

WEBVTT

NOTE duration:"00:22:50.9250000"

NOTE language:en-us

NOTE Confidence: 0.466538786888123

00:00:04.160 --> 00:00:06.100 Yeah.

NOTE Confidence: 0.871379911899567

00:00:10.460 --> 00:00:33.240 Alright hello, we can get started. We have a forum and everybody's already still quiet so I come to the first grand rounds of the year. It's my pleasure to introduce the speakers today, so right now. Lim will be our first speaker. She's assistant professor of ophthalmology and visual science and she's a director of the smilow cancer hospitals ocular oncology program.

NOTE Confidence: 0.888274133205414

00:00:33.780 --> 00:01:02.900 She received her MD from the State University of New York Downstate Medical School and also trained under Carol Shields and will die. Husband Philadelphia, Philadelphia and she completed 2 fellowships when an ocular plastic surgery and in ocular oncology and she is the director of the archaeology program and sees patients was common and rare malignancies of the eyes and will speak to us today about ophthalmic immune related adverse events, so by contacting him.

NOTE Confidence: 0.923393607139587

00:01:07.620 --> 00:01:26.650 Thank you so much for the kind introduction, my name is Ronald Lemon. Today I'll talk to you about the ophthalmic immune related adverse events and share our experience, I have no financial disclosures, although a few of my coauthors are consultants.

NOTE Confidence: 0.932679831981659

00:01:27.170 --> 00:01:57.720 Today we'll discuss the mechanism. The mechanism of action of checkpoint inhibitors and detail a few cases. We can all agree that the relationship between the immune system and cancer is complex with the realization that cancer finds ways to escape detection by the immune system trends in treatment have focused on methods to interrupt cancer tolerance and reactivate the immune system against tumor antigens.

NOTE Confidence: 0.935592234134674

00:01:58.480 --> 00:02:13.820 Target recognition by T cells is a 2 step process. The 1st is an interaction between the T cell receptor and that MHC complex or major histocompatibility complex displayed by tumor cells or antigen presenting cells.

NOTE Confidence: 0.91476845741272

00:02:14.430 --> 00:02:24.750 The 2nd event is a Co regulatory signal that determines whether the T cell becomes activated or down regulated and the 2nd event will be illustrated here.

NOTE Confidence: 0.902710139751434

00:02:25.520 --> 00:02:40.690 You can think of CTLA for a receptor on the surface of activated T cells as one of the brakes of the immune system because it functions to down regulate the T cells to help prevent autoimmunity an inflammation.

NOTE Confidence: 0.871075332164764

00:02:42.240 --> 00:02:59.570 When the interaction of B7 and CTL E4 takes place it's like stepping on the brakes inhibiting the TSLT cells also expressed another receptor called CD 28, which is Constitutively expressed and serves an opposing function to CTL A4.

NOTE Confidence: 0.896340906620026

00:03:01.410 --> 00:03:13.090 Triggering T cell activation when CD 28 binds to B7. It's like stepping on the gas pedal and the T cell remains active to go kill cancer.

NOTE Confidence: 0.866514205932617

00:03:14.060 --> 00:03:30.970 CTL A4 competes with CD28 for B7 binding, but CTL A4 has a much higher affinity to kill cancer cells. The cytotoxic T cell should remain active so how do we keep the T cell active?

NOTE Confidence: 0.907432973384857

00:03:31.630 --> 00:04:02.420 By preventing the binding of CtlA 4. NB 7 altogether in 2011. the FDA approved it belimo map a monoclonal antibody for treatment of advanced metastatic cutaneous Melanoma. It's been 9 years since approval of it be limam anti. PD one and P. DL1 way later approved by the FDA based on successful. Large, randomized, controlled clinical trials now immunotherapy is considered one of the pillars of cancer therapy.

NOTE Confidence: 0.931307196617126

00:04:03.210 --> 00:04:10.240 Prior to the introduction of immunotherapy the 10 year survival rate for metastatic Melanoma was less than 10%.

NOTE Confidence: 0.921700954437256

00:04:11.030 --> 00:04:38.730 Survival rates for Advanced Stage 3 or 4 unresectable metastatic cutaneous Melanoma are even better when combination therapy is employed. The five year data was recently published demonstrating that the overall survival of advanced metastatic Melanoma was 52% in the combination group of Nivolumab and if you have Nivolumab there are currently 7 FDA approved immune checkpoint inhibitors.

NOTE Confidence: 0.925406873226166

00:04:40.020 --> 00:05:03.180 And the indication for use of immune checkpoint inhibitors are continually growing to not only involve unresectable advanced metastatic cutaneous Melanoma, but squamous cell carcinoma of the head and neck. Merkel cell carcinoma of paddle cellular carcinoma renal cell carcinoma cervical cancer and the list continues.

NOTE Confidence: 0.927247226238251

00:05:04.290 --> 00:05:24.490 We recently published our experience with immunotherapy and the atomic immune related adverse events because the use of immunotherapy continues to grow the adverse events will expand and it's important to be mindful that there are ophthalmic immune related adverse events.

NOTE Confidence: 0.871325969696045

00:05:26.260 --> 00:05:46.560 We reviewed the charts of almost 1500 patients and 15 of them or 1% developed in al thalamic immune related adverse event. Most patients were treated with combination therapy. It belima map and Nuvola Mab, the most common ophthalmic immune related adverse event was uveitis.

NOTE Confidence: 0.911819398403168

00:05:47.390 --> 00:06:06.040 Interesting Lee all patients who had ophthalmic immune related adverse events also had concomitant systemic immune related adverse events such as colitis dermatitis arthritis. Hepatitis Hypophysitis and the list goes on.

NOTE Confidence: 0.919713139533997

00:06:06.780 --> 00:06:09.660 Now let's discuss a few unique cases.

NOTE Confidence: 0.915998518466949

00:06:10.840 --> 00:06:29.700 This is a 75 year old man with a history of left foot Melanoma, who developed widespread metastasis. He was treated with two cycles of hippie anevo and complained of seeing distorted images anterior segment examination showed an irregular pupil.

NOTE Confidence: 0.90445864200592

00:06:30.440 --> 00:06:46.210 And you can see a little bit of scarring and this is what we call posterior synechiae where the iris is adherent to the anterior lens capsule. This patient was managed with Topical Corticosteroids Topical Prednisone.

NOTE Confidence: 0.905015170574188

00:06:47.070 --> 00:06:53.540 And after one month you see release of the posterior sneaky and he now has around pupil.

NOTE Confidence: 0.88644403219223

00:06:54.260 --> 00:07:11.510 So I mentioned that uveitis was the most common ophthalmic immune related adverse event and I'd like to take a minute to just talk about what uveitis is it simply inflammation of the UV A and the uvea consists of the iris. The ciliary body and the choroid.

NOTE Confidence: 0.906818687915802

00:07:12.220 --> 00:07:24.940 Uveitis can manifest in many different ways patients can present with debris on the back of the Corneal. The Corneal endothelium and we call this keratic precipitates.

NOTE Confidence: 0.919482886791229

00:07:25.830 --> 00:07:37.560 Our patients can have cells in the anterior chamber. Usually, it should be white and quiet. Usually, it should be quiet. But when cells are present. We know there's some underlying inflammation.

NOTE Confidence: 0.833606064319611

00:07:38.360 --> 00:07:56.570 Or have posterior synechiae and that's anterior uveitis, but UV I just cannot affect the back of the eye. More and we call that posterior the ritis or core roditis and you can see inflammation affecting the choroid and sometimes the retinal vascular cherr.

NOTE Confidence: 0.928303778171539

00:07:57.450 --> 00:08:04.630 Here's another case a 57 year old woman with a history of choroidal Melanoma and you see a pigmented.

NOTE Confidence: 0.879042625427246

00:08:05.500 --> 00:08:35.570 At lesion affecting the choroid, she was treated with black breakey therapy and you see very nice regression of the pigmented lesion, however. Later, she developed liver metastasis. She was treated with hippie. Lumaban nuvola mab and receive just one cycle. She then developed a rash in 2 weeks later, she presented with left upper eyelid ptosis and diplopia a work up was performed and she had elevated CK levels.

NOTE Confidence: 0.900069117546082

00:08:35.570 --> 00:09:08.770 Myositis elevated proponents myocarditis an she had acetylcholine. Receptor antibodies and she was diagnosed with myasthenia gravis myositis and myocarditis. She was hospitalised and treated with intravenous corticosteroids immunoglobulins empire, it'll stick mean and she had complete resolution of her ophthalmic symptoms at 6 months. However, she did have progression of disease in later received radio embolization for worsening liver metastasis.

NOTE Confidence: 0.919232606887817

00:09:09.620 --> 00:09:42.050 This is a case report an I thought this was interesting because it's very similar to our patient an the authors described in 80 year old man with a history of cutaneous Melanoma metastatic to lymph nodes

who developed fatigue shortness of breath, Weakness After 2 weeks 2 weeks after starting nuvola. Mab the authors obtained baseline acetylcholine. Receptor antibody level in this patient had low levels of acetylcholine receptor antibodies.

NOTE Confidence: 0.901727259159088

00:09:42.050 --> 00:09:49.440 However, after treatment with nuvola mab, we can see a spike in the acetylcholine receptor antibodies in it.

NOTE Confidence: 0.911805033683777

00:09:51.210 --> 00:10:01.070 And after immunoglobulin you see the acetylcholine receptor antibody level decrease in the same was true for the CK levels.

NOTE Confidence: 0.923823058605194

00:10:02.230 --> 00:10:34.720 The patient had a skeletal muscle biopsy T cell receptor analysis using next generation sequencing identified infiltration of Clonally expanded T cell populations in skeletal muscle after treatment with nuvola mab and these high numbers of T cells found in the skeletal muscle biopsy suggest a strong T cell immune response against muscular skeletal, muscular cells. Here's another case a 43 year old woman with a history of metastatic cutaneous Melanoma.

NOTE Confidence: 0.848947167396545

00:10:34.720 --> 00:10:37.470 Received 3 cycles of it being evil.

NOTE Confidence: 0.924616575241089

00:10:38.190 --> 00:10:40.030 She complained of blurry vision.

NOTE Confidence: 0.923079252243042

00:10:40.540 --> 00:11:02.200 Fundoscopic examination showed choroiditis and you can see the areas of inflammation affecting the core ride. She was treated with systemic corticosteroids with improvement in her visual acuity and she achieved 20/20 vision in both eyes. An she had a complete response to treatment and is now followed every six months.

NOTE Confidence: 0.910990357398987

00:11:03.790 --> 00:11:32.040 Here's another case a 54 year old women with a history of Angel Melanoma with brain metastasis who is treated with combination therapy who also complained blurry vision, Visual Acuity was 20/70. In both eyes in the photos at the Top. This is called optical coherence tomography and this is our version of a see T scan of the eye and it essentially scans. The retinal layers and you can see fluid deep to the retina.

NOTE Confidence: 0.923568367958069

00:11:33.980 --> 00:11:44.670 This patient was treated with systemic corticosteroids with improvement in her visual acuity to 20/25 in both eyes. However, she had progression of her metastatic disease and is now deceased.

NOTE Confidence: 0.918784558773041

00:11:47.600 --> 00:12:07.720 This is another interesting case of a 61 year old woman with a history of metastatic cutaneous Melanoma who complained of blurry vision, especially of the left eye. Funduscopic examination showed bilateral disk adima you can see swelling of the optic nerves visual field testing showed severe constriction.

NOTE Confidence: 0.918518900871277

00:12:08.250 --> 00:12:30.900 Everything that you see outlined in black is an area of her visual field that she could not see so this patient was treated with systemic corticosteroids. However, there was no improvement in her best corrected visual. Acuity immunotherapy was stopped because the patient also had lowritis and floral Fusion, she had progression of disease, Ann is now deceased.

NOTE Confidence: 0.937171816825867

00:12:32.850 --> 00:12:46.050 This is another case of a 54 year old man with a history of metastatic cutaneous Melanoma who received one cycle of combination therapy and complained of progressive visual loss.

NOTE Confidence: 0.901277303695679

00:12:46.950 --> 00:13:03.900 Here you can see pockets of subretinal fluid and you see yellow material. It's forming a little bit of a meniscus. We call this patelliform material. So you see 1 central large pocket of fluid an multiple satellite pockets of fluid.

NOTE Confidence: 0.885353088378906

00:13:04.680 --> 00:13:18.090 This patient was diagnosed with acute oxidative polymorphous the Teleform Maculopathy, an the subretinal fluid was confirmed an optical coherence tomography.

NOTE Confidence: 0.87963479757309

00:13:21.190 --> 00:13:38.170 This is a report of a patient very similar to the one I just described but the patient developed acute exit dative polymorphism. Patelliform maculopathy after me. Rafa nib and pembrolizumab with similar clinical features, however, not as dramatic as our patient.

NOTE Confidence: 0.8952676653862

00:13:41.290 --> 00:13:53.330 A 79 year old women with metastatic cutaneous Melanoma complained of Photopsia. We're seeing flashes of light just after one cycle of a belimo mab and Nuvola Mab.

NOTE Confidence: 0.905980467796326

00:13:53.910 --> 00:14:11.060 Her funduscopic examination was completely normal there was no deviation from baseline. No evidence of chorditis know sub-

retinal fluid. No evidence of uveitis so she went on to receive another cycle of combination therapy. Then she developed transaminitis.

NOTE Confidence: 0.888502717018127

00:14:11.610 --> 00:14:22.320 Hypophysitis and Dermatitis as well as worsening of her ophthalmic symptoms, worsening photopsia and she had difficulty seeing at night nyctalopia.

NOTE Confidence: 0.894903242588043

00:14:23.970 --> 00:14:40.220 Because of her trans amanita sin hypopituitarism. She was treated with intravenous solu medrol with without resolution of her ophthalmic symptoms. At this point Melanoma associated retinopathy was high on the differential.

NOTE Confidence: 0.909739911556244

00:14:40.770 --> 00:14:58.770 So, an electroretinogram was performed and if you look to the left, you can see what a normal. I will look like the B wave has that very high amplitude indicated by the arrow. But in our patients right and left eye. She had a severely attenuated be wave.

NOTE Confidence: 0.906665027141571

00:14:59.520 --> 00:15:03.080 Which shows bipolar loss of bipolar cell function?

NOTE Confidence: 0.908144533634186

00:15:05.390 --> 00:15:13.440 Anti retinal antibodies were also obtained an were positive in our patient and she was diagnosed with Melanoma associated retinopathy.

NOTE Confidence: 0.877081751823425

00:15:14.340 --> 00:15:25.130 So how do we treat these conditions if mild and if uveitis is just anterior we can treat these patients with topical Prednisolone?

NOTE Confidence: 0.894618332386017

00:15:25.740 --> 00:15:59.430 In more advanced cases, we can administer steroids via injection. Perry ocular injections or intravitreal injections. An tored the right. You can see a Depot. The white material is kenna log and there's a Depot in his superior, temporal fornix here. Sometimes patients are managed with Prednisone others. Other times patients have to undergo treatment with corticosteroids or immunoglobulins an rarely do we use plasma pheresis?

NOTE Confidence: 0.924751102924347

00:16:02.470 --> 00:16:11.980 In summary immune checkpoint inhibitors are powerful agents, which allow cytotoxic T cells to remain active in attack cancer cells.

NOTE Confidence: 0.905138254165649

00:16:12.610 --> 00:16:16.080 The atomic immune related adverse events are real.

NOTE Confidence: 0.877071082592011

00:16:16.650 --> 00:16:28.660 The incidents is about 1% an can occur within weeks to months of therapy and can affect various parts of the eye and orbit.

NOTE Confidence: 0.880967438220978

00:16:30.740 --> 00:16:39.630 Patient can patients can have dry eye conjunctivitis keratitis uveitis serious retinal detachment optic neuritis.

NOTE Confidence: 0.899789810180664

00:16:41.450 --> 00:16:46.290 Autoimmune Retinopathy Choroiditis Myasthenia Gravis.

NOTE Confidence: 0.833107829093933

00:16:47.050 --> 00:16:51.190 An myositis so when these patients have dry eye.

NOTE Confidence: 0.928202211856842

00:16:51.750 --> 00:16:55.040 These can be managed with Topical Lubrication.

NOTE Confidence: 0.907674312591553

00:16:57.660 --> 00:17:16.220 Patients can present with conjunctivitis where you see redness of the conjunctiva and these are mild symptoms and can be managed with eyedrops. However, keratitis can be more visually debilitating in cause blurry vision. We actually had a patient who had a corneal perforation.

NOTE Confidence: 0.871054887771606

00:17:16.870 --> 00:17:23.640 Where the cornea actually opened and the intra ocular contents? Can then be extruded if the keratitis is severe?

NOTE Confidence: 0.84162974357605

00:17:25.130 --> 00:17:31.280 UV ritis we talked about posterior sneaky a we talked about anterior chamber cell.

NOTE Confidence: 0.885454595088959

00:17:33.320 --> 00:17:38.200 Serious retinal detachment swear there's fluid underneath the retina.

NOTE Confidence: 0.910981774330139

00:17:40.180 --> 00:17:47.750 We talked about optic neuritis or optic disc edema and loss severe loss of visual field function.

NOTE Confidence: 0.91027820110321



00:17:49.530 --> 00:17:56.630 Autoimmune Retinopathy again, these patients can have a normal I exam normal fundoscopic findings.

NOTE Confidence: 0.868023157119751

00:17:58.140 --> 00:18:06.110 ERG or electroretinogram will show an attenuated be wave, which show which signifies loss of bipolar cells.

NOTE Confidence: 0.899324834346771

00:18:07.340 --> 00:18:29.810 And we discussed Cora Dietis, where I remember the core right is part of the UV and so this is a type of posterior uveitis. Our patients who had a uveal Melanoma developed my senior gravis after just one cycle of combination therapy and she presented with left upper eyelid ptosis and double vision.

NOTE Confidence: 0.892078995704651

00:18:31.150 --> 00:18:40.490 And here's an example of what myositis looks like of the extraocular muscles. You see the medial rectus enlarged in axial in Corona views.

NOTE Confidence: 0.861285388469696

00:18:41.560 --> 00:18:45.690 Impatience can present with cranial nerve palsies as well.

NOTE Confidence: 0.937500178813934

00:18:47.300 --> 00:18:48.030 Thank you.

NOTE Confidence: 0.806050300598145

00:18:56.940 --> 00:18:59.550 Any questions with temple questions.

NOTE Confidence: 0.555100381374359

00:19:02.000 --> 00:19:03.080 So I have.

NOTE Confidence: 0.396336793899536

00:19:04.690 --> 00:19:07.450 Notice.

NOTE Confidence: 0.67575991153717

00:19:09.410 --> 00:19:10.280 How often do you?

NOTE Confidence: 0.775518774986267

00:19:12.470 --> 00:19:22.720 The perspective in comparison to the junior right? That's a great great question the question was.

NOTE Confidence: 0.932260632514954

00:19:23.220 --> 00:19:31.570 How does the use of immune checkpoint inhibitors differ for uveal Melanoma when compared to cutaneous Melanoma?

NOTE Confidence: 0.928935885429382

00:19:32.680 --> 00:19:51.010 Unfortunately, when uveal Melanoma metastasizes there is no great treatment. So we employ the use of immune checkpoint inhibitors. However, about 10 to 15% of patients will respond does not have a great overall survival that cutaneous Melanoma has.

NOTE Confidence: 0.907409310340881

00:19:51.940 --> 00:20:03.850 An in that patient, she actually still had progression of disease, she only received one cycle of combination therapy. But she had to undergo radio embolization.

NOTE Confidence: 0.673841238021851

00:20:05.510 --> 00:20:06.940 To be more questions.

NOTE Confidence: 0.924761235713959

00:20:07.670 --> 00:20:36.200 I've a question so do you see a correlation between the types of symptoms. You see in the eyes and their systemic side effects on in our study. We did not see that now. Some people hypothesize that if patients develop immune related adverse events that these patients are more likely to respond to immunotherapy and more likely to have an improvement in overall survival. But when looking at the ophthalmic immune related adverse event there was no correlation.

NOTE Confidence: 0.871134340763092

00:20:39.010 --> 00:20:57.360 As just wondering about the etiology of the optic neuritis. You don't biopsy anything there. So you're just seeing the papilledema or the disc edema right so do you know what's going on? Is it art easels infiltrating the optic nerve is an antibody mediated or nobody knows or not you know it's immune related I think that's what I meant.

NOTE Confidence: 0.921259224414825

00:20:57.930 --> 00:21:12.520 Well, in that we have to put the whole picture together in this setting of using immune checkpoint inhibitors in again. These patients when they present with a thaumic immune related adverse events. They also have other types of inflammation in the rest of the body so.

NOTE Confidence: 0.901526629924774

00:21:13.170 --> 00:21:20.360 Yeah, we can assume that this is all related to immunotherapy, but no one is.

NOTE Confidence: 0.901462614536285

00:21:21.880 --> 00:21:40.350 So, in that case, she did receive corticosteroids. However, there was no improvement in the vision vision. And that was a severe case. She had a severe constriction in her visual fields. So it's very difficult to have that normalized.

NOTE Confidence: 0.816836059093475

00:21:42.740 --> 00:21:47.400 Do you have any additional questions in the middle? I'm not sure I need to make it there?

NOTE Confidence: 0.634556651115417

00:21:48.050 --> 00:21:51.630 Hello.

NOTE Confidence: 0.369457751512527

00:21:57.100 --> 00:22:01.470 And.

NOTE Confidence: 0.905599892139435

00:22:03.780 --> 00:22:34.970 So the question was how long does it take between the diagnosis of Melanoma and the actual symptoms So what we looked at was not necessarily the time of diagnosis of Melanoma, but more when immune checkpoint inhibitors were started and from the time when the immune checkpoint inhibitors are started to the time of ophthalmic immune related adverse events.

NOTE Confidence: 0.924295842647552

00:22:34.970 --> 00:22:37.760 It varies from weeks to several months.

NOTE Confidence: 0.838917672634125

00:22:42.080 --> 00:22:43.210 More questions.

NOTE Confidence: 0.868698418140411

00:22:45.390 --> 00:22:48.420 No OK OK. Thank you very much.

NOTE Confidence: 0.495835602283478

00:22:48.920 --> 00:22:49.870 Right.