CASE REPORT

Follicular bronchiolitis in an HIV-infected individual on combination antiretroviral therapy with low CD4+ cell count but sustained viral suppression

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SUMMARY

A 36-year-old Danish man, living in Asia, was diagnosed with *Pneumocystis pneumonia* (PCP) and HIV in 2013 (CD4+ count: 6 cells/μL; viral load: 518 000 copies/mL). He initiated combination antiretroviral therapy. Later that year, he was also diagnosed with granulomatosis with polyangiitis and was treated with prednisolone. Despite complete viral suppression and increasing CD4+ count (162 cells/μL), he was readmitted with PCP in April 2015. Subsequently, he returned to Denmark (CD4+ count: 80 cells/μL, viral suppression). Over the following months, he developed progressive dyspnoea. Lung function tests demonstrated severely reduced lung capacity with an obstructive pattern and a moderately reduced diffusion capacity. High resolution computer tomography revealed minor areas with tree-in-bud pattern and no signs of air trapping on expiratory views. Lung biopsy showed lymphocytic infiltration surrounding the bronchioles with sparing of the alveolar septa. He was diagnosed with follicular bronchiolitis. The patient spontaneously recovered along with an improvement of the immune system.

BACKGROUND

The epidemiology of pulmonary diseases in HIV-infected individuals has changed since the advent of combination antiretroviral therapy (cART) in the mid-1990s.¹ Although classic HIV-related pulmonary diseases such as *Pneumocystis pneumonia* (PCP), tuberculosis, Kaposi's sarcoma and recurrent pneumococcal pneumonia remain rather common, smoking-related lung diseases has by far become the most important pulmonary diseases in HIV-infected people living in Western Europe and North America.^{2–5} Before cART, non-infectious, non-neoplastic conditions including lymphocytic infiltrative pulmonary disorders like lymphocytic interstitial pneumonitis (LIP) and the more frequent non-specific interstitial pneumonitis (NSIP) were seen. LIP is characterised by CD8+ lymphocyte infiltration of the lungs in the absence of opportunistic infection or neoplasm.^{6–10} In contrast, HIV-associated follicular bronchiolitis (FB) is a small airway disease, characterised by hyperplastic lymphoid follicles with reactive germinal centres distributed along the bronchioles.^{11–14} Contrary to LIP, FB is limited to the peribronchial area, with sparing of the alveolar septa, whereas LIP extends into the interstitium.¹² As such, these conditions are described as

a continuum of pulmonary lymphoproliferative diseases with overlapping histological patterns.^{6 13 15} Although rare after the introduction of cART,¹⁶ LIP mainly occurred in children with advanced HIV in the pre-cART era (~AIDS defining condition in children younger than 13 years of age).¹⁷ In contrast, only very few cases of FB has been described in HIV-infected children or adults during both the pre-CART and cART era.^{11 12 18–20}

We present an adult HIV-infected individual on cART diagnosed with FB.

CASE PRESENTATION

In September 2013, a 36-year-old Danish-born man, previous smoker, who was living and working in Malaysia and Thailand, was admitted to a local hospital with PCP and further diagnosed with HIV. His initial CD4+ count was 6 cells/μL, and the viral load (VL) was 518 000 copies/mL. cART was initiated with nevirapine, tenofovir and emtricitabine. Due to development of resistance mutations, the treatment was changed to zidovudine, tenofovir and lopinavir/ritonavir in November 2013. In November, the patient also developed symptoms of granulomatosis with polyangiitis (GPA) with sinusitis, severe kidney affection and positive anti-neutrophil cytoplasmic antibodies directed against proteinase 3 (PR3-ANCA) of 160 units/mL. No kidney biopsy was performed. Prednisolone 50 mg/daily was initiated with a good response. No other immunosuppressive therapy was initiated. In May 2014 (CD4+ count 140 cells/μL and VL <20 copies/mL), the patient developed several osteoporotic fractures of the spine, and he initiated treatment with calcium and teriparatide. Prednisolone and tenofovir were considered as possible contributing factors of the osteoporosis. As a result, the antiretroviral regimen was changed to raltegravir, lamivudine and lopinavir/ritonavir. In March 2015, the CD4+ count was 162 cells/μL and VL <20 copies/mL. In April 2015, the patient was readmitted with a new episode of PCP. After discharge, prophylactic treatment with sulfamethoxazole and trimethoprim was initiated.

In May 2015, he returned to Denmark. The VL was still suppressed, but the CD4+ count had dropped to 80 cells/μL. cART was kept unchanged. Since no symptoms or signs of GPA could be identified and PR3-ANCA measurement was negative, the prednisolone dose was further reduced from

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Figure 1 Immunestatus and viral load.

7.5 mg/day to 5 mg/day. Over the following months, he developed progressive dyspnoea. Three times he was acutely admitted at the Department of Cardiology; however, he had a normal echocardiography, heart CT scan and a normal chest X-ray, and it was concluded that he did not have cardiac failure, pulmonary embolism or acute myocardial infarction. Subsequently, he was referred to the Department of Respiratory Medicine for further investigation.

INVESTIGATIONS

The initial examination in the Outpatient Clinic (OPC) of Respiratory Medicine revealed no signs of interstitial lung disease. Lung function tests demonstrated a severely reduced lung capacity with an obstructive pattern (forced expiratory volume in 1 s (FEV₁): 1.6 L~35% of expected; forced vital capacity (FVC): 4 L~71% of expected; FEV₁/FVC ratio (index): 41%, normal total lung capacity: 105%) and a moderately reduced diffusing capacity (61% of expected). No significant reversibility was present. High-resolution CT (HRCT) further visualised minor areas with tree-in-bud pattern. Expiratory images revealed no signs of air trapping. Lung biopsy performed by video-assisted thoracoscopic surgery showed characteristic lymphocytic infiltration surrounding the bronchioles with sparing of the alveolar septa. At a subsequent multidisciplinary conference for interstitial lung diseases, the diagnosis of FB was agreed on.

Figure 2 Lung function test.

TREATMENT

Treatment of FB is mainly based on optimal treatment of the underlying condition and generally associated with a good prognosis.¹³ Due to the unique anti-inflammatory and immunomodulatory properties of macrolide antibiotics, treatment with azithromycin has also been recommended.^{21 22} In this case, the patient spontaneously recovered along with an improvement of the immune system on cART. Hence, azithromycin was not initiated.

OUTCOME AND FOLLOW-UP

At the subsequent visits in the OPC of Infectious Medicine and Respiratory Medicine, the patient's symptoms and clinical findings improved along with an improvement of the immune system (figure 1). Lung function tests improved during the follow-up period (figure 2). In January 2017, the following was measured: FEV₁: 3.6 L~77% of expected, FVC: 6.0 L~104% of expected and FEV₁/FVC (index): 60%. Diffusing capacity: 81% of expected. The pattern of the flow volume loop gradually changed from severe to moderate air flow limitation (figure 3).

During the period, no clinical symptoms or signs indicating recurrence of GPA was observed, and PR3-ANCA was repeatedly negative.

DISCUSSION

FB is mainly associated with immunodeficiency, or inflammatory, autoimmune or connective tissue diseases, but may in rare cases be idiopathic.¹¹⁻¹³ The pathogenesis remains poorly understood, although repetitive antigenic stimulation of the bronchial associated lymphatic tissue resulting in polyclonal lymphoid hyperplasia has been suggested.¹¹

In two case studies of 6 and 19 adults with FB, respectively,^{11 12} two HIV-infected individuals with advanced AIDS was identified (one patient was on cART for 2 months; one patient had unknown treatment status; both had unknown CD4+ count and VL). Three more cases of HIV-associated FB¹⁸⁻²⁰ have been identified. Theron *et al*¹⁹ presented the history of an HIV-infected child where the case clinically and radiologically mimicked miliary TB; however, after failure of TB treatment, an open biopsy revealed FB (CD4+ count, VL and treatment history not presented). Exley *et al*²⁰ reported FB in a 49-year-old Zambian woman experiencing recurrent bacterial pneumonias. In this case, minor features of LIP were also present according to pathology results. There was a satisfactory clinical and radiological response on cART.²⁰ Finally, Shipe *et al*¹⁸ presented a 38-year-old African American HIV-infected man (CD4+ count: 347 cells/μL, VL: 633 000 copies/mL and never on cART) who presented with several months of non-productive cough and radiology featuring miliary nodules. He was thoroughly examined, and there were no signs of TB, disseminated fungal disease or viral or bacterial pneumonia. An open lung biopsy revealed the FB diagnosis, and the patient improved clinically after 6 months of cART.¹⁸

In the presented case, the symptoms and radiological features were non-specific; however, lung function test results were consistent with significant small airway disease and subsequent lung biopsies confirmed the diagnosis of FB.

In accordance with the favourable effect of cART on LIP,²³ FB also seems to resolve on cART.^{18 20} Although the patient described in the case had achieved and sustained viral suppression on cART as measured on a number of occasions,

Figure 3 Flow volume loops. A: August 2015, B: October 2015, C: January 2016, D: January 2017.

he was probably severely immunocompromised due to a combined and probably additive negative effect of HIV and prednisone on CD4 lymphocyte number and function.^{24,25} It seems evident that a high pulmonary VL cannot explain the patient's development of FB and subsequent spontaneous improvement.

Prior to the initial presentation with symptoms of FB, the patient was admitted at another hospital abroad with presumed PCP. Unfortunately, we do not have access to the medical records from this admission and are therefore unable to determine how the PCP diagnosis was established. One might speculate whether the admission was the initial presentation of FB or FB developed as the result of PCP. In a study by Sattler *et al*,²⁶ NSIP was the most common pathology diagnosis (23.9%) in 67 of 251 HIV-infected individuals with presumed PCP that could not be confirmed by bronchial alveolar lavage or transbronchial biopsy. As such, NSIP and possibly also FB might mimic PCP in patients with HIV. Although the potential immune reconstitution syndrome following initiation of cART could potentially mimic the case,¹ the patient described in the case had been on cART since September 2013. Unfortunately, we are unable to provide any explanation for the underlying mechanism of FB under the condition of low CD4+ count and low VL.

Since the patient had previously been diagnosed and treated for GPA, relapse of GPA is a relevant differential diagnosis. The symptoms and signs, however, made GPA relapse less likely. Furthermore, PR3-ANCA remained negative on several occasions, and results of lung function tests, HRCT findings and pathology results were not typical for GPA. These findings and the spontaneous improvement without treatment make relapse of previous GPA unlikely.

Learning points

- ▶ Although rare, follicular bronchiolitis (FB) may present in HIV-infected individuals despite complete viral suppression on combination antiretroviral therapy (cART).
- ▶ Immunosuppression due to several factors at the same time, that is, HIV and glucocorticoids, may be a risk factor for FB.
- ▶ FB may clinically mimic obstructive lung diseases.
- ▶ In HIV patients with clinical signs of *Pneumocystis* pneumonia, interstitial lung diseases should be considered as a differential diagnosis

Smoking-related lung diseases, including chronic obstructive pulmonary disease (COPD), emphysema and lung cancer, are the most common lung diseases in HIV-patients following the introduction of cART.^{2–5} Since FB is a small airway disease, it may mimic more common obstructive lung diseases such as COPD. The possibility of FB should thus be kept in mind when the diagnosis of COPD is considered in a patient with HIV.

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REFERENCES

- 1 Calligaro GL, Gray DM. Lung function abnormalities in HIV-infected adults and children. *Respiology* 2015;20:24–32.
- 2 Diaz PT, King MA, Pacht ER, *et al*. Increased susceptibility to pulmonary emphysema among HIV-seropositive smokers. *Ann Intern Med* 2000;132:369–72.
- 3 Crothers K, Butt AA, Gibert CL, *et al*. Increased COPD among HIV-positive compared to HIV-negative veterans. *Chest* 2006;130:1326–33.
- 4 Helleberg M, Gerstoft J, Afzal S, *et al*. Risk of cancer among HIV-infected individuals compared to the background population: impact of smoking and HIV. *AIDS* 2014;28:1499–508.
- 5 Helleberg M, Afzal S, Kronborg G, *et al*. Mortality attributable to smoking among HIV-1-infected individuals: a nationwide, population-based cohort study. *Clin Infect Dis* 2013;56:727–34.
- 6 Travis WD, Fox CH, Devaney KO, *et al*. Lymphoid pneumonitis in 50 adult patients infected with the human immunodeficiency virus: lymphocytic interstitial pneumonitis versus nonspecific interstitial pneumonitis. *Hum Pathol* 1992;23:529–41.
- 7 Morris JC, Rosen MJ, Marchevsky A, *et al*. Lymphocytic interstitial pneumonia in patients at risk for the acquired immune deficiency syndrome. *Chest* 1987;91:63–7.
- 8 Solal-Celigny P, Couderc LJ, Herman D, *et al*. Lymphoid interstitial pneumonitis in acquired immunodeficiency syndrome-related complex. *Am Rev Respir Dis* 1985;131:956–60.
- 9 Lin RY, Gruber PJ, Saunders R, *et al*. Lymphocytic interstitial pneumonitis in adult HIV infection. *N Y State J Med* 1988;88:273–6.
- 10 Grieco MH, Chinoy-Acharya P. Lymphocytic interstitial pneumonia associated with the acquired immune deficiency syndrome. *Am Rev Respir Dis* 1985;131:952–5.
- 11 Yousem SA, Colby TV, Carrington CB. Follicular bronchitis/bronchiolitis. *Hum Pathol* 1985;16:700–6.
- 12 Romero S, Barroso E, Gil J, *et al*. Follicular bronchiolitis: clinical and pathologic findings in six patients. *Lung* 2003;181:309–19.

- 13 Tashtoush B, Okafor NC, Ramirez JF, *et al.* Follicular Bronchiolitis: A Literature Review. *J Clin Diagn Res* 2015;9:Oe01–5.
- 14 Guinee DG. Update on nonneoplastic pulmonary lymphoproliferative disorders and related entities. *Arch Pathol Lab Med* 2010;134:691–701.
- 15 Nicholson AG. Lymphocytic interstitial pneumonia and other lymphoproliferative disorders in the lung. *Semin Respir Crit Care Med* 2001;22:409–22.
- 16 Basu D, Williams FM, Ahn CW, *et al.* Changing spectrum of the diffuse infiltrative lymphocytosis syndrome. *Arthritis Rheum* 2006;55:466–72.
- 17 Centers for Disease Control and Prevention. 1992. MMWR-Recommendations and Reports. <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5710a2.htm>. 41[No. RR-17].
- 18 Shipe R, Lawrence J, Green J, *et al.* HIV-associated follicular bronchiolitis. *Am J Respir Crit Care Med* 2013;188:510–1.
- 19 Theron S, Goussard P. Follicular bronchiolitis in an HIV-positive child. *Pediatr Radiol* 2008;38:1031.
- 20 Exley CM, Suvarna SK, Matthews S. Follicular bronchiolitis as a presentation of HIV. *Clin Radiol* 2006;61:710–3.
- 21 Parnham MJ, Erakovic Haber V, Giamarellos-Bourboulis EJ, *et al.* Azithromycin: mechanisms of action and their relevance for clinical applications. *Pharmacol Ther* 2014;143:225–45.
- 22 Vos R, Vanaudenaerde BM, Verleden SE, *et al.* Anti-inflammatory and immunomodulatory properties of azithromycin involved in treatment and prevention of chronic lung allograft rejection. *Transplantation* 2012;94:101–9.
- 23 Dufour V, Wislez M, Bergot E, *et al.* Improvement of symptomatic human immunodeficiency virus-related lymphoid interstitial pneumonia in patients receiving highly active antiretroviral therapy. *Clin Infect Dis* 2003;36:e127–30.
- 24 Walzer PD, LaBine M, Redington TJ, *et al.* Lymphocyte changes during chronic administration of and withdrawal from corticosteroids: relation to *Pneumocystis carinii* pneumonia. *J Immunol* 1984;133:2502–8.
- 25 Sauma D, Mora JR, Fierro A, *et al.* Low-dose prednisone accounts for a transient reduction on CD4+ and CD8+ T cells in renal transplant patients under triple therapy. *Transplant Proc* 2002;34:3183–4.
- 26 Sattler F, Nichols L, Hirano L, *et al.* Nonspecific interstitial pneumonitis mimicking *Pneumocystis carinii* pneumonia. *Am J Respir Crit Care Med* 1997;156:912–7.

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