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CASE STUDY

Reactive airways dysfunction syndrome due to chlorine: sequential bronchial biopsies and functional assessment

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Reactive airways dysfunction syndrome due to chlorine: sequential bronchial biopsies and functional assessment. C. Lemière, J-L. Malo, M. Boutet. ©ERS Journals Ltd 1997.

ABSTRACT: Very little information is available on the acute histopathological bronchial alterations caused by reactive airways dysfunction syndrome (RADS). We had the opportunity to carry out sequential bronchial biopsies in a subject with RADS due to chlorine (60 h, 15 days, 2 and 5 months after the acute exposure), and also to assess spirometry and bronchial responsiveness to methacholine.

A 36 year old worker in a water-filtration plant (nonsmoker) abruptly inhaled high concentrations of chlorine on September 12, 1994. He experienced immediate nasal and throat burning, retrosternal burning and wheezing, and these symptoms persisted during and after the workshift. Two days later, he complained of retrosternal burning, dyspnoea and wheezing. Inspiratory wheezing was documented. His forced expiratory volume in one second (FEV_1) was 66% of predicted and the provocative concentration of methacholine causing a 20% fall in FEV_1 (PC_{20}) was slightly abnormal (2.5 $mg \cdot mL^{-1}$). On the following day, the patient underwent bronchial biopsies, which showed almost complete replacement of the epithelium by a fibrinohaemorhagic exsudate. The subject was prescribed inhaled steroids.

Fifteen days after the accident, the PC_{20} was improved to 6 $mg \cdot mL^{-1}$. Bronchial biopsies showed considerable epithelial desquamation with an inflammatory exudate and swelling of the subepithelial space. Five weeks after the accident, the PC_{20} was normal (57 $mg \cdot mL^{-1}$). Inhaled steroids were stopped. Two months after the accident, the PC_{20} deteriorated to 4 $mg \cdot mL^{-1}$. Biopsies then showed regeneration of the epithelium by basal cells and there was still a pronounced inflammatory infiltrate. Inhaled steroids were restarted. Three and five months later, the PC_{20} was normal (24 $mg \cdot mL^{-1}$). Bronchial biopsies showed a greatly improved epithelium and reduction of the inflammatory infiltrate.

This case report shows that reactive airways dysfunction syndrome can cause acute, marked, though partially reversible, histological abnormalities. Inhaled steroids may modulate changes in bronchial responsiveness in this condition.

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In 1985, BROOKS *et al.* [1] defined the reactive airways dysfunction syndrome as an asthma-like condition that arises after a single inhalation of miscellaneous irritant agents. Bronchial hyperresponsiveness is the key functional alteration, with airway calibre most often remaining normal. Chlorine is one of the main causal agents, as described in later case reports [2, 3] and a recent review [4]. The time course of functional and histological changes after acute inhalation of irritant agents is not yet well known. The effect of inhaled steroids on bronchial hyperresponsiveness caused by RADS is also unknown. We report the case of a subject who developed RADS after a single high exposure to chlorine. Serial functional assessment was carried out and bronchial biopsies were performed on four occasions (60 h, 15 days, 2 and 5 months) after acute exposure.

Case report

A 36 year old male had been employed for 10 yrs in a water-filtration plant. He mixed gaseous chlorine with sodium chloride, which reacted to produce chlorine dioxide (ClO_2), and had to mix this with water. Five years earlier, the subject had experienced symptoms of burning throat, cough, dyspnoea and wheezing after chlorine inhalation, but these symptoms had been transient and the subject had not been symptomatic since that event. He was a nonsmoker.

On September 12, 1994, when the subject mixed chlorine dioxide with water, he suddenly experienced a strong odour and nasal, throat and retrosternal burning. A chlorine detector alarm had sounded. He had to leave the room where he worked. After the room had been ventilated, he returned to work. The clinical, functional and bronchoscopic features of the following events are listed in table 1. One hour later, the subject started noticing wheezing, retrosternal burning and headaches. These symptoms worsened in the evening and he could not sleep until 03:00 h. On the following day, he went back to work, and again experienced chest wheezing and retrosternal burning.

He was seen by a physician. The chest radiograph was normal. He was prescribed salbutamol on demand.

Table 1. – Time course of clinical, functional and histological features after acute exposure to chlorine

	12/09/94 (accident)	14/09/94	15/09/94	21/09/94	27/09/94	19/10/94	17/11/94	14/12/94	14/02/95
Symptoms	Burning throat, dyspnoea, wheezing	Cough, dyspnoea, wheezing	Cough, dyspnoea, wheezing	None	None	None	Dyspnoea on exercise	None	None
FEV_1[#] L	ND	2.6	3.5	3.8	3.8	3.9	3.8	3.8	3.7
FVC[##] L		3.8	4.6 (4.9 post-BDT)	4.7	4.8	4.7	4.7	4.8	4.7
PC_{20} mg·mL^{-1}	ND	2.5	ND	16	6.4	57	4	21	24.5
Bronchial biopsies	ND	ND	73% epithelial desquamation, subepithelial haemorrhagic exsudate with swelling, 116 cells·mm^{-2}: HLA-DR (33%), CD45+ (27%)	ND	78% epithelial desquamation, subepithelial haemorrhagic exsudate, 42 cells·mm^{-2}: HLA-DR (48%), CD45+ (29%)	ND	59% desquamation of epithelium with regeneration (basal cells), 95 cells·mm^{-2}: HLA-DR (33%), CD45+ (23%)	ND	Ciliated epithelium, increased basal cells, 28% desquamation, subepithelial swelling, 36 cells·mm^{-2}: HLA-DR (47%)
BAL	ND	ND	Normal	ND	Normal	ND	Lymphocytosis (40% of 8×10^4 cells)	ND	Lmphocytosis (58% of 25.8×10^4 cells)
Treatment: inhaled budesonide µg·day^{-1}			1600	1600	800	800	800	800	800

[#]: predicted value 3.9 L [5]; [##]: predicted value 4.6 L [5]. FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; PC_{20}: provocative concentration of methacholine causing a 20% fall in FEV_1; ND: not done; BDT: bronchodilation therapy; HLA-DR: human leucocyte antigen-DR.

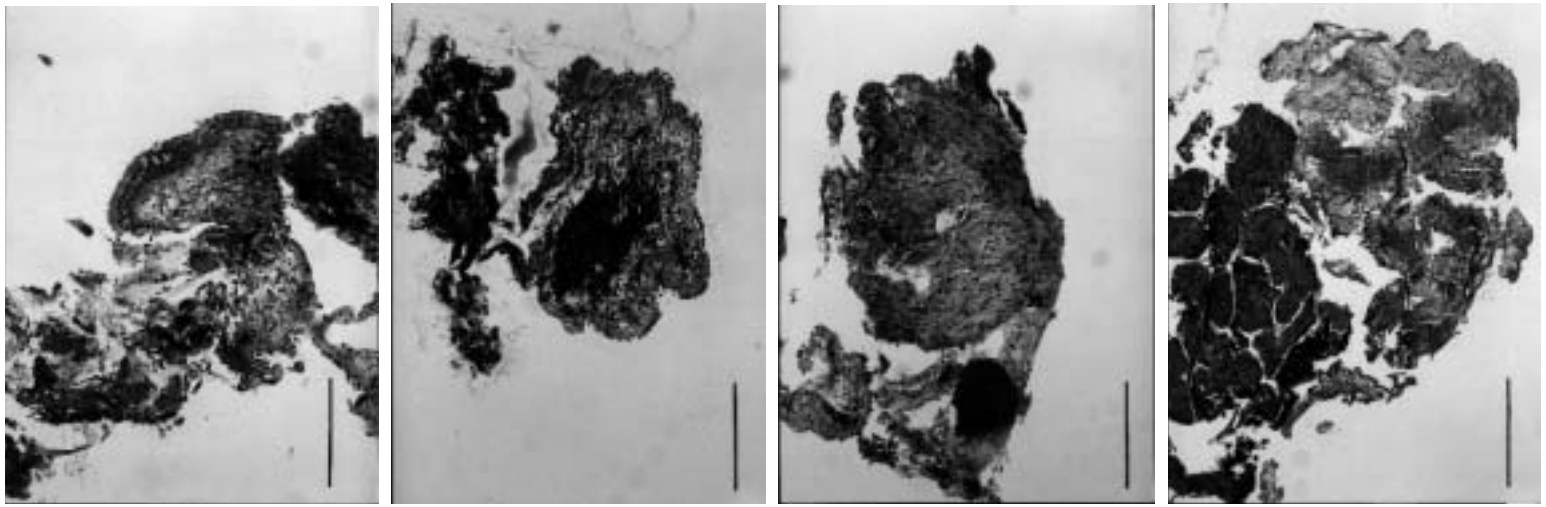

Fig. 1. – a) Almost complete desquamation of the bronchial mucosa (left and upper portion) with fibrinohaemorrhagic deposit (dark pink colour). Inflammatory influx of neutrophils (dark purple spots in the middle and upper portions). Normal smooth muscle (right hand side). (Weigert-Masson stain). b) Almost complete desquamation of surface epithelium. Oedema of the subepithelial zone with inflammatory infiltrate. (Weigert-Masson stain). c) Regeneration of basal cells. No ciliated cells. Oedema of the subepithelial zone with inflammatory infiltrate. (Weigert-Masson stain). d) Ciliated epithelium (left hand side) with increased basal cells. Oedematous subepithelial zone with inflammatory cells. (Weigert-Masson stain). Scale bars = 100µm.

On September 14, the subject was seen by a chest physician, who noticed inspiratory wheezing. Spirometry showed a reduced forced expiratory volume in one second (FEV_1) value of 2.6 L (67% of predicted value (3.9 L) [5]), and forced vital capacity (FVC) 3.8 L (83% of predicted value (4.6 L) [5]). The transfer factor of the lung for carbon monoxide was normal. The provocative concentration of methacholine causing a 20% fall in FEV_1 (PC_{20}) using a standardized procedure [6] (output of nebulizer = 0.14 $mL \cdot min^{-1}$) was 2.5 $mg \cdot mL^{-1}$ (mild bronchial hyperresponsiveness).

On September 15, *i.e.* 60 h after the acute exposure, a first bronchoscopy was performed. The bronchial mucosa was hyperaemic with mucoid secretions. Features of biopsies and bronchoalveolar lavage (BAL) are shown in table 1 and figure 1a. The subject was then prescribed inhaled steroids (budesonide 1,600 μg daily). He was reassessed on September 21 (Day 9). He was asymptomatic, with no bronchial obstruction, and methacholine challenge showed borderline bronchial hyperresponsiveness (table 1). A second bronchoscopy was scheduled on September 27 (Day 15). Hyperaemia of the bronchial mucosa was less pronounced than 12 days previously. Biopsies and BAL are described in table 1 and figure 1b. The dose of inhaled steroids was reduced to 800 μg daily. On October 19 (Day 43), the subject had normal spirometry and the methacholine test no longer showed bronchial hyperresponsiveness. Inhaled steroids were progressively decreased and stopped.

One month later, the subject complained of dyspnoea and retrosternal burning during exercise. Spirometry was normal, but the methacholine test showed mild bronchial hyperresponsiveness. Inhaled steroids were restarted (budesonide 800 μg daily). Bronchoscopy was repeated a third time, 2 months after the initial event. The bronchial mucosa was still hyperaemic. The abnormal features of biopsies and BAL are shown in table 1 and figure 1c. One month later, the subject was asymptomatic, and no longer had bronchial hyperresponsiveness. Inhaled steroids were maintained at the same dose. On February 14, 1995 (Day 166), the subject was completely asymptomatic and had normal respiratory function. A last bronchoscopy was performed. Features of bronchial biopsies and BAL are shown in table 1 and figure 1d.

Discussion

We report a case of RADS that occurred after acute exposure to chlorine. Although RADS secondary to chlorine has been described by several authors [3, 7, 8], we report for the first time, to our knowledge, serial measurements of spirometry and bronchial responsiveness combined with histological evaluation on four occasions, shortly after acute exposure to chlorine. The histopathological features are those of acute desquamation of the epithelium, with subepithelial haemorrhage and swelling, inflammatory infiltrates, and regeneration of the epithelium at a later stage (Day 72). Bronchial hyperresponsiveness appeared to be modulated and reversed by the use of inhaled steroids. Similar clinical, functional and histological features were recently described by our group in a subject who suffered RADS induced by exposure to an isocyanate [9].

Few authors [1, 8] have reported histological findings of RADS, and these were only documented at least one year after the acute exposure. They showed mild chronic inflammation and focal desquamation of the epithelial layer, as well as bronchial wall thickening. There is no report, to our knowledge, of the histological features shortly after acute exposure to a common causal agent, chlorine. In the various cases described in previous studies [1, 8], there was persistent histological damage at least one year after exposure. The subjects also had persistent airway hyperresponsiveness. The two subjects reported by BROOKS *et al.* [1], each of whom had bronchial biopsies 1 and 3 yrs after exposure, had persistent bronchial obstruction and airway hyperresponsiveness. Among the 15 subjects suffering from RADS studied by GAUTRIN *et al.* [8], five subjects with bronchial hyperresponsiveness underwent bronchoscopy with bronchial biopsies. These revealed desquamation of the epithelial layer, inflammatory infiltrate and extended fibrosis, which was the main feature. These authors did not perform biopsies in subjects who had returned to a baseline of normal responsiveness.

It is likely that persistent airway hyperresponsiveness is related, in this condition as for asthma, to persistent epithelial damage [10, 11], inflammation [12, 13], and/or structural changes. It has been shown in asthma that structural changes related to bronchial wall thickness with oedema and inflammation, or in airway smooth muscle can modify airway responsiveness [14, 15]. The present case also shows that functional integrity does not necessarily mean histological integrity. Indeed, this subject was no longer complaining of respiratory symptoms nor did he have airway hyperresponsiveness or airway obstruction, at a time when bronchial biopsies showed epithelial desquamation, inflammatory infiltrate and swelling of the subepithelial space, and BAL showed lymphocytosis. It is interesting to note that the lymphocytosis, detected at the time of the third and fourth bronchoscopies, only followed the appearance of inflammatory cells detected by immunohistochemistry within the bronchial layer at an earlier stage.

The differential diagnosis of this case includes all types of acute bronchitis, including that caused by viral infection, which shares some histological features (desquamation of epithelium, infiltrate of inflammatory cells) and for which inhaled steroids can also be of benefit. In the present case, the history was, however, directly related to chlorine exposure.

Inhaled steroids could have modulated the course of the disease. Indeed, after the first attempt to stop inhaled steroids, the subject again complained of respiratory symptoms when exposed to nonspecific irritants, and the PC_{20} fell from 57 to 4 $mg \cdot mL^{-1}$. He rapidly recovered after 1 month of inhaled steroid treatment. Inhaled steroids, therefore, seem to be efficacious in RADS, normalizing nonspecific bronchial hyperresponsiveness and improving symptoms. We do not know, however, what the functional course and histological changes would have been without inhaled steroids. The changes that were noted might represent the natural history of the disease, although it appeared that inhaled steroids modulated the course of bronchial responsiveness. Randomized studies on RADS using inhaled steroids *versus* placebo would be necessary to make a precise evaluation

of the efficacy of inhaled steroids, and also to determine the optimum dose and duration of treatment after acute exposure. Alternatively, the effect of parenteral or inhaled steroids could be first assessed in animal models of RADS.

In conclusion, this case report shows that reactive airways dysfunction syndrome can cause acute, marked, though partially reversible, histological abnormalities. Inhaled steroids may modulate changes in bronchial responsiveness in this condition.

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