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【 CASE REPORT 】

Clubbed Digits Presumably Caused by Lubiprostone

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Abstract:
Digital clubbing has been regarded as an important sign in medicine. A 33-year-old woman with no history of hepatic, pulmonary, or malignant disease was referred to our hospital. She had been taking lubiprostone every day for three years for constipation. Clubbing in her upper and lower limb digits began gradually about two years ago. The results of laboratory investigations were almost normal. We suspected the clubbed digits were a side effect of lubiprostone and confirmed that the levels of urinary prostaglandin E2 (PGE2), which can cause clubbed digits, were elevated. Thus, we instructed the woman to stop taking lubiprostone and monitored this lab value. However, the value continued to rise over 2 months to 41.9 μg/g Cr. During that time, she had been taking sennoside A B calcium instead of lubiprostone for constipation. Since sennoside A B calcium also has the effect of increasing PGE2, we ordered the discontinuation. Her urinary PGE2 to creatinine level normalized, and the clubbing improved after the discontinuation of these two medications.

Key words: digital clubbing, prostaglandin E2, lubiprostone, sennoside A B calcium

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Introduction

Digital clubbing, which was first described by Hippocrates (1) about 2,500 years ago in a patient with empyema, is an important clinical sign in medicine. Although having clubbed digits is rarely accompanied by other symptoms, clubbing often indicates the presence of serious underlying diseases (2). These major conditions are often lung diseases (75-80%), cardiovascular diseases (10-15%), diseases of the liver and gastrointestinal tract (5-15%), or miscellaneous causes (5-15%) (3).

In the pathogenesis of digital clubbing, vascular endothelial growth factor and platelet-derived growth factor have been shown to play a central role (4), but the exact mechanism is not fully understood. Uppal et al. (5) studied three Pakistani families with primary hypertrophic osteoarthropathy (PHO), a disorder in which clubbing is accompanied by painful joint enlargement, and went on to show that patients with PHO had chronically elevated levels of one particular prostaglandin, prostaglandin E2 (PGE2). Thus, the functions of PGE2 may provide a plausible explanation for the clinical features of clubbed digits, and measurements of PGE2 may be an important diagnostic tool.

We herein report a case of clubbed digits in which urinary PGE2 levels were elevated from the long-term use of lubiprostone, as the clubbing improved after lubiprostone discontinuation.

Case Report

A 33-year-old woman presenting with clubbed digits on both hands was referred to our hospital for a further examination. She had been taking medications for schizophrenia since the age of 23 and had been properly taking antipsychotic medicines (e.g., sodium valproate, levomepromazine maleate, lorazepam, olanzapine, risperidone). In addition, she had been taking lubiprostone and magnesium oxide every day for constipation for three years. Clubbing in her upper and lower limb digits began gradually about two years ago. She had no chest pain, syncope, palpitation, cyanosis, ankle swelling, or any gastrointestinal complaints other than constipation. She was not married and lived with her family; she had smoked tobacco for 10 years and denied alcohol consumption. Other members of her family had no history of clubbing. There was no history of hepatic, cardiopulmonary, or malignant disease.

On a physical examination, her body mass index was 21.6

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kg/m^2, pulse rate 61/min, regular, blood pressure 130/80 mmHg, and respiratory rate 18/min. There was no evidence of cyanosis, pallor, jaundice, or lymphadenopathy. An examination of her hands and feet revealed drumstick-type clubbing of her fingers and toes (Fig. 1). There was no swelling or tenderness of the wrists, elbows, ankles, or knees. Additionally, there was no thickening of the skin over the arms or legs. As shown in the Table, the results of laboratory investigations, including a complete blood count, urinalysis, and renal tests, were almost normal. Only alanine aminotransferase (ALT) increased to 70 IU/L, but ultrasonography revealed fatty liver and later confirmed its improvement. Rheumatoid factor and anti-nuclear antibody levels were within normal limits.

Because of the clubbing, we ordered chest X-ray, an electrocardiogram, pulmonary function tests, and echocardiography - all of which were normal. Computed tomography (CT) did not reveal any underlying malignancy. Given the above findings, the clubbed digits were suspected of being a side effect of the medications, including lubiprostone.

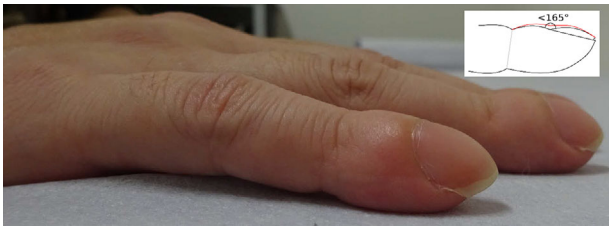

Figure 1. At the first visit to the hospital. Her digits showed a loss of the normal <165° angle (Lovibond angle) between the nailbed and the fold (cuticula), increased convexity of the nail fold, and thickening of the whole distal end of the finger (resembling a drumstick).

Uppal et al. (5) reported increased blood PGE2 levels as a cause of clubbed digits. Thus, we measured urinary PGE2 to creatinine (Cr) excretion, which reflected blood PGE2 levels. As shown in Fig. 2, the level of urinary PGE2 to Cr was remarkably high at 45.1 μg/g Cr [Japanese healthy controls: median 13.1, interquartile range 10.3-17.2 μg/g Cr as reported in previous studies (6)]. Thus, we instructed the woman to stop taking lubiprostone and monitored this lab value. However, the value at 2 months later had risen to 41.9 μg/g Cr. During that time, she had been taking sennoside A B calcium instead of lubiprostone for constipation. Since sennoside A B calcium also has the effect of increasing PGE2, we ordered its discontinuation as well. Her urinary PGE2-to-Cr level normalized to 15.3 μg/g Cr, and the clubbing improved after the discontinuation of these medications (Fig. 3).

Discussion

Clubbed digits have been associated with a number of neoplastic, pulmonary, cardiac, gastrointestinal, infectious, endocrine, psychiatric, and multisystem diseases (7). It is also part of the clinical triad, along with arthralgias and ossifying periostitis, known as primary or secondary hypertrophic osteoarthropathy (7). To our knowledge, this case is the world's first patient with clubbed digits presumably caused by the long-term administration of lubiprostone.

The pathophysiology underlying the development of clubbing remains unclear. A link between clubbing and laxative abuse has been reported several times in the literature, and all cases were young women who acknowledged taking high doses of senna tablets to control their weight (8). Many other previously reported clubbing cases have been associated with hypokalemia, chronic renal failure or fluid reten-

Table. Laboratory Data on the First Visit.

<Blood cell count>		T-BiL	0.4 mg/dL	Pi	4.4 mg/dL
WBC	7,700 /μL	AST	38 U/L	CRP	0.56 mg/dL
Neu	49.8 %	ALT	70 U/L	RF	(-)
Lymp	40.2 %	LDH	200 U/L	ANA	<40
Eosino	4.5 %	ALP	421 U/L	<Endocrinological examination>	
Baso	0.3 %	γ-GTP	19 U/L	TSH	4.690 μIU/mL
RBC	442×10^4 /μL	BUN	8 mg/dL	Free T3	1.14 ng/dL
Hb	12.6 g/dL	Cr	0.50 mg/dL	Free T4	2.75 pg/mL
Ht	38.2 %	SUA	4.8 mg/dL	Intact PTH	76 pg/mL
Plat	25.0×10^4 /μL	Na	142 mmol/L	<Urinary test>	
<Blood chemistry>		K	4.1 mmol/L	U-Pro	(-)
TP	7.8 g/dL	Cl	105 mmol/L	U-Glu	(-)
Alb	4.2 g/dL	Ca	9.3 mg/dL	U-Urob	(-)

WBC: white blood cell, Neu: neutrophil, Lymp: lymphocyte, Eosino: eosinophil, Baso: basophil, RBC: red blood cell, Hb: hemoglobin, Ht: hematocrit, TP: total protein, Alb: albumin, T-BiL: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: gamma-glutamyl transferase, BUN: blood urea nitrogen, Cr: creatinine, SUA: serum uric acid, CRP: c-reactive protein, RF: rheumatoid factor, ANA: anti-nuclear antibody, TSH: thyroid-stimulating hormone, PTH: parathyroid hormone, U-Pro: urinary protein, U-Glu: urinary glucose, U-Urob: urinary urobilinogen

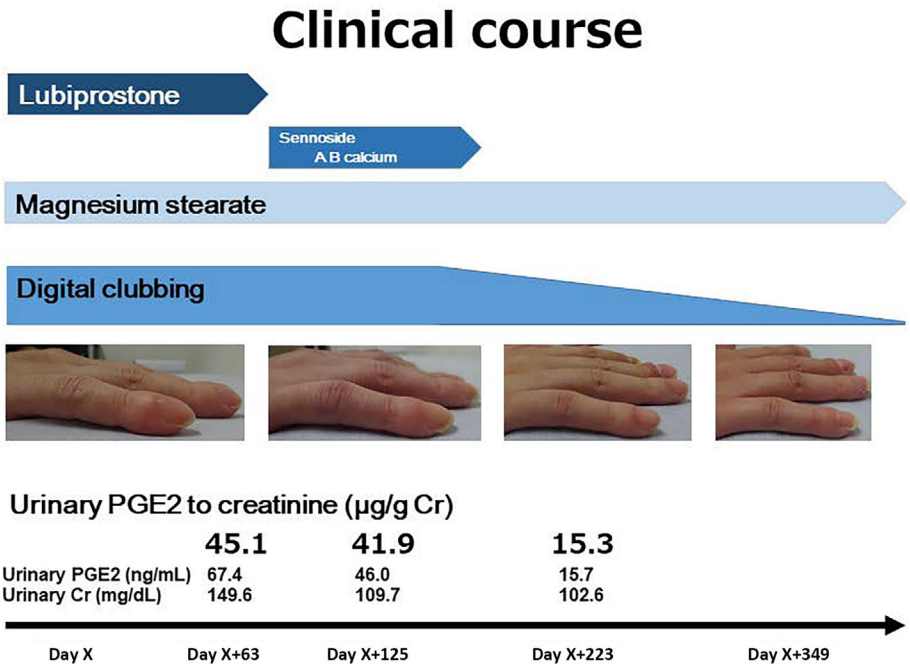

Figure 2. **Clinical course.**

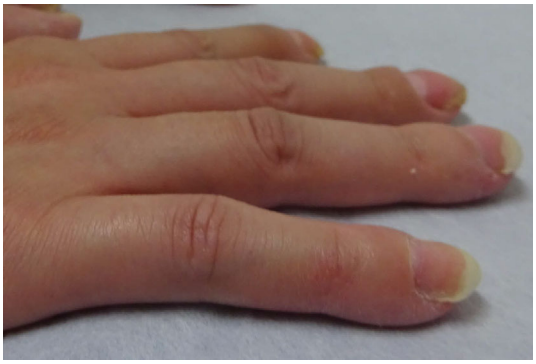

Figure 3. **Seven months after lubiprostone and sennoside A B calcium discontinuation. Her digits show a normal Lovibond angle between the nailbed and the fold and improved thickening of the whole distal end of the finger.**

tion, and hypercalcemia due to calcium in the senna tablets (9). However, the nature of this relationship is not fully understood. In this case, lubiprostone and magnesium oxide had been taken daily for constipation for three years. The patient had no history of hepatic, pulmonary, or malignant disease, and the results of her laboratory investigations were normal. Interestingly, her urinary PGE2-to-Cr level was remarkably high when she was referred to our hospital.

PGE2 is a strong vasodilator, inducing prolonged vasodilation in the distal digits associated with clubbing. This prostaglandin stimulates the activity of both osteoblasts and osteoclasts, thereby causing both bone deposition (periostosis) and resorption (acro-osteolysis) (10). PGE2 is a critical inflammatory mediator and a major cyclooxygenase product that plays a vital role in human physiology and tumor development and progression (11). However, it is difficult to measure PGE2 values directly in local tissue and blood due to its rapid metabolism (6). A recently developed radioimmunoassay kit (Institute of Isotopes, Budapest, Hungary) was used to measure the value of main metabolites of prostaglandin E (PGE-MUM: 7-hydroxy-5, 11-diketotetranor-prosta-1, 16-dioic acid) levels at SRL (Tokyo, Japan). The PGE-MUM levels were corrected by the urinary Cr concentration (expressed as μg/g Cr) because the PGE-MUM concentration depends on the urinary volume. In this case, the urinary PGE2-to-Cr level was remarkably high at 45.1 μg/g Cr at the first visit to our hospital, and her urinary PGE2-to-Cr level normalized to 15.3 μg/g Cr after discontinuation of the relevant medications (lubiprostone and sennoside A B calcium).

Lubiprostone is a bicyclic fatty acid metabolite analogue of prostaglandin E1 that belongs to a class of drugs known as type-2 chloride channel (ClC-2) activators. It works by increasing the amount of fluid within the intestines, making the passage of stool easier, and is used to treat certain types of constipation, including chronic idiopathic constipation and constipation associated with irritable bowel syndrome (12). Parentesis et al. (13) suggested that lubiprostone has very weak activity on PG receptors, and it has also been reported in up to 54% PGE2 activity on the PGE receptor 1 (EP_1). Recent studies have suggested that lubiprostone may also exert PG-based effects on non-gastrointestinal tissues (14). The link between clubbing and laxative abuse (e.g., senna) has been reported several times in the literature (8). Interestingly the clubbing was reported to resolve upon cessation of senna (15-17). Rhein anthrone, the active metabolite of sennoside A B calcium, also stimulates PGE2 release into the mouse colonic lumen (15). In the present patient, the urinary PGE2-to-Cr level decreased and normal-

ized three months after the discontinuation of lubiprostone and sennoside A B calcium.

This patient had been properly taking antipsychotic medicines (e.g., sodium valproate, levomepromazine maleate, lorazepam, olanzapine, risperidone). To our knowledge, the interaction of these drugs with lubiprostone and sennoside A B calcium and their direct effect on PGE2 production and/or clubbed digits have not been reported.

In conclusion, physicians should be aware of the potential for digital clubbing when patients take lubiprostone and sennoside A B calcium for extended durations.

The authors state that they have no Conflict of Interest (COI).

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