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Clinical case discussion on non-melanoma skin cancers - Part Two

Dr Tagliaferri: Welcome. Welcome to this session of European School of Oncology. This is the second edition on a clinical case discussion on non-melanoma skin cancer. And it is an honour to introduce you also my friends and colleagues as experts in this field, Dr Agata Rembielak, medical oncologist and radiation oncologist, and Alessandro Di Stefani, dermatopathologist and dermatologist. So, we can start and we can move to the first case. And I would like to ask to Francesca Sparano and Eleonora Cioli to start the presentation of the first clinical case. Thank you.

Dr Sparano: Thank you. Good evening, everyone. Today, we present a case of a rare and highly aggressive primary skin cancer that arises in the eccrine sweat glands treated with immunotherapy combination. We have no disclosure to declare. The patient we are talking about was a 28-years-old female with a performance status of zero, according to ECOG scale. She had no comorbidities or ongoing chronic treatment, and she was born in Romania. The patient underwent several biopsies from July to October, 2021 with the diagnosis of Hidroadenocarcinoma. At the PET/CT scan in October, 2021, we found out lesions at right arm, Xyphoid region and right leg, showing a first stage disease. Thanks to the opportunity to perform NGS Foundation One evaluation, we found out a single gene alteration. In particular, the loss of CDKN2A/B that is frequent in adnexal cancer but efficacy data of CDK4/6 inhibition therapy, actually, we don't have. Currently, we don't have any guidelines or a phase III randomised trial, so to decide the different subsequence of the treatment, we found in literature and we only found out some clinical cases or a single-Phase II Basket Trial. So, in October, 2021, our patient started a first-line treatment with Carboplatin and Paclitaxel. But in November, 2021, the disease progressed, and after we have, in December, 2021, the approval of the second-line with Nivolumab off-label, that the patient continued until February, 2022, when we can add also Ipilimumab in compassionate use. During this treatment, the best response is a stable disease that the patient performed in March, 2022. So, in this time, patient underwent also locoregional treatment. First, in November, 2021, when a surgical excision of the right arm lesion was performed. This is because of we wanted to avoid the functional impairment of the right arm. But as you can see in the photo, in December '21, there was a relapse at the scar. And in this site, patient underwent also two times electrochemotherapy and radiotherapy. Radiotherapy was also performed in the lesions, lymph node lesions and electrochemotherapy was performed also in Xyphoid region and left mammary region. In September, 2022, the CT scan showed a progressive disease with a bulk disease. And so, the patient clinical status was worsening. She was a PS 2 according to the ECOG scale, mostly due to pain when moving the arm and she was on treatment with morphine. At this point, we had some options, therapeutic option, Etoposide, or anti-angiogenic drugs, like Sunitinib, Adriamycin or Capecitabine. Our team decided to go for Etoposide, waiting for the approval of Sunitinib, off-label in Italy. Between October and November, 2022, the patient was treated with oral Etoposide. And then, in November, 2022, she started Sunitinib with adverse event oral mucositis and the skin rash, as you can see. But unfortunately, only just after one cycle of Sunitinib, the patient died due to progressive disease and worsening of clinical conditions. We have some questions. Would you have

considered immunotherapy treatment combined with locoregional strategies or chemotherapy? How we can study immunotherapy in rare cancer, giving the difficulty to design large clinical trials and our basket trials are unanswered? And which therapeutic option is the best in your opinion? Also taking into account the NGS assessment, and would you have repeated the NGS at progression if possible? Thank you very much for the opportunity and attention.

Dr Tagliaferri: Thank you very much. Very, very interesting case. And so, may I ask you to move to the question slide? So, we can discuss your proposal regarding the questions, but waiting for the slide, we have the opportunity to have as expert Alessandro Di Stefani. Alessandro is a dermatopathologist. So, I would like to ask him, first some information regarding the diagnosis regarding the hidradenocarcinoma and the differences with squamous-cell carcinoma. And maybe, you can also answer regarding the opportunity to repeat NGS at the progression. Please, Alessandro.

Dr Di Stefani: Yeah. So, thank you to all the organising committee and thank you, Luca, for the question. Of course, thank you to the two colleagues from Naples for this very interesting case because it's a very rare skin neoplasm, a malignant adnexal neoplasm. According to the pathological characteristics, it's still a morphological diagnosis, but, of course, it's important to have a skilled dermatopathologist to perform the evaluation. Now, in Naples, they have a very expert in the field, so there are some differences also in immunophenotypical expression, but most of all, in the characteristics of cells with this secretion unit, of course, it's a poorly differentiated tumour, but you can still recognise some ductal structures and ENE positivity also is useful. So, this is very first step, it's a very precise diagnosis. Then, of course, it's a very uncommon tumour and so, we have just this anecdotical experience. So, it would be very important to perform NGS, to perform this genetic study in order to find also some possible target that we can use in some basket trial whenever possible. So, I think that this would be the next future of the approach to this very rare skin neoplasm to even repeat NGS evaluation at progression because, sometimes, it could be also a selection of a new neoplastic clone, maybe showing some possible target for therapeutic options. So, this, it's a very deeply studied case and you can see how these kinds of tumours can be aggressive, very aggressive in the clinical behaviour.

Dr Tagliaferri: Thank you. Thank you, Alessandro. Very clear, your answer. So, Agata, Agata, you are a medical oncologist and radiation oncologist. We have other three minutes for this case. So, what about the association regarding local therapy and the systemic therapy, also in terms of abscopal effect, for example? Please.

Dr Rembielak: I mean, again, I have to echo what Alessandro has already shared. This is extremely rare situation and although we do see those patients in different countries, I don't think we will have enough patients to create a randomised clinical trial. And I think NGS is the right way to go. Maybe, we would not be able to help this patient specifically, but we can learn and maybe help patients in future. And although the unsolved issue is how and when to repeat NGS, whether at progression or we should do it at certain interval, I think we have to probably learn about this disease and definitely gather information, again, that can be used for future patients if we cannot help this patient. In terms of local strategies, because this patient, in this patient's obviously quality of life was an issue and I'm really sorry that unfortunately she passed away. Again, very limited evidence how radiotherapy can work for those cancers. They are regarded as not so sensitive to radiotherapy but I think, in terms of helping with pain, with discharge, with ulceration, radiotherapy can be a very good option, either in combination with palliative surgery or consideration of electrochemotherapy. I was wondering why you decided for some locations to go with radiotherapy and for other locations for ECT and whether you noticed any differences in response. So, this is something that would be also interested to know. There are also some tiny little fragments, almost, of evidence, that if we treat those patients with systemic treatment and then, we provide local treatment radiotherapy, actually, we can observe abscopal effect. It's not again well-published, but I understand that you didn't see this effect in this particular patient. But again, abscopal effect is completely different phenomenon, which we still are trying

to learn and I'm not sure whether I would have done anything differently. I think consideration of chemotherapy, then waiting for Sunitinib when you were allowed to use it. I think I would've probably decided to go in the same way. Large clinical trials, impossible in future. Basket trial, yes, providing that we have really good information on gene alterations and those mutations that can guide our management. It would be good at, and it should be really an international effort, to gather cases from different countries and some organisations are trying to address it under rare tumour initiative, including EORTC. So, that could be the one right way to go, but I think NGS is definitely our way to manage those patients.

Dr Tagliaferri: Thank you.

Dr Rembielak: Very interesting. Please consider writing up and maybe case presentation because I think it's really important that we share your experience with wider audience and then, in the next session, in future, we can say, "Or actually, there was a case from Naples presented and this is what our colleagues did." So, I would definitely recommend sharing this experience. Alessandro, you wanted to say something?

Dr Di Stefani: Yeah, yeah, yeah. Just anticipate my last comment, was to publish this case because it's important also to have this answer to IO combination and all the other treatments that were exposed to the patient.

Dr Tagliaferri: Thank you, Agata. Thank you, Alessandro. So, I would like to highlight the importance of interaction during this session. So, I would like to invite the attendees to use the specific tool in order to answer some questions also during the presentation. So, we can move to the second speaker, Dr Menna Fouda. And, please, you can show the second case regarding complex non-melanoma skin cancer, please.

Dr Fouda: Yeah, hello. My case is about metastatic Merkel cell carcinoma, which was treated with immunotherapy in elderly patients. My patient at 91-years-old, he presented with rapidly growing lesion in the left lateral forehead. He had a PET scan, which didn't show any distant metastases, and in terms of his comorbidities, he had hypertension, transient ischaemic attacks in 2017. He had the Parkinson's which was not diagnosed, actually, he presented with resting tremors, but he was not in any treatment at the time of his presentation and his performance status was one when he was presented to us. We had a biopsy from the lesion, which confirmed Merkel cell carcinoma and the recommended management was to do wide excision and staging of the neck with sentinel lymph node biopsy and neck dissection. But in terms of his age and comorbidities, we went through wide local excision for the primary site only, which was done and proved to have T4 Merkel cell carcinoma with local muscle invasion. It was a clear margin but there was carcinoma in-situ at the peripheral edge with LVI positive. At the time of the surgical resection for the lesion in the forehead, there was also right pinna basal cell carcinoma, which was removed. So, the first question we wanted to highlight is what treatment option should be next. And actually, when we discussed the case and the entity, there was a recommendation for post-operative radiotherapy and the patient had 50 Gy and 25 fractions radiotherapy session to the surgical bed and the lymph node and he completed his treatment in December, 2019, which actually he tolerated fairly well. The main side effect from the radiotherapy was irritation in the left eye, which improved after one month with local and topical treatment. His end of treatment scan didn't show any evidence of relapse and we continued surveillance for the patient. He had a CT scan in July, 2020 which did prove few small sub-centimetric lymph nodes, which was not of clinical significance. In March, 2021, the patient was presented to the team again with right hand lesion and the lesion in a temporal area as well. He had excision for both lesions and the one in the right hand showed to be squamous-cell carcinoma, which was completely excised with clear margin. And the right temporal lesion was basal cell carcinoma, but it was excised with positive margin. So, on this basis, we didn't offer the patient actually postoperative radiotherapy because of his comorbidities and health and we continued to monitor him. At the time of this presentation, with these lesions, we did a CT scan for the patient, which showed new 33 mm porto-caval lymph node, which was highly suggestive for a metastatic lesion. We did a PET scan, which was avid at this solitary area, and the patient at that time had a PS of 2. So, we again discussed in our MDT,

what we can do for the patient in terms of systemic treatment option. The MDT was convinced that it's unlikely that this lesion might be related to the basal cell carcinoma, the squamous cell carcinoma, which was recently excised. And the main concern was a relapsed Merkel cell carcinoma. So, we discussed to see the patient in the clinic to assess his fitness for systemic therapy and we offered him single agent Avelumab onto weekly basis. The patient was quite concerned with the long-term treatment. We offered him that we will assess any toxicity that might happen and also, we'll offer him some treatment breaks, in case that he had any toxicities. After cycle five Avelumab, had CT scan in July 21, did partial response to his treatment, reduction in the portocaval node and continue to have maintained response in this lymph node until November, 2021. It's just important to highlight that his resting tremors were getting worse since January 21. He also had some difficulty in mobility but otherwise, from the Avelumab perspective, he did very well and there was no, any concern of IO-related toxicities. His MRI brain didn't show any metastatic disease and at that point, we referred him for neurological review. The neurological review was done in April, 2022 and actually, the patient had these resting tremors getting worse over the last three years. He had some walking deterioration as well, and shuffling gait. So, the neurology was concerned, either it could be a central tremor or a kinetic rigid syndrome. So, they started for him Co-careldopa and then, after two months of Co-careldopa, the patient actually didn't improve, there was no benefit from this treatment. They started to increase the dose and they were convinced that the diagnosis is central tremor rather than any underlying a kinetic rigid syndrome. At that point, the patient in June, 2022, completed 24 cycles of Avelumab and we decided to discontinue the treatment because the main concern was his tremors, which were affecting his quality of life and the patient, actually, from the Merkel cell carcinoma perspective, was in remission. So, my question, first the question that I addressed at the first setting, would we consider radiotherapy? The second question, after 24 cycles, shall we continue the treatment or not? And the question number three, do you think that the patient was over-treated? Thank you for your attention.

Dr Tagliaferri: Thank you, thank you. Very interesting case, Merkel carcinoma. So, I have a question that I would like to ask to Agata. So, regarding this patient, the age is very important, 94-years-old. So, one preliminary question. After, in case of positive sentinel lymph node, in a very older patient, directly adjuvant radiotherapy or neck dissection?

Dr Rembielak: Yeah, very good question. I think the patient had local excision, so, postoperative radiotherapy to local, so forehead, and probably, I would do exactly the same. I wouldn't treat the whole neck because of his age and would narrow postoperative radiotherapy to level-2 lymph nodes. We know that these patients, even if they are fit at the start of radiotherapy, may develop some toxicity in the neck. So, I would definitely support you and wouldn't go with full nodal dissection, but of course, that needs to be discussed with the patient as well. There is a... if we have scans not indicating really risk and he had PET scan, you've done all scans, I think that's the right way to go. I wonder obviously, Luca, what you would advise for this kind of patient because obviously age is just only a number.

Dr Tagliaferri: Yeah, so it's important the performance status, of course, and the prognosis of the patient, maybe, maybe, adjuvant radiotherapy without nodal dissection in case of negative imaging could be taken in the account as an opportunity, non-invasive opportunity in alternative to nodal dissection. But of course, we need to evaluate the performance status of the patient and the aspect of the patient. So, there is a question for you, Agata, maybe, you can answer to this question and if ICI is not available, only chemo, would you use it in such a case or go for RT to the only lesion?

Dr Rembielak: If ICI is not available, only chemotherapy, go for radiotherapy? I'm really sorry, I don't understand this question, I'm just trying to read it.

Dr Tagliaferri: So, I can, maybe, it means that radiotherapy alone to metastatic lesion, for example, stereobody or also systemic therapy. So, we can also...

Dr Rembielak: We are now in pelvic metastatic disease.

Dr Tagliaferri: Yeah.

Dr Rembielak: So, if the question is, by all means, I think stereotactic radiotherapy should be considered for those patients. There is also another question from the same colleague, asking about oligometastatic Merkel cell carcinoma. As in our old experience, it's usually wildly metastatic, but we do see sometimes patients presenting with single oligometastatic disease before they develop further disease. And just only last week, I can say, I had a patient with oligometastatic disease and it was Merkel cell carcinoma in lining of the stomach and the patient concurrently with Merkel cell referral was investigated for active bleeding from her stomach. And so, it is still possible she didn't have any other side of disease, but I think if we don't start them on treatment, unfortunately, those patients would go very quickly on metastatic disease. So, the answer for the first one, yes, it's rare, but it happens. The answer to the second one, stereotactic radiotherapy is a valid option for those patients.

Dr Tagliaferri: Thank you, Agata. We have only another minute for the discussion, then, we need to move to the third case. Alessandro, what about the management of this case?

Dr Di Stefani: Yes, of course, is something we can share. I will just say one thing to the question number two, about the... if is the case to continue or not the treatment. We know very well that in this immunotherapy from other tumours, all the medical oncologists, they can confirm we have this kind of still continue activity of the immunotherapy after suspension. So, in case of these adverse events of severe importance, of course, the treatment can be interrupted. And the over-treatment of the patient, well, I don't think so, maybe, we can always consider quality of life. So, in this case the Parkinson's symptoms are the leading question to take into consideration, of course.

Dr Rembielak: There is also a query, whether we are observing actually, increased Parkinson's symptoms related to his Avelumab. So, this is another thing that we don't know to what extent those new drugs can actually increase risk. So, or it was just a natural progression. But I don't think he was over-treated, in my opinion. I think you offered him appropriate treatment with surgery, radiotherapy and then with Avelumab. And what's really important, what you highlighted in your talk, that he was discussed through MDT. It is of great importance that we communicate and we discuss those still rare cases with our colleagues through multidisciplinary interaction.

Dr Tagliaferri: Thank you. Thank you, Agata. Thank you, Alessandro. We are little bit late but the cases are very interesting, so, we need to discuss about the management and about this special situation. So, I would like to invite Ilhomidin Niyazov, to present the third and last case. Please.

Dr Niyazov: Okay, thank you. Good evening, dear faculty, dear professors, dear colleagues and everyone who are connected online. I'm Dr Niyazov and today, I'm going to talk about the case of Management of Advanced Squamous-Cell Carcinoma of the Head and Neck in Elderly patient. So, our patient is a 77-year-old gentleman. He was admitted on May, 2012 and his diagnosis was stage 3 skin cancer of the occipital and posterior of his neck. He was fit enough with the performance status of zero, but comorbid with grade 2 arterial hypertension. And he had a history of treatment with radiotherapy, 2 Gy per fraction, with a total dosage of 40 Gy in 20 fractions. And the effect of the treatment was the partial tumour regression. And due to some unknown reasons, the patient didn't come to the further treatment. On his second admission, which was on May, 2019, his complaints were of persistent tumour of the same side but with further progression of the disease and there was some pain and bloody discharge from the tumour. On clinical examination, there was a 6.5 to 5 cm exophytic tumour on the skin of the border of his neck and occipital region with ulcerative surface on palpation. The tumour was firm and fixed to the underlying tissues, which was the sign of locally advanced stage of disease, which were proven by both imaging. And pathology reports suggested the presence of non-keratinizing squamous-cell carcinoma, grade 2. Further work up, like neck ultrasound and imaging, revealed a clinically positive 1.5 cm right occipital lymph node. And the cytology report revealed cells with hyperplasia and nuclear polymorphism, which were both suggestive for either inflammatory or

metastatic. And the tumour board, this diagnosis was stage IV non-keratinizing squamous-cell carcinoma of the posterior of the neck and occipital region. So, here is a question to discuss on, what is the best treatment option regarding this patient?

Dr Rembielak: So, if I may start from radiotherapy hat on, the patient has had already radiotherapy, therefore, I don't think that would be my preferred option. The one comment I would only have is, the dose that the patient received for his T3 disease, in 2012, at the time of presentation, seems a little bit low for, you know, currently used doses. So, is it the standard, 40 Gy that you use for skin SCC?

Dr Niyazov: I guess it was given as a pre-operative setting to further to downstage the tumour and to go with surgery.

Dr Rembielak: Right, so, it was pre-operative radiotherapy but then the patient did not continue with follow-up and he was lost to follow-up?

Dr Niyazov: Exactly.

Dr Rembielak: All right. Okay. So, I'm worried about the extent of this disease. So, I think I would discuss with our colleagues within MDT regarding pre-operative chemotherapy to downstage this disease and then, consideration of surgery. But I'm really very interested what Alessandro and Luca are thinking.

Dr Tagliaferri: Yes, Agata. I completely agree with you. I would like to add to your previous comment regarding the dose to the squamous-cell carcinoma. I personally dislike pre-operative approach for squamous-cell carcinoma because the rate of complete response and the local control is very high with exclusive radiotherapy using the adequate dose. So, my personal opinion is that if we decide to use radiotherapy, we need to use exclusive radiotherapy without other treatment and we can consider surgery only in case of a failure of radiotherapy. Regarding this question, I completely agree with you, Agata, that chemotherapy will be an option, followed by surgery. And maybe if in the centre there are experts in brachytherapy, interventional radiotherapy. In this case, we can consider, because it's a re-treatment, a perioperative radiotherapy or interoperative radiotherapy or perioperative brachytherapy, in order to improve the local control. Alessandro, I don't know if you would like to add some comment now or at the end of the case?

Dr Di Stefani: Just quickly, of course, it's a stereotypical case that has to be discussed in a multidisciplinary tumour board. It's for sure a locally advanced squamous-cell carcinoma with this suspect nodal involvement. So, when surgery and/or radiotherapy may not be curative, of course, immunotherapy with Cemiplimab can be taken into consideration. So, this is just a comment of course of 2023, not being 2019.

Dr Tagliaferri: Yes, exactly. It's important that.

Dr Di Stefani: Yeah, maybe, also with neoadjuvant intent, but this is another point of view. So, let's move on to see what happens.

Dr Niyazov: Good points. So, our decision was to treat this patient with chemotherapy, as you said already. So, from December, 2019 until January, 2020, this patient took, received two cycles of Cisplatin-based chemotherapy and the effect of the treatment was partial response. So, the next question to discuss on, is what treatment options should be applied next?

Dr Tagliaferri: We have already answered to this question because maybe surgery could be an opportunity with or without intraoperative preoperative radiotherapy, in my opinion. But Agata, maybe, you are in line with this opinion regarding surgery, I understood. Okay.

Dr Di Stefani: It was a kind of downstaging, yeah. So.

Dr Niyazov: Yeah.

Dr Di Stefani: At least surgical downstaging.

Dr Niyazov: Yeah, our decision was made in favour of surgery. The surgery plan included excision of the primary tumour and the functional neck dissection from the right with the levels of two, three, and five of lymph nodes. And the surgical defect was reconstructed with the regional fasciocutaneous suprascapular pedicle flap, as you see here. And as you can see here, the flap was raised in the donor site and resected the surgical specimen from both sides, which is invading to the muscles of the neck and the final view of the surgical wound with the regional lymph nodes from the neck. As a result, the surgical wound healed with primarily intention. Histopathological report confirmed free surgical margins and there were no pathologically confirmed metastases in none of the lymph nodes, out of 15 ones. And the patient was discharged on the 10th day in postoperative period and he's being followed-up, up to date with no signs of local and regional recurrence. And the last questions to be addressed, was the patient over-treated, since the treatment plan included the neck dissection, but pathologists found no nodal metastases? And what can we do to differentially diagnose between clinically and pathologically nodal metastases?

Dr Tagliaferri: Thank you for this question. So, I would like to starting from the second question, I would like to ask to Alessandro, we have two, three minutes for discussion, but non-keratinizing squamous-cell carcinoma should be managed in a different way or in the same way of keratinizing squamous-cell carcinoma?

Dr Di Stefani: Okay, we have no guidelines regarding this topic because there is no already standardised the difference in between clinical behaviour, otherwise, the sarcomatous differentiation of cells, so spindle cells and the loss of pan-CK, cytokeratin markers can be found in pathological specimen. So, it's something that should be added in the discussion. And of course, the role of the pathologist in the multidisciplinary tumour board, it's important as well. In this case, we can see that we had a prior, if I can remember well, a prior biopsy of a non-keratinizing tumour. But then, G2, grade 2 differentiation, so moderately differentiated squamous cell carcinoma. Yeah, considering the difference of the pathologically or clinically lymph node that is very difficult to remain to the diagnosis of possible metastatic or possible inflammatory. So, probably, I would suggest in those cases to repeat a biopsy to have a more confident diagnosis of pathological involvement.

Dr Tagliaferri: Thank you, Alessandro. So, Agata, the time is over but I would like to invite you to share the last comment and the conclusion of this very interesting session.

Dr Rembielak: So, regarding over-treatment, I think opposite, we agreed that at the first phase of his treatment, he was actually under-treated and unfortunately, he didn't go on to having surgery. In the second phase, it was progression probably, I wouldn't call it recurrence because he didn't have really full treatment at the beginning. So, it was a very aggressive disease. In posterior aspect, you may consider whether actually bilateral neck dissection is required because of anatomy and drainage. So, it's really difficult in those locations to say that only right or left side is appropriate. I didn't have information about scans. They can help us, CT scans and MRI scans, to assess, and obviously we are now further down the line, in terms of years and there is more technology available. Sometimes scans can help us to distinguish regarding clinically involved or pathologically involved nodes or not. But the second phase, definitely he was not over-treated and I think the fact that he's now free from disease is really very good. And, you know, great case, again worth sharing with colleagues, especially surgical colleagues would be interested in terms of flap and how you reconstructed this quite big defect. So, yeah, definitely biopsy, repeated biopsy if we are of concern. But in view of 15 nodes, not involved in skin, not involved with metastatic disease, there is no indication for post-operative radiotherapy. So, close clinical monitoring. But I would do it with imaging, at least head and neck and chest.

Dr Niyazov: Okay, we'll do it. Thank you.

Dr Rembielak: And wrap it up and publish. Right, so we are reaching now the end of our session. The recording will be available and I would like to thank you very much, Luca, Alessandro, our speakers and attendees. Without your input it wouldn't be... the session would not be possible. And I would like also to thank you, ESO and the team, supporting us behind. Again, without your patience in getting everything done, this session wouldn't be possible. So, thank you very, very much and until next session then. Thank you very, very much.

Dr Tagliaferri: Bye-bye.

Dr Rembielak: Okay, thank you. Bye-bye, bye.

All: Bye, thank you.