Sitagliptin-induced diffuse alveolar hemorrhage mimicking pulmonary edema

Dear Editor,

We read with great interest the article entitled "Noncardiac pulmonary edema induced by sitagliptin treatment" by Belice *et al*.[1] published in this journal, and also a commentary on this article by Sureka *et al*.,[2] who discussed the pulmonary edema of unknown etiology in this patient. Through our recent clinical experience, we would like to point out diffuse alveolar hemorrhage (DAH) as another potential cause of "pulmonary edema" in the patient reported by Belice *et al*. Our patient, a 50-year-old Japanese male with diabetes mellitus who had been started on treatment with sitagliptin at the dose of 50 mg once a day 3 months earlier, was admitted to our hospital because of bloody sputum and worsening of dyspnea. He had previously been diagnosed as having interstitial pneumonia, but his respiratory symptoms had been stable before he started to receive sitagliptin. On admission, he had tachypnea and hypoxemia (SpO_2 75%), and chest examination revealed fine and coarse crackles in the lower lung regions on both sides. His chest X-ray [Figure 1a] and computed tomography (CT) [Figure 1b] revealed new-onset bilateral diffuse infiltrative and ground-glass opacities, in addition to the preexisting bibasilar reticular shadows due to interstitial pneumonia; the new opacities suggested the complication of pulmonary edema. However, there were no clinical signs suggestive of cardiogenic edema, for example, no pretibial edema, normal plasma brain natriuretic peptide levels, a normal 12-lead electrocardiograph, and normal cardiac function on echocardiography. In contrast, bronchoalveolar lavage fluid obtained by fiberoptic bronchoscopy showed a bloody appearance [Figure 1c], confirming the diagnosis of DAH as the cause of the acute respiratory insufficiency with the CT opacities suggestive of pulmonary edema. A positive result of the drug-induced lymphocyte stimulation test with sitagliptin strongly suggested that this drug was the cause of the DAH in our patient. Thereafter, sitagliptin was discontinued, and the patient was started on intravenous methylprednisolone pulse therapy (1 g/day), his symptoms improved, and the bilateral diffuse infiltrative and ground glass opacities on the chest CT almost disappeared.

We consider several possible mechanisms, by which sitagliptin could have caused alveolar hemorrhage in our patient. First, because the DLST for sitagliptin was positive, sitagliptin may have acted as a hapten and elicited allergic hypersensitivity reactions damaging the pulmonary vasculature. Second, sitagliptin may have directly modulated immune cell functions, because lymphocytes have been shown to express CD126 that has dipeptidyl peptidase (DPP)-4 activity.[3] A previous study showed that systemic inhibition of DPP-4 activity aggravated allergic inflammation in mice.[3] Third, sitagliptin may have increased vascular leakage by disrupting the endothelial cell-to-cell junctions through vascular endothelial cadherin.[4]

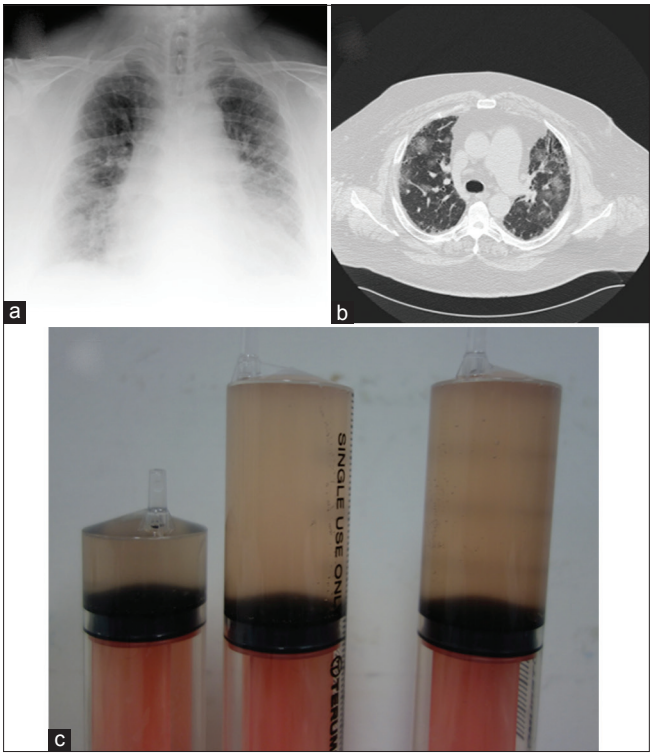

Figure 1: (a) Chest X-ray and (b) computed tomography revealing bilateral diffuse infiltrative and ground-glass opacities. (c) Macroscopic bloody appearance of bronchoalveolar fluid

In addition to sitagliptin, vildagliptin, another DPP-4 inhibitor, has also recently been reported to induce lung injury.[5] We suggest that lung injury is a rare but important adverse effect of DPP-4 inhibitors, and in patients receiving this class of drugs presenting with respiratory symptoms/signs, the possibility of DAH should be considered.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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References

1. Belice T, Yuce S, Kizilkaya B, Kurt A, Cure E. Noncardiac pulmonary edema induced by sitagliptin treatment. J Family Med Prim Care 2014;3:456-7.
2. Sureka B, Bansal K, Arora A. Pulmonary edema – Cardiogenic or noncardiogenic? J Family Med Prim Care 2015;4:290.
3. Stephan M, Suhling H, Schade J, Wittlake M, Tasic T, Klemann C, *et al.* Effects of dipeptidyl peptidase-4 inhibition in an animal model of experimental asthma: A matter of dose, route, and time. Physiol Rep 2013;1:e00095.
4. Lee CS, Kim YG, Cho HJ, Park J, Jeong H, Lee SE, *et al.* Dipeptidyl peptidase-4 inhibitor increases vascular leakage in retina through VE-cadherin phosphorylation. Sci Rep 2016;6:29393.
5. Ohara N, Kaneko M, Sato K, Maruyama R, Furukawa T, Tanaka J, *et al.* Vildagliptin-induced acute lung injury: A case report. J Med Case Rep 2016;10:225.

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Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_160_17

How to cite this article: Kikuchi R, Nakamura H, Aoshiba K. Sitagliptin-induced diffuse alveolar hemorrhage mimicking pulmonary edema. J Family Med Prim Care 2018;7:480-1.