

CASE FOR DIAGNOSIS

"Difficult-to-treat" asthma-like symptoms in a 12-yr-old atopic female

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Case history

A 12-yr-old Caucasian female was referred to the pulmonary disease department in July 1997 for progressive on-exertion dyspnoea, persistent nonproductive cough and wheezing. Her symptoms had started 6 months prior to admission and moderately aggressive treatment with high-dose inhaled steroids and short and long-acting β_2 -adreno-receptor agonists, associated with short courses of oral prednisone therapy, had not produced any significant improvement.

The most relevant data in her clinical history were the presence of a mild-to-moderate sensitivity to house

dust mites (not associated, in the past, with significant respiratory symptoms) and the appearance in December 1996, after menarche, of iron-deficiency anaemia treated with oral iron tablets, containing ferrous sulphate 525 mg (Ferrograd[®]). On January 17, 1997 after ingestion of an iron tablet, she complained of sudden dyspnoea, chest pain and nonproductive cough. She was admitted to the accident and emergency department of another hospital and, as a result of a normal chest radiograph and a partial improvement of her symptoms after bronchodilator treatment, she was sent home on inhaled steroids and short-acting β_2 -adrenoreceptor agonists. Ten days later, while coughing, she finally expectorated a

a)



b)



Fig. 1. – a) Posteroanterior; and b) lateral chest radiograph, performed on admission.

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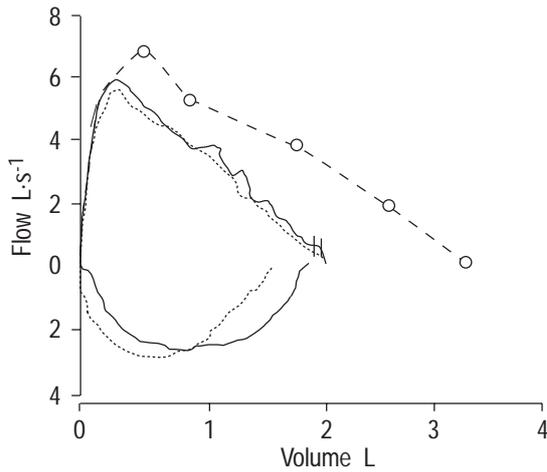


Fig. 2. – Flow/volume loop of the patient before (---) and after (—) inhalation of salbutamol (200 µg) compared to predicted values (○).

Table 1. – Pulmonary function test results

Parameter	Prebronchodilator			Postbronchodilator	
	meas	pred	% pred	meas	Δ %
FVC L	1.95	3.38	58	1.96	1
FEV1 L	1.90	3.12	61	1.95	3
FEV1/FVC %	97	84		100	2
MEF75% L·s ⁻¹	4.77	5.39	89	5.24	10
MEF50% L·s ⁻¹	3.58	3.82	94	3.83	7
MEF25% L·s ⁻¹	1.68	1.97	85	2.14	27
MEF L·s ⁻¹	5.62	6.89	82	6.04	7
FEF25–75% L·s ⁻¹	3.00	3.53	85	3.36	12
FIVC L	1.79	3.22	56	1.50	-16

meas: measured; pred: predicted. % pred: percentage of the pred value; δ: change; FVC: forced vital capacity; FEV1: forced expiratory volume in one second; MEF75%, MEF50% and MEF25%: maximal expiratory flow (MEF) when 75, 50 and 25% of the lung volume remains to be exhaled; FEF25–75%: forced mid-expiratory flow, FIVC: forced inspiratory vital capacity.

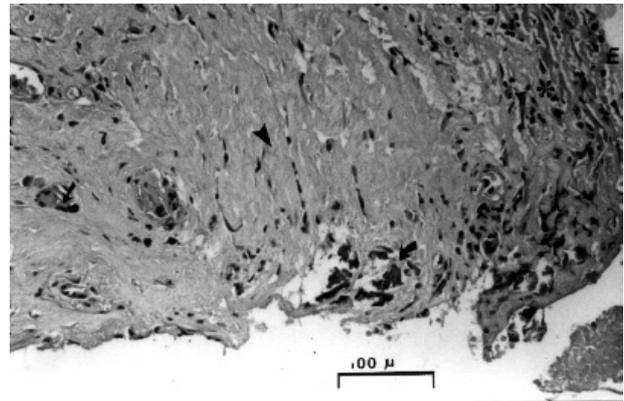


Fig. 4. – Bronchial biopsy specimen. (Haematoxylin and eosin stain; internal scale bar=100 µm.)

partially dissolved Ferrograd® tablet. However, the respiratory symptoms, which included on-exertion dyspnoea with cough and wheezing, persisted and got gradually worse.

On admission, 6 months later, physical examination demonstrated wheezes, rhonchi and rales over the two hemithoraces; a slight decrease in breath sounds was noticed in the areas corresponding to the middle and lower right lobes. The patient was afebrile. Routine blood test results were within normal ranges, including sedimentation rates, white cell counts, electrophoresis of serum proteins and immunoglobulin G levels. Transcutaneous blood gas concentration determination in room air showed normal arterial oxygen (PaO₂) and carbon dioxide tension. Skin-prick tests confirmed moderate sensitivity to *Dermatophagoides Pteronyssinus* and *D. Farinae*.

Chest radiography was performed (fig. 1), together with pulmonary function tests (fig. 2, table 1). These were followed by high-resolution computed tomographic (HRCT) scans (fig. 3) and fiberoptic bronchoscopy with bronchial biopsy (fig. 4).

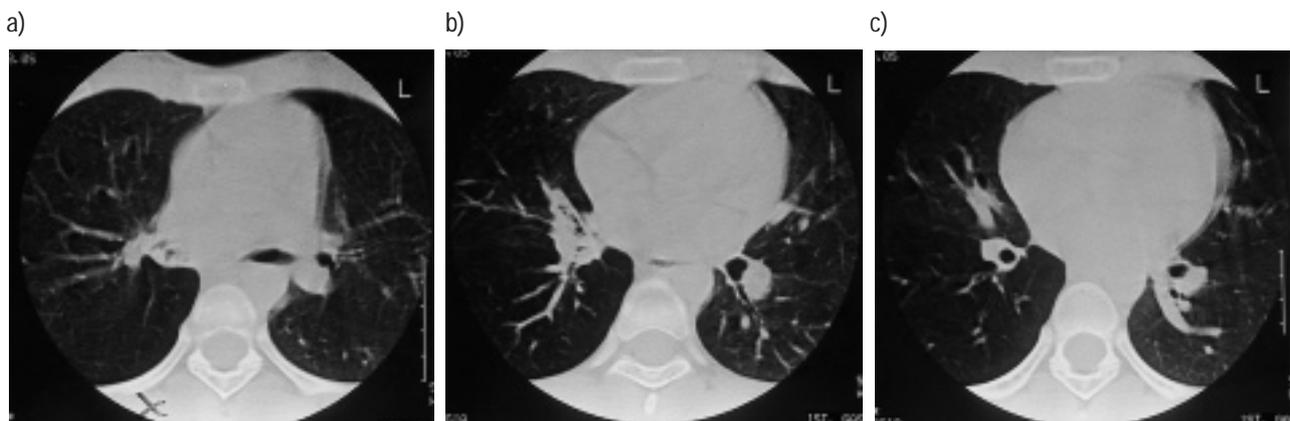


Fig. 3. – High-resolution computed tomography scans performed 1 week after admission: a) 1.5 cm; b) 3.2 cm; and c) 3.6 cm below the tracheal carina.

BEFORE TURNING THE PAGE, INTERPRET THE RADIOGRAPH, PULMONARY FUNCTION TEST RESULTS, HRCT SCANS, AND BRONCHIAL BIOPSY SPECIMEN AND SUGGEST A DIAGNOSTIC HYPOTHESIS AND THE FURTHER MANAGEMENT OF THE PATIENT

Interpretation

Chest radiographs

The posteroanterior chest radiograph, exposed at full inspiration, reveals mild overinflation of the lungs. The hilar shadow of the right hemithorax demonstrates prominent markings, extending into the lower portion of the lungs (fig. 1a).

The right lateral view shows thickening of the distal portion of the pleural fissure separating the middle lobe from the lower lobe (fig. 1b).

Pulmonary function tests

The results of the pulmonary function tests show: 1) a decreased forced vital capacity (FVC) (1.9 L (58% of the predicted value)); 2) a decreased forced expiratory volume in one second (FEV₁) (1.9 L (61% pred)); 3) a normal FEV₁/FVC ratio (97%); 4) a normal forced mid-expiratory flow (FEF_{25-75%}) (3.0 L (85% pred); and 5) a flow/volume loop indicating restrictive condition (table 1, fig. 2). There were no significant changes in the various parameters after inhalation of a β_2 -adrenergic drug (salbutamol 200 μ g).

High-resolution computed tomography

The HRCT scans of the chest demonstrate: 1) partial obstruction of the right intermediate bronchus; b) a bronchial/peribronchial infiltrate, with a homogeneous opacity involving the right middle lobe bronchus; and 3) a homogeneous linear opacity with segmental distribution in an area corresponding to a segment of the right middle lobe (fig. 3).

Fibreoptic bronchoscopy

Fibreoptic bronchoscopy revealed 80% concentric stenosis of the lower portion of the right intermediate bronchus, with involvement of the middle lobe bronchus orifice. The bronchial mucosa at that level was oedematous and hyperaemic, with disseminated greenish-yellow submucosal spots. Bronchial biopsy revealed epithelial damage with mild inflammatory infiltrates and subepithelial fibrosis (fig. 4). The infiltrates were characterized mainly by the presence of mononuclear cells; fragments of ferrous pigments (Perls' stain-positive) are seen as aggregates (arrows).

Diagnosis: "Bronchial obstruction of the right intermediate bronchus with segmental atelectasis of the middle lobe, induced by 'iron dusts'".

Treatment and clinical course

The endoscopic demonstration of stenosis of the lower portion of the right intermediate bronchus involving the middle lobe bronchus and the histological evidence of fibrotic changes induced us to consider laser therapy. The bronchial stenosis was therefore treated with neodymium-yttrium aluminium garnet (Nd-YAG) laser applications on

three subsequent occasions during fibreoptic bronchoscopy, 1 week, and 1 and 2 months later. A full and complete recanalization of the airways was achieved, the pulmonary function test results returned to normal values and the "asthma-like" symptoms disappeared.

Discussion

Foreign body aspiration is an alarming experience, which is often associated with acute dyspnoea and may be immediately followed by laryngeal oedema and asphyxia. This event occurs mainly in children and elderly people. In the adult population, it is seen only in patients with neurological disorders, unconsciousness, alcohol or sedative abuse, during local anaesthesia for dental procedures or following manipulations at tracheostomas or endotracheal tubes [1]. Unawareness of the inhalation, which can occur with small foreign bodies, or neglect of symptoms, can make diagnosis difficult, allowing the foreign body to stay in the lower airways (usually the right lower or the right middle lobe) for variable lengths of time.

The most common presentations after undiscerned foreign body inhalation include cough, expectoration, wheezing, dyspnoea, chest pain, fever and haemoptysis, which can lead to the mistaken diagnoses of bronchial asthma, bronchitis, chronic pneumonia and pulmonary embolism [2]. Indeed, an erroneous diagnosis of bronchial asthma had been made for the patient described here, prior to admission to our department, based on clinical symptoms (dyspnoea, chest pain, and nonproductive cough) and a history of allergic sensitization to ubiquitous inhalant allergens.

According to international guidelines, in order to establish a clear diagnosis of asthma, the clinician should determine not only that symptoms of episodic airway obstruction are present but also that the airflow obstruction is at least partially reversible and that alternative diagnoses can be excluded [3]. Pulmonary function tests performed in this patient demonstrated a clear restrictive pattern, with no changes after inhalation of salbutamol. Indeed, the lack of improvement after therapy with β_2 -adrenergic drugs associated with inhaled and oral steroids, although insufficient for making a diagnosis, should have induced the clinicians to carefully revise the patient's clinical history and take into account diseases other than asthma.

In addition to local obstruction and irritation, which can induce asthma-like symptoms, inhalation of ferrous sulphate or other chemically active compounds can lead to airway tissue necrosis with granuloma formation and fibrotic stenosis [4]. In the case presented here, the endoscopic appearance of the bronchial mucosa 6 months after iron inhalation was characterized by oedema and hyperaemia and disseminated greenish-yellow submucosal spots, corresponding to iron deposits.

Indeed, iron is a transition metal that is able to cause direct oxidative damage (such as lipid peroxidation) and to generate the extremely toxic oxygen radicals superoxide and hydroxyl [5]. Finally, transition metals may produce oxidative damage indirectly by recruiting and activating inflammatory cells, polymorphonuclear leukocytes and macrophages, which are the main sources of reactive oxygen species.

Nine cases of ferrous sulphate tablet inhalation have been described to date, all in females aged 12–80 yrs, who

had been prescribed oral ferrous sulphate tablet treatment [6, 7]. Review of these cases suggests that, if the iron tablet is not removed early after inhalation, local necrosis on an oxidative basis can occur, leading in some cases to established stenosis [8]. The clinical progression can be more favourable, with necrosis repair occurring spontaneously or after a short steroidal course. However, severe complications may occur, as recently reported for a 59-year-old patient who died owing to massive haemoptysis 10 days after aspiration, despite relatively early tablet removal [9]. Autopsy demonstrated the death to be due to deep necrosis of the intermediate bronchus and the walls of the pulmonary artery and the right upper vein, probably caused, at least in part, by local oxygen radical production [9].

In addition to medical treatment with anti-inflammatory agents, localized refractory stenosis of the tracheobronchial tree may be managed with segmental resection [8]. More extensive involvement may require prolonged endotracheal intubation, external tracheal splinting or the use of a Silastic tube prosthesis or metal stent [10]. Our experience demonstrates that neodymium-yttrium aluminium garnet laser therapy may be considered a good therapeutic approach to endobronchial lesions in airway granulomatous reaction to iron dusts. Finally, if iron supplementation is needed in high-risk (and also in low-risk?) persons, tablets should be avoided, preferring safer formulations such as syrups or soluble powders.

Keywords: Bronchial stenosis oxygen radicals transition metals YAG laser therapy

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References

1. Limper AH, Prakash UBS. Tracheobronchial foreign bodies in adults. *Ann Intern Med* 1990; 112: 604–609.
2. Hill SN, Main ANH, Fuggle WJ. Covert inhalation of tablet causing fatal pneumonia. *Postgrad Med J* 1988; 64: 66–67.
3. National Asthma Education and Prevention Program. Guidelines for the Diagnosis and Management of Asthma. Expert Panel Report 2. Publication No. 97-4053. National Institute of Health, National Heart, Lung and Blood Institute, 1997.
4. Lamaze R, Tréchet P, Martinet Y. Bronchial necrosis and granuloma induced by the aspiration of a tablet of ferrous sulphate. *Eur Respir J* 1994; 7: 1710–1711.
5. Poli G, Parola M. Oxidative damage and fibrogenesis. *Free Radical Biol Med* 1997; 22: 287–305.
6. Melillo G, Scala G, Chiummariello A, Palumbo U. Sténose de la bronchie principale gauche, secondaire à l'inhalation d'un médicament à base de sulfate ferreux. *Bronches* 1975; 25: 184–188.
7. Hirschler-Schlute CJW, Van der Wal AM, Edens ET. Aspiratie van Ferrogradumet. *Ned T Geneesk* 1981; 125: 15–17.
8. Mizuki M, Onizuka O, Aoki K, Tsuda T. A case of remarkable bronchial stenosis due to aspiration of delayed-release iron tablet. *Nippon Kyobu Shikkann Gakkai Zasshi* 1989; 27: 234–239.
9. Evrard C, Coffin O, Kaladji C, Brun J, Benard Y, Doumert J. Hémoptisie massive 10 jours après extraction bronchique d'un comprimé de sulfate ferreux inhalé accidentellement. *Presse Med* 1990; 19: 34–35.
10. Sacco O, Fregonese B, Oddone M, *et al.* Severe endobronchial obstruction in a girl with relapsing polychronidritis: treatment with Nd Yag laser and endobronchial silicon stent. *Eur Respir J* 1997; 10: 494–496.