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Editorial

Time to stand up; are Japanese prone to diffuse alveolar damage?

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Editorial

Diffuse alveolar damage (DAD) is a histological pattern commonly found in progressive lung disease [1]. It usually has several stages: 1) exudative phase which is similar to pulmonary edema when the alveoli become flooded with transudate, 2) production phase of hyaline membrane which are fibrous structures laid down to prevent oxygen diffusion through the damaged alveoli, and 3) organizing phase resulting in irreversible respiratory failure. Although DAD is seen in patients with pneumonia, sepsis, drug-induced lung disease, inhalation injury, and various other conditions, the most common diagnosis associated with it is acute respiratory distress syndrome (ARDS) (Table 1).

DAD is one of many pathologic patterns seen in drug-induced lung disease [2]. Since many cases with the disease are unable to undergo surgical lung biopsy, DAD is often diagnosed in clinical and radiological manners [3,4]. Response to corticosteroid therapy of drug-induced DAD is dependent on the inciting drug, severity of the reaction, and promptness of the therapeutic intervention. Gefitinib is an epidermal growth factor receptor (EGFR) inhibitor, which interrupts signaling through the EGFR in target cells. First-line gefitinib for patients with advanced non–small-cell lung cancer who were selected on the basis of EGFR mutations improved progression-free survival as compared with standard chemotherapy [5]. The most serious side effect of gefitinib is interstitial lung disease (ILD) with a reported incidence of 3.98% in Japan, which is about 13-fold higher than the corresponding rate, 0.3%, in the USA (Table 2) [6,7]. The ILD is radiologically and in some cases pathologically diagnosed as DAD [8]. Leflunomide is a disease-modifying anti-rheumatic drug that is used in moderate to severe rheumatoid arthritis and psoriatic arthritis. It reduces inflammation by suppressing the activity of immune cells responsible for the disease development and progression. Immediately after its introduction in Japan in 2003, ILD with a fatal outcome frequently developed under its use [9]. The incidence of leflunomide-induced lung injury in Japan was 1.81%, about 100-fold higher than the overseas rate of 0.017% (Table 2) [10]. The mortality rate from the drug-induced lung diseases by gefitinib or leflunomide was as high as 40%, with all deaths related to clinical and radiological DAD patterns. In addition, frequencies of ILDs induced by bleomycin, bortezomib, and erlotinib are also higher in Japan compared with the overseas rates (Table 2) [11-13].

Table 1: Clinical conditions associated with diffuse alveolar lavage.

Causes	Diagnosis
Idiopathic	Acute exacerbation of IPF, AIP
Infection (pneumonia)	ARDS
Sepsis	ARDS
Shock	ARDS
Trauma	ARDS
Collagen vascular diseases	CVD-associated ILD
Drug toxicity	Drug-induced pneumonia
Toxic inhalation	ARDS
Uremia	Uremic lung
Transfusion	TRALI

Abbreviations: IPF: Idiopathic Pulmonary Fibrosis; AIP: Acute Interstitial Pneumonia; ARDS: Acute Respiratory Distress Syndrome; CVD: Collagen Vascular Disease; ILD: Interstitial Lung Disease; TRALI: Transfusion-Related Acute Lung.

Idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic, progressive fibrosing ILD of unknown cause, primarily occurring in older adults. The natural history of IPF was thought to be a steady, gradual, and predictable decline in lung function over years. However, some patients may experience a more acute course accompanied by rapid progressive fibrosis and ultimately result in fatal outcome. When these acute declines develop without clinically apparent infection, left heart failure, pulmonary embolism, or other identifiable cause, the episodes of acute deterioration have been termed acute exacerbations of IPF [14]. In acute exacerbation of IPF, DAD superimposed on underlying usual interstitial pneumonia is the most common pathological finding [15]. The estimates of incidence and mortality rates of acute exacerbation of IPF are discordant among different studies, probably due to substantial variations in the definition of acute exacerbation. However, Japanese patients with IPF seem to suffer from acute exacerbation much more frequently than patients of other ethnic backgrounds [16-19]. In 2007, Collard et al. proposed a definition of acute exacerbation of IPF which includes an unexplained subjective worsening within the past 30 days, new bilateral radiographic opacities, and the absence of infection or another identifiable etiology causing lung injury [20]. More accurate estimates of incidence and mortality rates of the disease under the proposed definition should be expected in the future. Usually we cannot predict development of acute exacerbations of IPF, but surgical lung biopsy or lung resection may be a risk factor [21,22]. Sato et al. retrospectively analyzed 1763 patients with a clinical diagnosis of

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Table 2: Comparison of frequencies of acute lung injury between Japanese and non-Japanese.

Causes	Comments	References
Drug-induced	Frequency in Japanese /non-Japanese	
Gefitinib	3.98% (n=1,482) /0.3% (n=23,000)	6, 7, 8
Leflunomide	1.81% (n=3,867) /0.017% (n=861,860)	10
Bleomycin	0.66% (n=3,772) /0.01% (n=295,800)	11
Bortezomib	2.33% (n=3,556) /0.16% (n=106,832)	12
Erlotinib	4.52% (n=3,488) /0.7% (n=4,900)	13
Acute exacerbation of IPF	4.8% at median 76 week follow up in 168 Caucasians	16
	14.3% at 9 months in 35 Japanese	17
	25% for 10 years in 112 Japanese	18
	14.2% and 20.7% at 1 and 3 years in 461 Asians	19
ILD in clinically ADM		
	Rapidly progressive ILD reported predominantly in Asia, including Japan, Hong Kong, Taiwanand Korea.	29, 31, 32, 33
	Anti-CADM-140/MDA5 antibody primarily detectedin Japanese with ADM, but frequently found in non-Japanese with classic DM or severe vasculopathy.	44, 45

Abbreviations: IPF, idiopathic pulmonary fibrosis, ILD, interstitial lung disease, ADM, amyopathic dermatomyositis, DM, dermatomyositis.

ILDs and non-small cell lung cancer who had undergone pulmonary resection in Japan [23]. They found that acute exacerbation occurred in 164 patients (9.3%) with a mortality rate of 43.9%, which was the top cause of 30-day mortality (71.7%). Kutlu et al. reported that 3.9% of the patients who underwent pulmonary resection developed acute lung injury/ARDS, but their study did not mention anything about ILDs as a risk factor [24]. We need to examine how often pulmonary resection of lung cancer with ILDs provokes acute exacerbation in non-Japanese population by the consensus definition.

Dermatomyositis (DM) is an uncommon inflammatory disease marked by muscle weakness and a distinctive skin rash [25]. A form of DM termed amyopathic DM (ADM) is a condition in which patients have characteristic skin findings of DM with little or no evidence of myositis [26]. Patients with ADM sometimes develop rapidly progressive ILDs, which is often resistant to intensive therapy including high dose corticosteroids and immunosuppressive agents, resulting in fatal respiratory failure [27]. Although nonspecific interstitial pneumonia is the most common finding in the pathologic appearance of ILD in DM [28], DAD is often associated with rapidly progressive ILD in ADM [29,30]. Epidemiologically rapidly progressive ILD in ADM has been reported predominantly in Asia, including Japan, Hong Kong, Taiwan, and Korea [29,31-33]. Sato et al. identified a novel autoantibody, anti-CADM-140 antibody which recognized an antigen of an RNA helicase encoded by melanoma differentiation-associated gene 5 (MDA-5) [34,35]. Anti-CADM-140/MDA5 antibody titer could correlate with disease activity and predict the course of ILD associated with DM [36-41]. The antibody may be also a diagnostic and predictive marker for rapidly progressive ILD associated with juvenile DM [42,43]. A literature review indicates that anti-CADM-140/MDA5 antibody is primarily detected in patients with ADM in cohort studies conducted in Japan, but is frequently found in patients with classic DM or severe vasculopathy in non-Japanese cohorts [44,45].

Epidemiological data suggest the presence of ethnic differences between Japan and other countries and Japanese seem to be more prone to DAD due to various causes such as drug-induced lung disease, acute exacerbation of IPF, and rapidly progressive ILD associated with ADM. Some of Japanese researchers suspect that genetic factor (s) may be involved in the Japanese predisposition to DAD [11,18]. Instead of staying prone, it is time to stand up to clarify the underlying predisposition.

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