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Exceptional Case

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Sarcoid-like lung granulomas in a hemodialysis patient treated with a dipeptidyl peptidase-4 inhibitor

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Abstract
It has been reported that the inhibition of dipeptidyl peptidase-4 (DPP-4)/CD26 on T-cells by DPP-4 enzymatic inhibitors suppresses lymphocyte proliferation and reduces the production of various cytokines, including tumor necrosis factor (TNF)-α. A 72-year-old female with diabetic nephropathy on hemodialysis developed multiple lung nodules following the administration of vildagliptin. A biopsy demonstrated the histology of granulomas without caseous necrosis. The discontinuation of vildagliptin resulted in the disappearance of the granulomas within 4 months. As granulomatosis often develops in patients under anti-TNF-α therapy, the accumulation of DPP-4 inhibitors or its metabolites is possibly linked to unrecognized complications, such as sarcoid-like lung granulomas.

Keywords: dipeptidyl peptidase-4 inhibitor; granuloma; hemodialysis; vildagliptin

Background

Dipeptidyl peptidase (DPP)-4 degrades incretin hormones, such as glucagon-like peptide (GLP)-1, and reduces the glucose-dependent insulinotropic effects of incretins on pancreatic β cells. DPP-4 inhibitors are a new class of antidiabetic agents that improve glucose homeostasis by enhancing the actions of incretin hormones. Vildagliptin has a relatively shorter half-life than other DPP-4 inhibitors and therefore is preferably administered twice daily. Exposure to vildagliptin in patients with moderate-to-severe renal impairment is increased compared with that observed in control subjects. However, the degree of exposure to vildagliptin does not correspond to the severity of renal impairment. In contrast, the level of the primary metabolite of (DPP)-4 (M20.7) increases in association with declines of renal function; however, increases in the level of this metabolite have no clinically relevant consequences since M20.7 is pharmacologically inactive [1, 2]. Therefore, vildagliptin can be used without dose adjustment in patients with a creatinine clearance of >50 mL/min. Although vildagliptin is, in principle, contraindicated in patients with moderate-to-severe renal impairment, a recent 24-week study suggested that vildagliptin (50 mg once daily) therapy is effective and well tolerated in moderate-to-severe renal impairment patients and those on dialysis with type 2 diabetes mellitus (T2DM) [3, 4].

DPP-4 is also known as adenosine deaminase complexing protein 2 or CD26 (EC 3.4.14.5) and is expressed on the surface of several cell types, including lymphocytes and monocytes, where it exerts immunoregulatory effects. In addition, DPP-4 substrates are proline- and alanine-containing peptides, including various growth factors, chemokines, neuropeptides and vasoactive peptides. Due to these off-target mechanisms, the use of DPP-4 inhibitors may result in unexpected side effects related to immunological responses [5]. In this article, we report the first case, to our knowledge, of sarcoid-like lung granulomas in a hemodialysis patient treated with vildagliptin.

Case report

A 70-year-old female began to receive hemodialysis for end-stage renal disease due to diabetic nephropathy in August 2010. Her treatment regimen for T2DM was changed from insulin injections to the oral administration of vildagliptin (50 mg/day) in December 2011. Following the initiation of vildagliptin, the patient's level of HbA1c ranged between 6.0 and 6.3%, and no episodes of hypoglycemia were observed. In April 2012, multiple nodular lesions were incidentally detected on chest computed tomography (CT) screening for lung cancer, without subjective symptoms (Figure 1A). These nodular lesions were not apparent 1 year earlier (Figure 1B). The patient had no pets, was not a smoker, had no experience of traveling overseas or allergies to drugs or foods. A QuantiFERON®-TB (QFT) blood test was positive; however, repeated sputum cultures and polymerase chain reaction assays were negative for tuberculosis (TB). The multiple nodular

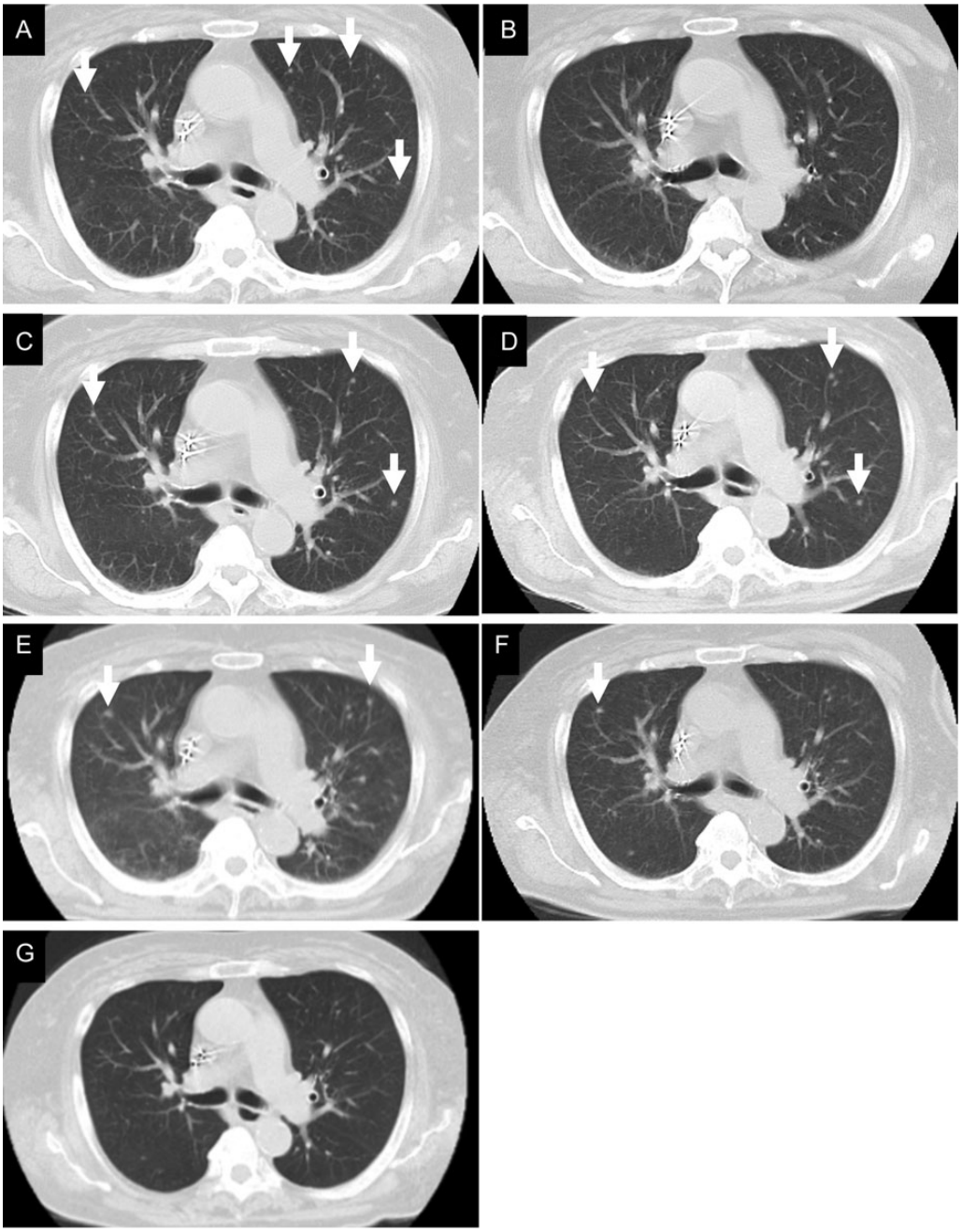

Fig. 1. Images of computed tomography of the chest. Multiple lung nodules were incidentally found in April 2012 (**A**); no lung nodules were seen in April 2011 (**B**). The size of the nodular lesions progressively increased in June 2012 (**C**) and September (**D**). In spite of the initiation of antituberculosis drugs in September 2012, the granulomas increased in size in October 2012 (**E**). In November 2012, 1 month after the discontinuation of antituberculosis drugs and vildagliptin, the size of the granulomas decreased (**F**). In February 2013, 4 months after the discontinuation of these drugs, most of the granulomas were no longer detectable (**G**).

lesions increased in size on CT after 2 months (Figure 1C); therefore, a CT-guided needle lung biopsy was performed, and granulomas without caseous necrosis were identified on a histological examination (Figure 2). No pathogenic microorganisms were detected on staining, including Grocott's methenamine silver and acid-fast staining. Furthermore, there was no evidence of TB on a culture of bronchial alveolar liquid (BAL). Because the presence of TB infection could not be completely excluded and the size of the granulomas progressively increased (Figure 1D), antituberculosis drugs, including rifampicin (450 mg/day), isoniazid (300 mg/day) and ethambutol (250 mg/two days), were administered empirically starting in September 2012. Nevertheless, the granulomas further increased in size on follow-up CT performed 1 month later (Figure 1E). Therefore, we discontinued both the antituberculosis drugs and vildagliptin. Following the discontinuation of vildagliptin, the size of the granulomas decreased within 1 month (Figure 1F), and most of the lesions were barely detectable after 4 months (Figure 1G).

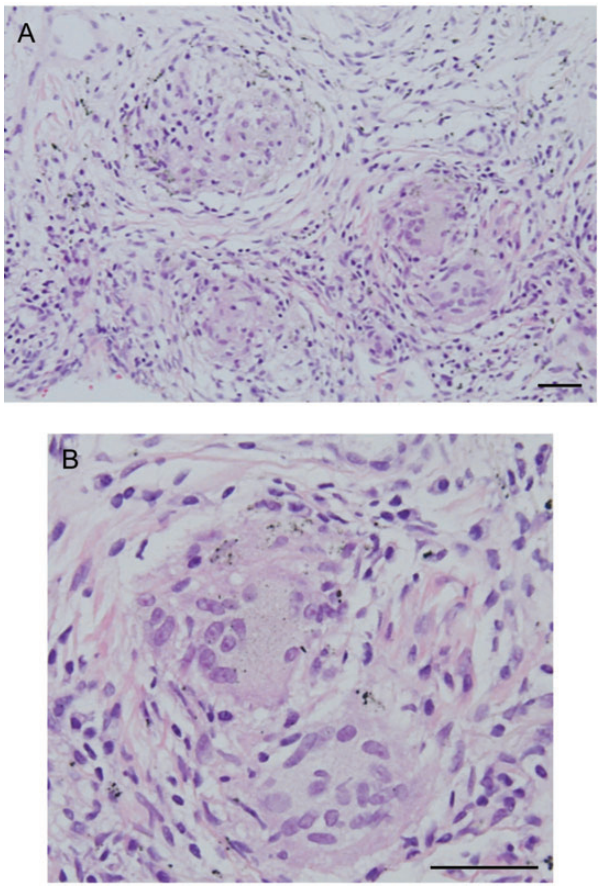

Fig. 2. Histological examinations of the lung nodules showing granulomas without caseous necrosis. (**A**) Hematoxylin-eosin, ×40. (**B**) Hematoxylin-eosin, ×400. Scale bars: 50 μm.

Discussion

We herein reported a case of sarcoid-like lung granulomas in a patient under hemodialysis who was treated with vildagliptin. To the best of our knowledge, this is the first case of granulomatosis related to the use of a DPP-4 inhibitor. In general, the incidence of adverse effects of DPP-4 inhibitors is lower than that of other oral hypoglycemic agents, and this case represents a very rare adverse effect of vildagliptin. The asymptomatic granulomas appeared following the initiation of treatment with vildagliptin and disappeared after its discontinuation. It is well known that dialysis patients have an increased risk of TB compared with the general population [6], with an often atypical pattern of development [7]. The current patient presented with positive findings for QFT, with no evidence of TB on cultures of the sputum and BALF or histology of the biopsy specimen. Although empiric therapy for TB was administered, the size of the granulomas did not change. The patient's laboratory findings and clinical course indicate that the granulomas were not caused by TB.

The occurrence of granulomatosis in patients treated with tumor necrosis factor (TNF) blockers has been previously reported [8]. It has also been speculated that modulation of the cytokine environment by anti-TNF therapy is related to the formation of granulomas. It was recently reported that the inhibition of DPP-4/CD26 on T-cells by DPP-4 enzymatic inhibitors selectively suppresses lymphocyte proliferation and reduces the production of various cytokines, including interferon-γ, interleukin-17 and TNF-α [9]. Similarly, other DPP family members, such as DPP-8 and DPP-9, play roles in immunoregulation [10]. In addition, it has been reported that GLP-1 inhibits inflammatory pathways [11], thereby increasing the level of GLP-1 via the inhibition of DPP-4, which may affect the inactivation of inflammatory pathways. Therefore, the effects of DPP-4 inhibitors may mimic those of anti-TNF therapies under certain conditions. Discontinuation of the anti-TNF therapies results in the resolution of granulomatosis in most cases. The granulomas also disappeared after the discontinuation of vildagliptin in the present case, suggesting similarities between the biological behavior of granulomas under these two conditions.

Vildagliptin can be administered without dose adjustment in patients with a creatinine clearance of >50 mL/min [2]. However, it has been reported that the plasma concentrations of vildagliptin and its metabolites are increased in patients with severe renal impairment [1, 12]. The accumulation of vildagliptin and its metabolites may affect the immune system and provoke unexpected side effects in dialysis patients with T2DM. Therefore, the use of non-renal excreted DPP-4 inhibitors, such as linagliptin, may reduce the risk of pharmacokinetic complications.

Since we ethically cannot readminister the drug in this case, other possible causes of granulomas remain, for example, a late response to therapy for TB or the spontaneous regression of sarcoidosis.

In conclusion, the administration of DPP-4 inhibitors in patients undergoing hemodialysis is possibly linked with the new onset of sarcoid-like granulomatosis. Hence, clinicians should be aware of such unexpected adverse effects.

Conflict of interest statement. None declared.

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