Linagliptin/metformin/pembrolizumab interaction

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Various toxicities: case report

A 77-year-old woman developed acute renal failure during concomitant administration of pembrolizumab and linagliptin/metformin. Additionally, she developed neurological disorders, polymyositis, diarrhoea, bilateral, diplopia, blepharoptosis, severe ocular-paresis and hyperthyroidism during treatment with pembrolizumab for skin melanoma.

The woman had hypertension and type 2 diabetes, and had been receiving treatment with lercanidipine/enalapril, pioglitazone, atorvastatin, aspirin [acetylsalicyclic acid] and linagliptin/metformin 2.5/850mg [*not all dosages stated; routes not stated*] after meals. In April 2021, she underwent the excision of a skin melanoma with axillary lymph node dissection. Subsequently, she started receiving pembrolizumab therapy (second dose on August 2021). In June 2021, she received vaccination against SARS-CoV-2 infection. About 96 hours after pembrolizumab administration, adverse effects like diffuse myalgia, asthaenia and diarrhoea, prompting her to seek medical assistance in hospital in Italy. She presented to the emergency department with hypoglycaemia and obtundation, which was treated with glucose [dextrose] infusions. Neurological examination was performed, which revealed blepharoptosis, severe ocular-paresis, bilateral diplopia and sever weakness of head and of proximal limb muscles (distal strength preserved), which led to diagnosis of polymyositis. No dyspnea, dysphonia and dysphagia was noted in her. Laboratory tests were performed, which showed sever metabolic acidosis, with hyponatraemia and hyperkalaemia (Na^+ 123 mmol/L, pH 7.13, HCO_3 8.5 mmol/L, K^+ 7.2 mmol/L , lactate 9.7 mmol/L), anuria, elevated CK, serum creatinine of 7.9 mg/dL and myoglobin (persistently above 1000 units/L). She was admitted in the ICU due to neurological adverse effects and acute renal failure due to pembrolizumab therapy. Acute kidney injury (AKI) was attributed to the overlapping of pembrolizumab and metformin.

The woman's treatment with linagliptin/metformin and ACE inhibitors were discontinued. She was treated with methylprednisolone. Subsequently, she underwent renal replacement therapy (CVVHDF) until an improvement in her renal function was confirmed clinically (restoration of diuresis >1 mL/kg/h) and two sessions of plasmapheresis. To maintain adequate level of plasma glucose, she received continuous infusion of rapid-acting insulin. During her ICU stay, no respiratory or haemodynamical problems were noted. After 48 hours of ICU stay, an improvement in renal function was observed, with the correction of electrolyte abnormalities and metabolic acidosis. Partial remission of blepharoptosis was noted, with proximal limb weakness and persistent ophthalomparesis. Thyroid function tests were performed, which showed high FT4 levels of 24 pg/mL, low TSH levels of 0.034 uU/mL with negative TSH receptor antibodies. From the thyroid function tests, hyperthyroidism was diagnosed. During the ICU stay, a chest X-ray was performed, which showed a shaded parenchymal thickening of the right inferior pulmonary lobe in the absence of fever or cough. Brain stroke or tumours were excluded by 2 CT scans of the brain. After 4 day stay in ICU, she was transferred from ICU to sub-acute care ward, where doses of methimazole and methylprednisolone were tapered. An improvement in her neurological symptoms were noted, and she started walking again. Finally, 20 days after admission, she was discharged from the hospital to a rehabilitation facility.

Fasano G, et al. Pembrolizumab-Related Side Effects: Acute Renal Failure and Severe Neurological Toxicity. Medicina (Kaunas, Lithuania) 58: No. 2, 30 Jan 2022. Available from: URL: http://doi.org/10.3390/medicina58020209

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