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Web Exclusive: Solving a Medical Mystery

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During medical school and residency, I was always fascinated by medical mysteries and the exercise of problem-solving. This is, of course, a routine part of medical education, and most of us take pride in getting the correct diagnosis in a very difficult test case.

But in real life, the correct diagnosis may be elusive. This can be frightening when the “unknown” is the origin of cancer that has spread. When I first heard the term “cancer of unknown primary,” or CUP, I found it hard to believe this could end up being the final “answer,” despite following the accepted guidelines for diagnostic tests and having expert oncologists, radiologists, and pathologists on the case.

What are the oncologist and patient to do for a case of CUP? How can a reasonable diagnostic and treatment plan be put together in a reasonable timeframe? Cancer is usually not an emergency, so days or even weeks should be taken to answer the question as best possible. The oncologist must also get a sense of the tempo of the cancer—how fast is it growing, what are the current symptoms, and what is the best sequence of tests. Sometimes, therapy might need to be initiated before the answer is clear, especially in a patient who is acutely ill due to their cancer.

These days, sophisticated imaging tests and expert pathology review, special tumor immunostains and even DNA-based tests like chromosomal studies and FISH (fluorescent in situ hybridization) can be done within a few days *if* an expert team is assembled quickly.

The first set of tests should be to determine whether this could be a more treatable and responsive tumor, like germ cell tumors (including testicular cancer) or high-grade lymphoma. If enough evidence emerges to classify these, potentially curative therapy can be started.

Clinical data such as the age of the patient, symptoms, location of the metastases, and blood tests should steer the team as to the best order of test—younger patients with midline tumors are more likely to have more treatable cancers like

germ cell tumors.

Older patients with tumors that resemble those that arise in glands (carcinomas) probably have one of the more common and less responsive cancers such as breast, prostate, colon, or lung cancers. However, they can still respond, especially if they have some of the known targets, such as hormonal therapies for estrogen, progesterone, or androgen receptors, or Herceptin (trastuzumab) if the HER2 gene is amplified or overexpressed. The key is to have the right team, a clear plan, and some degree of patience—in many cases, the last of these is the hardest.