Child with drug-resistant tuberculosis successfully treated

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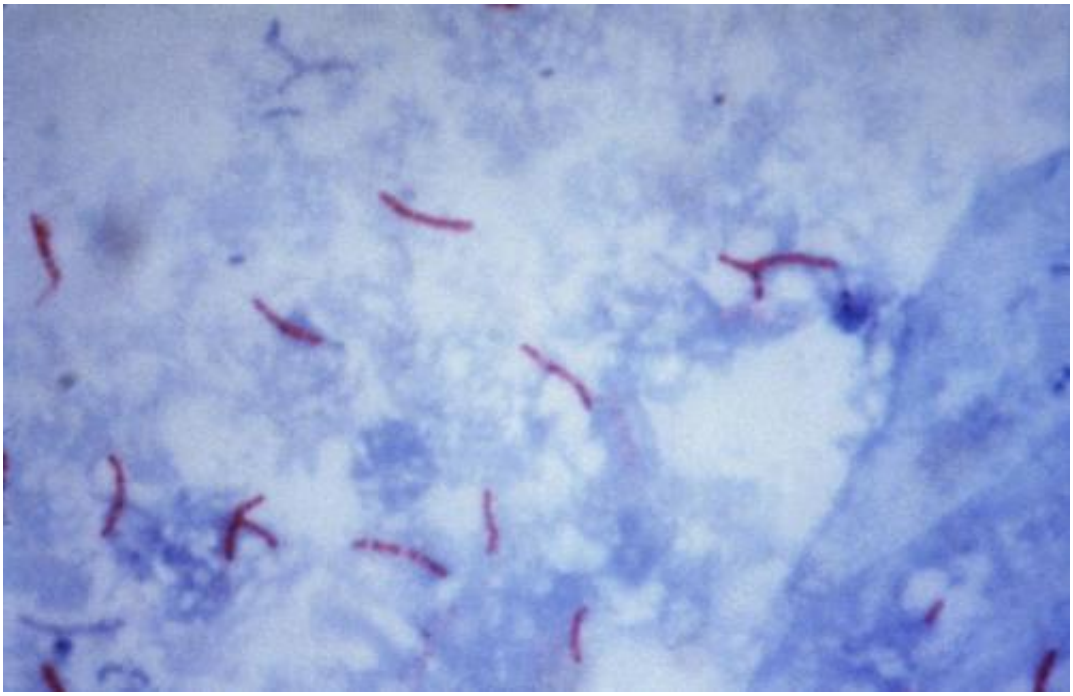

This photomicrograph reveals Mycobacterium tuberculosis bacteria using acid-fast Ziehl-Neelsen stain; Magnified 1000 X. The acid-fast stains depend on the ability of mycobacteria to retain dye when treated with mineral acid or an acid-alcohol solution such as the Ziehl-Neelsen, or the Kinyoun stains that are carbolfuchsin methods specific for M. tuberculosis. Credit: public domain

Johns Hopkins Children's Center specialists report they have successfully treated and put in remission a 2-year-old, now age 5, with a highly virulent form of tuberculosis known as XDR TB, or extensively

drug-resistant TB. The case, researchers say, provides the first detailed account of a young child in the United States diagnosed and treated for XDR TB.

The bug's resistance to most known TB drugs render it particularly challenging to treat in anyone but even more so in children, the Johns Hopkins team says, with only a handful of cases of children younger than 5 described in the medical literature worldwide.

Despite the successful outcome, the Johns Hopkins experts say the child's case underscores the shape-shifting nature of a bacterium increasingly resistant to drugs, and the serious challenges of monitoring and treating pediatric TB.

"We are thrilled that our patient is doing so well," says Johns Hopkins Children's Center pediatrician and TB expert Sanjay Jain, M.D. "But at the same time, this is a wake-up call to the realities of TB."

In an account of the case, published online Nov. 16 in *The Lancet Infectious Diseases*, the Johns Hopkins team describes the hurdles they faced throughout the child's treatment along with several "pearls" of clinical wisdom gleaned from it.

Mycobacterium tuberculosis, the bacterium responsible for TB, is estimated to cause almost 10 million new cases of TB disease worldwide each year, with strains impervious to drug therapies rapidly spreading. Experts estimate that a million children develop TB each year, but the real number may be higher given the difficulty of confirming the diagnosis in a child.

"Drug-resistant TB is a daunting disease to diagnose and treat in anyone, but in a child, it is infinitely more so," says Nicole Salazar-Austin, M.D., co-author on the report and a fellow in pediatric infectious disease at the

Johns Hopkins University School of Medicine.

The major difficulties in the case, Jain and colleagues say, stemmed from lack of fast, reliable diagnostic tools to spot and track drug-resistant forms of the disease, lack of reliable markers to help them monitor response to drug treatment, and lack of pediatric-friendly drug formulations tailored to the physiologic and metabolic needs of children.

Children with TB harbor far fewer TB bacteria in their bodies than adults, Jain says, which can render initial test results inconclusive, cause a false negative reading and lead to substantial delays in diagnosis. Diagnosis can be further complicated by unreliable laboratory techniques that may take weeks to yield definitive results.

The child was brought to The Johns Hopkins Hospital for evaluation of unrelenting fever and malaise upon her return from India, where she and a sibling spent three months. An initial battery of tests, including a throat swab and urine and bloodwork, showed no evidence of infection. But a chest X-ray revealed a suspicious lung spot, providing a telling clue.

Johns Hopkins pediatricians then performed a gastric aspiration—a procedure to retrieve swallowed mucus from the gut. The test is often used in young children because they cannot expel enough mucus from deep inside the lungs —the epicenter of disease—for a testing sample.

Even though initial test results came back negative, the Johns Hopkins pediatricians followed their hunch and forged ahead with preemptive treatment for TB anyway.

"Preliminary test results are notoriously unreliable and this case provides a perfect illustration of the need for swifter and more reliable techniques," Jain says.

Indeed, four weeks after the initial sample, test results suggested TB disease.

The child's symptoms improved rapidly with standard TB treatment, but a repeat X-ray revealed signs of persistent lung inflammation, underscoring the notion that clinical symptoms in children with TB can be misleading, Jain says.

Repeat lab tests ultimately showed the child harbored XDR TB. In all, conclusive identification of drug-resistant TB took 12 weeks, the researchers write.

Around that time, according to the case report, the child's condition worsened. Her fevers came back. A CT scan revealed worsening lung inflammation and another, more concerning, finding: spots showing that lung tissue was dying.

Clinicians initiated a new combination treatment with five drugs plus vitamin B6. But they faced yet another hurdle: no fast, reliable way to monitor how bacteria responded to the revised drug cocktail. Confirmatory lab tests could take weeks, and clinical symptoms would be a poor indicator of treatment response, the team reasoned, so they turned to CT imaging, an approach inspired by Jain and team's ongoing National Institutes of Health-funded experimental work in animals using a combination of CT and PET scanning technique to track TB's behavior in real time.

Using a low-radiation, child-friendly adaptation of the imaging technique, Jain and colleagues performed repeat CT scans over six months, gleaning rapid feedback of the progress of the disease. Each CT scan delivered a dose comparable to two or three months of natural background radiation from the environment.

"In the absence of reliable biomarkers for pediatric TB, the acute need for rapid readouts of treatment response and the dangers of treatment failure, we felt a CT scan was our best option," Jain says.

Child-friendly, low-dose CT scans are increasingly used by medical centers. They should become the norm for pediatric CT imaging, Jain and colleagues write, because recalibration of current devices can be achieved easily and cheaply.

The imaging approach, Jain adds, defied the clinical dogma that imaging tests always lag behind physical symptoms. In this case, symptom improvement occurred weeks after CT scans suggested declining lung inflammation and lower bacterial counts.

"Many factors made this a challenging case, including how physicians would monitor on a timely basis whether the drugs had reduced or eliminated the bacteria," says Antonio Sastre, Ph.D., program director at the National Institute of Biomedical Imaging and Bioengineering, one of the National Institutes of Health components supporting the research team. "The effective use of CT monitoring was first shown in the laboratory, with mice, and low-radiation CT imaging has provided a readily translatable solution for this case."

Given the child's good overall health and the fact that her disease is in full remission, the Johns Hopkins team says a reactivation of the infection is unlikely. Out of an abundance of caution, however, the researchers will continue to follow the child for another two years or so.

All of the child's family members, including a sibling, remain infection-free.

Provided by Johns Hopkins University School of Medicine