

Clinical features of secondary pulmonary alveolar proteinosis: pre-mortem cases in Japan

To the Editors:

Pulmonary alveolar proteinosis (PAP) is a rare syndrome that predominantly affects the lungs, and is characterised by the accumulation of surfactant lipids and proteins in the alveoli and terminal airways [1]. In 1999, we published findings that high levels of granulocyte-macrophage colony-stimulating factor (GM-CSF) neutralising autoantibodies were detected specifically in patients with idiopathic PAP [2]. Recently, as a result of the excellent sensitivity and specificity of GM-CSF autoantibody assays in identifying this form of PAP [3], it has been proposed that the nomenclature for this condition should be changed to “autoimmune PAP” rather than “idiopathic PAP” [4]. Secondary or hereditary PAP is not associated with

GM-CSF autoantibodies but develops as a consequence of a separate underlying disorder or genetic background [5]. Recently, we demonstrated that the characteristic high-resolution computed tomography (HRCT) findings in secondary PAP are distinct from those in autoimmune PAP [6]. However, physicians may not suspect secondary PAP, even when encountering unexplained pulmonary opacities on chest radiograph or computed tomography in patients with pre-existing haematological or infectious diseases, since there is little information available on the clinical features. Here, we outline the clinical features of adult-onset secondary PAP based on our database of 40 pre-mortem cases in which serum GM-CSF autoantibodies were negative, and compare them with other cases in the literature.

A total of 404 patients with pre-mortem cytologically or pathologically proven PAP were registered in our study group between 1999 and 2009. We obtained consent from all treating physicians for each identified case according to the guidelines for epidemiological studies from the Ministry of Health, Labour and Welfare [7], and all clinical data were de-identified. 360 (89%) cases were positive for serum GM-CSF autoantibody. The clinical features of 223 of the cases were previously published as a cross-sectional study [4]. 40 (10%) cases were negative for serum GM-CSF autoantibody, and were diagnosed as secondary PAP based on the existence of appropriate underlying diseases (table 1). Four (1%) cases remained as unclassified PAP.

Definitive diagnosis of secondary PAP was made using bronchoalveolar lavage (BAL) in 21 cases, transbronchial lung biopsy in nine cases, and video-assisted thoracoscopic surgery in 10 cases. All cases were diagnosed based on the pathological examination of lung biopsy specimens or BAL fluid cytology. At diagnosis, underlying diseases had been recognised in 30 cases; in the other 10, underlying disease was diagnosed at the same time as secondary PAP. The median (range) age at diagnosis was 49 (24–77) yrs and male sex was dominant (1.4:1). At diagnosis, 77% of the cases were symptomatic, with the most common symptom being dyspnoea on effort (40%) followed by fever (38%).

Haematological disorders constituted 88% of all underlying diseases. Among these, myelodysplastic syndrome (MDS) was the most frequent (65%). Interestingly, there were four cases of Behcet's disease complicated by MDS (two of which developed MDS during the treatment of intestinal Behcet's disease) and a single case of Behcet's disease alone [8]. The other non-haematological underlying diseases consisted of single cases of Wegener's granulomatosis, pulmonary tuberculosis, nontuberculosis mycobacterium infection, and microscopic polyangiitis.

At diagnosis, arterial blood gas analysis was performed in 29 cases and the mean \pm SD alveolar-arterial oxygen difference was 46.8 ± 55.6 mmHg. HRCT was performed in 27 cases, with the findings contributing significantly to a definitive diagnosis. In the present study, six new cases were added to the 21 cases from our previous study [6], and we reanalysed HRCT characteristics in all 27 cases. In accordance with our previous report, HRCT findings were classified into three patterns based on the nature of the observed ground-glass opacities. 17 (63%) cases showed a diffuse pattern in which the ground-glass opacities were evenly distributed with indistinct borders. In five (19%) cases, a patchy geographic pattern was seen, and a mixed pattern was seen in the remaining five (19%) cases. The so-called "crazy-paving" appearance was rare in secondary PAP (12%).

25 cases underwent pulmonary function tests at diagnosis of PAP. As is the case with autoimmune PAP, forced vital capacity and forced expiratory volume in 1 s were within normal limits, whereas the mean \pm SD diffusing capacity for carbon monoxide was markedly reduced to $46.2 \pm 13.8\%$ of normal. Serum levels of KL-6, surfactant protein (SP)-D, SP-A, and carcinoembryonic antigen were all elevated in a similar way to autoimmune PAP [4]. Among them, KL-6 was most

TABLE 1 Demographic characteristics and clinical features of our cases and cases from the literature[#]

| Characteristics | Our cases | | Literature cases |
|-------------------------------|-----------|------------|------------------|
| | APAP | SPAP | SPAP |
| Subjects n | 223 | 40 | 57 |
| Age yrs | 50 (9–89) | 49 (24–77) | 40 (24–74) |
| Sex n | | | |
| Males | 151 | 23 | 31 |
| Females | 72 | 17 | 26 |
| Clinical symptoms | | | |
| Asymptomatic | 70 (32) | 9 (23) | 0 (0) |
| Symptomatic | 150 (68) | 31 (77) | 21 (100) |
| Dyspnoea on effort | 116 (53) | 16 (40) | 10 (48) |
| Febrile | 2 (1) | 15 (38) | 14 (67) |
| Smoking habits | | | |
| Never-smoker | 93 (43) | 13 (37) | NA |
| Current or ex-smoker | 124 (57) | 22 (63) | NA |
| Underlying diseases | | | |
| Haematological disorders | None | 35 (88) | 43 (76) |
| Myelodysplastic syndrome | | 26 | 6 |
| Chronic myeloid leukaemia | | 2 | 16 |
| Myelofibrosis | | 2 | 1 |
| Acute myeloid leukaemia | | 1 | 8 |
| Acute lymphoid leukaemia | | 1 | 3 |
| Adult T-cell leukaemia | | 1 | 0 |
| Aplastic anaemia | | 1 | 1 |
| Lymphoma | | 1 | 3 |
| Multiple myeloma | | 0 | 1 |
| Plasmacytoma | | 0 | 1 |
| Alymphoplasia | | 0 | 1 |
| Essential thrombocytosis | | 0 | 1 |
| Infectious diseases | None | 2 (5) | 3 (5) |
| Autoimmune diseases | None | 3 (7) | 4 (7) |
| Post organ transplantation | None | 0 | 4 (7) |
| Non-haematological malignancy | None | 0 | 3 (5) |
| Diagnostic procedure | | | |
| Bronchoscopy | 208 (93) | 30 (75) | 27 (47) |
| Video-assisted thoracoscopy | 15 (7) | 10 (25) | 9 (16) |
| Open lung biopsy | 0 (0) | 0 (0) | 21 (37) |

Data are presented as median (range) or n (%), unless otherwise stated. APAP: autoimmune pulmonary alveolar proteinosis; SPAP: secondary pulmonary alveolar proteinosis; NA: not applicable. #: cases from the literature were identified using the search methods detailed in the main text.

strikingly elevated in both autoimmune and secondary PAP, but not specifically so, as it is known to be elevated in a number of other lung diseases [9].

A total of 35 cases with PAP secondary to haematological disorders were followed-up for 2 yrs after diagnosis. A survival rate of 46% was noted in this group. The median survival time for all cases was 16 months; 17 of the cases died within 2 yrs of the diagnosis of secondary PAP. In one case, PAP improved after cord blood transplantation. Whole lung

lavage was carried out in five cases, but three patients died within 2 months of the procedure (PAP was exacerbated in all three subjects with apparent progression of underlying disease in one of them). In one case, PAP was improved by bone marrow transplantation after whole lung lavage. Of the eight cases that underwent segmental BAL for treatment of PAP, four died within 6 months. In two cases, secondary PAP remained stable more than 5 yrs after diagnosis. Of the five cases with non-hematological disorders, only one patient with Behcet's disease died (13 months after diagnosis) due to respiratory failure caused by PAP.

Cases in the literatures were identified by searching Index Medicus for entries listed under "Lung Diseases" between 1958 and 1966, and by searching Medline for entries listed under "alveolar proteinosis", "alveolar lipoproteinosis", "pulmonary alveolar proteinosis" and "pulmonary alveolar lipoproteinosis" between 1966 and 2009. Proceedings of conferences and cases published only in abstract form were not systematically sought and were only identified if cited by other publications. The above search strategy identified 556 articles written in English on pulmonary alveolar proteinosis. Of those, we carefully selected 69 reports in which 139 cases with underlying diseases or states were described as the secondary development of pulmonary alveolar proteinosis. For the purposes of comparison with the present data, we excluded: 66 cases diagnosed *post mortem*; 10 cases in which the patient was <20 yrs old at diagnosis because our database does not include paediatric cases; and five cases that were also included in our present database. One case associated with dust inhalation was also excluded, given that our previous study demonstrated that this might in fact be due to autoimmune PAP [4]. Consequently, 57 cases were compiled into a database for meta-analysis (table 1). At 40 yrs of age, the median age at diagnosis was younger than in our sample. The male to female ratio was similar to ours, at 1.2:1. Consistent with our data, haematological disorders were the underlying disease in 75% of cases. Unlike our cohort, PAP secondary to MDS was only seen in six (11%) cases, all of which were reported after 2001 [10–12]. When we compared the clinical features of those who have secondary PAP from our study and from the literature, with those of the 223 cases with autoimmune PAP (table 1), we found that the age at diagnosis was older and the male to female ratio was higher in autoimmune PAP. In autoimmune PAP, age at diagnosis was older, and the male to female ratio was higher than those in with secondary PAP, but smoking habits were not distinctive. The proportion of symptomatic patients in autoimmune PAP was not different from those in both our cases and the cases from the literature, but febrile cases were rare. The median survival time after diagnosis in the cases from the literature (n=44) was 14 months, which was not significantly different from our data. In figure 1, the cumulative survival curve after diagnosis for our cases and for the cases from the literature demonstrates the consistently poor prognosis of secondary PAP.

Taken together, we conclude that haematological disorders are the major underlying disease in >75% of cases with adult-onset secondary PAP. The median age at diagnosis is typically in the fourth decade of life, with a greater incidence among males (1.2–1.4:1). Prognosis is very poor, with a median survival time of <20 months.

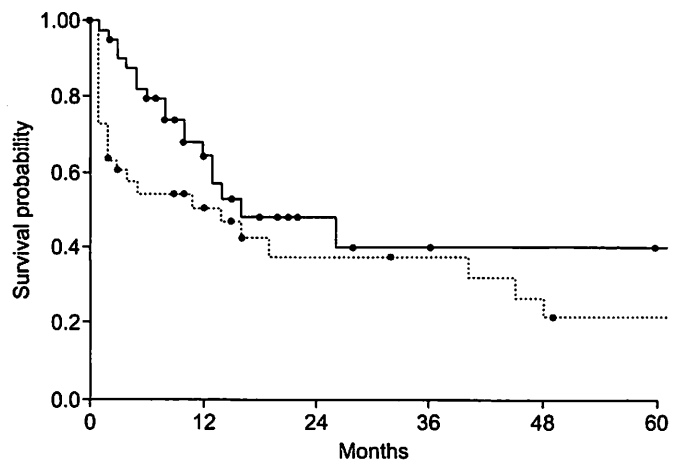


FIGURE 1. Overall survival probability of cases from our study (—) and cases from the literature (·····). The longest survival term from diagnosis of pulmonary alveolar proteinosis (PAP) was investigated in each case and data were analysed using SPSS 17.0 (SPSS, Chicago, IL, USA). In our original 40 cases, we could follow-up all cases. The longest terms of patient survival after diagnosis were confirmed in only 44 cases described in the literature.

This is the first report outlining the clinical features of secondary PAP. We believe that this information will contribute to the diagnosis and management of patients with secondary PAP.

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Support Statement: The present study was in part supported by grant Category B18406031 and B21406025 from the Japan Society for the Promotion of Science, and grant H21-Nanchi-Ippan-161 and H14-trans-014 from the Ministry of Health,

Labor, and Welfare of Japan, as well as grants from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

Statement of Interest: None declared.

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DOI: 10.1183/09031936.00092910