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

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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 (FEV1) was 66% of predicted and the provocative concentration of methacholine causing a 20% fall in FEV1 (PC20) was slightly abnormal (2.5 mg·mL⁻¹). On the following day, the patient underwent bronchial biopsies, which showed almost complete replacement of the epithelium by a fibrinohaemorrhagic exsudate. The subject was prescribed inhaled steroids.

Fifteen days after the accident, the PC20 was improved to 6 mg·mL⁻¹. Bronchial biopsies showed considerable epithelial desquamation with an inflammatory exudate and swelling of the subepithelial space. Five weeks after the accident, the PC20 was normal (57 mg·mL⁻¹). Inhaled steroids were stopped. Two months after the accident, the PC20 deteriorated to 4 mg·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 PC20 was normal (24 mg·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.

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 (ClO₂), 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

<table>
<thead>
<tr>
<th>Date</th>
<th>Symptoms</th>
<th>FEV1 L</th>
<th>FVC L</th>
<th>PC20 mg·mL⁻¹</th>
<th>Bronchial biopsies</th>
<th>BAL</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/09/94</td>
<td>Burning throat, dyspnoea, wheezing</td>
<td>ND</td>
<td>2.6</td>
<td>ND</td>
<td>73% epithelial desquamation, subepithelial haemorrhagic exudate with swelling, 116 cells·mm⁻²; CD45+ (27%)</td>
<td>ND</td>
<td>Normal 1600</td>
</tr>
<tr>
<td>14/09/94</td>
<td>Cough, dyspnoea, wheezing</td>
<td>2.6</td>
<td>3.5</td>
<td>ND</td>
<td>62% epithelial desquamation, subepithelial haemorrhagic exudate, 42 cells·mm⁻²; HLA-DR (48%), CD45+ (29%)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>15/09/94</td>
<td>Cough</td>
<td>3.5</td>
<td>4.6</td>
<td>ND</td>
<td>73% epithelial desquamation, subepithelial haemorrhagic exudate, 116 cells·mm⁻²; HLA-DR (48%), CD45+ (29%)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>21/09/94</td>
<td>None</td>
<td>3.8</td>
<td>4.7</td>
<td>ND</td>
<td>73% epithelial desquamation, subepithelial haemorrhagic exudate, 116 cells·mm⁻²; HLA-DR (48%), CD45+ (29%)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>27/09/94</td>
<td>None</td>
<td>3.8</td>
<td>4.8</td>
<td>ND</td>
<td>73% epithelial desquamation, subepithelial haemorrhagic exudate, 116 cells·mm⁻²; HLA-DR (48%), CD45+ (29%)</td>
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<td>ND</td>
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<tr>
<td>19/10/94</td>
<td>None</td>
<td>3.9</td>
<td>4.7</td>
<td>ND</td>
<td>73% epithelial desquamation, subepithelial haemorrhagic exudate, 116 cells·mm⁻²; HLA-DR (48%), CD45+ (29%)</td>
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<tr>
<td>17/11/94</td>
<td>None</td>
<td>3.8</td>
<td>4.7</td>
<td>ND</td>
<td>73% epithelial desquamation, subepithelial haemorrhagic exudate, 116 cells·mm⁻²; HLA-DR (48%), CD45+ (29%)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>14/12/94</td>
<td>Dyspnoea on exercise</td>
<td>3.8</td>
<td>4.7</td>
<td>ND</td>
<td>73% epithelial desquamation, subepithelial haemorrhagic exudate, 116 cells·mm⁻²; HLA-DR (48%), CD45+ (29%)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>14/02/95</td>
<td>None</td>
<td>3.7</td>
<td>4.7</td>
<td>ND</td>
<td>73% epithelial desquamation, subepithelial haemorrhagic exudate, 116 cells·mm⁻²; HLA-DR (48%), CD45+ (29%)</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

*: predicted value 3.9 L [5]; **: predicted value 4.6 L [5]. FEV1: forced expiratory volume in one second; FVC: forced vital capacity; PC20: provocative concentration of methacholine causing a 20% fall in FEV1; ND: not done; BDT: bronchodilation therapy; HLA-DR: human leucocyte antigen-DR.
On September 14, the subject was seen by a chest physi- 
cian, who noticed inspiratory wheezing. Spirometry 
showed a reduced forced expiratory volume in one sec-
ond (FEV1) 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 provoca-
tive concentration of methacholine causing a 20% fall 
in FEV1 (PC20) using a standardized procedure [6] (out-
put of nebulizer = 0.14 mL·min⁻¹) was 2.5 mg·mL⁻¹ (mild 
bronchial hyperresponsiveness).

On September 15, i.e., 60 h after the acute exposure, 
a first bronchoscopy was performed. The bronchial muc-
osa 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 asympto-
matic, with no bronchial obstruction, and methacholine 
challenge showed borderline bronchial hyperrespon-
siveness (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 (bude-
sonide 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 ster-
oids were maintained at the same dose. On February 14, 
1995 (Day 166), the subject was completely asympto-
matic and had normal respiratory function. A last bron-
choscopy 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 chlo-
rine has been described by several authors [3, 7, 8], we 
report for the first time, to our knowledge, serial mea-
surements of spirometry and bronchial responsiveness 
combined with histological evaluation on four occasions, 
shortly after acute exposure to chlorine. The histopatho-
logical features are those of acute desquamation of the 
epithelium, with subepithelial haemorrhage and swel-
ling, inflammatory infiltrates, and regeneration of the 
epithelium at a later stage (Day 72). Bronchial hyper-
responsiveness appeared to be modulated and reversed 
by the use of inhaled steroids. Similar clinical, func-
tional 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 stud-
ies [1, 8], there was persistent histological damage at 
least one year after exposure. The subjects also had per-
sistent 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 bron-
chial obstruction and airway hyperresponsiveness. Among 
the 15 subjects suffering from RADS studied by GAUTRIN 
et al. [8], five subjects with bronchial hyperresponsive-
ness 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 biop-
sies in subjects who had returned to a baseline of nor-
mal responsiveness.

It is likely that persistent airway hyperresponsiveness 
is related, in this condition as for asthma, to per-
sistent epithelial damage [10, 11], inflammation [12, 
13], and/or structural changes. It has been shown in asth-
ma that structural changes related to bronchial wall thick-
ness 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 symp-
toms nor did he have airway hyperresponsiveness or air-
way 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 lym-
phocytosis, detected at the time of the third and fourth 
bronchoscopies, only followed the appearance of inflam-
matory 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 (des-
quamation 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 
stereoids, the subject again complained of respiratory 
symptoms when exposed to nonspecific irritants, and the 
PC20 fell from 57 to 4 mg·mL⁻¹. He rapidly recovered 
after 1 month of inhaled steroid treatment. Inhaled ster-
oids, therefore, seem to be efficacious in RADS, nor-
malizing 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 mod-
ulated the course of bronchial responsiveness. Random-
ized 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.

Acknowledgements: The authors would like to thank C. Leblanc and M. Bélanger for technical support and L. Schubert for reviewing the manuscript.

References