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Mistaken Identity

BY CURTIS PESMEN

Preventing misdiagnoses of blood cancers is all in the details.

At first, it was an itch that a scratch couldn't fix. A typical teen's minor medical lament. Patch of redness on the skin now and then, no big deal. Maybe an allergy or psoriasis. It'll pass.

Well over a year later, in 2001, after four doctors hadn't sorted his symptoms correctly, college freshman Kyle Steuck, then 19 and living in Austin, Texas, started coughing up what he recalls as a sink full of dark red blood. From downstairs, his mom, unaware of the severity but aware he'd been feeling listless, called up to her son to ask if she should call the doctor. "I think you should call 9-1-1," he responded.

Within hours, Steuck received his shocking diagnosis in the emergency room of a nearby hospital: Hodgkin's disease. "I was probably symptomatic for 18 months before I was diagnosed," he says. "I was misdiagnosed with bronchitis, asthma, and psoriasis, all before being diagnosed with stage 4 Hodgkin's disease. And that included a visit to a G.P. the day before my tumor [basically] exploded inside my lungs. I'm not sure I'd believe it if I wasn't there."

Semi-conscious for part of that first night, Steuck recovered rather miraculously following a collapsed right lung caused by the bursting of the football-sized tumor and associated blood loss. He received seven units of blood and was on a ventilator for two days. Today, Steuck looks back at his predicament and care from the vantage point of a thrice-misdiagnosed six-year survivor. There's no apparent bitterness in Steuck's voice. Maybe he understands the nature of the disease a bit better now.

The fact is, leukemias and lymphomas, especially among children and young adults, are among the most frequently misdiagnosed cancers. Family doctors or general practitioners simply don't see—and thus don't expect—cancer at first glance (or first appointment). For some cancers, patients of a certain age automatically undergo regular or annual screenings, such as mammography for breast cancer and prostate-specific antigen testing for prostate cancer. In hematology, there aren't similar standards. And while there is no national cancer registry in the United States to track misdiagnoses, one recent estimate in the journal *Cancer* suggested at least 150,000 misdiagnoses may occur each year, apart from gynecological miscues.

[From General to Specific Symptoms](#)

Of the 115,000 or so cases of leukemia and lymphoma (the major “blood” cancers) diagnosed in the United States each year, some 71,000 are lymphomas, which include Hodgkin’s disease and non-Hodgkin’s lymphoma (B-cell and T-cell). The other 44,000 cases are leukemia, which has four main types. Add myeloma to the list—cancer of the bone marrow that’s diagnosed about 20,000 times each year—and you may appreciate why the average general practitioner may not, right away, focus on blood cancer when a teenager or adult mentions such non-specific symptoms as feeling tired, listless, achy, or, in Steuck’s case, itchy.

Leukemia, in brief, refers to cancer of the white blood cells that are primarily made in bone marrow and circulate in blood. They are classified as either lymphocytic or myeloid depending on their cell of origin—lymphocytes and neutrophils, respectively. Both lymphocytic and myeloid leukemia can be either fast (acute) or slow (chronic) growing. Lymphoma, on the other hand, afflicts the all-important lymph system of tissue replenishment and repair.

These diseases are rarely simple to diagnose. Doctors must consider a weighty, confusing array of possible symptoms, including fatigue, fever, weight loss (or loss of appetite), anemia, shortness of breath, increased bruising, bone and joint pain, or persistent infections.

However, from a specialist/pathologist’s point of view, “the leukemias, for the most part, are pretty straightforward,” says Scott Kogan, MD, associate professor of laboratory medicine at the University of California-San Francisco. “And as for the B-cell lymphomas [upon review], most of the time, I see them diagnosed properly. But in the world of hematopathology, T-cell lymphoma is the most difficult diagnosis for a number of reasons,” specifically because it accounts for only about 15 percent of all lymphoma cases.

❑ I think the thing that frustrates me is that there wasn’t much digging deeper. I’d bring up my symptoms, and there wasn’t any, ‘What else could it be?’ ❑

—Kyle Steuck

Dr. Kogan advises a second opinion from a specialist or cancer research center for patients who receive a diagnosis of T-cell lymphoma.

According to the World Health Organization’s updated classification system, known as REAL (Revised European American Lymphoma), there are more than 20 different leukemia and lymphoma subtypes, some of which are further subcategorized. Many of these classifications are separated by infinitesimal changes in the architecture of genetic proteins that go beyond simple blood tests or tissue stains on slides. Immunophenotyping, Dr. Kogan says, is the next stage of diagnosis, where blood cancers that look similar at first are teased apart by the architecture and specific receptors’ behavior on cancer cells. Researchers and

pathologists are discovering new cancer genes each year, and deciphering how they work together over time.

The good news: With more variety and precision in diagnosis, patients will eventually see better targeted gene array-based drugs for their exact cancer type. Breast cancer patients have already seen this with Herceptin (trastuzumab), and chronic myeloid leukemia patients are greatly benefiting from Gleevec (imatinib), which is used for other cancers as well.

Gaining Precision

What makes leukemia and lymphoma diagnoses even tougher compared with solid tumors are their wildly different prognoses. While some chronic leukemias can be managed or controlled for decades, acute leukemias, such as acute myeloid leukemia, require immediate treatment. If left unchecked or if misdiagnosed as another leukemia (or even flu), it can cause serious injury or death.

For 2007, the American Cancer Society estimates more than 13,000 new diagnoses of AML, resulting in almost 9,000 deaths. Experts say AML is often misdiagnosed as a common cold, but with timely and proper diagnosis and treatment, some AML patients can achieve remission.

“It is so important to have a very good pathologist,” says Elizabeth Rich, MD, assistant professor of medicine in hematology/oncology at the University of Chicago. “Sometimes what we see is a patient diagnosed with one type of leukemia, and treated for it, though it may, in fact, be another type.” In a report published in *Cancer* in 2005, researchers found errors in up to 12 percent of cancer diagnoses following tissue collection and biopsy, with wide variation between medical institutions and types of cancer.

Another problem arises when doctors reclassify a diagnosis from one type of leukemia to a different type—a change that may not be recorded, officially, as a misdiagnosis, Dr. Rich says.

These subtleties have led to another perhaps surprising finding: When patients have sued for malpractice, blood cancers don't jump to the top of the list. “The number of [medical malpractice] claims involving either the alleged misdiagnosis or clinical mismanagement of solid tumors far exceeds those for hematologic malignancies, including both Hodgkin's disease and non-Hodgkin's lymphoma,” says David Troxel, MD, past president of the American Board of Pathology and medical director of The Doctors Company, a California-based physicians' malpractice insurer.

In other words, it's not normal in the malpractice world for patients to file suit for misdiagnosis of a subtype of cancer that may still be murky or not universally recognized.

Patient and Survivor Steps

"I think the thing that frustrates me is that there wasn't much digging deeper," says Steuck. "I'd bring up my symptoms, and there wasn't any, 'What else could it be?' But the undercurrent of anger didn't set in until later. I was so relieved at the time that someone [finally] had figured out what was going on; that it was treatable and curable. I was one of those cases, even when being diagnosed with stage 4, where things still looked pretty good."

☒ I think [blood cancer] diagnoses are likely to be complicated for a long time. I won't treat a patient for a lymphoma unless an expert hematopathologist here has reviewed the slides. ☒

—James Armitage, MD

Because cancer diagnoses (and misdiagnoses) are by their very nature shocking, it's difficult or impossible for patients to think logically at first about action plans. Besides obtaining a second opinion soon after a lymphoma or leukemia diagnosis, patients can help prevent possible misdiagnoses or delays in treatment by specifically requesting a separate pathology team's diagnosis (as opposed to a second opinion solely from a medical oncologist).

It also bears repeating: No matter how minor the symptom, patients should make certain to repeat it to all doctors and oncology practitioners they may see. Odd combinations of symptoms often trigger thoughts of a more elusive diagnosis. If symptoms continue without any clear explanation, a re-evaluation, even if it means starting over with physical examinations and tests, may be warranted, say experts.

"In [looking at] most normal cells, you don't have a lot of actively dividing cells. With infections, you do," says Mitchell Smith, MD, a hematology/oncology specialist at Fox Chase Cancer Center in Philadelphia. "The difference is, when the infection is over, things settle down, as opposed to cancer cells [that don't]." When doctors look at lymphoma and where the field of diagnosis is heading, Dr. Smith says the differences between normal infections and lymphoma cells will be less about what they look like and more about their genetic makeup.

Since 2005, a new medical diagnosis program—a safety net of sorts—devised by Isabel Healthcare, has gained favor in the United States and Europe, where it was created. In short, doctors or other health care professionals key in symptoms, and an array of possibilities, including long-shot diagnoses, pop up almost instantly. It may be considered "artificial intelligence" by some, but at its core are actual case histories.

"This can be useful," says Dr. Kogan, as many doctors start their diagnostic thinking with, " 'I think it's this,' rather than saying, 'These are the possibilities.' " Though Isabel and new compatible systems, such as Patient Keeper, can cost hospitals upwards of \$80,000 per year (which may explain why the systems are not employed in cancer centers nationwide), diagnosis decision support system programs already have helped signal or re-diagnose countless lethal conditions,

including cancer, which might never have been diagnosed or corrected.

“I think [blood cancer] diagnoses are likely to be complicated for a long time,” says James Armitage, MD, professor of internal medicine at the University of Nebraska Medical Center and a specialist in blood cancers. “And probably general pathologists aren’t going to do that extra [testing] very often. That’s the reason I won’t treat a patient for a lymphoma unless an expert hematopathologist here [at the hospital] has reviewed the slides.

“I don’t know what percentage, but the number of [hematologic cancer] patients who have their diagnosis changed is substantial,” he adds. “If it gets called follicular lymphoma, it’s least likely to be changed. If it is a B-cell, not likely to be changed, although pathologists may disagree on a grade. But if it gets called a rare disease, the diagnosis is much more likely to get changed.”

Though such estimates are unsettling, the continued discovery of cancer subtypes—such as Burkitt’s lymphoma or HER2-positive breast cancer—and the precise, targeted drugs to treat them are surely what’s in store for the next phase of cancer diagnosis.