Missed diagnosis and delayed treatment of acromegaly in a patient with severe diabetes: A case report

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Abstract. The early stages of acromegaly are characterized by slow and progressive acral overgrowth without major systemic complications. Failure to diagnose acromegaly at an early stage may have devastating consequences on patient care. The case in the present report was a 44-year-old Japanese man, referred to Kuwana City Medical Center due to severe hyperglycemia detected in a general checkup. The patient had no acromegaly-related complaints. Laboratory data revealed high blood levels of hemoglobin A1c and glucose. Careful physical examination revealed enlargement of extremities and soft tissues. Laboratory investigation indicated a high blood concentration of growth hormone, and magnetic resonance imaging disclosed an enhanced pituitary tumor. The diagnosis was pituitary tumor-associated acromegaly with severe diabetic complications. The pituitary tumor became large and unresectable following 10 years of misdiagnosis. The patient was treated with somatostatin receptor ligands (lanreotide and pasireotide), as well as bromocriptine in Mie University Hospital. The tumor size was reduced following treatment, though it was still unresectable at the time of this report. The case highlights the importance of hyperglycemia and abnormal manifestations of the feet in patients with acromegaly. In addition, these findings highlight the need for a thorough examination of the feet in diabetic patients, and the critical importance of the early diagnosis of acromegaly for preventing the consequences of inappropriate patient care.

Introduction

The most frequent cause of acromegaly is pituitary hypersecretion of growth hormone (GH) (1). High levels of GH and insulin-like growth factor-1 (IGF-1) result in systemic alterations such as acral enlargement, skin thickening, soft tissue hyperplasia and excessive sweating (1). Acromegaly may also be associated with dyslipidemia, insulin resistance, diabetes mellitus and cardiovascular events (1-3). Previous reports have revealed increased overall mortality rates in patients with acromegaly compared with the healthy control population (4). Acromegaly-associated physical alterations may not be detected by the patients at the early stages of disease (5,6). However, health professionals may also misdiagnose acromegaly in patients exhibiting slow disease progression and limited symptoms (1). As previously reported, diagnostic error may notably impact therapeutic management, prognosis and patient quality of life (7). Diagnostic error has also been the cause of numerous lawsuits of medical malpractice (8). The present report outlines a case of acromegaly that was undiagnosed for multiple years, which affected the therapeutic management of the patient.

Case report

The case was a 44-year-old Japanese man referred to the Department of Internal Medicine, Kuwana City Medical Center (Kuwana, Mie, Japan) in October 2017 for severe hyperglycemia, which was detected during a general workplace checkup. The patient experienced mild hyperglycemia during a medical check-up five years before admission, without subsequent medical follow-up. The clinical findings during the examination were as follows: Height, 168 cm; body weight, 77 kg; body mass index, 27.3 kg/m^2; blood pressure, 110/64 mmHg; heart rate, 70 beats/min; and body temperature, 36.9˚C. The laboratory data revealed a hemoglobin A1c level of 15.8% and a random blood glucose level of 330 mg/dl (Table I). A routine physical foot examination for diabetic patients revealed enlargement of both feet (Fig. 1A). The feet had no pitting-edema and were not painful, red or warm. Additional physical examination disclosed hyperhidrosis, jaw malocclusion, prominent supraciliary arches and enlarged hands and tongue (Fig. 1A-C). The patient was transferred to the Department of Diabetes and Endocrinology of Mie University Hospital (Tsu, Mie, Japan) as he was suspected of having an endocrine disorder. A plain radiograph indicated hypertrophied terminal phalangeal tufts and soft tissue hypertrophy (Fig. 2A) with heel pad thickness (Fig. 2B).

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Table I. Endocrine parameters.

Variable	Value	Reference range
GH, ng/ml	870	<1.0
IGF-1, ng/ml	582	92-255
Random blood glucose, mg/dl	330	<200
HbA1c (%)	15.8	4.9-6.0
TSH[a] (μIU/ml)	0.84	0.35-4.9
Free T3[a] (pg/ml)	1.80	1.7-3.7
Free T4[a] (ng/dl)	0.79	0.70-1.48
LH[a] (mIU/ml)	0.44	0.57-12.07
FSH[a] (mIU/ml)	2.11	0.95-11.95
ACTH[a] (pg/ml)	43.4	7.2-63.3
Cortisol[a] (μg/dl)	8.3	4.5-21.1
PRL[a] (ng/ml)	5.9	3.6-12.8
AVP[a] (pg/ml)	1.7	<2.8
Serum osmolality[a] (mOsm/kg/H_2O)	295	275-295

[a]Parameters measured on the second visit. GH, growth hormone; IGF-1; insulin-like growth; HbA 1c, hemoglobin A1c; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine; LH, luteinizing hormone; FSH, follicle stimulating hormone; ACTH, adrenocorticotropic hormone; PRL, prolactin; AVP, arginine vasopressin.

Table II. Results of CRH and LHRH tests.

	Time of measurement		
Variable	0 min	30 min	60 min
CRH test			
ACTH, pg/ml	55.3	62.1	47.2
Cortisol, μg/dl	20.1	21.9	17.6
LHRH test			
LH, mIU/ml	0.56	4.91	7.29
FSH, mIU/ml	2.65	4.37	5.48

Parameters were measured on admission. CRH, corticotropin-releasing hormone; LHRH, luteinizing hormone releasing hormone; ACTH, adrenocorticotropic hormone; LH, luteinizing hormone; FSH, follicle stimulating hormone.

Table I describes the results of endocrine parameter analysis. There was an increased serum concentration of GH and IGF-I, and the serum level of luteinizing hormone was low. However, the circulating levels of adrenocorticotropic hormone, thyroid stimulation hormone, follicle-stimulating hormone, free triiodothyronine, free thyroxine and cortisol were within the normal range. The circulating levels of prolactin and arginine vasopressin, as well as the serum osmolality, were also within the normal range. As presented in Table II, a luteinizing-hormone releasing hormone test revealed that the levels of luteinizing hormone and follicle-stimulating hormone were also normal (6). Magnetic resonance imaging (MRI) revealed an enhanced pituitary tumor of 4.5 cm (Fig. 2C and D). Ophthalmic examinations revealed no vision loss secondary to the pituitary tumor or diabetic retinopathy (Fig. 2E). There were no symptoms of Cushing's syndrome, and the overall results of the corticotropin-releasing hormone stimulation test showed no significant abnormality (Table II) (9). A test for cortisol rhythm was not performed.

The patient was diagnosed with acromegaly, type 2 diabetes mellitus and acromegaly-associated exacerbation of diabetes mellitus. However, tumor removal will ultimately clarify whether type 2 diabetes mellitus is only secondary to acromegaly. Subsequent investigation disclosed the presence of sleep apnea, colon polyps and thyroid enlargement; based on a previous report (10). The summary of positive clinical findings of acromegaly in the present case was as follows: Pituitary gland tumor, acral enlargement, jaw malocclusion, hyperhidrosis, colon polyps, left ventricular hypertrophy, sleep apnea, diabetes mellitus, dyslipidemia and enlargement of tongue and thyroid gland (10). In the present case, the electrocardiogram demonstrated a first-degree atrioventricular blockade (PR interval, 212 ms; reported normal range, 120-200 ms) with no ST-segment changes (11). Echocardiography demonstrated a left-ventricular ejection fraction of 55% (using the modified Simpson method), diffuse mild left ventricular hypertrophy and mild thickening of the mitral valve (12). The right and left ankle-brachial indexes were 1.19 and 1.22 (reported normal range, 0.9-1.3), respectively (13). Carotid ultrasonography revealed no atherosclerotic changes. Based on previous studies (11-13), an expert (Dr K.S). from the Department of Cardiovascular Medicine (Mie University), recommended no further therapy for these mild cardiovascular changes.

The tumor was unresectable due to excessive enlargement and cavernous sinus invasion. Treatment with somatostatin receptor ligands (SRLs; lanreotide and pasireotide) were recommended, as these compounds can potentially reduce tumor size (14,15). As such, SRLs are the first treatment choice for patients with acromegaly (16). Lanreotide has a high affinity for both somatostatin receptor (SSTR) 2 and SSTR5, and a weak affinity for SSTR3 (16). Pasireotide is able to bind multiple SSTRs (SSTR1, 3, 5 and 2) and with a greater affinity than lanreotide (16). Initially, the use of lanreotide (90 or 120 mg) was indicated every 4 weeks. In addition to diet and exercise therapy, hypoglycemic agents are the first treatment of choice for those with type 2 diabetes mellitus (17). However, the blood glucose level of the current case was >300 mg/dl on admission, and the patient was therefore treated with insulin according to previous clinical guidelines (17). During follow-up and five months after starting therapy with lanreotide, laboratory data revealed decreased circulating levels of GH with increasing doses of lanreotide (Fig. 3A), and a MRI study demonstrated a reduction in tumor size (Fig. 3B-E). A previous study reported that serum GH levels of >10 ng/ml were not correlated with serum IGF-1 levels (18). This may explain the persistently high levels of IGF-1, despite the decreased levels of GH, observed in the present case (Fig. 3A). During follow-up, no therapeutic response to lanreotide was observed. Therefore, the patient was subsequently treated with pasireotide (40 mg every 4 weeks), in additional to 5 mg bromocriptine per day. Bromocriptine is a dopamine agonist

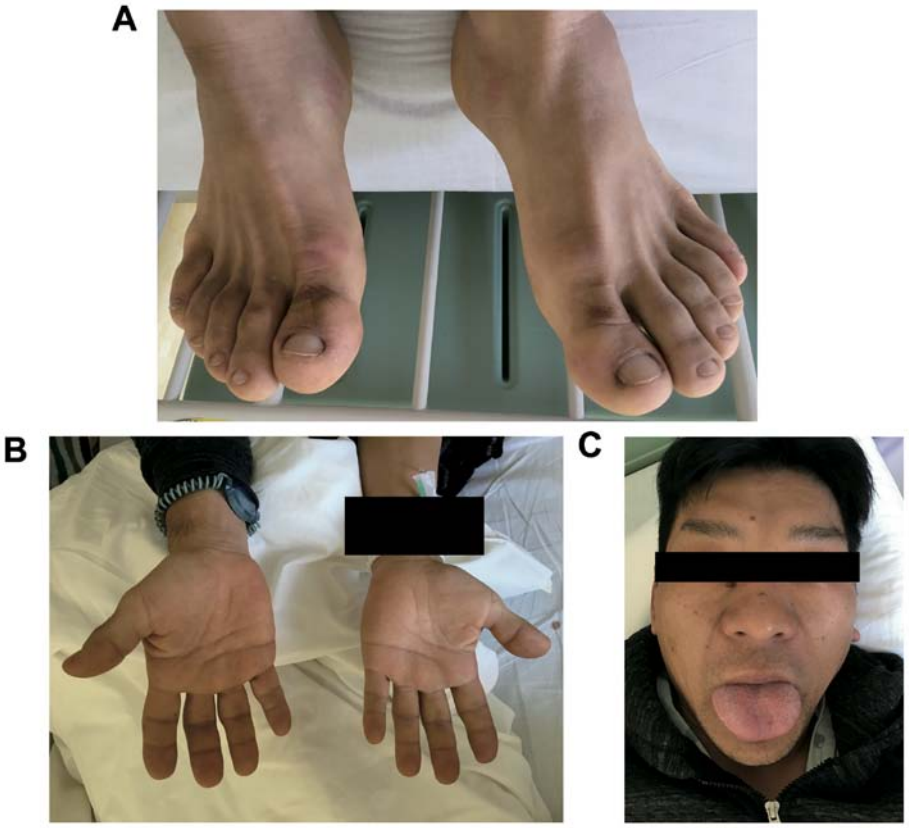

Figure 1. Patient physical examination. (A) Enlarged feet without pitting-edema or symptoms of infection, and enlargement of the (B) hands and (C) tongue.

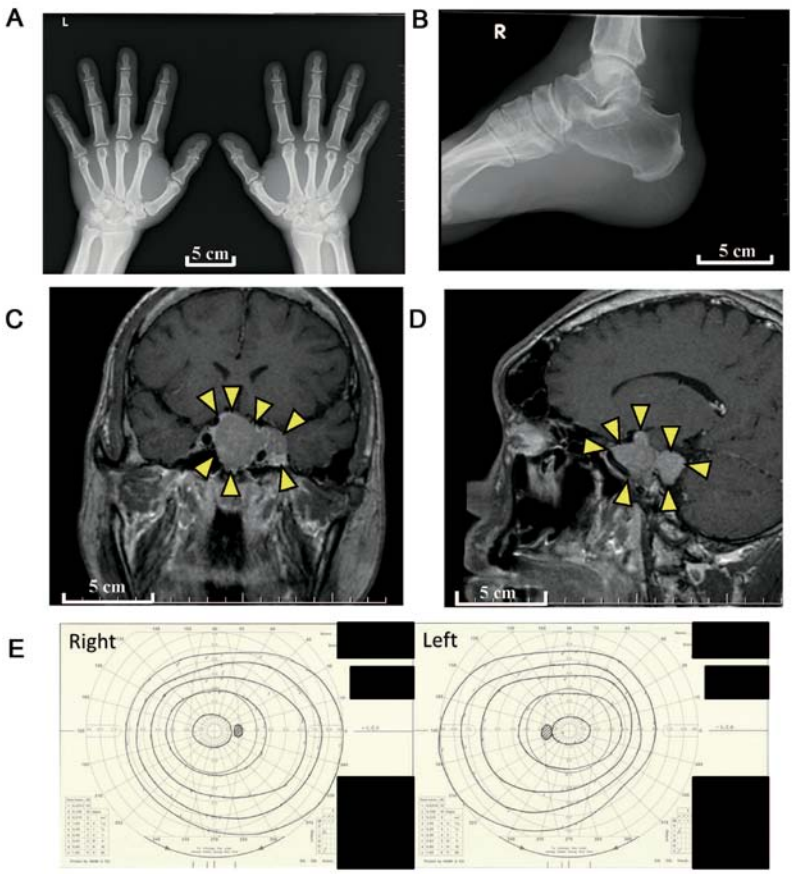

Figure 2. Radiographic and ophthalmic examinations. Radiographic imaging suggested (A) hypertrophied terminal phalangeal tufts and soft tissue hypertrophy, and (B) heel pad thickness. (C and D) Enhanced T1-weighted magnetic resonance imaging revealed a 4.5-cm pituitary tumor involving the left cavernous sinus. (E) Ophthalmic examinations demonstrated no vision loss secondary to the pituitary tumor.

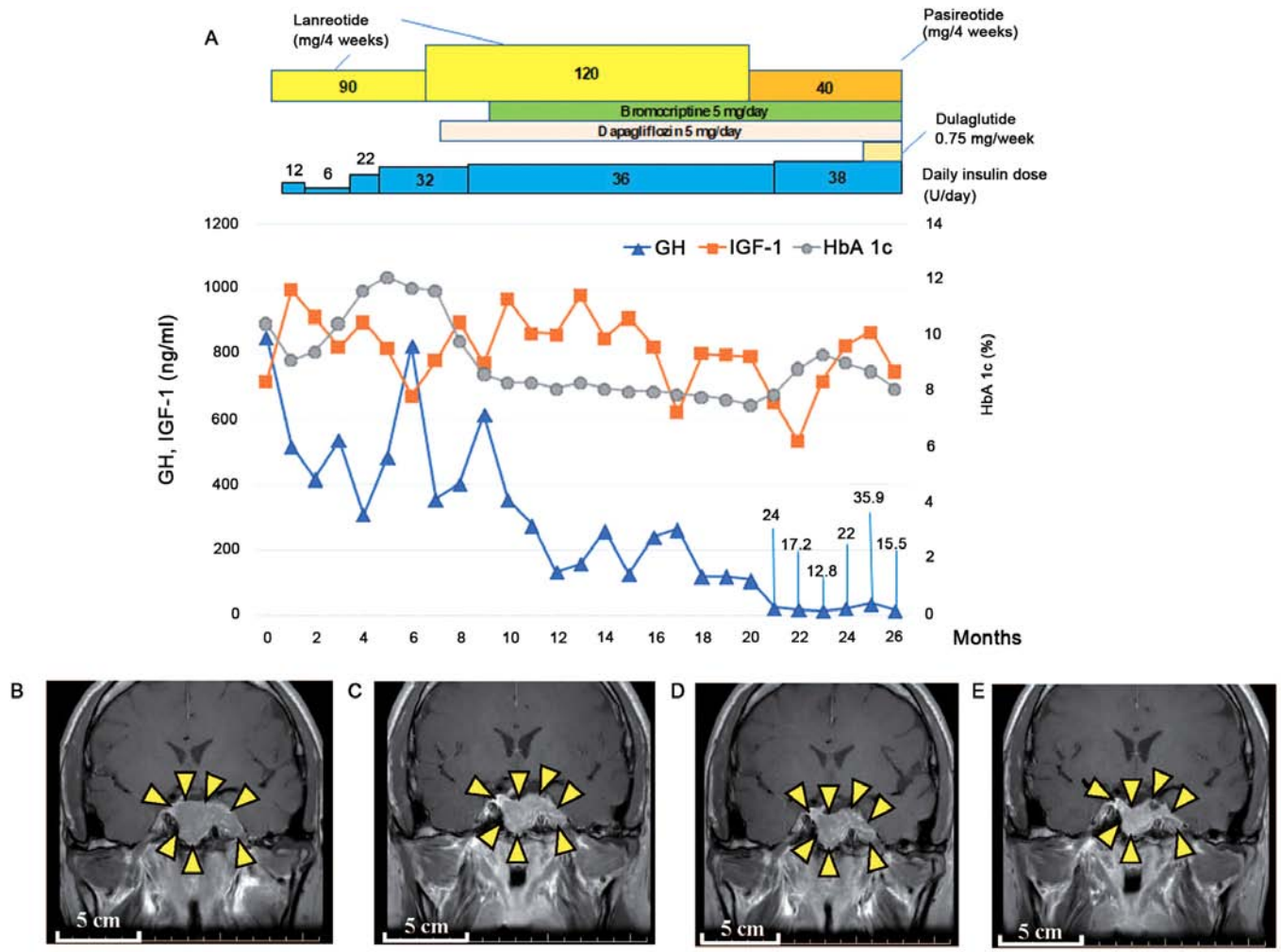

Figure 3. Clinical course of the patient (A) Patient clinical course and treatment, and the results of laboratory analyses. Magnetic resonance imaging demonstrating tumor shrinkage; images were captured (B) 5, (C) 12, (D) 18 and (E) 24 months after treatment. GH, growth hormone; IGF-1; insulin-like growth factor-1; HbA 1c, hemoglobin A1c.

that suppresses GH secretion by binding to the D2 receptor in the pituitary tumor (16). International consensus statement also recommend the use of cabergoline, a dopamine agonist (14). However, the Japanese Health Insurance System does not cover cabergoline, and therefore, bromocriptine was indicated in the present case (19). A previous report demonstrated the beneficial effects of bromocriptine in acromegaly-associated glucose abnormalities (16). Due to the large size of the tumor and the high levels of circulating of IGF-1, no surgical procedures were indicated at the time of the present report. Tumor debulking surgery will be indicated after appropriate tumor shrinkage.

Discussion

Acromegaly may reduce the life expectancy of individuals. Metabolic disorders associated with acromegaly accelerate arteriosclerosis and increase the risk of cardiovascular events (20). The first therapeutic option for acromegaly is surgical resection of the pituitary adenoma, although surgery is not feasible in patients with large tumors (6). Patients with unresectable tumors receive treatment with SRLs and GH receptor antagonists (20). However, the lack of an international consensus for the duration of therapy, the high economic burden for the patient and the potential adverse effects associated with the prolonged use of specific SRLs, make the routine indication of these drugs difficult in clinical practice (21). Therefore, the early diagnosis of acromegaly is imperative to successful treatment. However, subtle progressive physical alterations may go unnoticed by patients and attending physicians, leading to delayed or missed diagnoses with detrimental implications for patient care (22). Current clinical guidelines describe the importance of a thorough foot examination for the diagnosis of acromegaly (23); however, available guidelines lack a detailed description of the clinical disease presentations in the presence of comorbidities (such as diabetes mellitus) (23). The present case indicated that, in addition to diabetic foot, acral abnormalities (such as enlarged feet) should also be assessed during the routine examination of patients with untreated diabetes mellitus. The present report is an illustrative case of missed diagnosis of acromegaly that negatively affected medical treatment. Due to a missed diagnosis of acromegaly at the early stages (during routine medical check-ups over numerous years), the patient could not undergo debulking surgery of the pituitary tumor. Therefore, this case also underscores the critical

importance of early diagnosis for the management of patients with acromegaly.

Another point that could have prevented a missed diagnosis in the present case is the detection of hyperglycemia. Diabetes mellitus is a metabolic disorder that may be associated with acromegaly (20). A cohort study in a Mexican population revealed that, among patients with acromegaly, the incidence of diabetes mellitus appeared to be higher in women than in men (16). However, epidemiological data from other geographical areas revealed no differences between the sexes (4,24-28). Clinical suspicion of acromegaly is generally difficult during anamnesis of patients with diabetes mellitus, particularly in the absence of disease-related symptomatology. However, following routine checkpoints may prevent patients and practitioners from overlooking the signs of acromegaly. The American Diabetes Association recommends a comprehensive and routine foot examination during the initial visits of all diabetic patients (29,30). In addition to evaluating the presence of diabetic foot, peripheral artery disease or diabetic neuropathy, careful foot examination may also provide hints for the early diagnosis of acromegaly. In the present case, laboratory data during the medical check-up disclosed hyperglycemia that was indicative of diabetes mellitus. Failure to examine the foot of the patient, despite the suspicion of diabetes mellitus, was another contributing factor for the missed diagnosis of acromegaly. In the present case, improvement of glucose metabolism after surgical treatment may demonstrate that acromegaly was the cause of hyperglycemia (16). The patient is currently under clinical follow-up, and will undergo surgery when the tumor becomes operable.

Diagnostic error is a frequent cause of patient harm and adverse events in hospital practice and outpatient care (31,32). In 2015, the National Academy of Medicine stated that most individuals 'will experience at least one diagnostic error in their lifetime, sometimes with devastating consequences' (33-35). There are different types of diagnostic errors, such as the wrong diagnosis (misdiagnosis), failure to diagnose (missed diagnosis) and delayed diagnosis (32). Diagnostic errors may be detrimental to patient health, resulting in delayed or inappropriate therapy or diagnostic procedures (32,33). The current report is a typical case of acromegaly where, due to missed diagnosis over a number of years, the most appropriate treatment was not received.

The present report outlines a case of missed diagnosis of acromegaly associated with severe hyperglycemia. After 10 years of missed diagnosis, the associated pituitary tumor became inoperable due to invasive growth into the adjacent tissue. This case highlights the importance of hyperglycemia and abnormal feet in acromegaly. In addition, the case underscores the requirement for a careful examination of the feet of diabetic patients, and the critical importance of early diagnosis of acromegaly to prevent devastating consequences for patient care.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

KN was responsible for clinical treatment, follow-up in Kuwana City Medical Center and Mie University Hospital and preparation of the first draft of the manuscript. YY, TY and ECG contributed to the interpretation of the data and made intellectual contributions for the preparation of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of clinical details and images.

Competing interests

The authors declare that they have no competing of interests.

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