Hermansky-Pudlak Syndrome with Acute Hatred Idiopathic Pulmonary Fibrosis: All of the Patients of Oculocutaneous Albinism for Past 20 Years in Juntendo University Hospital

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Hermansky-Pudlak syndrome (HPS) is genodermatosis, which is one of syndromic oculocutaneous albinism (OCA). OCA categorizes 9 genes, and patients with mutations in HPS1 gene have greater likelihood of pulmonary fibrosis and granulomatous colitis for their 40s.

A 49-year-old man was referred to our hospital as his chest CT image indicated abnormal shadow for his age. At birth, he had white skin, blond hair, and blue iris. And he had not visual power. He was also easy to bleed and had disfunction of platelet. Skin biopsy and genetic test indicated he was diagnosed as HPS definitely and had mutations in HPS1 variation on DNA (c.398+5 G>A, homozygote), which is already known. After 4 months from his hospitalization, his respiratory function became worsen. Otherwise he took pirfenidone, pulmonary fibrosis progressed and he died of dyspnea.

In our university, 39 patients had diagnosed as OCA during past 20 years. Only 5 patients were conducted gene analysis. 3 patients were OCA1B, and 2 patients were HPS1. In OCA patients, there are some gene mutations which onset serious complications. Early detection by gene test and early treatment is important.

Key words: oculocutaneous albinism, Hermansky-Pudlak syndrome, HPS1, pirfenidone, pulmonary fibrosis

Introduction

Hermansky-Pudlak syndrome (HPS) is firstly reported by Hermansky and Pudlak1) in 1959 and autosomal recessive genodermatosis consisted of oculocutaneous albinism (OCA), platelet storage pool deficiency, and lysosomal accumulation of ceroid lipofuscin2). The symptom was thought to be developed by disfunction of lysosome, and 9 genes have been reported3).

In Japan, 8107 albino patients have come to hospitals every year, and 160 patients (2%) exhibit OCA4). OCA can categorize syndromic or non-syndromic types (Table 1). Non-syndromic type is simply called OCA, and 7 genes have been reported. Syndromic types divide into HPS, Chediak-Higashi Syndrome (CHS), and Griscelli syndrome (GS). In 160 OCA patients, 54 patients (34%) are OCA1, 38 patients (26%) are OCA4, 16 patients (10%) are HPS1, 12 patients (8%) are OCA2, 2 patients are OCA3, and 1 patient is HPS4).

Patients with mutations in the HPS1 gene tend to have greater likelihood of pulmonary fibrosis and granulomatous colitis for their 40s. Especially, progressive interstitial pneumonias (IP) link to the prognostic factor. We report here a case of HPS which developed acute progressive idiopathic pulmonary fibrosis (IPF). This case was approved
A 49-year-old man with a history of ulcerative colitis was pointed out abnormal shadow on chest CT image by medical checkup three years ago, and he was referred to department of respiratory medicine at our hospital for further examination. Since he had not any symptoms, he had been followed up examinations as a day-patient. As he had coughed for one year and breathed difficulty on working for one month, he was put into the hospital for survey and treatment. His chest CT image shadow indicated abnormal IP for his age (Figure 1). Involving other symptoms such as bleeding tendency and albinism, he was suspected of HPS and referred to ophthalmology, dermatology, and hematology department.

From childhood, his eyes are also blue, showed nystagmus, and easy to bleed at nose every other day. By fundus mirror, he had low pigments on eyeground, low growth on yellow spot. Visual acuity test, he had not any visual power (Right: 0.08, Left: 0.1). Clinical findings at presentation indicated his skin was completely white, his hair was

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**Report of a case**

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**Figure 1** Chest computed tomography scans
blond, and his iris were blue since being at birth (Figure 2). Skin biopsy indicated no melanocytes at epidermal basal layer. Genetic test was conducted at Yamagata University, and it showed variation on DNA (c.398+5 G>A, homozygote), which is already known, at HPS1, whereas his mother was heterozygote. Blood test indicated disfunction of platelet, and easy to bleed. According to the Japanese oculo-cutaneous albinism guidelines, he was diagnosed as HPS definitely and his symptom was serious.

Table 2 shows his respiratory function had come to been worsen, but considering hemorrhagic tendency, treatment using bronchoscope was difficult. He was young and resident to be taken operation, he was thought to be adjusted for lung implant. After two months, he had Pulmonary hypertension (PH) and took home oxygen therapy (HOT). After one month, he had chest pain causing by pneumothorax on right side. Treating by drain into thoracic cavity had no effect. In order to inhibit the progress of IP, pirfenidone started but worsen. As lung transplant was not in time of waiting and his family rejected to give their lung to him, he decided to take palliative medicine such as morphine. He died of dyspnea, but we don’t know the cause of death, how affect the drain into the lung. His family reject
the autopsy, so the reason why he died was unknown.

Discussion

HPS1 often complicates with IP and granulomatous colitis for their forties. Especially, progressive IP is the prognostic factor. In Japan, 70% of HPS patients complicated with IP\textsuperscript{10}. Almost all patients were there thirty-forties and came to hospitals with chief complaint of difficulty in breathing on working or dry cough. They died 1–6 years after occurring the IP\textsuperscript{11}. As the reason why they develop IP in their thirties is unknown, recent studies show this is linked to environmental factors such as exposition and inspiration poisonous substances\textsuperscript{12}. They had been treated by steroid or immunosuppressive agent, but not achieved. Since 2008, we can use pirfenidone as we expect not to be fibrotic\textsuperscript{13}. In 2002, RCT report at Puerto Rico indicated that pirfenidone could delay the developing IPF\textsuperscript{14}. However, later study showed that pirfenidone did not have availability for IPF\textsuperscript{15}.

In our university, we included all the patients with OCA in our hospital from 1\textsuperscript{st} June in 1989 to 2\textsuperscript{nd} September in 2019. 39 patients had diagnosed as OCA during past 20 years. Of the 39 patients, 10 were female and 29 were male. The mean age was 14.2. Then, 5 had some allergy, and 15 had same symptoms in relatives. Table 3 shows which department OCA patients came at first. Most of patients came to the department of ophthalmology at first, and they were recommended to receive gene analysis at other hospital. In our university, five patients were already conducted gene analysis. three were OCA1B, and two were HPS1. These patients were followed by ophthalmologists and/or dermatologists during their courses. These two patients had no symptoms at skin on birth. White skin and blond hair were noted in one patient at the age of thirty. Two patients developed pulmonary fibrosis at the age of forty and two died of complications of OCA in their early fifties.

Diagnose of HPS is so difficult that we often rule out by not showing any other symptoms. In this case, we learned the importance of genetic diagnosis, and take treatments as soon as possible such as lung transplant which needs wait in order. We expect 1\textsuperscript{st} department where patients visit to consider the possibilities of HPS as doctors at respiratory medicine noticed.

Conflict of interest

None declared.

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