CASE REPORT

Fever and generalised lymphadenopathy in an HIV-positive patient: a diagnostic challenge

Bernardo Neves,[1] Pedro Raimundo,[1] Pedro Farinha[2]

[1]Internal Medicine, Hospital da Luz, Lisboa, Lisboa, Portugal
[2]Pathology Anatomy, Centro Hospitalar de Lisboa Central EPE, Lisboa, Lisboa, Portugal

Correspondence to
Dr Pedro Raimundo,
p_oliveiraraimundo@yahoo.com

Accepted 28 July 2017

SUMMARY

Fever and generalised lymphadenopathy is a common presentation of a variety of diseases and a thorough investigation is often necessary for appropriate diagnosis.

We present a 53-year-old male patient admitted with fever, weight loss of 15 kg in 3 months and abdominal discomfort. Examination was only remarkable for axillary and inguinal lymphadenopathy. Blood tests showed normocytic normochromic anaemia, cholestasis and a previously unknown HIV-1 infection with lymphocyte CD4 +count of 239 cells/mm^3 and viral load 3.172.370 copies/mL. A body CT scan showed multiple axillary, mediastinal, lumbar, aortic, iliac and pelvic lymphadenopathy as well as hepatosplenomegaly. An excisional biopsy of the left axillary lymphadenopathy was performed and histology ultimately revealed multicentric Castleman's disease associated with Human Herpes Virus-8. After initiation of antiretroviral therapy, rituximab was given and progressive clinical improvement occurred.

BACKGROUND

Fever and generalised lymphadenopathy are frequently seen on HIV-positive patients, especially those who are unaware of their diagnosis. Because the differential diagnosis is broad and variable according to the degree of immunosuppression, a systematic approach should be taken to achieve a proper diagnosis. Infectious diseases including HIV infection itself and malignant lymphoid neoplasms are the biggest concerns with any patient with this presentation. On this clinical case, we illustrate a thorough clinical investigation that ended up on a rare but treatable entity, making this an educational clinical case. This is also a report of a successful clinical response of rituximab on this rare clinical condition.

CASE PRESENTATION

A 53-year-old male patient, Angolan, currently living in a malaria-endemic region of Ethiopia, was admitted with fever, asthenia and abdominal pain. He had been well 3 months before he developed intermittent fever, malaise, anorexia and diffuse abdominal pain. He noticed weight loss of 15 kg for the last 3 months and referred no other symptoms. His personal and familiar history was unremarkable and no travelling outside from Ethiopia was noticed before his presentation in a Portuguese hospital, 7 days after travelling from his country.

On examination, he was febrile (38.5°C), blood pressure was 110/80 mm Hg, cardiac frequency 90 bpm, respiratory rate 18 cycles per minute. Lung sounds were clear and abdominal examination was only remarkable for unpainful hepatosplenomegaly. Several axillary and inguinal mobile masses were noticed, the largest with 3 cm diameter on left axilla, without associated skin findings.

INVESTIGATIONS

The admission blood tests results showed normocytic normochromic anaemia (Hg 8,4 g/dL), leucocytosis with lymphocytosis (17.000x10^9/L and 9.100x10^9/L, respectively), platelets 163.000, peripheral blood smear was negative for parasites or any other abnormalities, C reactive protein 11 mg/dL and slight elevation of phosphatase alkaline and gamma-GT with a normal bilirubin. Protein electrophoresis showed a broad-base gamma peak and a bone marrow aspirate was performed showing 15% plasmocytes with a normal myeloid/erythroid ratio. Uroculture, sequential blood cultures, myeloculture both for bacteria and mycobacteria, acid fast bacilli staining and leishmania direct examination and PCR were all negative.

On the first days, haemoglobin decreased to 6.9 g/dL despite transfusion and brief haemodynamic deterioration occurred. At this time there were no clear signs of haemolysis, namely increasing lactate dehydrogenase, increasing unconjugated bilirubin or low haptoglobin, and the direct Coombs test was also negative. Because blood loss was a concern, upper endoscopy and colonoscopy were then performed and showed no abnormalities. Laboratory findings were also not consistent with adrenal failure and the patient spontaneously improved with no further therapy. A body CT scan was performed at this time and revealed multiple lymphadenopathy: mediastinal, hilar and, lumbar and aortic (figure 1).

The patient kept relapsing fever with no other complaints. An initially ordered fourth-generation HIV test was positive, which was later confirmed with positive western blot for HIV-1 infection. Lymphocyte T CD4 +count was 239 cells/mm^3 and viral load was 3.172.370 copies/mL.

Venereal Disease Research Laboratory (VDRL), Epstein Barr virus (EBV), cytomegalovirus (CMV), toxoplasmosis, hepatitis B virus (HBV) and hepatitis C virus (HCV) serology were all negative for recent infection.

A surgical biopsy was then performed on the left axillary nodal conglomerate which ultimately

To cite: Neves B, Raimundo P, Farinha P. *BMJ Case Rep* Published Online First: [*please include* Day Month Year]. doi:10.1136/bcr-2017-220740

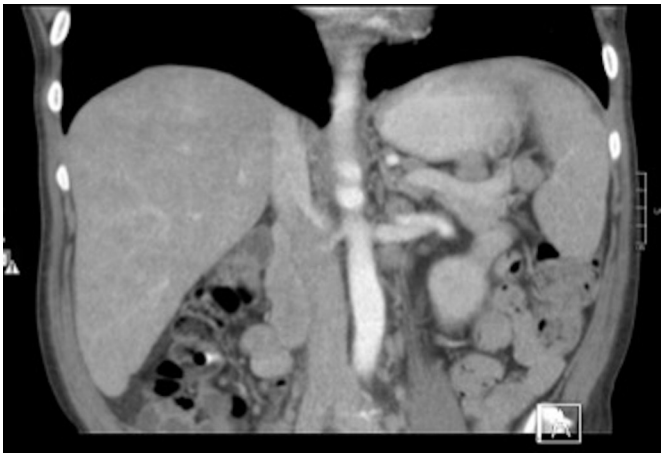

Figure 1 Body CT scan showing multiple lymphadenopathy.

showed a various lymphatic nodes with preserved nodal structure and involution of the germinal centres, interfollicular regions filled with plasmocytes and proliferating vascular growth. In some of the germinal centres and mantle zones, isolated and aggregated plasmablasts could be seen, expressing human herpes virus-8 (HHV-8), monotypical for lambda light chains. The remaining interfollicular plasmocytes were polyclonal. This findings were consistent with HHV-8-positive variant of multicentric Castleman's disease (MCD) (figure 2).

DIFFERENTIAL DIAGNOSIS

Most of the series of generalised lymphadenopathy on HIV-positive patients come from the pre-antiretroviral therapy (ART) era or from countries where tuberculosis is endemic, making mycobacterial infections the first cause of generalised lymphadenopathy on this population.[1] Because this patient came from Ethiopia, a country where tuberculosis is still endemic, this diagnosis must be ruled out. Tuberculous lymphadenitis is the most common extrapulmonary presentation of *Mycobacterium tuberculosis* infection and tends to occur inversely to CD4 +lymphocyte count. Cervical lymph nodes are the most common site and in 35% of patients multiple localisations are involved.[2]

Other Mycobacteria species infections could also have similar presentations. *Mycobacterium avium complex* infections are frequently associated with severe anaemia; however, generalised lymphadenopathy is less frequent and one should expect a lower lymphocyte CD4 +count (eg, <50 cells/uL).[3]

Blood and bone marrow cultures and in this case lymph node biopsy would be helpful for the diagnosis of mycobacterial infections.

HIV infection itself could be responsible for the clinical symptoms, either by acute or chronic infection. Acute viral infection was not present in this case because a positive western blot implies an infection of more than 3 months and also the symptomatology is consistent with a more indolent disease. Chronic HIV infection with this degree of immunosuppression could account for constitutional symptoms and generalised lymphadenopathy; however, this diagnosis should only be made after excluding other entities.

The slow onset of the clinical complains makes most bacterial and other acute infections less likely, however, HBV, HCV, Epstein-Barr virus (EBV), cytomegalovirus (CMV) and toxoplasmosis should be ruled out as they can present with similar complaints.

Visceral leishmaniasis could explain this clinical picture, specially fever and hepatosplenomegaly. Lymphadenopathies are however a rare finding in this entity.[4] For proper diagnosis, direct visualisation of parasites on bone marrow smear or positive culture are required.

Lymphoma is always a concern in any patient with lymphadenopathy, especially those with HIV infection. Such patients have higher risk of developing lymphomas and highly aggressive non-Hodgkin lymphomas such as Burkitt lymphoma and diffuse B cell are common.[5]

Classically, the risk of developing lymphoma is proportional to the degree of immunosupression with median lymphocyte CD4 +count 200 cells/mm^3 at diagnosis.[6] Some types of lymphoma are specially related to HIV infection, such as plasmablastic, oral cavity, pleural cavity lymphomas and HHV-8 related Kaposi sarcoma.[7]

Differently from HIV-negative patients, lymphomas usually present more acutely and on a highly aggressive way on HIV-positive patients, being more advanced at diagnosis and more frequently with associated B symptoms (ie, fever, weight loss and nocturnal sudoresis).[8]

An uncommon entity that can be easily confounded with a lymphoma is MCD, where lymph node histology is essential for establishing the correct diagnosis.

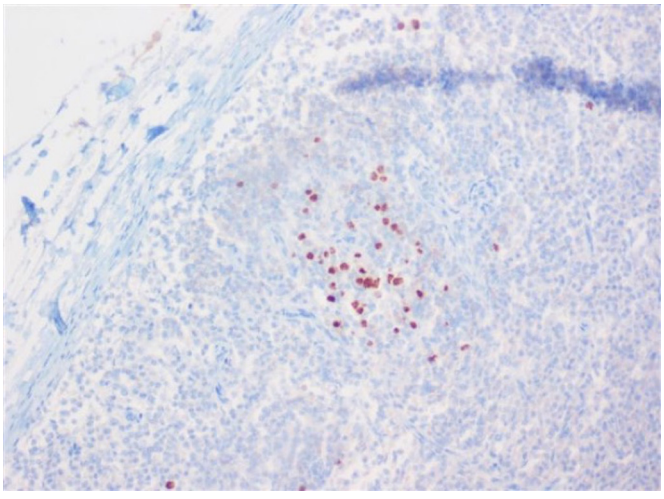

Figure 2 Lymph node biopsy showing diffuse plasmocyte infiltration with positive staining for HHV-8, human herpes virus-8.

TREATMENT

After diagnosis, antiretroviral therapy (ART) was initiated with efavirenz, tenofovir and emtricitabine with good tolerance and significant improvement of symptoms and anaemia. After 1 month, rituximab was then initiated (375 mg/m^2 weekly during 4 weeks) and an impressive response was observed on lymphadenopathy. Anaemia and weight also improved after four doses of this drug and no adverse effects were observed during the treatment period.

OUTCOME AND FOLLOW-UP

During the 8-month follow-up period, no adverse effects were noticed and symptomatology improved considerably with weight gain, haemoglobin improvement and lymphadenopathy resolution. After 5 years of follow-up, the patient is alive and without any evidence of recurring disease nor evolution into lymphoma.

DISCUSSION

Castleman's disease is a heterogeneous group of rare diseases which have in common augmented production of interleukin 6 with lymphoid hyperplasy. Both localised or unicentric and multicentric forms exist, being the later more commonly associated with HHV-8 and also with HIV infection. Annual incidence of MCD is 8.3/10.000 patients per year, a number that has raised after rising after the introduction of ART.[9]

Clinical presentation of multicentric disease is usually undistinguishable from a lymphoma with generalised lymphadenopathy and hepatosplenomegaly. Its pathophysiology is still not fully understood; however, HHV-8 plays a role as it is commonly found on biopsies.[10] Laboratory markers are unspecific, presenting commonly with anaemia, thrombocytosis, elevated erythrocyte sedimentation rate and hypergammaglobulaemia. Histological hallmark includes a polyclonal plasmocitary expansion with normal nodal structure and HHV-8 identification which is almost always present on HIV-positive patients.[11]

Although it is a benign histological entity, MCD accounts for significant morbidity and mortality, either because of bacterial infection predisposition or for the risk of developing associated malignancies such as Kaposi sarcoma and non-Hodgkin's lymphoma.[12] Histology in this patient additionally showed increased expression of lambda free light chains, a finding that had been suggested to be linked to increased susceptibility to developing a high-grade lymphoma.[13]

Because it is such an uncommon diagnosis, treatment experience is still sparse and only based on observational studies. In HIV-positive patients, treatment with rituximab showed good results with an overall low relapse rate and with acceptable safety profile.[14] Patients with low CD4 +counts and high viral loads should start ART before rituximab to decrease viral load. Some authors suggest the addition of chemotherapy to rituximab on severe cases including those with end-organ failure; however, benefit is still not clear comparing with rituximab monotherapy.[15]

Learning points

- Fever and lymphadenopathy is a frequent presentation of a variety of diseases and intensive investigation should be performed to achieve a proper diagnosis as many important and life-threatening conditions can present this way.
- HIV infection should be ruled out in these situations especially in patients coming from endemic areas.
- Differential diagnosis should take in account the level of immunosuppression but ultimately many conditions should be considered.
- Multicentric Castleman's disease is a rare entity that required a histology diagnosis and should be considered in patients with HIV with unexplained fever and generalised lymphadenopathy.
- Treatment of this condition is still not consensual but rituximab either on monotherapy or associated with chemotherapy has been showing good results.

Contributors BN has written the majority of this paper and had the greatest contribution (70%). PR reviewed the paper and contributed with some parts (20%). PF contributed with some parts of the paper (10%).

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Kamana NK, Wanchu A, Sachdeva RK, *et al*. Tuberculosis is the leading cause of lymphadenopathy in HIV-infected persons in India: results of a fine-needle aspiration analysis. *Scand J Infect Dis* 2010;42:827–30.
2 Bogoch II, Andrews JR, Nagami EH, *et al*. Clinical predictors for the aetiology of peripheral lymphadenopathy in HIV-infected adults. *HIV Med* 2013;14:182–6.
3 Naing C, Mak JW, Maung M, *et al*. Meta-analysis: the association between HIV infection and extrapulmonary tuberculosis. *Lung* 2013;191:27–34.
4 Domingues M, Menezes Y, Ostronoff F, *et al*. Coexistence of leishmaniasis and Hodgkin's lymphoma in a lymph node. *J Clin Oncol* 2009;27:e184–85.
5 Dal Maso L, Franceschi S. Epidemiology of non-Hodgkin lymphomas and other haemolymphopoietic neoplasms in people with AIDS. *Lancet Oncol* 2003;4:110–9.
6 Bower M, Fisher M, Hill T, *et al*. CD4 counts and the risk of systemic non-Hodgkin's lymphoma in individuals with HIV in the UK. *Haematologica* 2009;94:875–80.
7 Gloghini A, Dolcetti R, Carbone A. Lymphomas occurring specifically in HIV-infected patients: from pathogenesis to pathology. *Semin Cancer Biol* 2013;23:457–67.
8 Gabarre J, Raphael M, Lepage E, *et al*. Human immunodeficiency virus-related lymphoma: relation between clinical features and histologic subtypes. *Am J Med* 2001;111:704–11.
9 Casper C. The aetiology and management of Castleman disease at 50 years: translating pathophysiology to patient care. *Br J Haematol* 2005;129:3–17.
10 Powles T, Stebbing J, Bazeos A, *et al*. The role of immune suppression and HHV-8 in the increasing incidence of HIV-associated multicentric Castleman's disease. *Ann Oncol* 2009;20:775–9.
11 Oksenhendler E, Duarte M, Soulier J, *et al*. Multicentric Castleman's disease in HIV infection: a clinical and pathological study of 20 patients. *AIDS* 1996;10:61–7.
12 Oksenhendler E, Boulanger E, Galicier L, *et al*. High incidence of Kaposi sarcoma-associated herpesvirus-related non-Hodgkin lymphoma in patients with HIV infection and multicentric Castleman disease. *Blood* 2002;99:2331–6.
13 Wang H-W, Pittaluga S, Jaffe ES. Multicentric Castleman disease—where are we now? seminars in diagnostic pathology. *Elsevier* 2016:1–33.
14 Bower M, Newsom-Davis T, Naresh K, *et al*. Clinical features and outcome in HIV-associated multicentric Castleman's disease. *J Clin Oncol* 2011;29:2481–6.
15 Gérard L, Bérezné A, Galicier L, *et al*. Prospective study of rituximab in chemotherapy-dependent human immunodeficiency virus associated multicentric Castleman's disease: ANRS 117 CastlemaB trial. *J Clin Oncol* 2007;25:3350–6.