



## CT Image of Consolidation and Ground-Glass Opacification (GGO) of COVID-19 in Diabetic Patient

Katsunori Ogura<sup>1</sup>, Hiroshi Bando<sup>1,2ID\*</sup>, Yoshinobu Kato<sup>1</sup>, Hisako Yamashita<sup>1</sup>, Yoshikane Kato<sup>1</sup>

<sup>1</sup>Kanaiso Hospital, Komatsushima, Tokushima, Japan

<sup>2</sup>Tokushima University/Medical research, Tokushima, Japan

Corresponding Author: **Hiroshi BANDO, MD, PhD, FACP** [ORCID ID](#)

**Address:** Tokushima University /Medical Research, Nakashowa 1-61, Tokushima 770-0943, Japan; Tel: +81-90-3187-2485; Email: [pianomed@bronze.ocn.ne.jp](mailto:pianomed@bronze.ocn.ne.jp)

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### Abstract

The case involves a 70-year-old female with Type 2 Diabetes (T2D) who had been prescribed EquMet (vildagliptin/metformin) and had a stable HbA1c. In August 2022, she tested positive for real-time polymerase chain reaction (RT-PCR) without showing any symptoms. By November 2022, her HbA1c had increased to 7.4%, and a chest CT scan revealed a consolidation lesion in her left lower lung, suggesting post-inflammatory pathology of COVID-19. Imeglimin (Twymeeeg) was added to her treatment regimen, and it proved effective, resulting in a 0.9% reduction in HbA1c over 4 months without any gastrointestinal adverse effects (GIAEs). The combined treatment of EquMet and Twymeeeg was effective, and the interrelationship between T2D and COVID-19 will be followed up.

### Keywords

Real-Time Polymerase Chain Reaction, COVID-19, EquMet (vildagliptin/metformin), Imeglimin (Twymeeeg), Gastro-Intestinal Adverse Effects

### Abbreviations

RT-PCR: Real-Time Polymerase Chain Reaction; GIAEs: Gastro-Intestinal Adverse Effects

### Introduction

In March 2020, the World Health Organization (WHO) declared COVID-19 a pandemic disease and a public health emergency of international concern [1]. Interestingly, many people with positive real-time polymerase chain reaction (RT-PCR) results have been found to be asymptomatic. As a result, chest CT scans have played an important role in the early detection of pneumonia [2]. If RT-PCR results are false negative, CT scans can reveal probable abnormalities [3]. CT scans become a beneficial measure for early detection

of COVID-19 when a patient has symptoms for 3 days. However, during the first 2 days with symptoms, CT scans show normal findings in 56% of cases [4].

Authors and collaborators have been conducting clinical research and practice for a long time in various related fields, including primary care (PC), integrative medicine (IM), and various management of COVID-19 [5,6]. In many countries, including Japan, unexpected changes in COVID-19 have been detected over the years [7,8]. Additionally, we have covered medical

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fields such as type 1 and 2 diabetes (T1D, T2D), low-carbohydrate diets (LCDs), meal tolerance tests (MTTs), continuous glucose monitoring (CGM), and others [9,10]. Some reports have discussed the novel OHA, imeglimin (Twymeeg) [11,12].

We have come across meaningful case reports of patients with various pathophysiology [13] (Bando). Currently, we have observed an impressive case involving a patient with a positive COVID-19 test and T2D who experienced clinical benefits from imeglimin. This article will describe the general clinical progress and offer some perspectives.

### Case Presentation

#### Medical History:

This case concerns a 70-year-old female with Type 2 Diabetes (T2D) for 11 years. There is no history of hypertension, dyslipidemia, hyperuricemia, cerebral vascular accident (CVA), cardiovascular disease (CVD), or peripheral artery disease (PAD). Additionally, the patient has not shown any remarkable microangiopathy such as retinopathy, neuropathy, or nephropathy. Her HbA1c has been around 7.0% for years, and she has been treated with some oral hypoglycemic agents (OHAs).

Regarding her past medical history, the patient had no significant diseases until the age of 59. Her body weight remained stable at about 44 kg from the ages of 18 to 59. She has a son who has been diagnosed with T2D and has a physique of 180cm in height and 80kg in weight.

From January 2021, her general clinical progress was summarized in **Fig-1**. In September 2022, she underwent a chest X-ray, which had a negative result (**Fig-2a**). In March 2022, her OHA was changed from teneligliptin to EquMet, a combination of Vildagliptin (Equa) and Metformin, resulting in a decrease in her HbA1c level to 6.6% for 6 months. In early August 2022, her family was diagnosed with COVID-19 infection, and she tested positive for real-time polymerase chain reaction (RT-PCR) without experiencing any symptoms. She did not undergo a chest X-ray or blood test at that time. Her HbA1c level increased from 6.6% to 7.4% over the next 3 months. In November 2022, she underwent a chest X-ray as part of her routine annual check-up, which revealed the silhouette sign on the left margin of the heart (**Fig-2b**).

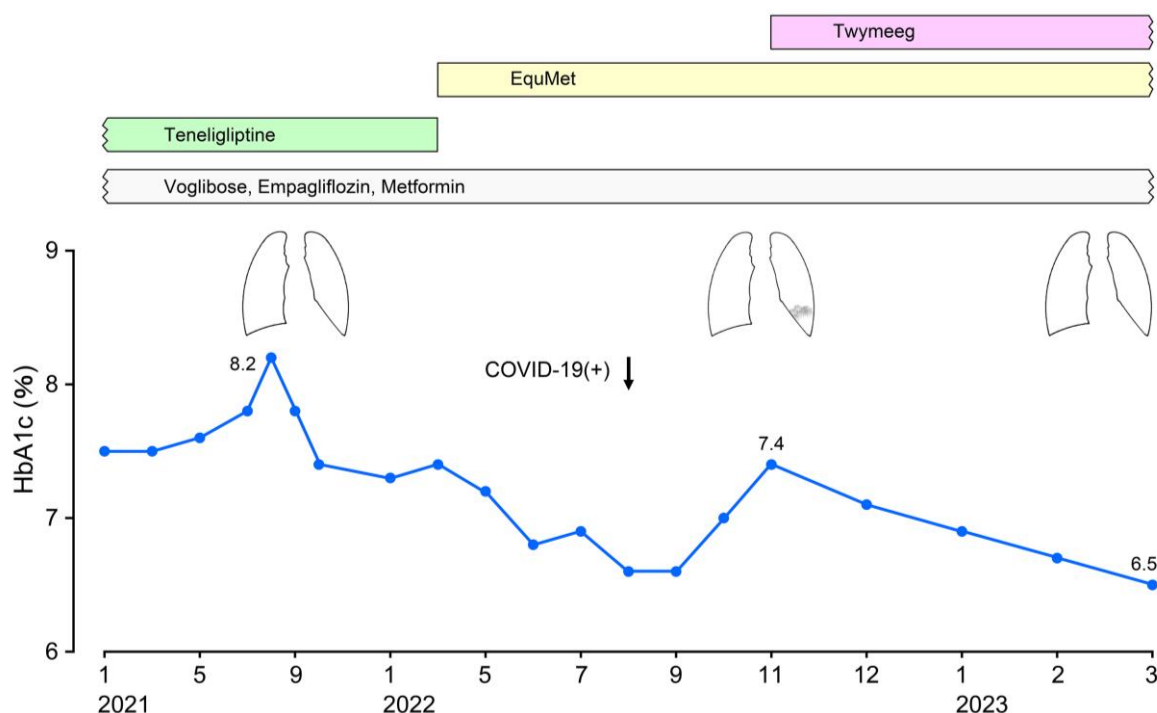


Fig-1: Clinical progress of HbA1c, chest X-ray and treatment

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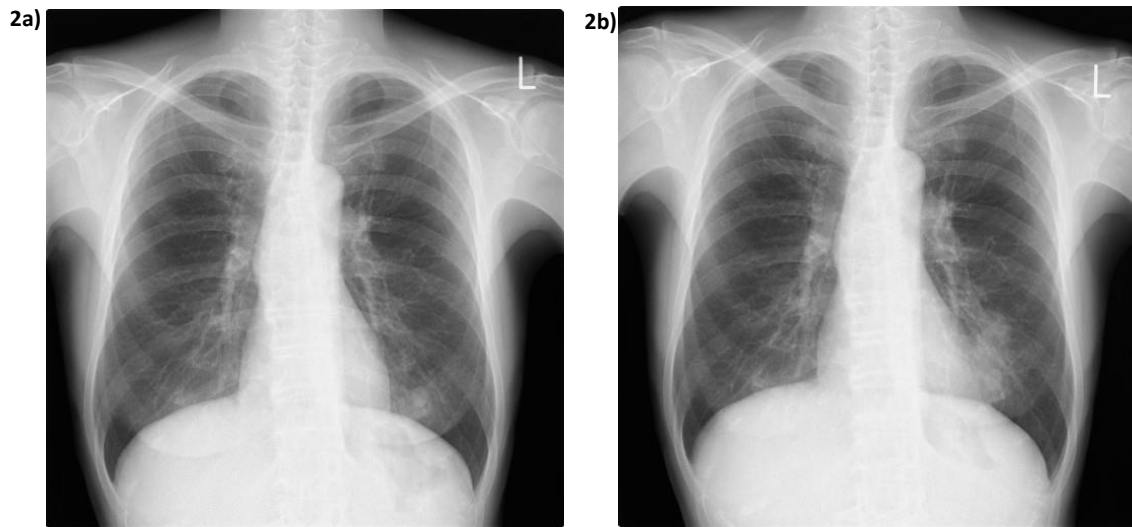


Fig-2: Chest X-ray

2a: standing chest image in Sep 2021

2b: standing chest image in Nov 2022

As a result, a chest CT scan was performed for a more detailed examination. When the chest CT image was analyzed under the condition of the mediastinum, consolidation and ground-glass opacification (GGO) were found in the lingual segment of the left upper lobe of the lung, with a slight tendency to shrink (Fig-3a and Fig-3b). This CT image indicated a previous history of pneumonia and some changes after pneumonia due to COVID-19. Furthermore, the chest CT image was expressed under the lung condition, and the consolidation lesion appeared to be rather wide (Fig-4a). When the

consolidation of the left lung was viewed in the coronal view, detailed heterogeneity was revealed (Fig-4b).

*Physical and Laboratory Exam:*

Her physical status in Nov 2022 was as follows: consciousness alert, speech normal, vitals within normal limits, SpO<sub>2</sub> 99%, head, neck, lung, heart, abdomen and neurological findings were negative. Her physique was height 157cm, weight 45kg with BMI 18.3 kg/m<sup>2</sup>.

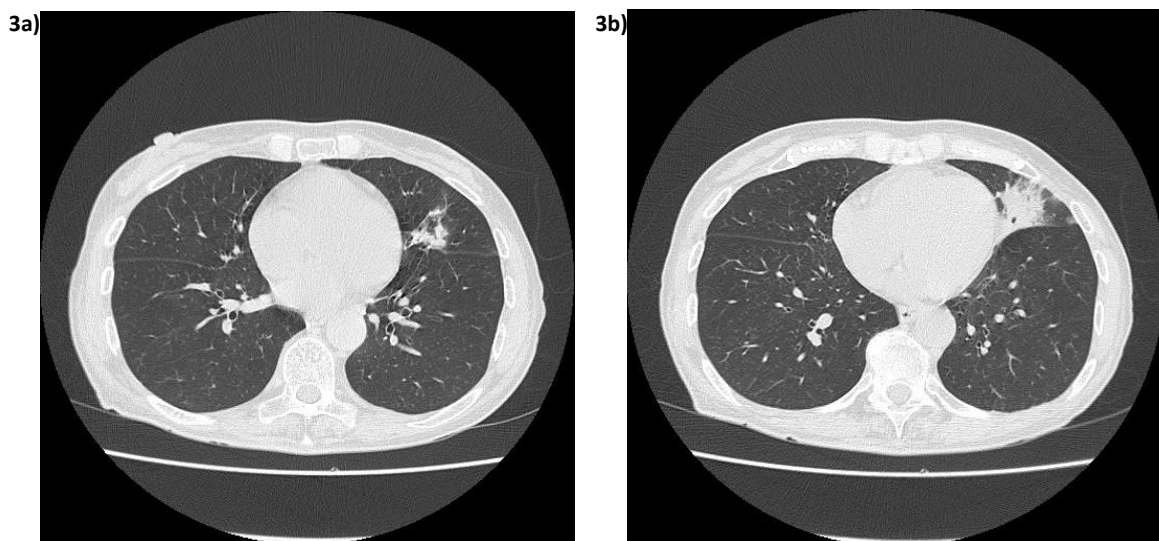
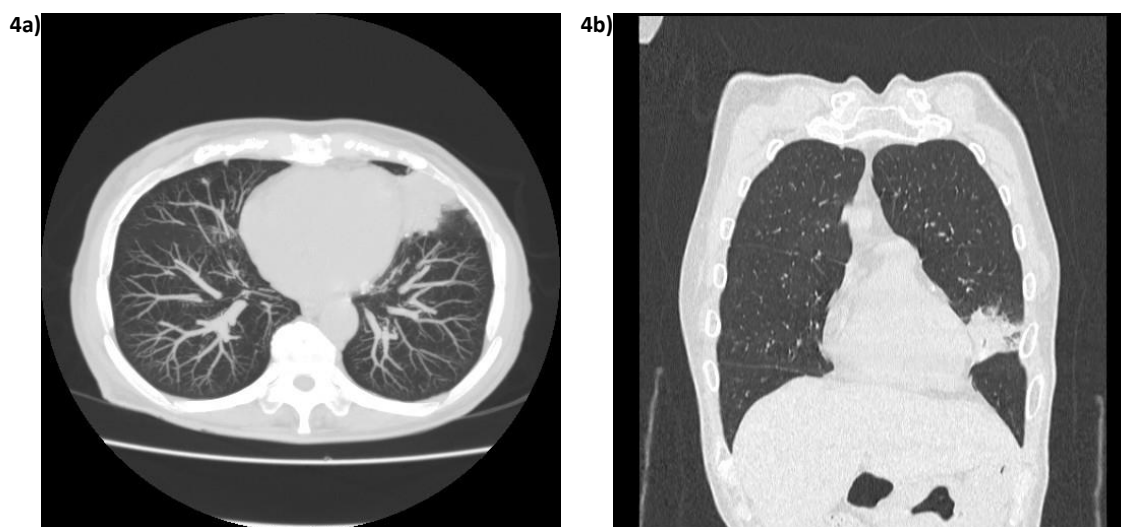


Fig-3: Chest CT scan

3a: the consolidation and ground-glass opacification (GGO) were found

3b: image of a few slices apart from 3a



**Fig-4: Chest CT scan**

*4a: axial plane image using lung image condition*

*4b: coronal plane image using the mediastinum condition*

The laboratory examination in Nov 2022 showed in the following: HbA1c 7.4%, pre-prandial blood glucose 124 mg/dL, RBC  $4.61 \times 10^6 / \mu\text{L}$ , Hb 14.5 g/dL, Ht 44.5 %, MCV 96.5 fL (80-98), MCH 31.5 pg (27-33), MCHC 32.6 g/dL (31-36), WBC 5000/ $\mu\text{L}$ , Plt  $22.7 \times 10^4 / \mu\text{L}$ , AST 24 U/L, ALT 19 U/L,  $\gamma$ -GTP 10 U/L, Uric acid 2.7 mg/dL, BUN 20 mg/dL, Cre 0.48 mg/dL, HDL 76 mg/dL, LDL 117 mg/dL, TG 53 mg/dL. Urinalysis: protein (-), glucose (+), urobilinogen (+/-), pH 6.0, ketone bodies (-), urinary Alb/Cre ratio 24.3 mg/g·Cre (0-30). Electrocardiogram (ECG) showed ordinary sinus rhythm, pulse 76/min, normal axis with no remarkable ST-T changes.

### Clinical Progress

Current case has showed elevated HbA1c value in Nov 2022, and then she began to take the novel OHA as imeglimin (Twymeeeg) 2000mg/day. After that HbA1c value was decreased from 7.4% to 6.5% for 4 months. She did not show any symptoms of gastro-intestinal adverse effects (GIAEs) from Twymeeeg. In Mar 2023, she received chest X-ray, chest CT and blood chemistry, which showed all negative results.

### Ethical Standards

This study was complied with the usual standard ethical guidelines from the Declaration of Helsinki. Moreover, several comments are included by the

protective standard regulation accompanied by personal information. The related principle has presented the ethic rule concerning the clinical research, that is involved in the matter of human being. Some guidelines are announced by Japanese government, which are from the Ministry of Education, Culture, Sports, Science Technology and the Ministry of Health, Labor and Welfare. The authors et al. established the ethical committee about this case. It existed in Kanaiso hospital, Tokushima, Japan. The committee included related hospital staffs and the person of legal professional. The members were the director, physician, nutritionist, head nurse, pharmacist, and radiologist. We discussed enough concerning the research protocol, and agreed the current protocol.

### Discussion

The characteristics of this case are as follows: i) COVID-19 infection was detected in August 2022 without any symptoms, ii) consolidation happened to be found by chest CT scan in November 2022, followed by improvement in March 2023, and iii) EquMet and Twymeeeg were effective in the treatment of diabetes. Consideration will be given in this order.

Firstly, chest X-rays seem to be insufficient for confirming COVID-19 infection [14]. A chest CT scan



would be required to diagnose the details of the pathology [15]. Characteristic CT features of COVID-19 pneumonia have been analyzed [3]. The characteristic features of COVID-19 for an initial CT scan include multi-lobar ground-glass opacification (GGO). It is observed for the posterior or peripheral region, which tends to be found in the lower lobes [16]. Clinical improvement is usually found after 2 weeks associated with a gradual resolution of the consolidative opacification. Regarding lung abnormalities in COVID-19 for survival analysis, the characteristic findings were predominant inferior lung involvement, nodular consolidations, linear consolidations, GGO, peripheral topography, and others [17]. From summarized data (n=515), pulmonary involvement degree ( $\geq 50\%$ ) and advanced age, nodular consolidations showed a Hazard Ratio of 2.25 for lower survival rates of 30 days in the hospital.

Secondly, abnormal consolidation image of CT scan was disappeared for 4 months. It was probably due to COVID-19 infection without symptoms. For pulmonary abnormalities of COVID-19, 84 cases were investigated for changes in GGOs and consolidations [18]. GGOs showed changes from 100% to 2% in 1 year, and consolidations has disappeared from 71% to 0% for half year. Consequently, pulmonary abnormalities of COVID-19 pneumonia were improved in 78/84 (93%) cases. Aged patients of COVID-19 (n=55) were investigated for their changes in chest CT scan [19]. For 6 months, GGOs were still found in 22% of cases, while consolidations were disappeared. Consequently, typical CT abnormal acute image of COVID-19 pneumonia would be almost resolved in the elderly.

Thirdly, the current case showed remarkable HbA<sub>1c</sub> decrease after starting Twymeeg for 4 months. Both of EquMet and Twymeeg are OHAs of providing twice a day (bis in die, bid). This bid administration would be known to show clinical efficacy of improving blood glucose profile for all day long [20]. From historical point of view, metformin has been used for T2D as first-line OHA for long [21]. As a similar molecular construction of metformin, imeglimin (Twymeeg) has been developed [22]. It shows

beneficial add-on treatment with other OHAs and insulin therapy [23].

This case was provided add-on treatment of Twymeeg and EquMet, which include imeglimin, vildagliptin and Meformin. According to the large clinical studies of imeglimin, the results of TIMES 1,2 and 3 were reported [24]. Clinical efficacy of add-on treatment of Twymeeg and other OHAs were in the following. They were monotherapy -0.46%, DPP4-I -0.92%, biguanides -0.67%, which were related to the current case. In addition, SGLT2i -0.57%, glinides -0.70%, sulfonyl urea -0.56% and alfa-GI -0.85% were reported. From TIMES 3, impressive result was observed, where add-on treatment of GLP-1RA showed only -0.12% [25]. Although SGLT2i and GLP-1RA have similar common pharmacological mechanisms, the actual difference of clinical effect was found [26]. Thus, related mechanism may have other route of pharmacological pathway [27]. From a recent report, precise profile of blood glucose with imeglimin was investigated by continuous glucose monitoring (CGM). Recent report showed the detail glucose variability by imeglimin using continuous glucose monitoring (CGM), in which remarkable decrease of glucose profile was found for 24 hours [28]. Thus, further research development of imeglimin will be expected [29]. As regards to EquMet, comparative study was conducted between EquMet (vildagliptin and metformin) and metformin only ( $\geq 1500\text{mg/day}$ ) [30]. It included 11 RCT with 8533 cases. The result showed combined treatment had higher efficacy of -0.59 of mean differences (MD).

Certain limitation may exist in this article. The image of consolidation and GGO in CT scan was likely from COVID-19 infection, and was disappeared in 3 months. She did not feel any symptoms for clinical progress, and then following up would be required in the future. Furthermore, interrelationship between infection and diabetes may be investigated for solving the pathophysiology.

In summary, 70-year-old female showed clinically complex problems of positive PCR, later development

of pneumonia, T2D, and medication of EquMet/Twymeeg. Current patient becomes one of the impressive beneficial case reports, that provides several problem-solving perspectives.

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### Conflict of Interest

The authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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