Powerful new cancer drugs are saving lives, but can also ignite diabetes or other autoimmune conditions

By **Jennifer Couzin-Frankel**Nov. 15, 2017 , 2:00 PM

Last week, Yale University immunologist Kevan Herold spoke about a few of his newest diabetes patients to an unlikely audience: oncologists and cancer researchers. At the Society for Immunotherapy of Cancer's annual meeting in Oxon Hill, Maryland, Herold and other speakers described how a novel class of promising cancer drugs is causing type 1 diabetes and other autoimmune diseases in some of those treated.

Known as checkpoint inhibitors, these medicines rev up the immune system and are rescuing people from deadly cancers. Physicians such as Herold, however, are now seeing a nasty, if treatable, side effect: the rapid onset of conditions such as thyroid disease, colitis, and type 1 diabetes, which all result from an immune attack on the body's own tissues. As cases mount, researchers across specialties are intensifying efforts to figure out whether certain cancer patients on checkpoint inhibitors are at higher risk—and to learn from this unusual side effect how autoimmune attacks erupt. "These [patients] are human experiments" of the autoimmune process, Herold says.

The first case walked into Herold's office a few years ago. She was 55 years old and had suddenly developed type 1 diabetes, which occurs when the body destroys cells in the pancreas that make insulin. Though the more common form of diabetes, type 2, is often diagnosed in middle age, type 1 is not. Herold learned that she had melanoma, and weeks earlier had received the checkpoint inhibitor nivolumab, an antibody that blocks the activity of a receptor called PD-1 on T cells.

"When you stop and think about it, you think, 'Oh of course this would happen,'" Herold says. PD-1 and the protein that

binds to it, PD-L1, help keep T cells in check. Cancer cells often sport PD-L1, suppressing attacks by these immune cells. Five checkpoint inhibitors on the market, approved since 2014, block either PD-L1 or PD-1, unleashing T cells against tumors.

That the immune attack can extend to normal tissue isn't surprising, in retrospect. Researchers had suspected a link between PD-1/PD-L1 and diabetes as far back as 2003, when a Boston team reported that mice engineered to lack one or the other fell prey to the disease.

Diabetes isn't the only condition triggered by the drugs. In Tennessee, a man and a woman in their 60s, both in clinical trials combining two checkpoint inhibitors for advanced melanoma, died of immune attacks on their heart. Other patients have come down with colitis, which occurs when the immune system targets the gut. Whereas the diabetes cases are linked almost solely to PD-1 and PD-L1 blockers, other autoimmune conditions have occurred with a different type of checkpoint inhibitor, ipilimumab, which blocks a T cell receptor called CTLA-4.

Groups within academic medical centers are starting to collaborate, with oncologists referring every patient who develops a particular autoimmune disease to a specialist in that condition. Herold has reached out to oncologists at Yale and the University of California, San Francisco (UCSF), to ask that all cancer patients treated with checkpoint inhibitors who then got type 1 diabetes be referred to him. His roster numbers 22 so far.

Some specialists, led by cardiologist Javid Moslehi at Vanderbilt University in Nashville, are trying to build a similar network for autoimmune attacks on the heart, called lymphocytic myocarditis. "There has to be some central way of reporting it," says Andrew Lichtman, a pathologist at Brigham and Women's Hospital in Boston who also spoke at the immunotherapy meeting.

The companies that make checkpoint inhibitors have stores of blood and biopsies from participants in their trials, along with clinical information. All could hold clues about who is susceptible to the autoimmune attacks, says UCSF immunologist Jeffrey Bluestone, who is president and CEO of the Parker Institute for Cancer Immunotherapy. He is seeking anonymized data and tissue samples from the companies and hopes to search for a genetic predisposition, for example, or biomarkers associated with these illnesses.

Bluestone is also designing a study that will evaluate cancer patients from Parker Institute–funded sites before and after they get checkpoint inhibitors and other immunotherapy treatments. This could help identify risk factors and track the onset of autoimmune diseases in real time.

Especially intriguing to scientists is the possibility that checkpoint inhibitors could help show how PD-1 contributes to auto-immune diseases in other patients. Work reported this week in *Science Translational Medicine* highlights the connection by **showing the flip side of PD-1 blocking**. A group led by Paolo Fiorina, an immunologist at Boston Children's Hospital, found that in mice with a form of type 1 diabetes, infusing the animals with blood stem cells that overexpressed PD-L1 reversed the disease. Further studies revealed that the animals had a defect in the RNA molecules that control PD-L1 expression, and that the cells of people with type 1 diabetes had the same defect.

For oncologists thrilled with the spectacular results that checkpoint inhibitors can deliver, the key is to walk "a very fine line" between treating cancer and causing autoimmunity, says immunologist Brian Fife of the University of Minnesota in Minneapolis. Fife, who has been exploring how the drugs can cause diabetes, believes "there's hope" that scientists will figure this out.

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