18. **Robinson M,** Daviskas E, Eberl S, et al. The effect of inhaled mannitol on bronchial mucus clearance in cystic fibrosis patients: a pilot study. Eur Respir J 1999;**14**:678–85.
19. **Jacques A,** Daviskas E, Turton JA, et al. Inhaled mannitol improves FEV$_1$ in cystic fibrosis. Chest 2008;**133**:1388–96.
20. **Rosenstein BJ,** Cutting GR. The diagnosis of cystic fibrosis: a consensus statement. Cystic Fibrosis Foundation Consensus Panel. J Pediatr 1998;**132**:589–95.
21. **American Thoracic Society**. Standardization of Spirometry, 1994 Update. Am J Respir Crit Care Med 1995;**152**:1107–36.
22. **Minasian C,** Wallis C, Metcalfe C, et al. Bronchial provocation testing with dry powder mannitol in children with cystic fibrosis. Pediatr Pulmonol 2008;**43**:1078–84.
23. **Equi A,** Balfour-Lynn IM, Bush A, et al. Long term azithromycin in children with cystic fibrosis: a randomised, placebo-controlled crossover trial. Lancet 2002;**360**:978–84.
24. **Southern KW,** Smyth RL. Design of clinical trials in CF. Lancet 2003;**361**:349–50.
25. **Equi A,** Balfour-Lynn IM, Bush A, et al. Author's reply. Lancet 2003;**361**:350.
26. **Rosenfeld M.** An overview of endpoints for cystic fibrosis clinical trials: one size does not fit all. Proc Am Thorac Soc 2007;**4**:299–301.
27. **Mayer-Hamblett N,** Bamsey BW, Kronmal RA. Advancing cystic fibrosis measures for the new era of drug development in cystic fibrosis. Proc Am Thorac Soc 2007;**4**:370–1.
28. **Suri R,** Metcalfe C, Wallis C, et al. Assessing the usefulness of outcomes measured in a cystic fibrosis treatment trial. Respir Med 2007;**101**:254–60.
29. **Quan JM,** Tiddens HA, Sy JP, et al. A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities. J Pediatr 2001;**139**:813–20.
30. **Daviskas E,** Anderson SD, Eberl S, et al. Effects of increasing doses of mannitol on mucus clearance in patients with bronchiectasis. Eur Resp J 2008;**31**:765–72.

Pulmonary puzzle

Once bitten, twice shy

CLINICAL PRESENTATION

A 46-year-old man of Ethiopian origin was admitted to hospital in 2008 for investigation of cough, increasing dyspnoea and weight loss over several weeks. He was known to be HIV positive. He had a history of several opportunistic infections, including *Cryptosporidium* diarrhoea, tuberculosis, *Mycobacterium avium* complex and *Pseudomonas* pneumonia. He had also been treated in 2005 for visceral leishmaniasis with liposomal amphotericin. His prescribed medication included trimethoprim–suxamethoxazole, clarithromycin, efarinez, lamivudine, zidovudine and folic acid. His compliance with highly active antiretroviral therapy (HAART) was known to be poor.

On physical examination he was afebrile. Aside from moderate tachypnoea (24 respirations/min), his vital signs were normal. General examination showed cachexia and marked parotid swelling. The abdomen was non-tender with hepatosplenomegaly. Cardiac/respiratory examination was normal.

Laboratory testing revealed a normal haemoglobin level (14.4 g/dl), leucopenia (total white cell count 1.46×10^9/l; neutrophils 1.0×10^9/l, lymphocytes 0.3×10^9/l, eosinophils 0.1×10^9/l) and thrombocytopenia (113×10^{12}/l). CD4 count was 34×10^6 cells/l. Other blood tests were within the normal range, except for hypoalbuminaemia and elevated liver enzymes in a cholestatic pattern.
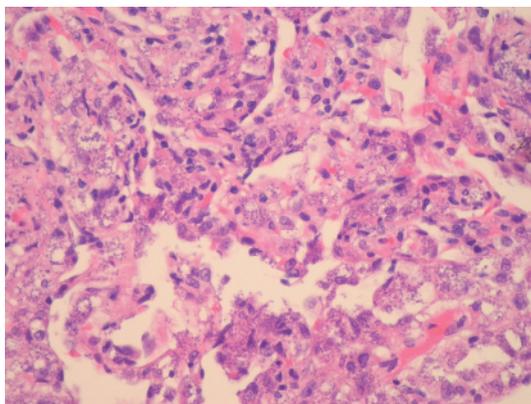

Figure 1 Transbronchial biopsy: the lung parenchyma is heavily infiltrated with mononuclear cells containing a large number of small purple/blue staining structures (H&E stain ×40 magnification).

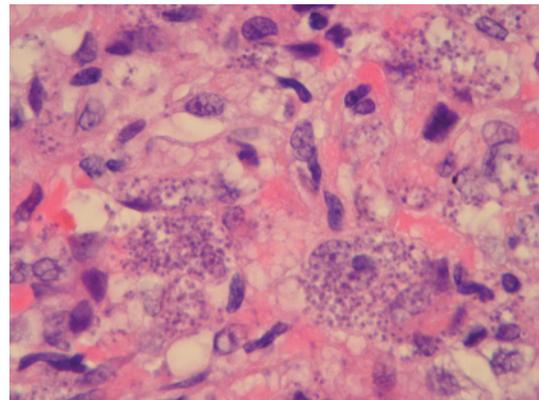**Figure 2** Transbronchial biopsy: as fig 1, but at higher magnification (H&E stain ×100 magnification with oil immersion).

On admission to our institution, the chest radiograph showed diffuse bilateral airspace opacities mainly in the left upper and right lower lobes (Supplementary fig 1 online). CT scan of the thorax performed elsewhere 1 month prior to his admission showed peripheral pulmonary consolidation throughout the left lung and bilateral areas of ground-glass opacities (Supplementary fig 2). Massive hepatosplenomegaly was noted (Supplementary fig 3). A transbronchial biopsy was performed (figs 1 and 2).

QUESTION

What is the diagnosis?

See page 90 for answer

B D Fox,[1] S Morgenstern,[2] A Grubstein,[3] S Pitlik,[4] M R Kramer[1]

[1] Pulmonary Institute, Rabin Medical Center, Beilinson Campus, Petach Tiqwa, Israel; [2] Pathology Institute, Rabin Medical Center, Beilinson Campus, Petach Tiqwa, Israel; [3] Department of Radiology, Rabin Medical Center, Beilinson Campus, Petach Tiqwa, Israel; [4] Internal Medicine C, Rabin Medical Center, Beilinson Campus, Petach Tiqwa, Israel

Correspondence to: Dr B D Fox, Pulmonary Institute, Rabin Medical Center (Beilinson Campus), Petach Tiqwa 49100, Israel; benfox@post.tau.ac.il

26. **Hurst JR,** Kuchai R, Michael P, *et al*. Nasal symptoms, airway obstruction and disease severity in chronic obstructive pulmonary disease. *Clin Physiol Funct Imaging* 2006;**26**:251–6.
27. **Braunstahl GJ,** Overbeek SE, Kleinjan A, *et al*. Nasal allergen provocation induces adhesion molecule expression and tissue eosinophilia in upper and lower airways. *J Allergy Clin Immunol* 2001;**107**:469–76.
28. **Braunstahl GJ,** Overbeek SE, Fokkens WJ, *et al*. Segmental bronchoprovocation in allergic rhinitis patients affects mast cell and basophil numbers in nasal and bronchial mucosa. *Am J Respir Crit Care Med* 2001;**164**:858–65.
29. **Sarin S,** Undem B, Sanico A, *et al*. The role of the nervous system in rhinitis. *J Allergy Clin Immunol* 2006;**118**:999–1016.
30. **Hurst JR,** Wilkinson TM, Donaldson GC, *et al*. Upper airway symptoms and quality of life in chronic obstructive pulmonary disease (COPD). *Respir Med* 2004;**98**:767–70.
31. **Dewan NA,** Rafique S, Kanwar B, *et al*. Acute exacerbation of COPD. Factors associated with poor treatment outcome. *Chest* 2000;**117**:662–71.
32. **McDougall CM,** Blaylock MG, Douglas JG, *et al*. Nasal epithelial cells as surrogates for bronchial epithelial cells in airway inflammation studies. *Am J Respir Cell Mol Biol* 2008;**39**:560–8.
33. **Devalia JL,** Sapsford RJ, Wells CW, *et al*. Culture and comparison of human bronchial and nasal epithelial cells *in vitro*. *Respir Med* 1990;**84**:303–12.
34. **Sridhar S,** Schembri F, Zeskind J, *et al*. Smoking-induced gene expression changes in the bronchial airway are reflected in nasal and buccal epithelium. *BMC Genomics* 2008;**9**:259.
35. **Karatzanis AD,** Samara KD, Tzortzaki E, *et al*. Microsatellite DNA instability in nasal cytology of COPD patients. *Oncol Rep* 2007;**17**:661–5.
36. **Meltzer EO,** Hamilos DL, Hadley JA, *et al*. Rhinosinusitis: developing guidance for clinical trials. *J Allergy Clin Immunol* 2006;**118**(Suppl):S17–61.

Pulmonary puzzle

ANSWER
From the question on page 56

The transbronchial biopsy showed large numbers of mononuclear cells in both bronchial and parenchymal tissue. The mononuclear cells were heavily parasitised with *Leishmania* amastigotes (figs 1 and 2). No granulomas were seen. *Leishmania* spp. were also identified in a parotid aspirate (Supplementary fig 4). Stains and cultures were negative for bacteria, fungi, mycobacteria, *Pneumocystis jirovecii* and cytomegalovirus.

Leishmaniasis is usually spread through sandfly bites, although direct human–human transmission may occur via needle sharing.[1][2] The *Leishmania* parasite resides free in the sandfly digestive tract in the proamastigote form. Upon entering the human host, the parasite is taken up by macrophages where it transforms to the obligate intracellular amastigote stage. Depending on the leishmaniasis species, macrophage traffic patterns and host immunity, the infection may remain localised in the skin (cutaneous leishmaniasis) or may disseminate systemically (visceral leishmaniasis or kala-azar as in this case). The typical systemic spread is throughout the reticuloendothelial system (bone marrow, spleen and liver) although any organ may be affected. Pulmonary involvement with kala-azar is uncommon, with very few cases reported.[3] Diagnosis is usually made by biopsy of the affected organs, although microbiological, serological and PCR techniques exist. Visceral leishmaniasis is treated with pentavalent antimony compounds or amphotericin B.[4]

Patients with advanced HIV disease frequently present with respiratory illness, and the differential diagnosis is extremely wide.[5] Asymptomatic hepatosplenomegaly is a common feature in patients with HIV, although in this clinical context its presence narrows the differential somewhat to cytomegalovirus, toxoplasmosis, leishmaniasis, schistosomiasis, endemic mycoses, *M avium* complex, miliary tuberculosis and HIV-associated lymphoma. The previous treatment for leishmaniasis was a "red-herring" since the parasite is difficult to eradicate completely and may recur, especially in immunosuppressed patients.[1]

REFERENCES
1. **Piscopo TV,** Mallia AC. Leishmaniasis. *Postgrad Med J* 2006;**82**:649–57.
2. **Cruz I,** Morales MA, Noguer I, *et al*. Leishmania in discarded syringes from intravenous drug users. *Lancet* 2002;**359**:1124–5.
3. **Sarker CB,** Chowdhury KS, Siddiqui NI, *et al*. Clinical profile of Kala-azar in adults: as seen in Mymensingh Medical College Hospital, Mymensingh, Bangladesh. *Mymensingh Med J* 2003;**12**:41–4.
4. **Alvar J,** Aparicio P, Aseffa A, *et al*. The relationship between leishmaniasis and AIDS: the second 10 years. *Clin Microbiol Rev* 2008;**21**:334–59.
5. **Huang L,** Stansell J. Pulmonary complications of human immunodeficiency virus infection. In: Mason RJ, Broaddus VC, Murray JF, *et al*, eds. *Murray and Nadel's textbook of respiratory medicine*. 4th edn. Philadelphia, PA: Elsevier Saunders, 2005:2111–62.