Changes in Electrocardiogram During Romidepsin Therapy: A Case Report

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Romidepsin is an intravenously administered antineoplastic agent, which acts by inhibiting histone deacetylases, thus preventing removal of acetyl groups from histones. The accrual of acetyl groups on histones causes cell cycle arrest and apoptotic cell death. It was approved for use in the United States in 2009 for treatment of refractory or relapsed cutaneous and peripheral T cell lymphomas [1-3].

The most common side effects are mild to moderate in severity and include nausea, vomiting, fatigue, fever, myelosuppression (e.g., anemia, neutropenia, thrombocytopenia), elevated liver enzymes, constipation, and rash. More severe adverse events can include marked neutropenia, thrombocytopenia, serious infections such as line sepsis, acute renal failure, tumor lysis syndrome, and cardiac arrhythmias [1].

PATIENT DESCRIPTION

A 72-year-old female with no cardiovascular risk factors or previous ischemic heart disease and who did not take any regular medications experienced electrolyte and electrocardiogram changes after treated with romidepsin.

On 2020 due to bicytopenia (thrombocytopenia and neutropenia) and splenomegaly, she was diagnosed with T cell lymphoma (T-NHL) with bony involvement. She underwent six cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) therapy and mid-treatment positron-emission tomography/computed tomography (PET/CT) showed complete remission. Two months later, severe thrombocytopenia was noted, and bone marrow biopsy revealed recurrence of the disease. She was treated with two cycles of salvage chemotherapy (ifosfamide, carboplatin, etoposide) with no response; therefore, she was treated with intravenous romidepsin.

The treatment was well tolerated, other than recurrent nausea and chills, and induced complete remission as shown by PET/CT in August 2021. She also had improvement of the cytopenia.

On 25 October 2021, she was hospitalized due to weakness and chills while undergoing treatment. She complained of nonspecific chest pain, heartburn, difficult swallowing, and dyspnea. These complaints occurred after each treatment.

The physical examination was normal. She was hemodynamically stable and did not have fever. Electrocardiogram recording revealed new T wave inversion on precordial leads (V1-6) that were not seen in a previous electrocardiogram recording from February 2021 [Figure 1A]. Chest X-ray was normal except for known fibrotic lung changes. Echocardiography revealed normal left ventricle size and function, mild mitral regurgitation, and diastolic dysfunction grade II.

On admission hemoglobin was 9.1 g/dl, platelets 56 × 109/L, white blood cells 1.1 ×109/L, potassium 3.24 mmol/L, and creatinine 1.07 mg/dl.

Because of the lymphoma and the evidence of a central line infection she was treated with antibiotics. There was a gradual rise in troponin levels from an initial level of 19 (0–14) to 49 after a few days. The rise of troponin was referred to the infective disease.

Follow-up electrocardiogram revealed the same T wave inversion in the precordial leads similar to the previous electrocardiogram; however, more prominent T wave inversion in the inferior leads was also noted. APCS with varying PR length, VPBS, and QT prolongation up to 560 msec were recorded [Figure 1B].

The electrocardiogram changes were attributed partially to the marked hypocalcemia (6.6 mg/dl) and mild hypokalemia (3.3 mmol/L). Correction of these electrolyte changes resulted in partial resolution of the electrocardiogram changes [Figure 1C].

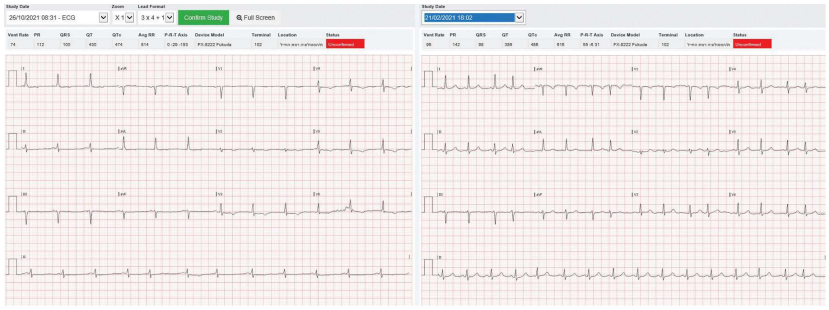
COMMENT

Cardiac toxicity of romidepsin may result in electrocardiogram changes and arrhythmias, as noted in our patient. Most arrhythmias were benign and only one case of cardiac arrest due to VF has been reported. In most cases the electrocardiogram changes were not associated with reduced left ventricular function by echocardiography, signs of heart failure, or evidence of myocardial infarction. Electrocardiogram changes were transient and resolved spontaneously [2].

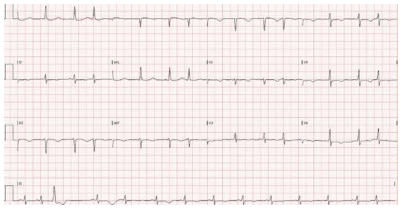
Romidepsin can also cause electrolyte changes, which include hypocalcemia, hypokalemia, and hypomagnesemia [3].

Figure 1. Electrocardiogram recording

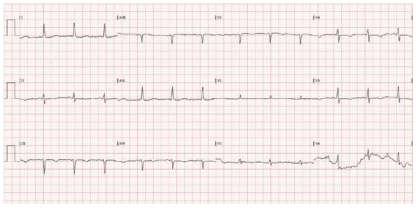
[A] Recording from October 2021 and February 2021



[B] Follow-up electrocardiogram with more prominent T wave inversion in the inferior leads noted



[C] Partial resolution of the electrocardiogram changes after electrolyte changes



These changes can aggravate those electrocardiogram changes.

Hypocalcemia can be seen in malignant diseases with a wide spectrum of mechanisms [4]. It prolongs duration of phase 2 of the action potential of cardiac muscle, which leads to change of serum calcium concentration and function of the myocyte calcium channels. Electrocardiogram conduction abnormalities are common and include mostly QTC prolongation, ST, and T wave changes. However, serious hypocalcemia-induced dysrhythmias (e.g., heart block and ventricular dysrhythmias, Torsades de pointes) are infrequent and mostly occur with additional confounder (e.g., QT prolongation drugs, and electrolyte changes) [5].

Our patient had evidence of electrolyte imbalance, which was probably chronic due to her oncologic background. The electrocardiogram changes observed during treatment were related to the romidepsin therapy and dynamic changes in electrolyte level. These changes should be addressed to assure prevention of higher-grade arrhythmias.

CONCLUSIONS

It is important to recognize the cardiac toxicity of romidepsin and the need for cardiac monitoring prior to and during treatment, especially in the presence of electrolyte imbalance.

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Capsule

Overcoming a barrier in prostate cancer

Prostate cancer is minimally responsive to most immunotherapy approaches because of the poor tumor infiltration of lymphocytes. Using mouse models of prostate cancer, **Zhu** et al. found that cancer cell expression of the chromatin effector Pygo2 promoted immunotherapy resistance by restraining tumor T cell infiltration and cytotoxicity. Pygo2's suppressive effects were mediated by promoting the expression of the receptor tyrosine kinase Kit and the activity of indoleamine 2,3-dioxygenase 1, which occurred independently of Wnt/β-catenin signaling. Genetic deletion or pharmacological inhibition of Pygo2 enhanced prostate tumor responses to a wide range of immunotherapies. Together, these results demonstrate that Pygo2 regulates cancer cell-extrinsic immune features and represents a potential target for reducing prostate cancer resistance to immunotherapy.

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