

Polyglandular Autoimmune Syndrome Type III with Primary Hypoparathyroidism

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Polyglandular autoimmune syndrome is defined as multiple endocrine gland insufficiencies accompanied by autoimmune diseases of the endocrine and nonendocrine system. After Schmidt introduced a case of nontuberculosis adrenal gland dysfunction with thyroiditis in 1926, Neufeld defined polyglandular autoimmune syndrome by I, II, and III subtypes in 1980 by their presentation of occurrence age, heredity methods, relationship with human leukocyte antigen, and accompanying diseases. We report a case of a 32-year-old female with polyglandular autoimmune syndrome III accompanied by type 1 diabetes mellitus that was treated with insulin (36 units per day) for 11 years. She had insulin deficiency and Hashimoto thyroiditis as an autoimmune disorder. In addition, she had several features similar to Albright's hereditary osteodystrophy including short stature, truncal obesity, round face, short neck, low intelligence (full IQ 84), and decreased memory. Although Albright's hereditary osteodystrophy is morphological evidence of pseudohypoparathyroidism or pseudopseudohypoparathyroidism, she had primary hypoparathyroidism on laboratory results. Here, we report a case of polyglandular autoimmune syndrome III with type 1 diabetes mellitus, autoimmune thyroiditis, and primary hypoparathyroidism, accompanied by clinical features similar to Albright's hereditary osteodystrophy.

Keywords: Polyendocrinopathies; Autoimmune; Primary hypoparathyroidism

INTRODUCTION

Polyglandular autoimmune syndrome (PAS) is defined as the functional disorder of two abnormal endocrine glands. In 1926, Schmidt reported a case in which nontuberculosis hypoadrenalism with autoimmune thyroiditis, and Neufeld et al. [1] divided the PAS into type I, II, and III according to the endocrinopathy occurrence age, heredity method, relationship with human leukocyte antigen (HLA), and the characteristics of accompanying disease. In 1980 [1], PAS type I corresponds to cases with at least two of the following: autoimmune Addison's disease, chronic mucocutaneous candidiasis, and idiopathic hypoparathyroidism, while PAS type II was defined as a dis-

ease group including Addison's disease, autoimmune thyroid disease, and type 1 diabetes [2]. PAS type III is not accompanied by Addison disease but includes other autoimmune diseases, such as type 1 diabetes together with autoimmune thyroid disease. In addition, Neufeld et al. [1] subdivided cases with both type 1 diabetes and autoimmune thyroiditis into PAS type IIIa. However, type I PAS is so rare that only 100 cases have been reported worldwide [3]. In Korea, some PAS cases with various clinical features including PAS III have been reported [4-8].

Albright's hereditary osteodystrophy (AHO) is a growth impairment-related congenital disease, accompanied by several pathognomonic features [9,10]. These somatic features are as-

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sociated with resistance to parathyroid hormone (PTH) including pseudohypoparathyroidism (PHP) I or pseudopseudohypoparathyroidism (PPHP) in an autosomal dominant inheritance [11]. Primary hypoparathyroidism is characterized as a deficiency or secretory disorder of PTH without underlying disorders including any prior neck surgery, chronic renal failure, alcoholism, gastrointestinal absorption disorders, or pathognomonic musculoskeletal abnormality such as AHO [12].

In the present case, the 32-year-old female with type I diabetes had autoimmune thyroiditis, and therefore we could diagnose her illness as having PAS type IIIa. At the same time, the present case was accompanied by primary hypoparathyroidism with clinical features similar to AHO and thyroid papillary cancer, and this is a rare case. Therefore, we report this valuable experience.

CASE REPORT

Patient: 32-year-old female.

Chief complaint: General weakness.

Present illness: She was receiving insulin injections for type 1 diabetes, but her symptoms had not been improved at all, which prompted her decision to come to our hospital.

Past history: She had been using 32 U insulin every day for type 1 diabetes for 11 years before her visit to our hospital.

Family history: All family members, including both parents and all siblings, had diabetes.

Physical examination: When she appeared, her blood pressure was 130/80 mm Hg, pulse rate was 74 beats per minute, and body temperature was 36.6°C. She had no other symptoms, except for general weakness and central obesity (body mass index 23.4 kg/m²). No tumor-like mass was checked at her head and neck, nothing was discovered in chest auscultation. When we checked her abdomen, neither any pain nor hepatosplenomegaly was observed. No skin or oral mucosa pigmentation was found. There was no edema in lower leg. The neurological examination results were also normal. She weighed 51.5 kg and was 148.2 cm tall, and she was somewhat short woman with a short neck and round face, similar to a clinical features of AHO, but there was no pathognomonic brachydactyly.

Laboratory results: The result of complete blood count was the hemoglobin 9.3 g/dL, the erythrocyte average volume 96 fL, leukocyte 5,720/mm³, and platelets 310,000/mm. The results of anemia work up were the total iron binding capacity 447.5 µg/dL, serum ferritin 35.11 ng/mL, reticulocyte count

2.89%, average erythrocyte hemoglobin density 32.6 g/dL, and vitamin B₁₂ 839.65 pg/mL. Her blood glucose level was 212 mg/dL, the level of hemoglobin A1c was 7.3%, and the simultaneous measurement of serum level of C-peptide showed decreased level of 0.13 ng/mL. Serum concentration of total calcium were 5.5 mg/dL (range, 8.7 to 1.4); ionized Ca 1.56 mg/dL (range, 2.3 to 2.58); phosphorus 6.7 mg/dL (range, 2.5 to 4.5); total protein 6.7 g/dL; albumin 3.3 g/dL; alkaline phosphatase 329 IU/L; aspartate aminotransferase 119 IU; alanine aminotransferase 65 IU/L. Intact PTH level was 13.32 pg/mL (range, 13 to 54). Serum adrenocorticotropic hormone (ACTH) and cortisol levels were 11.92 pg/mL (range, 10 to 60) and 0.94 (range, 9.4 to 26.1). The results of rapid ACTH stimulation test for adrenal function were normal. The results of thyroid function test were T3 99.01 ng/mL, free T4 0.85 µg/dL, and thyroid stimulating hormone 7.99 µIU/mL. The results for antimicrobial and antithyroglobulin antibody were positive (52.91 IU/mL, 132.57 IU/mL), and, both islet cell antibody and antiglutamic acid decarboxylase antibody tested negative. In the Ellsworth-Howard examination, urinary phosphoric acid was slightly increased (12.3 mg/dL) and the increase of cyclic adenosine monophosphate (cAMP) was sufficient (4,400 µmol/mL). There was no GNAS mutation. Serum levels of sodium, potassium, blood urea nitrogen, and creatinine were within normal limits at 144 mmol/L, 5.3 mmol/L, 8.2 mg/dL, and 1.0 mg/dL.

Radiological results: The chest X-ray showed no abnormal lesion. A brain computed tomography scan showed prominent calcifications in both basal ganglion and hypothalamus (Fig. 1). The thyroid sonogram discovered several nodules, sized 4.5×3.7 mm and 3.9×2.9 mm on each side that were suspected to be thyroid papillary cancer.

Treatment and clinical course: The patient came to the hospital experiencing general weakness, and she was diagnosed with hypocalcaemia on laboratory examination. At that time, both the levels of PTH and vitamin D were within normal range, but she had previously experienced spasm symptoms and the levels of previous intact PTH were low (4.38 to 10.66 pg/mL) 7 years ago. She has taken oral calcium medicine for treatment of idiopathic hypoparathyroidism because she had no underlying secondary disorders for hypocalcemia and low PTH level. Although she has no pathognomonic brachydactyly, her appearance was similar to AHO in clinical features including short stature, intelligence decline, round face, calcification on basal ganglion and hypothalamus, or obesity. Furthermore, she had a lower normal PTH level and hypocalcemia

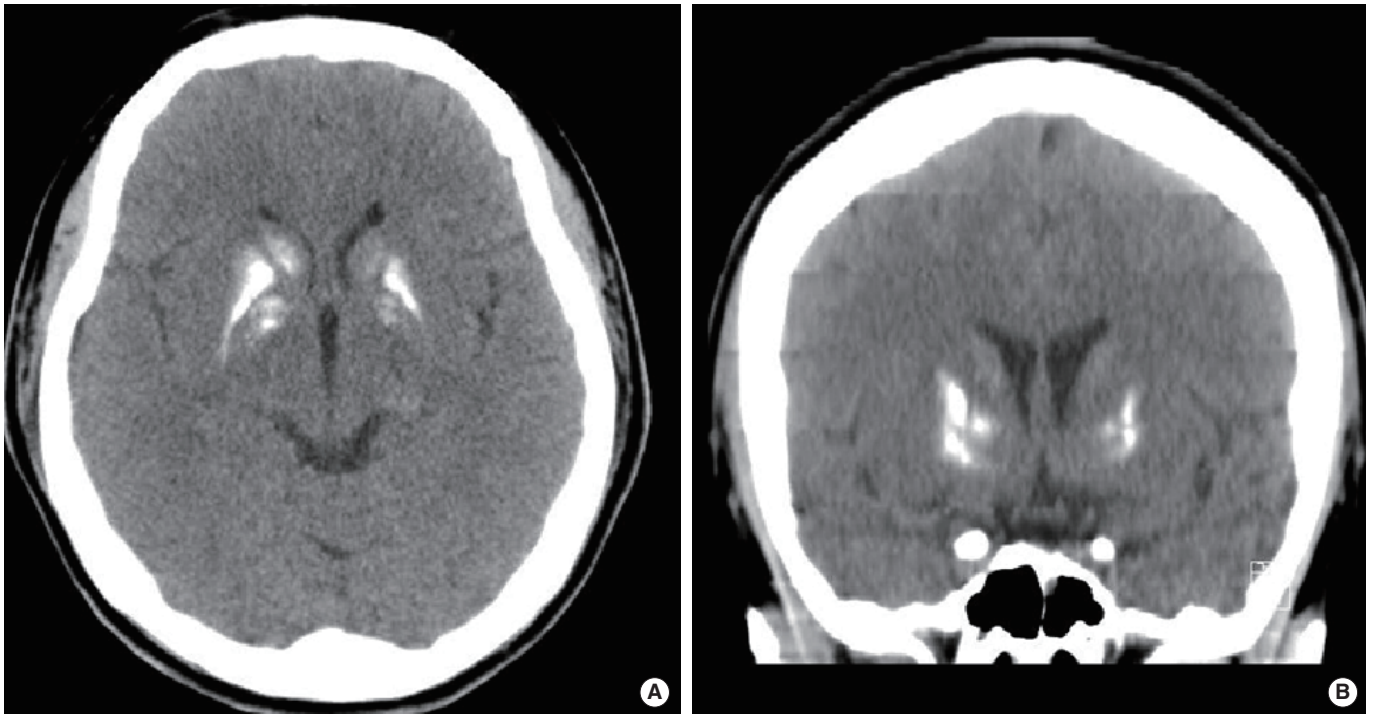


Fig. 1. Basal ganglia calcification. Brain computed tomography scan show prominent calcifications in both the basal ganglia and thalami.

on admission, and we decided to investigate the PTH resistance to identify PHP Ia or PPHP with AHO. In the Ellsworth-Howard examination for investigation of the PTH resistance, it was confirmed that there was no PTH resistance at the kidney and there was no sign of GNAS mutation. We diagnosed this case as hypocalcemia due to idiopathic hypoparathyroidism for lower serum calcium and traced intact PTH levels and began calcium and calcitriol medicine to treat the hypocalcemia. Subsequently, her symptoms were improved with normalization of ionized Ca at 2.32 mg/dL (range, 2.3 to 2.53). The results of fine needle aspiration on two nodules of thyroid were suggestive malignancy and she underwent a total thyroidectomy. The biopsy results were papillary microcarcinoma with lymphocytic thyroiditis for two suspicious nodules (sized 1.5×1.0 cm on the left and 2.0×1.0 cm on the right). Among the four parathyroid glands, the left inferior parathyroid gland was not discovered, and the remaining three parathyroid glands were remained during surgery. We used levothyroxine 0.05 mg medication for Hashimoto thyroiditis and insulin detemir 12 U and aspart 16 U for glucose control.

DISCUSSION

PAS was reported by Schmidt in 1922 when he conducted an autopsy of a patient who had died of adrenal insufficiency and

discovered that the lymphocyte had infiltrated into the thyroid and adrenal cortex, and thereafter, many cases have been reported in which both autoimmune endocrinopathy and nonendocrinopathy have been found in the same patient. In 1980, Neufeld et al. [1] classified the PAS into type I, II, and III according to age of endocrinopathy occurrence, heredity method, relationship with HLA, and accompanying disease, and this contributed greatly to screening and early diagnosis of PAS. PAS type I is also called autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, and it has been the topic of recent genetic research. This revealed that PAS type I is known to be associated with the abnormality of a single gene such as autoimmune regulator gene (AIRE) through autosomal recessive heredity [13,14]. In addition, the immune dysfunction, polyendocrineopathy, enteropathy, X-Linked (IPEX) syndrome is caused by serious immune damage with forkhead box P3 gene mutation at the regulatory T cell. PAS may be classified into three types including type I related with AIRE, type II related with HLA, and type III related with IPEX. Particularly, PAS type I is so rare that only 100 cases have been reported worldwide [3].

In Korea, some cases of PAS with various clinical features have been reported [4-8], but the type III case is not common. Seven cases of PAS type III have been reported; three cases of PAS with autoimmune thyroid disease and systemic lupus ery-

thematosis, two cases with autoimmune thyroid disease and rheumatoid arthritis, one case with pernicious anemia and insulin-dependent diabetes, and one case with autoimmune thyroiditis and leukopathy. The patient in the present case was diagnosed with type I diabetes (C-peptide 0.13) accompanied by insulin deficiency 11 years ago and thyroiditis was already under development according to thyroid ultrasonogram examination that was taken 7 years ago. After then, autoimmune thyroiditis was confirmed with the positive results of the thyroid autoantibodies and biopsy. Therefore the patient was diagnosed with PAS III with autoimmune thyroid disease and type I diabetes.

Primary hypoparathyroidism is characterized as a deficiency or secretory disorder of PTH without underlying disorders, including prior neck surgery, chronic renal failure, alcoholism, gastrointestinal absorption disorders, and pathognomonic musculoskeletal abnormality as stated by Albright [12]. AHO is known to be relatively rare in primary hypoparathyroidism, but one case with AHO and primary hypoparathyroidism has been reported in Korea [15]. AHO is a congenital disease associated with short stature, obesity, rounded face, subcutaneous ossification, and characteristic shortening and widening of long bones in the hands and feet, and less frequently, mental retardation [9,10]. Usually, AHO is associated with PHP I or PPHP with GNAS mutation [11]. Six cases of PPHP or PHP with AHO and two cases of PPHP or PHP without AHO have been reported in Korean [16,17]. The PPHP is considered when a patient has definite AHO evidences, a family history of PPHP, normal results on the Ellsworth-Howard examination, reductions in erythrocyte membrane Gs activity, GNAS mutation or a patient's father has AHO evidences [18,19]. The AHO patients with paternal inheritance may be diagnosed with PPHP without hormone resistance of PTH, but the patients with maternal inheritance may have PHP by hormone resistance [11]. The patient in the present case was confirmed with hypocalcemia, low PTH, and a previous history of spasms that might be associated with hypocalcemia. Based on laboratory results, we could consider this case as primary hypoparathyroidism. Interestingly, she had several clinical features similar to AHO including short stature, intelligence decline, round face, calcification on basal ganglion and hypothalamus, and obesity except pathognomonic brachydactyly, which might be considered as PHP or PPHP. Therefore, the Ellsworth-Howard examination was performed to investigate the resistance to PTH actions on target organs [20] but we diagnosed the patient with idiopathic hypoparathyroidism due to

the increase of urinary phosphoric acid, sufficient increase of cAMP by 20 times (4,400 $\mu\text{mol/mL}$), and no GNAS mutation. The subnormal response of urinary phosphoric acid might be due to variations of the basal level or diurnal excretion.

In conclusion, it is thought that this is a case of PAS type IIIa with autoimmune thyroiditis and type I diabetes required insulin treatment. At the same time, this case was accompanied by thyroid papillary cancer and primary hypoparathyroidism with clinical features that could be mistaken for AHO. This is a rare case and instructive experience for us and we report the case with the review of reference literature.

In the present case, the patient was young female who was diagnosed with type I diabetes as an absolute deficiency of insulin and required insulin supply for glucose control. She had also autoimmune thyroid disease, thyroid papillary cancer and primary hypoparathyroidism with clinical features resembled AHO. Here, we report a rare case of PAS type IIIa with autoimmune thyroiditis and type I diabetes, accompanied by thyroid papillary cancer and primary hypoparathyroidism with clinical features that could be mistaken for AHO.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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