

## ANSWER TO PHOTO QUIZ (PAGE 306)

MASSIVE LYMPHADENOPATHY IN A PATIENT WITH HUMAN  
IMMUNODEFICIENCY VIRUS INFECTION

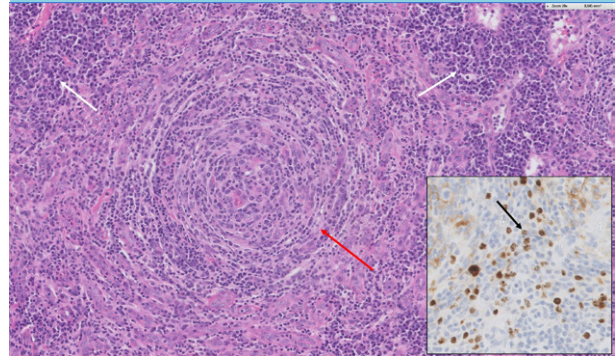
## DIAGNOSIS

The FDG PET/CT scan shows extensive lymphadenopathy and splenomegaly suggestive for multicentric Castleman's disease (MCD), although malignant lymphoma, opportunistic infections and sarcoidosis cannot be excluded. Histology and immunohistochemistry of an excised axillary lymph node confirmed the diagnosis of MCD and immunostaining for human herpesvirus-8 (HHV-8) on biopsy was positive (figure 2).

MCD is a recurring and remitting lymphoproliferative disorder with an incidence in HIV patients of around 8.3 per 10,000 patient-years, in which it is associated with HHV-8.<sup>1</sup> The pathogenesis is related to infection of HHV-8 in immunoblasts and the production of viral interleukin-6 (IL6), but the exact mechanism is unknown. CD4 counts and viral load at presentation can vary and are not associated with the risk of developing MCD. Patients typically present with fever and lymphadenopathy. Splenomegaly, hepatomegaly and fluid retention are also common findings and concomitant Kaposi sarcoma is found in approximately 70% of the patients.<sup>2</sup> Histologically, pathological variants of lymph node biopsies can be divided into three categories: The plasma cell variant and the mixed variant each represent approximately half of cases, the hyaline vascular variant represents 4%. HHV-8 testing on biopsy or serum is positive in 98% of cases associated with HIV. Diagnosis is made when clinical criteria as described by the French *Agence Nationale de Recherche sur le SIDA 117 CastlemaB* trial group are met, in combination with histological findings.<sup>1,2,3</sup>

Evidence on the treatment for MCD is of low quality, current expert opinion is to treat with rituximab. Multiple studies have combined rituximab with antiviral therapy or with chemotherapy, but evidence is of low quality due to small study populations. Anti-IL6(R) therapy shows promise as a second line regimen, but is still under investigation. Antiretroviral therapy (ART) needs to be initiated in newly diagnosed HIV patients and optimized in existing ones already on ART. However, MCD can also be provoked by a rise in CD4 count in the context of an immune reconstitution inflammatory syndrome, as could have been the case in our patient.<sup>2</sup> All-cause mortality for HIV patients with MCD is high, around 25% with a median follow-up of 27 months.<sup>1,3</sup> Imaging is not always necessary for diagnosis but an FDG PET/CT-scan can

**Figure 2.** Lymph node involved with multicentric Castleman's disease. The larger image shows a hematoxylin and eosin stain with in the follicle regression of the germinal center with increased vascularity and concentric arrangement of lymphocytes ('onion skin' pattern) (red arrow). In the interfollicular areas large sheets of plasma cells (white arrows). In the inserted picture human herpesvirus-8 (HHV-8) positive cells in the mantle zones with a finely stippled nuclear staining (black arrow)



assist in distinguishing from concurrent conditions, can aid in choosing a lymph node to excise and can confirm complete remission after initial treatment.<sup>4</sup> Our patient was treated with rituximab and valganciclovir for four weeks and showed complete remission on a follow-up FDG PET/CT-scan three months later.

## ACKNOWLEDGEMENTS

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## REFERENCES

1. Rokx C, Rijnders BJ, van Laar JA. Treatment of multicentric Castleman's disease in HIV-1 infected and uninfected patients: a systematic review. *Netherlands J Med.* 2015;73:202-10.
2. Mylona EE, Baraboutis IG, Lekakis LJ, Geogiou, Papastamopoulos V, Skoutelis A. Multicentric Castleman's disease in HIV infection: a systemic review of literature. *AIDS Rev.* 2008;10:25-35.
3. Reddy D, Mitsuyasu R. HIV-associated Multicentric Castleman Disease. *Curr Opin Oncol.* 2011;23:475-81.
4. Polizzotto MN, Millo C, Uldrick TS, et al. 18F-fluorodeoxyglucose positron emission tomography in Kaposi sarcoma herpesvirus-associated multicentric Castleman disease: Correlation with activity, severity, inflammatory and virologic parameters. *J Infect Dis.* 2015;212:1250-60.