An outbreak of extrinsic alveolitis at a car engine plant

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Background

Twelve workers from a car engine-manufacturing plant presented with extrinsic allergic alveolitis (EAA), with heterogeneous clinical, radiological and pathological findings. They were exposed to metalworking fluids (MWF) that cooled, lubricated and cleaned the machines.

Methods

They were characterized by history, examination, lung function testing, radiology, bronchoscopic lavage, lung biopsy and serology. Sera were tested for precipitins to a crude extract of used MWF and to reference cultures of bacteria suspected to be implicated.

Results

All were males and none were current smokers. All had dyspnoea, many had weight loss and cough, but only half had influenza-like symptoms. Only half had auscultatory crackles. Five had peak flow variability, four with an occupational component. There was overall restrictive spirometry, decreased lung volumes and reduced gas transfers. Ten had radiological evidence of interstitial lung disease. Seven (of eight) had lymphocytosis on bronchial lavage, including the two with inconclusive radiology. Seven (of 11) had lung biopsies showing inflammatory infiltrates, two with fibrosis and one with granulomas. Three (of 11) had strong positive precipitins to an extract of the used MWF from the plant. Molecular biological analysis of the MWF revealed Acinetobacter and Ochrobactrum. Precipitins to Acinetobacter were detected in seven of 11 workers tested (and four of 11 control workers). Precipitins to Ochrobactrum were detected in three of 11 workers tested (and three of 11 control workers).

Conclusion

This is the largest series reported in Europe of EAA due to an aerosol of microbiologically contaminated MWF in heavy manufacturing industry.

Key words

Extrinsic allergic alveolitis; factory; hypersensitivity pneumonitis; metal working fluids; occupational exposure; precipitins.

Introduction

Metalworking fluids (MWF) are a complex mixture composed of a water–oil emulsion containing biocides and various additives to improve performance and stability [1]. Their role is the lubrication and cooling of machines involved in operations such as cutting and drilling of metal parts, as well as aiding the removal of the waste metal.

The possible dangers of oil mist to respiratory health were first hypothesized by Jones in the 1960s [2]. The first report of a respiratory complication related to MWF was of lipoid pneumonia secondary to inhalation of the oils [3]. Outbreaks of extrinsic allergic alveolitis (EAA) secondary to presumed contamination of MWF have been reported in the USA. The first reported were six workers at a car parts factory in MI, USA [4], all of whom had precipitins to Pseudomonas fluorescens, which was also cultured from the MWF. The largest outbreaks of EAA secondary to MWF were 20 at a machine and assembly area of an engine-manufacturing plant in WI, USA [5], and 35 workers at a metalworking plant in CT, USA [6]. In the Wisconsin outbreak, there was a high incidence of precipitins to ‘used’ MWF (11 out of 14 tested) compared with unused MWF (none of the 14 tested). Therefore, it was suggested that there was a biocontaminant, but no specific organism was implicated. In the Connecticut outbreak, three sources of water-based aerosols were identified, but again no specific organism was identified. Other reports include eight clusters of EAA thought to be related to MWF in the mid 1990s [7], where nontuberculous Mycobacterium and Aspergillus species were identified as possible causative organisms. Finally, there
were five biopsy-confirmed cases in automobile production workers in MI, USA [8].

This paper reports a case series of 12 workers with heterogeneous presentations of EAA at a large car engine plant in the UK, secondary to presumed microbiological contamination of MWF.

Methods

There were 798 employees and 33 sub-contractors working in an open plan factory where car engines and transmissions were being machined and assembled. Operations included grinding, drilling, boring and cutting that required cooling, lubricating and cleaning with MWF. Most machines were supplied with MWF from one of four common sumps. There were a number of machines mostly working cast iron with single sumps. Photographs of the MWF in this factory are shown in Figure 1.

The referrals originated from hospital consultants (eight cases), the works occupational health department (two cases), a general practitioner (one case) and a firm of solicitors (one case). There were 12 workers that first developed symptoms in early 2003. One worker (Case 12) had symptoms dating back to 2001 but symptoms worsened significantly in early 2003. All were male, which reflected the predominance of male workers at the plant. There were six ex-smokers and six never-smokers, but no current smokers.

All workers were exposed to MWF: eight directly (working at machines that used MWF or cleaning these machines), four indirectly (working in the vicinity of machines that used MWF).

All cases were characterized by clinical history and examination, pulmonary function tests and thoracic computed tomography (CT) scan. Eight had bronchoscopy and lavage and 11 had either transbronchial or surgical lung biopsies. Serological tests performed included total immunoglobulin E (IgE), angiotensin converting enzyme (ACE), rheumatoid factor (RF), antinuclear cytoplasmic antigen (ANCA) and alpha-1-antitrypsin (A1AT) phenotype. Precipitin tests to *Aspergillus fumigatus*, *Micropolyspora faeni* and *Pseudomonas* species were performed. Further specialized precipitin tests were performed on blood samples from 11 of the workers. A crude extract was made from a sample of the used MWF from the largest common sump [9] and sera from the workers were tested for precipitins to this [10], as well as to an extract of *Mycobacterium* species (composed of equal protein concentrations of *Mycobacterium chelonae*, *fortuitum* and *immunogenum*). The sera were also tested against reference cultures of bacteria whose DNA was isolated from the used MWF.

Criteria for defining cases of EAA were adapted from Fox et al. [5]. There were seven criteria as follows, one point for each criterion reached:

(i) Clinician diagnosis of probable or definite EAA.

(ii) Onset of at least two pulmonary symptoms (cough, wheeze, chest tightness, shortness of breath) and one systemic symptom (fever, weight loss) since 1 January 2003.

(iii) Work relatedness of symptoms: symptoms worse at work and better on days off work, and recurrence of symptoms after at least 3 days away from work.

(iv) Restrictive pattern on spirometry: forced vital capacity (FVC) < 80% predicted and forced expiratory volume in 1 s (FEV₁)/FVC ≥ 70%.

Figure 1. (A) The MWF, which are composed of a water–oil emulsion, from which the top layer of ‘tramp oil’ is being skimmed off. (B) The MWF are sprayed over the machines in order to cool, lubricate and remove metal waste. (C) The MWF is returned to a common sump for cleaning before recirculation.
(v) Pulmonary diffusing capacity [gas transfer for carbon monoxide (TLCO)] < 80% predicted.

(vi) Chest X-ray or CT showing interstitial, reticulonodular or mosaic pattern.

(vii) Biopsy evidence of non-caseating granulomas on biopsy or lymphocytosis on bronchoalveolar lavage.

A patient with a score of ≥4 on the basis of the above criteria was considered as fulfilling the case definition. The diagnostic scores for each of the 12 workers fulfilled these criteria and are illustrated in Table 1. When these criteria were applied to the workers, five were definite (six or seven criteria met), six were probable (five criteria met) and one was possible (four criteria met).

### Results

All cases had work relatedness of symptoms: that is to say, they worsened clinically on a work day, deteriorated during the working week and improved during weekends, leave or factory shutdowns. All had breathlessness, 11 had weight loss and 9 had a cough. Half reported wheeze and only half recalled the influenza-type symptoms that are classically associated with EAA. A third experienced chest discomfort and a quarter produced sputum.

On examination at clinic, only half had audible crackles on auscultation of the chest (although some workers had already been removed from exposure prior to this assessment). None had audible wheeze on auscultation. Five had demonstrated peak flow variability >20% on serial self-recordings and four of these reached criteria for occupational asthma with an OASYS score >2.5 [11,12].

Pulmonary function test results are illustrated in the scatter plot in Figure 2. Although most results were within the ‘normal ranges’ (within two standard residuals of the mean), overall there was on average restrictive pattern spirometry (FEV₁ and FVC), low lung volumes [residual volume (RV) and total lung capacity (TLC)] and reduced gas transfers (TLCO). One patient (Case 5) had a degree of gas trapping secondary to coexistent chronic obstructive pulmonary disease and hence an outlying point for residual volume.

Twelve high-resolution computed tomography (HRCT) examinations of the lungs were reviewed by one radiologist experienced in their interpretation. Only one of these scans was reported as normal, although another had some minimal atelectasis as the sole abnormality. Of the other 10 abnormal HRCT examinations, the commonest finding was mosaic attenuation, seen in nine of the workers. Nine workers had evidence of ground glass opacity. In only one of these workers was there a suggestion of interstitial thickening and it is likely that most of the cases of ground glass opacity were due to an infiltrative disease process. Four workers demonstrated parenchymal nodules. In one of these, there were a few nodules with a centrilobular distribution suggesting bronchiolar dilatation and inflammation. In the others, there were nodules more widely distributed with a perilymphatic distribution, consistent with a granulomatous process. One worker demonstrated diffuse reticular opacity with traction bronchiectasis and some small peripheral honeycomb cysts, consistent with usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP) or chronic hypersensitivity pneumonitis. Other findings in this group included atelectasis (two patients) and centrilobular emphysema (one patient).

Examples of CT scans of four of the patients are illustrated in Figure 3.

Eight workers had bronchoscopy and lavage. In six of them high-volume lavage showed increased lymphocyte counts (median 46%, range 22–76%), including the two workers with indeterminate radiology (Cases 5 and 7).
One was reported qualitatively as showing lymphocytosis and one as showing inflammatory cells.

Lung biopsies were performed in 11 of the workers, eight by the transbronchial route at bronchoscopy and three by open-lung biopsy. Three of the biopsies (all transbronchials) were inadequate specimens, while six out of the remaining eight biopsies, including all the open-lung biopsies, showed evidence of interstitial or alveolar inflammatory cell infiltrate. Two of the six positive biopsies revealed evidence of established fibrosis. Only one of the biopsies had granulomas as used in the Fox case definition.

Of the three open-lung biopsies, Case 8 had the typical histological appearance of EAA with a lymphocytic interstitial pneumonia and numerous loose granulomas (Figure 4a). The other two had established fibrosis. A NSIP pattern was present in Case 12 (Figure 4b). However, the fibrosis showed mild bronchiolocentric accentuation and together with a loose granuloma was suggestive of chronic EAA. Temporal heterogeneity with fibroblastic foci in Case 1 (Figure 4c) imparted a UIP pattern of lung injury. Peribronchiolar metaplasia, a manifestation of bronchiolar injury, was prominent in this worker (Figure 4d) and was focally associated with loose intraluminal fibrous buds. Although no diagnostic histological features were noted, this bronchiolocentric pattern reflects the distribution seen in EAA.

Two patients had raised ACE (>52 U/ml), a non-specific marker of granulomatous disease. None had fungal precipitins and one patient had a strong precipitin reaction to *Pseudomonas*. There was no abnormality of ANCA or A1AT, but two patients had a raised RF (>20 U/ml) and two had a raised IgE (>100 U/ml).
Three of the 11 workers tested had strong positive precipitins to the MWF extract. None of 11 exposed controls had precipitins to the same extract (workers from the same working environment without respiratory symptoms). Sixty-five non-exposed controls (Health and Safety Laboratory staff) were all negative for precipitins to the MWF extract.

Preliminary microbiological analysis of the MWF yielded no culturable bacteria, including *Mycobacterium* species or fungi. However, DNA extracted from the MWF and characterized by polymerase chain reaction showed that there was evidence of DNA from two gram-negative bacteria: *Acinetobacter* and *Ochrobactrum*. Serum from 11 of the 12 workers was therefore tested against reference cultures of these two bacteria. Seven out of the 11 workers tested had precipitins to *Acinetobacter*; however four out of 11 controls (workers from the same working environment without respiratory symptoms) also had precipitins to *Acinetobacter*. Three out of the 11 workers had precipitins to *Ochrobactrum*, but similarly three of the 11 controls also had precipitins to *Ochrobactrum*. None of the 65 non-exposed controls had precipitins to either of these bacterial species.

In addition, the sera from the workers were tested against an extract of *Mycobacterium* species (*chelonae*, *fortuitum* and *immunogenenum*) and this was all negative, as well as the sera for the 11 exposed and 65 non-exposed controls. The precipitin results are illustrated in Figure 5.

An epidemiological investigation was commenced in June 2004 in order to investigate the extent of respiratory disease at the plant and to attempt to identify the causal factors. As part of the interventions to improve workers’ health, MWF in the central sumps were completely drained, machines were steam cleaned and MWF replaced. Respiratory protection equipment was provided for all

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**Figure 4.** (A) A poorly formed granuloma consisting of loose clusters of giant cells admixed with epithelioid cells and lymphocytes. Crystalline inclusions are seen within the cytoplasm of some of the giant cells (Case 8). (H&E stain 400×). (B) Uniform fibrosis is present associated with mild chronic inflammation (Case 12). (H&E stain 100×). (C) A UIP pattern with established fibrosis adjacent to a fibroblastic focus of loose organizing connective tissue (Case 1). (H&E stain 200×). (D) Peribronchiolar metaplasia with extension of metaplastic bronchiolar epithelium along mildly thickened and fibrotic alveolar walls (Case 1). (H&E stain 100×).

**Figure 5.** Graph illustrating precipitins to used MWF extract in the cases’ sera and to isolates of *Acinetobacter* and *Ochrobactrum*. DNA of these two bacteria was isolated from the used MWF and the cases’ sera were tested against reference cultures of these bacteria. Eleven out of the 12 workers were tested for precipitins.
symptomatic staff. Surveillance of the rest of the workforce was initiated via the works occupational health department.

Ten of the 12 workers were off sick long term, made redundant or relocated. Nine of these 10 clinically improved after leaving the working environment. Two still continued to work (Cases 7 and 11) and both continued to be symptomatic despite respiratory protection.

Six of the workers had received treatment with oral corticosteroids (Cases 1, 2, 3, 4, 8 and 10). The worker with typical histology for UIP (Case 1) relapsed despite leaving work and required treatment with azathioprine in addition to the corticosteroids. The six workers not treated with oral corticosteroids all received inhaled corticosteroids.

Discussion

The 12 workers in the reported outbreak were diagnosed as cases of EAA using the criteria adapted from the Fox paper [5]. These are a combination of clinical, physiological, radiological and pathological findings. We added the cytological criterion of lymphocytosis on bronchoalveolar lavage to the histological diagnosis of granulomas on biopsy, since there were reservations about performing lung biopsies on patients that were already thought to have EAA on clinical grounds. Although useful for definitive confirmation (especially in investigations of an outbreak), there is a good argument that lung biopsies are unnecessary (and indeed possibly unethical) if clinical, radiological and pathological criteria already point strongly to the diagnosis of EAA. Indeed, a prospective cohort study of 116 patients with EAA showed that six criteria taken from history, examination and presence of precipitating antibodies could predict the presence or absence of EAA with good specificity and sensitivity without resort to surgical biopsy or bronchoalveolar lavage [13].

Among the 12 workers, there was quite marked variation in clinical presentation (shortness of breath, cough, wheeze, influenza-like symptoms) radiological patterns (alveolar, nodular, fibrotic, mosaic) and histological findings (granulomatous, fibrotic, lymphocytic/mosaicic), leading to speculation as to why different individuals react differently to the same antigenic stimulus. This was noted in the study of Hodgson et al. [6], where it was commented that many workers had other lung disease such as asthma, and there was at least one case of UIP and a case of sarcoidosis at the same plant. Different manifestations of lung disease related to the same exposure have been reported in a fibre-manufacturing plant [14] (asthma, EAA and humidifier fever), a damp office building [15] (asthma, EAA and UIP), a car engine-manufacturing plant [16] (asthma, bronchitis, EAA) and print works [17,18] (asthma and EAA). This illustrates a different reaction in different individuals to the same antigenic exposure, possibly resulting from genetic differences. It is interesting that five of the workers had peak flow variability consistent with asthma, four of which had evidence of a work-related pattern. Many patients in the study of Hodgson et al. [6] were noted to have both asthma and hypersensitivity pneumonitis. An overlap syndrome of interstitial lung disease and asthma has been described for cobalt-associated hard metal lung disease [19]. In the present study, whether this airways obstruction was true coincident asthma, or whether it was secondary to a bronchiolitis related to the EAA, is unclear.

In a recent study of surgical lung biopsies of 26 patients with bird fancier’s lung [20], there was a marked heterogeneity in the histological appearances including cellular and fibrotic NSIP, bronchiolitis obliterans organizing pneumonia and UIP that tended to occur in a centrilobular distribution consistent with a hypersensitivity pneumonitis. Moreover, this study found a correlation between the histology and the disease course, with the patients with UIP type lesions having a more insidious onset and worse outcome. This is consistent with the present study where there was also heterogeneity in the histological presentation. The two patients with the fibrotic changes on histology (Cases 1 and 2) had the lowest gas transfers in the whole group. The patient with the typical UIP type histology (Case 1) clinically deteriorated despite treatment with corticosteroids and immunosuppressive agents. In contrast, the patient with the typical granulomatous appearance on histology (Case 8) made a good response to therapy with corticosteroids.

The finding of precipitins to the used MWF in a quarter of the workers with disease would support the presence of a microbiological contaminant in the MWF to which they reacted. This is consistent with the Fox study [5] where there was a significantly higher prevalence of positive precipitin reactions to used MWFs. In the present study, although no viable bacteria were cultured from the used MWF (probably due to the presence of biocides), DNA tests showed the presence of two gram-negative bacteria, Acinetobacter and Ochrobactrum. The former is a well-known respiratory and urinary pathogen but the latter is a more obscure organism that has been related to opportunistic infections. Precipitins to Acinetobacter and Ochrobactrum were present in some of the workers’ serum, but they were also present in a similar proportion of exposed control workers without disease at the same plant, which suggests the precipitin reaction was also a marker of asymptomatic exposure. Previous studies have implicated gram-negative bacteria in the aetiology of outbreaks of EAA (e.g. Pseudomonas [4], Acinetobacter lwoffii [16]).

In the present study, the presence of precipitins to the used MWF, or to the two gram-negative bacteria studied, did not appear to correlate with any physiological, radiological or histological findings. It is interesting to note that one patient (Case 10) had strong positive precipitins to used MWF, Acinetobacter, Ochrobactrum and Pseudomonas pseudoalcaligenes. This may suggest that the presence of
precipitins may be a non-specific marker of a primed immune system, and therefore their use in defining a specific causative antigen may be limited. Indeed, in the Fox study [5], precipitins to Aspergillus and Penicillium species (as well as to used MWF) were associated with the workers who developed EAA, even though these were not thought to be the causative organisms.

Non-tuberculous Mycobacterium species have been implicated in a number of outbreaks of EAA [7,21]. These include Mycobacterium chelonae, a taxon related to Mycobacterium chelonae and abscessus, a Mycobacterium chelonae and fortuitum complex and Mycobacterium immunogenum [22]. In the present study, prolonged culture and polymerase chain reaction studies of the MWF revealed no Mycobacterium. No sera from the workers tested positive for Mycobacterium.

Non-smoking has been shown to be associated with EAA in 18 workers in the 1970s compared with the normal population [23]. It is interesting to note than none of our 12 workers smoked (six were ex-smokers). This compares with a background rate of 27% current smokers, 28% ex-smokers and 44% never-smokers in 500 out of 554 workers at the plant that responded to questionnaires.

In summary, details have been presented of an outbreak of EAA in 12 people working in the same area of a large car engine-manufacturing plant in the UK. This was probably related to exposure to aerosols of contaminated MWF and is the first such outbreak of EAA secondary to MWF reported in Europe.

Conflicts of interest
None of the authors have any conflict of interest to declare in relation to this paper. Sherwood Burge has acted as an expert witness in the case of one of the workers in the study.

References