Recurrent flu-like illness with migrating pulmonary infiltrates of unknown aetiology

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Migrating pulmonary infiltrates present a difficult diagnostic and therapeutic challenge. We report on eight patients (mean age 51 years, range 32–78 years), with a prolonged history of migrating pulmonary infiltrates of unknown aetiology despite a very elaborate search for infectious causes, hypersensitivity pneumonitis or inhalation fever due to occupational or domestic exposure to fungi, or to other environmental causes, and for humoral or cellular immunological incompetence. These patients (one male, seven females) presented with recurrent episodes (mean 6, range 2–13) of a flu-like illness, often with cough, wheezing and pleuritic chest pain, but without systemic involvement. Previous medical histories were unremarkable. There was no relation with smoking habits, occupation, drug use or other possible exposures. Biochemical data were non-specific. There was no peripheral nor pulmonary eosinophilia; total IgE was normal, with negative RASTs and precipitins to a variety of antigens. Cultures and serological tests for bacteria, viruses, fungi, etc were non-contributory. Chest X-ray and computed tomography (CT) scan showed bilateral migratory pulmonary infiltrates, with a predilection for the middle and lower lung zones, often with a minor-to-moderate pleural effusion. Lung function tests were usually normal; at the most a slight decrease in diffusing capacity was noted in some patients. There was no or only a slight response to antimicrobials; systemic corticosteroids were not given. Further evolution was benign with patients being asymptomatic between the episodes. Despite elaborate investigations, the cause of these ‘pneumonias’ remains frustratingly unknown.

Key words: migrating infiltrates; pneumonitis; flu-like illness.

Introduction

‘Recurrent’ pulmonary opacities, i.e. clearing followed by a return of pulmonary opacities in the same lung zones, are well recognized in certain diseases: for example, chronic eosinophilic pneumonia, partially treated bacterial pneumonia and endobronchial obstructions impairing airway clearance.

There are, however, only few diseases in which fleeting or migratory pulmonary infiltrates are common, and often they present a difficult diagnostic and therapeutic challenge. This is seen in syndromes associated with peripheral and/or pulmonary eosinophilia (simple pulmonary eosinophilia or Loffler’s syndrome, hypersensitivity to drugs, parasitic infections or fungus-induced), and in Wegener and Churg-Strauss vasculitis. Fleeting infiltrates have also been noted in several case series of idiopathic bronchiolitis obliterans with organizing pneumonia (BOOP). Nevertheless, it can be very difficult to make a definite diagnosis because sometimes all tests remain inconclusive despite very extensive investigations.

We report on eight selected patients (mean age 51 years, range 32–78 years) with a history of migrating pulmonary infiltrates. In these cases a definite diagnosis could not be made despite elaborate search for a specific cause, especially for infections, for immunological or toxic reactions to environmental agents, and for collagen vascular diseases. We followed most of them over a period of several years and they all had a benign evolution and were asymptomatic between the episodes.

Review of cases

We retrospectively reviewed the records of all patients with flu-like illness and recurring infiltrates presenting at our outpatient clinic over a period of 6 years. In most of them a definite diagnosis could be made, which mostly was diffuse interstitial lung disease (especially idiopathic interstitial pneumonia or associated with collagen vascular disease), infection, hypersensitivity pneumonitis or another form of inhalation pathology or drug reaction, and sometimes...
eosinophilic pneumonia or migratory BOOP (e.g. after chest wall irradiation for breast tumour).

In eight patients, i.e. about one-fifth of these cases with flu-like illness and recurring infiltrates, no final diagnosis could be made. In general, each of the insults in these eight patients were less debilitating than those which had led to a specific diagnosis and especially no residual abnormalities could be retained. These eight ‘idiopathic’ forms of flu-like illness and recurring infiltrates are briefly described in the following paragraphs.

CASE 1
A 59-year-old housewife experienced three acute episodes of a flu-like illness, with high fever (38.5°C), wheezing and pleuritic chest pain. Radiological examination showed bilateral reticulomicronodular infiltrates on chest X-ray, most often in the lower lung zones (Fig. 1) and patchy consolidation in the posterior lung zones on CT scan (Fig. 2). The total amount of cells in the bronchoalveolar lavage (BAL) fluid was slightly increased (372,093 ml⁻¹), with a predominance of neutrophils (37%) and lymphocytes (48.5%), and a CD4/CD8 ratio of 2.44. The diffusing capacity was slightly decreased during acute exacerbations (77% predicted).

Environmental, mainly mycological, investigations by the Institute of Public Health revealed no specific findings.

CASE 2
A 43-year-old housewife reported at least four acute episodes of a flu-like illness, with high fever (38.5°C), dyspnoea, wheezing and pleuritic chest pain, over the last 2 years. We noted bilateral infiltrates in the middle and lower lung zones, with a moderate pleural effusion. The total amount of cells in BAL fluid was slightly increased (311,429 ml⁻¹), with a predominance of macrophages (93%). Lung function tests were normal. There was a mild hypoxaemia (PO₂: 69 mmHg) with an increased A–aO₂ gradient (38.9 mmHg), during one acute episode.

CASE 3
A 78-year-old housewife experienced two acute episodes of a flu-like illness, with anorexia and weight loss, general
weakness and fatigue. Respiratory symptoms (dyspnoea, cough) were of minor importance. Bilateral migrating infiltrates were noted in the middle and lower lung zones with a BOOP-like consolidation in the left dorsobasal segments, and a moderate pleural effusion. There was a mild decrease in diffusing capacity (74% predicted) during acute episodes. Arterial blood gases revealed a mild hypoxaemia (PO₂: 72 mmHg) with a discrete increase of the A–aO₂ gradient (26-6 mmHg).

CASE 4
A 54-year-old housewife experienced six acute episodes of a flu-like illness, with low-grade fever (37.5°C), fatigue and sometimes also pleuritic chest pain. Again, respiratory symptoms were of minor importance. Pulmonary X-ray and CT scan showed bilateral migrating infiltrates, especially in the middle and lower lung zones, with a moderate pleural effusion. Lung function tests were normal. Environmental studies by the Institute of Public Health revealed no specific abnormalities.

CASE 5
A 32-year-old female dentist reported 13 acute episodes of a flu-like illness, with high fever (38.5°C), dyspnoea, wheezing and pleuritic chest pain. There were bilateral migrating patchy infiltrates in the middle and lower lung zones (Fig. 3), sometimes with a discrete pleural effusion. BAL fluid examination showed a normal amount of cells, with a normal differentiation. Lung function tests were also normal.

There was no correlation with professional activities; radio-allergo sorbant tests (RASTs) on isocyanates were all negative. Environmental studies by the Institute of Public Health revealed the presence of different fungi in several rooms of the house. However, serological tests remained negative and we could not demonstrate a lymphocytic alveolitis. Furthermore, the last episodes occurred after she had moved to another house.

CASE 6
A 65-year-old female, a former administrative worker, experienced three episodes of a flu-like illness, with fever (38°C), fatigue and only minor respiratory symptoms. There were again bilateral migrating infiltrates in the middle and lower lung zones (Fig. 4). BAL evaluation showed a marked increase of the total amount of cells (539·189 ml⁻¹), with a lymphocytic predominance (49%) and an eosinophilia of 6·5. The CD4/CD8 ratio was 0·5. The eosinophil count in the peripheral blood was not elevated (0%). Lung function tests were normal. There was no hypoxaemia and the A–aO₂ gradient was not increased. Thoracoscopic lung biopsies revealed an infiltration with mononuclear cells, mostly lymphocytic, and one small epithelioid granuloma.

Environmental studies by the Institute of Public Health revealed no specific findings.

CASE 7
A 36-year-old female dentist experienced 12 acute episodes of a flu-like illness, with fever (38.5°C), a dry cough and pleuritic chest pain. Radiological evaluation revealed rather diffuse migrating infiltrates, with moderate pleural effusion. BAL evaluation showed a normal amount of cells, with a normal differentiation. Lung function tests were normal. There was no correlation with professional activities. Environmental studies by the Institute of Public Health revealed no specific findings.

CASE 8
A 40-year-old sports teacher experienced nine episodes of a flu-like illness, with fever, mild dyspnoea and pleuritic chest pain. Pulmonary X-ray and CT scan showed migrating infiltrates, mostly in the middle or lower lung zones at the left (Fig. 5) or at the right. BAL evaluation showed a normal amount of cells, with a normal differentiation. Lung function tests were normal.

Environmental studies by the Institute of Public Health revealed no specific findings.

Results
PATIENT CHARACTERISTICS
We studied eight selected patients, one male and seven females, with a mean age of 51 years (range 32–78 years) (Table 1). They all presented with repeated flu-like illnesses which included fever in all but one, sometimes also shortness of breath, cough with occasional production of purulent sputum, often wheezing (cases 1, 2 and 5) and pleuritic chest pain (cases 1, 2, 4, 5, 7 and 8).
Furthermore there was myalgia and arthralgia, general fatigue, anorexia and minimal weight loss. Crackles were not noted.

Previous medical histories were unremarkable. There was no relation with smoking habits, occupation, hobbies or contact with pets, including birds.

There was no history or evidence of exposure to medications, risk factors for human immunodeficiency virus infection, or recent travel. In two dentists (cases 5 and 7) there was a professional exposure to chemicals including isocyanates, but the flu-like symptoms also occurred outside the working environment in both cases.
Laboratory data were non-specific (Table 2): inflammatory parameters were not raised, there was no eosinophilia in the peripheral blood, total IgE was normal, with negative RASTs on occupational allergens, house mite, pollen and fungi, and negative precipitins for fungi and avian proteins.

Mild hypoxaemia was present in two of five patients in whom arterial blood gases were measured. The alveolar–arterial oxygen gradient was normal, except in these two patients with mild hypoxaemia, in whom it was slightly elevated.

We could not demonstrate any abnormality in the cellular or humoral immune response.

**MICROBIOLOGY**

In all patients at least two blood cultures had been obtained before a possible antibiotic therapy was started. If available, sputum was collected and in six patients BAL was performed. Blood, sputum and lung aspirates were sent for conventional cultures as well as for selective culture for mycobacteria (Löwenstein-Jensen). Gram-, Ziehl–Neelsen and silver stain was obtained from every sample. Antigen detection tests and specific cultures for respiratory viruses (adenovirus, herpes virus, RSV, influenza virus, para-influenza virus) were performed on BAL fluid, as well as silver stain and immunofluorescence testing for *P. carinii*, and direct fluorescent antibody (DFA) test for detection of *Legionella* antigen. Acute and convalescent sera were tested by immunofluorescence for IgG antibodies to *Mycobacterium pneumoniae* and by microimmunofluorescence for IgG antibodies to *Chlamydia pneumoniae*. Polymerase chain reaction (PCR) techniques were not used. All these microbiological tests were non-contributory (Table 3).

**RADIOLOGY**

Chest radiograph and CT scan were performed in all eight patients. They both showed migratory infiltrates possibly in both lungs, with a predilection for the middle and lower lung zones. In five patients (62%), a moderate pleural effusion was noted.

Sinus X-ray or CT scan was performed in seven patients and never showed any inflammatory changes or other abnormalities.
LUNG FUNCTION TESTS

Lung function, including volumes [vital capacity (VC), forced expiratory volume in 1 sec (FEV\(_1\)), total lung capacity (TLC)] and diffusing capacity (DL\(_{CO}\)), was measured according to the guidelines of the European Respiratory Society (ERS) (1,2), and expressed in percentage of the predicted values proposed by the ERS (2).

The results of these tests were mostly normal (Table 4). In two patients, a slight decrease in the diffusing capacity was noted during an acute phase of their pulmonary disease, although not consistently during each exacerbation. After the acute episode, the diffusing capacity always returned to normal values.

BRONCHOALVEOLAR LAVAGE

Lavage with 4 × 50 ml saline was performed in six patients. Immunological evaluation of the BAL fluid showed variable results (Table 5): the total amount of cells was raised in only two patients, with most often a predominance of macrophages. In two patients (cases 1 and 6) we noted a preponderance of lymphocytes (49%) with a decreased CD4/CD8 ratio (0-5%) and some eosinophilia (6-5%) in one of these two patients.

Neither microbiological agents nor other foreign substances were found. Neither could we demonstrate any sign of malignancy.

HISTOLOGY

Transbronchial biopsies were performed in five patients (cases 1, 3, 6, 7 and 8) and never showed any specific abnormality. One patient (case 6) underwent a video-assisted thoracoscopy, during which several lung biopsies were taken. These revealed an infiltration with mononuclear cells, mostly lymphocytic, and one small non-specific epithelioid granuloma.

### Table 3. Microbiology

<table>
<thead>
<tr>
<th>Cultures (bacteria, fungi, mycobacteria, viruses)</th>
<th>Sputum</th>
<th>BAL</th>
<th>Blood</th>
<th>Pleural fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycoplasma pneumoniae</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Serology</td>
<td></td>
<td></td>
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<tr>
<td>Tuberculin skin test</td>
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</tbody>
</table>

### Table 4. Lung function tests (during acute exacerbations)

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
<th>Patient 7</th>
<th>Patient 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV(_1) (% predicted)</td>
<td>85</td>
<td>95</td>
<td>90</td>
<td>91</td>
<td>105</td>
<td>108</td>
<td>84</td>
<td>101</td>
</tr>
<tr>
<td>TLC (% predicted)</td>
<td>114</td>
<td>129</td>
<td>89</td>
<td>111</td>
<td>98</td>
<td>93</td>
<td>104</td>
<td>107</td>
</tr>
<tr>
<td>DL(<em>{CO})/K(</em>{CO}) (% predicted)</td>
<td>77/66</td>
<td>81/77</td>
<td>74/101</td>
<td>85/90</td>
<td>87/91</td>
<td>89/93</td>
<td>87/81</td>
<td>110/113</td>
</tr>
</tbody>
</table>

### Table 5. Bronchoalveolar lavage

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Range</th>
<th>Normal values (29)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-smokers</td>
<td>Smokers</td>
<td></td>
</tr>
<tr>
<td>Cells (millions)</td>
<td>16.9</td>
<td>9.8-39.9</td>
<td>15-20</td>
</tr>
<tr>
<td>Fluid recuperation after instillation of 200ml saline (ml)</td>
<td>89</td>
<td>35-150</td>
<td></td>
</tr>
<tr>
<td>Cells (103 ml(^{-1}))</td>
<td>255</td>
<td>67-539</td>
<td>100-150</td>
</tr>
<tr>
<td>Macrophages (%)</td>
<td>65</td>
<td>14.5-93</td>
<td>85-93</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>9</td>
<td>2-37</td>
<td>0-2</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>1</td>
<td>0-6.5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>25</td>
<td>5.5-49</td>
<td>7-12</td>
</tr>
<tr>
<td>D4/CD8 ratio</td>
<td>1</td>
<td>0.5-2.44</td>
<td>1.5-2.0</td>
</tr>
</tbody>
</table>
TREATMENT AND OUTCOME

Treatment consisted mostly of antibiotics, bronchodilating drugs and anti-pyretics; systemic corticosteroids were not given. There was little to no immediate response to medication and most often, spontaneous regression of symptoms and radiological signs occurred within 2 weeks.

Further evolution was benign, with all patients being asymptomatic between episodes. The mean follow-up period was 40 months (range 12–72 months), during which several exacerbations were noted (mean 6, range 2–13).

Discussion

We report on eight patients with a history of recurrent flu-like illness and migrating pulmonary infiltrates. In all cases, investigations were non-contributory and despite an elaborate search, the cause of these infiltrates remained unknown. Spontaneous recovery always occurred within 10 days to 2 weeks, with complete resolution of the radiological abnormalities in most cases. Further evolution was benign, with all patients being asymptomatic between episodes.

The differential diagnosis of recurrent migrating infiltrates is broad and includes especially infectious causes, hypersensitivity pneumonitis due to occupational or domestic exposure to fungi or to other environmental causes, acute and chronic eosinophilic pneumonia, BOOP, drug-induced lung disease, neoplastic disorders and even pulmonary vasculitis.

All these potential causes will now be considered but, as further evidence will show, all these disease entities were ruled out with reasonable confidence.

Pulmonary infection can have an acute, subacute or insidious onset, with fever and chills, a cough with purulent sputa and dyspnoea. The infection can be exogenous or may reflect a reactivation of latent endogenous pathogens. A number of pulmonary roentgenographic patterns can be seen, either alone or in combination.

Known specific infectious causes of our patients’ recurrent pulmonary disease are unlikely because routine and special stains did not demonstrate a predominant pathogen, serological tests remained negative, immune depression was not present and there was no beneficial effect of antibiotic therapy. Indeed, although antibiotics were often prescribed during the first period of febrile illness, they were withheld in most of the following episodes and we always noted a benign evolution with a fast and total regression of all symptoms.

Hypersensitivity pneumonitis (HP) is an immunologically-mediated inflammation of the lungs caused by repeated inhalation of organic dusts or other agents by a susceptible host (3, 4). A diagnosis of acute presentations of HP was considered in several patients (e.g. cases 1 and 6 with high lymphocytosis on BAL) but this could not be confirmed, both on the grounds of the clinical history (recurrence after avoidance of suspected agent) and absence of supportive data (no serological signs of hypersensitivity reaction).

Allergic bronchopulmonary aspergillosis or other fungal disease (5–7) was excluded because the patients in whom this was considered had no history of atopy nor bronchial asthma, because there were no signs of hypersensitivity nor eosinophilia and because the presence of fungi could not be demonstrated.

In patients with diffuse air-space disease, acute or chronic eosinophilic pneumonia must be considered in the differential diagnosis. In our series we noted a slight elevation of eosinophils (6-5%) in one patient with a lymphocytic predominance on BAL (case 6). Lung biopsies, taken during video-assisted thoracoscopy only revealed an infiltration with mononuclear cells, mostly lymphocytes, and one small non-specific epithelioid granuloma. The absence of eosinophilia, both pulmonary and peripheral, and the exclusion of known causes, allows us to reject the diagnosis of eosinophilic pneumonia in our patients (8–11).

BOOP presents with cough, fever, dyspnoea, malaise, bibasilar crackles, and bilateral, non-lobar, patchy alveolar and interstitial infiltrates (12–14). In most cases, the disorder is idiopathic, but it can develop after a viral illness, mycoplasma infection, inhalation of irritant fumes, high-dose chemotherapy or radiotherapy, or a variety of other diseases. In most cases CT scan reveals areas of consolidation that are frequently peripheral and may be triangular, with the base of the triangle at the pleural surface, and which do not tend to disappear spontaneously (15).

Infiltrates can, however, be migratory, especially in the idiopathic form of BOOP (13, 16, 17). BAL reveals foamy macrophages, a predominance of lymphocytes or a rather colourful pattern with elevation of lymphocytes, but also of neutrophils and eosinophils, and a decreased CD4/CD8 ratio. A restrictive lung function pattern with a decrease in the carbon monoxide diffusing capacity can be observed in most cases (13).

Although there are some similarities between the findings in our patients and those in BOOP, the very mild clinical picture despite extensive radiological lesions, the absence of any sign of inflammation, the normal physiological findings and the spontaneous recovery after each acute exacerbation, argue strongly against a diagnosis of idiopathic BOOP.

Recurrent lipoid pneumonia deserves consideration in the diagnostic setting of diffuse air-space disease that occupies the inferoposterior portions of the lung. Aspiration while using mineral oil or oily nose drops is the usual cause. The clinical and roentgenographic findings vary from an asymptomatic pulmonary mass or infiltrate to features resembling infection (18). BAL typically reveals lipid-laden macrophages (19).

In our series, no patient mentioned the use of oily products. Furthermore, the extent of the lung disease and the absence of specific BAL fluid findings, rule against this diagnosis.

Certain neoplasms can result in diffuse air-space disease and there have been reports of pulmonary lymphoproliferative disorders that give rise to recurrent infiltrates as early as 5 years before the definite diagnosis is made (20–23). However, lung involvement without thoracic lymph-node involvement is extremely rare (22). No patient...
had severe systemic symptoms nor signs of multiple-organ system involvement. Further follow-up showed a benign evolution in all our patients.

The only connective tissue or vasculitic disorder that perhaps merits discussion in these cases is Wegener’s granulomatosis. In the limited from of the disease, glomerulonephritis and destruction of the upper respiratory tract are absent (24,25). In this instance the disease may be clinically subacute as in our patients. However, in the case of limited Wegener’s granulomatosis, one would expect to find raised inflammatory parameters, a positive test for antineutrophil cytoplasmatic antibodies (ANCA) and a history of haemoptysis, all of which were absent in our patients.

In any febrile or afibrile patient with unexplained chest radiographic abnormalities, the possibility that the observed abnormalities are drug-induced must be kept in mind. The physician’s alertness to possible drug toxicity, a meticulous drug history and the evolution of disease after withdrawal of the drug, are most important in making a correct diagnosis. The clinical manifestations of drug-induced lung disease are protean and the radiographic manifestations are entirely non-specific. BAL fluid shows either an eosinophilic or lymphocytic predominance (26–28). None of our patients were taking known pneumotoxic drugs at the time of diagnosis. During their ensuing follow-up period, most of the medication was stopped, but recurrences of the flu-like disease with pulmonary infiltrates were still noted.

We also have no arguments for inhalation fever nor for toxic or chemical pneumonitis since we never could document any history of high exposure to organic or anorganic environmental agents, and in the few suspected cases, symptoms persisted after stopping any possible work- or hobby-related exposure or even moving house.

The eight patients of the present study, presenting with a recurrent flu-like illness and migrating pulmonary infiltrates, do not fit well into any of the above-mentioned diseases. Despite an elaborate search, we could not find any evidence for infection, humoral or cellular immunological incompetence, hypersensitivity pneumonitis or eosinophilic pneumonia. Although there are some similarities with the findings in idiopathic BOOP, several disease features weigh against this diagnosis.

We admit that in some patients investigations could have been incomplete. However, taking into account the minimal affect of the disease on the patients’ general condition and the self-limiting nature of these disorders, we believe that all the necessary tests of ‘good clinical practice’ were performed.

In conclusion, the cause of these pneumonias remains frustratingly unknown and we are left with a describing definition of a ‘syndrome of idiopathic migrating pulmonary infiltrates’.

References


