Supplementary

Appendix 1

Questions

1. Do you agree that radiation-induced lung injury and CTLI exhibit similarities in clinical symptoms, diagnostic tests, and imaging findings?

Biniam Kidane: Yes.

Elena Bignami: Yes.

Fumio Sakamaki: I almost agree with this consideration.

Giandomenico Roviello: Yes.

Hirokazu Taniguchi: Yes.

Kyeongman Jeon: Yes, I agree that the both exhibit similarities.

Lenko Saric: Yes, I agree that radiation induced lung injury and CTLI can have many similarities in symptoms as well as in diagnostic testing and image findings.

Miguel Ariza-Prota: Yes, I agree that radiation-induced lung injury (RILI) and cancer treatment lung injury (CTLI) exhibit similarities in clinical symptoms, diagnostic tests, and imaging findings. Both conditions often present with nonspecific respiratory symptoms like cough, dyspnea, and chest pain, which can make early differentiation difficult.

In terms of diagnostic tests, both conditions can show abnormalities on pulmonary function tests (PFTs), such as a restrictive pattern and reduced diffusion capacity. Imaging, particularly CT scans, reveals overlapping features, such as ground-glass opacities, consolidations, and fibrosis. These patterns can be similar in both RILI and CTLI, although their distribution may vary depending on the radiation field or the specific cancer treatment.

Given these similarities, a detailed clinical history, including prior exposure to radiation or immune checkpoint inhibitors, is essential for accurate diagnosis and appropriate management. However, the underlying mechanisms differ (radiation-induced inflammation *vs.* immune-mediated injury), which can influence treatment strategies.

Ninh M. La-Beck: Yes.

Nobuhiro Kanaji: If cancer treatment-related lung injury (CTLI) is a concept that includes a wide range of cancer treatments, then radiation-induced lung injury (RILI) is one of the CTLIs. Although there are some similatities between drug-induced lung injury and RILI, there are also many differences. RILI is diagnosed primarily on imaging findings, which can be based on the fact of irradiation, the site of irradiation, and the time of onset. However, RILI that extends beyond the irradiated area can be more severe, although such case is less common.

Satoshi Watanabe: I agree. In addition, when RP appears early, such as during radiation therapy, or outside the irradiated field, it can often be more severe and associated with a poorer prognosis.

Takehito Shukuya: First of all, it would be better to clarify the definition of CTLI. CTLI is defined as cancer treatment related lung injury, but does cancer treatment include surgery, radiation, and drug therapy? Or is it only drug therapy? Even if it is only drug therapy, I think that the image patterns that occur and the prognosis will differ depending on the type of drug, such as ICI, molecular targeted drugs, and ADCs such as HER2-Dxd. I think that some drugs are similar to radiation-induced lung injury.

Tomohiro Akaba: Yes. Rather than being a separate category, I believe that radiation-induced lung injury may fall under the broader category of CTLI.

Tracy L. Leong: Yes.

Wolfgang Gesierich: I very much agree with this point. In our ILD service and ILD conference we face both RILI and CTLI rather frequently.

Also, we frequently see reactions which exceed the irradiated area or even generalize in the lungs with COP- or AIP/ARDS-patterns. This has to be much more emphasized in the text as these forms are usually symptomatic and also life threatening and thus very relevant to the patient and on the other hand radiation therapists are usually reluctant to accept, that they can induce of-target effects with irradiation, which are presumably immunologically mediated. This can lead to improper diagnosis of these reactions and awareness has to be raised. A nice paper to support this would be the following: Thomas *et al.* support a series of 82 patients with RILI (119). In 82% CT changes extended beyond the expected radiation field, which is the majority. These patients tended to have high-grade and even lethal pneumonitis.

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Yasuhiko Koga: Yes.

Yoshinori Tanino: Partially agree. As mentioned in the text, the typical imaging changes of radiation-induced lung injury are confined to the area of radiation exposure and do not align with the anatomical distribution of lung fields or segments. This distribution is different from CTLI. However, radiation can induce imaging alterations outside the irradiated area. The distribution and imaging pattern of the findings are quite similar as those of CTLI.

Yuji Uehara: Yes. Radiation-induced lung injury and CTLI exhibit similarities in clinical symptoms, diagnostic tests, and imaging findings.

2. Do you agree with the importance of an MDT in the diagnosis and management of CTLI?

Biniam Kidane: Yes.

Elena Bignami: Yes.

Fumio Sakamaki: I almost agree with this.

Giandomenico Roviello: Yes.

Hirokazu Taniguchi: Yes.

Kyeongman Jeon: Sure, the MDT approaches are very important.

Lenko Saric: Yes, I agree with the importance of an MDT for these patients. As is the case with other complex patients and diseases, a multidisciplinary approach is very important for making timely diagnosis and starting correct treatment as soon as possible to avoid possible complications. In this case, MDT would consist of oncologist, radiologist, thoracic surgeon and possibly anesthesiologist and palliative care specialist.

Miguel Ariza-Prota: Yes, I fully agree with the importance of an MDT (multidisciplinary team) in the diagnosis and management of CTLI (checkpoint inhibitor-induced pneumonitis). CTLI is a complex immune-related adverse event that requires careful coordination between pulmonologists, oncologists, radiologists, and pathologists.

A multidisciplinary approach ensures:

- ❖ Accurate diagnosis, by integrating clinical, radiological, and pathological findings, which is crucial as CTLI symptoms often overlap with infections or cancer progression.
- ❖ Tailored management plans, which may involve corticosteroids, immunosuppressive therapy, or modification of the cancer treatment regimen.
- ❖ Minimized risk of complications, as CTLI can escalate if not managed promptly, and immunosuppressive therapy needs careful monitoring for secondary infections.

This collaborative approach improves patient outcomes by enabling timely interventions and comprehensive care.

Ninh M. La-Beck: Yes.

Nobuhiro Kanaji: I agree with this opinion (the importance of an MDT in the diagnosis and management of CTLI). However, it is a prerequisite for MDT to have more than one physician with a great deal of experience. If junior doctors are not able to give their opinions to senior doctors, the conclusion will ultimately be based on the opinion of the senior doctor alone. It is important to respect each other's opinions within the team to avoid such a situation.

Satoshi Watanabe: Partly. The primary physician should not diagnose or determine the treatment plan alone. However, a full MDT approach is not necessary, as in most cases, the diagnosis and treatment plan for CTLI are decided through a conference in the respiratory department.

Takehito Shukuya: I think MDT is important for CTLI. In particular, in situations where respiratory physicians are not involved, for example, because chest X-rays are not routinely taken, there is a concern that CTLI may be detected late. Also, in terms of diagnosis, I think that the involvement of radiologists will enable a range of differential diagnoses to be made.

Tomohiro Akaba: I partly agree. While it is not necessary in all cases, MDT can be useful in situations where diagnosis is challenging.

Tracy L. Leong: Yes.

Wolfgang Gesierich: I strongly agree with this point. Just what I responded to question 1. It underscores the need for a multidisciplinary view on CTLI.

Also, as these treatments are increasingly used, it is getting more likely that pulmonologists are faced with CTLI in their daily practice where they need exchange with oncologists to fully understand the clinical picture. On the other hand,

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oncologists need pulmonolgists for a complete workup of the broad differential diagnosis. Eventually there has also to be a shared decision on treatment.

Yasuhiko Koga: Yes.

Yoshinori Tanino: Completely yes. I believe an MDT can improve the accuracy of the diagnosis and efficacy of the management of CTLI.

Yuji Uehara: Yes. An MDT is essential in the diagnosis and management of CTLI.

3. Do you agree with the type- and stage-specific management strategies for CTLI? Please remember that your comments and suggestions are welcome.

Biniam Kidane: Yes. These should be done within context of MDT and also documented ideally as part of a prospective study.

Elena Bignami: Yes.

Fumio Sakamaki: I almost agree with this.

Giandomenico Roviello: Yes.

Hirokazu Taniguchi: Yes.

Kyeongman Jeon: I agree and support all of what is described in the text.

Lenko Saric: Yes, I agree that management of CTLI should take into consideration type- and stage-specific characteristics as every type and stage has its own specificity.

Miguel Ariza-Prota: Yes, I agree with the type- and stage-specific management strategies for cancer treatment-related lung injury (CTLI). These strategies are crucial because CTLI can manifest in varying severities, from mild to life-threatening, and different types of lung injuries require distinct approaches. Tailoring the treatment to the severity and stage of the injury helps optimize patient outcomes and minimize risks.

For example:

- Mild (grade 1) CTLI can often be managed with close monitoring and, in some cases, temporarily halting cancer treatment.
- Moderate to severe (grade 2–4) CTLI often requires more aggressive interventions, such as corticosteroids or even the use of additional immunosuppressive therapies if symptoms persist. In these cases, the decision to continue or stop cancer treatment depends on the balance between controlling the lung injury and the cancer's progression.

Adopting a type- and stage-specific strategy ensures that treatment is effective while minimizing the adverse impact on the patient's overall cancer therapy. This approach is supported by current clinical guidelines, including those from oncology and respiratory societies.

Ninh M. La-Beck: Yes.

Nobuhiro Kanaji: I agree with this opinion (the type- and stage-specific management strategies for CTLI). In cases of drug-induced lung injury, improvement is often achieved only by drug discontinuation. However, in cases of respiratory failure, intensive treatments are required; hospitalization, oxygen, corticosteroids and other immunosuppressive drugs, and ventilator management in some cases.

Satoshi Watanabe: I agreed with the grade-specific management strategies for CTLI. However, the treatment strategy for CTLI should be adjusted on the causative agent. For example, in cases of CTLI caused by trastuzumab Deruxtecan, GC treatment should be considered starting from grade 1. For CTLI induced by gefitinib, which has a high fatality rate, high-dose GC should be considered early. On the other hand, CTLI caused by osimertinib can sometimes improve without treatment, so even at grade 2, monitoring without GC use may be appropriate.

Takehito Shukuya: I agree. I think that the prognosis of CTLI can be predicted by the type of drug and the imaging pattern, and that the treatment strategy will differ accordingly.

Tomohiro Akaba: Yes. Given that the severity and clinical course vary among cases, it is essential to determine the treatment strategy for each instance of CTLI individually.

Tracy L. Leong: Yes.

Wolfgang Gesierich: The three-way split into grading, typing, and staging gives the reader orientation, is very helpful for therapy planning in CTLI and can be easily implemented in clinical practice. Tables and figures support the text in an optimal

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way and make the information easily accessible. I very much agree with this system and the therapeutic suggestions derived from this.

I would only recommend to elaborate a bit more on the typing. The pure and mixed types are obvious and easy to understand. The induced type, however, does not get clear to the reader in the present form of the text. I am not familiar with the classification system of Lin *et al.* (180) and also looking into the cited paper it's not easy to grasp, what is meant by "induced type". So, this type should be explained more concisely in simple words. It might also be helpful, to have a table, where the characteristics of the three types are clearly displayed.

Also, diagnostics and therapy of this type remain a bit nebulous and should be described in more detail in the section "type-specific management". Which viruses to test for? Which other precipitants we have to think of? Which antiviral medication can be used? Also, this could be presented in a table, or integrated in *Figure 2*.

The wording: "…suspected inducing agents should be discontinued…" seems a bit unfortunate. Viruses cannot be "discontinued", they can only be treated.

Yasuhiko Koga: Yes.

Yoshinori Tanino: Yes, I do. The management should be changed according to the type and stage of CTLI. It is known that prognosis of CTLI is different according to the type of CTLI. Because CTLI with DAD has poor prognosis, it must require the intensive treatment. Regarding the stage of CTLI, some mild CTLI may improve after discontinuation of the candidate drug.

Yuji Uehara: Yes. Type- and stage-specific management strategies are necessary for CTLI.

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