

Occupational Hypersensitivity Pneumonitis Due to Isocyanates: Mechanisms of Action and Case Reports in Japan

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Abstract: Isocyanates are very useful chemicals, and these are important for our daily life. Various products, especially urethane resin, are made from these chemicals. There is no substitute for isocyanates at the present. Isocyanates are potent agents to provoke immunological responses. This article deals with the case reports of hypersensitivity pneumonitis (HP) induced by isocyanates in Japan. It is said that HP is one of the rare diseases induced by isocyanate with very low frequency so far in the world. Certainly there are rare cases of isocyanate-HP also in Japan, but these are the cases only in large enterprises that pay attention to their working places. In Japan, there are several cases of isocyanate-induced HP, which happened in minor enterprises such as those with less than 50 workers. In clinical appearance, there are few conflicts with Western studies. The best choice for sensitized people is isolation from working places. It is important for the workers to understand the diseases. In these days, several tests for diagnosis are developed. It is indispensable to put these tests for prevention of these diseases and improvement of their working places.

Key words: Di-isocyanate, Immunology, Hypersensitivity pneumonitis (HP), Review, Japan

Introduction

Development of chemical industry contributed to our daily life. But we should not forget the fact that the products of the chemical industry elicit many symptoms in the workers who participate in their production¹.

Hypersensitivity pneumonitis (HP), or extrinsic allergic alveolitis, is a descriptive phrase that characterizes a spectrum of lymphocytic and granulomatous interstitial and alveolar filling pulmonary disorders associated with intense and often prolonged exposure to a wide range of inhaled organic dusts and related occupational antigens. The traditional sources of antigen in the classic forms of this disease, such as farmer's lung and bagassosis, have been decaying, actinomyceteladen composts such as moldy hay and bagasse. A wide range of

vegetable and animal dust, and some inorganic and organic simple chemicals are now known to cause the disease^{2,3}. HP is an immunologically induced lung disease caused by inhalation of a variety of environmental agents^{4,5}. HP is not a uniform disease but rather a complex syndrome characterized by varying intensities of responsiveness to different antigens leading to an immunopathology with variable clinical presentation and natural history^{3,6,7}.

In many industrialized countries, chemicals of isocyanate family are required for commercial products, including insulation materials, automobile upholstery, furniture, and surface coatings². Isocyanates such as toluene diisocyanate (TDI), 4,4'-methylenediphenyl diisocyanate (MDI) and 1,6'-hexamethylene diisocyanate (HDI) are most commonly utilized in industry as cross-linking and polymerizing agents in the manufacture of urethane products¹.

Recently, the cases of HP induced by inhalation of organic

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substances such as isocyanates vapor are reported in Western countries⁸⁻¹³) and also in Japan¹⁴⁻³⁶). Isocyanate asthma is the major allergic disease induced after isocyanates exposure. A HP type of reaction has also been reported but only in a few isolated cases¹³). It is about 1% of workers inhaled isocyanates³⁷). However, it is important for solutions of mechanisms of action after isocyanates exposure to investigate that HP induced by inhalation of low molecular organic substances such as isocyanates vapor^{2, 38}). Perhaps, appearance of asthma or HP is based on individual variations.

Hypersensitivity Pneumonitis due to Isocyanates

Inhalation of organic materials induces HP. There are some patients of HP due to isocyanates in urethane foam workers or car painter. However, in spite that large quantity of these chemicals is used in various industries, frequency of this disease is rather rare. Weak antigenicity of isocyanates themselves or short fixation of working is thought for this reason³⁹). TDI is known as the major cause material in Japan, and MDI or HDI is the minor one. On the other hand, in Western case reports, the major cause material is MDI. It is because, MDI has low vapor pressure and weak antigenicity than TDI⁴⁰). In this reason, MDI is more frequently used than TDI in the West.

Investigations of HP in Western Countries

HP has been reported in workers exposed to isocyanates^{8-13, 41-47}). Two studies based on 1,780 workers from different isocyanates processing company³⁷) and 167 workers in a wood shipboard manufacturing plant¹²) provided evidence that isocyanates cause this chronic lung disease. Vandenplas *et al.* demonstrated occurrence of HP in 4.7% of the workers exposed to a resin containing MDI or MDI-prepolymers using specific inhalation challenges hypersensitivity pneumonitis¹²), whereas Baur found a frequency of approximately 1% among symptomatic isocyanates workers³⁷). Baur³⁷) evaluated case histories of 1,780 isocyanate workers and concluded that occupational exposure to isocyanate vapors and aerosols induces typical HP in at least 1% of isocyanate workers with symptoms. In both studies, MDI or MDI-prepolymers were found to be the main causal factors. Typical symptoms include work-related dyspnea, malaise, and fever several hours after work with isocyanates. The existing literature consists of case reports in which the relationship to measured exposures cannot be determined, although in the opinion of some experienced observers, HP results from circumstances of

high exposure concentrations¹²). There is no quantitative basis for estimating either the risk or the severity of this response in relation to exposure.

Case Reports of HP in Japan

As occupational respiratory diseases due to isocyanates, especially due to TDI, bronchial asthma has been well known. In spite of low frequency, HP occupies the attention of the whole world today. It is because, HP is thought respiratory disease induced by isocyanates with different immunological mechanisms from asthma^{8-13, 39-45}). In Japan, several cases of HP have been reported. The first case in Japan was reported in 1981, but it was not an original paper⁴⁸). From 1982 to 1998, there are twenty-three original papers of HP¹⁴⁻³⁶). Thus, from a viewpoint of clinical medicine and working health, this paper reviews those reports and at the same time, considers the problems of HP due to isocyanates.

Chronic HP due to isocyanates is rare^{31, 36}) and sometimes severe³²). Early detection and early isolation from allergens are important for treatment^{14, 15, 18, 24, 28, 35, 36}). In clinical appearance, there is no conflict with Western studies. Specific IgE antibodies cannot be detected except one case³⁰) (Tables 1 and 2). The prognosis is reported as good in most (but not all) cases provided exposure ceases. In one reported case, clinical improvement occurred in spite of continuing exposure²³). Duration of less than 6 months is 12/23 (52.2%), that of 7 months to 1 year 1/23 (4.4%) and that of more than 1 year is 10/23 (43.5%). Chest X-ray findings are the same as other HP, but they have mild lesions. In pulmonary histological findings, frequency of the presence of epithelioid sarcoma is low (6 cases per 19 cases: 31.6%) (Tables 3, 4).

In Asia-Pacific region, isocyanate industry is becoming as important as in Japan. The occurrence of the similar HP cases in these countries should be avoided. The existing isocyanate industries have a duty to inform of these problems to developing countries and for checking the health problems.

Mechanisms of action

HP is a granulomatous inflammatory reaction in terminal airways, alveoli, and surrounding interstitium. Extensive information on the pathology of this disorder was obtained by open lung biopsies and by analysis of BALF (Bronchoalveolar lavage fluid)⁵). According to the pathogenesis, there are several lines of evidence supporting the involvement of both type III immunity (IgG-dependent; which may lead to the formation of immune complexes and the activation of the complement cascade) and type IV immunity (cellular; antigen-responsive T cells with

Table 1. Original case reports of hypersensitivity pneumonitis (HP) in Japan (1982–1998): Immunologic diagnosis and findings (1)

Reference	sex/age	allergy	work/duration	respiratory dysfunction	immunological tests	workplace association	cause materials
Hanawa <i>et al.</i> (1982)	M/49	(-)	piano factory manager/4yr	restrictive, diffusible	ND	provocative test (+)	MDI
Dosaka <i>et al.</i> (1984)	M/62	(-)	car repairer /3mon	restrictive, diffusible hypoxemia	TDI-GPSA** specific IgG(+), IgE(-)	(+)	TDI
Fujimura <i>et al.</i> (1984)	F/52	nc*	painter /13yr	restrictive, diffusible peripheral respiratory obliteration	TDI-HSA, TMI-HSA‡ skin test (+)	(+)	TDI
Kimura <i>et al.</i> (1985)	M/44	nc*	car painter /25yr	restrictive	specific IgE (-)	provocative test (+)	HDI
Kato <i>et al.</i> (1986)	M/32	(-)	agriculture /1mon	restrictive	ND	(+)	paint
Narita <i>et al.</i> (1987)	M/46	nc*	painter /28yr	diffusible, hypoxemia	ND	provocative test (+)	paint
Takazakura <i>et al.</i> (1989)	M/42	(-)	founder/3mon	hypoxemia	MDI-HSA(+)(±)(+)† TDI-HSA(-)(-)(+)† TMI-HSA(+)(+)(+++)†‡	(+)	MDI
	M/49	(-)	founder/2mon	hypoxemia	MDI-HSA(++)(±)(-)† TDI-HSA(-)(-)(+)† TMI-HSA(+)(±)(+)†‡	(+)	MDI
Hosono <i>et al.</i> (1989)	M/65	(-)	car repairshop manager/6yr	diffusible	MDI patch test (+)	(+)	MDI
Nozawa <i>et al.</i> (1989)	M/46	nc*	painter /29yr	restrictive, diffusible	MDI-HSA, TDI-HSA skin test (+)	provocative test (+)	TDI
Yoshizawa <i>et al.</i> (1989)	M/41	(-)	car painter /1wk	hypoxemia	MDI-HSA specific IgG(+), IgE(-)	(+)	TDI

*nc: not clear, **GPSA: guinea pig serum albumin, ‡ TMI: p-tolyl-isocyanate, † results of (skin test) (peripheral lymphocyte stimulation test) (Ouchterlony test) in order.

conjugates of isocyanates and human serum albumin are present both in BALF²³⁾ and in peripheral blood^{49, 50)} (Fig. 1). Although the individual pathogenetic role of these responses is not clear, it can be assumed that diagnostic parameters, such as specific IgG antibodies and antigen-specific lymphocytic reactions, are operative in this chronic interstitial lung disease³⁷⁾.

Immediately after exposure to isocyanates (ex. after workplace related challenge tests) during the acute stage, an elevated neutrophil count in the BALF is often detectable, overlapping lymphocytic alveolitis⁵⁰⁾. The analysis of T cell subsets showed that CD8-lymphocytes (suppressor and cytotoxic) are the predominant cells retrieved from the BALF of these patients^{51, 52)}. Data on the characteristics of these CD8+ -cells⁵³⁾ in isocyanates induced HP is not available

and the cytokines generated by these lymphocytes have not been studied yet. It is likely that they are the cytokines associated with delayed hypersensitivity and IgG antibody production.

In addition, BALF macrophages of HP patients are in an activated state and produce not only the cytokines responsible for lymphocyte activity but also toxic reactive oxygen species such as superoxide⁵⁴⁾. Corresponding to the experiences with patients suffering from farmer's lung or humidifier lung, the strong preponderance of isocyanates alveolitis in non-smokers is notable [70%³⁷⁾]. This suggests that the nonsmoking status is associated with an increased risk of isocyanates alveolitis. Evidence suggests that smokers have a reduced immune response to inhaled antigens, and effector functions alveolar macrophage are significantly impaired

Table 2. Original case reports of hypersensitivity pneumonitis (HP) in Japan (1982–1998): Immunologic diagnosis and findings (2)

Reference	sex/age	allergy	work/duration	respiratory dysfunction	immunological tests	workplace association	cause materials
Kobayashi et al. (1990)	M/47	nc*	founder /4mon	hypoxemia restrictive, diffusible	TDI-HSA (+)¶ MDI-HSA, HDI-HSA (-)¶	challenge test (-)	isocyanate
Idezuka et al. (1991)	M/41	(+)	painter /6mon	diffusible, FVC, FEV1 normal	TDI-HSA (+)¶ MDI-HSA, HDI-HSA (-)¶	(+)	TDI
Akimoto et al. (1992)	M/68	(-)	painter /3mon	restrictive	TDI-HSA(+) MDI-HSA(+)	(+)	TDI, MDI
Nagai et al. (1992)	M/65	(-)	car repairshop manager/5mon	diffusive, hypoxemia	patch test (+)	patch test (+)	MDI
Suzuki et al. (1992)	M/64	nc*	car factory manager/7mon	restrictive, diffusible	TDI-HSA(+)(+)(-)+† MDI-HSA(+)(-)(-)+† HDI-HSA(-)(-)(-)+† specific IgE (+)	patch test (+), provocative test (+)	paint
Usui et al. (1992)	M/60	(-)	car painter /1mon	diffusible	TDI-IgG, TDI-IgA (+) HDI-IgG, HDI-IgA (+)	(+)	HDI
Bando et al. (1993)	M/50	nc*	painter /nc	mixed	TDI-HSA(±)(-)(+)+†	provocative test (+)	TDI
Nakamura et al. (1995)	M/55	nc*	car repairman /35yr	hypoxemia	TDI-IgG (++)	(+)	TDI
Nakagawa et al. (1996)	M/40	nc*	car painter /5yr	restrictive, diffusible, hypoxemia	TDI-HSA, MDI-HSA specific IgG, IgA (-)	(+)	isocyanate
Abe et al. (1997)	M/69	nc*	machine manufacture /3mon	restrictive, diffusible	TDI-IgG(+)(-)# HDI-IgG(-)(±)#	(+)	isocyanate
Kaji et al. (1997)	M/42	nc*	soft urethane production/5yr	restrictive	TDI-HSA, MDI-HSA specific IgG (-), IgA (-)	(+)	TDI
Nomura et al. (1998)	M/54	nc*	vinyl manufacture /3mon	restrictive, diffusible	isocyanate (+)(+)+‡	(+)	isocyanate
Yoshimura et al. (1998)	M/51	nc*	polyurethane painter/10yr	mixed, hypoxemia	challenge test (-) MDI-IgG, IgA (+)	provocative test (-)	MDI

*nc: not clear, **GPSA: guinea pig serum albumin, #: results of detection in (BALF) (serum) in order, † results of (skin test) (peripheral lymphocyte stimulation test) (Ouchterlony test) in order.

by smoking⁵⁵). In BALF cell finding also in not-isocyanates-induced HP, smoking is the most important factor⁵⁶).

It should be mentioned that the presence of isocyanate-HSA-specific IgG antibodies is, by themselves, not a reliable indicator of isocyanates induced allergic alveolitis, since they can be detected in the serum of affected subjects as well as in exposed workers without symptoms^{45, 47}).

In Japanese cases, there are no conflicts with Western studies. It is thought that type III or IV allergy participates in isocyanate-induced HP. However, investigating case reports, findings have not only similarities but also differences in several points. For example, isocyanates-HSA are detected

in most cases, histological findings are same. In other hand, respiratory dysfunctions and detection of specific antibodies (IgG, IgE) are different. So, it is difficult to draw a clear line between these two types by investigation of the findings. There are some cases where type III immunity is dominant^{22, 25, 35}. In most cases, these immunities act simultaneously, and complicatedly in this disease^{14, 16, 18-21, 27, 28, 30}).

Which is more relevant to the appearance of HP? concentration or duration? In animal study, it is clear that concentration, duration and inhalation routes are important factors for the appearance of the disease⁵⁷).

Table 3. Original case reports of hypersensitivity pneumonitis (HP) in Japan (1982–1998): Respiratory function and pulmonary findings (1)

Reference	sex/age	Chest X-ray*	Thoracic CT*	BALF**	TBLB*
Hanawa <i>et al.</i> (1982)	M/49	ground-glass appearance in the right upper and bilateral lower lung field with several thick linear shadows just above the diaphragm	nd	nd	nd
Dosaka <i>et al.</i> (1984)	M/62	diffuse particle and patchy shadows in bilateral lung fields	nd	nd	Masson body (+) alveolitis
Fujimura <i>et al.</i> (1984)	F/52	diffuse small granular shadows with upper field shrinkage	nd	lymphocyte ↑	nd
Kimura <i>et al.</i> (1985)	M/44	diffuse microparticle pattern in birateral down area	nd	lymphocyte ↑	lymphocyte ↑ fibrosis mononuclear cell invate
Kato <i>et al.</i> (1986)	M/32	diffuse small nodular shadows	diffuse small nodular shadows	lymphocyte ↑	inflammation cell invasion Masson body (–) sarcoma (–)
Narita <i>et al.</i> (1987)	M/46	increase markings with diffuse small particle pattern in bilateral area	nd	nd	random tylosis, organization of exudate, Foamy cell in alveolus Masson body (+)
Takazakura <i>et al.</i> (1989)	M/42	small nodular shadows	nd	nd	alveolitis epithelioid sarcoma (+) Masson body (+)
	M/49	small nodular shadows	nd	nd	alveolitis epithelioid sarcoma (+) Masson body (+)
Hosono <i>et al.</i> (1989)	M/65	diffuse microparticle pattern in bilateral lower fields	nd	CD4/CD8<1	lymphocyte infiltration, increasing macrophage hypertrophy in alveolus
Nozawa <i>et al.</i> (1989)	M/46	diffuse microparticle pattern in bilateral lower lung fields	diffuse small nodular shadows	lymphocyte ↑ CD4/CD8<1 total cel number ↑	alveolitis without fibrosis edematous thickness of alveolar septum and infiltration of mononuclear cells Masson body (+) granuloma (–)
Yoshizawa <i>et al.</i> (1989)	M/41	nd	nd	IgA (+) IgG (+)	alveolar edema and lymphocytic infiltrates in alveolar and bronchiolar walls

*nd = not done **↑ = increase in number.

Diagnosis

Diagnoses of the symptoms possibly caused isocyanates are clinical recording, work recording, measure of lung function, and inhalation tests⁵⁸. Especially, question and answer is important, relation between clinical recording and work recording and change of symptoms and work⁵⁹. If

there is an acute response in and after exposure of dust and gas, or symptoms appear periodically, or recover in weekend and the day not working, the case needs attention. Symptoms involve dry cough, roaring, dyspnea, and strangulation of chest are frequent. Measuring of PEF_R (Peak expiratory flow rates) before and after working and change within one

Table 4. Original case reports of hypersensitivity pneumonitis (HP) in Japan (1982–1998): Respiratory function and pulmonary findings (2)

Reference	sex/age	Chest X-ray	Thoracic CT*	BALF**	TBLB*
Kobayashi <i>et al.</i> (1990)	M/47	diffuse small particle pattern in all lung field	diffuse small particle pattern in all lung field	lymphocyte ↑ CD4/CD8<1	infiltrate of inflammation cells
Idezuka <i>et al.</i> (1991)	M/41	diffuse ground-glass pattern in bilateral middle down area	bilateral diffuse microgranular shadows, mainly in the middle and lower fields	T lymphocyte ↑ CD4/CD8<1	Masson body (–) sarcoma (–) alveolitis
Akimoto <i>et al.</i> (1992)	M/68	diffuse granular and reticular shadows	irregular distribution of reticular and small nodular shadows	lymphocyte ↑	Masson body (+) cell infiltration in the alveoli mild accumulation of macrophages
Nagai <i>et al.</i> (1992)	M/65	diffuse reticulogranular shadows in the bilateral lower lung fields	nd	T lymphocyte ↑ CD4/CD8<1	accumulation of macrophages lymphocyte infiltration
Suzuki <i>et al.</i> (1992)	M/64	ground-glass interstitial pattern	ground-glass interstitial pattern	T lymphocyte ↑ CD4/CD8<1	Masson body (+) diffuse alveolitis
Usui <i>et al.</i> (1992)	M/60	diffuse ground-glass infiltrates	focal fine nodular infiltrates in the lung fields	Total cell number ↑ specific IgG and IgA (+) (TDI and HDI)	nd
Bando <i>et al.</i> (1993)	M/50	interstitial shadows in the bilateral lower lung fields	diffuse non-uniform increase in intensity and micronodular shadows in the bilateral lung field	T lymphocyte ↑ CD4/CD8<1 macrophage ↑	thickening of alveolar speta and infiltration of eosinophils and lymphocytes into alveolar speta and bronchioles
Nakamura <i>et al.</i> (1995)	M/55	small nodular and reticular shadows in both lung fields	reticular and ringed shadows in both lung fields	T lymphocyte ↑ CD4/CD8<1	not clear (open lung test was done) alveolitis and fibrosis infiltration of mononuclear cells Masson body (–), granulomas (–)
Nakagawa <i>et al.</i> (1996)	M/40	ground-glass pattern nodular opacity	light patchy shadows in the bilateral lung field	lymphocyte ↑ CD4/CD8<1	alveolitis with lymphocyte infiltration
Abe <i>et al.</i> (1997)	M/69	diffuse reticular shadows in the bilateral middle lower lung fields	ground-glass interstitial funicular and linear pattern	lymphocyte ↑ CD4/CD8<1	Masson body (+), sarcoma (–) lymphocyte infiltration
Kaji <i>et al.</i> (1997)	M/42	irregular macular pattern in the lung fields	focal fine nodular infiltrates in the lung fields	lymphocyte ↑	Masson body (–), sarcoma (–) fibrosis
Nomura <i>et al.</i> (1998)	M/54	small particle pattern	small particle pattern in bilateral back lower lung field	lymphocyte ↑	alveolitis
Yoshimura <i>et al.</i> (1998)	M/51	diffuse patchy infiltrative changes in both lung fields	patchy air-space opacification, air bronchograms in both lung fields, honeycombing in the subpleural area	Total cell number ↑ lymphocyte ↑ CD4/CD8<1	lymphocyte infiltration macrophages infiltration epithelioid sarcoma (+)

*nd = not done, **↑ = increase in number.

week for several months, confirms the relationship between work and symptoms. If needed, under supervision watch, inhalation challenge test can be done²⁶⁾. If origin is not clear or gas and mixture, work at workplace of patients, observation of symptoms appearance and change of lung function; an

environment provocative test may be appropriate^{60, 61)}. If causative allergens are clear, they may be used to see skin reaction and detect specific IgE antibody. And except that, using inhalation of histamine and acetylcholine, or diagnosis asthma using airway reactive test.

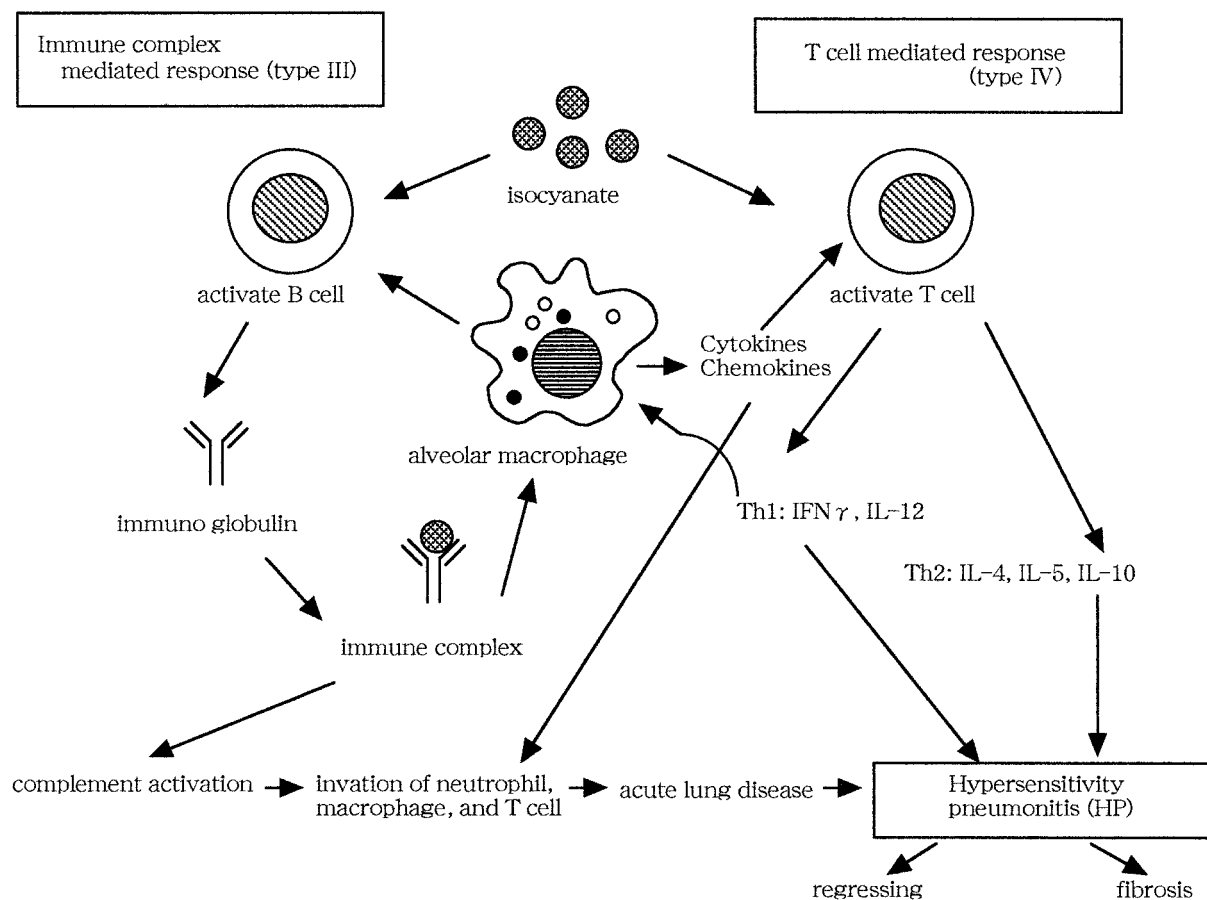


Fig. 1. Mechanisms of hypersensitivity pneumonitis (HP) due to isocyanate.

According to the pathogenesis of hypersensitivity pneumonitis (HP), there are several lines of evidence supporting the involvement of both type III and IV immunity. It is now clear that CD4⁺ Th cells have two different profiles of cytokine production, such as Th1 (Th1 helper T cell) and Th2 (Th2 helper T cell), and those patterns select between the two basic types of response mediated by CD4⁺ T-helper cells. Typical human Th1 cytokines include interferon- γ (IFN γ) and interleukin 12 (IL-12), and so on. By contrast, Th2 cells are typified by the production of interleukin 4 (IL-4), interleukin 5 (IL-5) and interleukin 10 (IL-10) also commonly produced.

In diagnosis, careful work recording is needed. Lung function test detects obstructive disorder or normal appearance. After exposure, airway flow and airway reactivity (methacholine and histamine challenge test) change fugitive, the symptoms may be isocyanate asthma⁶². Classically, the clinical presentation of HP has been divided into acute, subacute, and chronic forms on the basis of clinical features. The clinical features of chronic HP are subjective complaints of cough and dyspnea on exertion, imaging and pulmonary function abnormalities, and poor prognosis with a strong resemblance to idiopathic pulmonary fibrosis (IPF). In isocyanate-HP, clinical presentations are similar to other HP. Diagnosis was confirmed by restrictive ventilatory patterns, reticular or nodular lung patterns in the chest X-ray film, and serum IgG antibodies specific to isocyanate-HSA conjugates. Additional typical findings are lymphocytic

alveolitis with CD8 predominance in the BALF analysis (CD4/CD8-ratio<1.0), lymphohistiocytic patterns, mostly associated with mild fibrosis in lung histology³⁷, and Masson body and epithelioid granuloma are detected in TBLB³⁸. Thoracotomy was done in two cases^{16, 31}. Such an invasive test is burden for those patients, so it should not be done.

In various tests for diagnosis, skin test, especially patch test, is simple and useful^{21, 27}. However, mechanisms of action of HP are complex, and there is also a case that asthma and HP appear simultaneously³⁰.

For differentiation of isocyanate-induced HP, chest X-ray, chest CT, and analysis of BALF or TBLB (Trans bronchial lung biopsy) are done. These noninvasive tests are useful and important, and for more accurate diagnosis, immune tests (for example, skin test or detecting specific antibody, etc) are also necessary.

Treatment and prevention

In general, without quitting the workplaces (continuing isocyanates exposure), symptoms do not recover. There are lethal cases because of continuing work^{26,32}. For this reason, for the process of improving working health, such as by adjustment and improvement of workplace, it is important to remove cause materials completely⁶³.

In one case that lung function improve after avoidance of causative materials, hypersensitivity is slight. In addition exposure period is short and showing delay reaction, the prognosis is good. However, when not exposing to causative materials, there is NSBH (non-specific bronchial hyperresponsiveness), symptoms do not recover⁵⁵. Symptoms do not recover when airway wall structure of sensitized patients change, such as subepithelial fibrogenesis and hypertrophy⁶⁴.

In most cases, if causative materials are removed, prognosis is mostly good^{14, 15, 18, 24, 28, 35, 36, 65}. If complete removal is impossible, the second-best measure is decreasing exposure concentration^{66, 67}. This may be achieved, in workplaces, by improvement of working practice, consideration of workplace layout, construction and ventilation, for the employee, mask (filter mask), protection may be needed. Wearing a mask is already shown to be useful^{25, 68}, and development of more protective mask is ongoing. However, in almost all the cases, concentrations of isocyanates in workplaces were not measured. In Japan, there is only one case where the concentration of workplace was measured³⁴. In animal study, concentration is important for sensitization⁵⁷. Thus, measure of concentrations in workplaces is important for prevention. Once a worker is sensitized, the only safe course is to remove them from exposure. As is seen with rarely reported fatalities, death may occur when sensitized patients continue to be exposed to the diisocyanate. Even wearing masks is not sufficient protection for sensitized patients. Masks in the workplaces are for the protection of healthy workers, to prevent sensitization.

Certainly, there is a clinical presentation under TLV (5 ppb)³⁴, but concentration is low enough (<1 ppb), diseases do not appear⁶⁹.

Conclusions

The analysis of BALF or TBLB, and soluble mediators (cytokine) from isocyanates workers and the correlation with clinical parameters have provided some insights into the pathogenesis of HP induced by isocyanates. Some features such as cell and mediator composition are similar to other HP, but others are different. Inflammatory cells (especially

eosinophils) and T cells (CD4 and especially CD8 cells) and their interaction and cooperation seems to be important. It has to be considered that the degrees of exposure to allergen is processed and presented to T cells may have important implications for the quality of immune response induced. Data concerning exposure-response relationship between diisocyanates and the induction of sensitization and elicitation of the relevant immunological processes.

Based on the observation of Vandenplas *et al.*¹², systemic symptoms in their study population was severe. Because of this, affected subjects had to leave the plant shortly after the onset of symptoms, an underestimation of HP in previous cross-sectional surveys due to the healthy worker effect is most likely¹³.

Comparison with Japanese and Western countries case reports, race does not contribute to the appearance of HP.

In general, basic research on immunology, molecular, and cellular biology, together with detailed clinical examinations, brought the light to the future on these major concerns of occupational health today.

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