ISOCYANATE EXPOSURE - AN UNUSUAL CASE OF SPRAY PAINTER'S LUNG

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ABSTRACT
Isocyanates are most commonly responsible for occupational asthma and rarely cause hypersensitivity pneumonitis (HP). Spray painters are particularly at high risk of developing these adverse respiratory outcomes associated with exposure to isocyanates. Hypersensitivity pneumonitis is a poorly understood entity characterised by a variety of clinical presentations, which can also overlap with other lung diseases. There are no validated diagnostic criteria for HP. Specific IgE to isocyanates will only be found in a minority of symptomatic individuals while specific IgG for isocyanates seem to be merely an indicator of exposure. Sensitisation may occur due to skin or inhalational exposure. This case report highlights the insidious onset of the disease associated with progressive respiratory impairment and symptoms that can occur without clearly documented acute episodes, as well as the complex diagnostic and management aspects related to isocyanate induced HP. A high index of suspicion, a careful history and a multidisciplinary approach is key to accurate diagnosis. Avoidance of exposure to the offending agent is the mainstay of treatment and prevention of progression to chronic disease. The Compensation for Occupational Injuries and Diseases Act (COIDA) recognises HP due to toluene diisocyanate (TDI) as an occupational disease. Workplace exposure risk management is required to protect the affected worker as well as other unaffected workers.

INTRODUCTION

Polyisocyanates, a group of low-molecular weight cross-linking agents, are industrial chemicals containing highly unsaturated N=C=O groups.[1,2] They are unique in their ability to catalyse the production of polyurethane, a product of great commercial importance. Toluene diisocyanate (TDI), hexamethylene diisocyanate (HDI) and methylene diphenyl diisocyanate (MDI) are the most frequently used diisocyanate monomers.[2] Important industry uses include flexible and rigid foams, sealants, adhesives, external coats and paints, lacquers, inks, insulating materials, varnishes, rubber modifiers, and bonding and vulcanising agents.[3] Polyisocyanates are the most commonly identified cause of occupational asthma (OA) worldwide, but exposure can result in a spectrum of adverse health effects including reactive airways dysfunction syndrome (RADS) or irritant-induced asthma, hypersensitivity pneumonitis (HP), irritant bronchitis, rhinitis, and dermatitis, as well as pulmonary oedema.[3-6]

PRESENTING COMPLAINT

A 54-year old man complained of a dry cough and shortness of breath accompanied by decreased effort tolerance over a period of 2 years. His original baseline effort tolerance was 10 kilometres (km) on a flat surface and currently this was reduced to 2 km. He denied any nasal symptoms. He had been working in the automobile spray painting industry for 38 years. Initially, he only experienced symptoms during and after spray painting at work. There was no acute episode that was associated with these symptoms, instead the symptoms were of insidious onset over the previous 2 years. He noticed his symptoms were much better when he was on vacation or away from work for more than two days. The symptoms had worsened after spray painting at work, but over time his dry cough persisted during weekends when he was off work as well.

MEDICAL HISTORY

The worker had been previously diagnosed with liver and lung abscesses by a pulmonologist, for which he had been fully treated. He had also undergone a thoracoscopic lung biopsy and lung resection during this period for the same symptoms that he currently reported. The worker had had a pacemaker inserted 10 years ago for which he could not remember the exact indication. There was no family history of allergy or lung problems, nor was he on any medication.

SOCIAL HISTORY

He was a non-smoker and there were no smokers in the home. He lived with his wife and children in a brick house

with modern amenities. They had no birds or any other pets in the home that may have pointed to any organic dust exposures.

OCCUPATIONAL HISTORY OR EXPOSURES

The worker had worked for his current company for 5 years. He worked a 40 hour week, Monday to Friday, from 07h30 to 16h15, for a heavy duty construction and mining vehicle manufacturing company of bulldozers and dump trucks as a spray painter. He had recently been put off work for 3 months due to his illness prior to him being seen at our clinic. He was exposed to spray paint chemicals for 4 to 6 hours per day. The spray paints included hexamethylene diisocyanate (HDI) that was present in Carbothane 134 paint and curing agent, Ducol 2K fast hardener and epoxy resins in Carbomastic 15 paint. His personal protective equipment (PPE) included an overall top and trousers, safety boots and a full face respirator. Although, he was initially supplied with a half face respirator with cartridges, this was replaced with a full face respirator with cartridges in the past 3 years. Prior to his current job, he performed spray painting activities for another company as a contractor for 7 years and in other automobile panel beating shops for a further 26 years.

CLINICAL EXAMINATION

He appeared generally well. General examination revealed early clubbing of his fingers. He weighed 78 kilograms (kg) and had a body mass index of 30. Nasal examination revealed 50% bilateral turbinate swelling. On cardiovascular examination he had a raised blood pressure of 200/110 with a regular pulse of 72 and was haemodynamically stable with no evidence of cardiac failure. However, he was tachypnoeic having a respiratory rate of 24/minute. His oxygen saturation on room air was 98%. He had bilateral mildly decreased breath sounds posteriorly, but no crackles nor any wheeze. His abdominal and central nervous system examination was unremarkable.

SPECIAL INVESTIGATIONS

Pulmonary function tests revealed a mild restrictive pattern, with a carbon monoxide (CO) diffusing capacity within normal limits, as shown in Table I. There were no changes suggestive of asthma.

Original chest radiographs showed an increased cardio-thoracic index, left ventricular configuration and prominent bronchial markings. The images repeated a year later on presentation to our clinic showed increased bilateral reticular shadows, which were more profuse over the bases with some veiling of the cardiac shadow, as seen in Figure 1. The pattern remained relatively unchanged over this period.

Figure 1. CXR showing predominantly basal bilateral reticular shadows.

High resolution CT scan (HRCT) done during this period showed a patchy mosaic pattern, diffuse ground glass

Table I: Pulmonary function tests

	Predicted	Pre-bronchodilator (% of predicted)	Post-bronchodilator	Percentage change
FEV_1 (L)	2.87	1.89 (66%)	2.06 (72%)	9
FVC (L)	3.53	2.65 (75%)	2.84 (80%)	7
FEV_1/FVC %		71%	73%	2
TLCO (ml CO/min/mmHg)	24.7	18.17 (73%)		
KCO	4.28	4.91 (115%)		

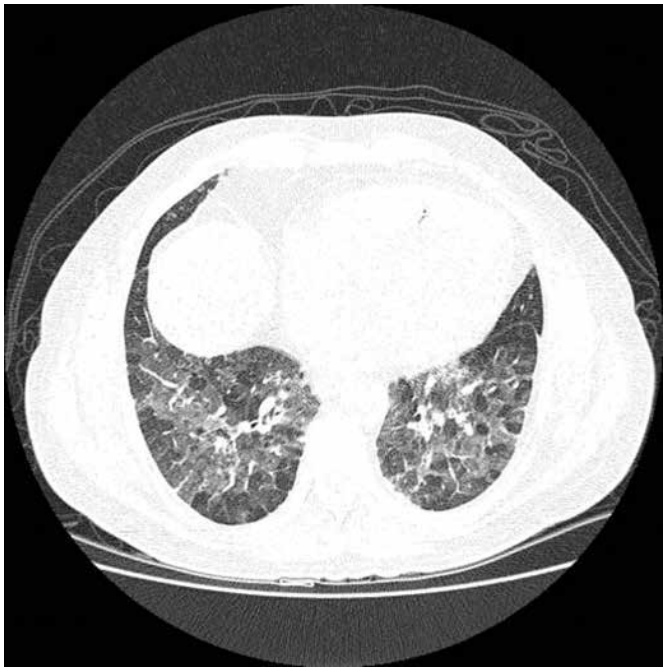

Figure 2. HRCT showing diffuse ground glass opacification.

opacification and air trapping affecting predominately the middle and lower zones (Figure 2).

Histology of pathology specimens obtained from the left lower lobe lung biopsy and resection demonstrated an interstitial fibrosis (Figure 3) and peribronchial distribution of bronchial metaplasia (Figure 4). The pathology report indicated that this was likely to be a late stage fibrotic hypersensitivity pneumonitis with the absence of granulomas and honeycomb changes.

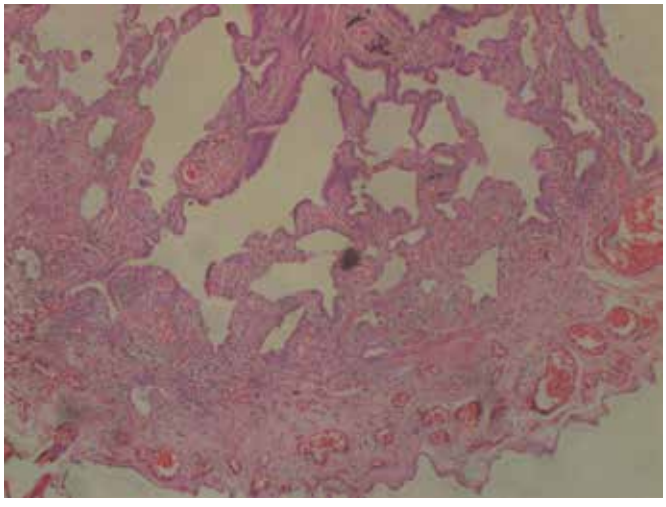

Figure 3. Left lung lower lobe biopsy showing interstitial fibrosis.

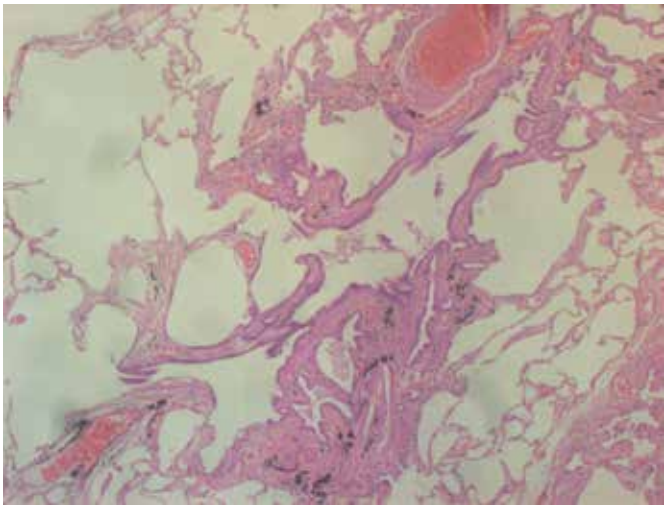

Figure 4. Left lung lower lobe biopsy showing peribronchial distribution of bronchial metaplasia.

INITIAL ASSESSMENT

The initial assessment was that of late stage hypersensitivity pneumonitis (extrinsic allergic alveolitis) secondary to isocyanate exposure from spray painting. Material safety data sheets (MSDS) were requested from the employer. No treatment was given initially. The IgE ImmunoCAP test for methylene diphenyl diisocyanate (MDI), toluene diisocyanate (TDI) and hexamethylene diisocyanate (HDI) were all <0.10 kU/L (negative). Isocyanate IgG levels were requested and are pending.

CLINICAL COURSE AND MANAGEMENT

On follow up 2 months later, the patient's symptoms persisted and he had started getting episodes of tight chest as well. He had not been back to work during this period. After it was recommended to his employer that he be removed from spray painting activities, he returned to work in the stores department. He commenced treatment with Salbutamol as required and Ipratropium Bromide 80 mcg twice a day but demonstrated no significant clinical improvement. His treatment was then reviewed and a daily dose of prednisone (10 mg) was added, but his pulmonary function tests (PFTs) continued to deteriorate. Four months later the prednisone dose was increased to 20 mg daily and 15 mg of methotrexate was added, but his symptoms remain unchanged. His last PFTs showed a deterioration from baseline of the FEV_1 to 1.55 L (55% predicted), FVC=2.18 L (62% predicted) and ratio of 71%.

WORKPLACE VISIT

A workplace visit was conducted, followed by a meeting with the line supervisor to ascertain the general conditions at

the workplace, to identify sources and duration of exposure, existence of current workplace controls and to determine if alternative placement for the worker was appropriate. The line supervisor was a health and safety representative and was partially aware of the health risks associated with spray-painting. Two large rooms (similar to garages) were used to station the huge mining trucks, while spray painting was done. These rooms had local exhaust ventilation (LEV) extraction at the one end opposite the door. The walls and floors were visibly stained with paint. The visit revealed that health risk assessments and occupational hygiene surveys had not been done. However, each new spray painter had undergone an induction programme. Personal protective equipment (PPE) including overalls, raincoats, safety boots, hearing protection devices, gloves, and safety goggles and respirators were provided. The use of half face respirators with vapour cartridges had been practiced for 5 years while the full face respirator with cartridges had been introduced only in the last 3 years. The source of the isocyanates was confirmed to be from the paints used during spray-painting. One truck typically involved 14 days of work, with 5 days for preparation and 2 to 3 days of spray-painting and the remaining days for finishing. During spray-painting a strong smell of solvents was apparent during the visit.

The workplace visit confirmed that the employee had been accommodated in an alternative job in the tool stores. This job entails handling spare parts from the parts store and transferring them to the mechanical workshop where the tools are issued to other workers. There was no spray paint exposure in this new department.

FINAL ASSESSMENT

A final diagnosis of chronic hypersensitivity pneumonitis (HP) was made based on the pattern of symptoms, exposure to a known causative agent (isocyanate), exposure having preceded the development of the condition, a restrictive impairment on pulmonary function tests and an interstitial lung pattern on histology. This case was submitted to the Compensation Commissioner according to Compensation of Occupational Injuries and Diseases Act (COIDA) as it is a listed under schedule 3 of compensable diseases.

DISCUSSION

Although it is well known that exposure to isocyanate is recognised as one of the major causes of occupational asthma, in contrast, hypersensitivity pneumonitis (HP) due to isocyanates is a rare condition.[7] According to various observational occupational studies, the prevalence of isocyanate-induced HP may vary from 4 to 27% in exposed workers.[8,9] Two major groups of international experts (HP Study Group and National Heart, Lung, and Blood Institute in collaboration with the Office of Rare Diseases (NHLBI/ORD)) have not been able to arrive at a consensual definition of HP.[10] Hypersensitivity pneumonitis accounts for between 4-15% of all interstitial lung diseases in Europe,[11] however the local incidence is unknown.

Antigens responsible for HP usually arise from organic sources such as bacteria, moulds, yeasts or fungi. However chemicals can also act as haptens and induce HP (see Table II).[10] Common occupations involving these antigens include agriculture, detergent manufacture, machine operators, automobile spray painting, and bird breeders. New antigens inducing HP are described every year for both home and work exposures.[12]

Hypersensitivity pneumonitis is an immunologically mediated inflammatory disease of the lung parenchyma due to a combined type III and IV hypersensitivity reaction, which is induced by inhalation of an antigen to which a person has become sensitised.[12] Although many individuals

Table II: Major causes of HP*

Type of Antigen	Examples of Sources
Mushrooms, fungi, yeasts	Contaminated wood, humidifiers, central hot air heating ducts, mouldy hay or grain
Bacteria	Dairy barns, detergents
Mycobacteria	Metalworking fluids, saunas, hot tubs
Bird proteins	Pigeons, dove feathers, ducks, parakeets
Chemicals	Isocyanates, zinc, dyes, anhydrides

*Modified from Lacasse et al.[10]

are exposed to environmental antigens known to induce HP, only 5-15% will develop disease.[11] This suggests that trigger factors such as viruses[13] endotoxins,[14] b-glucan[14] as well as host genetic and immune co-factors may be required to induce disease.[12] Clinical subtypes include acute, sub-acute and chronic depending on the onset and duration of symptoms and there are histological features for each subtype.[15] HP is characterised by a lymphocytic alveolitis and granulomatous pneumonitis and complete improvement if early exposure avoidance is implemented. Chronic exposure can cause irreversible inflammatory processes and lung fibrosis which may lead to progressive HP despite removal from the offending antigen (as illustrated in this case).[16]

Pronk et al. found in their study of 581 spray painters that respiratory symptoms were more prevalent in exposed workers than among comparison office workers.[17] The acute effects of isocyanate exposure are usually eye, nose and throat irritation, coughing, dyspnoea with chills, fever, malaise and earache which is frequently misdiagnosed.[16] Chronic health effects include asthma, HP, pulmonary oedema and dermatitis and recurrent low level exposure may result in an insidious onset with progressive respiratory impairment and symptoms without acute episodes.[16] Serum immunological tests in the form of precipitating serum specific IgE and IgG antibodies to TDI-human serum albumin (HSA) conjugate have been found to have diagnostic value in studies by Park et al.[18] Commercially available HDI-specific IgE and IgG antibodies like ImmunoCAP assay (Phadia, Uppsala, Sweden) and isocyanate-specific IgE and IgG enzyme immunoassay with HDI–HAS conjugates are available overseas,[17] but are unfortunately not available locally. The prevalence of specific IgE sensitisation was found to be low in spray painters (up to 4.2%), while the prevalence of specific IgG was higher (2-50.4%) and strongly associated with exposure.[17] In animals, isocyanate skin exposure is an efficient route to induce sensitisation, with subsequent inhalation challenge resulting in asthma-like responses. Several lines of evidence support isocyanate skin exposure as an efficient route to induce sensitisation.[19,20]

While there are a number of proposed diagnostic criteria for HP, none have been validated.[10] Inhalation challenge tests and broncho-alveolar lavage (BAL) can provide useful, supportive elements in the diagnosis, but both these tests lack standardisation[10] and were not done in this case. The mainstay of management of HP is antigen exposure avoidance, but this may be difficult to achieve in some cases. Systemic corticosteroids are recommended for sub-acute or chronic forms of HP, but do not influence long term outcome.[10] Prognosis is highly variable and dependent on duration, type, exposure intensity, lung pathological changes and possible genetic factors.[10] Overall, there is an increased mortality in patients with HP compared with the general population (hazard ratio = 2.98), even though these individuals are less likely to smoke.[21]

Aside from the clinical management instituted, the following recommendations to employers for exposure control were made:

- Engineering controls: This included providing adequate ventilation in terms of airflow and extraction in the spray-painting rooms. There also needed to be regular maintenance checks and filter changes of the ventilation/extraction system.
- Administrative controls: Measures to limit the number of workers exposed to spray-painting needed to be implemented. An induction program for all workers that included hazard education and standard operating procedures for safe work practices was also advised.
- Workplace health risk assessments should be done every 2 years (according to the Hazardous Chemical Substances Regulations of the Occupational Health and Safety Act). Occupational hygiene measurements of chemicals hazards (airborne levels of isocyanates) may be indicated.
- A medical surveillance program of spray painters was required to be conducted under the supervision of an occupational medical practitioner.
- Personal protective equipment (PPE): This included disposable coveralls, chemical safety goggles, impervious gloves and appropriate respirators (for gas and vapour filtering) according to the specifications in the material safety data sheets.

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DECLARATION OF CONFLICT OF INTEREST

The author declares no conflict of interests.

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1. Duolin HFA Inhaler Package Insert
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