

Japanese summer-type hypersensitivity pneumonitis: studies using *Cryptococcus* antigen

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Summary

Sixty-six patients, diagnosed as Japanese summer-type hypersensitivity pneumonitis at Osaka Prefectural Habikino hospital between 1973 and 1980, were studied. The diagnosis was based on the clinical features and summer-seasonal nature of the disease. The presence of an aetiological agent within patients' home environment was suggested by the recurrence of acute symptoms of high fever, cough and dyspnoea 5–8 hr after coming home from hospital, and by spontaneous improvement on leaving home. Immunological studies revealed the presence of anti-*Cryptococcus* antibody in sixty-four of sixty-five patients' sera, by indirect immunofluorescence against *Cryptococcus neoformans*. Precipitating antibody against culture supernatant protein-antigen of *Cr. neoformans* was detected in more than 80% of sera obtained from patients during the active stage of the disease. The positive result on inhalation provocation-challenge, using culture supernatant protein-antigen, suggested that *Cr. neoformans* or antigenically related *Cryptococcus* species may cause Japanese summer-type hypersensitivity pneumonitis.

Introduction

Hypersensitivity pneumonitis (HP) is an immunological disorder characterized by the presence of granulomatous interstitial pneumonia, due to exposure to occupational or environmental antigens. Organic dusts containing fungi, bacteria and animal-derived protein are known to cause HP (Pepys, 1969; Mahon *et al.*, 1967; Johnson *et al.*, 1980). Thermophilic *Actinomyces* are aetiological agents for farmer's lung (Pepys & Jenkins, 1965), bagassosis (Seabury *et al.*, 1968), air-conditioner disease (Fink *et al.*, 1971, 1976) and humidifier disease (Sweet *et al.*, 1971). Bird breeder's disease results from exposure to avian droppings (Fink *et al.*, 1968; Hargreave *et al.*, 1966).

Recent studies reveal that patients with HP have been increasing during the past 10 years in Japan. Hypersensitivity pneumonitis in Japan, including our cases, was

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characterized by a high incidence in the summer season. The aetiological agent was unknown in the majority although a few cases were identified as due to *Candida albicans* (Kimura et al., 1979; Dobashi et al., 1980) and *Aspergillus fumigatus* (Toyama et al., 1981). We have demonstrated the presence of anti-*Cryptococcus* antibody in forty-one of forty-two patients with summer HP, observed at Habikino hospital (100% in sera tested) and in about 65% of sera of their family (Miyagawa, Ochi & Takahashi, 1978). Hypersensitivity pneumonitis with certain clinical and immunological characteristics was called summer-type HP and distinguished from other causes of HP (Ochi et al., 1978, 1980).

The relation of the *Cryptococcus* to summer-type HP was suggested, although inhalation provocation-challenge, using antigen extracted from *Cryptococcus neoformans* was unsuccessful.

In this paper we describe the clinical and immunological features of Japanese summer-type HP including case reports, and results of inhalation provocation-challenge using culture supernatant protein-antigen of *C. neoformans*.

Case reports

Patient 1 (M.S.), a 38-year-old bus driver, had symptoms of common cold in June 1980. Cough and shortness of breath increased gradually. On 19 July he was admitted to a hospital with severe dyspnoea. He had a fever of 38–39°C for several days prior to admission. On the second hospital day, he became afebrile. He recovered without specific medications. On 23 July he was discharged home, when he had a recurrence of his symptoms. He was admitted to Habikino hospital on 25 July. On examination temperature was 37.6°C and respiration was 21/min. Physical examination revealed crepitation at both lung bases. The chest x-ray revealed bilateral diffuse micronodular-infiltration. The leucocyte count was 9500/mm³ with 80% of neutrophils and 3.0% of eosinophils. Blood sedimentation rate (ESR) was 35 mm/hr. C-reactive protein (CRP) was not detected. Pulmonary function tests revealed forced vital capacity (FVC) of 85% of predicted value and the forced expiratory volume in 1 sec (FEV₁) of 92% of FVC. The single breath diffusing capacity of lung for carbon monoxide (DLCO) was 15.0 ml/min mmHg⁻¹, 41% of predicted value, while PaO₂ was 55.6 mmHg and PaCO₂

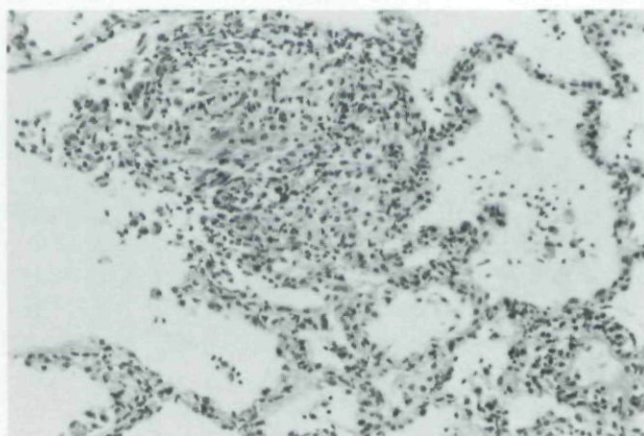


Fig. 1. Photomicrograph of lung biopsy obtained from M.S., demonstrating a granulomatous interstitial pneumonitis (H.E.).

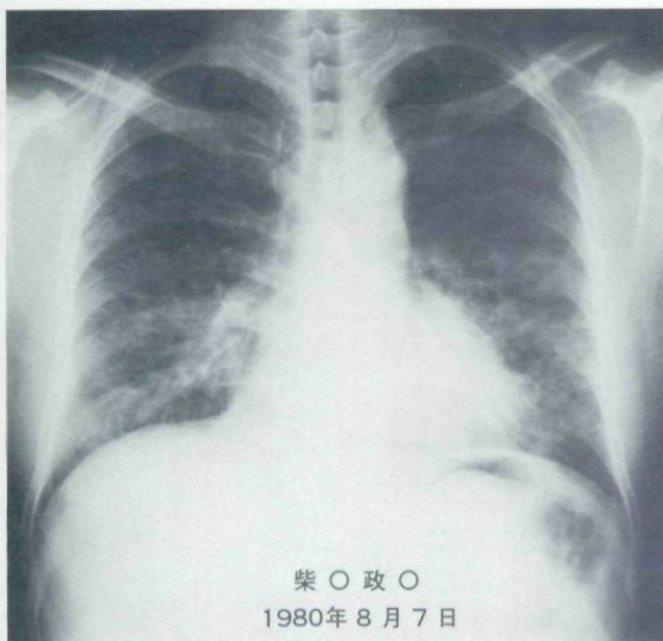


Fig. 2. Chest x-ray of M.S. on 7 August 1980, 1 day after exposure to his home environment, showing diffuse interstitial infiltration in bilateral lung.

was 26.4 mmHg. Skin reaction to PPD was negative. Anti-*Cryptococcus* antibody was positive by indirect immunofluorescence and precipitation reaction. He was diagnosed as having summer-type HP. On 29 July a transbronchial lung biopsy was done (Fig. 1). On 5 August the PaO_2 improved to 78 mmHg and laboratory findings became almost normal. The chest x-ray also markedly improved. On 6 August he was allowed to go home to see whether his illness would relapse on exposure to his home environment. Within 5 hr after returning home, he experienced a recrudescence of symptoms with high fever, 39°C , cough, dyspnoea and general fatigue. He became dyspnoeic and cyanotic. He had haemoptysis and the chest x-ray revealed the reappearance of interstitial pneumonia (Fig. 2); PaO_2 was 48.8 mmHg and PaCO_2 was 22.8 mmHg. The leucocyte count was $28\,000/\text{mm}^3$ with 80% of neutrophils. Blood sedimentation rate (ESR) was 21 mm/hr; CRP was 6+. Forced vital capacity (FVC) was 65% of predicted value and FEV_1 was 90% of FVC; DLCO was 33% of predicted value. Intranasal oxygen and prednisolone produced rapid improvement of symptoms, laboratory findings, chest x-ray and pulmonary functions except gas transfer. On 8 September exposure to his home environment for 3 hr resulted in recrudescence of high fever, cough and dyspnoea, increase of interstitial infiltration in chest x-ray, worsening in laboratory tests and pulmonary functions. He was treated with 20 mg prednisolone for 1 week and he became asymptomatic. On 20 October inhalation provocation-challenge was done (Fig. 3a). He has had no obvious worsening by exposure to his home environment since November 1980. He was discharged and has changed his residence.

Patient 2 (H.E.), a 16-year-old boy, was well until mid-August 1980, when coughing attacks developed with fever and malaise. He noticed dyspnoea on exercise on 18 September. During several days before admission dyspnoea progressed and he

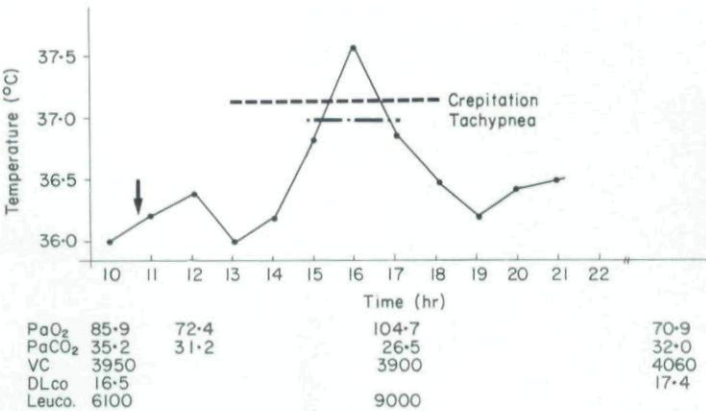


Fig. 3a.

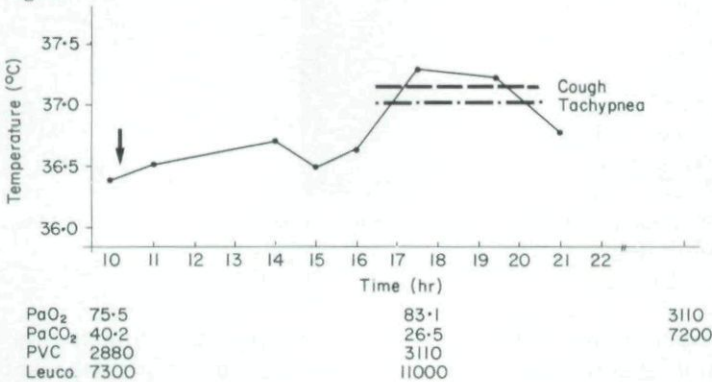


Fig. 3b.

Fig. 3a. Patient 1 (M.S.) & Fig. 3b Patient 2 (H.E.). Inhalation provocation-challenge of patients M.S. and H.E., showing late pyrexia reaction induced by challenge of culture supernatant protein-antigen of *Cr. neoformans*.

had a temperature. He was admitted to hospital on 26 September with his parents, who had suffered a similar illness since early August. On examination he was cyanotic and dyspnoeic; temperature, 37.5°C; respiration, 30/min. Crepitations were heard at both lung bases. Chest x-ray revealed diffuse micronodular-infiltration in both lung fields (Fig. 4). The leucocyte count was 12 000/mm³ with 75% of neutrophils and 1.0% of eosinophils; ESR was 32 mm/hr; CRP was 2+; PaO₂ was 49.8 mmHg and PaCO₂ was 30 mmHg; FVC was 24% of predicated value and FEV₁ was 100% of FVC. A tuberculin test with PPD was negative. On the second hospital day he was afebrile. His symptoms improved gradually with nasal oxygen inhalation for 5 days. He and his parents were diagnosed as summer-type HP, with anti-*Cryptococcus* antibody, detected in their sera by the indirect immunofluorescence and precipitation reaction. Transbronchial lung biopsy was done on 1 October (Fig. 4). Administration of 20 mg/day prednisolone was started on the sixth hospital day and resulted in rapid improvement of clinical, laboratory, physiological and radiological findings. He went home on 15 and 23 October and 1 November, when mild to severe acute symptoms of cough, dyspnoea, chillness and high fever appeared 6–8 hr after returning home from hospital. The presence of the aetiological agent within his home environment was suggested. Inhalation provocation-challenge was performed on 11 November (Fig. 3b).

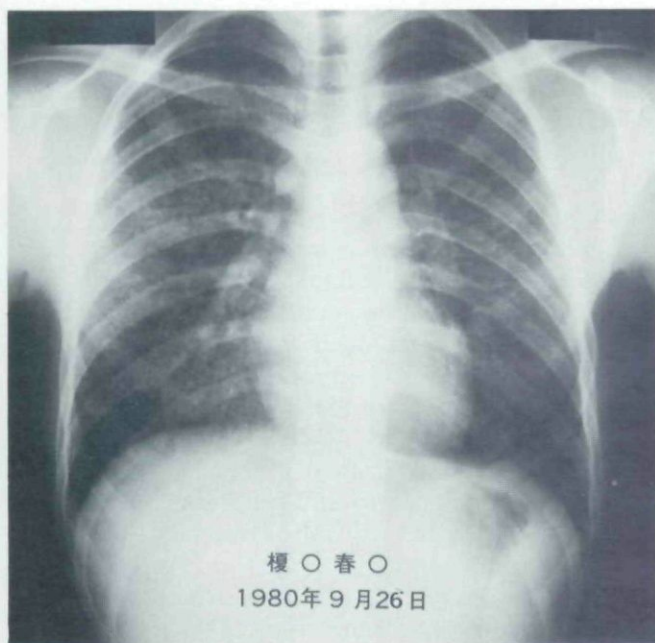


Fig. 4. Chest x-ray of H.E. on 26 September 1980, showing diffuse interstitial micronodular infiltration in bilateral lung.

Materials and methods

Patients

Sixty-six patients, twenty-four males and forty-two females who were suspected of summer-type HP from history between 1973 and 1980 at Habikino Hospital were studied. Examination of chest roentgenogram, pulmonary functions were made in all the patients. A transbronchial or open lung-biopsy was performed in seventeen patients. Serum samples were tested for anti-*Cryptococcus* antibody.

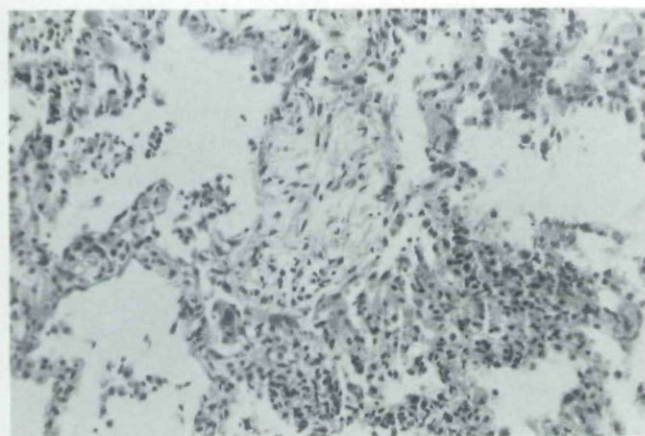


Fig. 5. Photomicrograph of lung biopsy obtained from H.E., demonstrating a granulomatous interstitial pneumonitis (H.E.).

Immunological studies

Anti-*Cryptococcus* antibody was tested by the method of indirect immunofluorescence technique and double diffusion in agar gel described in a previous paper (Miyagawa *et al.*, 1978). A culture supernatant protein-antigen of *Cr. neoformans* was employed as antigen for precipitation reaction.

Preparation of culture supernatant protein-antigen of Cr. neoformans

Cr. neoformans IFO 0608 strain, a thin capsular form of serotype A, was supplied by the Institute of Fermentation, Osaka, Japan. A 1-week-old culture on Sabouraud glucose agar was seeded to 500 ml culture flasks containing 250 ml of culture fluid, having the following composition in g/l. de-ionized water: glucose, 30; NaNO₃, 3.0; KH₂PO₄, 1.0; MgSO₄, 0.5; KCl, 0.5; FeSO₄, 0.01; and a dialysable component of 5.0 g neopeptone. Culture fluid was autoclaved at 110°C for 15 min. The cells were cultured on a shaker at 25°C for 5 days, then killed by heating at 56°C for 1 hr and separated by centrifugation at 5000 rev/min for 10 min. A method of ammonium sulphate precipitation was used to separate protein from supernatant. The precipitate produced between 30 and 60% saturation was collected and redissolved in saline, followed by extensive dialysis in saline. The antigen solution thus prepared was lyophilized and stored at 4°C until use. The protein concentration was 0.55 mg/10 mg dry weight determined by Lowry's method (Kabat, 1964). 10 mg/ml of solution was passed through a sterilizing milipore filter before clinical applications.

Skin reaction

Intradermal skin-test was performed with 0.1 ml 1:1000 or 1:10 000 dilution of antigen in saline. The skin reaction was assessed at 15 min and 8, 24 and 48 hr.

Inhalation provocation-challenge

Inhalation provocation challenge was carried out in three patients. Each patient (M.S., H.E.) received approximately 1.5 mg of protein in 5.0–6.0 ml of saline in nebulized form by Nissho's nebulizer apparatus in 30–40 min. A patient (N.E.) received 2.0 ml of antigen solution containing about 75 µg of protein in 10 min. Pulmonary function, blood gas, leucocyte count and body temperature were measured before and after testing.

Results

The incidence of summer-type HP was concentrated during 4 months from June to September with sixty-six new cases and nineteen relapsed cases. No patients have been observed during the 6 months from November to April in the following year. Tables 1 and 2 show the clinical and laboratory findings in sixteen cases studied during 1980. Six were relapsed cases, and five were followed as outpatients. The familial occurrence was present in five members of two families. The clinical symptoms and signs in these patients were similar to those of HP already described and in farmer's lung and bird breeder's disease (Hargreave *et al.*, 1966; Fink *et al.*, 1968, 1976).

The clinical course of HP could be divided into three forms, acute, subacute (insidious) and chronic, according to mode of onset (Pepys, 1969, Fink *et al.*, 1968, 1976). In the summer-type HP, most patients had symptoms of common cold, such as cough without sputum, general fatigue and low grade fever lasting 5 days–2 months before high fever and progressive dyspnoea appeared. Some patients had gradually

TABLE 1. The clinical features of patients with summer-type HP studied during 1980.

Patient	Age	Sex	Occupation	Onset	Clinical form of disease	Main symptoms	Previous history of summer-type HP	Acute attacks after exposure to home environment
M.S.	38	M	Bus driver	June	Acute	Fever, cough, dyspnoea		Positive
K.Y.	13	M	School boy	August	Acute	Fever, cough, dyspnoea		Positive
H.I.	38	F	Housewife	June	Acute	Fever, cough, dyspnoea		
C.O.	47	F	Housewife	September	Subacute	Fever, cough, dyspnoea		
N.E.*	45	M	Carpenter	August	Acute	Fever, cough, dyspnoea		Positive
C.E.*	42	F	Housewife	August	Acute	Fever, cough, dyspnoea		Positive
H.E.*	16	M	School boy	August	Acute	Fever, cough, dyspnoea		Positive
K.I.	50	F	Housewife	July	Acute	Fever, cough, dyspnoea	1977, 1978, 1979	Positive
H.U.††	68	M		August	Subacute	Shortness of breath	1979?	1978, 1979
S.U.††	33	F	Office girl	August	Subacute	Cough, sputa	1979	Positive
H.N.	65	M		June	Acute	Fever, cough, dyspnoea	1979	Positive§
H.I.‡	51	M		August	Subacute	Shortness of breath	1974, 1975, 1978, 1979	Positive§
H.T.‡	65	F	Housewife	June	Subacute	Shortness of breath	1979	Positive§
M.M.‡	50	F	Housewife	July	Subacute	Cough, shortness of breath	1979	Positive§
K.I.	10	M	School boy	August	Acute	Fever, cough, shortness of breath	1979	

* Patients related to each other.

† Patients related to each other.

‡ Outpatients.

§ Positive in past history.

TABLE 2. Laboratory, physiological, pathological and immunological findings at the time of diagnosis.

Patient	Leucocyte ($\times 10^3/\text{mm}^3$)	CRP (mm/hr)	ESR (mm/hr)	PaO ₂ (mmHg)	PaCO ₂ (mmHg)	FVC (%)	FEV ₁ /FVC (%)	DLCO (%)	Anti- <i>Cryptococcus</i> antibody precipitin	Pathology of lung specimens			
										Epitheloid granuloma	Masson's body	Alveolitis	IFA* titre
M.S.	9500	—	35	55.6	26.4	85	92	41	+	+	+	+	256
K.Y.	15 600	4+	15	53.1	31.1	50	88		+				128
H.I.	9500	±	41	61.0	27.6	53	100	68	+	+	+	+	512
C.O.	7000	—	41	85.7	30.0	82	87	56	+				128
N.E.	9900	1+	25	64.1	31.9	90	63	66	+	+	+	+	128
C.E.	4700	—	12	87.8	38.8	42	100	38	+				128
H.E.	12 900	2+	32	49.8	30.5	24	100	45	+	+	+	+	256
K.I.	5700	2+	36	76.7	32.9	86	96	46	+				64
H.U.	12 100	2+	40			59	86	67					128
S.U.	13 300	±	20			88	86	89					256
H.N.	6400	—	58	59.0	28.1	54	100	39	+	+	+	+	512
H.I.		2+		64.1	24.0	80	95	71					64
H.T.	4600	—	24	66.8	22.8	70	85	50					128
M.M.	9300	2+	38	62.7	32.6	104	83	55	+	+	+	+	64
K.I.	6200	1+	32	67.3	36.6	32	100	71	—	?	+	+	64

* Indirect immunofluorescent antibody titre, normal range: < 16

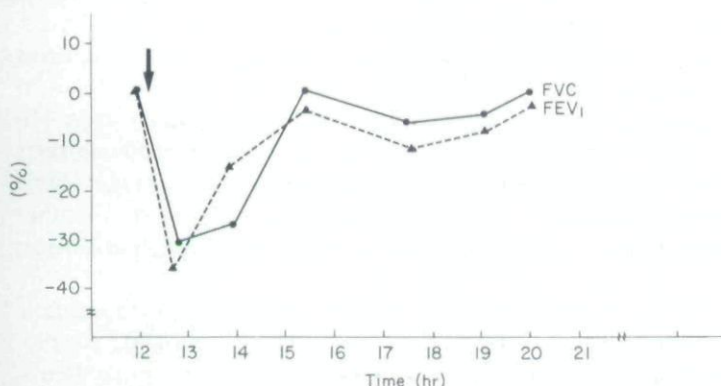


Fig. 6. Inhalation provocation challenge of patient N.E., showing immediate reaction induced by challenge of culture supernatant protein-antigen of *Cr. neoformans*.

increasing cough, dyspnoea, low grade fever, general fatigue and weight loss without obvious symptoms of acute attacks. These symptoms improved spontaneously while they were away from their home, but in the majority, acute symptoms of high fever, general fatigue, cough and dyspnoea reappeared 5–8 hr after returning home from hospital. These symptoms were similar to those of acute attacks experienced in patients with other HP, when exposed to the appropriate antigen (Pepys, 1969; Fink, 1968). The cessation of exposure to antigen, by leaving home, resulted in a spontaneous improvement in mild cases, but administration of steroid hormone was necessary in severe cases.

Anti-*Cryptococcus* antibodies were demonstrated in sixty-four of sixty-five cases by the indirect immunofluorescence and in forty-two of fifty-one cases by the precipitation reaction to culture supernatant protein-antigen of *Cr. neoformans*. The results of precipitation reaction and anti-*Cryptococcus* antibody titre in indirect immunofluorescence are shown in Table 2 for patients studied during 1980.

The results of inhalation provocation-challenge were shown in Fig. 3a and b, and in Fig. 6. A late febrile reaction, accompanied with leucocytosis and mild respiratory symptoms, was reproduced in two patients (M.S. and H.E.). However, the change of pulmonary functions was small in these experiments. The immediate reaction was accompanied by an increase of coughing attacks and crepitations, decrease of FVC and FEV₁ were produced in patient N.E. with a small antigen-challenge. This patient showed immediate and late reactions, after exposure to his home environment. Late febrile reaction was not induced with this antigen dose. The immediate and Arthus-type skin reaction to culture supernatant protein antigen was positive in these three patients.

Discussion

More than 200 patients have been diagnosed as summer-type HP on a clinical basis during the past 10 years in Japan (Kurihara *et al.*, 1976; Shishido *et al.*, 1977, Ochi *et al.*, 1978, Murao *et al.*, 1980). Summer-type HP was widely distributed except for northern parts of the country, but the majority of cases were observed in Osaka district and its surroundings. Immunological studies revealed no distinct causative antigen in these cases, therefore the presence of some new antigenic material was suspected, but unidentified.

We observed a patient's serum which reacted with polysaccharide antigen of *Cr. neoformans* in precipitation reaction in the previous study. The application of indirect immunofluorescence technique, using *Cr. neoformans* cells, revealed the presence of anti-*Cryptococcus* antibody in almost all sera from patients with summer-type HP (over 100 patients) and in about 65% of sera from their family members, and contrasts with less than 10% of sera from healthy subjects and various lung diseases (Miyagawa *et al.*, 1978). However, microbiological studies revealed no *Cr. neoformans* or other *Cryptococcus* species in sputum or lung specimens obtained by transbronchial or open lung-biopsy.

The presence of anti-*Cryptococcus* antibody in symptomatic and asymptomatic members of the same family suggested the possibility of existence of some *Cryptococcus* species or antigenically related organism during summer season within patients' home environments. Exposure and sensitization to such organisms might have caused the summer-type HP. Anti-*Cryptococcus* antibody titres changes in correlation with clinical course of summer-type HP (Miyagawa *et al.*, 1978).

According to Phaff and Fell, genus *Cryptococcus* consists of seventeen species and six varieties. Most *Cryptococcus* species have been isolated from our surroundings as saprophytes (Phaff & Fell, 1970). *Cryptococcus* species other than *Cr. neoformans* have generally been considered to be non-pathogenic, and infections caused by these organisms have rarely been reported in humans (Cuhna & Lusins, 1973; Melo *et al.*, 1980; Krumholz, 1972, Lynch *et al.*, 1981). During the present study, several strains of *Cryptococcus* species which appeared to biologically belong to *Cr. albidus*, *Cr. uniguttulatus* and *Cr. lactivorius* were isolated from patients' homes. However, these strains showed only weak agglutination reaction with sera from patients with summer-type HP.

It has been reported that some *Cryptococcus* species have a shared antigen, common to *Cr. neoformans* (Tsuchiya, Kawakita & Udagawa, 1963; Pidcoe & Kaufman, 1968). Similar cross-reaction was observed between patients' sera and several strains of *Cryptococcus* species in agglutination reaction and indirect immunofluorescence, particularly between *Cr. neoformans*, *Cr. albidus* and *Cr. terreus* cells. We also observed similar cross-reactivity in agglutination reaction using anti-*Cryptococcus* antibody prepared in rabbits against *Cr. neoformans* IFO 0608 strain. We have not succeeded in isolating the causative *Cryptococcus* from patients' home environments.

Antigen extracted from *Cr. neoformans* cells consisted mostly of capsular polysaccharide. Precipitating antibody against polysaccharide was detected in less than 40% and inhalation provocation-challenge with this antigen failed to elicit a positive reaction. Therefore culture supernatant protein-antigen of *Cr. neoformans* was used. Precipitating antibody against culture supernatant protein-antigen was detected in more than 80% sera of patients with active summer-type HP. Arthus-type skin reaction was also elicited in 80% of patients tested. These results were consistent with those of farmer's lung, bird breeder's disease and other HP to aetiological agents (Pepys & Jenkins, 1965; Fink *et al.*, 1968; Salvaggio, Seabury & Buechner, 1967).

The inhalation provocation-challenge with this protein antigen gave a positive result. The late febrile reaction with mild respiratory symptoms and leucocytosis, or immediate and late reaction in some cases, has been reported in the studies of antigen inhalation provocation-challenge in farmer's lung and bird breeder's disease (Pepys &

Jenkins, 1965; Hargreave & Pepys, 1972; Hendrick *et al.*, 1980). Perhaps a proper concentration of antigen is required for patients to get a typical reaction.

From the immunological studies of patients' sera and inhalation provocation-challenge, we concluded *Cr. neoformans* or antigenically related *Cryptococcus* species could be responsible for Japanese summer-type HP studied in this report. The detection of antigenic material in patients' homes would confirm this conclusion.

Acknowledgments

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References

- CUHNA, D.T. & LUSINS, J. (1973) *Cryptococcus albidus* meningitis. *South Medical Journal*, **66**, 1230.
- DOBASHI, K., NAKAZAWA, T., NAGASAWA, T., UMEGAI, Y., INAZAWA, M., TOMIOKA, S., FUEKI, R. & KOBAYASHI, S. (1980) A case of hypersensitivity pneumonitis caused by *Candida albicans*. *Nippon Naika Gakkai Zasshi*, **69**, 40.
- FINK, J.N., SOSMAN, A.J., BARBORIAK, J.J., SCHLUETER, D.P. & HOLMES, R.A. (1968) Pigeon breeders' disease. A clinical study of a hypersensitivity pneumonitis. *Annals of Internal Medicine*, **68**, 1205.
- FINK, J.N., BANASZAK, E.F., THIEDE, W.H. & BARBORIAK, J.J. (1971) Interstitial pneumonitis due to hypersensitivity to an organism contaminating a heating system. *Annals of Internal Medicine*, **74**, 80.
- FINK, J.N., BANASZAK, E.F., BARBORIAK, J.J., HENSLEY, G. T., KURUP, V.P., SCANLON, G.T., SCHLUETER, D.P., SOSMAN, A.J., THIEDE, W.H. & UNGER, G.F. (1976) Interstitial lung disease due to contamination of forced air system. *Annals of Internal Medicine*, **84**, 406.
- HARGREAVE, F.E., PEPYS, J., LONGBOTTOM, J.L. & WRAITH, D.G. (1966) Bird breeder's (fancier's) lung. *Lancet*, **i**, 445.
- HARGREAVE, F.E. & PEPYS, J. (1972) Allergic respiratory reaction in bird fanciers' provoked by allergen inhalation provocation tests. *Journal of Allergy and Clinical Immunology*, **50**, 157.
- HENDRICK, D.J., MARSHALL, R., FAUX, J.A. & KRALL, J.M. (1980) Positive 'alveolar' responses to antigen inhalation provocation-tests: their validity and recognition. *Thorax*, **35**, 415.
- JOHNSON, C.L., BERNSTEIN, I.L., GALLAGHER, J.S., BONVENTRE, P.F. & BROOKS, S.M. (1980) Familial hypersensitivity pneumonitis induced by *Bacillus subtilis*. *American Review of Respiratory Disease*, **122**, 339.
- KABAT, E.A. (1964) In: (Eds) Kabat and Mayer. Estimation of protein with Folin-ciocalten phenol reagent. *Experimental Immunochemistry*. 2nd ed, p. 556, Charles C. Thomas, Illinois, U.S.A.
- KIMURA, I., TANIZAKI, Y., UEDA, N., HOSOKAWA, M., NAKAMURA, Y., SASAKI, Y., HARADA, H., AKAGI, K. & TAKEYAMA, H. (1979) *Allergy*, **28**, 640.
- KURIHARA, N., GOTO, T., FUJIMOTO, S., ICHIHARA, H., TOYAMA, T., OGAWA, K., HAMADA, A., SHIOTA, K. & HOJO, K. (1976) A case of hypersensitivity pneumonitis found in residents in Osaka city area. *Nippon Kyobu Rinsho*, **35**, 531.
- KRUMHOLZ, R.A. (1972) Pulmonary cryptococcosis, a case due to *Cryptococcus albidus*. *American Review of Respiratory Disease*, **105**, 421.
- LYNCH, J.P., SCHABERG, D.R., KISSNER, D.G. & KAUFFMAN, C.A. (1981) *Cryptococcus laurentii* lung abscess. *American Review of Respiratory Disease*, **123**, 135.
- MAHON, W.E., SCOTT, D.J., ANSELL, G., MANSON, G.L. & FRASER, R. (1967) Hypersensitivity to pituitary snuff with miliary shadowing in the lungs. *Thorax*, **22**, 13.
- MELO, J.C., SRINIVASAN, S., SCOTT, M.L. & RAFF, M.J. (1980) *Cryptococcus albidus* meningitis. *Journal of Infection*, **2**, 79.
- MIYAGAWA, T., OCHI, T. & TAKAHASHI, H. (1978) Hypersensitivity pneumonitis with antibody against *Cryptococcus neoformans*. *Clinical Allergy*, **8**, 501.
- MURAO, M. *et al.* (1980) A clinical study of hypersensitivity pneumonitis in Japan. *Nippon Kyobu Shikkan Gakkai Shi*, **18**, 373.
- OCHI, T., MIYAGAWA, T., OSUGI, T., FUJITA, K., YAMAMOTO, H., KIKUI, M. & TAKAHASHI, H. (1978) Studies on forty-two cases of hypersensitivity pneumonitis. *Nippon Kyobu Shikkan Gakkai Shi*, **16**, 320.
- OCHI, T., MIYAGAWA, T., KIKUI, M., OSUGI, H., IZUMI, T., TACHIBANA, M., KONDO, A., HOSODA, Y. & MIKAMI, R. (1980) A new type of hypersensitivity pneumonitis in Japan, sarcoidosis and other granulomatous diseases. Alpha Omega Publishing Ltd, Cardiff, U.K. p. 705.

- PEPYS, J. & JENKINS, P.A. (1965) Precipitin (F.L.H.) test in farmer's lung. *Thorax*, **20**, 21.
- PEPYS, J. (1969) Hypersensitivity diseases of the lung due to fungi and organic dusts. *Monograph of Allergy*, **4**, 69.
- PHAFF, H.F. & FELL, J.W. (1970) *Cryptococcus*. In: *The yeast*. (Ed.) J. Lodder, p. 1088, North Holland Publishing Co. Amsterdam, Holland.
- PIDCOE, V. & KAUFMAN, L. (1968) Fluorescent antibody reagent for the identification of *Cryptococcus neoformans*. *Applied Microbiology*, **16**, 271.
- SALVAGGIO, J.E., SEABURY, J.H. & BUECHNER, H.A. (1967) Bagassosis: demonstration of precipitins against extracts of thermophilic actinomycetes in sera of affected individuals. *Journal of Allergy*, **34**, 476.
- SEABURY, J., SALVAGGIO, J., BUECHNER, H. & KUNDUR, V.G. (1968) Bagassosis. III. Isolation of thermophilic and mesophilic actinomycetes and fungi from moldy bagasse. *Proceedings of the Society of Experimental Biology and Medicine*, **129**, 351.
- SHISHIDO, S., IWAI, K., TAKAHASHI, S. & KAMEDA, K. (1977) Extrinsic allergic alveolitis observed in a father and his daughter in the same season every year. *Nippon Kyobu Rinsho*, **36**, 512.
- SWEET, L.C., ANDERSON, J.A., CALLIES, Q.C. & COATES, E.O. (1971) Hypersensitivity pneumonitis related to a home furnace humidifier. *Journal of Allergy*, **48**, 171.
- TOYAMA, J., NAKOMOTO, M., KONDO, A. & ARAKAWA, M. (1981) A case of hypersensitivity pneumonitis due to *Aspergillus fumigatus*. *Nippon Kyobu Shikkan Gakkai Shi*, **19**, 402.
- TSUCHIYA, T., KAWAKITA, S. & UDAGAWA, M. (1963) Rapid identification of *Cryptococcus neoformans* by serology. *Sabouraudia*, **2**, 209.

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