
CHRISTOPH D SPINNER\textsuperscript{15}, SEBASTIAN NOE\textsuperscript{1}, CHRISTIANE SCHWERDTFEGER\textsuperscript{15}, ANTONIA TODOROVA\textsuperscript{25}, JOCHEN GAA\textsuperscript{3}, ROLAND M SCHMID\textsuperscript{1}, DIRK H BUSCH\textsuperscript{46}, MICHAEL NEUENHAHN\textsuperscript{46}

Department of Medicine II\textsuperscript{1}, Department of Dermatology and Allergy\textsuperscript{2}, Department of Radiology\textsuperscript{3} and Interdisciplinary HIV Centre (IZAR)\textsuperscript{5} at UNIVERSITY HOSPITAL KLINIKUM RECHTS DER ISAR

UNIVERSITY HOSPITAL KLINIKUM RECHTS DER ISAR, Ismaningerstr. 22, 81675 Munich\textsuperscript{1,3,5}
UNIVERSITY HOSPITAL KLINIKUM RECHTS DER ISAR, Biedersteiner Str. 29, 80802 Munich,\textsuperscript{2}

Institute for Medical Microbiology, Immunology and Hygiene, TECHNISCHE UNIVERSITAET MUENCHEN (TUM), Trogerstr. 30, 81675 Munich\textsuperscript{4}

German Center for Infection Research (DZIF)\textsuperscript{6}

Correspondence address:

Dr. Christoph D. Spinner, Department of Medicine II, University Hospital Klinikum rechts der Isar, Ismaningerstr. 22, 81675 Munich, christoph.spinner@lrz.tum.de, phone +49 (89) 4140-5236, fax +49 (89) 4140-4958

Alternative correspondence address:

Dr. Michael Neuenhahn, Institute for Medical Microbiology, Immunology and Hygiene Technische Universitaet Muenchen (TUM), Trogerstr. 30, 81675 Munich, michael.neuenhahn@mikrobio.med.tum.de, phone +49 (89) 4140-7454, fax +49 (89) 4140-4131

E-mail addresses of all authors:

christoph.spinner@lrz.tum.de, sebastian.noe@lrz.tum.de, christiane.schwerdtfeger@lrz.tum.de, antonia.todorova@lrz.tum.de, jochen.gaa@tum.de, dirk.busch@mikrobio.med.tum.de, michael.neuenhahn@mikrobio.med.tum.de.

Key words:

HIV, MSM, syphilis, hypopituitarism, hypophysitis.
ABSTRACT

BACKGROUND Sexually transmitted diseases and most notably syphilis-infections are rising among men who have sex with men. In HIV-co-infected patients, an accelerated clinical course of syphilis neurological involvement is known. CASE PRESENTATION A HIV-positive male patient presented to our emergency department with acute fever, rapidly progressive cephalgia, neck stiffness and photosensitivity. Palmar skin efflorescences evoked an active syphilis infection and a reactive TPPA with positive Treponema pallidum-specific IgG/IgM immunofluorescence and highly reactive VDRL confirmed the diagnosis. Liquor pleocytosis, liquor protein elevation and a highly positive VDRL test in CSF were interpreted in context of the clinical symptoms as neurosyphilitic manifestations. Interestingly, endocrine laboratory analysis revealed hypopituitarism explaining a prolonged general weakness episode. Cranial nuclear magnetic resonance scans of the sella turcica showed signs of hypophysitis like pituitary gland enlargement and inhomogeneous contrast enhancement. 14 days intravenous antibiotic treatment and levothyroxine- and hydrocortisol-substitution led to a complete disappearance of all clinical symptoms. 2 months later, nuclear magnetic resonance scan showed normal pituitary size and syphilis serology had normalized.

CONCLUSION We here report to our knowledge the first case of an acute hypophysitis with consecutive hypopituitarism during an early neurosyphilis infection in a HIV-positive MSM. Antibiotic treatment and levothyroxine- and hydrocortisol-substitution led to disappearance of all clinical symptoms. We strongly recommend syphilis diagnostic in every unclear clinical situation in HIV-patients, especially when additional risk factors are known.

CASE REPORT

BACKGROUND

Sexually transmitted diseases (STD) and in particular syphilis infections, caused by the spirochete Treponema pallidum (subspecies pallidum), are on the rise since the beginning of this century. [1, 2] Men who have sex with men (MSM) are by far the most affected group in the western world and Human immunodeficiency virus (HIV) co-infected MSM have been described to show an accelerated and more complicated course of syphilis infections with neurological involvement. [3-5] Notably, cerebrospinal fluid (CSF) and neurological abnormalities (e.g. meningitis) correlate with low (<=350/µl) CD4 cells counts in HIV seropositive individuals.[6] Syphilis infection has also been linked to a specific pituitary inflammation, named granulomatous hypophysitis, but obviously just in analogy to other granulomatous infectious aetiologies. [7-9] We here describe to our best knowledge the first clinical case of acute hypophysitis during an early syphilis infection. Though a rare disorder, physicians should be aware of the possibility of pituitary inflammation secondary to syphilis, since a potential secondary adrenal insufficiency may develop that can be lethal if unrecognised and not treated adequately and immediately.
We here report a case of acute hypophysitis and consecutive hypopituitarism due to active neurosyphilis infection in a 46-year old HIV-positive MSM patient. The patient presented to our emergency department with acute fever (39 °C), rapidly progressive cephalgia, neck stiffness and photosensitivity. Beside the combined antiretroviral therapy with Abacavir, Lamivudin and Efavirenz no other medication was taken. HIV load had been below detection level (< 40 cps/ml) at his last outpatient visit and a recent CD4-count was above 350/µl. Besides the known HIV-infection, STD history was unremarkable. Six months ago, a screening test for syphilis co-infection using the Treponema pallidum particle agglutination assay (TPPA) had been negative. Drug abuse was denied and other medical pre-existing conditions were not known.

The patient was hospitalized from emergency department and on assumption of acute meningitis a calculated antimicrobial therapy with intravenous Ceftriaxone (4g per day on day 1, followed by 2g per day), Amoxicillin (3 x 5 g per day) and Aciclovir (3 x 10 mg/kg body weight per day) was immediately initiated. An emergency cranial computed tomography excluded signs of intracranial pressure. Lumbar puncture showed mild pleocytosis (10 cells/µl) and high protein levels (1040 mg/l). The liquor/serum-albumin-quotient was elevated indicating blood-CSF barrier dysfunction (13 x 10^{-3}). Initial laboratory diagnostics revealed hyponatremia (130 mmol/l), mild C-reactive protein elevation (2.1 mg/dl) and hepatopathy (ALT 68 U/l, AST 85 U/l). Endocrine laboratory analysis was performed due to general weakness and showed hypopituitarism with low levels for TSH (0.15 µIU/ml), fT3 (2.5 pg/ml), fT4 (0.4 ng/ml), LH (< 0.1 IU/l), testosterone (< 0.1 IU/l), basal cortisole (0,2 µg/dl) and IGF-1 (74 ng/ml). Nuclear magnetic resonance (NMR)-imaging of the sella turcica showed pituitary and pituitary stalk enlargement with inhomogeneous contrast enhancement (Figure 1A). Stereotactic biopsy and histopathological assessment to exclude malignancy of the pituitary enlargement was refused by the patient.

Subsequent microbiological and viral analysis by nucleic acid amplification excluded infection of the central nervous system for Mycobacterium tuberculosis, Herpes simplex-, Cytomegalo-, Epstein-Barr-, Varicella- and Enterovirus. Aerobic and anaerobic liquor cultures were sterile. HIV PCR from peripheral blood showed low-level viremia (47 Geq/ml), but was negative in cerebrospinal fluid. Upon clinical examination erythematous maculae with distinct edges occurred on the palms and soles. Consistent with these skin manifestations, a disseminated syphilis infection was postulated. Syphilis infection was serologically confirmed by reactive TPPA (1:10240) and positive Treponema pallidum-specific IgG immunofluorescence (IgG-FTA abs) test. The detection of Treponema pallidum-specific IgM (IgM-FTA abs and immunoblot) together with high titres in the Venereal Disease Research Laboratory (VDRL) microfloculation test (1:512) in patient serum indicated high activity of the syphilis infection. Because of the meningitis symptoms and the known accelerated clinical course of syphilis in HIV-patients specific liquor diagnostics were performed. Syphilis-specific liquor serology showed a positive TPPA (1:64) and a highly positive VDRL test (1:512) in CSF. However, TPPA-liquor/serum index (TPPA-index) was normal (1.15) and a retrospectively performed Treponema pallidum-specific NAT in CSF was negative. The empirically started Ceftriaxone therapy (2 g per day) led to rapid resolution of meningitis symptoms and was continued for a total course of fourteen days for neurosyphilis treatment. After exclusion of cerebral Listeria and HSV infection, treatment with Aciclovir and Ampicillin was stopped. Hormone substitution
therapy with levothyroxine (75 µg per day) and hydrocortisone substitution (50 mg per day) was started for the hypopituitarism and laboratory ranges normalized within days. Under ceftriaxone therapy and levothyroxine and hydrocortisone substitution all clinical symptoms completely resolved. A NMR scan of the sella turcica two months later showed a normal pituitary size (Figure 1B) and the patient remained asymptomatic. Hormone substitution was reduced gradually and then completely stopped. Hormone laboratory results (TSH, fT3, fT4, cortisone basal level) stayed in the follow consistently normal. Syphilis serology confirmed 6 month after hospitalization with a significantly reduced TPPA (1:320), negative IgM (Immunofluorescence) and normalized VDRL (<1:2) in patient serum successful antibiotic treatment.

CONCLUSION

We report to our knowledge the first case of a HIV-positive MSM patient with acute hypophysitis and hypopituitarism coincidental to active syphilis infection. In the context of the clinical symptoms (meningitis and disseminated cutaneous exanthema) and a negative syphilis screening history (only 6 months before hospitalization) we interpreted the clinical picture as a confirmed early secondary syphilis (according to ECDC definitions).[10] The high activity of the infection was illustrated by positive Treponema pallidum-specific serum IgMs and high VDRL serum titres (1:512). In order to treat the presumably syphilitic lesions in the pituitary gland and the neurological symptoms sufficiently, we decided to continue intravenous antibiotic treatment for 14 days according to national treatment guidelines.[11] CSF abnormalities with blood-CSF-barrier disturbance, CSF pleocytosis, high liquor protein levels (total protein 1.040,0 mg/l) and in particular a very high CSF VDRL reactivity (1:512) were in line with early neurosyphilis in accordance to CDC guidelines.[12] However, symptomatic bacterial replication in the central nervous system could not be formally proven according to national diagnostic criteria, because the ITpA index was not elevated.[11] A retrospectively performed Treponema pallidum-specific NAT from CSF was also negative, but a recent meta-analysis reported low sensitivity (47%) in retrospective CSF PCR samples from patients with neurosyphilis.[13] In any case, the complete neurological, endocrinological and serological recovery after antibiotic treatment may probably count as the strongest argument for Treponema pallidum-caused hypophysitis and consecutive hypopituitarism.

We strongly recommend syphilis diagnostic in every unclear clinical situation in HIV-patients, especially when additional risk factors are known. Syphilis-specific CSF diagnostic should be performed whenever any additional signs of neurosyphilis occur. A CSF VDRL test could be helpful to diagnose a neurosyphilis when other signs of neurosyphilis are missing.

LITERATURE


**FIGURE LEGEND**

**Fig 1A**
Contrast-enhanced coronal T1-weighted nuclear magnetic resonance (NMR) scan of the sella turcica showing pituitary and pituitary stalk enlargement with inhomogeneous contrast enhancement.

**Fig 1B**
Contrast-enhanced coronal T1-weighted nuclear magnetic resonance (NMR) scan of the sella turcica two months after hypophysitis demonstrates normal pituitary size.

**AUTHORS’ CONTRIBUTION**

We declare that all authors contributed relevant to the manuscript and read and approved the final version. AT cared for the dermatological diagnostics, SN cared for the endocrinological diagnostics and therapy and CSp cared for the infectious counselling and whole clinical care and treatment of the patient. JG cared for radiology diagnostics, especially the NMR and cranial CT-scan. MN cared for microbiological
laboratory and serological diagnostics. CS and MN wrote the manuscript with equal contribution. In addition, CSc was relevantly involved in data interpretation, additional retrospective liquor analysis and manuscript composition. RS and DB supervised clinical and laboratory diagnostics and therapy, as well as manuscript preparation.

ACKNOWLEDGMENTS

No further acknowledgements are declared.

COMPETING INTERESTS

We declare for all authors that there is no competing interest.

CONSENT STATEMENT

Written informed consent was obtained from the patient for publication of this report and accompanying images. A copy of written consent is available for review by the Editor of this journal.
Contrast-enhanced coronal T1-weighted nuclear magnetic resonance (NMR) scan of the sella turcica showing pituitary and pituitary stalk enlargement with inhomogeneous contrast enhancement.

Contrast-enhanced coronal T1-weighted nuclear magnetic resonance (NMR) scan of the sella turcica two months after hypophysitis demonstrates normal pituitary size.