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A Blood Test for Lung Cancer?

LYMPHOCYTE GENE EXPRESSION

Your patient's chest x-ray comes back with a nonspecific nodule. Is there any way that you can prevent this patient from needing to undergo a biopsy to determine the etiology of this finding? I am your host Dr. Lee Freedman, and with me today is Dr. Anil Vachani, Assistant Professor of Medicine in the Pulmonary and Critical Care Division of the University of Pennsylvania Hospitals in Philadelphia.

DR. FREEDMAN:

Dr. Vachani, thank you very much for being with us.

DR. VACHANI:

Thank you for having me.

DR. FREEDMAN:

Today Dr. Vachani and I will be talking about his very interesting work that may help us one day to use the blood test to decide, which patients might have a malignant lesion on their chest x-ray or more benign lesion. Dr. Vachani, tell us about the theory behind having a blood test that will help us make this distinction?

DR. VACHANI:

So I think that the importance of a blood test is to clear for people who have a lung nodule on their chest x-ray or CT scan because we know that the majority of patients who have a nodule are likely to have benign disease and it is not going to be malignant. The problem that we have currently is that many of these patients require ongoing repeated CAT scans of the chest or chest x-rays, or may require having a biopsy done either through surgery, or another invasive procedure such as bronchoscopy. We believe that using a blood test as a diagnostic tool can be very useful to help determine which patient should go on to more invasive testing and allow for patients who have, who are deemed to have low risk of disease to continue to be followed with less invasive testing going forward.

DR. FREEDMAN:

And it almost sounds too good to be true. Is this something like a PSA for prostate cancer, or is it more involved than that?

DR. VACHANI:

It is. I think blood test for cancer can be divided up into 2 broad categories. One is blood test that can be used for screening purposes. So you can take people who are asymptomatic who have no evidence of disease who then undergo a blood test to determine whether they may have some early signs or indications of a cancer, and so PSA was originally developed in that realm in the screening realm. It has worked to some degree, though there are clearly controversies surrounding the use of PSA for prostate cancer screening as well. I think that people are interested in developing blood tests for screening for lung cancer as well; although, there have been many stumbling blocks along the way. Most importantly there has not yet been a single blood test that has been able to identify all people with lung cancer. Lung cancer tends to be a very heterogeneous disease and it does not appear that all lung tumors produce one unique protein that can be easily identified in the blood. We have approached it a little bit differently in trying to identify a blood test that can be used for people who already have an abnormality, people who have already been shown to have a lung nodule on a CAT scan or a chest x-ray will then need additional testing to prove whether that nodule is either benign or malignant.

DR. FREEDMAN:

What direction have we gone since there does not seem to be a single unique protein to malignant cells in the lung?

DR. VACHANI:

Our theory was that as opposed to looking for something that is released by the tumor cell like a shed protein, which is how PSA was discovered, we decided to focus on the immune response to a tumor. This is not really a novel idea. Clearly people have worked on evaluating tumor immune responses and how lymphocytes affect a tumor, and how lymphocytes can be used in sort of a therapeutic fashion against tumors the whole area of immunotherapy. By using the effects of the immune system as a diagnostic tool is relatively a recent development. I will say that the senior investigator on this project is a woman named, Louise Showe. She works at the Wistar Institute here in Philadelphia and who is my main collaborator and she has worked on looking at the immune response in various tumors for a majority of her career, and we did some preliminary work in looking at the blood of patients with lung cancer and people who did not have lung cancer, sort of healthier controls, and we were able to identify that there appeared to be some sort of difference in the gene expression of these lymphocytes from the cancer patients. That led to this larger study that we have done now to determine whether there really is this measurable response within the circulating lymphocytes of patients with lung cancer to see if it could really be used as a diagnostic tool.

DR. FREEDMAN:

So we are not looking at some protein or other product intrinsic to the malignancy itself, but rather looking at the immune response, specifically in this case the genes of the lymphocytes that respond to this and is this an easy process? It sounds somewhat daunting to me.

DR. VACHANI:

You are correct in that the technologies for measuring this are relatively new. So what we use and what is generally used to do a broad gene expression profiling of any sort of system are these things called gene expression arrays. What they do is you can take a sample whether it is blood or whether it is tissue, you can isolate the RNA from those cells and then ultimately hybridize them to these arrays, which allow you to actually measure the individual quantity of every specific RNA for every specific gene that is present in the sample. These things generally interrogate what we think of is the whole genomes. We think we are measuring approximately, you know, 25,000 to 30,000 genes at a single time point from each patient. Though the technologies are relatively new and it is complicated by the fact that the processing has to be sort of just right, the RNA has to be prepared just correctly, and the steps of actually doing the array you know have to go well. So there can be lots of technical issues, but most of the things are easily conquerable when done by an appropriately trained laboratory. I have also mentioned that there are still lots of issues in terms of commercializing these products for actual clinical use. There are only a few very limited examples that I could provide you today where expression arrays have been incorporated into clinical practice. Most of these things are still in early development and are still going through the process of validation and ultimately FDA approval.

DR. FREEDMAN:

And so with the work that you are doing at this point still is mostly sponsored by academic grants and the like as opposed to pharmaceutical companies and Genentech type companies?

DR. VACHANI:

Correct. So our work was actually funded by the State of Pennsylvania approximately 5 years ago. We proposed doing a large-scale analysis of gene expression in the peripheral blood lymphocytes of patients with lung cancer and controls, and we, you know, over the course of the last 4 years have collected blood samples from around 140 patients with cancer and about 90 controls. I will mention here that the choice of controls in these sorts of studies are very important. It would obviously be very easy to compare a 60-year-old patient who is a smoker and has a lung nodule to a 20-year-old healthy person and shows some differences, but those differences are probably not due to the tumor or to the nodule, but may be differences due to an age, you know, overall healthy state, smoking status, things like that. So what we have tried to do is do a very controlled matched study where we taken older patients, matched them for age, matched them for smoking status, matched them for gender and race and try to really focus in on the effects of whether the tumor is causing changes in the lymphocytes or not. At least in our results preliminarily, we think we found a signature that is relatively accurate; though I do believe that is going to require some more refinement prior to moving forward with validation studies.

DR. FREEDMAN:

Tell us about the signature that there is something that seems to differentiate benign from malignant?

DR. VACHANI:

Yeah, I would say that based on our current results, we are able to differentiate lung cancer patients from appropriately matched controls with about 87%-88% accuracy. It is not 100% because there is still a fair amount of heterogeneity, you know amongst this population, but with about an 88% accuracy and that breaks down to about our current study shows that we have a sensitivity of approximately 85% and a specificity of about 87%. So we are approaching numbers that are relatively reasonable for a diagnostic test. Most authorities think that you need to start getting into sensitivities and specificities of around 90% that those numbers are going to translate to a clinically effective diagnostic tool. We do believe that there are probably some opportunities for improving our algorithm if we do some additional analysis, but we believe that our results at least offer a perfect principle that the immune response, the cellular immune response to lung cancer is detectable and certainly has the potential for the use as a diagnostic tool.

DR. FREEDMAN:

And will the next steps be in refining this particular gene signature, or going back to look for a different signature? How do we go from here?

DR. VACHANI:

Right, so I think the most important steps going forward are to continue to refine our algorithm. So I think that even though we have this technology now where we can measure 20,000 or 30,000 genes at a single time point from a single patient, the statistical algorithms to analyze these data are still being developed; though we use various complicated statistical algorithms that I won't go into today to analyze these data and we think we have one that works well, but there are clearly new algorithms being developed all the time, new statistical methods that come online quite regularly and so we would like to continue to refine our statistical methods on analyzing these data, and the second big approach really is to validate these data in other independent validation sets. So we have established a collaboration with a couple of other institutions outside of the University of Pennsylvania to collect the samples from cancer patients and controls at their locations and allow us to measure the gene expression in their samples using the same arrays and see how well this works, and then to use those new data to be able to continue to refine the genes that we need to use in our algorithm. It is certainly possible that because of the added heterogeneity that might come in to play from the patients at other places, that is always the case when you go out and validate a diagnostic tool, but we might require a larger number of genes that might work to maintain our level of accuracy that we have now.

DR. FREEDMAN:

It sounds like it is a rather time-consuming analysis to do each one of these patients, and I would imagine somewhat costly, what is the pace that we can expect to see new algorithms and new arrays and gene signatures?

DR. VACHANI:

You sort of hit the major issue on the head here, which is that the time and effort that is required to do these studies is fairly intensive. Collecting these samples and isolating the RNA, doing the arrays and doing the statistical algorithms is somewhat of a costly procedure and it does take time. I don’t anticipate a test like this being ready for clinical use for at least 5 to 10 years to be perfectly honest. I think that there are going to be hard to being able to show that this actually works as a clinical tool. We were going to need to do some further validation studies here locally and that will probably require a large prospective study to be done at multiple centers, what I would call a multicenter validation study and those things are going to require additional funding. We are going to need to prove to the scientific community that it is worth investing the money into developing these sort of tests, and so I would anticipate that we are in the very early stages of development of a lymphocyte gene expression tool for cancer.

DR. FREEDMAN:

The proof of the concept to me is extremely exciting going from cancer that we really do not have any way to screen for, and even when we have an abnormality, it is very often difficult clinically to know what to do, and the diagnostic choices are often invasive. This is quite exciting work!

DR. VACHANI:

Thank you. I mean, I think that the other issue that you pointed out I will add to, which is that you know screening for lung cancer, there is no screening tool for lung cancer at the moment. There is a large trial being conducted in the United States currently that is evaluating the use of CAT scans for lung cancer screening and that study is ongoing though recruitment has completed and we should start to see some initial results from that study in the next, I think, 2-3 years; that's the National Lung Screening Trial. But as we sort of began this talk, the one thing that we do know that study will lead to is that if CT screening is started in United States is proven to be effective that many patients will undergo an annual CAT scan of the chest and many of these CAT scans will identify a lung nodule, an indeterminant lung nodule, and all of these patients will need to have some sort of followup that will ultimately decide whether or not they have a malignant or a benign lesion in their lung, and what we are hoping to do is to spare many patients from having to undergo invasive testing and that is why we have devoted the last several years of our work to identifying and hopefully developing a blood test that can be used in conjunction with CT scanning of the lung.

DR. FREEDMAN:

Well I want to thank Dr. Anil Vachani, Assistant Professor of Medicine in the Pulmonary and Critical Care Division at the University of Pennsylvania for discussing with us what I think is a very exciting technology that is on the horizon, lymphocyte gene expression, it is something that Dr. Vachani outlines that we have proof of the principle that it does seem to work that the lymphocytes and their genes are different in patients with malignancies versus those who don't have malignancies, and as work goes forward, we may in the not too distant future have a blood test that can help us differentiate benign disease from more malignant disease, really very exciting stuff.

This is ReachMD XM157, the Channel for Medical Professionals. I thank you for listening.