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Breast Implant Associated - Anaplastic Large Cell Lymphoma (BIA- ALCL)

Dr Rocco: Thank you, and good afternoon, or good evening, or good morning to all of you. And thank you to e-ESO for offering me the opportunity of discussing with you a very relevant and debated issue as the breast implant associated anaplastic large cell lymphoma is. And thank you to Dr Astrid Pavlovsky to kindly offer to be a discussant for this session. Well, breast implant associated anaplastic large cell lymphoma, BIA-ALCL, for the sake of brevity, I will address to this disease as ALCL during this session. Well, ALCL, BIA-ALCL is an uncommon neoplasia occurring in women with either cosmetic or reconstructive breast implants with an estimated risk of 1-3 per 1-million persons a year with breast implants. And the first case of a ALCL was reported in 1997, and since that time a growing body of literature on the potential association between breast implants and anaplastic large cell lymphoma has been published. However, the real incidence and risk for developing ALCL is difficult to estimate as the prevalence of women with breast implants worldwide is unknown. In 2011, the Food and Drug Administration advised the scientific community about the potential association between breast implants and the development of ALCL. And as of January 2020, the Food and Drug Administration received a total of 733 medical device reports for ALCL associated to breast implants, including 36 deaths globally. And the currently estimated incidences of BIA-ALCL in the United States is 2.3 per 1-million persons a year with breast implants. This incidence has been calculated in 2017. In Europe, the European Taskforce on BIA-ALCL, composed of authorities, competent authorities for this received 398 BIA-ALCL reports of which 345, that is around 90%, were confirmed BIA-ALCL cases from various European countries. Numbers have grown in the last years with a reported incidence in Italy, in 2018, of 2.8 per 100,000 person a year, that is an incidence 10-year higher than previously reported. I remember to all of you that you can use the Q&A function of Zoom at any time during my presentation to send your questions and comments, and we could also try to answer to your

questions during my presentation. I don't know, Astrid, if there are some questions now at the moment?

Dr Pavlovsky: No, thank you Nicola, no questions so far.

Dr Rocco: Okay, so I will go ahead with the presentation. So, what is BIA-ALCL? Well, the World Health Organisation, in 2016, classified breast implant associated anaplastic large cell lymphoma as a new form of lymphoma associated to breast implants. And the NCCN established some evidence-based consensus guidelines for the diagnosis and treatment of this disease. And these guidelines developed by the NCCN were recognised by the FDA, and many international plastic surgery societies to help physicians understanding this disease and providing reliable diagnosis and treatment. This is an overview of these guidelines, but we will go through them in the next slides. Obviously, a multidisciplinary team approach is essential for the management of BIA-ALCL. This disease is generally indolent and localised, with an excellent prognosis when patient receive surgical excision of disease. Anyway, it remains unclear whether a timely diagnosis can mitigate an invasive disease, or whether there is a biological variability of the tumour, and this could affect prognosis. Anyway, advanced disease may require adjuvant treatment, such as chemotherapeutic agents, radiotherapy, and also stem cell transplant, depending on pathology, stage of disease, and disease recurrence. But what is the Etiopathogenesis of BIA-ALCL? Well, several assumptions have been proposed, but the mechanisms that are behind the aetiology and pathogenesis of BIA-ALCL are not well understood yet. There are several hypotheses that include genetic drivers, and chronic inflammation. Chronic inflammation could derive from bacterial contamination, or also, shell shedding of particulates from the shell of the implant, or shell surface characteristics that could lead to friction, or also, implant-associated reactive compounds. Anyway, several studies have been also conducted to investigate the potential association between ALCL and textured implants. And textured implants seem to be able to promote a chronic inflammation as a potential etiological factor, even though, some cases of ALCL have been also described in patients with smooth implants, even though very few cases, but there are some cases described and reported to the FDA. Well, so, chronic, bacterial, antigen stimulation could be one of the possible etiopathological pathways towards the development of BIA-ALCL. And we know that chronic inflammation and bacteria could promote lymphoma development as demonstrated in Helicobacter pylori associated primary gastric lymphoma. There is also a genetic predisposition. Some studies identified the presence of some somatic mutation, mainly in genes of the JAK/STAT signalling pathway, or also the TP53, and DNMT3A, and also, some HLA polymorphisms can

confer an increased risk for the development of BIA-ALCLs, as in other form of lymphoma. Also, an increased prevalence of BRCA mutation, BRCA 1 and BRCA 2 mutation have been described in patients with anaplastic large cell lymphoma of the breast. So, I remember you again to use the Q&A button to send your questions and comments. Are there some questions, Astrid?

Dr Pavlovsky: No, we'll just leave the questions for the end, so we can listen to your whole presentation, thank you.

Dr Rocco: Okay, perfect, so, I will go direct to the end of presentation, then, we will have our discussion. What is the clinical presentation, and how to perform a correct diagnosis of breast implant associated ALCL? Well, the most common presentation of BIA-ALCL is a large, spontaneous periprosthetic fluid collection that is called late seroma, occurring at least one year, and on average, 7-10 years following cosmetic or reconstructive implantation with breast implant. In some cases, in addition to delayed seromas, 8-24% of patients will present an associated palpable mass, and 4-12% could also show a lymphadenopathy. There are also few cases, less than 5%, in which there are systemic symptoms, including skin rashes, fevers, and capsular contracture. Anyway, patients with large fluid collection may have fluid levels around an implant, the breast implants, and they may be misdiagnosed with an implant rupture. Anyway, we must have in our mind that as a general rule implant ruptures do not increase the overall volume of a breast, that occur in case of a late seroma. And we also think that other common aetiologies for a delayed seroma could be infections, or also, a recent trauma to the chest wall that should be investigated and excluded. Anyway, we must remember, then, every implant will have a minimal amount of surrounding fluid, around 5-10 ml, and this finding in asymptomatic patients does not require any biopsy or any further investigation. However, the initial workup for an enlarged breast should include an ultrasonographic evaluation for the fluid collection, for any breast mass, or any enlarged regional lymph node. The most common lymph node involvement is in the axillary level, but also, internal mammary lymph nodes could be involved, as supraclavicular lymph nodes. Involvement of non-regional lymph nodes is very, very uncommon. When US is equivocal, so, when the ultrasonography is equivocal, MRI is recommended for further characterization of disease, and then, ultrasound guided fine needle aspiration is the optimal method to sample a periprosthetic fluid collection. As much fluid as possible should be collected, a minimum of 50 ml is recommended to aid the diagnosis of disease and also, all suspicious masses require tissue biopsy, and thorough evaluation. Remember that all specimens should be sent for cell morphology by cytology, CD30 immunohistochemistry, and flow cytometry for the evaluation, the quantification,

and the characterization of T-cells within the specimens. Remember then CD30 immunohistochemistry is fundamental, but not pathognomonic of this disease. Because CD30 expression is nonspecific, and CD 30 can be expressed on benign inflammatory cells as well. Moreover, rare CD30 positive lymphocytes with normal morphology is considered a normal finding and does not require any further investigation. So, the diagnosis of BIA-ALCL requires a careful clinico-pathological correlation, and it is extremely important to exclude other malignancies or other benign processes that may mimic BIA-ALCL. Sometimes, additional biomarkers may be required to establish the diagnosis, and exclude other malignancies. Most of all, anaplastic lymphoma kinase, ALK, because remember that BIA-ALCL is always ALK negative. Anyway, other systemic and cutaneous forms of ALCL could be ALK negative, so, this finding alone does not establish a diagnosis of BIA-ALCL. Anyway, hematopathology consultation at a tertiary cancer centre is encouraged to establish or exclude a diagnosis of BIA-ALCL. So, I remember again to use the Q&A box and button to send your questions and comments, and we will reply to all your answers at the end of the session. So, what is the pre-operative workup in confirmed ALCL cases? So, I remember again that we have the need of a multidisciplinary team approach to have a diagnosis of this disease. So, oncologists, pathologists, surgical oncologists, and plastic surgeons will have to work together towards a diagnosis. So, we can start from a complete blood count with differential, comprehensive metabolic panel, lactate dehydrogenase, and also, in rare cases, also a bone marrow biopsy, when high suspicion of a systemic ALCL. Patients with aggressive local invasions or lymph node metastasis, not for every patient with an early-stage diagnosis. And also, pre-operative PET or CT scan could be useful to demonstrate associated capsular masses you can see here in this figure, this image, and also, to demonstrate chest wall involvement. This could be a very useful roadmap for surgical excision. What is the classification? We know that non-Hodgkin lymphomas are usually staged with the Lugano Modification of the Ann Arbour Staging System. And that IE disease is usually limited to a single extra nodal site, that could be breast or implant capsule, and IIE are diffuse to extra nodal disease with spread to local lymph nodes. Anyway, this classification does not account for the capsular invasion, or capsule penetration, so, a TNM, solid tumour staging system has been proposed. As you can see in this table, the majority of cases of ALCL from 35-70% are IA stage, that is a T1 stage, so, the disease is confined to an effusion around the implant, or a layer on the luminal side of the capsule. Around 3-11% of cases are IB, according to the TNM classification. That is T2 N0 M0 disease, it is an early capsular infiltration. From 8-13% of this disease is IC, that is T3 N0 M0, that is the presence of cell aggregates, or sheets infiltrating the capsule. From 8-25% is IIA disease, that is T4, that is infiltration beyond the capsule

that is present around the implants. Around 3-5% is IIB disease. That means T1, to T2 or T3, and N1 disease, so, one regional lymph node involved. And then, Stage III, that is from the 3-9% that is T4 and N1 or N2 disease. Remembering that N2 is multiple regional lymph nodes involved. And then Stage IV that is the presence of distant spread, spread to other organs. And only 1-4% of patients have been diagnosed with Stage IV breast implant associated anaplastic large cell lymphoma. Anyway, remember that the overall survival rate is of 94% at three years, and 91% at five years. And that solid tumour TNM staging predicts survival and recurrence more accurately than the Ann Arbour Staging. Anyway, remember that although indolent at early-stage breast implant associated anaplastic large cell lymphoma is a malignancy, and should not be considered benign at any stage. So, what is the best treatment for breast implant associated anaplastic large cell lymphoma? It's surgical treatment with en bloc explanation. What is en bloc explantation? The goal of our surgery should be to remove the implant with the surrounding fibrous capsule and any associated capsule mass. As you can see in this figure, you should remove the capsule together with the implant, without opening the capsule, and together with any associated mass. And complete surgical excision improves overall survival and event-free survival compared with all other therapeutic intervention. Remember also to orientate surgical specimens to allow the anatomic location of disease for the pathologist. There is no role for mastectomy, or sentinel lymph node biopsy, but en bloc explanation is the right surgical treatment for BIA-ALCL. And all attempts should be made to obtain a complete surgical excision, because retained or unresectable disease indicates the need for adjuvant treatments. And also, I would like to remember to all of you that in the case of a unilaterally diagnosed disease, a contralateral prophylactic implant removal with a total capsulectomy and an en bloc explantation is recommended, as there have been several cases of bilateral disease reported worldwide. Anyway, this is a very important message in non-symptomatic patients with textured implants, or implants with any kind of surface, implant removal, with or without total capsulectomy, capsulectomy for the single purpose of prophylaxis of breast implant associated ALCL is not recommended due to the very low incidence of this disease. Anyway, we know that some patients may request removal of the implant and capsule, particularly patients with manufacturer recalled implants, or the reported high-risk breast implants that are textured implants. Anyway, we know that any surgery should follow an informed-consent discussion on the related surgical risks. And remember the patients that the risk of BIA-ALCL may also persist following surgery, even though with a very, very low risk. What about adjuvant treatments? Well, we know that no prospective trials are available to guide the management of patients with disseminated disease of BIA-ALCL, and treatment

paradigms are generally extrapolated from the treatment of primary cutaneous and systemic ALCL. Radiation therapy for involved site, or in case of positive margins, or unresectable disease with chest wall invasions following surgery is request with 24-36 Gray and is suggested for patients with residual disease. Systemic therapy is requested for patients with Stage II-IV, that is TNM IIB-IV, so with nodal involvement or spread with distant metastasis. Anyway, oncologists can consider a standard approach for systemic ALCL following the NCCN guidelines for first-line therapy for a peripheral T-cell lymphoma. That is a combination of an anthracycline-based chemotherapy or a combination with a monoclonal antibody that is brentuximab vedotin, that is directed towards CD30. But I think that Astrid could help us better in going through these kinds of issues. What about disease surveillance? Patients with a complete response with treatments can be monitored every 3-6 months for two years, and then, also as clinically indicated. And also, the use of routine radiographic surveillance is unclear. Anyway, a chest, an abdominal, and pelvic CT scan with contrast, or PET scan could be considered every six months for two years, and then, only as clinically indicated. So, I, again, remember to you to use the Q&A function of Zoom for your questions, and we will answer to the questions later on. So, remember that breast implant associated anaplastic large cell lymphoma is an uncommon, extremely uncommon, T-cell lymphoma occurring in women with breast implants. It's generally indolent and localised disease, with an excellent prognosis when patients receive a complete surgical excision of disease an en bloc explanation of the implant and capsule, and any associated mass. Remember also that the most common presentation of breast implant associated anaplastic large cell lymphoma is a late seroma, that is a large, spontaneous periprosthetic fluid collection occurring at least one year, and from 7-10 years following implantation with a breast implant. The method, the optimal method to sample a periprosthetic fluid collection is an ultrasound guided fine-needle aspiration. And all specimens should be sent for cell morphology by cytology, CD30 immunohistochemistry and flow cytometry for the evaluation, quantification, and characterization of T-cells within the specimen. And although, several assumptions have been proposed for the aetiology and pathogenesis of this disease, the exact mechanisms are not well understood yet. There are several hypotheses, including genetic drivers and chronic inflammation resulting from bacterial contamination, shell shedding of particulates from the envelopes of implants, shell surface characteristics leading to friction, or implant-associated reactive compounds. Anyway, in order to improve our knowledge on this disease, remember that reporting of new cases to the national clinical registries is critically important for any patients with a breast implant. Thank you.

Dr Pavlovsky: Okay, thank you, thank you very much, Dr Rocco, you have gone over all of the very important features on this disease. I think the most important thing is to keep a high level of awareness of the existence of this disease. I want to clarify that I am a specialist, an onco-haematologist, I am not a surgeon. So, I see these patients when they are already diagnosed, so many times I see patients that have gone through different consultations before their diagnosis. So, maybe, the most important thing is to keep a high-level of awareness of the existence. And regarding this comment, I would like to ask you, because most of the patients I have seen and I have read about, are patients that, as you mentioned, present with disease with delayed seromas, meaning many years, as you mentioned, maybe 8 or 10 years after their implant surgery. So, within this group of patients that has seromas, delayed seromas, is it a high proportion that finally end up with this diagnosis, or is it common to see late seromas?

Dr Rocco: Thank you, Astrid, for your comment. And I absolutely agree with you when you underline how the awareness of this disease is extremely important. Awareness of both doctors, of both medical physicians and patients, because we saw that this disease is almost indolent if early diagnosed. So, patients must be aware of this possibility, and must be aware that late seroma could be the first sign of this disease. Anyway, as you asked, late seromas are not only associated, obviously, to breast implant associated anaplastic large cell lymphoma, and they are quite diffuse. And I see late seromas associated to trauma to the breasts, so, there are late seromas. And also, you can have late seromas without an association with anaplastic large cell lymphoma. So, not all late seromas are associated to this disease. There are some kinds of implants that are particularly associated to develop late seromas, and also, double capsules, and I see these in my experience then. But anyway, a correct examination of any fluid collection should be performed in order to exclude this disease. So, even though there are few cases, every late seroma should be thoroughly investigated.

Dr Pavlovsky: Thank you, and also, I want to add, and maybe, listen to your opinion, that there are lots of false negative when we are examining the liquid, the seroma, both in cytology, so it's important to ask for flow cytometry, but even then, there are a proportion of false negatives. So, then again, I think, sometimes, the decision to do the removal of the implant has to be made. So, can you comment on this?

Dr Rocco: Yes, yes, also, my pathologist told me about this, the possibility of false negative, and they asked me to collect as much fluid as possible.

Dr Pavlovsky: Exactly.

Dr Rocco: Yes, this is very, very important to have a big amount of fluid to examinate, anyway, in case of a persistent seroma, also after the evacuation, the complete evacuation, and the persistent formation of late seroma, I suggest to remove the implant and the capsule, even though a diagnosis has not been done, a diagnosis of breast implant associated (-ALCL). Also, I completely agree with you that we must be aware of the possibility of false negatives. So, recurrent late seromas should be investigated, and perhaps, it is a good option to consider the removal of breast implant and breast capsule in recurrent late seromas.

Dr Pavlovsky: And also, regarding diagnosis, we have another question saying that if ALK status is positive on a breast cancer patient with late seroma after breast reconstruction with textured implant. Is this enough to say that breast implant associated anaplastic lymphoma is not the diagnosis?

Dr Rocco: Well, sorry, I didn't catch the beginning of your question, if, if?

Dr Pavlovsky: If ALK status is positive, as you mentioned, all of these patients have ALK negative anaplastic large cell lymphoma. So, this question is regarding what if we find an ALK positive? Is this enough to rule out this diagnosis?

Dr Rocco: According, you can also, from your experience, but anyway, from the literature I see that all breast implant associated anaplastic, large cell lymphoma are ALK negative.

Dr Pavlovsky: Exactly. I think that it will exclude this association. Maybe, the patient has another anaplastic large cell lymphoma, which can be ALK positive, but all of the reported, at least reported up to now, anaplastic large cell lymphoma associated to breast implants are ALK negative.

Dr Rocco: Yeah, yeah, yeah, yeah.

Dr Pavlovsky: So, considering this from a onco-haematological point of view, ALK negative is associated with a worse prognosis. So, for us, when we diagnose anaplastic large cell lymphoma, which are ALK negative, you know, we think about very bad prognosis for these patients. But still, I want to emphasise what you have mentioned many times, that most of these patients, although, they are ALK negative, have a very good prognosis, especially, when they are treated rapidly and correctly with the whole removal of the capsule and the implant.

Dr Rocco: Yes, absolutely.

Dr Pavlovsky: Now, recently we had a patient who had a large mass associated. We're not sure whether it was a late diagnosis, or whether it was the biology, but this patient

had a Stage IV diagnosis with also PET positive images in bone, and had a large mass, which was associated to the capsule. So, the big discussion between surgeons, and onco-haematology department, was whether all of this mass should be removed or not, because it was a big surgery. She had also axillary adenopathy, cervical adenopathies, and this big mass, which was the way she was diagnosed. She was diagnosed because of the mass, the visible mass. So, in these cases, is it also necessary to remove the whole mass, even though this means it's a more complex surgery?

Dr Rocco: Yes, according to the evidence from literature, you should perform the most radical surgery as possible for the breast, for the capsule, and for any associated mass. We will not go to remove any positive lymph nodes, obviously, this is left to the adjuvant therapies, but you should try to perform the removal of all the mass, if feasible, if there is an infiltration of the chest wall, it could be unfeasible. And in that case, also, the opportunity of performing radiotherapy could be considered. I don't know what was your choice in that case?

Dr Pavlovsky: No, well, in this case she had a bone, a metabolic lesion, she had lots of adenopathies, so, she had to go on to chemotherapy. Another important thing regarding this disease is that, as haematologists, when we see anaplastic large cell lymphoma, ALK negative, we also categorise the prognosis, whether they are DUSP22 positive or negative, and these patients are all DUSP22 negative. So, in my mind, and I think that maybe although, we are calling these diseases the same when they are not associated to breast implant, or when they are, they have the same name, I am sure that these have different aetiology, or different biology, mainly due to the prognosis of these patients.

Dr Rocco: Yeah, yeah, yeah, yeah. I totally agree that the prognosis of breast implant associated anaplastic large cell lymphoma is a very good prognosis compared to other lymphomas, so.

Dr Pavlovsky: So, and at the same time, as we are trying to raise the awareness of this disease, we also don't want to provoke too much scare regarding this disease. So, in a patient that has already had implants, are there any specific recommendations, or do they have to have a special follow-up? Would you do any recommendation regarding the existence of this disease?

Dr Rocco: Yes, yes, I, after the more diffuse awareness on this disease, I added to my informed consent for any patient, for both reconstructive and cosmetic surgery, a thorough discussion about this disease, even though, underlining that it is a very rare, rare disease associated to implants. But for patients who already had implants, I recalled everyone I operated in my hospital, and also, many, many colleagues are

doing like this, and asking for performing annual clinical and ultrasonographical controls, because patients who underwent surgery for reconstructive reasons following mastectomy are in follow-up with oncologists, so, they perform periodic controls. But patients undergoing cosmetic augmentations usually forget their controls. So, it must be underlined by every plastic surgeon that patients undergoing cosmetic surgery using breast implants should be aware on the first signs of this disease, and anyway should perform an annual control of their breasts, clinical and with imaging, that could be an ultrasonography before 40 years, and also, mammography that could absolutely be performed also, with the implants after the age of 40. So, I think that patients should be aware of the disease, aware that the disease is not, it is an indolent disease if early diagnosed, and they should be aware that they should perform yearly control, clinical and with imaging.

Dr Pavlovsky: Now, have you been able to, looking at the literature, determine any prognostic factors to try to determine which patients have a higher risk of developing this disease?

Dr Rocco: Only, there are only some genetic drivers, some genetics, some HLA polymorphisms, or also, few studies also found an association between BRCA mutation and lymphoma, and this kind of lymphoma, but there are no particular characteristics of patients that have been found associated. But most of all, there are some characteristics of the implants that have been found associated. So, it's, as I told you, in particular, some studies from New Zealand, and also, from the United States, there is the report by Peter Cordeiro from the Memorial Sloan Kettering Cancer Centre reported a strong association between some kinds of textured implants, so-called macro-textured implants, and the development of breast implant associated anaplastic large cell lymphoma. But we also have to underline how these experiences are not confirmed in other centres, where these strong association has not been found. So, some authors argued that there is also some, there could be some other factors that are not known at the moment, because there are many cases associated to, in some centres, and there are some centres that have never seen a breast implant associated anaplastic large cell lymphoma. This could be also a problem of underdiagnose, but we actually do not have a particular framework of a patient that will more likely develop a breast implant associated anaplastic large cell lymphoma.

Dr Pavlovsky: Now, a frequent question that we face from some patients, patients that have had already this disease, that have had their implant removed, now, do they have a higher risk to develop it again? Would you recommend if they want to have a new implant?

Dr Rocco: This is a very interesting question. We discussed it with the Italian Society of Plastic Surgery, and we advise not to re-implant these patients, even though, there are not, there are not evidence, but perhaps those patients had a higher risk of developing that, will have some genetic mutations, also some genetic characteristics, or other characteristic that we do not actually know, but as they already developed an anaplastic large cell lymphoma associated to implants, we advise not to use again. So, if we remove the implants, if for reconstructive reason, we can consider a flap, autologous tissue, and for cosmetic reason we advise not to use implants anymore, even though there is no evidence about it.

Dr Pavlovsky: Okay. Well, I think, Dr Rocco, we have covered almost all aspects of this disease. We are learning every time because this is a very recent, as you mentioned, this has been included as a provisional entity in the WHO classification in 2016, and now it is a new entity. And we are, I think the whole haematological, and also, the surgeons, we are learning. So, I think many countries have registries on these diseases. I think this helps everyone to learn more about this disease. I think you've mentioned how many patients have been registered in Italy, can you mention about that?

Dr Rocco: 22, yes, yes, there are 22 patients in Italy, and around 348 in Europe. And yes, however, I would like to underline how it's very important, as this night, to have a dialogue between haemato-oncologists and surgeons. Because they learn a lot from you, and I don't know if you can learn from surgeons, but anyway.

Dr Pavlovsky: No, we learned a lot, obviously, yes.

Dr Rocco: Very, very important, because this disease should be treated as every oncological disease in a multidisciplinary approach.

Dr Pavlovsky: Absolutely, absolutely. And also, I want to mention that we have an Argentinian Registry of this disease, and there's also an international registry on T-cell lymphoma, in which we are also including this disease, because it's part of the T-cell classification, so, I think, we also have a task there, so, we can keep on learning. There is no doubt that we... from this disease is the first time that I am in contact with breast surgeons, so, I have also learned a lot from all of you. So, thank you very much. I don't know if you want to add any further comments, but I think we've covered almost everything.

Dr Rocco: Yes, yes, no. Thank you to you for this great discussion. I hope it has been useful for all the participants to this webinar. Thank you.

Dr Pavlovsky: I'm sure, very useful, and thank you very much.

Dr Rocco: Thank you, bye-bye everyone.

Dr Pavlovsky: Bye-bye.