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Case report

HTLV-1c associated bronchiolitis in an Aboriginal man from central Australia

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ABSTRACT

We describe the first case of HTLV associated bronchiolitis to be associated with HTLV-1c subtype infection. An Aboriginal man with HTLV-1 infection was repeatedly admitted to Alice Springs Hospital, central Australia, with hypercapnic respiratory failure from the age of 28 years. High resolution CT chest findings were consistent with bronchiolitis and large numbers of lymphocytes were found in bronchoalveolar lavage fluid (BALF). After extensive investigations failed to find a cause, he was tested for HTLV-1 and found to have a high HTLV-1c proviral load (6.8 %) in peripheral blood leukocytes and in BALF (4.7 %). The administration of systemic corticosteroids resulted in a rapid clinical response; however, he did not continue treatment after discharge and died due to respiratory failure in the community.

Case report

A 30-year-old Aboriginal man from central Australia who was infected with the Human T-cell leukemia virus type 1 (HTLV-1) and presented to Alice Springs Hospital with severe acute dyspnea, productive cough and fever. On examination he was febrile (38.2 °C), dyspneic, with tachypnea (respiratory rate, 32 breaths per minute) and hypoxia (oxygen saturation, 42 % on room air). Fingers and toes were clubbed and chest auscultation revealed widespread expiratory wheezes with bibasal coarse crackles. Cardiovascular examination revealed an elevated jugular venous pressure, a loud P2 and peripheral edema. Initial investigations showed that he had hypercapnic respiratory failure with arterial blood gas showing a pO2 of 49.8 mm Hg and pCO2 of 80 mm Hg. Chest high resolution computed tomography (cHRCT) showed centrilobular nodules, patchy ground glass opacity, thickening of bronchovascular bundles and mild bibasal bronchiectasis (Fig. 1). He was admitted to the intensive care unit and treated with non-invasive bi-level positive airway pressure ventilation. Empirical antibacterial for chest infection and high dose corticosteroids (intravenous hydrocortisone 100 mg every 6 hourly) were commenced. However, he did not improve and required invasive ventilation. While intubated, bronchoscopy was performed and bronchoalveolar lavage fluid (BALF) obtained for analysis. This revealed a predominant lymphocytic infiltration (total leukocytes, 4.05×10^5/ml; lymphocytes, 95 %; neutrophils, 5%), and a diagnosis of lymphocytic bronchiolitis was therefore made.

The patient first developed respiratory problems approximately 2 years prior to this presentation. He played competitive Australian Rules football prior to his respiratory symptoms onset. In the previous 2 years, he was hospitalised 4 times with severe acute dyspnea and hypercapnic respiratory failure. On each occasion, he promptly responded to high dose corticosteroids, but was not adherent to corticosteroid therapy as an out-patient.

A final diagnosis of HTLV-1c associated bronchiolitis (HAB) was made on the basis of positive HTLV-1 serology, with a confirmatory HTLV-1 western blot and high HTLV-1 proviral loads (PVL) in peripheral blood (6.8 HTLV-1 DNA copies per 100 peripheral blood leukocytes) and BALF (4.7 HTLV-1 DNA copies per 100 BALF lymphocyte). The HTLV-1 virus in blood and BALF was HTLV-1 subtype C which is endemic to the Indigenous population of

Abbreviations: HTLV, Human T cell leukemia virus; NIV, Non-invasive ventilation; CT, Computed tomography; CTPA, Computed tomography pulmonary angiography; HAB, HTLV associated bronchiolitis; ASH, Alice Springs Hospital; ATL, Adult T cell leukemia-lymphoma.

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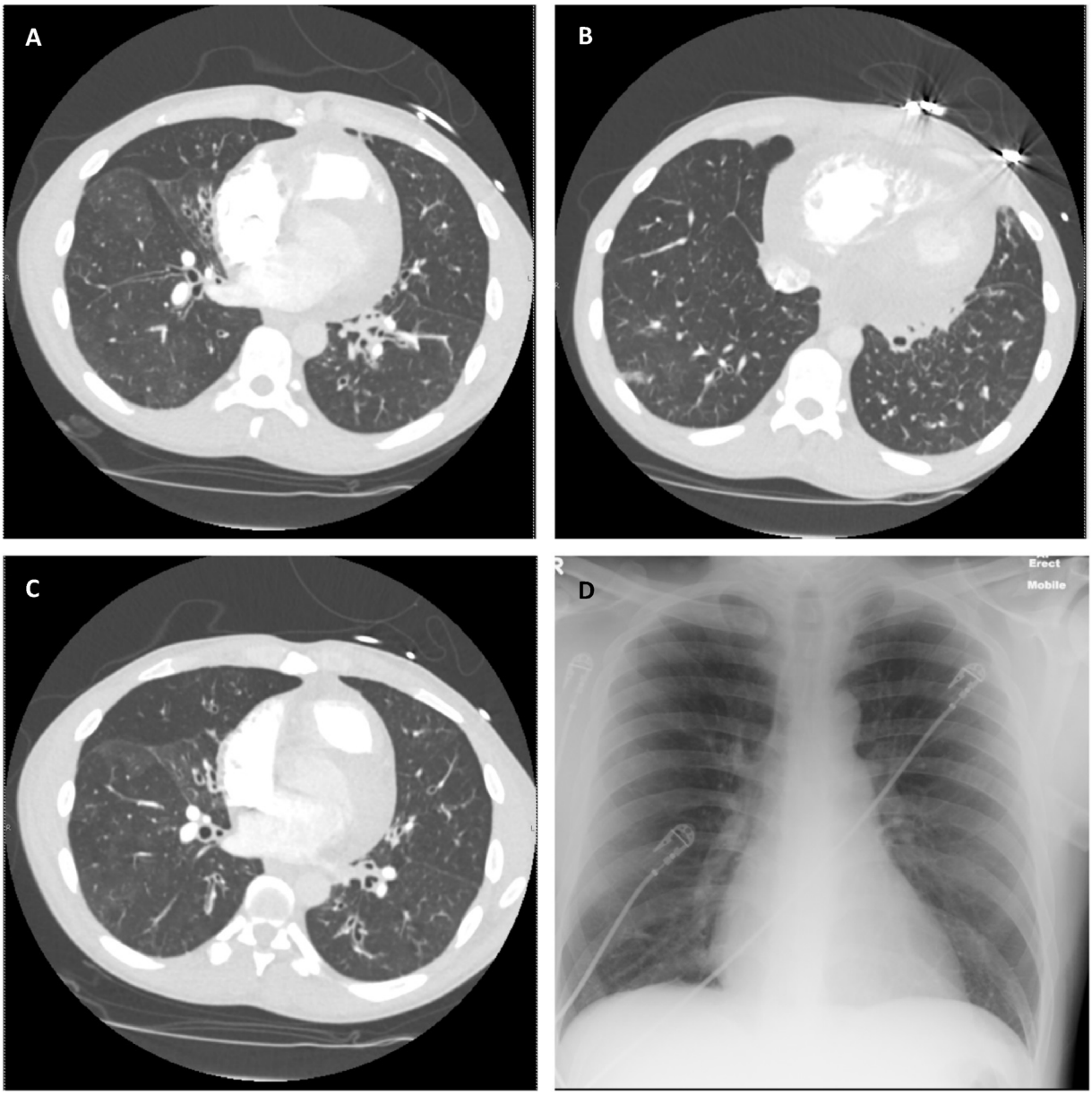

Fig. 1. A, B, C: CT chest showing centrilobular nodules, patchy ground glass opacity, thickening of bronchovascular bundles and bibasal bronchiectasis. D: Bilateral pulmonary micronodules.

central Australia. Extensive investigations excluded other causes of bronchiolitis/bronchiectasis and cardiac investigations failed to find a cardiovascular cause for his right heart failure (Table 1). These findings were consistent with HTLV-1 associated pneumopathy, manifesting as a multi-lobar bronchiolitis and bi-babasal tubular bronchiectasis, complicated by cor pulmonale.

The patient responded well to treatment with intravenous hydrocortisone 100 mg every 6 hourly. He was extubated after 4 days of assisted ventilation, at which time intravenous hydrocortisone was ceased and oral prednisolone 50 mg daily commenced. Unfortunately, he did not attend outpatient follow-up and died in his community 8 months later after again developing respiratory distress and not seeking medical assistance.

Discussion

HTLV-1 is an oncogenic human retrovirus that preferentially infects CD4 + T cells [1]. HTLV-1 infects up to 20 million people worldwide who predominantly dwell in areas of high endemicity in south-western Japan and developing countries of the Carribean basin, South America, and sub-Saharan Africa [2]. An endemic focus is also present in central Australia where infection with the Australo-Melanesian HTLV-1 subtype C is prevalent [4].

Central Australia is a sparsely populated region covering 830,000 km^2. Approximately 40 % of the population are Aboriginal Australians, the majority of which live in isolated remote communities [15]. HTLV-1 is endemic in central Australia and has the highest recorded regional prevalence of HTLV-1 infection worldwide; more than 40 % of adults are infected with HTLV-1 subtype C [4] in some remote Indigenous communities [5]. HTLV-1 is the recognised cause of Adult T cell leukemia-lymphoma (ATL) and HTLV-1 associated myelopathy (HAM) [1]. It is also associate with a range of inflammatory diseases involving the lungs, eye and skin [6]. Risk of complications of HTLV-1 is strongly associated with a higher HTLV-1 PVL [1].

HTLV-1 associated pulmonary diseases include a range of disease entities including alveolitis, bronchiolitis, bronchitis and

Table 1
Other investigation findings.

Pulmonary function tests	Severe obstructive ventilator defect not significantly improved with bronchodilator therapy. Reduce DLco (33 mmol/kPa/min) and increased residual volume(1.8 L). Marked oxygen desaturation at 88 % on room air.
Electrocardiography	Sinus rhythm, P pulmonale
Transthoracic echocardiogram	Ejection fraction 46 %. Dilated right ventricle with reduced function. Mild right ventricular hypertrophy.
Cardiac magnetic resonance imaging	Severe right ventricular systolic dysfunction
Coronary angiography	Minimal coronary artery disease. Less than 20 % circumflex disease. Mild pulmonary hypertension, mean pulmonary artery pressure 24 mm Hg, wedge pressure 7 mm Hg.
Alpha 1 antitrypisin	1.51 g/L (normal)
Human immunodeficiency virus	Negative
Blood cultures (3 sets)	No growth
Pan-respiratory viruses PCR on BALF	No virus detected
BALF mycobacteria cultures	No growth
BALF fungal cultures	No growth
BALF bacterial cultures	Haemophilus influenza
Aspergillus IgE precipitins	Not detected
Immunoglobulins	Total IgG 17.1 g/L (6.50–17.0) IgG1 15.55 g/L (3.40–9.20) IgG2 1.71 g/L (1.40–7.50) IgG3 0.95 g/L (0.20–1.20) IgG4 0.19 g/L (< 1.50)

bronchiectasis [7]. Pathological studies from lung biopsy and autopsy specimens reveal infiltration of small airways by lymphocytes and high numbers of infected lymphocytes have been recovered in BALF [7,8]. Similar to other HTLV-1 associated inflammatory diseases, HTLV-1 associated bronchiolitis (HAB) is thought to be caused by inflammation mediated by HTLV-1-infected $CD4^+$ T cells. Inefficient cytotoxic T lymphocyte response in host leads to pervasive dissemination of HTLV-1 virus in substantial quantity of HTLV-1-infected T-lymphocytes clones, which is reflected in high HTLV-1 PVL [9]. HTLV-1 infected Treg cells produce interferon gamma, which is thought to establish a positive inflammatory feedback loop in affected tissues [10]. This is consistent previous reports that a higher HTLV-1 PVL is associated with more extensive radiologically defined pulmonary injury [11]. The HTLV-1 PVL in our patient was very high (6.8 %) and this was associated with extensive bronchiolitis, which may be the precursor to mild bronchiectasis in this case [9]. A high HTLV-1 PVL predicts death due to bronchiectasis in this population [9,11]. Infection with HTLV-1c significantly increases the risk of bronchiolitis in central Australia [9]; however, this is the first description of the clinical presentation of this condition.

There are currently no guidelines to direct the management of HTLV-1 associated lung diseases. As demonstrated in this case report, HAB responds rapidly to treatment with corticosteroids, which suppress the pro-inflammatory cytokines and chemokines produced by the infected T cells. However, steroid related complications have encouraged the addition of corticosteroids sparing agent in the longer term such as cyclosporine, azathioprine, salazopyrine and methotrexate [16]. Most recently, a Japanese group has demonstrated the efficacy of mogamulizumab (anti-CCR4) as a means to reduce the HTLV-1 PVL and the inflammatory response associated with a high HTLV-1 PVL [13]. Unfortunately, there are no effective antiretroviral agents for HTLV-1 infection which replicates by clonal proliferation in chronic infections [14,16].

In conclusion, this is the first clinical description of HAB resulting from infection with HTLV-1 subtype C. Clinicians should consider HTLV-1 associated pulmonary disease as a potential cause of bronchiolitis in patients with HTLV-1 as treatment with corticosteroids can be lifesaving. There is also a need to better understand the pathogenesis of this condition in order to develop better targeted therapies.

Author statement

The authors have no competing/conflicting interests to declare in this article. Article processing fee for this article was funded by Baker Heart and Diabetes Institute Central Australia, Alice Springs, NT, Australia.

References

[1] Verdonck K, Gonzalez E, Van Dooren S, Vandamme AM, Vanham G, Gotuzzo E. Human T-lymphotropic virus 1: recent knowledge about an ancient infection. Lancet Infect Dis 2007;7(4):266–81.
[2] Gessain A, Cassar O. Epidemiological aspects and world distribution of HTLV-1 infection. Front Microbiol 2012;3:388.
[4] Cassar O, Einsiedel L, Afonso PV, Gessain A. Human T-cell lymphotropic virus type 1 subtype C molecular variants among indigenous australians: new insights into the molecular epidemiology of HTLV-1 in Australo-Melanesia. PLoS Negl Trop Dis 2013;7(9):e2418.
[5] Einsiedel LJ, Pham H, Woodman RJ, Pepperill C, Taylor KA. The prevalence and clinical associations of HTLV-1 infection in a remote Indigenous community. Med J Aust 2016;205(7):305–9.
[6] Martin F, Taylor GP, Jacobson S. Inflammatory manifestations of HTLV-1 and their therapeutic options. Expert Rev Clin Immunol 2014;10(11):1531–46.
[7] Sugisaki K, Tsuda T, Kumamoto T, Akizuki S. Clinicopathologic characteristics of the lungs of patients with human T cell lymphotropic virus type 1-associated myelopathy. Am J Trop Med Hyg 1998;58(6):721–5.
[8] Setoguchi Y, Takahashi S, Nukiwa T, Kira S. Detection of human T-cell lymphotropic virus type I-related antibodies in patients with lymphocytic interstitial pneumonia. Am Rev Respir Dis 1991;144(6):1361–5.
[9] Einsiedel L, Pham H, Wilson K, Walley R, Turpin J, Bangham C, et al. Human T-Lymphotropic Virus type 1c subtype proviral loads, chronic lung disease and survival in a prospective cohort of Indigenous Australians. PLoS Negl Trop Dis 2018;12(3):e0006281.
[10] Yamano Y, Coler-Reilly A. HTLV-1 induces a Th1-like state in CD4(+)CCR4(+) T cells that produces an inflammatory positive feedback loop via astrocytes in HAM/TSP. J Neuroimmunol 2017;304:51–5.
[11] Einsiedel L, Pham H, Au V, Hatami S, Wilson K, Spelman T, et al. Predictors of non-cystic fibrosis bronchiectasis in Indigenous adult residents of central Australia: results of a case-control study. ERJ Open Res 2019;5(4).
[13] Sato T, Coler-Reilly ALG, Yagishita N, Araya N, Inoue E, Furuta R, et al. Mogamulizumab (anti-CCR4) in HTLV-1-associated myelopathy. N Engl J Med 2018;378(6):529–38.
[14] Taylor GP, Goon P, Furukawa Y, Green H, Barfield A, Mosley A, et al. Zidovudine plus lamivudine in Human T-Lymphotropic Virus type-I-associated myelopathy: a randomised trial. Retrovirology 2006;3:63.
[15] Department of Health and Families. Central Australia regional plan 2010–2012. [accessed 10 November 2019].
[16] International Retrovirology Association guidelines for the management of HTLV-1-associated myelopathy/tropical spastic paraparesis; 2018. [accessed 10 Nov 2019].