Dr. Linda Yin:

Hi there. Welcome to another episode of ENT in a Nutshell. I'll be your host today. My name is Linda Yin, and I am joined by laryngologist Dr. Aaron Friedman. Dr. Friedman, thank you so much for being on the show.

Dr. Aaron Friedman:

Thank you for having me, Linda.

Dr. Linda Yin:

Perfect. And today we're going to talk about recurrent respiratory papillomatosis, otherwise known as RRP, and we recognize that this disease can affect both children and adults, but we're going to be talking about it sort of as a whole, starting off with presentation. So what is the typical presentation of a patient with RRP that comes to your office, Dr. Friedman?

Dr. Aaron Friedman:

So the presentation varies somewhat depending on the age of the patient that's affected, but in general, hoarseness and breathing problems are the two main symptoms that I think about with patients with RRP. In children, the symptoms can sometimes be a little bit more non-specific, chronic cough, and sometimes wheezing or other elements of respiratory distress, stridor sometimes as well. But in general, for most adults, voice issues are the primary complaint.

Dr. Linda Yin:

Good. And we've already started touching on this with children and adults, but tell me a little bit about the epidemiology of this disease. How common is it and what kind of population does it affect?

Dr. Aaron Friedman:

So the disease itself is actually relatively uncommon, and there's some data to actually indicate that it's becoming even more uncommon as time is going on. I'm sure we'll touch base on that, but effectively in children, the numbers are classified into what's called juvenile onset and adult onset RRP, but we'll back up to the pediatric population, the juvenile onset. Incidence is somewhere in the neighborhood of about two to four per 100,000 patients. And so there was a study I think, done about 10, 15 years ago that found that in the U.S., that came out to be somewhere in the neighborhood of 700 to 800 new cases in the entire country.

Dr. Aaron Friedman:

In adults, it's thought to be even a little bit more rare, so the adult onset versions. There actually aren't a lot of great studies out there looking at this surprisingly, but the incidence again out of a hundred thousand is somewhere in the neighborhood of one to two. So again, very rare. And we refer to this as a orphan disease in the context that it is very rare in the general population.

Dr. Linda Yin:

Gotcha. Now, even though it is rare, are there any identifiable risk factors that we have for people getting this disease and risk factors specifically we should focus on when taking a history from a patient?

Dr. Aaron Friedman:

Sure. So I'm sure we'll touch on this a little bit more, but the risk factors mainly relate to ways of transmission of the disease. So for instance, this is a sexually transmitted disease through the human papilloma virus, and so a sexual history can be pertinent in a adult patients. Birth history as well is germane to the pediatric population. And that primarily relates to issues of whether the newborn was a first-born, whether there was prolonged labor and in the history of the mother, if there is any sort of history of anogenital warts.

Dr. Linda Yin:

Great. After we take the history now, moving on to the physical exam, what are some features that you're looking for? And again, I assume most of this will be through a scope exam, but general exam as well, anything to pay attention to?

Dr. Aaron Friedman:

Right, so as you indicated, a laryngoscopy is really key, but even listening to the patient in terms of their breathing, in terms of their voice, those are things that you can pick up on that might give you some clue that a patient might have RRP. Obviously, if there's any sort of respiratory distress, you may pick up on elements of stridor, but as you alluded, the diagnosis is really dependent upon a laryngoscopy. And that can be challenging obviously in pediatric patients, depending on the age of the patient, but in adults, which is the primary patient population that I treat as a laryngologist, a flexible laryngoscopy is usually the examination of choice when you're suspecting something like this.

Dr. Aaron Friedman:

And in terms of what you might see, there is a predilection for the disease to be in the larynx and particularly along the vocal folds, but the disease can actually affect any mucosal surface of the upper aerodigestive tract. And so, you may on occasion, see sometimes even incidental, even on a oral exam, but we can find them anywhere from the nasal cavity all the way down to the pulmonary parenchyma. I've even had the experience of seeing it in the hypopharynx, and I'm sure that there are cases of this in the esophagus as well, too.

Dr. Linda Yin:

When you perform an exam or when you take a history and you see some of these signs and symptoms that we already talked about is RRP the only thing you think of, or is there anything else that should be on your differential diagnosis?

Dr. Aaron Friedman:

Like I said, I think it's in the adult population. One of the things that some of the other diseases that can mimic RRP include cancers, actually can look very similar. So squamous cell carcinomas of the larynx can look similar and also pre-cancerous, particularly dysplastic lesions of the vocal folds, can sometimes be challenging to interpret. So those would be the top two diseases that I would think of in terms of a differential diagnosis. In children, I think it can be more challenging. And again, because the ability to do a laryngoscopy may be somewhat diminished depending upon the age of the patient. So there can be other pathologies as well, that it might be mistaken for, including asthma, croup, laryngitis, those types of things.

Dr. Linda Yin:

Good. Okay, now moving on to the pathophysiology. So, from my rudimentary understanding, this is particularly crucial to RRP, so we've already talked about HPV, the human papilloma virus. Can you briefly tell us what HPV is and how it can lead to the development of RRP?

Dr. Aaron Friedman:

So HPV stands for human papillomavirus. Now, I think there are close to 170 or 180 different viral subtypes of this disease. It is a sexually transmitted virus, and it's actually the most common, sexually transmitted disease in the world. It's a DNA virus, and it has a particular affinity for squamous cells. The different subtypes that we talked about are really divided into low versus high risk because the higher risk forms of HPV are responsible for cervical cancer, certain types of oropharyngeal malignancies, but the RRP subtypes are predominantly six and 11. Those are also the subtypes that cause anogenital warts, and they are considered low risk because they, in general, do not result in malignancy. So six and 11 are the viral subtypes that are responsible for the majority of RRP. And some studies have suggested that subtype 11 is a little bit more aggressive, but it's not definitive that that's the case.

Dr. Linda Yin:

So we talked about HPV being a sexually transmitted disease, but we also know that children can get it. Can you talk a little bit about the methods of transmission and how patients acquire the infection that eventually leads to RRP?

Dr. Aaron Friedman:

Right. So the methods of transmission in children are primarily what are termed vertical transmission, so from the mother to the newborn. It's thought to occur at the time of birth when the child acquires it while passing through the contaminated birth canal of the mother. The presence of active warts at the time of delivery actually has been shown to increase the risk of developing RRP by more than 200 times. The presence of prolonged labor has been shown to, I think, about double the risk. And it's also a higher risk of transmission in first-borns. Nevertheless, even though these risks are increased, it's only about one in 400 newborns that develop it in the context of being exposed to genital warts. The other thing that's interesting is that there have been some studies finding that caesarian section isn't always preventative. And so there are some thoughts that there may actually be cases of in-utero transmission.

Dr. Linda Yin:

Interesting. So elaborating a little bit more on the virus. We did say that the high risk subtypes of HPV, which we know is an oncogenic virus can cause different types of malignancies. So for example HPV-positive oropharynx cancer, which is big in head and neck right now, but you mentioned that this is rare for RRP because of the serotype. How rare is it? Is it not possible at all? Or is there still a potential that we need to think about?

Dr. Aaron Friedman:

No. So I think the general rate that I believe is relevant is about a 2% chance of malignant transformation of quote, benign RRP into malignancy. And so what that really translates into is we see it more commonly, oftentimes in patients that have had RRP for decades where this cumulative risk goes up. So in the unfortunate few patients that do develop that, it's oftentimes patients who've had juvenile onset RRP that have the disease persist into adulthood, and then in their adult lives develop malignant progression. There are also cases of papillomatosis that are affiliated with the higher risk viral subtypes, such as 16 and 18. And those would be more likely obviously to progress into malignancy.

Dr. Linda Yin:

Right. Now on histopathology pathology, I understand these lesions have a pretty distinct appearance. So what do they look like?

Dr. Aaron Friedman:

So histologically, they are exophytic masses. They can either be sessile or pedunculated. We actually see that even in terms of their gross laryngoscopic appearance during office and operative exams. If you look at the histological level, there are multiple fronds of these fibrovascular stocks that are covered by stratified squamous epithelium. And there's thickening of the basal layer. That's consistent with HPV infection. And we know that that is the layer of epithelium that is targeted by HPV. We also see a delayed maturation of the epithelium as well.

Dr. Linda Yin:

And because this is a disease that's caused by a virus, do we think about the immune system and how this might factor into the pathogenesis of RRP?

Dr. Aaron Friedman:

Absolutely. And I think this is an area that we don't fully understand, but there is certainly a connection between the immune system and HPV. Studies show actually that HPV infection is actually quite common, meaning that most people actually do have an HPV infection, but they don't develop the phenotype of expressing the papillomatosis. And when patients are immunocompromised, there are case reports of papillomatosis, of RRP in particular, becoming much more aggressive. And so the immune system, it's thought to be sort of a selective immune defects, but research has really ongoing into that. And it's an area that, at this point, isn't really understood what that particular immune deficiency is.

Dr. Linda Yin:

Now moving on to work-up. So a patient comes into your office with some of these signs and symptoms that we talked about that are pretty classic for RRP. What kind of additional work-up do you need to conduct?

Dr. Aaron Friedman:

So in terms of work-up, we're really looking at the distribution of the disease. And as we talked about before, in the office, a flexible laryngoscopy becomes key. As a laryngologist, we also will often perform a video stroboscopy to look at the effect of the disease on the vibratory mechanics of the vocal folds. The disease can occasionally, as we talked about before, spread more distally in the aerodigestive track, particularly in the trachea or actually into the pulmonary parenchyma.

Dr. Aaron Friedman:

So getting a chest x-ray is not unreasonable, but oftentimes you won't see much on his chest x-ray. But patients that have had RRP for long periods of time, it's not uncommon if you get a CAT scan of the chest to find a small evidence in the lungs. Certainly, if patients have dyspnea that is disproportionate to what you might see on a laryngoscopic exam, then I have a low threshold to get a CAT scan of the chest, and sometimes we will pick up pulmonary parenchymal disease that was previously undiagnosed. But in general, I wouldn't say that a CT scan of the chest is a necessary component, though the flexible

laryngoscopy becomes the main tool to perform the work-up, and then obviously you need a biopsy for diagnosis.

Dr. Linda Yin:

Yeah. So, what about the biopsy? Do you do that in the office, and what are you testing for? Does it matter what subtype it is? Are you asking the pathologist to look at that?

Dr. Aaron Friedman:

So a biopsy in the office is not unreasonable if it's going to change your management, but oftentimes if a new patient presents with what you suspect is papillomatosis, you're going to go to the operating room anyways, because you will both obtain a biopsy and perform a treatment at the same time. So if it isn't going to change what you suspect your management is, then I often don't perform them in the office in adults. It's not to say there aren't exceptions to that. I think in children, obviously it becomes much more challenging to perform an awake biopsy in the office, and so that would generally be performed in the operating room.

Dr. Aaron Friedman:

And one of the things that I wanted to back up now, and I'm thinking a little bit more about it too, is that you would presumably perform a biopsy if you are concerned about some other pathology. We talked about the differential between, for instance, squamous cell carcinoma and papillomatosis, but one of the key things from an exam that often can help differentiate that is the distribution of the disease. If you see multiple areas, particularly in the larynx that are involved with normal intervening tissue, it makes the diagnosis of something like a malignancy much less. In general, malignancies don't skip around, whereas the distribution of RRP is often multi-focal within a given organ system and within the larynx in particular.

Dr. Linda Yin:

Now, if patients with RRP, if they were to receive no types of treatment at all, what is, in general, the natural course of this disease?

Dr. Aaron Friedman:

So the natural course really depends on timeframe, but in general, the disease will obviously not involute spontaneously, and it will continue to grow. And the rate that that occurs is quite variable from patient to patient. But in general, if patients present with dysphonia as their primary complaint, you would expect that to worsen over time. At some point, the airway can become restricted, obviously, and in children, that is much more likely to happen, just the small caliber of their airways. And so in that context, the natural history is to have breathing problems and ultimately it could be fatal. But in general, like I said, very few folks don't treat this disease once it's identified.

Dr. Linda Yin:

When you do treat it, what are your goals for treatment?

Dr. Aaron Friedman:

We say the term treatment, but really it's management because we don't have a cure. We can't cure this disease in any known reproducible way in every patient. So management is really the better word and

that relates to preserving voice quality and also breathing. So in that context, the treatment is directed towards improving those two symptoms. And there's different ways to do that from a surgical perspective and also through adjuvant therapies as well too.

Dr. Linda Yin:

Now focusing on surgery. So when surgery is performed, is it always done in the operating room under general anesthesia, or are there smaller procedures that you can manage in the office? And what do those look like?

Dr. Aaron Friedman:

Right. So surgery, or I should say debridement of papillomatosis, is generally done at least initially in the operating room. Number one, particularly if there's no diagnosis because you can perform a biopsy, but certainly once the diagnosis has been made, and if there is extensive disease in the larynx, it often makes sense to treat that in the operating room under general anesthesia. Once a patient has the diagnosis, and when they have limited amounts of laryngeal disease that recur, we do have the option of treating it in the office. And that's something that's usually reserved more for adult patients with RRP rather than pediatric ones, but there are obviously exceptions to that as well.

Dr. Linda Yin:

And we won't focus too much on surgical technique, but when you do treat these in the operating room, what sorts of instruments or tools are you using to debride the papillomas?

Dr. Aaron Friedman:

So the basic distinction comes down to using what we call cold instruments versus lasers, and lasers, we think of as generating heat, so the opposite would be cold. And the cold instruments are usually either in this day, micro-debriders or more rarely people will actually use just microlaryngoscopic instruments, scissors, and suctions and forceps and things like that. The latter doesn't work well for extensive laryngeal disease. So for disease on the vocal folds, some may still default to that, but really lasers have become a workhorse in treatment of this disease, both in the operating room and in the office.

Dr. Aaron Friedman:

The carbon dioxide laser is very commonly used by some surgeons to treat this disease. Yet, of course it has the wavelength that is best absorbed by water. And the other laser that surgeons use is the KTP laser, which has a different target. And so the target of that is actually oxyhemoglobin. And so in that context, because papillomatosis is a disease which requires a blood supply to grow, it's become quite popular in managing this disease. But the key thing that has to be remembered regardless of the surgical instrument that you use, is you want to preserve the normal structures around the disease, and in particular for disease on the vocal folds, this is an epithelial disease. This does not involve the vibratory layers below the epithelium. So surgery really has to focus on maximally preserving the lamina propria, the superficial layer of the lamina propria below the vocal fold epithelium. Otherwise you can end up with a permanent hoarseness.

Dr. Linda Yin:

And when you do perform some of these procedures in the office, as you mentioned, it's going to be primarily on adult patients, but are there any special considerations and what kind of techniques are you using there in the office?

Dr. Aaron Friedman:

So the office treatment of papillomatosis is generally done through a flexible laryngoscope with a working channel in it, and a laser that's delivered on a flexible fiber. And generally that means using the KTP laser. There are obviously flexible fiber CO2 lasers, but the diameter of those fibers isn't small enough in my understanding to be used in the office on a consistent basis.

Dr. Aaron Friedman:

So you need to have a patient obviously that is able to tolerate an office-based procedure and not every patient is in my experience, but really the way the procedure is done is under just topical anesthesia. So getting the patient and their larynx and their throat appropriately anesthetized is really key. And then again, trying not to do too much in one setting. There's kind of a limited window that you can treat. I think if you try to get too aggressive in the office, you're often not as successful.

Dr. Aaron Friedman:

So we know that office treatment will not accomplish as much in a given timeframe as a surgery would. So the expectation that it's going to change the cadence of the disease may not be a realistic one, but the nice thing about it is that it's not done under general anesthesia. Patients can leave right after the procedure. It usually takes about 10 minutes. And oftentimes it can increase the interval in between general anesthetics.

Dr. Aaron Friedman:

We know that in this disease, there's a wide variety of the severity of the disease. And so some patients may only require a handful of surgeries over their lifetimes. Others may require hundreds. And so for those that are requiring many, many surgeries using an office-based treatment to diminish the need for general anesthesia can be really advantageous and improve their quality of life.

Dr. Linda Yin:

Whenever you're using a laser, when you're using it, whether it's in the office or in the operating room, does that pose a risk? Because I would imagine you're vaporizing the virus. And so does you or all the surgical staff in the room, are there any special considerations for that?

Dr. Aaron Friedman:

Yeah, it's a great question. Absolutely. There is some documented risk of viral particles actually being aerosolized in the plume of the smoke that happens after papillomatosis is treated with the laser. Of course, anytime that you use a laser, we also want to think about eye production. So everybody, whether it's the operating room or for an office procedure, needs eye protection, including the patient. And then the smoke itself from the laser should be suctioned away. There are masks as well too, that are deemed laser-safe masks that are less likely to allow those aerosolized viral particles to be inhaled. So use of those masks would be strongly recommended.

Dr. Linda Yin:

And what about more aggressive surgical procedures or more invasive maybe I should say, outside of endoscopic laser or cold steel instrument management? I can imagine the disease progressing to a point of airway problems as you alluded to. Do we perform tracheostomies as a way to bypass that?

Dr. Aaron Friedman:

So generally we try to avoid them. This becomes more of an issue in pediatric patients because of the smaller diameter of the airways, and so they have less tolerance. And certainly tracheostomies have been performed and probably will continue to be performed for the most severe cases of RRP. But generally the goal is to try to avoid that. So if that means that you need to increase the frequency of your operative interventions, then that may be a reasonable alternative. There's some evidence that tracheostomies may actually promote more distal spread of the disease. And so in that context, again, we'd like to avoid that.

Dr. Aaron Friedman:

There are also cases, particularly with more with malignant transformation of the disease, where more aggressive surgical techniques may be required, whether it's in the larynx or sometimes even in patients, unfortunately that have diseases present to the pulmonary parenchyma. Some of those patients do actually need to undergo open lung surgery.

Dr. Linda Yin:

We've briefly mentioned adjuvant therapies already, and I've read a lot about potential adjuvant therapies. It seems like there's always new ones being studied, but can you talk a little bit about when we start considering adjuvant therapy in these patients in addition to surgery?

Dr. Aaron Friedman:

Yeah, there's not what I would say is a great consensus about it, and it probably depends upon what type of adjuvant therapy you're talking about. There are local adjuvant therapies in that there are more systemic ones. But in general, people talk about having more than four surgical procedures in a year as potentially an indication for using an adjuvant therapy, or if you find the disease just regrows rapidly, that may be an indication for it. As I said before, if it's spreading distantly and it's in multiple parts of the airway, in the trachea and pulmonary parenchyma, that might be an indication for considering a more systemic adjuvant therapy.

Dr. Linda Yin:

And of the adjuvant therapy options that we have available, what are some of the more promising ones we can highlight for the listener?

Dr. Aaron Friedman:

So there's been a lot of studies of things that people have tried over the years. A lot of them have been intralesional delivery of adjuvant therapies. And I would say the two most popular today of the intralesional class are still cidofovir, which has been used for decades now. And then more recently bevacizumab, which goes by the trade name Avastin, has been used intralesional.

Dr. Aaron Friedman:

In the context of cidofovir, there are studies showing that it improves control of papillomatosis. There is some risk of malignant transformation, although there's been some recent studies, I think in animal models, showing that that seems to be potentially not the case. There's also some concern about scarring related to use of cidofovir, and that also again in an animal model has been shown, at least in a porcine model is my recollection, not to be the case.

Dr. Aaron Friedman:

On the other hand, Avastin is a antibody. And so the studies to date have really shown no evidence of local toxicity or scarring or diminished vibratory capacity of the vocal folds. And the limited literature that's out there seems to suggest a benefit, at least in some proportion of the patients. But I would say that neither of these two adjuvant therapies are home runs. And again, they're just tools to be used in a local sense.

Dr. Aaron Friedman:

There are more systemic adjuvant therapies. We talked about Avastin. There is some impressive case reports of patients receiving intravenous Avastin actually, and having their disease melt away. The problem is that when they stop the Avastin, that the disease can sometimes come back and sometimes come back with a vengeance. And so the end point of that isn't really quite clear.

Dr. Aaron Friedman:

Interferon is another medication that's been given systemically, but it has significant side effects. And so it's not a perfect treatment either.

Dr. Linda Yin:

And we now have an HPV vaccine. And in fact, I think we have a recent expansion of who can get the vaccine. Given the fact that some of the patients who get the disease get it as neonates in the birth canal, is the vaccine effective at preventing RRP?

Dr. Aaron Friedman:

So the data that we have suggests that it is effective, not in the context, obviously, for the neonate who wouldn't be a candidate for the vaccine, but for the maternal transmission of it. So if there's less disease, fewer anogenital warts in the general population, then the risk of vertical transmission from mother to child goes down.

Dr. Aaron Friedman:

And in fact, there was a study that came out, I think about two years ago, looking at incidence of juvenile onset RRP in Australia. They have a particularly high rate of use of the vaccine in Australia. And what they found from years 2012 to 2016, is that they had a population database and found that there were only 15 new cases of juvenile onset RRP in the entire country. And that rate had diminished from seven new cases in 2012 down to just one in 2016. So the idea being that the vaccine does have a effect as a preventative strategy.

Dr. Linda Yin:

Well, those are all the questions that I had about this disease. Is there anything else that we haven't covered that you think will be really important for the listener to know?

Dr. Aaron Friedman:

I think we've covered a fair amount of what's out there. So I think we're pretty good.

Dr. Linda Yin:

Good. Okay, we're going to move on to the summary section, and I'll just summarize some of the key points that we talked about here. So RRP is a disease that typically presents with hoarseness, but the symptoms can be rather non-specific, especially in the pediatric population. We know that RRP has somewhat of a bi-modal distribution in terms of its epidemiology. We have the juvenile form that usually presents in young children, and this form can tend to be pretty aggressive and have a high recurrence rate.

Dr. Linda Yin:

Adults can also get the disease and this usually presents later in life, as a result of sexual transmission. RRP is caused by HPV, otherwise known as the human papilloma virus. In children, again, the transmission is vertical, so that means from the mother to the newborn, and this often occurs at the time of birth. In adults, the virus is transmitted sexually, usually through oral genital contact.

Dr. Linda Yin:

The potential for malignant transformation is low, as low as 2%. Even with the lower risk subtypes, it is possible and should always be something that is on our differential and carefully scrutinized with exams.

Dr. Linda Yin:

On pathology, these lesions usually exhibit multiple fronds of finger-like projections with fibrovascular stalks that are covered with stratified squamous epithelium.

Dr. Linda Yin:

The natural course of disease can be variable in terms of severity, but in general, without treatment, the disease will continue to progress and the lesions presumably grow larger and higher in number.

Dr. Linda Yin:

There is no known cure for RRP, but treatment is directed towards essentially debridement of these lesions with the goals in mind of improving the patient's voice, protecting their airway, and improving their general quality of life.

Dr. Linda Yin:

For surgery, some of the common techniques are instruments that are used include the CO2 laser and the KTP laser, as well as some cold steel instruments. Surgical procedures can be done in the operating room as well as in the office. Usually for the first surgical treatment of the RRP lesion, that's often done in the operating room, but especially for patients that need to come back for frequent treatment, in office procedures should certainly be explored and considered.

Dr. Linda Yin:

Adjuvant therapy should be considered as well in patients that require many surgical procedures a year or those who have rapid rebirth or the papillomas. Types of adjuvant therapy that we talked about are two main types that are commonly used. And the first is antiviral by the name of cidofovir. And the second is an antibody targeting the inhibition of angiogenesis called bevacizumab or Avastin, and both have shown really promising results when given in intralesional fashion.

Dr. Linda Yin:

Okay, we'll move on to the question session now. So I'm going to be asking Dr. Friedman a few questions to highlight some key points, and we'll give the listener about a five second pause to think about the answer before we give it. So Dr. Friedman, what is the primary age group affected by RRP?

Dr. Aaron Friedman:

RRP generally has a bi-modal distribution, so juvenile onset and then also adults in their 30s to 40s.

Dr. Linda Yin:

What is the primary stereotype of HPV that can cause RRP?

Dr. Aaron Friedman:

The primary types of HPV that cause RRP are six and 11.

Dr. Linda Yin:

What are the goals of surgical management of RRP?

Dr. Aaron Friedman:

The goal of surgical management is to preserve and improve voice and breathing and overall improve quality of life.

Dr. Linda Yin:

And finally, what are some commonly used adjuvant therapies for RRP?

Dr. Aaron Friedman:

Commonly used adjuvant therapies for RRP include cidofovir, bevacizumab, also know as Avastin and interferon.

Dr. Linda Yin:

All right, and that's our talk. Thank you so much again for being here.

Dr. Aaron Friedman:

Thank you for having me.