Hazards of the 'hard cash': Hypersensitivity pneumonitis

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Hypersensitivity pneumonitis (HP) is a nonimmunoglobulin E-related immune-mediated parenchymal lung disease. A 45-year-old woman who was a lifelong nonsmoker with a six-month history of frequent episodes of cough and dyspnea was admitted to hospital. She had been working as a money counter for 20 years at a central bank. Bibasilar crackles on lung auscultation, ground-glass opacities and a mosaic pattern on high-resolution computed tomography, restrictive abnormality on pulmonary function tests and mild hypoxemia were the prominent findings. Bronchoalveolar lavage fluid analysis revealed a predominance of CD4-positive T cells, and she tested positive on her natural challenge test. She was diagnosed with subacute HP based on established criteria. She was advised to discontinue counting fresh banknotes. Prednisolone was commenced, then tapered to discontinue in the ensuing six months. Clinical and radiological improvement was achieved within two months. To the authors' knowledge, the present report is the first to describe 'hard cash HP', possibly caused by chipping dust or printing dye.

Key Words: *BAL; Hard cash; Hypersensitivity pneumonitis; Interstitial lung diseases*

Les dangers de la monnaie : La pneumopathie d'hypersensibilité

La pneumopathie d'hypersensibilité (PH) est une maladie parenchymateuse pulmonaire à médiation immune non liée à l'immunoglobuline E. Une femme de 45 ans qui n'avait jamais fumé, mais qui avait de fréquents épisodes de toux et de dyspnée depuis six mois a été hospitalisée. Elle travaillait comme compteuse d'argent dans une banque centrale depuis 20 ans. Des crépitations bibasilaires à l'auscultation pulmonaire, une hyperdensité en verre dépoli et un motif en mosaïques à la tomodensitométrie à haute résolution, des anomalies restrictives aux explorations fonctionnelles respiratoires et une hypoxémie bénigne étaient les principales observations. L'analyse du liquide de lavage bronchoalvéolaire a révélé une prédominance de lymphocytes T positifs aux molécules CD_4, et le test de provocation naturelle s'est révélé positif. On a diagnostiqué une PH subaiguë d'après les critères établis. On lui a conseillé d'arrêter de compter des billets de banque neufs. On a entrepris un traitement de prednisolone, dont on a ensuite progressivement réduit la dose pour l'arrêter au cours des six mois suivants. On a constaté une amélioration clinique et radiologique au bout de deux mois. En autant que le sache l'auteur, le présent rapport est le premier à décrire une PH à la monnaie de papier, peut-être causée par la poussière d'effritement ou la teinture d'impression.

Patients with hypersensitivity pneumonitis (HP) may present with a wide variety of clinical findings depending on the nature of the inhaled dust, the immunological response of the host, and concomitant bacterial or viral infections. HP can be categorized into acute, subacute and chronic forms according to clinical presentation and radiological findings (1-4).

We present a case involving a 45-year-old woman, who worked as a money counter and was diagnosed with subacute HP due to exposure to freshly minted banknotes – an occupation that has not been previously linked with HP.

CASE PRESENTATION

A 45-year-old woman who was a lifelong nonsmoker was admitted with a six-month history of recurrent bouts of productive cough and dyspnea. She had been working as a money counter for 20 years at a central bank. She complained of strong odour and dust, especially while counting freshly minted banknotes, that was often followed by dry cough and chest tightness. She denied any other occupational exposure, contact with birds or animals, or having peculiar hobbies.

The bank notes she handled were delivered directly from the mint, stored in the vault and were never in the general circulation. However, details regarding the exact date of printing of the notes were not available. The vault maintained a constant temperature, with humidity at 38%. In earlier years, she counted all notes manually; for the past five to six years, the notes were being counted by a machine and manually. Her workplace was centrally air conditioned, with a humidifier in close proximity to her desk. Her job was unique in nature and no other coworker reported similar symptoms.

Her physical examination was normal except for bibasilar fine crackles on auscultation of her lungs. On laboratory analysis, her C-reactive protein (CRP) and immunoglobulin (Ig) G levels were high (77 mg/L and 236 g/L, respectively). A chest x-ray (CXR) showed bilateral reticulonodular infiltration predominantly involving the middle and lower zones of the lung. High-resolution computed tomography (HRCT) demonstrated ground-glass opacities involving bilateral upper lobe apical and apicoposterior segments (Figure 1); lower lobe basilar segments were involved and demonstrated a mosaic pattern.

Pulmonary function tests (PFTs) revealed mild restriction (forced expiratory volume in 1 s of 75% predicted, forced vital capacity of 78% and a forced expiratory volume in 1 s/forced vital capacity ratio of 81) and a normal diffusion capacity. She had mild hypoxemia (PO_2 = 68 mmHg) while breathing ambient air.

Diagnostic bronchoscopy exhibited edematous bronchial mucosa involving both endobronchial trees. Bronchoalveolar lavage (BAL) fluid analysis revealed lymphocytosis (80%) with a predominance of CD4-positive ($CD4^+$) T cells. Transbronchial lung biopsy revealed a very small fragment of lung tissue with lymphoctes bundled in the interstitial septae, without any granuloma formation, along with a small fibrotic area.

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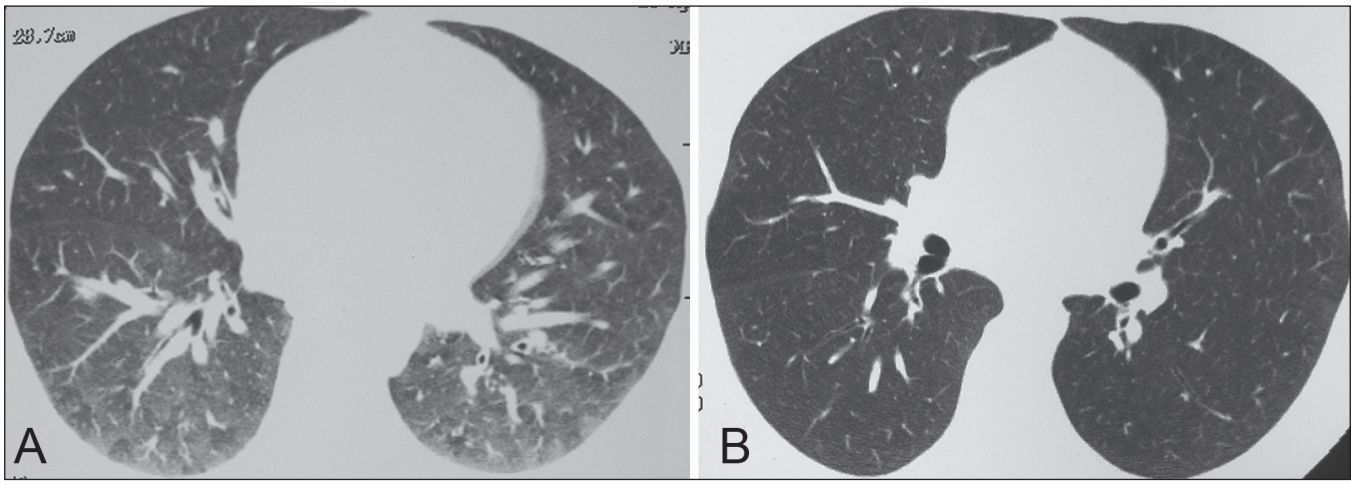

Figure 1) *High-resolution computed tomography scan of the patient before treatment* (**A**). *Ground-glass opacities involving bilateral upper lobe apical and apicoposterior segments, lower lobe basilar segments showed a mosaic pattern. Total resolution of the infiltrates were seen after treatment* (**B**)

Because the antigen that caused HP was unknown in the present case, a natural challenge test was performed by re-exposing the patient to a suspected antigen in her natural environment. Her peak expiratory flow rates (PEFRs) were checked at the beginning (morning) and at the end of the work day (evening) for one week. The values were best in the early mornings (75% of predicted), became worse as the day progressed and were worst at the end of the week (60% of predicted), thus confirming the relationship between her occupation and her symptoms (Figure 2).

A diagnosis of subacute HP was verified according to the established major and minor criteria (Table 1). She was prescribed prednisolone 1 mg/kg/day to be tapered to discontinue within the following six months. She was also advised to avoid exposure to freshly minted banknotes. HRCT performed after two months of therapy revealed total resolution of the lung infiltrates (Figure 1B). After three months of therapy, she retired and her PEFRs have remained optimal over the duration of her follow-up.

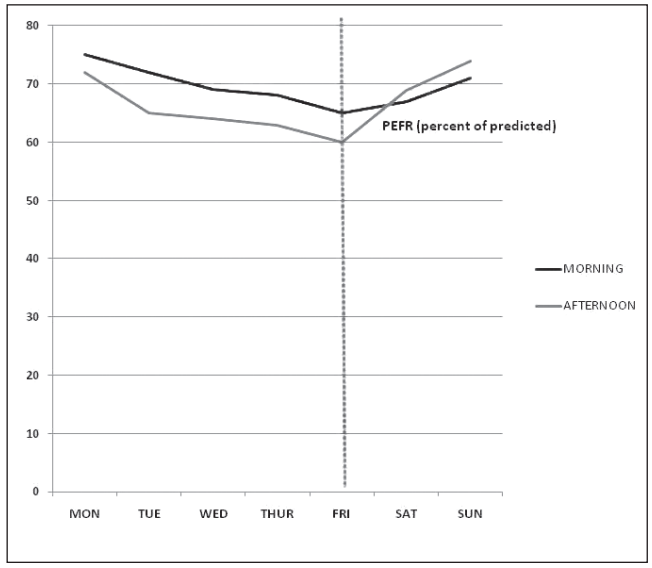

Figure 2) *Natural challenge test. Note the higher per cent of predicted peak expiratory flow rate (PEFR) in the morning versus evening, and on Monday (Mon) versus Friday (Fri)*

DISCUSSION

HP represents a heterogeneous group of diseases resulting from repeated inhalation of and sensitization to various dispersed antigens (1-5). Patients with HP may present with a variety of clinical abnormalities (5). Clinically, HP can be categorized into three different forms (1,4,6-8).

Acute HP typically occurs after a high-level, intermittent exposure to the offending antigen over a short period of time. Subacute HP is characterized by the gradual development of symptoms that occur during weeks to months after repeated low-level exposure. Chronic HP may develop in different settings – either chronic insidious or chronic recurrent HP. The former involves continuous long-term, low-level antigen exposure leading to irreversible pulmonary damage without major acute attacks. There may be a delay in seeking medical care for several months or years after illness onset (1,4,8-10). Physical examination often reveals fine crackles; clubbing can be seen in 20% to 50% of patients. Pulmonary hypertension or cor pulmonale develops in only advanced stages of chronic HP (1,8-11). Our patient worked at a bank as a money counter for many years, with low-level antigen (printing dye or typesetting water) exposure. Over the years, she was hospitalized on several occasions with respiratory symptoms, and received subjective treatment. With low-dose antigen exposure over many years, we suspected she developed subacute HP. An environmental exposure challenge test and cessation of exposure to the suspected offending agent further supported our diagnosis.

Combinations of several subjective and objective parameters are essential in most patients to establish a conclusive diagnosis. The recommended criteria for the diagnosis are listed in Table 1 (1,7,8). There is usually a marked blood neutrophilia and lymphopenia in acute HP. Elevation of CRP, erythrocyte sedimentation rate and serum lactate dehydrogenase may be present. Elevated rheumatoid factor may be detected in more than 50% of patients. Increased serum IgA, IgG and IgM levels have been reported in HP patients (1,2,4). Our patient

TABLE 1
Diagnostic criteria for hypersensitivity pneumonitis (HP)

Major criteria (four major criteria should be presented)
History of symptoms compatible with HP
Evidence of exposure to the offending antigen by history or through detection in serum or bronchoalveolar lavage fluid antibody
Changes characteristic of HP on chest radiograph (reticulonodular infiltrates, linear opacities) or high-resolution computed tomography of the chest (ground-glass opacities, micronodules, honeycombing, linear opacities, airtrapping)
Demonstration of bronchoalveolar lavage fluid lymphocytosis, if bronchoalveolar lavage analysis is performed
Demonstration of histological changes consistent with HP, if lung biopsy is performed, such as alveolitis, noncaseating granulomas, giant cells, foamy alveolar machrophages or fibrosis
Positive 'natural challange' that produces symptoms and objective abnormalities either through controlled inhalational challange or after re-exposure to the offending environment
Minor criteria (two minor criteria should be presented)
Bibasilar rales
Decreased diffusion capacity
Arterial hypoxemia either at rest or with exercise

consistently matched these criteria and also had elevated levels of CRP and IgG.

Specific serum precipitating antibodies are found in many patients with HP (7,9). The presence of these antibodies indicates exposure and sensitization to respective antigens, but not necessarily the presence of the disease. It should be noted that 40% to 50% of asymptomatic individuals exposed to the same antigens will also have serum IgG antibodies. For the diagnosis of HP, the precipitin test is reasonably sensitive, but it is nonspecific and should be ordered selectively (7,9,10,12). Because the actual antigen was unknown, we were unable to detect precipitating antibodies. Instead, a natural challenge test was performed by exposing the patient to the offending environment, which led to the diagnosis of hard cash HP.

Restrictive patterns with a decrease in diffusion capacity, hypoxemia and bronchial hyper-reactivity due to bronchiolitis can be encountered in patients with HP. Early diagnosis and avoidance of antigen exposure are the mainstays of treatment (1-4,7,10,13). Our patient showed a mild restriction, with unaffected diffusion capacity along with hypoxemia at rest due to impaired gas exchange compatible with the findings seen in patients with HP. Avoidance of exposure to the antigen resulted in improvement in her symptoms and PEFR. There has been no recurrence of her symptoms since her retirement.

Radiographic findings in HP correlate with the stage of the disease. In subacute form, fine linear or reticulonodular infiltrates can be found on CXR; however, normal CXR findings can also be seen in the acute form of HP (1-4). HRCT features include centilobular nodules associated with larger areas of ground-glass opacity as well as air trapping and mosaic pattern. Occasionally, thin-walled cysts can be noticed in patients with subacute HP. The sensitivity of HRCT for the diagnosis of HP is greater than that of CXR (14-17). The present case demonstrated ground-glass attenuation in a mosaic pattern and centrilobular nodules on HRCT.

Analysis of BAL fluid reveals lymphocytosis of predominantly $CD8^+$ T cells with a decrease in the $CD4^+/CD8^+$ ratio. However, BAL findings may vary depending on clinical presentation, the timing of the most recent antigen exposure and the attainment of BAL fluid. A predominant accumulation of $CD8^+$ T cells seems to be a feature in acute or subacute HP, whereas a prevalent elevation of $CD4^+$ T cells is found in the chronic form of the disease (1-4,8-9). The present patient demonstrated lymphocytic BAL fluid with $CD4^+$ T cell predominance, suggesting chronic exposure to the antigen over many years. She may have been demonstrating a transition from the subacute form, slowly converting to the chronic phase based on her BAL findings.

The characteristic histopathological findings of subacute HP are diffuse interstitial infiltrates with lymphocytes, macrophages, mast and plasma cells, scattered noncaseating granulomas and cellular inflammation of bronchioles – findings seen in 50% to 75% of patients. Other typical histopathological findings in the subacute form of HP are plasma cells, mast cells and foamy alveolar machrophages. Fifteen per cent to 25% of patients may exhibit bronchiolitis obliterans with organizing pneumonia on biopsy (1-4). Surgical biopsy may be misleading if considered in isolation and without the integration of clinical and radiological information. In HP, it is now known that the typical histological appearances are absent only in a minority of cases (18). In the present case, although we could not capture the granulomas in the transbronchial lung biopsy, clinical and radiological findings helped us to establish the diagnosis.

Parenteral steroids are indicated for patients with abnormal PFTs and radiographs, or with hypoxemia. They have been shown to improve symptoms and hypoxemia, and not to affect long-term prognosis (1-4,7,10). In our patient, oral prednisolone 1 mg/kg/day was started and tapered within six months. In the second month of treatment, her improvement both clinically and radiographically was dramatic.

CONCLUSION

The present case fulfills the diagnostic criteria for HP according to medical history, evidence of exposure to the antigen, physical findings, PFTs, hypoxemia on blood gases, demonstration of BAL fluid lymphocytosis, and compatible histological changes as well as a positive natural challenge test. To our knowledge, HP from an exposure to freshly minted banknotes (hard cash HP) has not been previously reported. In the literature we found a condition similar to that of the present case – 'Bible printer's lung' (19,20) – in which the offending antigen was mouldy typesetting water/printing dye. We believe that either the printing dye or the paper dust could have been the culprit in the development of 'hard cash HP' the present case.

REFERENCES

1. Kurup VP, Zacharisen MC, Fink JN. Hypersensitivity pneumonitis. Indian J Chest Dis Allied Sci 2006;48:115-28.
2. Bertorelli G, Bocchino V, Oliveri D. Hypersensitivity pneumonitis. Eur Respir Mon 2000;14:120-36.
3. Costabel U, Guzman J. Less common diseases: Hypersensitivity pneumonitis. In: Baugman RP, Du Bois RM, Lynch JP, Wells AU, eds. Diffuse Lung Disease. A Practical Approach. London: Arnold, 2004:203-12.
4. Selman M. Hypersensitivity pneumonitis: A multifaceted deceiving disorder. Clin Chest Med 2004;25:531-47.
5. Burge PS, Finnegan M, Horsfield N, et al. Occupational asthma in a factory with a contaminated humidifier. Thorax 1985;40:248-54.

6. Lacasse Y, Selman M, Costabel U, et al. Clinical diagnosis of hypersensitivity pneumonitis. Am J Respir Crit Care Med 2003;168:952-8.
7. Schuyler M, Cormier Y. The diagnosis of hypersensitivity pneumonitis. Chest 1997;111:534-6.
8. Patel AM, Ryeu JH, Reed CH. Hypersensitivity pneumonitis: Current concepts and future questions. J Allergy Clin Immunol 2001;108:661-70.
9. Sharma OP, Fujimura N. Hypersensitivity pneumonitis: A non-infectious granulomatosis. Semin Respir Infect 1995;10:96-106.
10. Fink JN. Hypersensitivity pneumonitis. Chest 1992;13:303-9.
11. Ohtani Y, Saiki S, Sumi Y, et al. Clinical features of recurrent and insidious chronic bird fancier's lung. Ann Allergy Asthma Immunol 2003;90:604-10.
12. Erkinjuntti-Pekkanen R, Reiman M, Kokkarinen JI. IgG antibodies, chronic bronchitis and pulmonary function values in farmer's lung patients and matched controls. Allergy 1999;54:1181-7.
13. Küpeli E, Karnak D, Kayacan O, Beder S. Clues for the differential diagnosis of hypersensitivity pneumonitis as an expectant variant of diffuse parenchymal lung disease. Postgrad Med J 2004;80:339-45.
14. Lynch DA, Rose CS, Way D, King TE. Hypersensitivity pneumonitis: Sensitivity of high-resolution CT in a population based study. AJR Am J Roentgenol 1992;159:469-72.
15. Gotway MB, Reddy GP, Webb WB, Elicker BM, Leung JWT. High-resolution CT of the lung: Patterns of disease and differential diagnosis. Radiol Clin North Am 2005;43:513-42.
16. Glazer CS, Rose CS, Lynch DA. Clinical and radiologic manifestations of hypersensitivity pneumonitis. J Thorac Imaging 2002;17:261-72.
17. Silva CSS, Müller NL, Lynch DA, et al. Chronic hypersensitivity pneumonitis: Differentiation from idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia by using thin-section CT. Radiology 2008;246:288-97.
18. Branley HM, Egan JJ, Greaves MS, et al. British Thoracic Society Interstitial Lung Disease Guideline Group, British Thoracic Society Standards of Care Committee; Thoracic Society of Australia; New Zealand Thoracic Society; Irish Thoracic Society. Interstitial lung disease guideline: The British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax 2008;63(Suppl 5):v1-58.
19. Schueter DP. Infiltrative lung disease hypersensitivity pneumonitis. J allergy Clin Immunol 1982;70:50.
20. Selman M. Hypersensitivity pneumonitis. In: Schwarz MI, King TE, eds. Interstitial Lung Diseases. Hamilton: BC Decker, 1998:393-422.