Study details rare cardiac side effects of immune checkpoint cancer therapies

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Combination therapy utilizing two approved immunotherapy drugs for cancer treatment may cause rare and sometimes fatal cardiac side effects linked to an unexpected immune response.

In a study led by Vanderbilt University Medical Center (VUMC) investigators and published in the Nov. 3 issue of The New England Journal of Medicine, researchers describe two cases of acute and unexpected fatal myocarditis (inflammation of the heart muscle) that occurred in melanoma patients following treatment with a combination of ipilimumab and nivolumab.

Both drugs are FDA-approved immune checkpoint inhibitors which stimulate an anti-tumor response in cancer patients. Ipilimumab is an anti-cytotoxic T-lymphocyte- associated antigen 4 (CTLA-4) antibody, and nivolumab, an anti-programmed death-1 (PD-1) antibody.

The use of these immune checkpoint inhibitors, especially in combination using two such therapies, has enhanced the treatment of several types of malignancy.

Common side effects of these agents such as inflammation of the skin, colon, liver, endocrine glands and lung, are thought to arise from off-target activation of T cells in the immune system.

In the two study cases, a 65-year-old woman and a 63-year-old man, both with metastatic melanoma, were hospitalized nearly two weeks after
initiation of the combination therapy.

Javid Moslehi, M.D., assistant professor of Medicine, director of the Cardio-Oncology Program at VUMC and corresponding author of the study, said both patients had seemingly mild symptoms at the time of hospitalization.

"The patients came with rather vague symptoms including fatigue and muscle aches. What made us take notice, however, were blood tests for cardiac damage that were extremely elevated and the electrocardiograms (EKG) that were abnormal in both cases. The problems quickly advanced such that the patients each needed a pacemaker to control the heart's electrical activity. The degree of cardiac arrhythmia was striking," Moslehi explained.

"Even aggressive combinations of these immune therapies are usually well tolerated with very selective activity against the tumor instead of self," said study first author Douglas Johnson, M.D., M.S.C.I., assistant professor of Medicine and clinical director of Melanoma. "But we occasionally observe these cases of wildly dysregulated autoimmune activation."

Johnson said VUMC physicians quickly treated the patients with high-dose corticosteroids (methylprednisolone). Despite aggressive treatment, both patients died from myocarditis.

The two similar cases stimulated a cross-disciplinary effort at VUMC to investigate the mechanisms of toxicity and potential treatments for patients with such rare reactions. The investigators collaborated with colleagues at Harvard Medical School, Johns Hopkins School of Medicine, and Bristol-Myers Squibb, the company that makes both drugs.
Justin Balko, Pharm.D., Ph.D., assistant professor of Medicine and Cancer Biology and leader of Molecular Oncology in the Center for Cancer Targeted Therapies at Vanderbilt-Ingram Cancer Center (VICC), said on autopsy and biopsy of the cardiac tissue it was clear that there was an immune reaction to the heart. VUMC pathologists found robust T cell and macrophage infiltrates. Importantly, there were shared populations of T cells infiltrating the myocardium which were identical to those present in tumor and skeletal muscle.

"One hypothesis based on the data is that essentially the body is seeing the heart and muscle tissue as foreign, just like the tumor," Balko said. "This gives us a starting point to develop a model to see how consistent this is with other cases as they appear and once we have that model, determine the right way to intervene so that we can keep other patients safe."

Study authors said global data reveal that myocarditis has occurred in less than one percent of patients treated with the ipilimumab/nivolumab combination therapy to date, suggesting this is a rare, potentially fatal T cell-driven drug reaction.

Johnson suggested "presumably the treatment strategy would involve high-dose steroids and possibly other intensive immune-suppressive drugs, as well. The best regimen is unclear at this point."

Provided by Vanderbilt University Medical Center

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