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# WHAT'S NEW IN KAPOSI SARCOMA?

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## **What's New in Kaposi Sarcoma?**

### **[video transcript]**

[00:00:01] Welcome to Physicians Research Network. I'm Jim Braun the Course Director of the monthly meetings of PRN in New York City. Since their beginning in 1990, PRN has been committed to enhancing the skills of our members in the diagnosis, management, and prevention of HIV disease as well as its co-infections and complications. We hope this recording of Susan Krown's presentation 'What's New and Kaposi Sarcoma?' will be helpful to you in your daily practice. And we invite you to join us in New York City for PRN live meetings in the future. PRN is a not for profit organization dedicated to peer support and education for physicians, nurse practitioners, and physician assistants. And membership is open to all interested clinicians nationwide at our website PRN.org. Now allow me to introduce Susan Krown, vice-chair for International Activities at the AIDS Malignancy Consortium and Member Emerita of the Department of Medicine at Memorial Sloan-Kettering Cancer Center in New York City.

[00:01:02] So we're going to start out with a little bit of history and go through the types of KS and the cause of KS and how the virus that causes KS gets transmitted, etc. and then get into some of the clinical spectrum of disease, and finally end up with some treatment and some complications. So it's named after Moritz Kaposi who was born Moritz Kohn, but there were a whole bunch of Moritz Kohn's in Vienna practicing medicine at the time. And he took his name from where he was born in Kaposvar, Hungary. And he first described this disease that would end up being called by his name in 1872. And what's interesting is that he described this as a disease that leads to death and does so within a short period of two to three years. And he described it as an incurable deadly disease, which is not really what we know as classic Kaposi's sarcoma today but I think it highlights the point that Kaposi's sarcoma can be an invasive, widespread, deadly disease even in people who are not profoundly immunosuppressed from diseases like HIV and people who have had major immunosuppressive therapy. So I think people forget that. And actually as an oncologist the first person I ever saw with Kaposi's sarcoma was an elderly man who had KS on his leg and he ended up having bone invasion and then presented with a small bowel metastasis. So, it happens.

[00:03:19] So there are basically four recognised epidemiological forms of KS and I'll go through them briefly. There is the classic form which is the one that usually is described as an indolent disease in older people, more often in men than in women, usually in certain ethnic or regional groups from either the Middle East or Eastern Europe and the Mediterranean. And one thing I want to mention is that it's been quite clear for a number of years that MSM who are HIV negative are at increased risk for developing KS. The absolute risk is not clear and they generally develop this at a younger age than your average person with classic KS, but the disease behaves very much like classic KS and usually is relatively limited and slowly progressive. There is another type of KS that's been described as endemic in sub-Saharan Africa and this occur both in children where it can be quite aggressive, as well as adults. In children it occurs in both boys and girls, in adults it occurs as in classic KS more often in men. And resembles classic KS

although it can present in some locally invasive forms. There's a third type of KS that is referred to as iatrogenic or allograft-related. It's usually cutaneous but can involve mucosal surfaces and internal viscera. And you know the classic appearance is in somebody who's had a solid organ transplant who is under immunosuppressive therapy, often with a drug like cyclosporine, and it's more common in people who've had multi-organ transplants or if you have a heart-lung transplant and you need that kind of major immunosuppression. But there are also other situations where this iatrogenic KS can appear and that includes people who've been treated with large doses of corticosteroids and I've personally seen it in some older individuals who were given drugs like enbrel for arthritis who developed KS. I've seen a 40-something year old HIV negative man who had severe asthma and was intubated on high dose steroids and ended up with disseminated KS that responded well to withdrawal of the steroids. So it's not just allografts and I think that it's important to remember that corticosteroids and other drugs that suppress immune function can precipitate development of KS in a susceptible individual. And then finally there is so-called epidemic or AIDS related KS and this again occurs across a spectrum of disease, can be very limited disease but can also be widely disseminated in the skin, mucosal surfaces, viscera and is often characterized by severe tumor-associated edema which can be quite debilitating. There's an increased risk with declining CD4 counts and as I'll show later the risk decreases with the use of antiretroviral therapy.

[00:07:33] So it's been well described for a number of years now that the cause of KS is a virus known as the Kaposi's sarcoma herpesvirus or human herpesvirus 8. And without this virus you don't develop KS. So the important thing to remember about this virus is that because it's a herpesvirus, infection is lifelong and this is similar to all other herpesviruses because these viruses can establish latency in B cells and endothelial cells, and that's why you can treat you know an acute episode where there's lytic virus with drugs like acyclovir, but once it's latent those drugs are no longer effective. And what's fascinating about this virus is that the genome contains multiple human gene homologs that encode proteins that are involved in cell cycle regulation and signaling. And this leads to the overexpression of certain angiogenic and inflammatory cytokines and growth factors and their receptors and a variety of other molecules including vascular integrins and matrix metalloproteinases that break down barriers between cells, but these are also exciting targets for therapy. And the virus also encodes proteins that inhibit apoptosis and immune responses to the virus, so it sort of perpetuates itself.

[00:09:17] There are a number of diseases that are caused by this virus. Kaposi's sarcoma is of course the prototype, but there are several other diseases including primary fusion lymphoma, Multicentric Castleman Disease, and most of the HIV-associated cases of MCD are related to this virus. And some of those MCD patients will go on to develop a large B cell lymphoma that is also KSHV related although most other lymphomas are not. And then there is a so called KSHV inflammatory cytokines syndrome which clinically is similar to MCD but without MCD when you do a lymph node biopsy, but it's not clear whether this KICS syndrome is really very different from what happens in KS-IRIS. I'll talk about KS-IRIS a bit at the end of my talk.

[00:10:32] OK. So let's talk a little bit about epidemiology and transmission.

[00:10:39] So these two maps, the first on the right shows KSHV seroprevalence rates and on the left you see KS age-standardised incidence rates and basically what these maps show you is that where there's a lot of KSHV, there's a lot of KS and that it's pretty much proportional. And you know the other take home message is that probably 90 percent of the world's KS is in sub-Saharan Africa. Although, you can see that you know the U.S. and South America and parts of Eastern Europe and the Mediterranean also have relatively higher rates of KS. But clearly in the southern and eastern part of Africa is where the most of the action is.

[00:11:39] Transmission of KSHV is sort of an interesting topic and specific routes of transmission are not really very well understood. But it is very clear that KSHV can be detected in blood and sometimes in semen, although even people with KS don't always have KSHV detectable in their blood. But saliva is the body fluid that most commonly harbors the virus, and it's believed to be the main route of spread. And so outside Africa, MSM are at the highest risk of KSHV infection and KSHV associated diseases. And it's not clear how that happens, whether it's because people use saliva as a lubricant, or because they have oral-anal sex, or from deep kissing. People are not really sure how that happens. But there have been those and Jeff Martin, one of Peter's colleagues in San Francisco, has made a point that maybe we should be at least counseling MSM about the existence of KSHV and the possibility of spread through saliva so that people can potentially take precautions not to spread the virus. You know it's not clear that that is the thing to do, but I know Jeff feels very strongly about it. In Africa on the other hand, non-sexual horizontal transmission in childhood is the main route of spread in the highest KSHV prevalence areas. And in these cases there are a number of different potential routes for salivary exposure.

[00:13:49] And this is from a very interesting study where they looked at KSHV seroprevalence in African children starting at the age of one and a half and going up to eight years. And they looked in two different countries, on the top in South Africa and on the bottom is Uganda. And then they looked at children in urban settings in rural settings. And what's very interesting is that in South Africa, the rates of infection did not seem to increase. By the time they were two years old, either they were infected or they weren't. Whereas in Uganda, rates were going up and up and up over time. And there are places in Uganda where the seroprevalence rate approaches 90 percent by the time people are 20 years old. So it's probably saliva, but it's not necessarily always the same way with saliva, and it's an interesting area. In the US the overall KSHV seroprevalence is less than 10 percent, but it's much higher in MSM and in people who have immigrated from endemic areas and I think that's important while we still have immigration in this country, in a place like New York where there are a lot of immigrants from Eastern Europe. When I was seeing patients I saw a lot of classic KS and a lot of my patients were elderly Russians and some Italians, and you know these are big populations in New York City especially the Russian population. Many of whom are fairly recent immigrants. But in HIV positive MSM, the seroprevalence rate has been estimated anywhere from 30 to 60 percent. But it's also as high as 20 to

30 percent in HIV negative MSM. And so we need to think about the implications of that for an aging population and I'll get to the issue of aging in a minute.

[00:16:28] Now this is taken from a recent paper published last year showing the decrease in KS incidents in the U.S. population over the past 10 or 15 years and it's clear that it's been going down. And I think everybody is aware of that. However, the same study looked at subgroups both regionally and by race, you see this one line that's going in the upward direction is for African-Americans in the south. So everywhere else in the U.S. rates are going down, but there may be subpopulations within the United States where the rates of KS are increasing. So it's not a uniform issue everywhere, even within this country.

[00:17:38] There's been a very interesting recent study that was done with a huge cohort from the IeDEA and COHERE cohorts looking at cancer incidence and this was again published in CID last year, and they looked at the comparison in different parts of the world of KS risk with relation to when people started ART and they looked at issues like age, gender, etc. And so what you see here is that in each of the areas that they looked at which included South Africa, Latin America, North America, and Europe the risk in women who were on ART was less than in men. But if you look at South Africa, the risk in women was significantly higher than anywhere else in the world. And if you also look at age, in North America and Europe, the risk increased with age whereas the opposite was true in South Africa and Latin America. And I can't say that I understand this but what I think the take home message is, that there may be other factors going on that are regionally specific and we can speculate on what they might be.

[00:19:24] Another interesting thing from this paper is they looked at the risk of developing KS depending upon where the CD4 count was. And it was pretty clear that the highest risk was, no matter where you were in the world, was in people with CD4 counts less than 50. But what's really fascinating to me is that whereas in Latin America and North America and Europe the risk continued to decrease as the CD4 count increased, in South Africa although the risk was lower in people whose CD4 count was higher than 50 it didn't really matter if your CD4 count was 52 or 700. It just suggests that there are other complex factors that influence the risk of KS and it's not just a matter of CD4 count or age or gender, etc. It's multifactorial and it may vary by location and what other things are going on in those people's lives.

[00:20:51] So the question comes up. Why doesn't everyone infected with KSHV develop KS? And in fact it's only a relatively small percentage of people who are infected who actually develop the disease. And you know we've already talked about immunosuppression as a factor and that can be acquired, such as in acquired immune deficiency disease, it can be treated iatrogenic and that is usually drug-induced either because you're getting immunosuppressive therapy for a transplant or you're getting some other treatment for some other condition. But that's not the whole story, obviously everybody who has a

kidney transplant develops KS even if they're infected with KSHV. Gender seems to be quite important and there is some fascinating studies about how genes on X and Y chromosomes and sex steroids have differential effects on immune responses and disease susceptibility. And there's a wonderful review article that I've cited here. There were also non-gender related genetic polymorphisms that regulate immune responses. There's the issue of age and Peter is going to talk about immunosenescence and that certainly seems to be a factor for classic KS, at least in North Americans and Europeans with HIV-associated KS but maybe not so much everywhere else. There are inflammatory conditions such as asthma and certain chronic infections that people have associated with an increased risk of KS. Oddly there have been a couple of studies that showed a protective effect of smoking on the development of KS and this does not mean that you should tell your patients to go out and start smoking. But it raises some interesting questions about how smoking affects the immune system and the inflammatory milieu. And there may be other social and demographic factors that we don't yet understand. People have speculated about walking barefoot in volcanic soils in eastern East Africa, but you know I think there's a lot to be learned.

[00:23:46] OK so let's talk about clinical manifestations. I think everybody's aware that the skin is the most common site of involvement, but there is frequent oral involvement. I will show lots of pictures in a minute. Lymphedema is quite important, not just in HIV positive people but also in elderly people who have KS confined to the lower extremities. Tremendous impact on quality of life, particularly when people have a lot of visible lesions and it's been pretty stigmatizing in certain situations. Lymph node involvement, if you go looking for it is very common but it does not have the same negative prognostic importance as lymph node involvement does in most other solid tumors. And I think people have to understand KS as a multifocal neoplasm some that may arise simultaneously in multiple parts of the skin and the mouth and lymph nodes. But it's not the same as having let's say, colon cancer that metastasizes to regional lymph nodes in the liver. It's a different story. Visceral involvement, at least in HIV-associated KS, back in the bad old days and certainly still in Africa is quite common. Gastrointestinal KS is often asymptomatic. Back in the 80s we used to scope everybody and we would find lots of occult lesions that were asymptomatic and we found that these didn't really have much of an effect on outcome, prognosis, etc. And so the general trend has been not to investigate in asymptomatic people but clearly to look for signs of things like occult GI bleeding, etc. Pulmonary KS is often a bad actor, it's usually symptomatic and can manifest in various ways. Multiple other organs can be involved, although less commonly. If you see a brain lesion in somebody who has KS assume that it's not KS and that it's something else and you should start looking for other reasons people develop brain lesions.

[00:26:25] OK so here's some lovely pictures and these are all patients that I cared for at one time or another in my life and you can see that skin disease can range from you know small pigmented papules to these you know big nodules, and ulcerated lesions, and little plaques, and then these these big infiltrative plaques that you see on the on the far right. You have to take my word for it that the lesion up in the upper left is KS, but certainly in a dark skinned individual a fibroma look like that. And that's why I'm going to stress in a minute that the biopsy is very important.

[00:27:18] Often the skin lesions will follow skin folds, like on the right you see somebody with pretty severe lymphedema and big plaques on his legs.

[00:27:31] Now these are two chest x-rays of patients that I took care of. And again you have to take my word for it that these are people who had biopsy proven pulmonary KS. I show these because I think it's very important to realize that the differential diagnosis is very broad and it's challenging. And you might suspect that this is KS in somebody who had KS elsewhere, but you could suspect that it was tuberculosis or cryptococcosis or whatever. And particularly in low resource environments like Africa where things like TB and bacterial pneumonias and cryptococcus are very common, it's sometimes very difficult to figure out what is going on there.

[00:28:34] Sometimes a CT can help because you see more nodular lesions.

[00:28:39] This is a picture of a fairly typical oral KS where flat plaques on the hard palate and some small nodules.

[00:28:50] But then there are other oral KS presentations, such as this on the upper gingiva of a large palate mass. A big tongue lesion. And this is like grapes all over. And the good news is all these people responded really well to treatment and it all got better.

[00:29:19] So I think I just want to stress that although you may see lesions that look very typical and you say, well this is obviously KS, I still think it's important that a biopsy be done for definitive diagnosis. And I think it's particularly important in the U.S. now because people see KS so much less frequently that people are not used to seeing it. So if you see something suspicious, it's not that hard to get a punch biopsy. And this is just data from a study that was done in Africa, with pathologists at UCSF where they showed that there were many other diseases, some of which have major implications like secondary syphilis, etc. and squamous cell carcinoma that you would want to know about and you wouldn't treat the same way as you treat KS.

[00:30:25] So I think I will skip over this other than to say you know this is what KS looks like under the microscope and you can do some immunohistochemistry to confirm the diagnosis.

[00:30:38] So let's talk a bit about the KS staging and the case definition. And this is taken from WHO guidelines on the treatment of skin and oral HIV-associated conditions which I contributed to. And it's adapted from the old so called ACTG staging which classifies patients as either good risk or poor risk tumors. And so basically the mild or moderate KS corresponds to good risk or T0 and the severe KS corresponds to T1 or advanced KS. So that's basically how we think about the disease rather than typical cancer staging.

[00:31:48] So as I mentioned before KS is multi centric and even when lesions are localized, let's say to an extremity, etc. there's no primary site as in other solid tumors. And the spread of KS doesn't follow typical primary, regional node, visceral metastases kind of pattern which means that if you have skin lesions on multiple body sites this doesn't necessarily indicate a poor prognosis. So you can have lesions on the leg and lesions on the arm and etc. and it's not like 'oh my, you know you've got stage 4 disease.' Again lymph node involvement does not imply a particularly poor prognosis, but it's important that the initial evaluation for visceral disease should include a chest x-ray and stool hemoccult as a minimum. And then follow up as needed. Chest CT can be helpful if the chest x-ray is abnormal. GI endoscopy should be performed if indicated based on symptoms or abnormal findings, let's say a positive hemoccult and you don't know where it's coming from. But CT scan is not really very good for picking up gastrointestinal lesions and an endoscopy is a whole lot better.

[00:33:18] All right, treatment. Basically, everybody who has HIV and KS needs to be on good ART and if they're not you should start to do it. And if they are and it's ineffective, you should optimize it. But there's no conclusive evidence that any particular regimen is better for treating or preventing KS. There are however some data that suggests that protease inhibitors and specifically nelfinavir may have KS activity that is separate from its anti-HIV activity, and that's actually being tested right now in a clinical trial which is including people who are HIV positive and HIV negative to try and dissect out is there anything about nelfinavir that has to do with the HIV infection. And so we'll see what happens. But I wouldn't add nelfinavir empirically to anybody's treatment right now. And I know that there used to be people who would switch somebody to a PI regimen when their case was progressing. I think there's no data to support that. I know that there are recommendations, let's say for people who are diagnosed simultaneously with TB and HIV, to start the TB treatment and delay starting ART. This is not the recommendation for KS particularly for advanced KS, and most people would start chemotherapy and ART at the same time. One thing I would stress though is that if you anticipate the need for systemic KS treatment in your future, that it is always good to have your patient be seen by an oncologist early on and coordinate treatment so that you don't run into potential drug-drug interactions and overlapping toxicities. And I think it's always good even if you don't anticipate an immediate need for KS treatment to get the patient at least connected with an oncologist or somebody who has some experience with treating KS.

[00:36:00] Treatment modalities. There are topical, intralesional treatments, excisions. I think these are primarily for cosmetic use. I don't think that they address the big problem but they're fine if somebody has a particularly difficult lesion. Radiation also is fine for locally bulky disease when you don't really need to give systemic therapy, but I would say that most people with advanced KS probably would benefit from systemic chemotherapy. But there were also a whole bunch of investigational therapies that are under evaluation, and I think that having patients referred to places where such investigations are going on can offer them access to some very promising treatments.

[00:37:06] I'm not going to go through all of this but there are recent National Comprehensive Cancer Network guidelines that have been developed for AIDS-related KS and they are divided into limited cutaneous KS depending upon whether it's symptomatic or cosmetically unacceptable or asymptomatic. And they have these diagrams as to what you do next. And certainly if people have cosmetically unacceptable lesions and they're distressed by them, I think that that's an important indication for therapy because it's a major quality of life issue. For people who are asymptomatic and have limited disease, they can be started on ART and be observed and if they don't respond or become symptomatic they can get treatment later. For people with more advanced disease, I think those are the people that really need to get to an oncologist quickly and either have them put on systemic therapy or evaluated for a clinical trial.

[00:38:32] And you know there are a number of factors that influence the selection of chemotherapy, which include both the intrinsic anti-tumor activity of the chemotherapy agents, their effects on quality of life. I mean you want to minimize the negative effects of chemotherapy on quality of life and also anything that might negatively influence somebody's adherence to their ART. And so you don't want things that are going to cause a lot of nausea, vomiting, etc. but fortunately there are. I think that in the past the potential drug-drug interactions that are important, but I think with modern ART regimens that's less of a problem and I think that's a good thing. Ease of administration, I think patient acceptance is very important and that's why a lot of the new investigational therapies which are oral are very exciting because I think people will find it much more acceptable to be treated. Cost probably needs to be considered, it certainly is an issue in resource constrained settings, as is availability of drugs.

[00:40:06] So in high resource settings, the first line chemotherapy is still liposomal doxorubicin, paclitaxel to some extent. Liposomal doxorubicin probably cost ten times as much as paclitaxel, maybe more. I just got a recent quote for a 50 milligram vial, which is what you need probably for one treatment, of slightly under four thousand dollars. But there are second line alternatives if those don't work, which I've listed here.

[00:40:40] In lower resource settings, liposomal anthracyclines are rarely available and far too expensive. And they have limited resources for administration of IV chemotherapy and so people have mostly relied on combinations like bleomycin/vincristine, sometimes with non-liposomal doxorubicin. And that sort of led us to do a study that the AIDS Malignancy Consortium did with the ACTG, mostly in Africa where we looked at combinations of ART with paclitaxel with B.V. and etoposide. And basically the take home message here is that paclitaxel was the winner by far and was far better than the standard B.V. regimen, and a lot better than oral etoposide. So interesting.

[00:41:39] There are a whole bunch of investigational clinical trial approaches that are being studied right now and have shown promise including tyrosine kinase signalling inhibitors, immunomodulatory imide drugs, thalidomide and son and daughter of thalidomide that are really exciting, and a variety of other drugs. All of which have shown some anti-KS activity but none are approved and are still actively being investigated which is why it's nice to refer patients to clinical trials.

[00:42:22] Two words on KS-IRIS and then I'll be done. KS immune reconstitution inflammatory syndrome refers to the abrupt worsening of KS often with a prominent inflammatory component and/or increase in edema, accompanied by evidence of HIV suppression and/or improved immunocompetence after ART initiation. Problem is there's no standardized case definition and that's why the reported incidence is all over the place. But most current definitions include these events occurring within the first 12 weeks of starting ART with a certain minimum decrease in viral load and/or increase in CD4 count. But they don't really specify the inflammatory characteristics of KS progression and some of this I really believe it's just the natural history of the disease. But it's certainly more common in low resource settings. It's more common in people with more advanced KS and high RNA levels at baseline and it's much less common in people who are receiving concomitant chemotherapy with their ART. It's associated with poor long term treatment outcomes and the management is not well established. It may regress with continued ART without further intervention, but I would warn you that rapid progression with visceral involvement and a lot of symptoms can be life-threatening and the addition of chemotherapy has been associated with overall improved survival. And warning, corticosteroids may make the KS-IRIS worse and are not recommended, which is very different from all other IRIS events so I think you should know that. So I'm done now. I have a list of resources that I'm happy to share with people if that's going to be on your website because various guidelines and that nice article on how sex and age affect immune responses. And I will do my shameless plug for the Malignancy Consortium and we are a NCI supported clinical trials group, we've been around for a long time. There's a website, we have sites now around the world and I've been sort of shepherding the African and Latin American sites over the past several years. And there are four sites in New York. And so you should look at the website. And if you have patients, you should think about referring them. Thanks.

[End]