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TRANSCRIPT

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Cases We Don't Forget: Treating a Patient with RET-Mutated NSCLC

Announcer:
Welcome to *Closing the Gaps in Non-Small Cell Lung Cancer* on ReachMD, sponsored by Lilly.

Dr. Caudle:
Although no more than two percent of patients with non-small-cell lung cancer have a rare genetic mutation involving the RET gene, it's still essential that we as physicians are aware of how this specific mutation impacts our diagnostic and treatment approach. That's why today we're going to be taking a look at this topic through the lens of a real-world patient case. Welcome to *Closing the Gaps in Small-Non-Cell Lung Cancer* on ReachMD. I'm your host, Dr. Jennifer Caudle, and here to share an interesting patient case from his own experience is Dr. Michael Shafique, an Assistant Professor of Thoracic Oncology at the Moffitt Cancer Center in Tampa, Florida. Dr. Shafique, welcome to the program.

Dr. Shafique:
Thanks so much for, having me.

Dr. Caudle:
So, without further ado, Dr. Shafique, let's just dive right into your patient case. Can you give us some basic background information on one of your patients with RET-mutated non-small-cell lung cancer?

Dr. Shafique:
Oh, absolutely. So, I think the most notable case involved a 54-year-old male. He was a practicing physician in Florida, and he was a never-smoker. He presented after experiencing several weeks of blurry vision, most notably when he was trying to interact with the electronic medical record in his office, and he was finding it very difficult to complete patient notes and place his orders on a day-to-day basis.

Dr. Caudle:
Okay, excellent. Now, obviously you now know that this patient has RET-mutated non-small-cell lung cancer, but before he was diagnosed, what symptoms other than the ones you mentioned did he present with?

Dr. Shafique:
He actually had very few other associated symptoms. I think the primary thing that worried him, you know, being a practicing

physician, was the pretty dramatic onset of blurry vision, but he did not have any associated weight loss, cough, bloody sput, or trouble breathing, so it was never really at the forefront of his mind that he would ever be diagnosed with lung cancer.

Dr. Caudle:
Sure, and just for the sake of background information, did he have any particular health history that we should be aware of?

Dr. Shafique:
He was really only being treated at the time for essential hypertension, but he was otherwise a very healthy individual and would exercise several times a week, which I think is important to note with some of these genetic mutations because they commonly happen in never-smokers or non-smokers. Oftentimes, these patients are feeling very good and are in their normal states of health and usually present with pretty advanced disease.

Dr. Caudle:
Now you mentioned some of the symptoms that he had was this blurred vision. Are those the typical symptoms that are associated with RET-mutated non-small-cell lung cancer?

Dr. Shafique:
I do think it's relatively common that these patients either present or develop during the course of their disease metastatic lesions to the brain, but I think more commonly they will present with respiratory and pulmonary symptoms. Typically, they tend to have smaller primary tumors, but they do present more commonly with very extensive nodal metastases, so the tumor itself has already shown and demonstrated a propensity to metastasize through the lymphatic system, and so it's very common for them to present with metastatic lesions not only in the brain but in other places, the liver, the bone, for example.

Dr. Caudle:
Well, with this particular patient, how did you go about diagnosing him with RET-mutated non-small-cell lung cancer, and what types of diagnostic testing did you perform?

Dr. Shafique:
Probably the most important thing to remember about these patients is the most accurate way to diagnose these molecular abnormalities is through biopsy tissue, and so we ended up performing a bronchoscopy first for this patient. We sampled several mediastinal lymph nodes, and although it's common at a large cancer center like Moffitt, we were able to run most of these mutation tests in our own pathology lab. I think in the community setting, some hospitals or community cancer centers may not have access to very quick molecular testing, and so sometimes the only way to test for the RET mutation is through outside testing from a FoundationOne panel or another next-generation sequencing test like that, but here, we were able to run the most common molecular abnormalities, for example, the mutations in either KRAS or the EGFR genes, rearrangements in ROS1 or ALK, and then, of course, we ran the testing for the RET fusion, which is what he ended up testing positive for, and the patient who gets diagnosed with lung cancer, and, in his case, after the biopsy, we specifically subtyped it as adenocarcinoma. It's important to test for these other genetic mutations like EGFR, ALK, and KRAS because most of these patients will test positive for one of these genes.

Dr. Caudle:
For those who are just tuning in, you're listening to *Closing the Gaps in Non-Small-Cell Lung Cancer* on ReachMD. I'm your host, Dr. Jennifer Caudle, and today I'm speaking with Dr. Michael Shafique about his experiences treating patients with RET-mutated non-small-cell lung cancer. So, Dr. Shafique, earlier you spoke about diagnosing a non-small-cell lung cancer patient, and that's certainly what we've been talking about with a RET mutation, but now let's shift over to how this type of genetic mutation impacts your treatment approach. So, going back to this patient case, how did you treat him, and what factors did you consider when selecting a treatment?

Dr. Shafique:
I think the most important factors to consider for this patient would be the speed at which you can get this testing done, and so at our center we can get results from these mutation tests in about a week or so, but in some community centers or if community hospitals

have to send this testing to be done at a different site, it can sometimes take up to three weeks to get results back, and so I think if you have a patient who's very symptomatic, it would be wise to send the tissue testing off but then to proceed with maybe more of a standard first-line treatment option and then wait for the mutation testing to come back. Most guidelines, for example, the NCCN, the National Comprehensive Cancer Network guidelines will be supportive of them changing to more targeted therapies if a mutation does turn up on subsequent testing. So for this patient, we sent off the testing because he was very symptomatic from his brain metastases. He ended up electing to undergo a radiation to the brain first and that seemed to help the majority of his symptoms, and we were waiting for the mutation testing to come back in the meantime.

Dr. Caudle:
So, what are the associated outcomes in patients with RET-mutated non-small-cell lung cancer, and what was this particular patient's outcome?

Dr. Shafique:
Yeah, so RET-mutated lung cancer represents about 1 to 2 percent of non-small-cell lung cancers, and so it's a very rare subtype of adenocarcinoma. I think the general outcomes aren't well established, and I also think the general treatment approaches aren't well described, either, so it does make it important that we look at sort of the general approach to lung cancer, and so for this patient we ended up electing to treat him with a standard first-line treatment for adenocarcinomas, and we didn't pursue RET-targeted treatment right up front, and so for him we ended up treating it with a combination of carboplatin, pemetrexed, and Keytruda, which is a combination of chemotherapy and immunotherapy. The response rates generally are about 50 percent if not more in most of these, and an unselected population of non-small-cell lung cancer patients, current RET inhibitors that we could use for RET-mutated lung adenocarcinoma, all have response rates ranging from 18 to 38 percent, and so just judging by the numbers, it made more sense to select an untargeted treatment upfront. However, more importantly, there are more potent inhibitors for RET, coming down the drug pipeline, and so those response rates are upwards of 60, approaching 80 percent, and so I think in the future the outcomes will be much better, and we will potentially be using RET-targeted therapies upfront. So, for this patient, he progressed after four cycles of the initial chemo plus immunotherapy combination, and he required some palliative radiation to a spine lesion. We subsequently were able to enroll him on a clinical trial for one of these newer RET-targeted therapies, and he enjoyed quite a dramatic response not only in the bulk of his mediastinal tors and and spine lesions, but he had a relapse of his brain metastases, and most of his brain metastases responded very well to this treatment.

Dr. Caudle:
Well, you know, this has been really helpful, you talking through your patient's case and the different treatments that he received and treatment options now and hopefully in the future. Before we wrap up, Dr. Shafique, what are some important considerations for all of us to keep in mind when managing patients with RET-mutated non-small-cell lung cancer?

Dr. Shafique:
Probably the most important things to keep in mind is I think with some lung cancers, there're some mutations that, that tend to be mutually exclusive. For example, if patients have a certain mutation, chances are, you know, they wouldn't have any other concurrent mutation. However, in RET--mutated lung cancers, other mutations are more commonly seen as well, and so it would be important to constantly reevaluate your patient for additional mutations, and so I think that's an important point for oncologists to consider. I also think for physicians in general, understanding that these patients are non-smokers, they're never-smokers. Their disease can be very aggressive and can progress very rapidly with brain metastases and other metastases, and so just because they don't fit the typical profile of a patient with lung cancer, their disease can be just as aggressive if not more, and finally I do think even though we do have newer RET inhibitors coming through the approval process, these patients still do respond at about the same rates as you would expect in an unselected lung cancer population, and so even though it's a targeted mutation, I do think it's important to know that even the standard treatments can and do offer good treatment outcomes for these patients as well.

Dr. Caudle:
Excellent, and, and thank you so much for that. You know, even though this type of genetic mutation is rare in non-small-cell lung

cancer patients, it's still so incredibly important for us to keep this on our radars, and I'd like to thank my guest, Dr. Michael Shafique, for sharing this interesting patient case with us today that demonstrates how we can go about diagnosing and treating it. Dr. Shafique, it was wonderful having you on the program.

Dr. Shafique:
Please to be with you. Thank you.

Announcer:
This program was sponsored by Lilly. To revisit any part of this discussion and to access other episodes in this series, visit ReachMD.com/N-S-C-L-C, where you can Be Part of the Knowledge. Thanks for listening.