CASE REPORT

Completely reversible respiratory insufficiency with persisting ultrastructural ciliary abnormalities

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Completely reversible respiratory insufficiency with persisting ultrastructural ciliary abnormalities. I. Malysse, M. Jorissen, E. Verbeken, C. Vaerenberg, M. Demedts. ©ERS Journals Ltd 1994.

ABSTRACT: A male nonsmoker, born in 1946, suffered from hypersecretory bronchitis and recurrent upper and lower respiratory tract infections since adolescence. In 1983 he developed pulmonary insufficiency. In 1984, some months after daily occupational exposure to printing inks and glues, forced expiratory volume in one second (FEV₁) was 1.1 l (28% pred) and arterial oxygen tension (Pao₂) 44 mmHg (5.9 kPa). Open lung biopsy showed a centri-acinar bronchiolitis-alveolitis suggestive of an airborne toxic pathology. Ultrastructural examination of the bronchial mucosa revealed microtubular abnormalities in about 10% of the cilia. Treatment consisted of stopping work from December 1985, oral corticosteroids until 1988, bronchodilators on a regular basis and intermittent antibiotics (1 week/month). The evolution was remarkable because: 1) from a severe pulmonary insufficiency, refractory to bronchodilators and corticosteroids for several years, lung function slowly improved to supernormal values, without residual functional signs of small airways disease; and 2) a repeat ultrastructural nasal mucosa examination in 1992 still showed persisting microtubular abnormalities in about 10% of the cilia, which disappeared on sequential monolayer-suspension culture, thus indicating secondary ciliary abnormalities.

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Chronic obstructive pulmonary disease (COPD) leads to a progressive respiratory functional deficit. We are unaware of publications on patients with COPD who deteriorated to respiratory insufficiency but, over several years, improved to a completely normal lung function.

However, neither in COPD, nor in reversible diseases (such as respiratory infections), has the severity of clinical disease been well correlated to the ultrastructural abnormalities; yet secondary ultrastructural abnormalities characteristically subside after resolution of the inflammation.

The following case report describes the unusual course in a man with hypersecretory bronchitis who suffered from respiratory insufficiency for half a decade following occupational exposure to printing inks but who afterwards showed a slow improvement of lung function to supernormal values, although secondary ciliary abnormalities persisted.

Case report

A 47 year old, lifetime nonsmoker, male blue collar worker, born in 1946, suffered since adolescence from chronic rhinitis, sinusitis, hypersecretory bronchitis with

nonspecific hyperreactivity and recurrent respiratory infections, for which he frequently used antibiotics and underwent several surgical procedures on the nose and sinuses. He was found fit for military service. His father, one uncle and one sibling (of four), all smokers, suffer from chronic bronchitis. He has one daughter who suffers from hay fever. In 1966 he started working in a small printing shop where he handled printed books (e.g. assemblage, distribution). There was no known exposure at the workplace or at home to organic or inorganic substances which may have caused inhalation pathology.

In 1982 he moved to another printing firm where he became involved in the printing process and had regular contact with inks (containing resins and aliphatic carbohydrate solvents) and glues. Within six months he developed severe, acute airway inflammation with persistent purulent expectorations, dyspnoea on exercise, and weight loss of 30 kg, for which he was hospitalised in May 1983. Clinical examination then showed diffuse coarse and also fine inspiratory rales particularly at the lung bases, moderate clubbing and cyanosis. There was a slightly restrictive lung function defect (forced vital capacity (FVC) 3.7 l (69% pred), forced expiratory volume in one second (FEV₁) 2.5 l (62% pred), total lung capacity (TLC) 5.7 l (80% pred)) and an arterial

Fig. 1. — Evolution of lung function, and periods of exposure and treatment with oral corticosteroids. Columns are dose of methylprednisolone (mg per day). For the lung function indices the predicted values of the European Community for Coal and Steel are used [11]. +: FVC; forced vital capacity (% pred); Δ : FEV₁; forced expiratory volume in one second (% pred); ■: DLCO; single breath carbon monoxide diffusing capacity (% pred); ○: PaO₂; □: PaCO₂.

oxygen tension (PaO₂) of only 46 mmHg (6.1 kPa) (fig. 1). Bronchoscopy revealed an acute purulent bronchitis and growth of *Pseudomonas aeruginosa* on culture. Bronchography demonstrated dilated bronchial mucous glands in the central bronchi and narrowed bronchioli without bronchiectases.

With antibiotics and theophylline the condition improved, but after resuming his job in January 1984 the respiratory complaints worsened again and he was admitted in May 1984 for respiratory insufficiency with a severe obstructive defect (FEV₁ 1.1 l = 28% pred) and a minor restrictive defect (TLC 4.6 l = 70% pred) with a PaO₂ of 44 mmHg (5.9 kPa) and a single breath carbon monoxide-diffusing capacity (DLCO) of 60% pred. *Klebsiella ozenae* was cultured from his sputum. Extensive immunologic investigation revealed no immediate or delayed type allergy by skin tests, specific IgEs and precipitins nor humoral or cellular deficiencies. The sweat test gave normal values (Cl⁻ = 9 mEq·l⁻¹). An open lung biopsy was performed, showing a widespread chronic interstitial inflammation with an intra-alveolar desquamative component, both almost exclusively confined to the centri-acinar regions. Some interstitial collagenosis was already present. No granulomas were detected. A polymorphonuclear exudate was seen in the bronchiolar lumen and in some adjacent parenchymal airspaces. This was considered to be suggestive for small airways disease due to an airborne toxin with superimposed infection possibly from a viral origin. Treatment with methylprednisolone (tapering off from 32 mg), antibiotics and bronchodilators was instituted with

initially markedly favourable effects on his physical condition.

In 1985 he tried several times to resume his work but each time he was forced to stop after some weeks due to recurrence of acute respiratory complaints. He was readmitted in March 1986. The chest X-ray showed thickening of bronchial walls and multiple ill-defined micronodular opacities. There was growth of *Haemophilus influenzae* on sputum culture. Methylprednisolone was increased to 64 mg per day (fig. 1) and antibiotics were added, but the FEV₁ only improved to 1.6 l (42% pred) with airway resistance (Raw) of 2.3 cmH₂O·l⁻¹·s, a DLCO of 66% pred, a PaO₂ of 56 mmHg (8.5 kPa) on air (and 423 mmHg (56.4 kPa) with 100% O₂), a static lung compliance at functional residual capacity (FRC) of 0.3 l·cmH₂O⁻¹, and an elastic recoil pressure at TLC of 26 cmH₂O. Bronchial mucosal biopsies were examined ultrastructurally; the interpretation at that time was that there were no abnormalities in axonemal pattern, that the outer dynein arms were shortened or absent, and that the inner dynein arms, radial spokes and nexine links were not clearly visible. Ultrastructural examination of a nasal biopsy showed squamous cell epithelium.

The patient stopped working in 1986 and has not required admission to a hospital since; the dyspnoea and other respiratory complaints slowly regressed while methylprednisolone was tapered off and finally stopped in 1988. He used inhaled salbutamol, ipratropium bromide and oral theophylline on a regular base. Lung function did not improve until 1988; then it slowly improved, attaining normal levels in 1991 (fig. 1) with

Fig. 2. — Maximal expiratory flow volume-curves in May 1986 and May 1992. In 1986 all expiratory flows were markedly reduced; in 1992 all flows were normal or supernormal: from left to right the black circles correspond with the predicted values of peak expiratory flow, maximum expiratory volume 75, 50 and 25%, and residual volume.

FEV₁ 4.1 l (113%), FVC 5.5 l (120%), TLC 8.6 l (120%), DLCO 120% pred, a normal Raw of 2.4 cmH₂O·l⁻¹·s, with no signs of small airways disease on the maximum expiratory flow volume (MEFV)-curve (fig. 2), Pao₂ of 77 mmHg (10.3 kPa), and a good exercise tolerance. He used antibiotics (amoxicillin-clavulanate or co-trimoxazole) for about one week each month, especially when the hypersecretory bronchitis became more purulent, preventing the occurrence of severe acute respiratory infections. Routine clinical examination in 1992 revealed only coarse rales which disappeared after coughing; the chest X-ray showed only minor signs of bronchitis without micronoduli. Endoscopy of the nasal and paranasal cavities showed chronically inflamed and hypersecretory mucosae combined with postoperative sequelae. Ultrastructural examination of a nasal biopsy revealed mostly peripheral microtubular abnormalities in 9% of the cilia (fig. 3) and the ciliary beat frequency was 5.5±1.6 Hz. Ciliary alignment was normal. After *in vitro* ciliogenesis in the sequential monolayer-

Fig. 3. — Transmission electron microscopy of the nasal biopsy in 1992. It shows one normal cilium (top), one with a supplementary peripheral microtubule shifted towards the centre (left), and one with two supplementary peripheral microtubules located right laterally (right). No abnormalities in ciliary alignment were found. (× 156,000). Bar line: 0.1 μm).

suspension culture [1, 2], ultrastructural abnormalities were no longer detectable and a ciliary beat frequency of 7.9±2.1 Hz, within the normal range, was found (table 1); thus confirming the diagnosis of secondary ciliary abnormalities on the biopsy. On revision of the bronchial biopsy taken in 1986 (by M.J.) microtubular abnormalities in about 10% of the (central and peripheral) cilia were considered to be the only pathology, while the dynein arms, spokes or nexines were found to be normal (table 1). No abnormalities in ciliary alignment were found.

Discussion

This case report contains two interesting aspects: a) a toxic bronchiolitis-alveolitis improving over about 4 years from severe respiratory insufficiency to a completely normal lung function, and b) the ultrastructural demonstration of secondary ciliary abnormalities which persisted, despite clinical recovery.

This nonsmoker, who since his youth suffered from rhinitis-sinusitis and hypersecretory bronchitis, from

Table 1. — Ultrastructural ciliary examination of bronchial and nasal biopsies

	Normal values*	Bronchial biopsy 1986 (revision in 1992)	Nasal biopsy 1992 (direct)	Nasal biopsy 1992 (after culture)
Number cilia examined		96	97	15
Outer dynein arms/cilium n	7-9	8.2±1.0	8.4±0.7	8.3±0.7
Inner dynein arms/cilium n	1-7	2.3±0.9	3.7±1.3	3.2±1.2
Spokes/cilium n	2-7	4.7±1.5	4.4±1.5	5.8±1.0
Membrane abnormalities %	≤3	3	2	0
Central pair abnormalities %	≤2	5	0	0
Peripheral microtubular abnormalities %	≤5	5	9	0
Disorganisation %	≤1	3	1	0

*: taken from [1-3]. Mean±SD.

the age of 37 year to 42 year presented a definite respiratory insufficiency with a severe obstructive and minor restrictive lung function pattern, a moderate CO-diffusing defect and a marked hypoxaemia with a shunt of about 15%. These severe abnormalities in middle age were related to the occupational exposure to resins and aliphatic hydrocarbonic solvents in inks and glues. The pathological basis was a particular, centri-acinar bronchiolitis and alveolitis which was very much in agreement with inhalation toxicity. The course, after exposure was stopped and systemic steroid therapy was instituted, was extremely unusual. The respiratory insufficiency with severe airway obstruction had persisted for 4–5 years and was refractory to maintenance therapy with bronchodilating and anti-inflammatory agents including high dose oral corticosteroids; then, lung function progressively normalised over a 3–4 year period, even after the corticosteroids were withheld; it, finally, reached supernormal values even without signs of small airways disease on MEFV-curves. To the best of our knowledge a similar normalisation of a severe COPD-pattern over a period of several years has not been previously described. No underlying cellular, humoral deficiencies, hypersensitivities, systemic diseases could be detected. Electron microscopy of bronchial mucosa (in 1986) and of nasal mucosa (in 1992) revealed, however, abnormalities in about 10% of the cilia (central and peripheral in 1986, exclusively peripheral in 1992), with a lowered ciliary beat frequency in the 1992 nasal biopsy. The percentage of ultrastructural ciliary abnormalities in this patient (10%) is at least double the value we find in controls (<5%) [4, 5]. In addition, these abnormalities are more frequent than observed in allergic or chronic rhinitis, sinusitis or in chronic bronchitis, where no consistent increase in ciliary abnormalities has been reported [6, 7].

One could question whether these ciliary abnormalities are primary or secondary. Central and peripheral microtubular abnormalities have been reported as the cause of primary ciliary dyskinesia. Most cases (80%) are inner and/or outer dynein arms deficiencies. Spoke deficiencies and central microtubular pair deficiencies each account for about 6% of the cases. Yet, when the central pair of microtubules is missing, the abnormality is found in approximately 1/3 of the cilia [3] while in the present case this was found in only 5% in 1986 and 0% in 1992. An increase of peripheral microtubular abnormalities (>10%) has also been reported as a cause of primary ciliary dyskinesia in a limited number of cases. This lesion is, however, not widely accepted as a primary defect [3] and its occurrence in our patient (5%) was too low in 1986. Therefore, the abnormalities found here can not be interpreted as the ultrastructural correlate of primary ciliary dyskinesia. Finally, this is confirmed by the normal ciliary beat frequency and the normal ciliary ultrastructure after ciliogenesis in the *in vitro* sequential monolayer-suspension culture system. Additional arguments in favour of secondary ciliary abnormalities are the facts that the patient had no major respiratory problems during the first 10 years of his life.

The cause of these abnormalities is not evident. Toxic agents preferentially cause membrane abnormalities, such as intracytoplasmic, compound, naked or disorganized cilia [6, 8, 9], which are virtually absent here. Also, chronic bronchitis and sinusitis are not characterized by an increase of microtubular abnormalities [6, 7]. Furthermore, severe acute respiratory infections can cause transitory central microtubular pair abnormalities [10] but our patient was in a stable condition when the biopsy was taken in 1992. Finally, the persistence of microtubular abnormalities in the nasal mucosa could be due to previous surgical procedures, resulting in scar tissue, mucostasis, bacterial colonization and ciliary abnormalities. However, experimental data or clinical studies supporting this hypothesis are lacking.

Not only is the explanation for the occurrence of the ciliary abnormalities uncertain, even the clinical relevance of these ultrastructural abnormalities is not clear. These abnormalities probably contributed to the development of the severe respiratory insufficiency after exposure to the occupational toxins and to the delay of the recovery after cessation of exposure and introduction of corticosteroid therapy. On the other hand, the degree of ultrastructural abnormalities was not clearly related to the severity of the clinical symptomatology *i.e.* the ultrastructural abnormalities were similar in 1986 and 1992 but lung function differed dramatically. This makes the clinical and physiological significance of these ultrastructural findings uncertain.

In conclusion, this case demonstrates an unusual course from severe respiratory insufficiency to complete functional recovery over several years. In our opinion, the accompanying ciliary abnormalities are secondary to the chronic rhinitis-sinusitis and bronchitis with recurring infections. Furthermore, this may have predisposed the patient to the markedly harmful effects of the occupational exposure because of a possible secondary ciliary dyskinesia with hampered removal of inhaled toxins. We did, however, not measure mucus clearance. The ciliary abnormalities did not inhibit the ultimate normalisation of the pulmonary function in middle age even after several years of severe respiratory insufficiency, despite persistence of the ultrastructural abnormalities. This demonstrates, again, that ultrastructural ciliary defects do not relate to the severity or course of the clinical symptomatology.

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