Rare genetic cause of peritoneal mesothelioma points to targeted therapy

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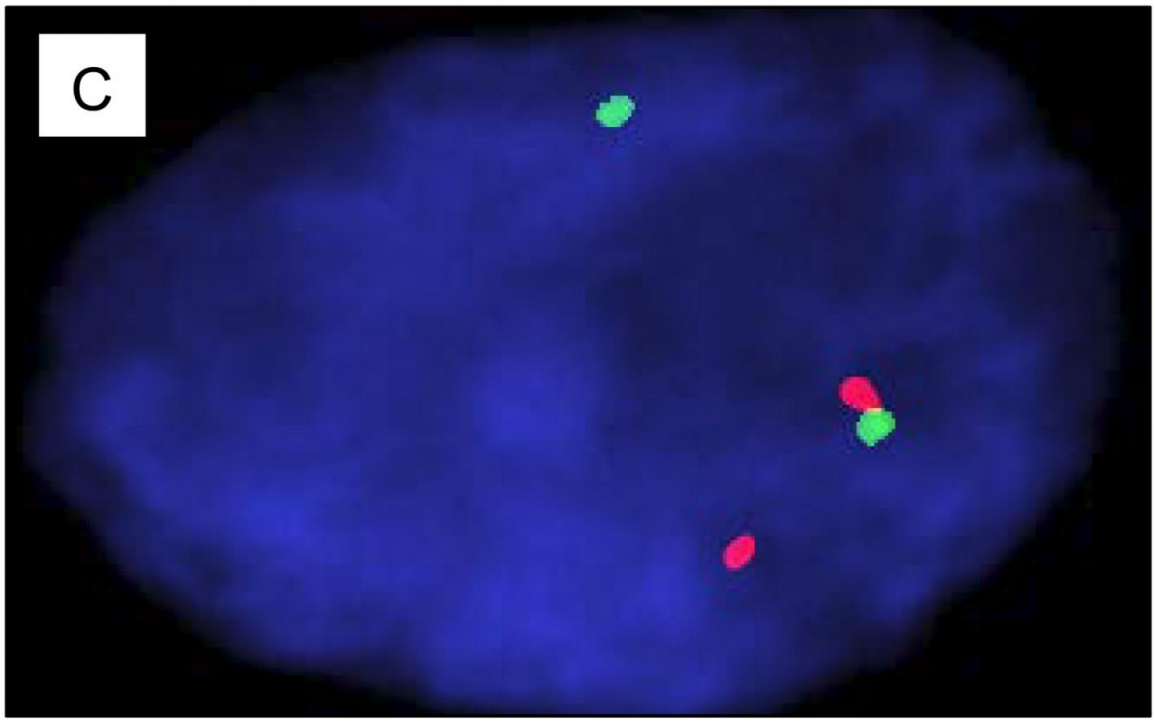

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Immunohistochemistry for ALK in peritoneal mesothelioma shows separation of the 5' (green) and 3' (red) probe signals in each of the 3 cases with diffuse strong ALK expression, indicating bona fide ALK rearrangement Credit: *JAMA* Network copyright 2017 American Medical Association

Mesothelioma is a rare and aggressive tumor that, in many cases, results from exposure to asbestos. But over the last several decades, other causes of the disease have emerged, including treatment with high-intensity therapeutic radiation and, more recently, an inherited genetic mutation. Now, through an unexpected observation and a meticulous study of patients seen at Brigham and Women's Hospital, BWH investigators have added a fourth cause to the list: a genetic rearrangement in the ALK gene, observed in three patients with peritoneal mesothelioma. Unlike previously known causes, this new discovery points to a potential therapeutic approach for those few patients whose tumors harbor the mutation.

The team's findings are published in *JAMA Oncology*.

"Mesothelioma is highly lethal and has no cure. Often, it is not diagnosed until at a late stage, when many tumors have already formed," said principal investigator Lucian Chirieac, MD, a thoracic oncology pathologist in the Department of Pathology at BWH and associate professor at Harvard Medical School. "Although this mutation only exists in a small percentage of cases, this discovery points to a potential therapeutic avenue for these patients."

There are about 3,000 new cases of mesothelioma each year in the U.S., and only about 300 of those are peritoneal mesothelioma, which forms in the lining of the abdomen. Most cases of mesothelioma result decades after exposure to asbestos or radiation therapy. But in rare cases, young patients who have never been exposed to either risk factor are diagnosed with the disease. One such case led Chirieac and his colleagues to their unexpected finding.

"This was a serendipitous discovery. We had a young patient with peritoneal mesothelioma that was difficult to diagnose. We extended our molecular diagnostics to test for a genetic rearrangement that had been

reported in lymphoma and lung cancer, but never in mesothelioma. When it came back positive, we were intrigued," said first author Yin (Rex) Hung, MD, PhD, the Corson Thoracic Pathology Fellow in the Department of Pathology at BWH and HMS.

Hung and Chirieac collaborated with other physicians and scientists at BWH and Massachusetts General Hospital to confirm their observation. They carefully examined samples from 88 consecutive patients with peritoneal mesothelioma who had been seen at BWH between 2005 and 2015. They identified ALK-positive mesotheliomas by immunohistochemistry; confirmed with fluorescence in situ hybridization; and performed targeted next-generation sequencing of tumor DNA and RNA to get a full picture of the exact genetic rearrangement underpinning the disease.

Three patient samples were positive for ALK—these patients with peritoneal mesothelioma were women with no history of asbestos or radiation therapy exposure. They also looked in samples collected from patients with pleural mesothelioma—the more common form of the diseases—but none of those samples were positive for ALK.

The ALK gene is important during embryonic development of the nervous system but should be inactive later in life. Previous studies of genetic alterations in lymphoma and lung cancer have found that certain genetic mutations—specifically when part of a gene breaks off and gets fused to another—can inappropriately switch on ALK, driving cancer cells to grow and divide. Targeting ALK with therapeutic drugs can turn that switch back off, blocking cancer progression—at least temporarily - without harming healthy cells. The FDA has approved several ALK inhibitors for treating non-small cell lung cancer. While the costs of targeted therapy may remain high, the cost of diagnostic testing for such genetic rearrangements is low.

Chirieac and colleagues hope to extend their study of ALK-positive mesotheliomas in a global patient population. In his own practice, Chirieac is routinely examining for the presence of ALK rearrangements for patients with mesothelioma and educating his residents about this new finding."When I teach my residents about the causes of mesothelioma, I talk to them about asbestos, radiation therapy and an inherited mutation," said Chirieac. "We believe this paper adds a fourth cause to that list - one that is potentially clinically actionable."

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