the general population, especially those with HIV. Owing to their rarity, the association between CD and TTP remains insufficiently understood. In this study, we present a case of a 53-year-old patient with controlled HIV infection who presented with fever, lymphadenopathy, severe anaemia, and thrombocytopenia. After a series of tests, the diagnosis was concurrent human herpesvirus 8 (HHV8)-related multicentric CD (MCD) and TTP. Only four male patients were previously reported having this association, with HHV8 present in four and HIV in three patients, suggesting that coinfection with HHV8 and HIV is a pivotal factor in MCD with TTP occurrence.

KEYWORDS

Castleman's disease, thrombotic thrombocytopenic purpura, HHV8, HIV, autoimmune hypoglycaemia

LEARNING POINTS

- Castleman's disease (CD) and thrombotic thrombocytopenic purpura (TTP) are rare diseases, and their association remains extremely uncommon.
- We report a case of multicentric CD (MCD) with TTP in a 53-year-old male patient with HIV.
- Only five patients, including ours, have been reported as having both MCD and TTP, with all five having HHV8 and four having HIV. Thus, coinfection with HHV8 and HIV may be a potential pivotal factor in the occurrence of MCD with TTP.

INTRODUCTION

Castleman's disease (CD) and thrombotic thrombocytopenic purpura (TTP) are rare diseases that can affect the general population as well as patients with HIV. Currently, the association between CD and TTP remains insufficiently understood. In 2017, epidemiological data on CD were updated with new diagnostic criteria[1-3]. CD comprises a heterogeneous group of lymphoproliferative disorders with

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distinct aetiologies, pathologies, and clinical presentations. The involved lymph nodes exhibit various degrees of lymphoid proliferation featuring hyperplastic or atrophic germinal centres along with hyperplastic or involuted follicular dendritic cell meshwork, vascular proliferation and interfollicular plasmacytosis. The primary subtypes include unicentric CD (UCD), idiopathic multicentric CD (iMCD) and human herpesvirus 8 (HHV8) or Kaposi's sarcoma-associated herpesvirus (KSHV) associated multicentric CD (HHV8 MCD)[1-3]. HHV8 is a gamma herpesvirus with a seroprevalence of 5% in western countries and 50% in east and central Africa[4]. It is mainly transmitted sexually or vertically from mother to child. HHV8 can lead to Kaposi's sarcoma, mainly among immunocompromised populations, particularly in patients with HIV[4,5]. In addition, HHV8 can trigger Kaposi sarcoma inflammatory cytokine syndrome, bone marrow failure and hepatitis. Therefore, MCD is a systemic disease that affects multiple lymph nodes, classified according to HHV-8 presence or absence. It is a challenging diagnosis, requiring the use of criteria described in 2017 by the international evidence-based consensus diagnostic criteria for HHV-8–negative/idiopathic multicentric Castleman disease[5] and exclusion of other infectious, tumoral or inflammatory pathologies. MCD diagnosis can be reached using two major criteria (multicentric lymph nodes, histology compatible with MCD) and at least 2 of the 11 minor criteria, including at least one biological abnormality (fever, weight loss, oedema, pleural effusion, hydrops, lymphocytic interstitial lung disease, biological inflammatory syndrome, anaemia, thrombocytopenia and polyclonal hypergammaglobulinemia). Its common histological features include hyperplastic lymphoid follicles with atrophying lymphoid germinal centres, hypervascularisation and plasmacytosis. HHV8 infection is more common in males than in females (three males for one female), especially those who are immunocompromised, and 50% of them have concurrent HIV/AIDS[1,2]. HHV8 is also known to worsen MCD prognosis.

Acquired TTP is an autoimmune disease characterised by the accumulation of platelet microthrombi occluding the arterial capillaries of vital organs secondary to ADAMTS13 inhibition by anti-ADAMTS13 antibody. Patients who exhibit thrombotic microangiopathy (TMA) with haemolytic anaemia and thrombocytopenia associated with acute renal failure reportedly experience lower ADAMTS13 activity (<10% – <5%), which is sometimes associated with a positive dosage of anti-ADAMTS13 antibodies[6]. Although TTP appears to be idiopathic in some cases, it has been linked to medication, pregnancy, HIV, or autoimmune disease. Therefore, HIV infection is a significant risk factor for both TTP and MCD, particularly among individuals with severe immunosuppression caused by this virus.

Here, we report a case of a 53-year-old male African patient with HIV hospitalised for febrile bicytopenia, leading to the discovery of concomitant MCD and TTP. Only four patients were previously reported having this association in the literature[6], with HHV8 present in four and HIV in three patients, suggesting that coinfection with HHV8 and HIV is a pivotal factor in MCD with TTP occurrence.

CASE DESCRIPTION

A 53-year-old Malian patient was hospitalised with febrile diarrhoea associated with a dry cough and dyspnoea. The symptoms occurred four months after travelling in West Africa. His medical history included the following: HIV infection in 2014 treated with dolutegravir/lamivudine, thereby undetectable for 8 years; cured hepatitis A and B infection (HBs negative, total anti-HBc positive, anti-HBs positive); syphilis and malaria. Upon admission, physical examination revealed left axillary lymphadenopathy. Laboratory test results were as follows: elevated creatinine level (147 µmol/l; glomerular filtration rate 46 ml/min/1.73 m^2), thrombocytopenia (54 G/l), non-haemolytic anaemia (haemoglobin, 10.4 g/dl), hyperleukocytosis (12.84 G/l) with neutrophilia (9.24 G/l), C-reactive protein (CRP) (134 mg/l) and absent haemolysis signs. Microbiological investigations for malaria, SARS-CoV-2, Cytomegalovirus, Pneumocystis, Aspergillus and histoplasmosis infections were all negative. In addition, the HIV viral load was undetectable, the CD4+ T-cell count was 505/mm^3 and the viral load for Epstein–Barr virus was 893 copies/ml.

A thoracic computed tomography (CT) scan and positron emission tomography (PET) revealed bilateral posterobasal subpleural condensation with interstitial images *(Fig.*

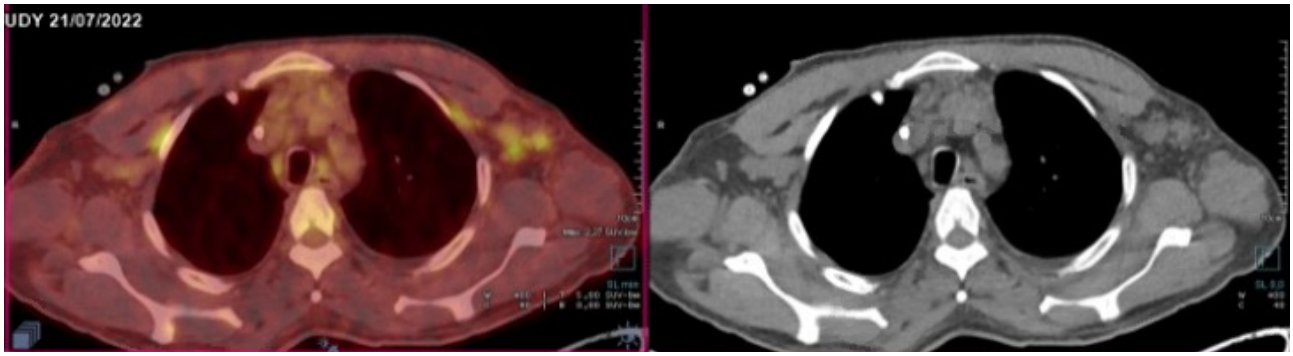

Figure 1. Mediastinal sections of whole-body positron emission tomography scans showing innumerable moderately-to-intensely hypermetabolic bilateral cervical, retro pectoral, axillary and juxta-centimetric external iliac, numerous bilateral inguinal lymph nodes and hypermetabolic splenomegaly.

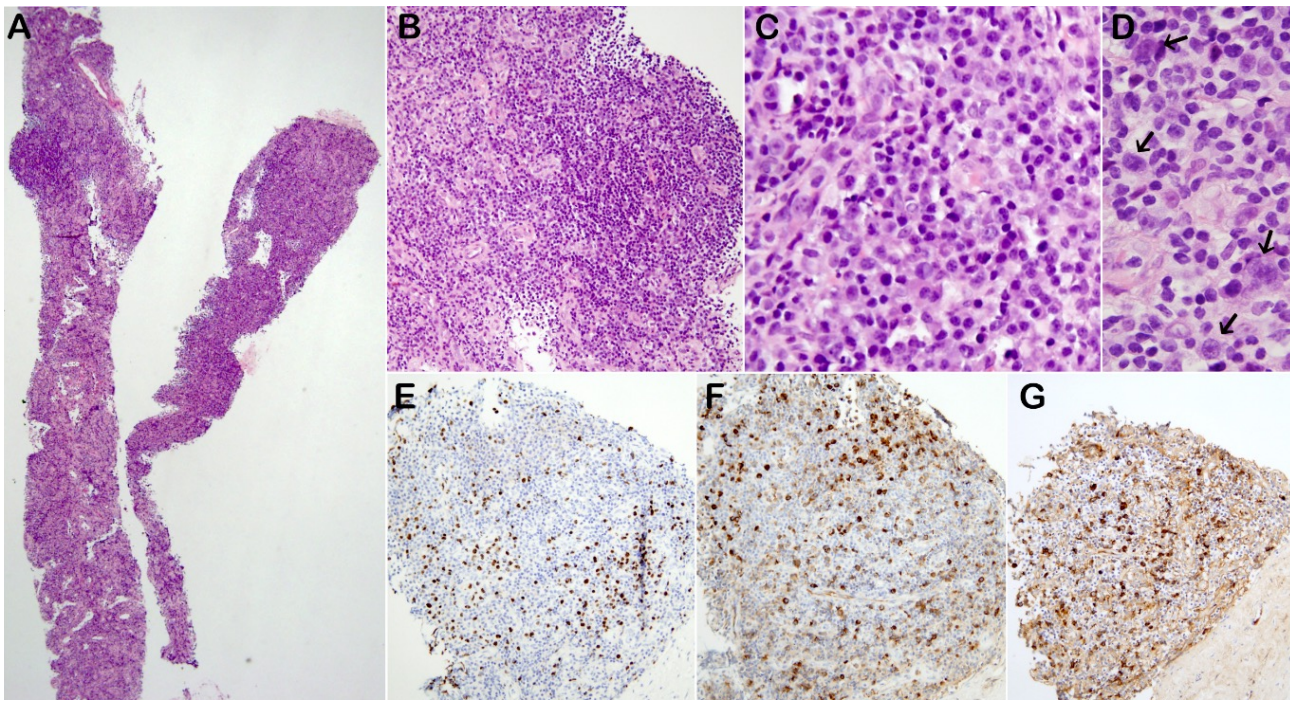

Figure 2. HHV8-associated MCD diagnosed in the axillary lymph node. A) Core needle biopsies show altered lymph node architecture with expansion of the paracortical and medullary areas, and B) atrophic lymphoid follicles. C) Marked medullary plasmacytosis displaying mature plasma cells. D) Scattered large plasmablasts (arrows) are observed in the residual mantle zone and focally clustered in the subcapsular area. E) Phenotypically, the plasmablasts show HHV8 positivity and exhibit monotypic immunoglobulin (Ig) lambda light chain and F) IgM heavy chain, G) restriction.

1), multiple moderately-to-intensely hypermetabolic lymphadenopathies (mediastinal, cervical, axillary, external iliac and inguinal) and hypermetabolic splenomegaly.

Subsequently, oxygen therapy, intravenous ceftriaxone (2 g/day), and spiramycin (3 MIU three times per day) were administered. However, after a few days the patient's condition did not improve, with obnubilation occurrence, worsened renal function (creatinine 233 µmol/l), anaemia (haemoglobin 6.9 g/dl) and thrombocytopenia (21 G/l). The haptoglobin level decreased to 0.10 g/l, with 1.25% schizocytes and a positive (++) IgG Coombs test result with the detection of anti-ADAMTS13 IgG, the *ADAMTS13* activity decreased to 5%, confirming the diagnosis of TTP.

Moreover, an axillary lymph node biopsy showed atrophic

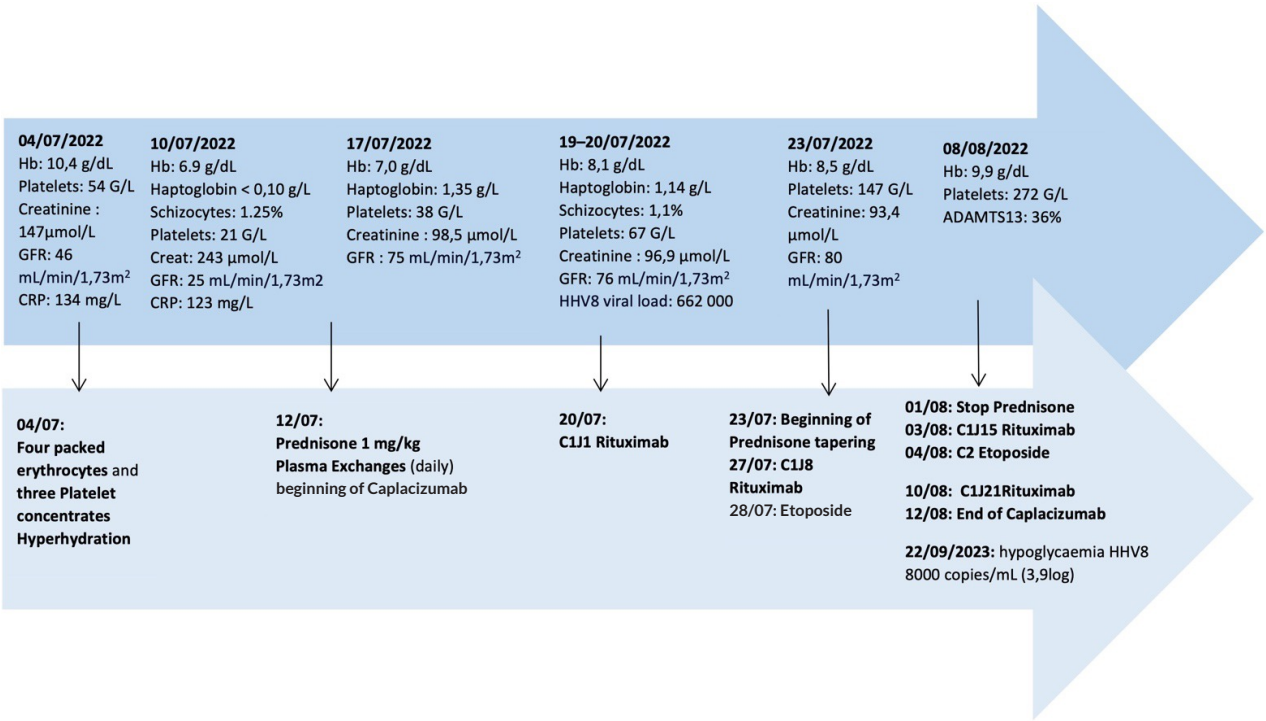

Figure 3. Timeline of blood count, renal function, anti-ADAMTS13 activity, HHV8 viral load and treatment from diagnosis to hospital discharge. Abbreviation: Hb, haemoglobin; CRP, C-reactive protein; GFR, glomerular filtration rate.

lymphoid follicles, vascular proliferation, interfollicular plasma cell hyperplasia and HHV8-positive monotypic lambda plasma blasts, consistent with HHV8-positive MCD (*Fig. 2*). The HVV8 viral load in the blood also significantly increased (662,000 copies/ml [5.8 log]).

Therefore, the patient underwent plasma exchange and treatment with caplacizumab, prednisone (1 mg/kg) and four doses of rituximab 375 mg/m^2 together with etoposide (two doses). Consequently, confusion and fever were resolved, and the laboratory test results improved (haemoglobin 9.9 g/dl, platelets 272 G/l), including renal function with *ADAMTS13* activity. Hence, prednisone and caplacizumab were discontinued. Meanwhile, the anti-HIV therapy was modified for tenofovir alafenamide/emtricitabine/bictegravir because of the patient's past history of hepatitis B virus. Patient status and treatments during hospitalisation are summarised on a timeline shown in *Figure 3*.

The patient remained asymptomatic for one year with an almost complete morpho-metabolic response. In October 2022, PET revealed the persistence of a hypermetabolic cervical lymph node without enlargement or effect on the patient's bloodline. However, the HHV8 viral load remained detectable during the follow-up. One year later, the patient developed another autoimmune complication related to a new HHV8-positive MCD flare and autoimmune hypoglycaemia, which also responded favourably to rituximab (four doses).

DISCUSSION

This study describes a case of HHV8-positive MCD and TTP in an African patient with controlled HIV replication. MCD and TTP are rare diseases, and their association is exceptionally uncommon. In France, among patients with HHV8-positive MCD, 50% are HIV+[1,2]. MCD can develop in individuals with controlled or uncontrolled HIV replication, with immunosuppression being its aggravating factor[2]. In immunosuppressed patients with HIV, the average age of diagnosis is 30–40 years, whereas in HIV-negative individuals, it develops considerably later in life, often around the age of 60.

TTP in HIV-infected patients is related to both *ADAMTS13* inhibitors and endotheliitis secondary to chronic inflammation, opportunistic infections and complement activation. Hence, TTP presents in two types among patients with HIV. The most common type is diagnosed among severely HIV-positive immunocompromised patients presenting with opportunistic infections. It shows a progressive onset, detectable *ADAMTS13* activity and a poor prognosis, with a mortality rate of 50%, primarily attributed to TTP[6]. TTP in mild immunosuppressed patients displays an abrupt onset with severe *ADAMTS13* deficiency of less than 5%, but the prognosis is better.

Since the introduction of antiretrovirals, TMA/TTP incidence and TTP-related cytopenia correction have been decreased among patients with HIV. Notably, relapses are observed when antiretroviral treatment is discontinued, underscoring the significant role of HIV replication and immunosuppression in TTP pathogenesis[7].

Currently, only four patients associated with MCD and TTP have been reported. *Table 1* summarises the details of these patients, with all being positive for HHV8 and four positive for HIV[6]. In our case, replicative HHV8 was consistently found in all five cases, and four were HIV positive, suggesting the potential role of HHV8 and its relationship with HIV in the association between MCD and TTP[6,8]. HIV increases the risk of TTP and MCD – it is a confounding factor[6]. However, if TTP usually occurs in uncontrolled HIV replication, the four HIV patients had either a low or undetectable HIV replication in opposition to a high level of HHV8 replication[9]. Studies found low *ADAMTS13* activity and high HHV8 viral load. Among the four patients with MCD, none experienced new TTP relapses, except during a CD flare in one patient, suggesting a causality between TTP and MCD flare[8].

Interestingly, our patient had persistent HHVV8 replication

Test	Patient 1	Patient 2	Patient 3	Patient 4	Our Patient	Median
Age	56	44	52	42	53	52
Sex	Male	Male	Male	Male	Male	
HIV (years before diagnosis)	Negative	4.6	11.3	13.4	7.9	12.35
HIV viral load (copies/ml)	Negative	*300*	48	*397*	*<40*	174
CD4 cells/mm^3	1,562	538	252	313	505	505
HHV8 viral load (copies/ml)	77,359	10,111	Positive§	151,189	662,000	114,274
ADAMST13 activity	<5%	<5%	<5%	<5%	<5%	<5%
ADAMTS13 activity at 3 years	Positive	Positive	Positive	Positive	Positive*	-

Table 1. Sociodemographic and biological features of five patients, including our patient, with MCD and TTP[10]. The median duration of HIV infection at presentation was 11.2 years, and all patients had been treated with antiretroviral therapy for a median duration of 11.1 years.
*§ qualitative PCR; *1 year of follow-up.*

and experienced a possible flare in the form of autoimmune hypoglycaemia, a rare but previously described cause of MCD[10].

CONCLUSION

In conclusion, this study describes a rare association between MCD and TTP, with only four male cases reported to date. All five patients, including ours, were HHV8 positive (PCR+ with a high level of HHV8 replication), and four were HIV positive (3 out of 4 with low detectable viral load), underlying the potential role of the coinfection of HHV8 and HIV in MCD with TTP development. Although the involvement of HHV8 in MCD pathogenesis is well established, its precise role in TTP biology remains unclear. The unique co-occurrence of MCD and TTP should be considered when evaluating HIV-positive patients presenting with undetermined thrombocytopenia accompanied by renal failure and/or thrombotic microangiopathy, along with general symptoms and polyadenopathy. Additionally, ADAMTS13 activity and HHV8 viral load should be promptly assessed.

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