Struggling to find a foothold with NAFLD

Karen Titus

March 2020—For pathologists, a first look at nonalcoholic fatty liver disease can be jarring.

Purva Gopal, MD, associate professor of pathology, UT Southwestern Medical Center, has seen her share of initial biopsies on patients whose “livers are already cirrhotic,” she says.

So has Cynthia Guy, MD, professor, Department of Pathology, and chief of the liver and GI surgical pathology section, Duke University Health System. It’s not a good look, obviously, so it’s one she’s doing her best to share with clinical colleagues.

At her institution, pathologists have built a strong connection with the hepatologists and gastroenterologists, she says, and NAFLD is part of the regular show-and-tell. “That raises awareness,” says Dr. Guy, who is also director of the GI/liver surgical pathology fellowship program. “Because we do have those discussions about the 30-year-old, overweight but otherwise apparently healthy patient who turns out to have cirrhosis from NAFLD. And just talking about that case points out that this didn’t just happen last year. They probably had this problem all during their 20s—and now it’s in the very, very severe end stage.”

How does such advanced disease make it past the warning signs of laboratory tests and the eyes of concerned clinicians?

How much time do you have?

“It’s multifactorial; it’s very complex,” Dr. Guy warns.

Arjmand Mufti, MD, transplant hepatologist, UT Southwestern Medical Center, agrees. “It’s a complicated disease, with lots of things contributing to it. There are lots of moving parts that need to be in play,” he says, then adds: “There are no sound bites for this story.”

The answer is simple yet complicated, like a Shakespeare plot. As Brutus learned, it was easy to kill Caesar, but bringing order to the postmortem Republic was not. And while those portents of doom seemed obvious in retrospect (shrieking ghosts, ghastly women, disinterested lions), they were also easy to misinterpret, making it feasible for Caesar to go forth on March 15.

Likewise, tackling NAFLD has the appearance of being straightforward. Use basic tests (ALT, AST) and follow up abnormal results. Calculate surrogate markers for fibrosis with tests that have already gained a strong foothold outside the United States, such as the NAFLD fibrosis score, Fibrosis-4 test,

Enhanced Liver Fibrosis, or FibroTest. Refer patients to hepatologists. Perform a liver biopsy, which is the gold standard for diagnosing nonalcoholic steatohepatitis. (NAFLD encompasses simple steatosis and NASH.) Intervene early with appropriate treatments.

Dr. Amit Singal (from left), Dr. Purva Gopal, and Dr. Arjmand Mufti at UT Southwestern Medical Center. The broad goal for nonalcoholic fatty liver disease patients, Dr. Mufti says, is to get care providers to think about the possibility of a NAFLD diagnosis sooner and to use basic tests to differentiate those who will progress. “Right now,” he says, “care is too fragmented.” (Photo: Reid Horn)

And yet, as the experiences of Drs. Gopal and Guy show, failures can occur at each step.

The goals are clear, says Amit Singal, MD, associate professor of medicine, clinical chief of hepatology, and medical director of the liver tumor program at UT Southwestern, but the steps to improving response to NAFLD can seem daunting.

“The ideal thing would be to decrease obesity and diabetes in the population and make NAFLD less prevalent,” Dr. Singal says. Prevention is key, in other words, with healthier lifestyles or some degree of medication that prevents liver fibrosis from developing even in the presence of metabolic syndrome. But that’s not happening. Score that medicine 0, NAFLD 1.

The next step would be a medication to treat both metabolic syndrome as well as liver inflammation and fibrosis, he says. Such a drug doesn’t exist. Score: 0–2.

The third step, Dr. Singal says, is a serum biomarker to accurately predict development of fatty liver disease in patients with metabolic syndrome and obesity. 0–3.

Finally, he’d like to see better biomarkers for noninvasive assessment of fibrosis. “There are several that are good. None are perfect,” says Dr. Singal. 0–4.

Make things too simple, and any useful meaning is lost. Richard III is just a cranky uncle in the market for a new horse. King Lear needs better estate planning. The Macbeths should not be hosting dinner parties.

The more complicated story demands exploration, say NAFLD experts. The disease already affects far too many patients, and the problem is likely to get worse. NAFLD has already replaced hepatitis C as the No. 1 reason for liver transplants. As the hepatic manifestation of metabolic syndrome, NAFLD is tightly bound to the continual rise in obesity and type two diabetes. “Some people consider this to be an epidemic almost worldwide,” Dr. Gopal says.

The consequences for patients are severe. Some 70 to 75 percent of patients with NAFLD will have isolated fatty liver, says Dr. Mufti, with no to minimal progression to fibrosis. But the rest will have NASH. “These are the patients

we need to identify, because they have increased cardiovascular death, they have increased malignancy, they have increased liver death. And if you have fibrosis, that is the thing that portends a worse diagnosis.

“This is where I think we could do a better job,” continues Dr. Mufti, who is also fellowship program director for digestive and liver diseases.

Who, exactly, needs to do a better job is also a bit complicated. The predicted explosion of the disease could alter the practices of pathologists and clinicians. Pathologists who aren’t liver specialists may find themselves being asked to perform more liver biopsies. And if there aren’t enough hepatologists to handle referrals, more primary care physicians could find themselves on the frontlines of trying to care for patients with the disease.

“This is not an issue that’s going to go away,” Dr. Mufti says. “It’s only going to grow.”

The first step is to continue to build awareness of NAFLD, says Dr. Guy. In her view, primary care physicians, focused on hypertension, hyperlipidemia, prediabetes, obesity, and other symptoms of metabolic syndrome, may not be aware of an underlying liver problem.

Laboratories can help point the way. But there is, naturally, no single diagnostic test for NAFLD. “Right now, it remains largely a diagnosis of exclusion,” Dr. Singal says. “Providers have patients who have chronic liver disease with elevated liver enzymes or other signs of chronic liver disease, and they must exclude the presence of viral hepatitis, other metabolic liver diseases, alcohol abuse. And then in the right clinical setting, such as somebody with obesity or metabolic syndrome, they can make a diagnosis of NAFLD.

“There are the patients who may have ‘lean’ NASH—they won’t have the phenotype that makes you think of NASH,” he continues. “But they have chronic liver disease and the testing for other liver diseases is negative. In those cases you may consider a biopsy to make a diagnosis.”

Often the initial tests for NAFLD—its iambic pentameter, if you will—are ALT and AST. While not specific for NAFLD, their presence in routine panels can offer early clues to possible problems. Both are poor markers of liver function, however, and physicians may not make the connection to possible NAFLD.

“If the ALT is elevated, then that’s informative, whether or not the patient has metabolic conditions,” says Elizabeth M. Brunt, MD, emeritus professor of pathology, Department of Pathology and Immunology, Washington University in St. Louis. “But if it’s not elevated, it’s not informative. It’s hard for people to understand that this disease can be quiet. If the patient is not obese, that doesn’t necessarily clear them of the possibility of having the disease. And if they have other metabolic problems, they can still have this disease.”

‘Often it takes an astute clinician to realize that perhaps the liver tests are elevated. And unfortunately, the liver tests aren’t always

elevated.'
Elizabeth Brunt, MD

Even when liver enzymes are indicative of a problem, it's not uncommon for physicians to look at AST and ALT in isolation, says Dr. Mufti. Nor is it uncommon for these results to be only very mildly elevated, prompting clinicians to say, in essence: *Nothing to see here—we'll just follow them when you come back for your next visit.*

"That's what a lot of people do now," Dr. Mufti says. But if that low-key response happens year after year, "That's where we get into trouble. We have patients who've had mildly abnormal liver function tests for 15 years, and they've had ongoing inflammation, and then they come in with cirrhosis."

It can be an understandable response, however. Sometimes that blinking of the "check engine" light is merely annoying.

Says Dr. Brunt: "Often it takes an astute clinician to realize that perhaps the liver tests are elevated. And unfortunately, the liver tests aren't always elevated." And if they are, it doesn't necessarily point to NAFLD. Certain medications, for example, can raise liver enzymes, as can viral hepatitis and other chronic liver diseases.

It's also possible for someone to have cirrhosis without the red flag of elevated enzymes—they can normalize in a patient with advanced fibrosis, says Dr. Gopal. "But hopefully they'd have some other clinical manifestation of cirrhosis that the clinician would pick up on."

Even if liver function tests are normal, patients with risk factors for metabolic syndrome can benefit from simple lab tests. The questions are straightforward, Dr. Mufti says: What's happened to the platelet count? *Was the platelet count ordered? Have the albumin levels fallen? Has the bilirubin been rising? Is there anything that is telling you that the patient may have evidence of portal hypertension based on labs?* "You don't even have to have imaging," Dr. Mufti says. "A lot of this is based on labs."

But without an awareness of the disease itself, clinicians may not put the pieces together to see the full picture. And laboratories aren't necessarily putting them together for the clinician, either, Dr. Brunt says. "But we're often not asked to."

Even if someone were assembling the pieces, it can be hard to see the full picture, Dr. Guy says. Because NAFLD is a systemic inflammatory disorder, patients often have elevated autoantibodies, such as antinuclear antibody or anti-smooth muscle antibody. Someone less familiar with that nuance might be tempted to assume autoimmune hepatitis. "Which it could be," Dr. Guy acknowledges. "But almost a third of fatty liver disease patients will have low-titer positivity for ANA and SMA."

Patients with fatty liver disease can have elevated alkaline phosphatase and gamma-glutamyl transferase, Dr. Guy continues, which typically points to a biliary problem. "And we don't understand exactly why, but 20 to 25 percent of [people] with NAFLD can have an elevated alkaline phosphatase and GGT."

Dr. Guy continues: "Even with a patient sitting in front of a very experienced hepatologist [who] has the full panel of labs, they may not know exactly what disease the patient has." In her observation, "That's why a lot of the really good hepatologists get a liver biopsy toward the beginning of the workup, because they know they can be fooled by the labs alone."

That assumes, of course, that a patient is indeed sitting in front of a physician. Dr. Gopal says when she sees a cirrhotic liver, "It's not necessarily because the physician isn't picking up on it sooner." Patients don't always have routine checkups and may see a physician only once they're feeling ill.

Even a discussion of normal/abnormal can create confusion.

As Dr. Mufti ponders this, he talks about the upper limits of normal for ALT. He looks to the guidelines from the

American Association for the Study of Liver Diseases, which uses 29 to 33 for men, and 19 to 25 for women; in practice, “We’re really looking at 35 for men and 25 for women, just to keep it simple.”

Nevertheless, he continues, it’s not uncommon for lab results to report an upper limit of normal of 50 or 60. “So if we get a lab value of 50, it’s considered normal,” even though upper limits of normal of 25 and 35 are most useful to him. Moreover, a patient with a 45 one year, followed by 70 the following year, doesn’t necessarily mean “it’s a thing,” as he puts it. “We need to keep in mind that these are all abnormal, and to think about what being abnormal means.”

The broader goal, he says, is to get care providers to think about the possibility of a NAFLD diagnosis sooner, and then to use basic tests to differentiate those who will progress.

“We use a spectrum of things to assess someone’s risk,” Dr. Mufti says. “The important thing to remember from our perspective is that normal liver function tests on their own do not mitigate someone from having significant risks.”

A patient with other risk factors—metabolic syndrome, diabetes, hypertension, hyperlipidemia—are at higher risk for NAFLD. Dr. Mufti cites data that suggest that among patients with type two diabetes and who have normal liver enzymes, about half may have NAFLD, while half of those patients will have nonalcoholic steatohepatitis. “So we may look to triglycerides and lipid levels,” Dr. Mufti says, noting that serum triglycerides are significantly higher in patients with NASH.

Surrogate markers for fibrosis are the next level of testing. Dr. Mufti says his regular practice is to “get a baseline, noninvasive marker in every single patient I see in clinical practice,” as a way to screen for fibrosis.

Among the tests he considers are Fibrosis-4, a score comprising AST, ALT, platelet count, and age; FibroTest/FibroSure (the same test, marketed under different names in Europe and the U.S.), which is a panel containing total bilirubin, GGT, α2-macroglobulin, haptoglobin, and apolipoprotein A1; and the AST to platelet ratio index. He also relies on FibroScan ultrasound. “If they have elevated numbers on their fibrosis score, along with some risk factors, then I would have a low threshold to biopsy those patients.”

The various tests and markers aren’t the only things physicians need to juggle. Given the seriousness of metabolic syndrome, it’s understandable that primary care physicians may find it tricky to balance urgent issues (lowering risk of cardiovascular disease, say) with non-life threatening liver disease. Physicians may not realize the liver is being damaged, Dr. Brunt says. “That can go on for years and years.”

That’s also why, says Dr. Singal, “Something like an elevated AST or ALT can get lost in the shuffle.”

But as Dr. Mufti points out, NAFLD does carry risk of malignancy. “It’s the one thing people often forget,” he says. In fact, he adds, it’s the leading cause of death for the disease—about 28 percent—followed by heart disease (about 25 percent) and liver disease itself (around 13 to 14 percent). Moreover, he says, community-diagnosed NAFLD has an increased risk of mortality.

Given all this, might there be new ways to balance how primary care physicians, hepatologists, and laboratories manage NAFLD? “We do need to think about these patients more systematically,” Dr. Mufti says. “Right now care is too fragmented.”

Dr. Singal is intrigued by the idea of laboratories somehow being able to highlight AST and ALT abnormalities with an eye toward better management of NAFLD. “That would be great,” he says. “But I’m not sure how to do that logistically.” After all, abnormal results are already highlighted. And without knowing the clinical scenario, the laboratory won’t otherwise be able to say if the results might be indicative of NASH. At the same time, he says, just as these results can get lost in the primary care shuffle, “I think sometimes people in the lab similarly have that issue.”

Dr. Mufti predicts that the future will bring about one-stop clinics, where NAFLD patients will see a hepatologist,

cardiologist, endocrinologist, and a nutritionist or dietician. UT Southwestern has already started moving in this direction, he says.

Likewise, Duke has a well-established regional NAFLD program, says Dr. Guy, which serves patients primarily from North and South Carolina, Virginia, and Tennessee. The program is involved in multiple clinical trials, and Dr. Guy has managed the database and biorepository "over the past too many years," she jokes. An exercise scientist also recently joined the program, she reports. But his first week on the job provides a small window into the challenges of this disease. "He's a young guy, he's very fit, and loves to work out," she says. "And he was so fired up about it—but after his first week of being in the liver clinic, he was completely demoralized. Because people just don't want to work out."

If a primary care physician does not pick up on NAFLD early on, patients may not get referred to a hepatologist, which is another concern, Dr. Guy says.

Chimes in Dr. Singal: "We do know NASH is often underrecognized, particularly by clinicians who don't manage it regularly. So that can lead to underdiagnosis and undertreatment in many cases."

Should patients be seeing hepatologists sooner? Dr. Mufti is, in fact, starting to see that. He reports primary caregivers often fast-track patients to his clinic. "They see an abnormal liver function test and send them [the patients] to us, and we do the whole workup here."

Is that the right thing to do? Dr. Mufti pauses. "That's a *really* good question," he says.

In fact, that's not necessarily what happens in Europe, he says, where noninvasive markers such as AST to platelet ratio index and FibroScan are used more routinely. A patient with low fibrosis will continue to be screened by a primary caregiver; referral to a specialist would come only with higher levels of scarring. This model might make more sense in the United States as well, especially as the incidence of NAFLD continues to grow.

"I also struggle with this issue of referrals," Dr. Singal says. "While I think that's ideal, it may oversimplify the issue." Currently more than one-third of Americans are obese, he says, and one recent modeling study suggested that figure would rise to one-half over the next decade. "If that's the case, you're talking about half the U.S. being at risk for fatty liver. It far exceeds the capacity of hepatologists to see those patients. It's almost like saying, anyone with an elevated glucose should see an endocrinologist."

Instead, Dr. Singal would like to see primary care providers become more comfortable with making the diagnosis.

Dr. Mufti agrees, not only for handling current patients but those they'll see in the not-too-distant future. "Do we prescreen this huge influx of referrals that we're going to get, and then only take the patients who have more advanced scarring? And have primary care physicians manage the others and see them on a less frequent basis?"

If primary care providers take on a more active role in managing NAFLD-adjacent patients, will labs have a larger role in helping these clinical colleagues put the pieces together?

"I think yes and no is the right answer," Dr. Mufti jokes.

Some primary care physicians are hyperaware of NAFLD and its complexities, he says. And those who aren't are slowly becoming more familiar.

But even with awareness, "It doesn't mean they themselves are comfortable managing it," Dr. Mufti says. "Many still want a specialist to first say everything is okay, and then they may be happy to take some of these patients back."

And only recently—the past five years—have some of the noninvasive markers become more widely available in the United States. "We didn't have FibroScan in our clinic until two years ago," he says, though it's been available in Europe for at least 10 years, not to mention part of European guidelines.

“It’s changing,” Dr. Mufti says. “But it hasn’t changed fully yet. And there still needs to be a lot of education—you can gauge the degree of fibrosis, calculating a score from very routine blood tests, and based on that, make a referral. Although if someone is diabetic or has other risk factors, it probably makes sense to make a referral no matter what some of these tests show.”

If the lines between primary care and hepatology are blurring, so might the lines in anatomic pathology. Says Dr. Brunt: “We don’t have enough well-trained, dedicated liver pathologists, in my opinion.”

That could be problematic. Dr. Mufti predicts: “I think in the future we will increase the number of biopsies we’re doing for patients with nonalcoholic steatosis. While noninvasive markers are very good when we have low scarring or lots of scarring, there’s this huge range in the middle. And especially when these patients have risk factors, we’re leaning toward biopsy.”

Dr. Guy seconds that prediction, especially as more therapies become available and more clinical trials are done. “I’m thinking liver biopsies are going to become more common for pathologists, even those who aren’t liver experts.” With apologies to Cole Porter, anatomic pathologists might want to brush up their liver expertise, especially if it’s been years since their training.

Fat in the liver, in and of itself, doesn’t mean the patient has the “bad” type of fatty liver, Dr. Guy says, i.e. NASH. The thinking on that has changed. In the early days, “We all thought that having fat in the liver was bad, and that it was the first hit of the ‘two-hit’ hypothesis—first you had fat buildup in your liver, and then something else happened, and then all of a sudden you’ve got really bad liver disease.”

Now, however, it’s thought there may be a protective component to accumulating fat, she says. “Which just funnels back into needing a liver biopsy to look for inflammation and damage.”

If more pathologists are drawn into performing liver biopsies, what will their clinical colleagues be looking for?

Dr. Brunt, recalling the consults she received (the majority from clinicians), says, “I thought it was important for them to understand the full scope of the disease. I would ask, *Does your patient have any of these features of metabolic syndrome? Does your patient drink alcohol? Is your patient on a certain medication?”* Pathologists can lead the way in those discussions, she says, especially if more primary care physicians take on the role of managing NAFLD.

Dr. Gopal says her clinical colleagues are most worried about fibrosis, because it’s the main histologic factor that predicts mortality. “How much fat am I seeing? How much fibrosis am I seeing?” They also may have questions about ballooning degeneration of hepatocytes, which is a histologic feature of steatohepatitis, as well as lobular inflammation.

Many pathologists, including Dr. Gopal, use the NAFLD activity score (Kleiner DE, Brunt EM, et al. *Hepatology*. 2005;41[6]:1313–1321), which combines the three aforementioned features. “Our clinicians like to have that score included in their reports. Usually that answers the majority of their questions,” she says, although “occasionally they’ll have something specific they want us to review.”

Clinicians may also order a biopsy because they suspect another chronic liver disease in addition to steatohepatitis, Dr. Gopal says. “So they’ll ask me if it’s NAFLD or NASH only, or might there also be another form of hepatitis superimposed upon the fatty liver disease, depending on a particular patient’s clinical and laboratory findings.”

Beyond that, she says she takes great care to annotate all the findings and provide a useful interpretation.

This can be especially challenging for pathologists who might not be liver experts. “They might use some fuzzy reporting terminology that leaves the hepatologist confused,” Dr. Guy says. “If the path report isn’t clear, it causes a big problem.” She speaks from experience, based on the consults she receives from hepatologists confused by an earlier biopsy report. “I think maybe pathologists are less aware of this burgeoning disease than hepatologists,”

she says.

Pathologists who are not liver experts, she suggests, may be more attuned to “the era where the big bad liver disease on the liver pathology block was viral hepatitis—all the biopsies used to be viral hepatitis C.”

But the histologic features of NASH and alcoholic liver disease overlap, says Dr. Gopal. “Essentially, for the most part, we can’t tell the difference between the two. So that’s another reason having good clinical information is paramount in these situations—so that this can be labeled correctly, alcoholic steatohepatitis versus nonalcoholic.”

Dr. Singal is familiar with these blurred lines. NASH inherently means no alcohol involvement, but “It’s hard to find these patients and fit things into these clean buckets.” What he and his colleagues will see instead is a patient with metabolic syndrome who occasionally drinks alcohol and has signs of NASH. The distinction between NASH and ASH, “while it’s clean in textbooks, is much less clear in clinical practice. This is a spectrum, and most people lie somewhere in the middle.”

Given that, says Dr. Guy, “Liver pathologists really need to be aware of the nuanced pathologies, and try to help the patient by having sound pathology reports. Because clinicians are confused to begin with. So we can do a lot to help them.”

A good place to start is to look for metabolic liver disease CME courses. “They may not be highlighted the way breast, prostate, luminal gut GI courses are, but they’re often available. They may just draw a smaller number of people,” Dr. Guy says.

This could be crucial for any pathologist who interacts with primary care physicians, especially if, as some suggest, those same caregivers will be shouldering a heavier load when it comes to NAFLD. “The onus is on us pathologists to keep current with diseases that are trending and becoming more problematic,” Dr. Guy says.

Dr. Brunt offers another piece of advice: “You can’t go wrong following the guidelines of the major societies. They’re well thought out, they’re vetted by the leaders in the field,” she says. Another bonus: There’s nothing controversial about them. Recalling her own work on guidelines, she says, “You write something you think is as bland as Melba toast, and [commenters] respond: ‘You can’t say that!’” The final result is a well-honed, practical document (Chalasani N, et al. *Hepatology*. 2018;67[1]:328–357; European Association for the Study of the Liver, et al. *J Hepatol*. 2016;64[6]:1388–1402).

Another useful avenue is the multidisciplinary conference, Dr. Guy says. “That could be an avenue where pathologists could remind their colleagues about fatty liver disease.” As she noted, that’s a major topic of discussion when she and her pathology colleagues meet with their gastroenterology fellows. “We want them, when they go out to practice, to understand our words, our reports. That’s the best way we can help our patients.”

Given all that has been discussed, it may feel easier to sort through Shakespeare’s Henry plays. But ask the experts what they’d like to see happen, and the answer may surprise. “It is starting to change,” says Dr. Guy, crediting the efforts being made by hepatologists to improve awareness of the disease.

Dr. Brunt says they’re making “serious headway” into increasing awareness of NAFLD. “We have some very strong clinicians in this field who have worked hard to reach across different professional societies and make a lot of noise about it. People are becoming aware.”

NAFLD is a relatively new disease in terms of medical years. Though it has been studied more intensively for the past two or three decades, “That’s not a really long time in the medical world,” Dr. Gopal says. “So there’s still a lot of work being done to understand this disease. There’s still a lot of variation between both clinicians and pathologists, I think, in how we interpret things. But the reason for that is because we’re still gathering data on what certain things mean.” Was Caesar a hero or a tyrant?

The liver itself is a complex, sophisticated organ, and it sits right in the middle, so to speak, of a complex disease. “But it’s all interlinked, and we’re just beginning to understand that,” Dr. Guy says. “The heart and the liver are

kind of communicating back and forth, participating together in this horrible dance. So is kidney disease. So many things are interlinked, and it's fascinating."

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