

Dr. Mody 02-22-2021

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Dr. Sanj Kakar

Welcome, everyone to Mayo Clinic Q&A. I'm Dr. Sanj Kakar. The gallbladder is a small pear-shaped organ on the right side of the abdomen and sits just beneath the liver. It sometimes can become cancerous and when discovered early, there is a good chance for a cure. Unfortunately, however, most gall bladder cancers are discovered a late stage and the prognosis can be poor. Cancer can also form in the bile ducts, which are the slender tubes that carry bile fluid. This type of cancer is called cholangiocarcinoma. February is Gallbladder and Bile Cuct Cancer Awareness Month. And joining us to discuss this today is Dr. Kabir Mody, who is past co -hair of the hepatobiliary disease group at the Mayo Clinic Cancer Center. Welcome to the program. Dr. Mody.

Dr. Kabir Mody

Thank you so much. Pleasure to be here.

Dr. Kakar

Dr. Mody, how common is this?

Dr. Kabir Mody

Yeah, so um, you know, cholangiocarcinoma, which encompasses gallbladder cancer and bile duct cancer, uniformly is, is pretty uncommon, you know, represents only about 3% of GI cancers overall, but is one of the few cancers that is actually rising in incidence globally, and including here in the United States.

Dr. Kakar

And so what causes it?

Dr. Kabir Mody

So, this is caused by you know, as with most cancers, you know, the bile ducts are these little slender tubes, as you said, that start in the liver. They, they migrate and coalesce, as they go through the liver down into one single bile duct to exit the liver. And that bile duct goes and empties into the small intestine, small bowel. And so the cholangiocarcinoma can occur anywhere along this, it occurs when cells the cells that line these bile ducts called cholangiocytes, they develop changes in their genetic code mutations is another word for that, which changed the instructions for how that cell behaves and eventually becomes cancerous when those cells turn to growing too much. And basically, what happens is it becomes a tumor within the bile duct. And then that tumor as it progresses will invade

through the wall, the bile duct and into the liver. Which is why you know, many of these cancers when we when we do find them appear as a mass within the liver, but they really coming from those cells that line the bile duct. And gallbladder cancer works similar. So, from the lining of the gallbladder, these cells turn cancerous and frequently, once when they become more advanced, will invade through the wall, the gallbladder and up into the liver where the gallbladder meets with the liver underneath.

Dr. Kakar 03:09

So are there genetic causes? Or are there certain behaviors that may lead to an increased risk of these forms of cancer?

Dr. Kabir Mody

Yeah, so there are some risk factors for cholangiocarcinoma. Many of them are shared between all forms of cholangiocarcinoma, others seem to be more specific for different subtypes. And maybe more important in some, some areas of the world versus the other. So, we know there's different incidence rates and mortality rates around the globe with geographic variations, probably because of some environmental factor, or perhaps different genetic etiologies. But in terms of risks, risk factors, common ones would be, you know, primary sclerosing cholangitis, which is a condition that causes hardening and narrowing of the bile ducts and a lot of inflammation, chronic liver disease, scarring of the liver, which can be caused by chronic hepatitis and, and other things, you know, frequently known as cirrhosis, older age, diabetes, smoking, obesity, and in some areas of the world, there are parasites which in fact, and live in the bile ducts that cause significant inflammation and changes there that that lead to cholangiocarcinoma. Additionally, you know, gallstones, chronic gall stones, those can raise the risk for cause chronic inflammation and, you know, perhaps bile gall bladder cancer. And then some patients have what we call a coloductal cysts, which are chronic cysts that form in these bile ducts as they can in most any duct in the body. And, and those can create an environment where cancer can develop as well.

Dr. Kakar

And so when you say cirrhosis, you know, we think of cirrhosis as disease of the liver, and one of the common causes of that is alcohol. Have you seen a link between excessive alcohol consumption and the development of these cancers?

Dr. Kabir Mody

Well, certainly, you know, chronic alcohol use can lead to chronic scarring in the liver and cirrhosis over time. I will say, when I say cirrhosis and chronic liver disease, you know, think more, more frequently, we mean, hepatitis B and C, chronic infection. Alcohol consumption can raise the risk for cholangiocarcinoma by about two to three times in retrospective looks. Chronic hepatitis C and chronic hepatitis B, maybe slightly more, maybe be four or five times the risk. And, and then, you know, one of the things that we haven't talked about a lot but need to going forward because of its significantly rising incidence is natural or non-alcoholic steatohepatitis, which basically means fat accumulation in the liver, which is drastically growing in this globally, actually with the obesity epidemic and addressing it growing as a cause for chronic liver disease. And it's certainly taking over as a leading cause of not only cholangiocarcinoma, but hepatocellular carcinoma, which is another type of liver cancer.

Dr. Kakar

So we're learning more and more about the Coronavirus and how it affects different organ systems. For example, the heart, the lungs, the brain, have you seen it affect the liver?

Dr. Kabir Mody

I don't know if I can answer that question. I haven't seen too many Coronavirus patients, but I have not seen, at least we don't really know whether Coronavirus can chronically affect the liver, right? So, if there was a situation where the virus causes changes that are ongoing chronically and cause chronic inflammation in the liver, then that would be a situation in which, you know, certainly it could raise your risk for cancers.

Dr. Kakar

Okay. And so let's talk about the symptoms, what would a patient, how would they feel if they're developing this because we talked about the earlier the detection, the better chance of the better prognosis? So, what symptoms may a patient be experiencing?

Dr. Kabir Mody

So I mean, I think, you know, part of the problem here is the liver. The liver is generally very resilient. And so a lot of patients won't have any symptoms when they have, you know, maybe very small tumors. Most commonly, patients will have symptoms that relate to obstruction of the bile ducts. And so those can happen that can happen within the liver, it can happen outside the liver and the gallbladder for sure. So yellowing of the skin, otherwise known as jaundice, or the whites of your eyes, a lot of itching, which is caused by higher level of the bilirubin pigment in your blood, and that's very, you know, can irritate the skin. Light lighter colored stools, even white colored doors, always known as clay-colored stores darkening of the urine, these are all symptoms of bilirubin backing up into the bloodstream. Otherwise, not pretty nonspecific symptoms, you know, more fatigued than normal, maybe some abdominal pain. Usually on the right side could be anywhere, unintended weight loss. In terms of gallbladder cancer, there's a you know a percentage of patients who have a gallbladder tumor that's diagnosed just simply when they go in for to have their gallbladder removed. You know, they go in with symptoms of a gallbladder infection, the surgeon goes in to take that out, and pathological you find a tumor, or the surgeon finds a tumor and has to decide what to do at that point. And that's incidentally noted gall bladder cancer so that can be particular to gallbladder cancer itself.

Dr. Kakar 9:57

So given how vague the symptoms are, what what tests How do you diagnose these, these conditions?

Dr. Kabir Mody

Yeah, so a lot of patients will come in saying My doctor found that my liver tests were elevated. And, you know, this is something that's routinely done usually doing a routine physical or follow up, follow up exam by your primary care physician perhaps. And, and then usually what we'll do is, you know, get a CAT scan, right everyone who comes with a with abdominal pain to the emergency room usually gets a CAT scan or an ultrasound of the abdomen, and that will show signs of a, of a mass in the liver. A lot of times we'll get MRI, at least in our practice here. MRIs can help to delineate, you know, the tumor relationship to the bile ducts and critically, relationship to blood vessels with all the blood vessels within

the liver, which are important when we're trying to decide whether something can be taken out surgically or not. It also will identify very small, you also want to identify a very small, what we call satellite lesions, which happen very frequently with bile duct cancers. So, you can have like a, you know, a main tumor in the liver, but then there's satellite lesions elsewhere that we really want to know about. So frequently, we see a main tumor, and then we see satellite lesions elsewhere in the liver. And that's, we want to know that that's important when we're trying to plan for different therapeutic options that we might have, like surgery or other things.

Dr. Kakar

Why is that important to diagnose the satellite lesions? Are you talking about metastases or just lesions elsewhere in the liver?

Dr. Kabir Mody 12:48

So they could be considered intra metastasis within the liver. r their other, just other separate tumors, right? So, remember that bile duct cancers is developing in this environment that's pervasive throughout the liver, presumably, right? Chronic inflammation across the liver, and that so that, that environment, you know, present all over all over the bile ducts. And so you could get separate tumors that develop, you know, all over the place, or their or their intrahepatic metastasis. But it's important to know that because if you have, you know, if you see only one small tumor here, and you don't see the satellite tumor over here, and then you go and try and take this main tumor out surgically, for example, then, you know, certainly that that other tumor is going to start to grow after surgery, right, when you stop adjuvant or post-operative therapy, and that sort of thing so that person is at higher risk. But we want to know, the totality of the disease as best as possible. So that will include getting a CAT scan of the chest as well to make sure that there's no spread of the disease to the chest, also.

Dr. Kakar

So, Dr. Mody, you touched upon some of the treatments, surgical interventions, can you can you talk about the sort of spectrum of treatments that a patient can be expected to have?

Dr. Kabir Mody

Sure. So, surgery and taking out all the diseases the ideal way to treat this, treat this tumor. And really the only way to offer the patient the potential for cure. And, and as we said before, you know, it's unfortunately not common enough that we find these situations where we see a tumor that can be taken out right away. In addition to surgical resection, Mayo Clinic did pioneer the advent of transplantation or liver transplant for particular cholangiocarcinomas that occur where the bile ducts come down of the liver. So, it's a particular location We got these tumors and we, we have pre-operative treatment where we apply chemotherapy and focused radiation, and then put patients on a maintenance chemotherapy that goes on until they get their liver transplant. And that's been life changing for, you know, a lot of patients with this particular bile duct cancer. Short of surgery, if surgery is not an option, then depending on where the disease is, and how extensive it is, we can we can employ chemotherapy or systemic therapies, which we'll probably talk about in a couple of minutes. But in addition to that, radiation, and there are different forms of radiation that that we can do, we can do radiation that comes from outside the body of traditional radiation that people hear about, or we can do radiation that is deployed on little glass beads or resin particles that we can deploy by a catheter to the

tumor directly, and deliver high doses of radiation that way. So, a lot of different things we can do. But sometimes that treatment leads to significant response that enables the patient to then go on to have a surgical surgery to take it out. And that's, that's fantastic when that happens. And sometimes it doesn't.

Dr. Kakar 15:22

And what about proton beam, has that had any role in the treatment of these liver cancers or bile duct cancers?

Dr. Kabir Mody

That's still that is still being ferreted out. You know, the pros and cons to proton and I'm not a radiation oncologist, so I'm not going to wax poetic about that. But, you know, certainly there, there could be a role, but it's something that's being more explored. Finding ways to, I think the crux of that question is really, how can we find a way to get more radiation to that tumor and spare normal liver. That's the ideal situation. And so we can do that protect potentially with, with proton, we can also do that with the with the beads and very particular mapping and dosing that way as well.

Dr. Kakar

So let's talk about what Mayo Clinic is doing for treatments, you touched upon the surgical sort of nuances tell us what Mayo Clinic is leading in terms of treatments for these type of cancers?

Dr. Kabir Mody

Well, so I think, you know, what we what we try to do best here is a multidisciplinary approach with faculty who are truly all in and focused on cholangiocarcinoma. And so we have surgeons who are, who were that way, we have medical oncologists like myself who do the same thing. We have radiation oncologists who are focused on liver cancers, and an individual radiologists, too, who are passionate about this topic. And also, part of that team, our folks in the lab, and we have a number of labs at Mayo that are doing groundbreaking research on, you know, the immune environment of cholangiocarcinoma and bile duct tumors... Targeted, you know, sort of signaling pathways to take advantage of and the true nitty gritty biology of how these tumors, you know, grow and survive, and how we can target that. Also, how can we model the disease better so that we can evaluate treatments better. And, you know, we're doing work down here, across the enterprise on modeling in specific, tiny little, what we call micro cancers and being able to test different things that way, and hopefully innovate treatments outside the patient before we get into a clinical trial

Dr. Kakar

So given this sort of multidisciplinary, innovative type of treatments, are you, if I was a patient, and I wanted to get for example, a second opinion or learn about the latest treatments? How does one go about doing that?

Dr. Kabir Mody

Yeah, so I think in terms of bile duct cancers, as a patient, it's incredibly important to have the opinion or have the evaluation of a team that sees a lot of this disease, because as we said, it's not very common. And, you know, many oncologists across the country will only see a couple over the course of their career. And so, I think it's incredibly important that patients, you know, at least get the opinion of

someone who, who sees a lot and can help to develop a treatment plan. Hopefully an innovative one that that can be employed as a team, and that includes their local oncology team, for sure. So, there's lots of patients I see from, you know, all over the country that I partner with, with their oncologist to deliver particular chemotherapy or targeted therapies. And, you know, we have touch points back and forth regarding repeat imaging, and all sorts of stuff that we can participate in.

Dr. Kakar 19:23

And I think that's good for patients to hear that they can have their treatment close to home, but still connected with Mayo Clinic.

Dr. Kabir Mody

Yeah. I mean, for there are a lot of cancers and bile duct cancer is one of them, where we know there are survival advantages, if you have the involvement of a dedicated specialized, multidisciplinary team. And again, we're not trying to exclude anyone, right, we're just trying to offer our opinion and our expert recommendations. Because, you know, cancer is moving so quickly now. There's so much happening in every disease, that it's not possible for one, you know, oncologist to who does who treats everything, a general oncologist to know the nitty gritty about every single one. And so, we're just here to help and provide, you know, that updated nuanced information to each particular case in a personalized way.

Dr. Kakar

So Dr. Mody, with the as you mentioned, the rapid developments that's happening, how has that changed the prognosis of this condition?

Dr. Kabir Mody

Yeah, good question. So I think cholangiocarcinoma and liver cancers in general, is one of these things where there's been a lot of development over the last couple of years. And it stems from biology and learning biology, and genomics, particularly. So, a few years ago, when we were able to finally you know, sequence the tumor genome and learn more about the biology of the disease from the genetics, we learned a lot about cholangiocarcinoma. So we learned primarily, one of the biggest updates is that, you know, we learned that there are particular genetic alterations that drive these tumors, and they differ between the different subtypes. So intrahepatic cholangiocarcinoma, differs from extrahepatic cholangiocarcinoma, differs from gall bladder. And the genetics differ among these three. And those genetic alterations have lent themselves to different new therapeutic options that patients did not have before. And the pharmaceutical industry has followed suit and done research and development and then developed drugs that are now on the market and much more to come to offer patients significant responses and, and disease control. So, it's really exciting. That's one of the biggest things, so you know, every patient with bile duct cancer should have their tumors genetically sequenced, which is easily done now. And so they know they know the genetic nature of their disease.

Dr. Kakar

So as we talk about variations and genetic variations, have you noticed healthcare disparities, and how that affects that both the diagnosis and the treatment and prognosis of patients with liver or gall bladder cancer?

Dr. Kabir Mody

I think it's a great question. I think this, you know, the healthcare disparities that exist for pretty much cancer in general and cancer care, you know, apply to other cancers as well. In the United States, you know, the incidence of cholangiocarcinoma is higher in older folks, older than 45-50 years old, than it is for younger, although it's rising for younger folks. It's higher for Hispanic individuals compared to non-Hispanic individuals. And the five-year survival is worse for both of these populations. There is a worse overall survival rate for reported for African Americans, American Indians and Alaskan Native groups as well, that we've, we've seen in large database studies. And like I said before, globally, there's geographic variations. And so, there are differences in delivery of health care that that can affect the treatment that folks at different groups might have access to. And, and we're definitely trying to change that by reaching out to the community and providing services to them to get them the knowledge that they need to be their own patient advocates, hopefully, in asking for this stuff. So, one example is, you know, the genetic mutations and a number of academic institutions including ours have, you know, worked with cleanser, Cholangiocarcinoma Foundation, which is a patient advocacy group that's done a huge campaign on how mutations matter in this disease and really tried to educate the cholangiocarcinoma patient population. And that hopefully goes out to groups of all kinds all over the country all over the world, actually. So they can advocate for themselves in treatment options that they otherwise wouldn't have.

Dr. Kakar

Yeah, that's incredibly important work. And thank you for sharing that with us. So, what when we when we have these disparities that exist, what are we doing for screening?

Dr. Kabir Mody

Right, so screening for cholangiocarcinoma is not really a single screening test yet. There's obviously a lot of work going on in the field to try and avail ourselves of an easy test. Unfortunately, it doesn't exist. But when it does, it will be incredibly important to get that knowledge out to communities all over the world and make those tests readily available. That's the second part, you can educate people, but you got to get that test to be readily available to them. But that'll be that'll be incredibly important. But from a screening standpoint, right now, there's not really a defined screening test for that. And that is one thing that's being worked on here, in particular, in addition to many other places, and trying to find genetic changes in the bile that we can sample endoscopically, or even hopefully, in the blood, that signal, a very high likelihood that there's a cancer hiding out somewhere, and then to be able to go look for it. So, we'll see.

Dr. Kakar

Dr. Mody, anything else that you want to share with us that we haven't touched upon?

Dr. Kabir Mody

No, I think I thank you for the opportunity to talk about a rare cancer, but one that's passionate, a lot of us here at Mayo Clinic and we're spending a lot of time working on and we do have a very large NIH grant that's dedicated to these cancers that's exploring all sorts of really exciting stuff. And so, hope to bring a lot more innovation to these patients in the in the near future.

Dr. Kakar

Well, that's tremendous. We've been discussing gallbladder and bile duct cancer with Dr. Kabir Mody, past co-chair of the variability disease group at Mayo Clinic Cancer Center. Dr. Modi, thank you for being with us today.

Dr. Kabir Mody

Thank you very much.