# STAGE III:
## NSCLC CASE LIBRARY

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## Table of Contents

# Prologue

Stage III non-small cell lung cancer (NSCLC) includes a highly heterogeneous group of patients with differences in the extent and localization of disease. Many aspects of the treatment of stage III disease are controversial. Unfortunately, the data supporting treatment approaches in specific patient subsets are often subject to a number of limitations, for example that the trials involved heterogeneous patient populations; the definition of stage III disease has changed over time; and early studies were frequently inadequately powered to detect small differences in therapeutic outcome, were not randomized, or had limited duration of follow-up.

Major improvements in therapy, including the use of more active chemotherapy agents and refinements in radiation and surgical techniques, also limit the interpretation of earlier clinical trials. Finally, improvements in pretreatment staging have led to reclassification of patients with relatively minimal metastatic disease as stage IV rather than stage III, leading to a prolonging in the apparent overall survival of both stage III and IV patients

Despite multimodality treatment, the prognosis for unresectable stage III NSCLC remains poor, with five-year OS rates of approximately 15 percent. Therefore, newer treatment paradigms have evolved; for example, incorporation of immunotherapy.

For patients with unresectable, stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and RT, the PD-L1 antibody durvalumab, which is approved by the US Food and Drug Administration (FDA) and Taiwan FDA for this indication. However, the potential for toxicities associated with immunotherapy, some experts may reasonably not to use immunotherapy in this setting, pending further data. Taiwan Lung Cancer Society hereby develop the Stage III Lung cancer Case Library to address how to  managing by case-based instruction.

Yuh-Min Chen 陳育民

***Professor Yuh-Min Chen MD, PhD***

President of Taiwan Lung Cancer Society

The heterogeneity of stage III NSCLC means there is not a one-size-fits-all strategy for patients. Rather, a multidisciplinary approach is required to optimally utilize the available tools of chemoradiation, immunotherapy, and surgery.

In general, stage III NSCLC is a pretty challenging disease. It's the most heterogeneous of all the stages that we deal with. Early-stage and stage IV lung cancer is pretty straightforward. Stage III really necessitates a true multidisciplinary approach.

Certainly, for all stage III patients, chemoradiotherapy is one of the major parts of treatment regardless of whether they’ re going to have surgery, or immunotherapy therapy. For resectable patients, our typical approach is to give them induction chemoradiation, restage tumors, and then operation. For unresectable patients, based on updated NCCN guideline, they get definitive chemoradiation in conjunction with durvalumab, the first immunotherapy drug for stage III non-small cell lung cancer, which has the potential to make an even bigger impact on patient survival.

Taiwan Lung Cancer Society has developed this case-based instruction for our colleagues to handling the treatments of Stage III Lung Cancer with an easily approach.

Te-Chun Hsia 夏德鈞

***Professor Te-Chun Hsia MD, PhD***

Chief Editor

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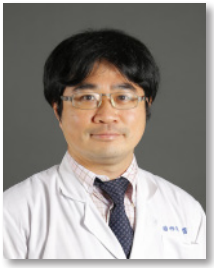

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# I.The Stage III lung cancer

# Introduction to AJCC 8 staging system of NSCLC

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An evidence-based cancer staging system is a tool for communicating and assessing the prognosis of cancer patients. After 10 years, in 2017, the International Association for the Study of Lung Cancer (IASLC) has released a revision of the staging system for lung cancer, the 8th edition of the Tumor-Node-Metastasis (TNM) staging system. In 2018, Taiwan officially implemented the new staging system, named AJCC 8. The AJCC 8 staging system is not only based on the actual data of more than 90,000 patients in five continents, but also incorporates some new specifications.

The main objectives of the following sections are to describe the most important changes introduced in the 8th edition (Refer to Table 1: Descriptors in AJCC 8th Ed. vs AJCC 7th Ed.) and to highlight the clinical and research implications of the new classification.

Table 1:Descriptors in AJCC 8th Ed. vs AJCC 7th Ed.

| Descriptor | Seventh Edition | Eighth Edition |
|---|---|---|
| T component | | |
| 0 cm (pure lepidic adenocarcinoma ≤3 cm total size) | T1a if ≤2 cm; T1b if >2-3 cm | Tis (AIS) |
| ≤ 0.5 cm invasive size (lepidic predominant adenocarcinoma ≤3 cm total size) | T1a if ≤2 cm; T1b if >2-3 cm | T1mi |
| ≤ 1cm | T1a | T1a |
| > 1-2 cm | T1a | T1b |
| > 2-3 cm | T1b | T1c |
| > 3-4 cm | T2a | T2a |
| > 4-5 cm | T2a | T2b |
| > 5-7 cm | T2b | T3 |
| > 7 cm | T3 | T4 |
| Bronchus < 2 cm from carina | T3 | T2 |
| Total atelectasis / pneumonitis | T3 | T2 |
| Invastion of diaphragm | T3 | T4 |
| Invation of mediastinal pleura | T3 | - |
| N component | | |
| No assessment, no involvement, or involvement of regional lymph nodes | NX, N0, N1, N2, N3 | No change |
| M component | | |
| Metastases within the thoracic cavity | M1a | M1a |
| Single extrathoracic metastasis | M1b | M1b |
| Multiple extrathoracic metastases | M1b | M1c |

Abbreviations: AIS, adenocarcinoma in situ; mi, minimally invasive adenocarcinoma; Tis, tumor in situ.

Modification of the T component

- The T component has many descriptors, such as tumor size, endobronchial location, atelectasis/pneumonitis, and the invasion of the many anatomic structures around the lung. The size decreased for several T categories, and some new pathology-based categories were introduced. Unlike the previous version, the current concept is" every centimeter counts." For each centimeter up to 5 cm, there is a corresponding T category. Tumors between 5 and 7 cm in size were reclassified from T2 to T3, and tumors larger than 7 cm were reassigned to T4, with larger tumors predicting a worse prognosis. Accurate measurement of tumor size is very important; thus, there are also specifications in the guidelines. It is necessary to measure the largest dimension of the solid portion clinically by computed tomography; the pathological measurement is focused on the invasive portion of the tumor. Using the maximum diameter in any of the three orthogonal planes to define the size of solid lesions is recommended. Use of the lung window is suggested to minimize underdiagnosis.

- Unlike the AJCC 7th edition, in this updated version, tumors involving the main bronchus without involving the carina, total collapse, or pneumonitis are defined as T2 lesions. It is recommended that visceral pleural invasion should be confirmed by elastic staining of pathological specimens if there is uncertainty. Additionally, in response to the increasing application of low-dose CT screenings, the new version added two new categories, Tis (AIS) and T1mi, which represent pathologically proven adenocarcinoma in situ and minimally invasive adenocarcinoma, respectively.

Modification of the N component

- The N component represents the staging of the lymph nodes. Lymph node staging is judged according to the American Thoracic Society mapping scheme. The current N descriptors at clinical and pathological staging clearly separate tumors with different prognoses. Hence, no modifications were made for the updated AJCC 8th edition.

Modification of the M component

- The M component represents distant metastasis of lung cancer. New M categories were introduced regarding extrathoracic metastatic disease. Based on available evidence, the number of distant metastases is more important than the location or the organ involved. Metastasis within the chest, such as to the pleura, pericardium, or lung to lung metastasis between contralateral

lobes is still defined as regional metastatic disease (M1a). M1b was reclassified as tumors with a single extrathoracic metastasis, and the new category M1c was introduced for tumors with multiple extrathoracic metastases in one organ or several organs.

Clinical and research implications on lung cancer stage

- There are some modifications in AJCC 8 stage grouping. Stage IA is now divided into stages IA1, IA2, and IA3 to include T1a, T1b, and T1c N0M0 tumors. Stage IB now contains T2aN0M0 tumors and stage IIA now contains T2bN0M0 tumors. All N1M0 tumors together with T3N0M0 tumors are now grouped into stage IIB, except for T3-4N1M0 tumors, which are grouped into stage IIIA.
- For stage III, in the AJCC 8th edition, there were some modifications. T3-4N1M0 and T4N0M0 tumors, which originally belonged to the IIB stage, were upgraded to IIIA. T3-4N3M0 tumors are now classified into the new IIIC stage. Although there is no survival difference between stages IIIC and IVA, as the tumors have different disease extents (loco-regional vs metastatic), they are identified by different stages (Table 2, AJCC 8$^{th}$ Lung Cancer Staging Instruction).

Table 2: AJCC 8th Lung Cancer Staging instruction.

| AJCC 8th Edition | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| T Component | | N0 | N1 | N2 | N3 | M1a[b] Any N | M1b[c] Any N | M1c[d] Any N |
| T1 | T1a ≤ 1cm | IA 1 | IIB | IIIA | IIIB | IVA | IVB | IVB |
| | T1b > 1-2cm | IA 2 | IIB | IIIA | IIIB | IVA | IVB | IVB |
| | T1c > 2-3cm | IA 3 | IIB | IIIA | IIIB | IVA | IVB | IVB |
| T2 | T2a Central, Visceral Pleura | IB | IIB | IIIA | IIIB | IVA | IVB | IVB |
| | T2a > 3-4cm | IB | IIB | IIIA | IIIB | IVA | IVB | IVB |
| | T2b > 4-5cm | IIA | IIB | IIIA | IIIB | IVA | IVB | IVB |
| T3 | T3 > 5-7cm | IIB | IIIA | IIIB | IIIC | IVA | IVB | IVB |
| | T3 Invasion | IIB | IIIA | IIIB | IIIC | IVA | IVB | IVB |
| | T3 Satellite | IIB | IIIA | IIIB | IIIC | IVA | IVB | IVB |
| T4 | T4 > 7cm | IIIA | IIIA | IIIB | IIIC | IVA | IVB | IVB |
| | T4 Ipsilateral Nodule | IIIA | IIIA | IIIB | IIIC | IVA | IVB | IVB |
| | T4 Invasion | IIIA | IIIA | IIIB | IIIC | IVA | IVB | IVB |

Abbreviations: AIS, adenocarcinoma in situ; mi, minimally invasive adenocarcinoma; Tis, tumor in situ.

- In summary, the innovations in the AJCC 8th edition define new tumor size groups and establish a new category for single extrathoracic metastasis. Adapting to the new version is crucial as it increases our capability to refine prognosis and improve tumor stratification in future trials.

***Reference***

1. Rami-Porta R *et al*. Lung cancer - major changes in the American Joint Committee on Cancer eighth edition cancer staging manual CA Cancer J Clin. 2017 Mar;67(2):138

# II.Surgical intervention strategy in stage III lung cancer

Stage III non–small-cell lung cancer (NSCLC) have locally advanced disease at diagnosis. Surgery with pre- and postoperative chemotherapy has been the preferred local treatment for patients with resectable disease. Targeted therapy, immunotherapy, and other non-cytotoxic agents are also being investigated for the combination with surgery, and may play a greater role in the future. Surgical resection should be considered once the mediastinal lymph nodes (N2 nodes) were proved as negative, and predicted postoperative pulmonary function was adequate. The differentiating between synchronous multiple primary lung cancers and intrapulmonary metastasis requires a combination of morphological, immunohistochemical, and molecular studies of the surgical specimens.

Although an upper anterior chest wall pain and numbness remind us of upper lobe lung cancer with brachial plexus involvement, almost complete absence of symptoms of superior sulcus carcinoma may happened. Therefore, chest radiography is required in such condition. MRI imaging provides further information of the tumor's spread and provide a guide for surgery. Now trimodality is treated as a standard management for such presentation of lung cancer.

***Reference***


1. Guerrero, M. Pancoast Tumor Imaging https://emedicine.medscape.com/article/359881-overview. 2015.
2. Sethi, S. Pancoast Tumor, Cleveland Clinic https://www.clevelandclinicmeded.com/online/monograph/lung-cancer/pancoast-tumor.asp. .

# Non-N2, clinical stage IIIA, T4N0M0 lung cancer (two or more separate tumor nodules in different lobes of the same ipsilateral lung)

***Wu-Wei Lai***

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## *Patient profile*

Case presentation

- A non-smoking 63-year-old woman had a history of right side breast cancer and had undergone post-total modified radical mastectomy (MRM) at 61 years of age (03/05/2011).
- A patch over the left middle lung field was noted during routine follow-up for breast cancer (12/04/2012), and had also been observed on a previous CXR (01/25/2011).
- Chest CT on 12/10/2012 revealed the following: 1) two new LUL lesions (3.2 and 0.9 cm, respectively), and one new LLL (1.2 cm) ground glass lesions, 2) no enlarged mediastinal lymph nodes, 3) left adrenal gland thickening, and 4) a liver cyst.
- CT-guided lung biopsy of the largest lesion in the LUL was performed on 01/09/2013. Pathological examined indicated adenocarcinoma.
- PET-CT performed on 01/22/2013 revealed no abnormal FDG uptake in the biopsy-proven LUL adenocarcinoma, and no abnormal FDG uptake in the LUL (0.9-cm lesion), LLL (1.2-cm) ground glass lesions, left adrenal gland, liver, or bone.
- The clinical staging of this patient was cT4N0M0, non-N2 cIIIA. Preoperative tumor markers (CEA and CA125) were within the normal range.
- The pulmonary function of this patient was normal:

$FEV_1$: 1.58 (87%), FVC: 2.02 (90%), $FEV_1$%: 79, and TLC: 96%. Therefore, surgical resection was planned and performed on 02/19/2013.

- The operative procedures were as follows: 1) CT-guided wire-localization of the LLL lesion, 2) wedge resection of the LLL, and 3) resection of the left upper division of the LUL.
- The final pathologic report showed that there were two separate tumors in the resected section of the upper division of the LUL, one measuring 1.6x1.2x0.6 cm and another measuring 0.9x0.6x0.4cm. We observed many papillary glandular structures lined by atypical hyper-chromatic non mucin-producing cells with recognizable mitotic activity, and some of the glands showed invasion into the stroma. Moderately differentiated adenocarcinoma was the diagnosis.
- One tumor measuring 0.5x0.5 cm in the left lower lobe was also noted, and was also determined to be moderately differentiated adenocarcinoma.
- With regard to lymph node metastasis, the mediastinal N2 (group 5: 0/3; group 6: 0/1), and N1 (group 10: 0/5; group 11: 0/4) lymph nodes were all free of tumor metastasis.
- *EGFR* mutation assay of the two lesions in the LUL revealed that they both harbored the L858R(CTG → CGG) point mutation.
- *EGFR* mutation assay of the LLL tumor revealed that it was wild type.

- We observed multiple synchronous primary lung cancers. The pathologic staging of the LUL tumors was pT3N0M0, pIIB, with *EGFR* exon 21 (L858R) mutation, and the LLL tumor was pT1aN0M0, pIA, with wild-type *EGFR* .
- The postoperative plan is observation with regular follow-up with chest CT every 6 months. She has survived 5 years and 8 months (02/19/2013-10/15/2018) with no evidence of disease.

Figures

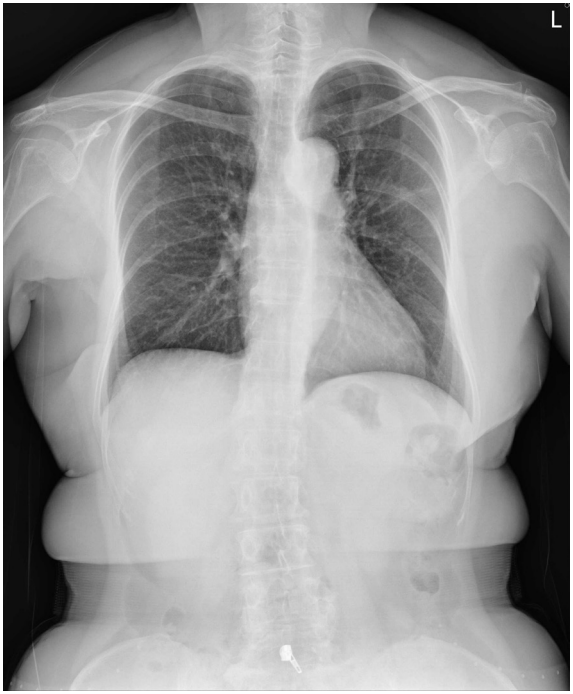


Figure 1: Pre-treatment chest radiograph (12/04/2012): a patch shadow over the left middle lung field .

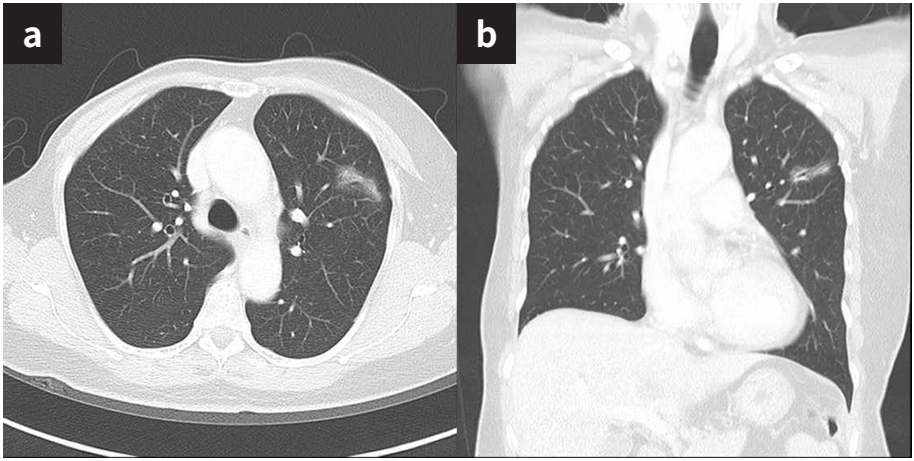


Figure 2: The largest GGO lesion on the upper division of the LUL: (a) horizontal and (b) coronary view.

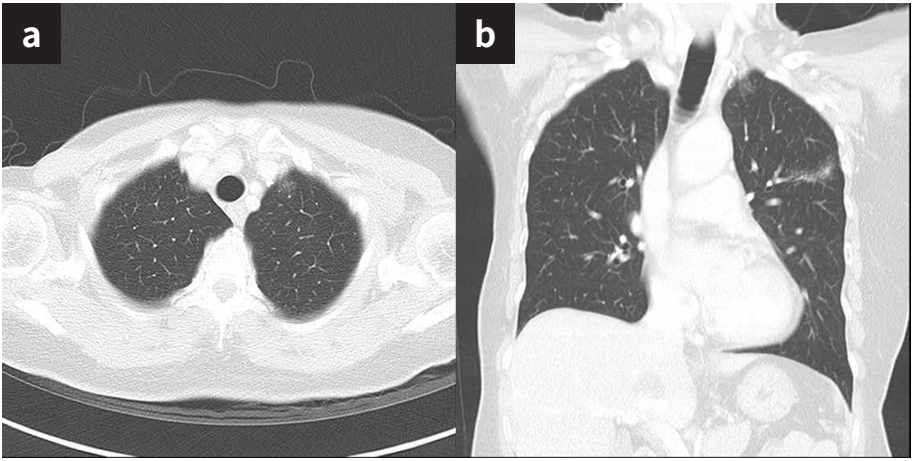


Figure 3: The smaller GGO lesion in the upper division of the LUL: (a) horizontal and (b) coronary view.

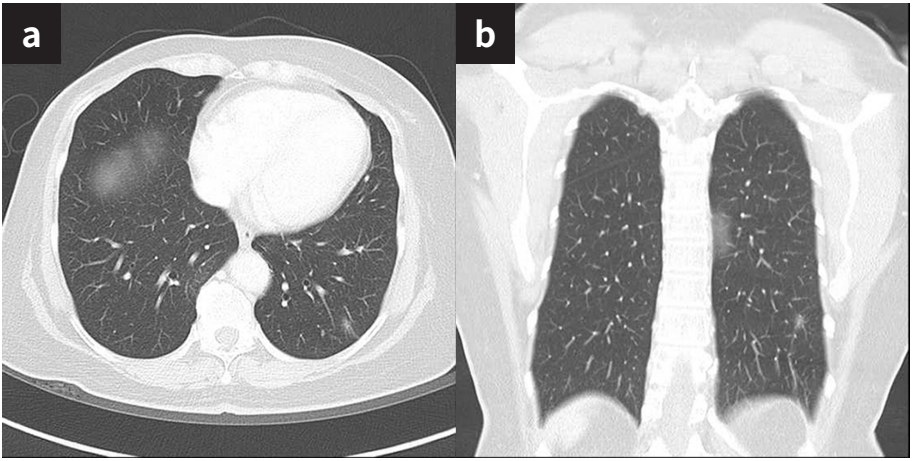


Figure 4: The GGO lesion in the LLL: (a) horizontal and (b) coronary view.

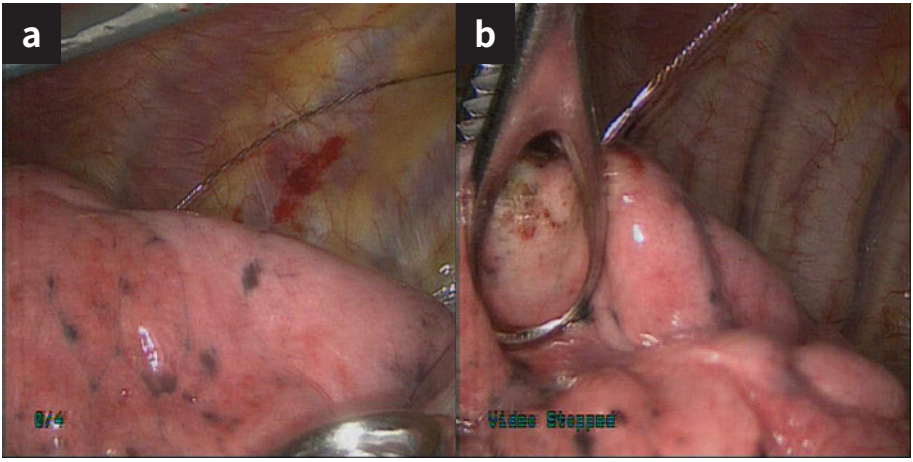


Figure 5: Wire-localization of the LLL lesion.(a) the wire was set with the assistance of CT. (b) the lesion was grasped with a ring forcep.

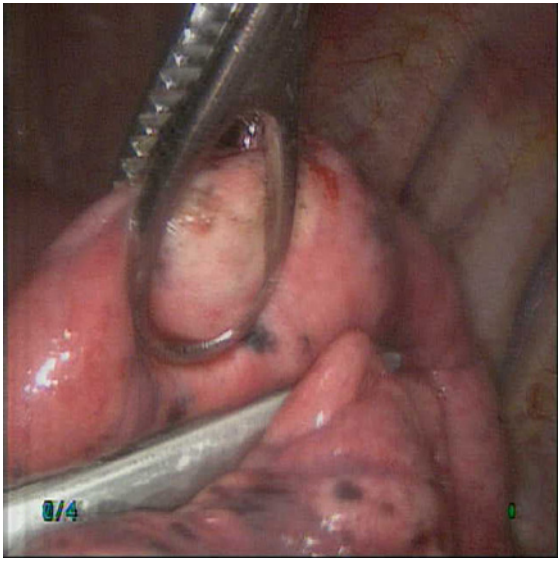

Figure 6: Surgical resection of the LLL lesion with endo-GIA.

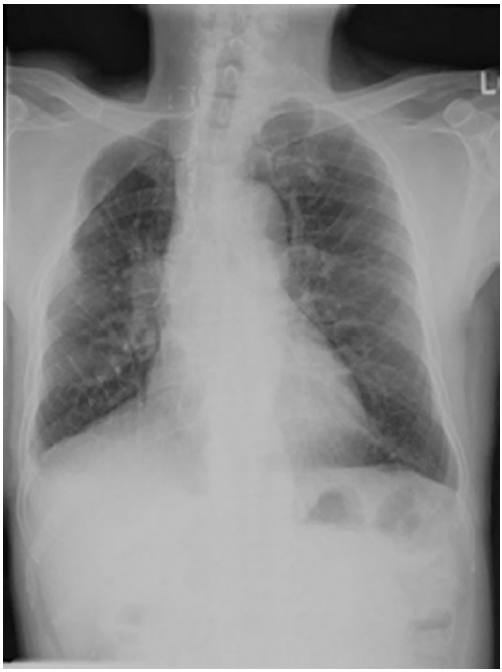

Figure 7: CXR 8 months postoperatively

## *Clinical Pearls*

- In this type of non-N2 clinical stage IIIA NSCLC (T4N0M0), the cancer has not spread to distant organs, but may or may not have spread to the lymph nodes within the lung and/or the area where the bronchus meets the lung (N1/N0).
- A major clinical challenge is determining whether this tumor type is non-N2 clinical stage IIIA. Negative findings in the mediastinal lymph nodes should be proven by the combined use of CT, PET-CT, EBUS-TBNA, and even mediastinoscopy before a treatment plan is made.
- Surgical resection should be considered once the mediastinal lymph nodes have been proven negative and predicted postoperative pulmonary function is adequate.
- Differentiating between synchronous multiple primary lung cancers and intrapulmonary metastasis requires a combination of morphological, immunohistochemical, and molecular studies of the surgical specimens.

# The Pancoast tumor (Superior sulcus tumor)

***Wu-Wei Lai***

Department of Surgery, National Cheng Kung University Hospital, Tainan, Taiwan.

## *Patient profile*

Case presentation

- A 61-year-old man with a smoking history of 2.5 packs per day x 40 years.
- Intermittent fever around 38.5°C -39°C noted for 1 month.
- Lingering right upper anterior chest wall pain and numbness over the upper inner aspect of the upper extremity were noted. An abnormal right upper lung shadow with cavitation (Figure 1) was noted upon radiography at an outside clinic, and he was referred to our hospital.

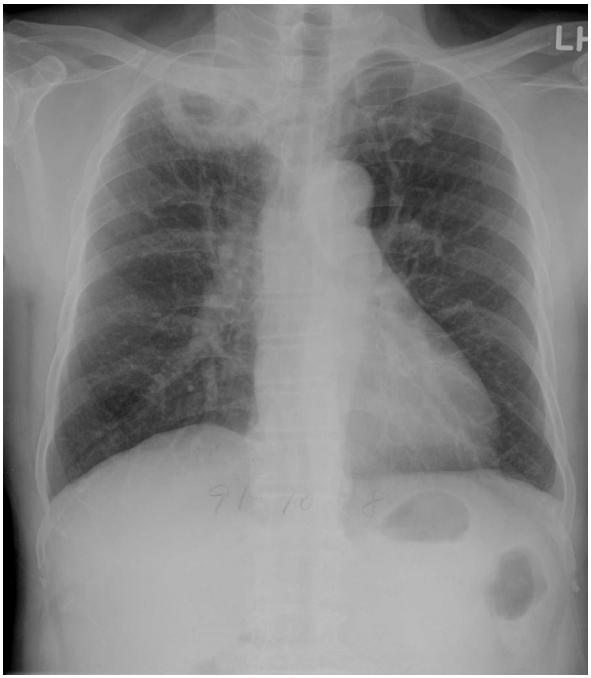

Figure 1: Pre-treatment chest radiograph.

- A series of examinations were performed, including chest CT,CT-guided lung biopsy, bone scan, chest MRI, and tumor markers. The results indicated central necrotic squamous cell carcinoma over the apical region of the right upper lobe (Figure 2) with extrathoracic extension into the right lower neck with involvement of the brachial plexus (Figure 3). Evidence of vascular encasement, mediastinal lymphadenopathy, and bone metastasis were not observed.

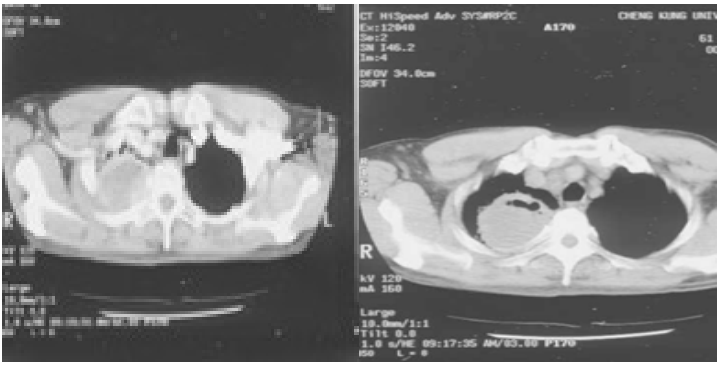

Figure 2: Pre-treatment chest CT: SqCC of RUL with central necrosis

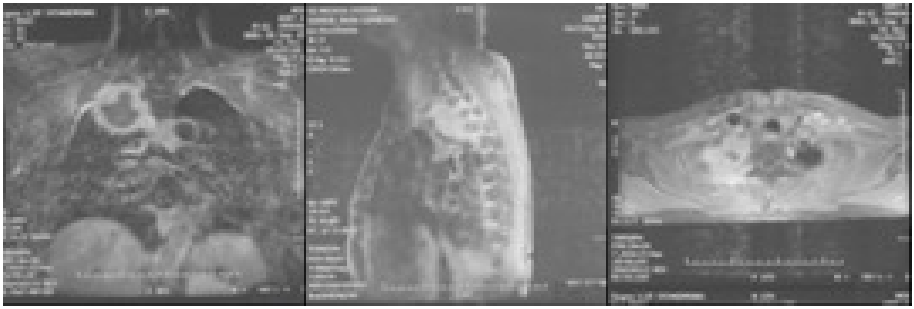

Figure 3: Pre-treatment MRI: extrathoracic extension into the right lower neck to the involvement of the brachial plexus

- The clinical stage of this case was diagnosed as cT4N0N0, cstage IIIA.
- Preoperative R/T with 3000 cGy was administered. Combined surgical resection was performed 3 weeks after completion of R/T.
- Surgical access was via high right thoracotomy from the neck root (the level of the C7 spine) downward to the anterior chest wall (Figures 4 & 5).
- The surgical approach to removal of the rib head was by transection of the transverse process of the T-spine and via the costotransverse foramen (Figures 4 & 5).

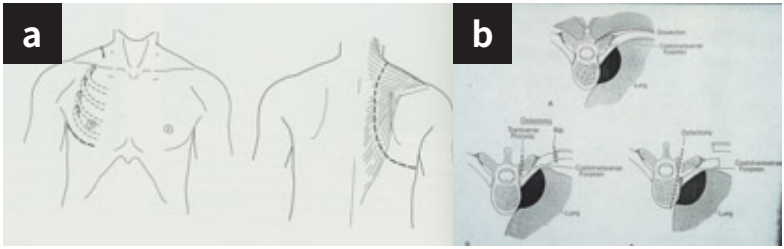


Figure 4: (a) High posterolateral thoracotomy. (b)The surgical approach for removal of the rib head was transection of the transverse process and via the costotransverse foramen.

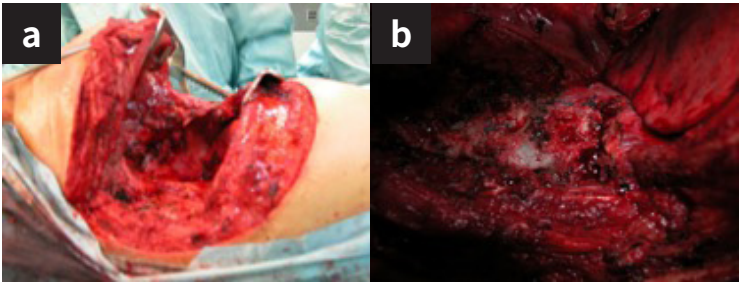


Figure 5: (a) Overhead view of the high right posterolateral thoracotomy. (b) Closed view of the thoracic vertebral body after removal of the transverse processes and ribs.

- Surgical procedures consisted of the removal of the RUL of the lung with its associated chest wall structures (1st-4th transverse process and ribs) (Figures 5 & 6), as well as mediastinal lymphadenectomy. The tumor size was 5.5 cm. The final pathologic stage was ypT3N0M0 (8th ed), yp IIB. Postoperative chest radiography was performed (Figure 7).

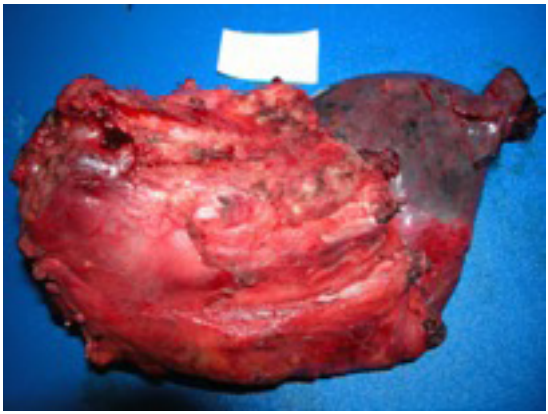

Figure 6: Resected specimen: RUL of the lung with the 1st-4th ribs

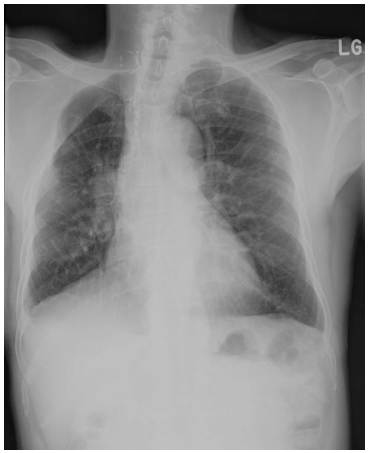


Figure 7: Chest radiography 8 months postoperatively

## *Clinical Pearls*

- The surgical approach for the Pancoast tumor[4, 5]. A high posterolateral(Shaw-Paulson)approach for the posterior-located Pancoast tumor(Figure 4a). Anterior-manubrial sternal approach for anterior-located Pancoast tumors, particularly those invading the subclavian vessels(Figure 4b).
- The prognostic factors of the Pancoast tumor[6, 7].Multivariate regression analysis: N2/N3 disease and methods of therapy. Method of therapy: Induction chemoradiotherapy plus surgery is preferred.
- Clinicians should consider upper lobe lung cancer with brachial plexus involvement when adults present with upper anterior chest wall pain and numbness over the upper inner aspect of the upper extremity along the distribution of the T1 dermatome.
- However, the almost complete absence of symptoms from the lung and this special initial clinical manifestation of superior sulcus carcinoma with shoulder pain are responsible for the observed delay in diagnosis in most cases, because patients are initially evaluated for cervical arthritis, shoulder bursitis, or rotator cuff injury from orthopedic surgeons, neurologists, and rheumatologists. Therefore, chest radiography is required as the initial survey when a diagnosis of Pancoast tumor is suspected [1].
- Magnetic resonance imaging (MRI) can show the tumor's spread and provide a guide for surgery [2].

- Treatment for Pancoast tumors is varied and involves a combination of chemotherapy, radiation, and surgery. The treatments have shifted from a bimodal regimen (preoperative radiotherapy [R/T] + surgery) to trimodal treatment (induction chemoradiotherapy plus surgery), and now trimodality is considered standard treatment[3]. Therefore, chemotherapy and R/T are the first steps before surgery. Then the tumor is reevaluated with another CT scan or other imaging test. Surgery ideally takes place 3 to 6 weeks after chemotherapy and radiation before any scarring might complicate the surgical procedure.

***References***


1. Foroulis, C.N *et al*. K. Superior sulcus (Pancoast) tumors: current evidence on diagnosis and radical treatment. J. Thorac. Dis., 5 Suppl 4 (Sep 2013), S342-358.
2. Guerrero, M. Pancoast Tumor Imaging https://emedicine.medscape.com/article/359881-overview. 2015.
3. Sethi, S. Pancoast Tumor, Cleveland Clinic https://www.clevelandclinicmeded.com/online/monograph/lung-cancer/pancoast-tumor.asp.
4. Dartevelle, P. and Macchiarini, P. Surgical Management of Superior Sulcus Tumors. Oncologist, 4 (1999), 398-407.
5. Barbetakis, N. Pancoast Tumors: Surgical Approaches and Techniques. 2012.
6. Attar, S *et al*. J. S. Superior sulcus (Pancoast) tumor: experience with 105 patients. Ann. Thorac. Surg., 66 (Jul 1998), 193-198.
7. Arcasoy, S. M *et al*. S. E. Superior pulmonary sulcus (Pancoast) tumors - UpToDate https://www.uptodate.com/contents/superior-pulmonary-sulcus-pancoast-tumors. 2018.

# Resection of a stage III non-small cell lung cancer with an endobronchial lesion

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## *Patient profile*

Case presentation

- 52-year-old woman
- Public servant
- Complained of cough for 1 week with some whitish sputum
- Hemoptysis noted off and on for several days

Medical history

- No known systemic disease
- No history of tobacco, alcohol, or drug use
- No pets
- Unremarkable family history

Physical examination

- Heart rate: 100 BPM
- $SpO_2$: 97% under ambient air
- No obvious wheezing or crackle over either lung
- No clubbing fingers
- No leg edema

Laboratory panels

- Normal CBC and biochemistry
- CEA: 1.2 ng/mL, SCC: 0.7 ng/mL, TPA: 34.0

## Chest radiograph (Figure 1)

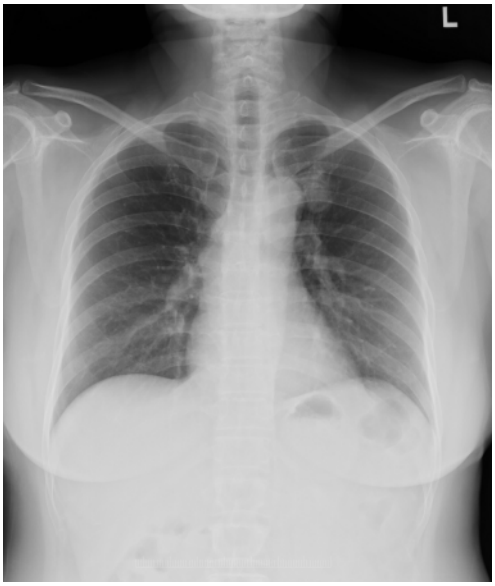


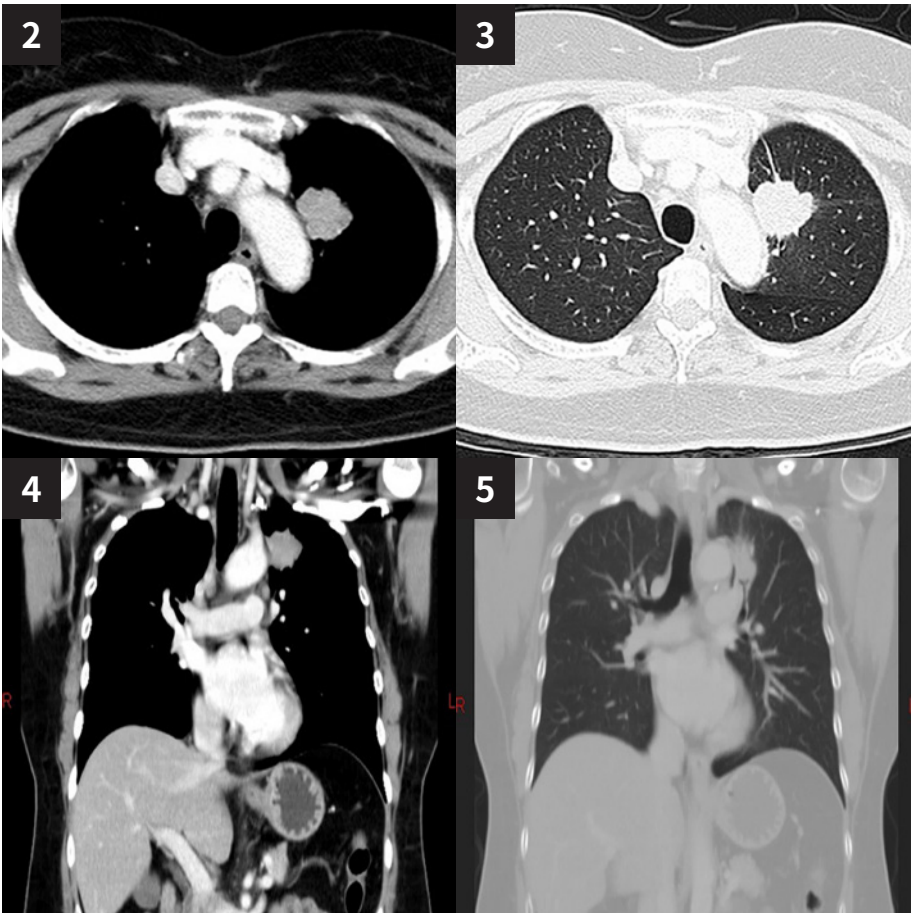

Figure 1: CXR: Left upper lobe nodule

## Pulmonary function test

| Parameter | Value (% predicted) |
|---|---|
| FVC | 97.4 |
| $FEV_1$ | 103.5 |
| $FEV_1/FVC$ | 90.49 |
| $FEF_{25\%-75\%}$ | 125 |
| Conclusion: normal pulmonary function | |

## Cardiac evaluation

- Impaired LV relaxation
- Mild mitral valve and tricuspid valve regurgitation
- Interventricular septal thickness hypertrophy




(Figure 2-5): Chest CT: Bronchogenic tumor in the left upper lobe of the lung

- Tumor size: 2.5 cm (greatest dimension)
- Visceral pleura invasion (+)
- Left upper lobe bronchus invasion (+)

Diagnostic process

- Chest CT revealed a mass-like lesion in the left upper lobe, which was suspected to be lung cancer, clinical stage T2aN0MB (according to the AJCC cancer staging 7th ed., 2010), stage IB.
- Bronchoscopy revealed an endobronchial lesion in the left upper lobe bronchus, with atypical mucosa change under AFI and heterogeneous consolidation lesion under EBUS (Figure 6).
- Pathology of the endobronchial biopsy specimen revealed adenocarcinoma, which was positive for TTF-1.
- Left upper lobe lobectomy by VATS and lymph node dissection were performed, and the pathological report revealed pT2aN2Mx, stage IIIA.
- After surgery, four cycles of vinorelbine/cisplatin were administered for adjuvant chemotherapy.
- After adjuvant chemotherapy, the patient's disease condition remained stable, and the patient is still followed up regularly at our OPD.

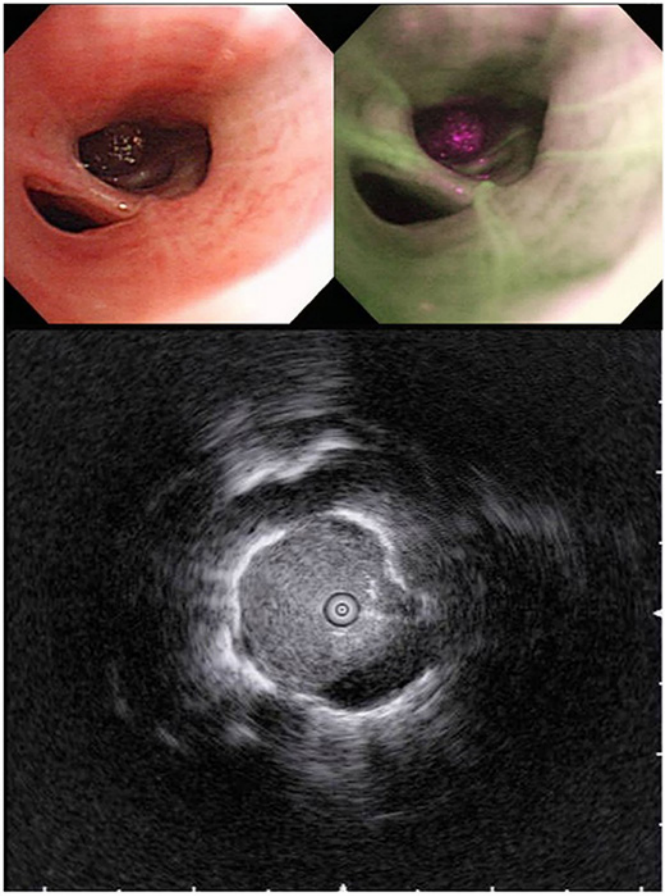


Figure 6: Bronchoscopy: endobronchial lesion in the left upper lobe bronchus

- AFI: peripheral mucosa invasion with magenta pattern
- EBUS: peribronchial heterogeneous consolidation pattern Tumor size: 2.5 cm (greatest dimension)

## *Clinical Pearls*

- Approximately one-third of patients with non–small-cell lung cancer (NSCLC) have stage III, locally advanced disease at diagnosis.
- Surgery with pre- and postoperative chemotherapy has been the preferred local treatment for patients with resectable disease.
- Targeted therapy, immunotherapy, and other non-cytotoxic drugs are also being investigated, and may play a greater role in the future.

***Abbreviations***

CBC, complete blood count; CEA, carcinoembryonic antigen; SCC, squamous cell carcinoma antigen; TPA, tissue polypeptide antigen; $FEV_1$, forced expiratory volume in one second; $FEF_{25\%-75\%}$, forced expiratory flow at 25-75%; FVC, forced vital capacity; CT, computed tomography; AJCC, American Joint Committee on Cancer; AFI, autofluorescence Imaging; EBUS, endobronchial ultrasound; TTF-1, thyroid transcription factor-1; VATS, video-assisted thoracic surgery; OPD, ; CXR, chest radiography

***References***


1. Antonia SJ *et al.* Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med. 2017 Nov 16;377(20):1919-1929.
2. Yoon SM *et al.* Therapeutic management options for stage III non-small cell lung cancer. World J Clin Oncol. 2017 Feb 10;8(1):1-20.

# III.Treatment of inoperable Stage III lung cancer

Unresectable stage III NSCLC has a wide range of disease conditions, including bulky mediastinal LNs, locally advanced tumor with vital organ involvement, and metastasis to the ipsilateral lobe. For patients with those conditions, primary resection may not be possible; instead, they will need to be treated by various treatment modalities. Local radiation therapy may be insufficient. Definitive CCRT is the current standard of care for unresectable locally advanced NSCLC patients, especially if they lack a driver mutation. However, the ideal concurrent chemotherapy regimen has not been determined. The most commonly used regimens are etoposide-cisplatin, cisplatin-vinorelbine, and carboplatin-paclitaxel, or cisplatin-pemetrexed for non-squamous histologies. Although maintenance chemotherapy has no role after CCRT, emerging evidence on the use of immunotherapy in such settings is growing. Durvalumab in the PACIFIC study is a good example. Treatment with durvalumab led to a significant increase in progression-free survival in patients with unresectable local advanced NSCLC who received chemoradiotherapy. We should emphasize the need of multi-disciplinary team discussion involving specialists in the relevant fields to assist in decision making and patient care.

***References***


1. Bezjak A *et al.* Definitive and Adjuvant Radiotherapy in Locally Advanced Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Evidence-Based Clinical Practice Guideline. J Clin Oncol. 2015 Jun 20;33(18):2100-2105.
2. Antonia SJ *et al.* Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med. 2017 Nov 16;377(20):1919-1929.

# A case of unresectable locally advanced NSCLC treated with definitive concurrent chemoradiotherapy

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[3]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, China Medical University Hospital, Taiwan

## *Patient profile*

Case presentation

- 65 y/o man
- NSCLC diagnosed in routine health exam without active complaint

History

- Gastritis and colon polyps
- No regular medication
- Smoker
- Unremarkable family history

Physical exam

- Performance status 0
- Body weight 68.8 kg [baseline 72 kg; < 5% loss]
- No neck mass
- No wheezing during chest breathing examination

Laboratory findings

- Complete blood count and biochemistry largely normal

CXR(Figure 1)

- 3/14/2015: bulging right mediastinum
- 3/23/2018: mild fibrosis in the bilateral hilum

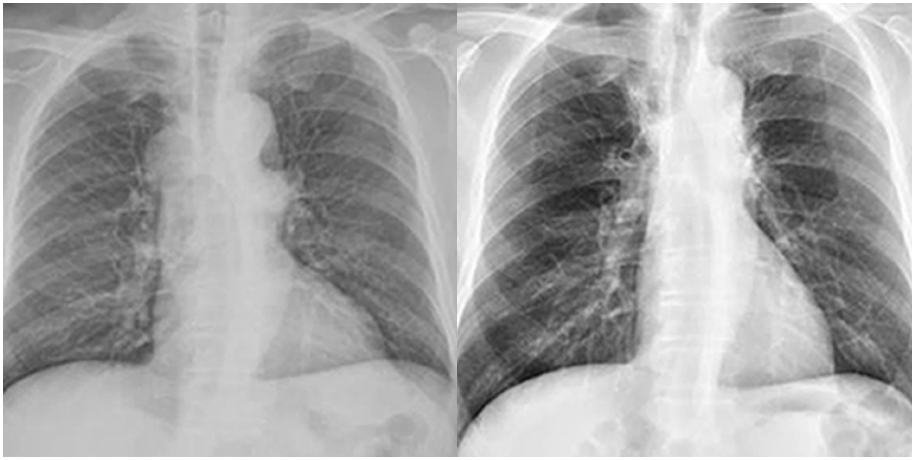


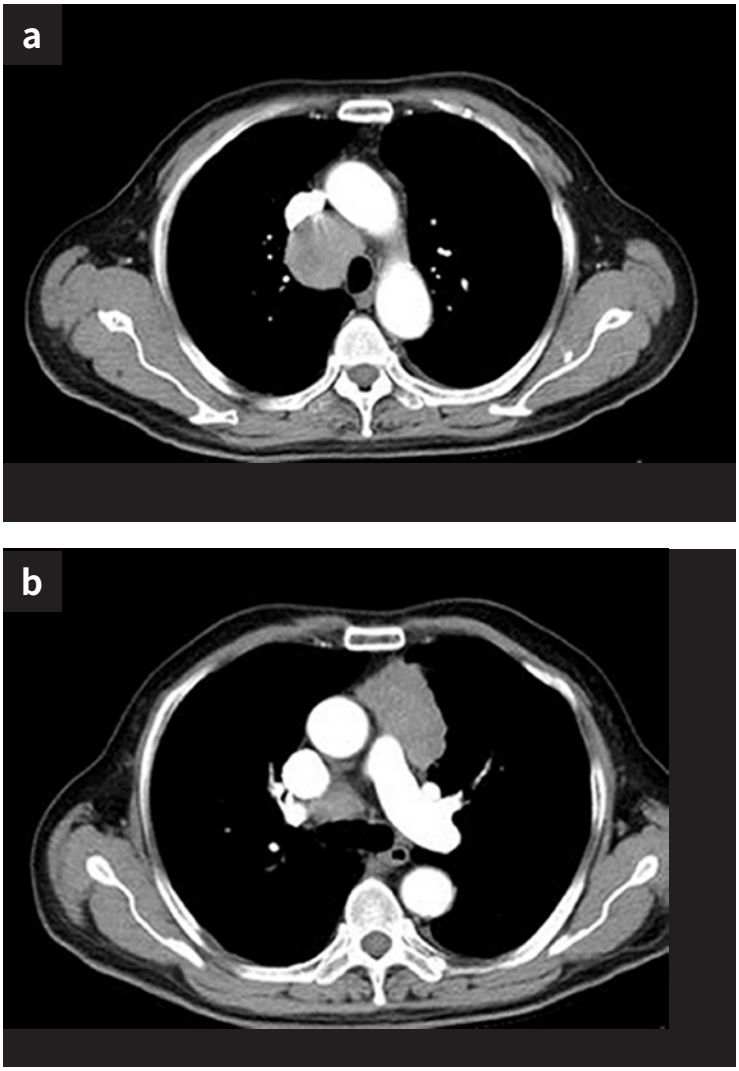
Figure 1: CXR performed on 04/08/2015 and 03/23/2018

PFT

- 3/13/2015 $FEV_1$= 2.58 (L) = 98.9% prediction

CT

- 4/8/2015 report: bilateral mediastinal masses(Figures 2a & 2b)




Figures 2a & 2b: CT performed on 4/8/2015. 2a: upper/middle; 2b: lower/coronal

- 8/4/2017 report: stable disease; 6/15/2018 report: partial response (Figures 3)

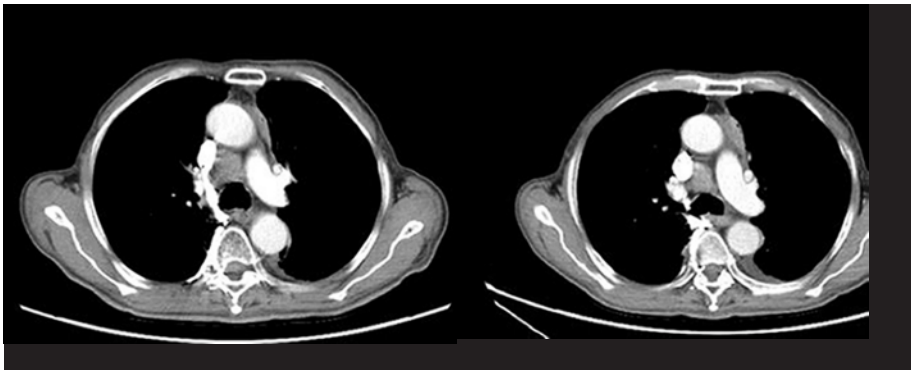


Figure 3: CT performed on 8/4/2017 and 6/15/2018

PET

- 4/29/2015 report: malignancy at the LUL/left anterior mediastinum and bilateral mediastina (Figures 4)

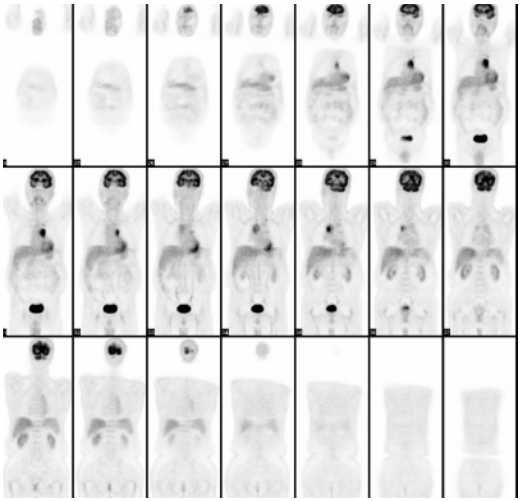


Figure 4: PET performed on 4/29/2015

Pathology

- 4/22/2015 4R LN EBUS biopsy indicated no malignancy; aspiration cytology indicated adenocarcinoma; subsequent LUL biopsy in Nov 2015 indicated adenocarcinoma, wild-type *EGFR, ALK*-negative

Stage

- AJCC 7th cT4 (mediastinum invasion) N3 (contralateral) M0 stage IIIb (6/10/2015 lung board) [AJCC 8$^{th}$ cT4N3M0 stage IIIC]

Treatment

- C/T Taxotere/Carboplatin 5/6/2015–10/28/2015
- RT: LUL mass and involved LN 60 Gy in 30 Fx: 6/10/2015–7/21/2015 (adaptive RT after 36 Gy due to mild weight loss (68.6 kg on 6/4/2015 to 66.9 kg on 7/16/2015) and loose RT fixation)(Figures 5)

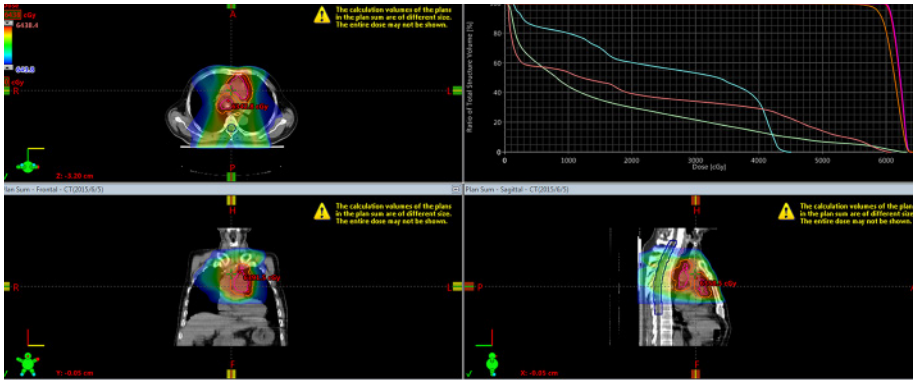


Figure 5: RT planning (summed) isodose and dose volume histogram

- No obvious ≥ grade III non-hematological toxicity during CCRT; no ER visit or hospital admission during CCRT

Follow-up

- Regular FU by chest physician, last FU 9/13/2018: stable disease; no ER visit or admission after CCRT

## *Clinical Pearls*

- Upfront definitive CCRT is the current standard of care for unresectable locally advanced NSCLC patients with "good" status [1,2], especially if no driver mutation is identified [3].
- Long-term [up to 1 year] FU might be needed (at least for some cases) to ascertain the disease status [4,5].
- For current patients who show no progression after CCRT, consolidative durvalumab should be considered, as suggested since the 2017 NCCN NSCLC guidelines [6].

***Abbreviations***

AJCC: American Joint Committee on Cancer; ALK: anaplastic lymphoma kinase; C/T: chemotherapy; CCRT: concurrent chemoradiotherapy; CT: computed tomography; CXR: chest radiography; EBUS: endobronchial ultrasound; EGFR: epidermal growth factor receptor; ER: emergency room; $FEV_1$: forced expiratory volume in one second; FU: follow-up; Fx: fraction; LN: lymph node; LUL: left upper lobe; NCCN: National Comprehensive Cancer Network; NSCLC: non-small cell lung cancer; PET: positron emission tomography; PFT: pulmonary function test; RT: radiotherapy

***References***


1. Bezjak A *et al.* Definitive and adjuvant radiotherapy in locally advanced non-small-cell lung cancer: American Society Of Clinical Oncology clinical practice guideline endorsement of the American Society For Radiation Oncology evidence-based clinical practice guideline. J Clin Oncol. 2015 Jun 20;33(18):2100-5.
2. Cardenal F *et al.* Concurrent systemic therapy with radiotherapy for the treatment of poor-risk patients with unresectable stage III non-small-cell lung cancer: a review of the literature. Ann Oncol. 2015 Feb;26(2):278-88.
3. Hsia TC *et al.* Comparative effectiveness research of concurrent chemoradiotherapy vs epidermal growth factor receptor tyrosine kinase inhibitor in the treatment of clinical stage IIIb lung adenocarcinoma patients with mutant EGFR. Thorac Cancer. 2018 accepted . doi: 10.1111/1759-7714.12847
4. Senan S *et al.* Literature-based recommendations for treatment planning and execution in high-dose radiotherapy for lung cancer. Radiother Oncol. 2004 May;71(2):139-46.
5. De Ruysscher D *et al.* European Organisation for Research and Treatment of Cancer recommendations for planning and delivery of high-dose, high-precision radiotherapy for lung cancer. J Clin Oncol. 2010 Dec 20;28(36):5301-10.
6. Antonia SJ *et al.* Durvalumab after Chemoradiotherapy in Stage III non-small-cell lung cancer. N Engl J Med. 2017 Nov 16;377(20):1919-29.

# A case of lung squamous cell carcinoma, cT4N3M0, stage IIIc in which standard concurrent chemoradiation therapy was performed

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## *Patient profile*

Case presentation

- A 65-year-old man with a history of smoking
- Initial symptoms included fever, hoarseness, easy choking, and body weight loss over 5 kg in the previous 6 months
- CXR showed a prominent left hilum and several nodules in the left lung field

Medical history

- A retired car factory worker
- Cigarette smoking 1 pack per day over 40 years
- Frequent exposure to incense and burning paper-money
- Betel nut history for over 40 years
- Moderate obstructive sleep apnea (AHI: 20.4/hr)
- Thalassemia
- Denied other systemic disease
- No regular oral medication
- Unremarkable family history

Physical examination

- Eastern Cooperative Oncology Group (ECOG) performance status: 0
- $SpO_2$: 97-99% under ambient air
- Left vocal cord paralysis
- Clear breathing sound, crackle(-), rale(-), wheezing(-)

Laboratory panels

- Microcytic anemia, other biochemistry data unremarkable
- Tumor marker SCC: 9.6 ng/mL (normal < 2.5 ng/mL)

Chest radiograph (Figure 1)

- Enlarged left hilum and several nodules in the left lung field

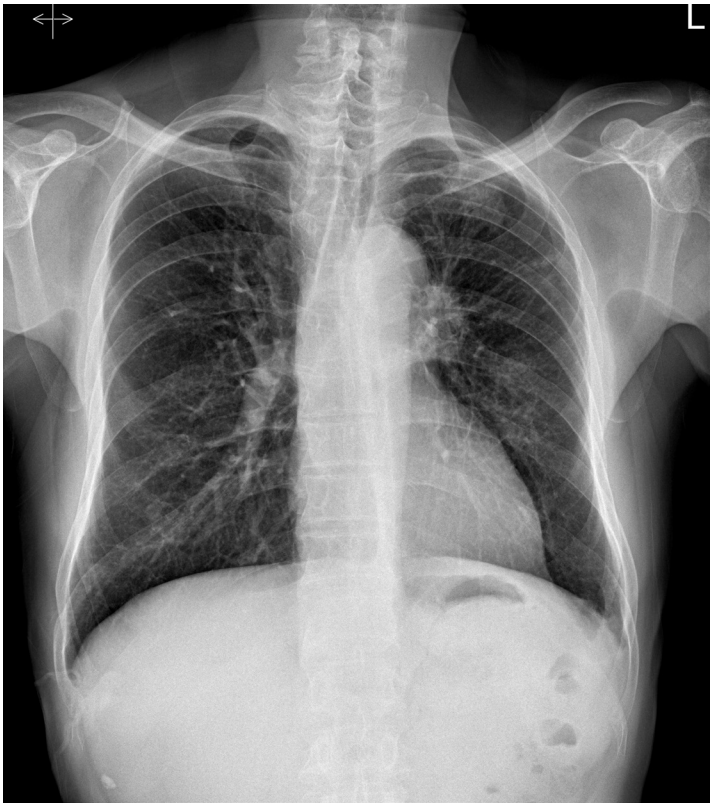
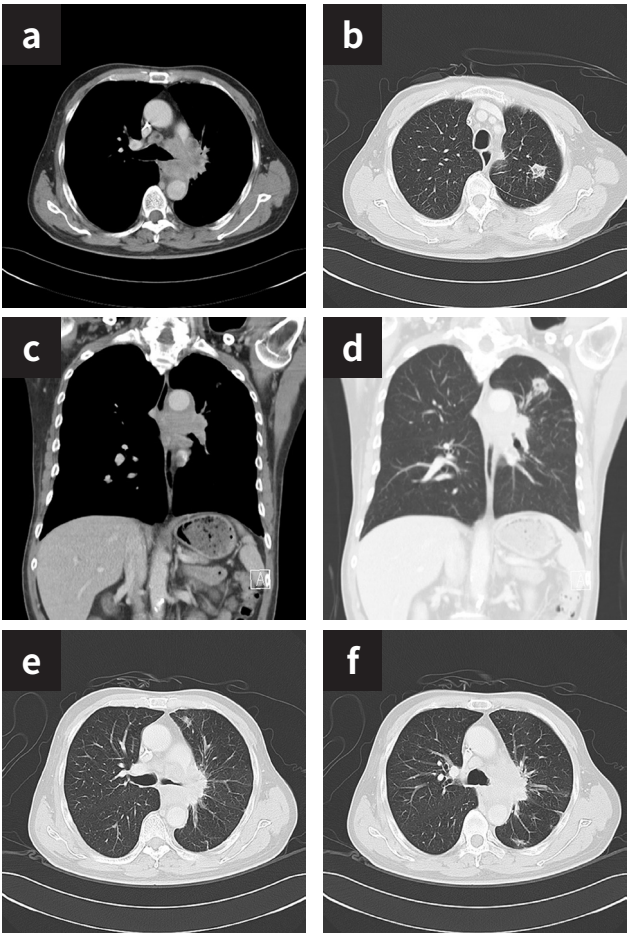



Figure 1

Chest CT findings (Figures 2a-2f)

- (2a-2b) A 5.3 x 4.2-cm spiculated mass at the left pulmonary hilum with mediastinum invasion, left main bronchus encasement, and confluent lymphadenopathy
- (2c-2f) Ground glass with solid component radio-opacity in the left lung, suspected metastasis.




Figures 2a-2f

Diagnostic process

- Bronchoscopic biopsy indicated squamous cell carcinoma
- Whole body bone scan confirmed no bone metastasis. Brain MRI confirmed no brain metastasis. The clinical stage was cT4N3M0, stage IIIC (AJCC 8$^{th}$ Ed.)

Treatment course

- Radical intent definitive concurrent chemoradiation, total 6000 cGy in 30 fractions was delivered to the left hilar and left upper lobe lesions concurrent with chemotherapy cisplatin and vinorelbine.
- Durvalumab for maintenance therapy was scheduled.

Radiation therapy planning map (Figure 3)

- 6000 cGy in 30 fractions with the ARC technique for the left hilar tumor and left upper lobe metastatic lesion

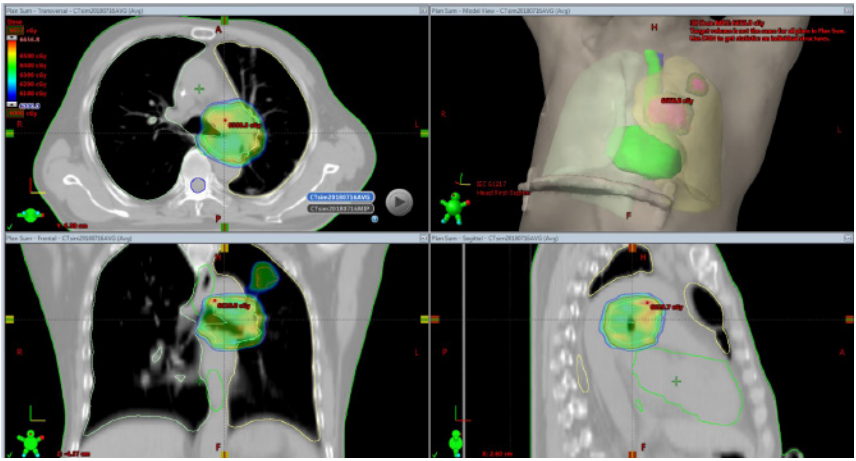


Figure 3

## *Clinical Pearls*

- Various treatment modalities are available for stage III non-small cell lung cancer (NSCLC).
- For stage III NSCLC patients with separate lung nodules in different lobes, whether to treat with standard concurrent chemoradiation therapy or chemotherapy alone remains controversial.
- Multidisciplinary team discussion involving specialists in the relevant fields is vital for decision making and patient care.

***References***

1. Antonia SJ *et al.* Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med. 2017 Nov 16;377(20):1919-1929.
2. Curran WJ Jr *et al.* Sequential vs Concurrent Chemoradiation for Stage III Non–Small Cell Lung Cancer: Randomized Phase III Trial RTOG 9410. J Natl Cancer Inst. 2011 Oct 5;103(19):1452–1460.

# Case III – Durvalumab treatment in unresectable T4N3M0 non-small cell lung cancer

***Hung-Jen Chen***

Division of Pulmonary and Critical Care, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan.

## *Patient profile*

Case presentation

- A 66-year-old man had a smoking history of one pack a day over 30 years.
- A 6.6-cm mass in the left upper lobe of the lung was observed incidentally on chest radiography when he was hospitalized due to duodenal ulcer with active bleeding.

Medical history

- Unremarkable medical and family history

Physical examination

- No neck lymphadenopathy
- Mild decreased breath sound and wheezing over the bilateral lung fields

Laboratory panels and pulmonary function test

- Normal biochemistry except high LDH (328 IU/L) and low sodium (129 mmol/L)
- CEA: 21.41 mg/dL (<5 mg/dL = Negative)
- SCC: 0.9 ng/mL (<2.0 ng/mL = Negative)
- $FEV_1$/FVC (Pred): 79% (70%); $FEV_1$ (%P): 1.14 L (50%)

## Chest radiography (Figure 1)

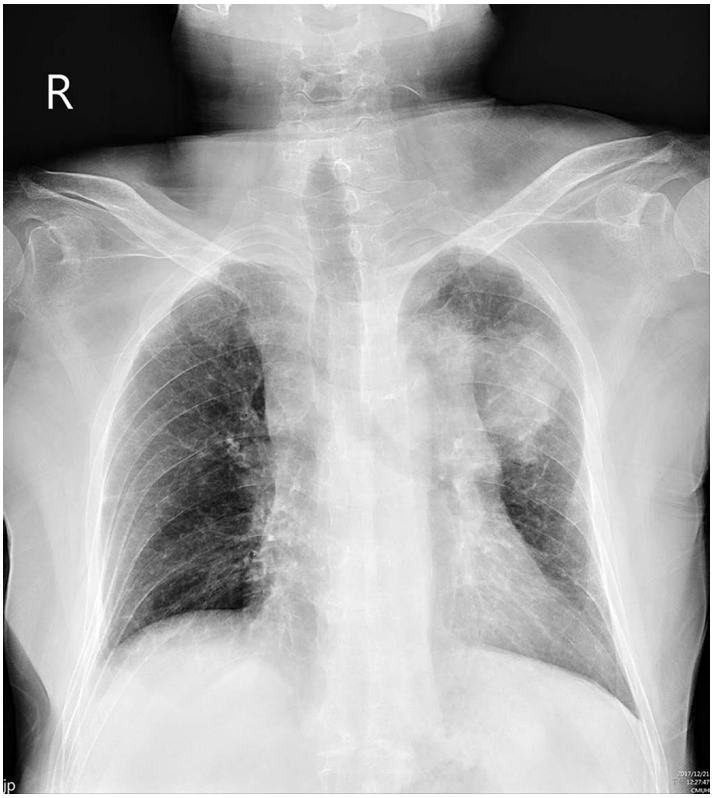



Figure 1:Chest radiography revealed a mass over the left upper lobe of the lung.

Diagnostic process

- Computed tomography (CT)-guided 18-gauge core needle biopsy was performed.
- The pathological findings indicated non-small cell carcinoma with clear cell change. The immunohistochemical findings were focally positive for p40 and negative for TTF-1. Staining with the DAKO 22C3 antibody for PD-L1 was negative (tumor proportion score <1%).
- Positron emission tomography (PET) with 2-[fluorine-18] fluoro-2-deoxy-D-glucose (FDG) showed uptake in the primary tumor in the left upper lobe with invasion to the left mediastinum (T4 disease) and multiple hilar and mediastinal nodes on the left and right sides. Intense FDG uptake was also observed in the right supraclavicular region (N3 disease). The patient was classified as having T4N3M0 clinical stage IIIb ($7^{th}$) (stage IIIc ($8t^{h}$)) disease (Figure 2).

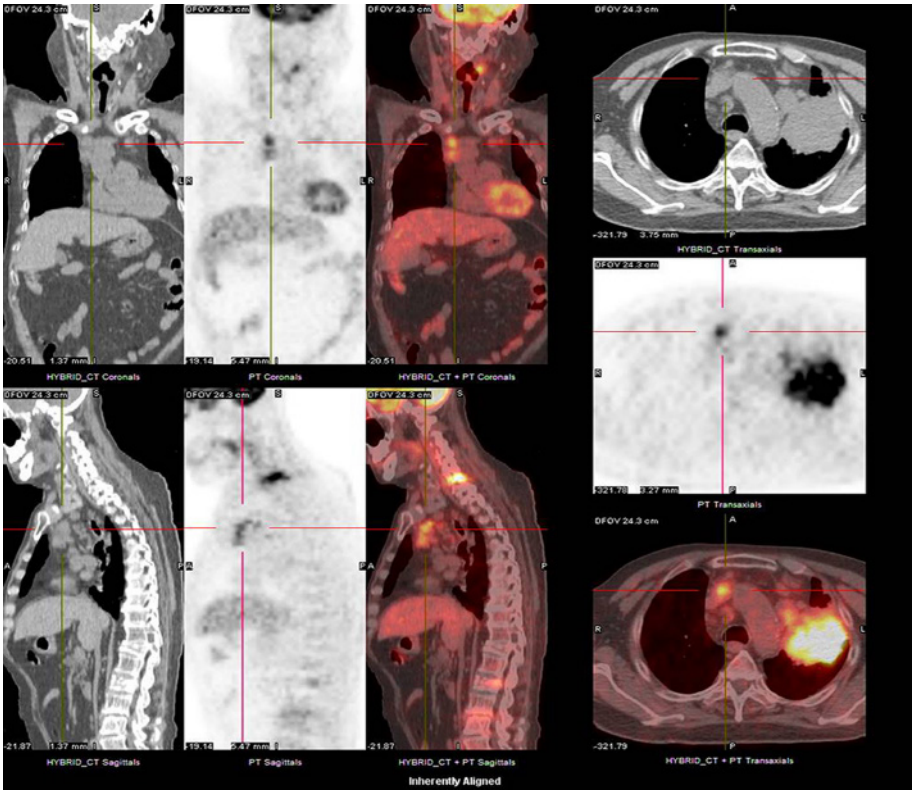



Figure 2:Positron emission tomography with 2-[fluorine-18] fluoro-2-deoxy-D-glucose (FDG) showed uptake in the primary tumor in the left upper lobe with invasion to the left mediastinum (T4 disease) and multiple hilar and mediastinal nodes on the left and right sides. Intense FDG uptake was also found in the right supraclavicular region (N3 disease).

Treatment process

- Etoposide 50 mg/m2 on days 1-5 and cisplatin 50 mg/m$^2$ on days 1 and 15 every 4 weeks for two cycles.
- Concurrent thoracic intensity-modulated radiotherapy with 54 Gy in 30 fractions (lung mean dose 14.25 Gy, spinal cord maximum dose ≤ 45.5 Gy) (Figure 3).

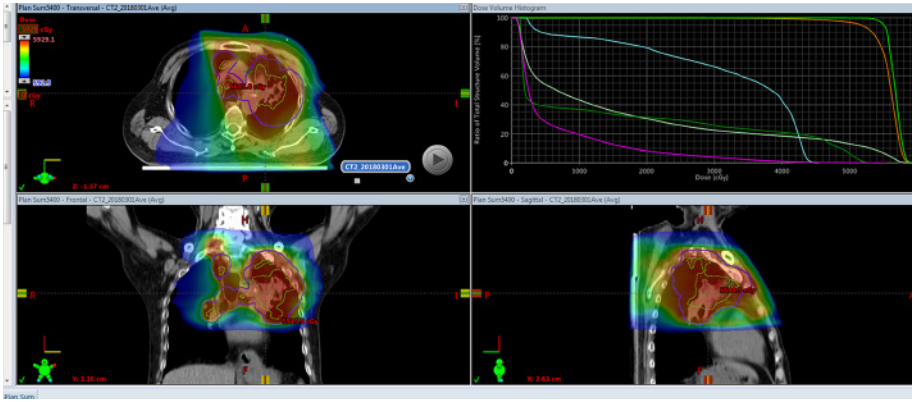


Figure 3:Concurrent thoracic intensity-modulated radiotherapy of 54 Gy in 30 fractions (lung mean dose 14.25 Gy, spinal cord maximum dose ≤ 45.5 Gy).

- CT revealed partial response after chemoradiotherapy (Figure 4).
- Durvalumab (10 mg per kg body weight intravenously) every 2 weeks was administered 48 days after the patient had received chemoradiotherapy.
- Three months later, CT revealed stable disease with durvalumab treatment (Figure 4). CEA declined to 5.05 mg/dL. The patient experienced no durvalumab-specific side effects.

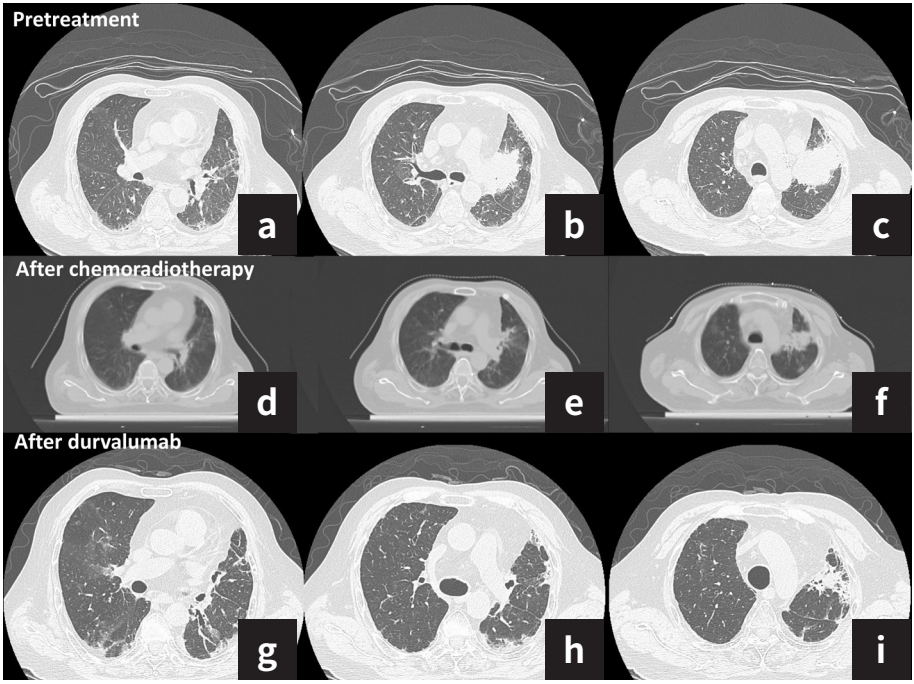



Figure 4:Computed tomography revealed a mass over the left upper lobe with mediastinal nodes (a)-(c), partial response after chemoradiotherapy (d)-(f), and stable disease with durvalumab treatment (g)-(i).

## *Clinical Pearls*

- Concurrent chemoradiotherapy is the treatment of choice for patients with unresectable local advanced non-small cell lung cancer (NSCLC).
- The ideal concurrent chemotherapy regimen has not been determined. The most commonly used regimens are etoposide-cisplatin, cisplatin-vinorelbine, and carboplatin-paclitaxel, or cisplatin-pemetrexed if the tumor has non-squamous histology[1].
- The PACIFIC study showed a significant increase in progression-free survival with durvalumab treatment in patients with unresectable local advanced NSCLC who had received chemoradiotherapy[2].

***References***

1. Postmus, P. E *et al.* Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 28.suppl_4 (2017): iv1-iv21.
2. Antonia, S.J *et al.* Durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer. N Engl J Med. 377.20 (2017): 1919-1929.

# IV.CCRT AE management

Definitive CCRT is the current standard of care for unresectable locally advanced NSCLC patients, although it comes at the cost of increasing side effects. Acute treatment-related morbidities include neutropenia, anemia, lung damage (pneumonitis), and esophagitis.

The incidence of grade 3 or higher pneumonitis accounts for 1% to 16% in those receiving concurrent treatment. Radiation-induced damage to the lung parenchyma remains a dose-limiting factor in chest radiotherapy. The presence of pneumonitis should be carefully evaluated in patients who develop respiratory symptoms or signs, such as dyspnea, cough, fever, malaise, auscultatory crackles, or a pleural rub. When closely comparing the pre-treatment CT, irradiation dosimetric information, and diagnostic CT images, the areas of the lung indicating radiation pneumonitis by CT typically closely align with the irradiated area.

The incidence of grade 3 or higher esophagitis ranges from 0% to 48% in those receiving concurrent treatment. Although esophagitis can be alleviated by empirical symptomatic treatment,endoscopic confirmation may occasionally be helpful.

Steroids,such as prednisone 40 to 60 mg/day, remain the treatment of choice for radiation pneumonitis in the first 2 weeks. Steroid treatment should be tapered slowly over 3 to 12 weeks.

***References***


1. Bezjak A *et al.* Definitive and adjuvant radiotherapy in locally advanced non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline endorsement of the American Society for Radiation Oncology evidence-based clinical practice guideline. J Clin Oncol. 2015 Jun 20;33(18):2100-5.
2. O'Rourke N *et al.* Concurrent chemoradiotherapy in non-small cell lung cancer. Cochrane Database Syst Rev. 2010 Jun 16;(6):CD002140.

# A case of radiation esophagitis during concurrent chemoradiotherapy for clinical stage III NSCLC

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[3]Division of Hematology and Oncology, Department of Internal Medicine, China Medical University Hospital, Taiwan

## *Patient profile*

Case presentation

- 62 y/o man
- Diagnosed in routine surveillance for head and neck cancer; No active c/o

Medical history

- Head-and-neck cancer (oropharynx squamous cell carcinoma) treated with chemoradiotherapy starting 7/29/2011; he experienced local relapse and was treated with salvage surgery 6/14/2016 and UFT.
- The patient quit alcohol/betel/smoking.

Physical exam

- Performance status 1
- Body weight 62.1 kg (6 months previously 61 kg)
- Neck fibrosis
- Chest breathing sound clear

Laboratory

- Complete blood count & biochemistry on 2/2/2015 were unremarkable

PFT

- $FEV_1$ = 2.2 L = 79 % prediction

CXR

- 1/1/2014 & 4/2/2015 indicated increased density in the RLL (Figure 1)

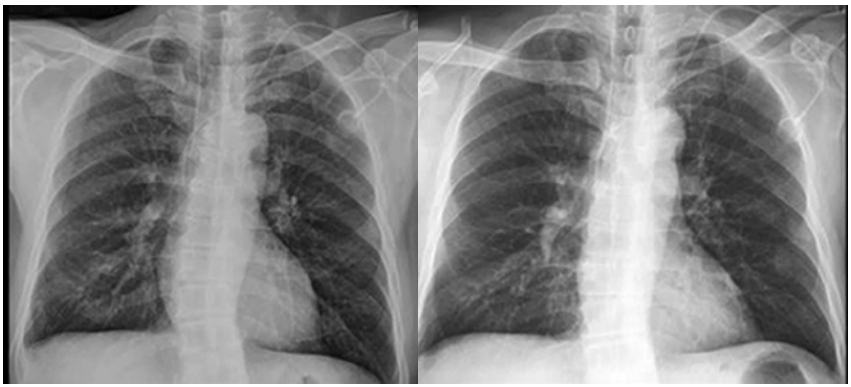

Figure 1: CXR on 1/1/2014 and 4/2/2015

CT

- 7/3/2013 a tiny nodule in the RLL abutting a major fissure [not the one favored later] (Figure 2)

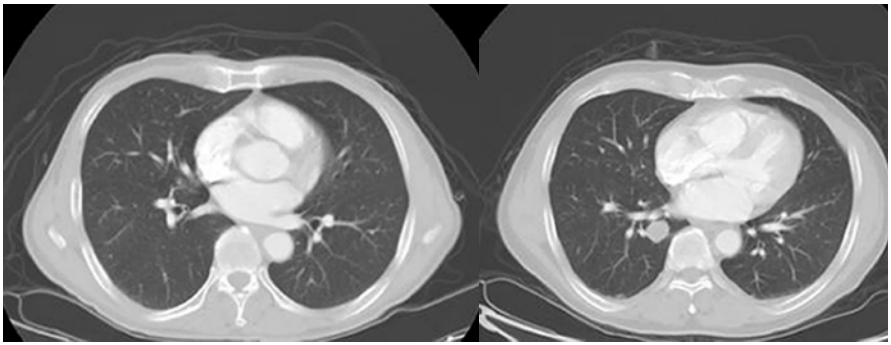

Figure 2: CT on 7/3/2013 and 2/4/2015

- 2/4/2015 report: RLL mass and metastases to the right hilum and subcarinal LNs (Figures 2 & 3a & 3b)

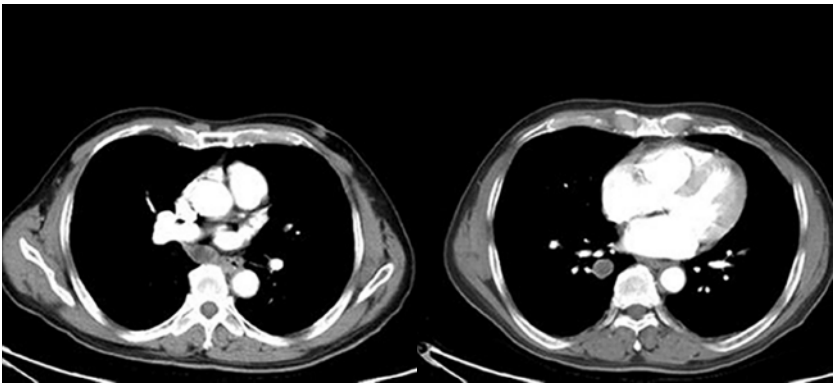

Figure 3a: CT on 2/4/2015: upper and middle

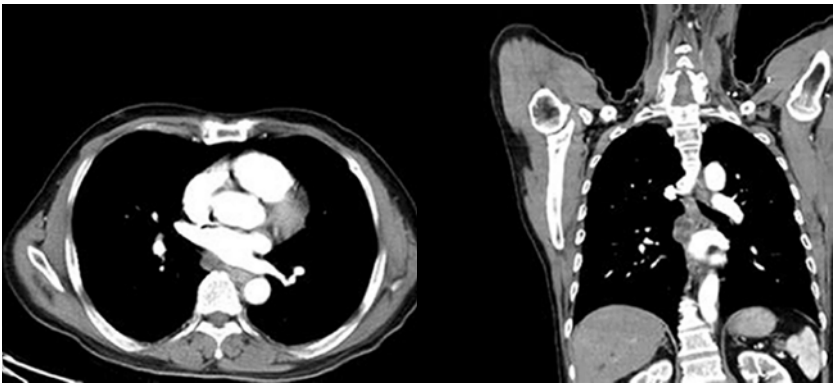

Figure 3b: CT on 2/4/2015: lower and coronal

- 5/25/2015 report: partial response
- 8/28/2015 report: tumor progression

Pathology

- 3/4/2014 EBUS biopsy for Group VII LN: squamous cell carcinoma

ENT

- Clinic 5/5/2015: neck fibrosis, no residual LN metastasis

PET

- 2/24/2015 malignancy in the right lower lung, right hilum/subcarinal, and left upper neck (Figure 4)

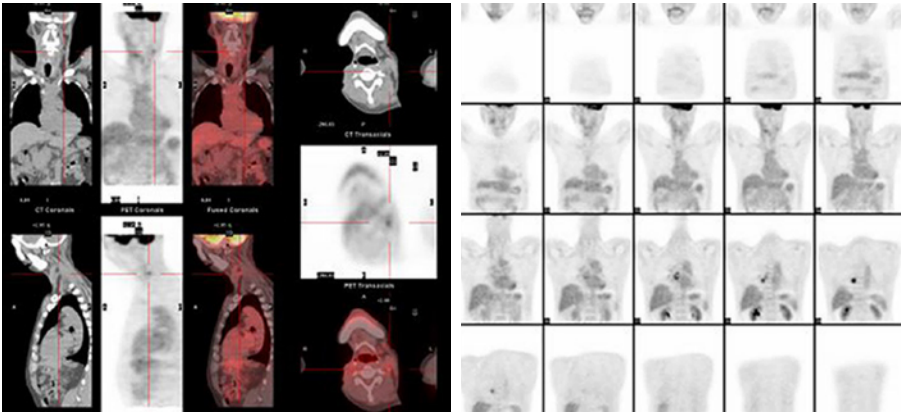

Figure 4: PET on 2/24/2015

Lung board 3/11/2015 indicated AJCC 7th NSCLC cT1N2M0 stage IIIA [AJCC 8th cT1N2 stage IIIA]

Treatment

- C/T paclitaxel & cisplatin 3/3/2015–4/29/2015
- RT: Right lung mass and involved LNs 60 Gy in 30 Fx 3/5/2015–4/15/2015 (Figure 5). Esophageal dose: mean 9.5Gy; maximal 62.2Gy

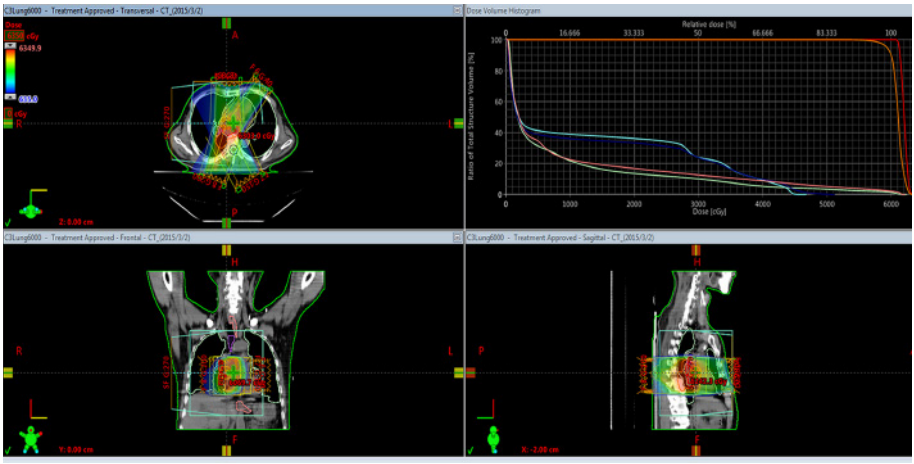

Figure 5: RT isodose distribution and dose volume histogram

- EGD 3/23/2015: 30–33 cm site mucosal oozing of whitish material. Biopsy was performed (Figure 6), and the pathology report indicated ulceration and candidiasis.

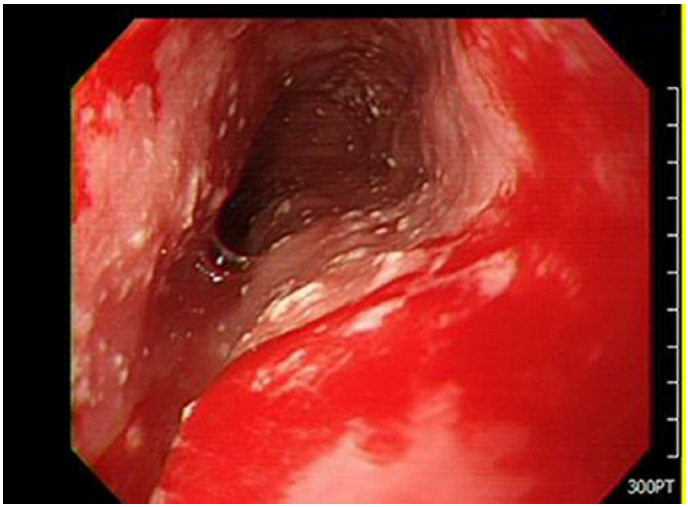


Figure 6: EGD on 3/23/2015

- He complained of odynophagia but had no need of intravenous fluid supply, feeding tube, or hospitalization [Common Toxicity v5: esophagitis grade 2]. Fluconazole 200 mg/day for 14 days was administered starting 4/2/2015 in addition to nystatin gargle. Acetaminophen/tramadol and proton-pump inhibitor were administered, after which symptoms and signs improved.

FU

- Best supportive care after progression in Aug 2015; the patient died on 6/22/2016.

## *Clinical Pearls*

- Upfront definitive CCRT is the current standard of care for unresectable locally advanced NSCLC patients with"good" status [1,2], but carries the cost of increasing side effects like severe acute esophagitis (relative risk 4.96 when compared to sequential chemoradiotherapy)[3]. Usually it can be alleviated by empirical symptomatic treatment [4], but endoscopic confirmation may be occasionally helpful.
- Field cancerization is common in the upper aerodigestive tract [including the lung][5]. It is sometimes difficult to differentiate metastatic and primary lung squamous cell carcinoma.
- For current patients who showed no progression after CCRT, consolidative durvalumab could be considered as suggested since the 2017 NCCN NSCLC guideline[6].

***Abbreviations***

AJCC: American Joint Committee on Cancer ; C/T: chemotherapy; CCRT: concurrent chemo-radiotherapy; CXR: chest radiography; CT: computed tomography; EBUS:endobronchial ultrasound; EGD: esophago-gastroduodenoscopy; ENT: ear, nose, and throat; $FEV_1$: forced expiratory volume in one second ; FU: follow-up; Fx: fraction; H/N: head and neck; LN: lymph node; NCCN: national comprehensive cancer network; NSCLC: non-small cell lung cancer; PET: positron emission tomography; PFT: pulmonary function test; RLL: right lower lobe; RT: radiotherapy

***References***


1. Bezjak A *et al.* Definitive and adjuvant radiotherapy in locally advanced non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline endorsement of the American Society for Radiation Oncology evidence-based clinical practice guideline. J Clin Oncol. 2015 Jun 20;33(18):2100-5.
2. Cardenal F *et al.* Concurrent systemic therapy with radiotherapy for the treatment of poor-risk patients with unresectable stage III non-small-cell lung cancer: a review of the literature. Ann Oncol. 2015 Feb;26(2):278-88.
3. O'Rourke N *et al.* Concurrent chemoradiotherapy in non-small cell lung cancer. Cochrane Database Syst Rev. 2010 Jun 16;(6):CD002140
4. Yazbeck VY *et al.* Management of normal tissue toxicity associated with chemoradiation (primary skin, esophagus, and lung). Cancer J. 2013 May-Jun;19(3):231-7.
5. Wei ZH *et al.* The concept of field cancerization and its clinical application. Zhonghua Kou Qiang Yi Xue Za Zhi. 2016 Sep;51(9):562-5.
6. Antonia SJ *et al.* Durvalumab after chemoradiotherapy in stage iii non-small-cell lung cancer. N Engl J Med. 2017 Nov 16;377(20):1919-29.

# CCRT-related pneumonitis

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## *Case Report*

We present a case of non-small cell lung cancer that initially presented as chronic cough for months in a 41-year-old man with a smoking history. He visited our chest clinic, and a right lower lobe lung nodule around 1 cm in size was incidentally observed on chest CT scan in April 2016. He received serial follow-up chest imaging examinations, which showed enlargement of the right lower lung nodule and mediastinal lymphadenopathies. Lung cancer was highly suspected based on imaging findings. Further FDG-PET scan showed a focal hypermetabolic nodule at the basal right lower lung and hot areas at the right hilum, right paratracheal, and subcarinal lymph nodes, compatible with lung cancer. Video-assisted thoracic surgery (VATS) lobectomy with mediastinal lymph node dissection was performed on 8/24/2017. The final pathological report indicated lung adenocarcinoma, AJCC 7$^{th}$ pT1aN2, stage IIIA, with free surgical margins.The genetic testing indicated that the tumor genotype was *EGFR* wild-type and *ALK* translocation-negative. Further staging brain MRI disclosed no brain metastases. Under the impression of IIIA, N2 disease, he received adjuvant chemoradiation with 5400 cGy in 30 fractions with vinorelbine and cisplatin from September 2017 to November 2017. He underwent all treatments smoothly with minimal acute toxicity.

Two months after radiotherapy, he suffered from mild fever and progressive dry cough. Chest radiography showed increasing right hilum infiltration (Figure 1a).

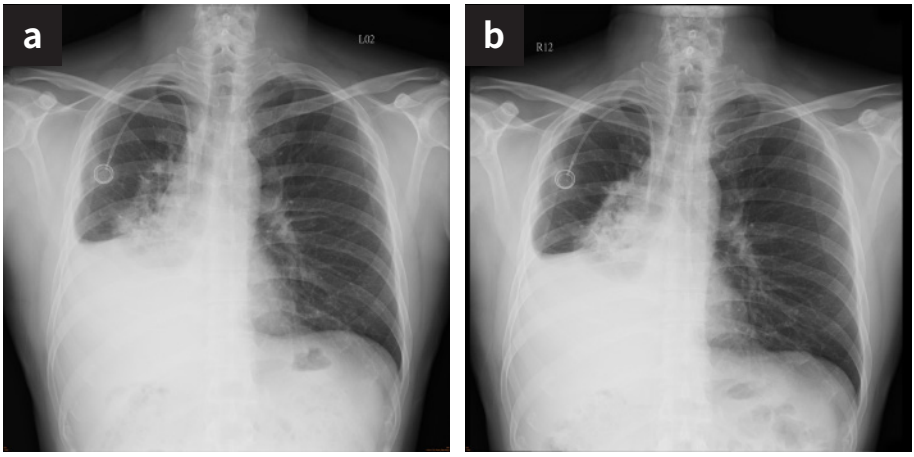


Figure 1: Chest radiograph indicating radiation pneumonitis. (a) First finding of right hilar infiltration and (b) increasing infiltration over the right hilum after antibiotic treatment.

There was no obvious leukocytosis or other signs of infection. He was treated for pneumonia first with oral antibiotics; however, the signs and symptoms progressed over the next 2 weeks with increasing infiltration on follow-up imaging (Figure 1b). Further chest CT scan (Figure 2) revealed ground glass opacity and air space consolidation over the right lung and restricted to the previous irradiated field. Radiation pneumonitis was suspected. Prednisone was administered with an initial dose of 20 mg twice daily with gradual tapering. His symptoms subsided within 2 weeks. Steroids were tapered off over 2 months.

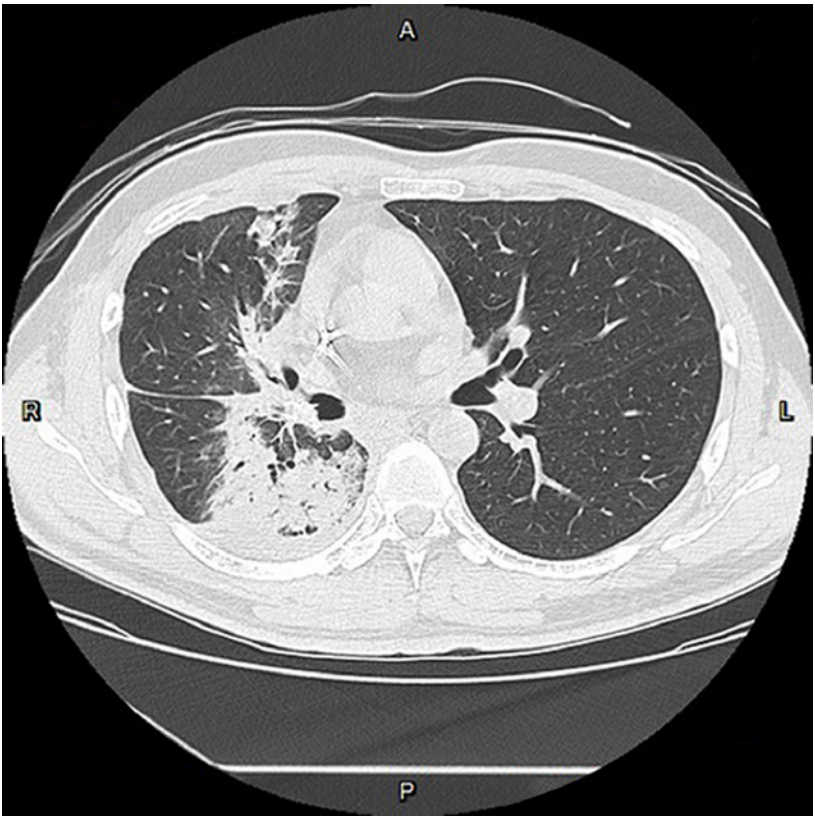


Figure 2: Chest computed tomography scan showed typical radiation pneumonitis findings with lung consolidation restricted to the radiation field across different lobes.

Three months after radiation pneumonitis was diagnosed, chest CT (Figure 3) showed that the consolidation had resolved, with residual post-irradiation changes in the treatment field. Ten months later, post-chemoradiation follow-up indicated no disease recurrence or major toxicity.

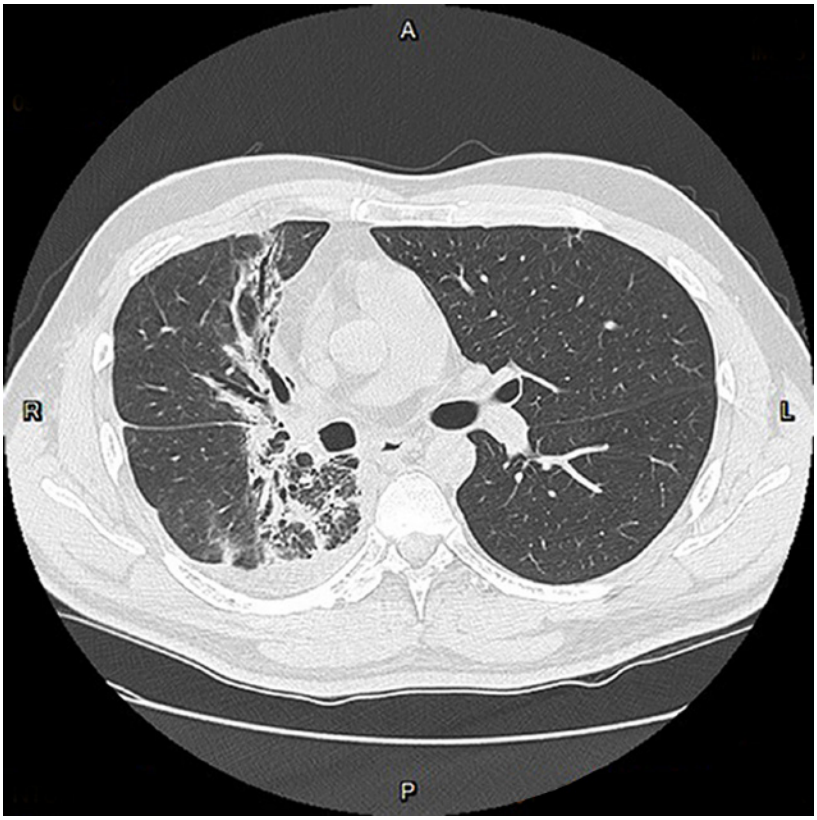


Figure 3: Chest computed tomography scan after steroid treatment for radiation pneumonitis. Lung consolidation resolved with residual post-irradiation change.

## *Summary and Recommendations*

- Radiation-induced damage to the normal lung parenchyma remains a dose-limiting factor in chest radiotherapy.
- Radiation-induced lung injury should be suspected when a patient who has undergone thoracic irradiation develops symptoms or signs such as dyspnea, cough, fever, malaise, auscultatory crackles, or a pleural rub.
- Symptoms caused by acute radiation pneumonitis usually develop approximately 4 to 12 weeks following irradiation, whereas symptoms of late or fibrotic radiation pneumonitis develop 6 to 12 months after radiotherapy.
- The key step in the evaluation of radiation pneumonitis is comparison by the radiation oncologist of pretreatment CT images, containing irradiation dosimetric information, with diagnostic CT images obtained at the time of symptom presentation. Lung involvement of radiation pneumonitis in CT images typically aligns closely with the irradiated area.
- Prednisone (approximately 40 to 60 mg/day) is generally administered for 2 to 4 weeks, with a gradual taper over 3 to 12 weeks.

# V.irAE management

Immune checkpoint inhibitors (ICIs) have demonstrated dramatic improvement in outcomes for select patients with metastatic non–small-cell lung cancer (NSCLC). Though these treatments are generally well tolerated, serious immune-related adverse events (irAEs) can occur. IrAEs tend to occur within 3 months of starting therapy, but some toxicities can occur earlier, such as skin and liver toxicities, whereas gastrointestinal toxicities and endocrinopathies tend to occur after the initial weeks of therapy. Pneumonitis induced by PD-1–directed agents occurring beyond the first 3 to 6 months is extremely uncommon. When PD-1–directed agents are combined with anti–CTLA-4 antibodies, the incidence of irAEs is higher, and the onset of toxicities can be earlier than with PD-1–directed agent use alone. For early detection of irAEs, patients receiving ICIs should undergo routine blood tests, including for renal function, liver function, thyroid function, electrolytes, complete blood count, ACTH, and cortisol levels, at baseline and regularly during treatment.

Fatigue is the most common irAE, followed by nausea.Hypothyroidism is also common, occurring in approximately 8% of patients. Other irAEs, occurring in less than 3% of patients, include hyperthyroidism, hepatitis, adrenal insufficiency, myositis, myocarditis, and type I diabetes. Pneumonitis has been observed in 1% to 5% of patients, and grade 3 or higher pneumonitis occurs in approximately 1% of patients.

The main treatment for irAEs is steroids. High-dose corticosteroids effectively reverse most grade 3 to 4 irAEs when administered early. In patients with severe symptoms, the use of immunomodulatory agents should not be delayed. Tapering of steroids should be performed very slowly over 6 weeks or longer to avoid relapse of

irAEs during tapering. Rechallenging with PD-1–directed agents in patients who have experienced irAEs should be performed with caution. The toxicity should generally resolve to grade 1 before considering restarting ICIs. If grade 3 or 4 toxicity occurs, these drugs should not be restarted. If the patient's cancer is well controlled, there may not be a need to restart the drug.

***References***


1. Zimmermann S *et al*. Immune checkpoint inhibitors in the management of lung cancer. Am Soc Clin Oncol Educ Book. 2018 May 23;(38):682-695.
2. Haanen JBAG *et al*. ESMO Guidelines Committee. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017 Jul 1;28(suppl_4):iv119-iv142.

# A case report-immune-related pneumonitis

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## *Patient profile*

Case presentation

- A 55-year-old man with no smoking or specific occupation history was diagnosed with left upper lobe lung cancer, adenocarcinoma, cT4N3M1b, stage IV (AJCC 7$^{th}$), with bone, multiple lung, LN, left pleura, and probable liver metastases (01-11-2017) (Figure 1). He was healthy prior to diagnosis.
  - *EGFR* mutation: not detected
  - *ALK* (Ventana anti-*ALK* D5F3 IHC assay): negative
  - PD-L1 (Dako anti-PD-L1 22C3 IHC assay): TPS 90%, high expression

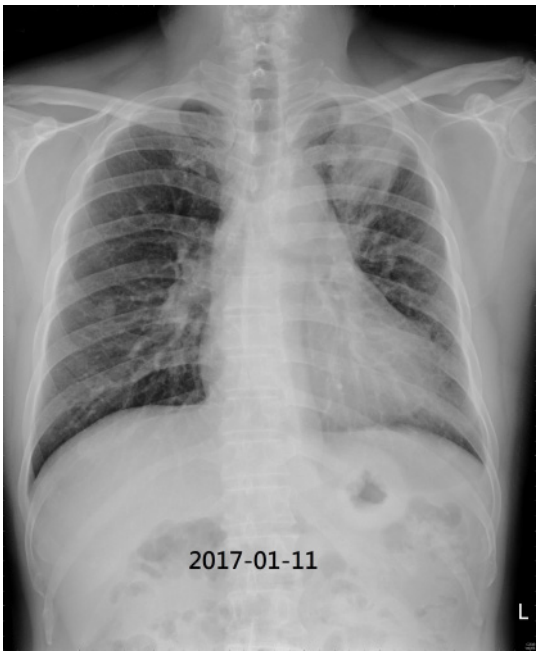


Figure 1: Chest radiography (07-21-2016)

Clinical course

- Taxotere and cisplatin were administered starting 02-10-2017.
- Progressive dyspnea and tumor progression based on imaging results were noted after one cycle of taxotere and cisplatin (Figure 2).

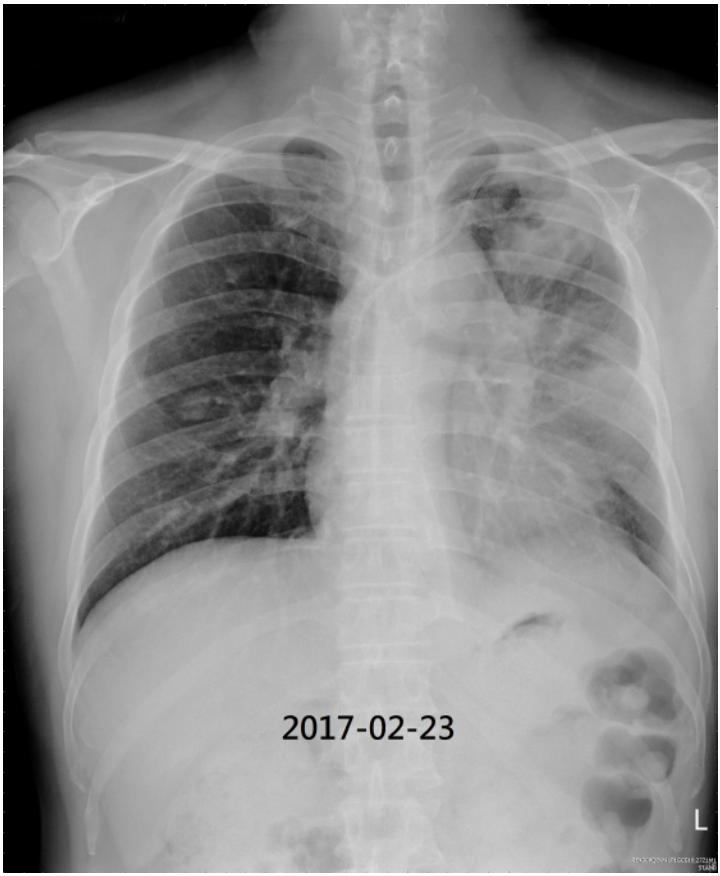


Figure 2: Chest radiography (02-23-2017) after one cycle of taxotere and cisplatin.

- Pembrolizumab was administered starting 03-03-2017 (cycle 1, 03-03-2017; cycle 2, 04-18-2017).
- After two cycles of pembrolizumab, the clinical symptoms and imaging results were improved (Figure 3).

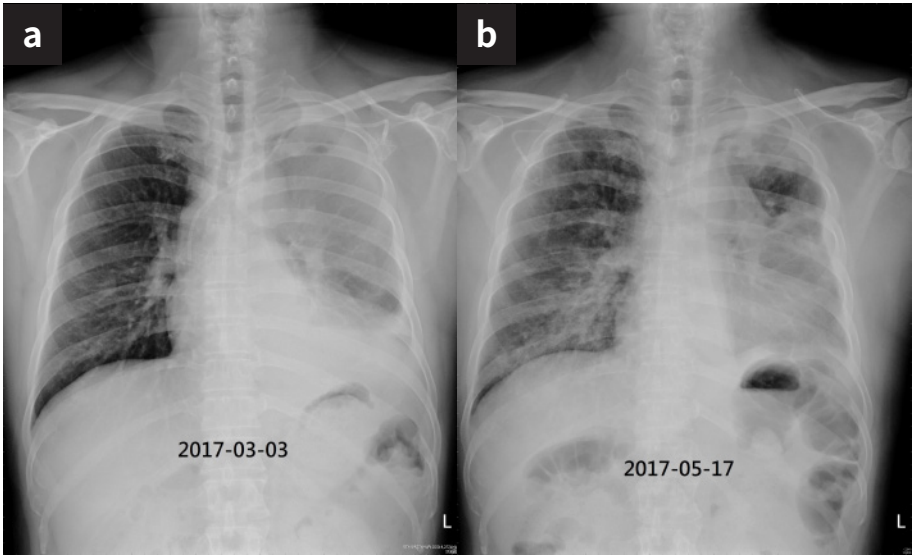


Figure 3: Chest radiography (03-03-2017 and 05-17-2017) after two cycles of pembrolizumab.

- Unfortunately, progressive dyspnea was noted on 05-18-2017. Chest radiography indicated bilateral diffusive consolidation (Figure 4).

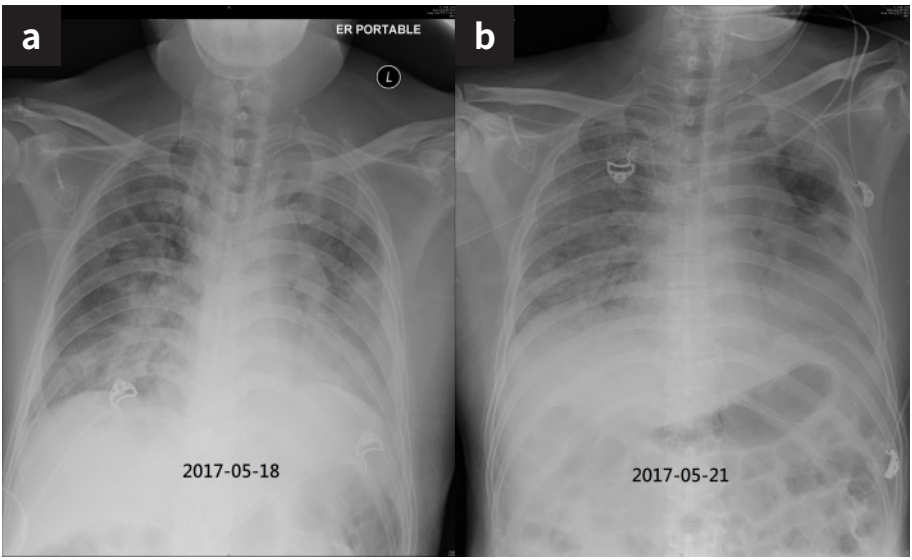


Figure 4: Chest radiography (05-18-2017 and 05-21-2017) showing bilateral diffusive consolidation.

- Chest CT was performed on 05-24-2017 (Figure 5b). The LUL lung cancer lesion had regressed (compared to the chest CT image from 04-28-2017; Figure 5a), but bilateral diffusive consolidation was also noted. Therefore, interstitial pneumonitis was diagnosed.

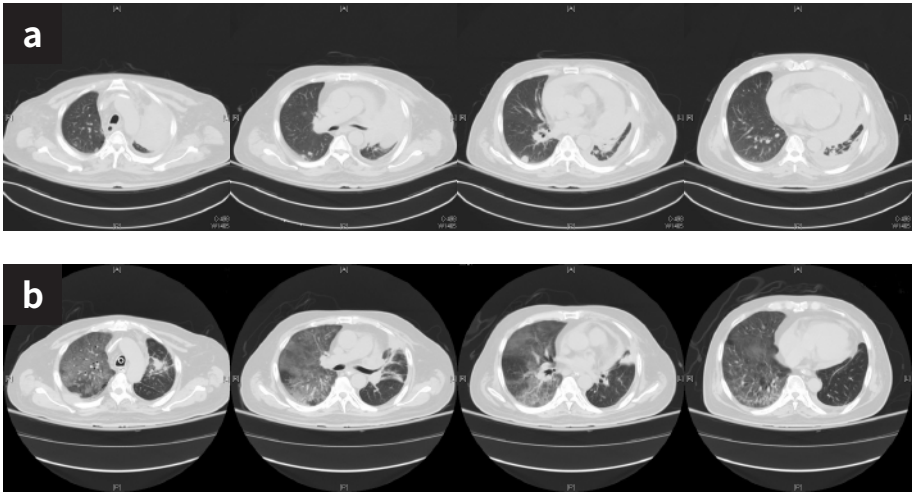


Figure 5: Chest CT (5a, 04-28-2017 and 5b, 05-24-2017). The left upper lobe lung cancer lesion had regressed (compared a to b), but bilateral diffusive consolidation was also noted.

- Both antibiotics and prednisolone were administered starting 05-18-2017. However, the clinical symptoms deteriorated, and imaging results indicated progression (Figure 6).
- The patient died on 06-02-2018.

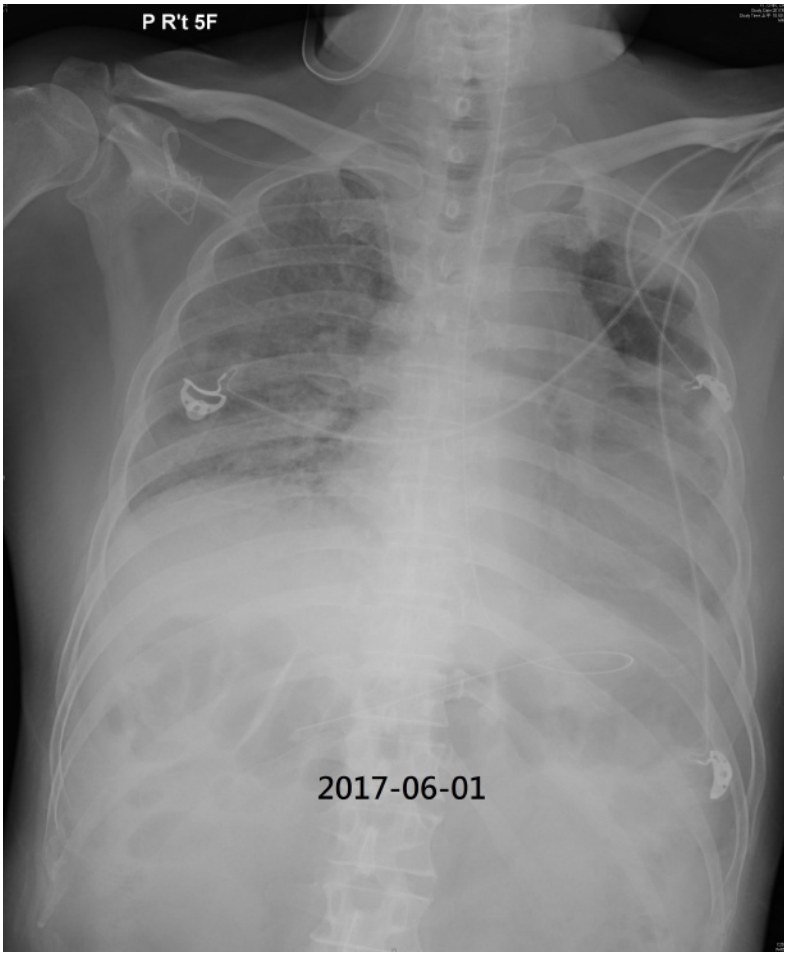


Figure 6: Chest radiography (06-01-2017).

## *Clinical Pearls*

- A 55-year-old man had complications of interstitial pneumonitis after two cycles of immunotherapy (pembrolizumab). Despite prednisolone administration, the patient still expired after 2 weeks. The initial prednisolone dose was 5 mg BID, which may not have been sufficient.
- The first generation of novel immunotherapies consists of antagonistic antibodies that block the specific immune checkpoint molecules cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein (PD-1) and its ligand PD-L1. Targeting these checkpoints in cancer patients has led to long-lasting tumor responses. However, by creating imbalances in the immune system, these new immunotherapies can also cause dysimmune toxicities, called immune-related adverse events (IRAEs), that mainly involve the gut, skin, endocrine glands, liver, and lung, but can potentially affect any tissue.
- IRAEs can develop at any time during treatment: at the beginning, during treatment, and after immunotherapy termination.
- Select treatment-related AEs occur in 49% of patients and are most commonly observed in the skin (34%) and GI tract (13%); select grade 3 to 4 treatment-related AEs have been reported in 4% of patients.

- The median time to onset for treatment-related pulmonary AEs of any grade is 8.9 (range, 3.6-22.1) weeks.
  Select pulmonary AEs generally resolve within several weeks (median 6.0 weeks; range 1.0-10.1 weeks).
- Before the initiation of corticosteroids or other immunosuppressive drugs, it is necessary to rule out any associated infection. Antibiotic prophylaxis with oral trimethoprim/sulfamethoxazole (400 mg qd) should be considered in order to prevent opportunistic infections in patients under long-term exposure to immunosuppressive drugs.

***References***


1. Michot JM *et al.* Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer. 2016 Feb;54:139-148.
2. Champiat S *et al.* Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. Ann Oncol. 2016 Apr;27(4):559-574.
3. Postow MA *et al.* Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med. 2018 Jan 11;378(2):158-168.
4. Weber JS *et al.* Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. J Clin Oncol. 2017 Mar;35(7):785-792.
5. Spain L *et al.* Management of toxicities of immune checkpoint inhibitors. Cancer Treat Rev. 2016 Mar;44:51-60.

# Immune-related colitis

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## *Patient profile*

Case presentation

A 77-year-old man with hypertension and chronic hepatitis C came to our clinic due to hoarseness sensation and productive cough with mucous sputum. He had quit smoking 6 months previously. Chest radiography and computed tomography (CT) revealed a large right upper lung mass and two small nodules in the left upper lobe. Echo-guided biopsy was performed, and the pathology indicated squamous cell carcinoma.

Immunohistochemistry for PD-L1 22C3 showed membrane staining in 10% of the tumor cells with weak to moderate intensity. The initial diagnosis was right lung squamous cell carcinoma, with lung to lung metastasis, cT4N3M1a, stage IVA (American Joint Committee on Cancer ver.8). Therefore, he received gemcitabine (1000 mg/m$^2$) on days 1, 8, and 15, combined with carboplatin (AUC 4) on day 1. Dose reduction and blood components transfusion was performed due to grade 3 anemia and grade 3 thrombocytopenia. Re-evaluation showed partial regression of the right lung lesion after four cycles, and he was followed up at our clinic.

Follow-up CT 4 months later indicated new metastatic hepatic tumors. The patient was informed of the disease progression, and he considered immunotherapy because of the adverse effects of second-line chemotherapy. The anti-programmed cell death receptor 1 (PD1) agent nivolumab (3 mg/kg) was prescribed every 2 weeks.

There was no acute reaction after the first and second cycles, although he did experience mild fatigue and anorexia. However, diarrhea 6-7 times a day developed after the third cycle of nivolumab.

There was no fever, abdominal tenderness, or rebounding pain. Chest radiography showed a partial response in the right lung tumor (Figure 1a and 1b).

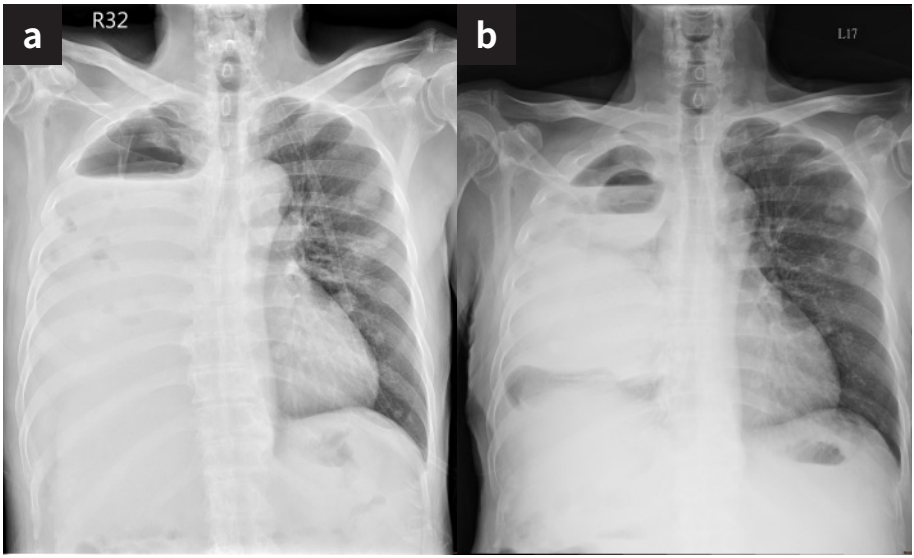


Figure 1a: Chest radiography at lung cancer diagnosis

Figure 1b: Chest radiography after three cycles of nivolumab

Abdominal radiography showed no dilated bowel gas (Figure 2). Laboratory data showed that hemogram, biochemistry, and electrolytes were all within normal limits.

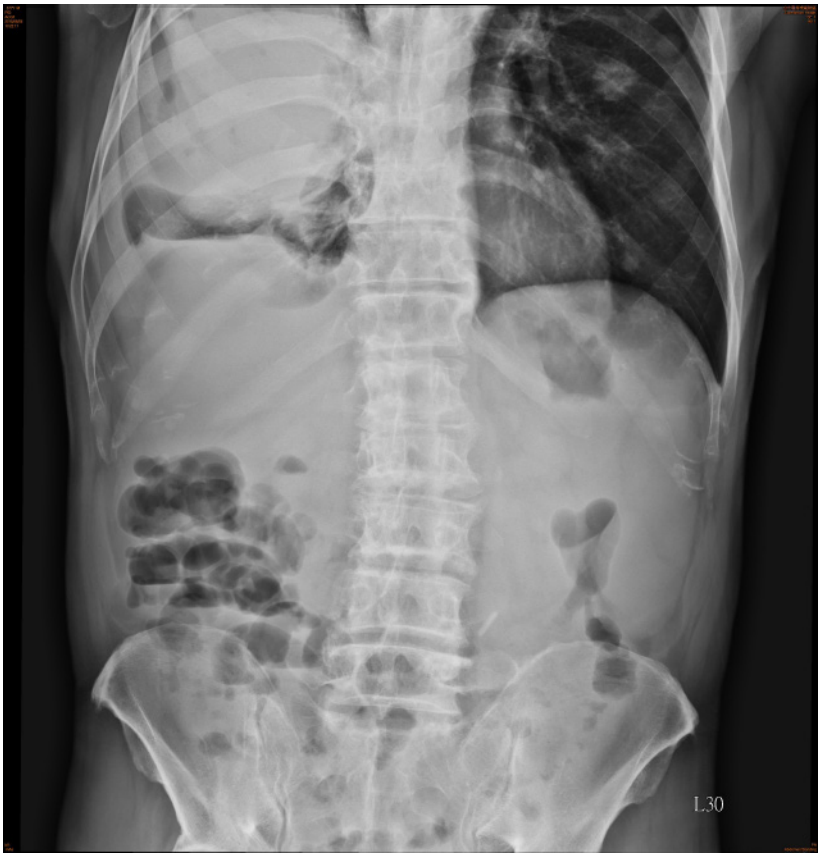


Figure 2: Abdominal radiography

Stool pus cells were not found, and stool cultures for Salmonella spp. and Clostridium spp. were negative. Immunotherapy-related colitis was considered. The anti-laxative medication loperamide was prescribed, and while the frequency of diarrhea decreased,it still persisted. Oral prednisolone 20 mg per day was prescribed, and the diarrhea improved within days. The steroid was tapered over 2 weeks, and the fourth cycle of nivolumab was administered smoothly.

## *Immune-Mediated Gastrointestinal Adverse Reactions*

- Diarrhea is a common clinical complaint in patients undergoing treatment with immune checkpoint-blocking antibodies. The incidence of diarrhea is much higher in patients receiving cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)-blocking antibodies (grade 3/4 < 10%) than in those receiving inhibitors of PD-1 (grade 3/4 1-2%).
- Diarrhea/colitis most commonly presents approximately 6 weeks into treatment, which is later than the presentation of dermatologic toxicity.
- The differential diagnosis of patients with diarrhea who are receiving an immune checkpoint inhibitor includes infections with Clostridium difficile and other bacterial/viral pathogens.
- Diarrhea (increase in stool frequency) is related to but clinically distinct from colitis (abdominal pain and radiographic or endoscopic findings of colonic inflammation).
- Management:
  - Mild (grade 1) symptoms (fewer than four stools per day over baseline) can be managed symptomatically.
  - Colonoscopy may be helpful if grade 2 symptoms (four to six stools per day over baseline) or greater occur or in situations where the diagnosis is unclear. Treatment should be initiated if colitis is observed.

- For patients with severe or life-threatening enterocolitis (grade 3/4, seven or more stools per day over baseline or other complications), immunotherapy should be permanently discontinued. High doses of corticosteroids should be administered.
- If patients do not improve with intravenous corticosteroids after approximately 3 days on IV steroids, infliximab at a dose of 5 mg/kg once every 2 weeks is typically recommended.
- In very rare cases, colitis can result in bowel perforation, potentially requiring colostomy.

## *Summary of Immune-Mediated Gastrointestinal Adverse Reactions*

| | **Grade 1** (Diarrhea: < 4 stools per day over baseline;Colitis: asymptomatic) | **Grade 2** (Diarrhea: 4–6 stools per day over baseline; IV fluids indicated< 24 hours; not interfering with ADL;Colitis: abdominal pain, blood in stool) | **Grade 3–4** (Diarrhea [G3]:≥ 7 stools per day over baseline; incontinence; IV fluids ≥ 24 hours; interfering with ADL; Colitis [G3]: severe abdominal pain, medical intervention indicated, peritoneal signs;[G4]: life-threatening, perforation) |
|---|---|---|---|
| Treatment with Immunotherapy | Continue treatment | With hold dose | Grade 3: Withhold dose<br>Grade 4: Permanently discontinue |
| Symptomatic Treatment | Administer | Administer | |
| Steroids | | For Grade 2 colitis > 5 days<br>• 0.5 to 1 mg/kg/day prednisone equivalent followed by corticosteroid taper over at least 1 month | 1 to 2 mg/kg/day prednisone equivalent followed by corticosteroid taper over at least 1 month |
| GI Tests | | | Consider lower GI endoscopy |

| | **Grade 1** (Diarrhea: < 4 stools per day over baseline;Colitis: asymptomatic) | **Grade 2** (Diarrhea: 4–6 stools per day over baseline; IV fluids indicated< 24 hours; not interfering with ADL;Colitis: abdominal pain, blood in stool) | **Grade 3–4** (Diarrhea [G3]:≥ 7 stools per day over baseline; incontinence; IV fluids ≥ 24 hours; interfering with ADL; Colitis [G3]: severe abdominal pain, medical intervention indicated, peritoneal signs;[G4]: life-threatening, perforation) |
|---|---|---|---|
| Follow-up | | | |
| | Close monitoring for worsening symptoms. Educate patient to report worsening immediately. | If improved to Grade 1<br>• Resume treatment<br>• If steroids have been administered, taper steroids over at least 1 month before resuming treatment<br>• Permanently discontinue for recurrent colitis upon re-initiation of immunotherapy. | If improved from Grade 3<br>• When at Grade 1, taper steroids over at least 1 month before resuming treatment. Permanently discontinue for recurrent colitis upon re-initiation of immunotherapy. |
| | If symptoms worsen<br>• Treat as Grade 2 or 3–4 | If worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day prednisone equivalent. | If symptoms persist > 3 to 5 days or recur after improvement, add non-corticosteroid immunosuppressive medication. |

IV: intravenous; ADL:activities of daily living ;
GI: gastrointestinal

# Why am I so tired after immunotherapy? A case of immunotherapy-induced acute hepatitis

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## *Patient profile*

Case presentation

- A 32-year-old woman, non-smoker, with no major systemic disease
- Initial presentation with a 3-month history of headache
- Chest images showed a right lower lung tumor (Figure 1a & 1b)

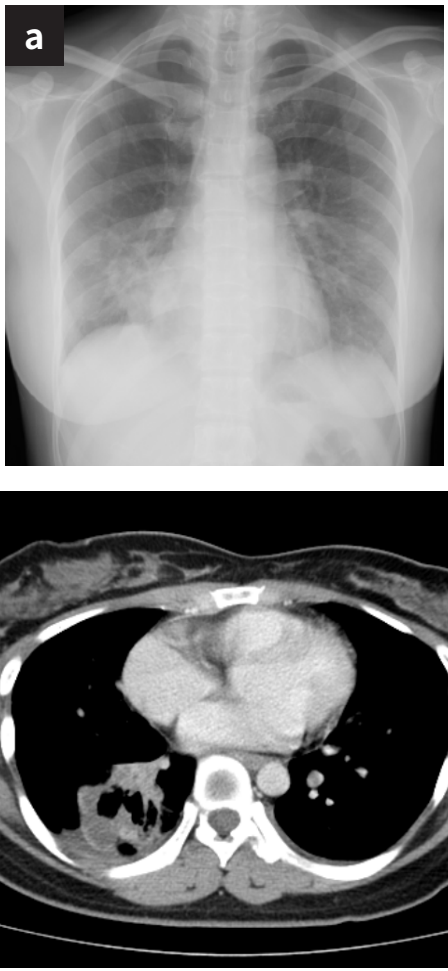



Figure 1a&1b: Chest radiography (a) and computed tomography (b) revealed a consolidative mass lesion over the right lower lung field.

- Lung adenocarcinoma was diagnosed by bronchoscopic biopsy, and the initial stage was T2N0M1b, stage IV, with brain and bone metastases.
- Negative for *EGFR* mutation and *ALK* rearrangement

Physical examination

- BW: 55 kg, BH: 162.5 kg
- Blood pressure: 110/72 mmHg, Heart rate: 76 bpm
- Other findings were unremarkable

Treatment process

- She received PD-L1 targeted immunotherapy as first-line therapy
- She felt malaise 1 week after the 1$^{st}$ dose of immunotherapy
- Laboratory tests revealed a grade 4 elevation of bilirubin and liver enzymes
- She received methylprednisolone 1 mg/kg/day but showed no significant improvement
- We increased the dose of methylprednisolone to 2 mg/kg/day and added MMF 500 mg 2# bid later
- Liver function improved gradually and returned to normal 1 month later
- Viral hepatitis and autoimmune hepatitis were excluded after a series of workups

- Computed tomography of the chest disclosed that the lung tumor had regressed (Figure 2)
- Nevertheless, the drug was permanently discontinued due to grade 4 toxicity
- She received subsequent chemotherapy after liver function improved
- The patient died of lung cancer progression 2 years later

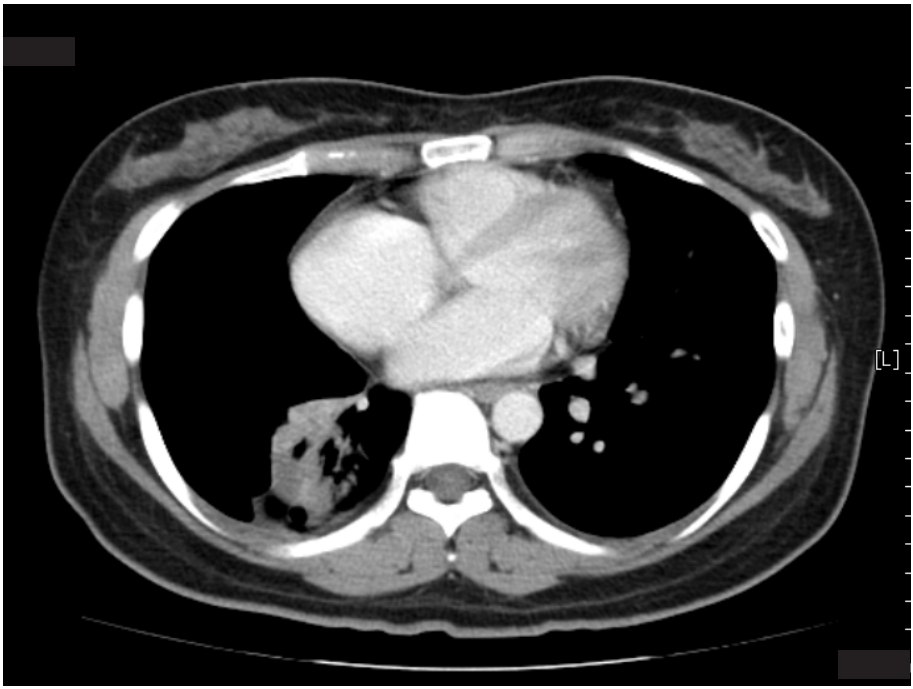
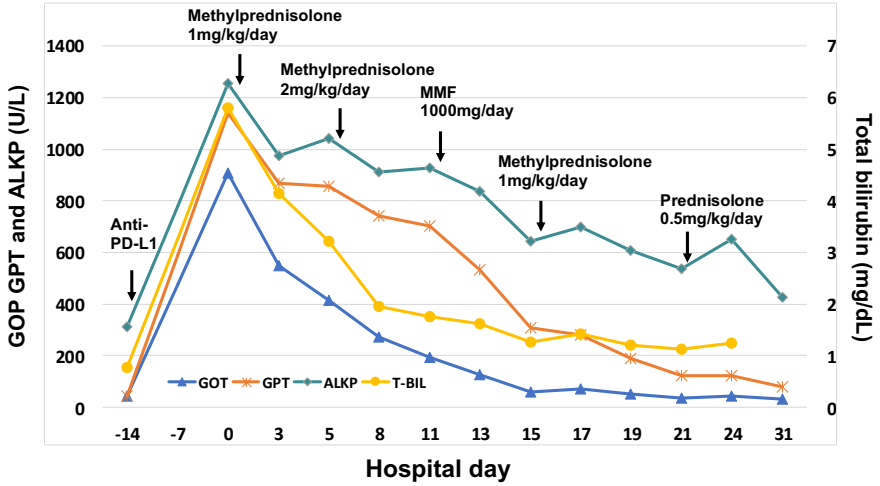



Figure 2: Computed tomography of the chest revealed regression of the lung tumor after the 1st dose of PD-L1 targeted immunotherapy.

# Liver function during hospitalization



## *Clinical pearls*[1,2]

- Immunotherapy-induced hepatotoxicity has been reported in 2%-10% of patients treated with monotherapy (of which 1%-2% is grade 3), and up to 30% of patients receiving combination treatment (of which 15% is grade 3).
- Onset of abnormal liver function typically occurs within the first 6-12 weeks after initiation of treatment.
- Prednisolone or equivalent at 0.5-1 mg/kg/day is the mainstay of treatment for patients with grade 1 or 2 hepatotoxicity.
- For patients with grade 3 or 4 toxicity, 1-2 mg/kg/day of methylprednisolone or equivalent should be administered, and the addition of mycophenolate mofetil (MMF) is recommended if no improvement is seen after 3 days of steroid administration.
- Initial follow-up to assess liver function should be performed every 3 days, and hepatitis is usually resolved within 4-6 weeks. Steroids should be tapered under close monitoring over at least 1 month.

***References***


1. Haanen J *et al.* Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2017;28(suppl_4):iv119-iv142.
2. Brahmer JR *et al.* Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018;36(17):1714-1768.

# Case IV – irAE-related endocrinology disorder: islet deficiency

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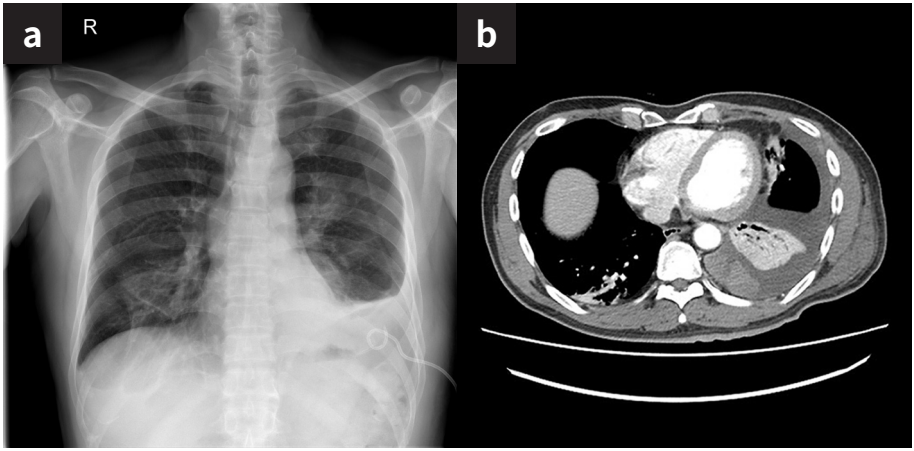
## *Patient profile*

Case presentation

- A 65-year-old man presented with left side chest pain and hoarseness.
- Chest radiography and computed tomography (CT) showed a left-sided pleural effusion and a patchy opacity in the left lower lobe (Figure 1a & 1b).




Figures 1a & 1b: Chest radiography and chest computed tomography revealed a mass in the left lower lobe of the lung with pleural effusion.

- The patient was diagnosed with stage IV squamous cell lung carcinoma. Therefore, chemotherapy was administered as anti-cancer treatment.
- However, the patient had disease progression after five courses of first-line platinum-based chemotherapy and five courses of second-line treatment with docetaxel.
- He received immunotherapy (nivolumab) combined with vinorelbine as salvage therapy.

- He was diagnosed with T1DM after developing hyperglycemia after eight cycles of immunotherapy (nivolumab).
- His blood sugar was controlled after receiving insulin therapy and switching to immunotherapy with atezolizumab.

Medical history

- Hypertension and hypertensive cardiovascular disease-Taxotere and cisplatin were administered starting 02-10-2017.

Physical examination

- No neck lymphadenopathy
- Mild decreased breath sound over the left lower lung fields

Laboratory panels

- SCC 1.3 ng/mL
- Glu 333 mg/dL
- HbA1c: 9.0%
- C-Peptide: 2.13 ng/mL

Diagnostic process

- CT-guided 18-gauge core needle biopsy was performed (Figure 2).

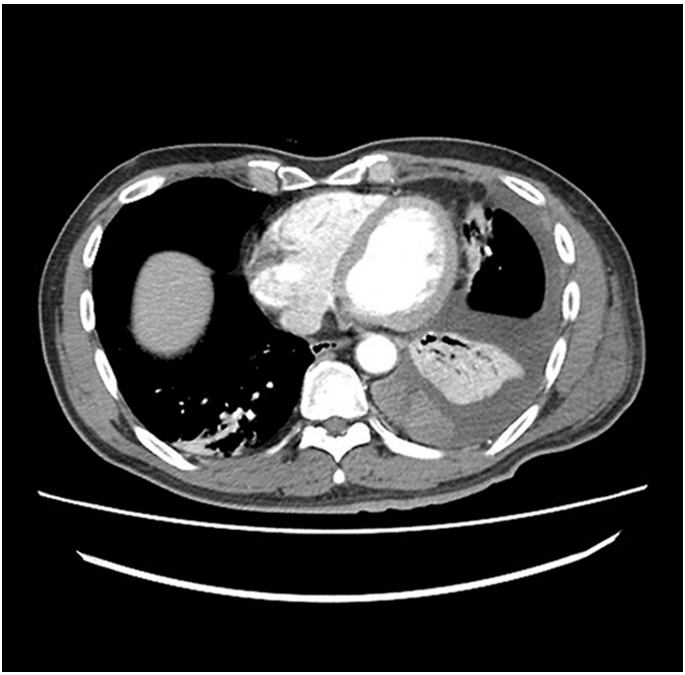


Figure 2: Computed tomography-guided 18-gauge core needle biopsy was performed.

- Pathology reported squamous cell lung carcinoma.
- The patient was classified as having T3N2M1a clinical stage IVa ($7^{th}$) (stage IVa ($8^{th}$).

Treatment process

- Gemcitabine 1200 mg/m$^2$ and cisplatin 60-75 mg/m$^2$ on days 1 and 8 every 4 weeks for 5 cycles. Chest CT showed stable disease after first-line chemotherapy (Figure 3).

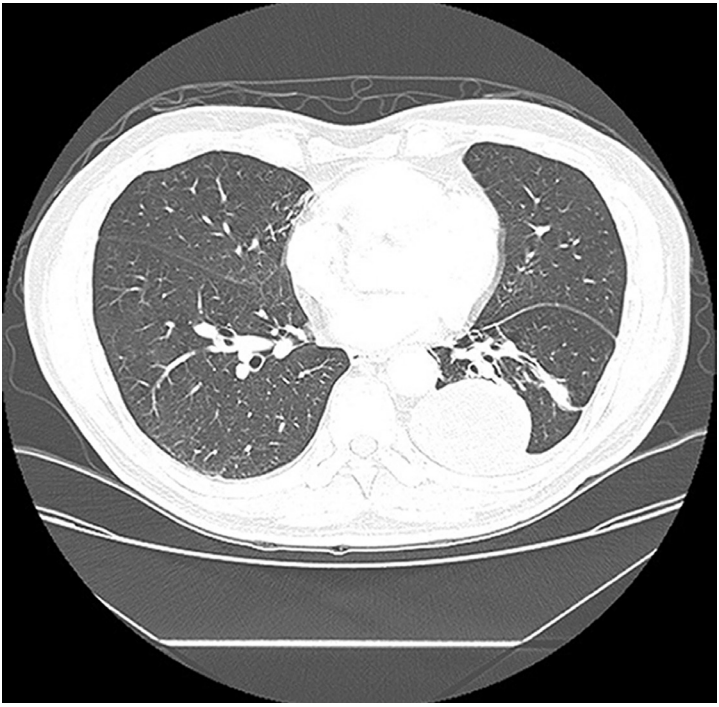


Figure 3: Chest computed tomography indicated stable disease after first-line chemotherapy.

- Six months later, chest CT revealed growth of the left lower lung mass, indicating disease progression (Figure 4).
- Second-line treatment with docetaxel 30 mg on days 1 and 8 every 3 weeks for 5 cycles.

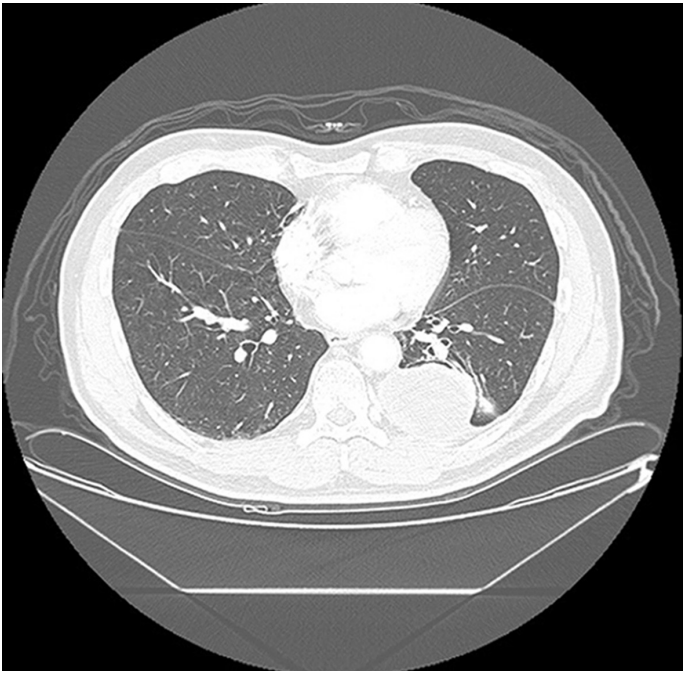


Figure 4: Chest computed tomography revealed growth of the left lower lung mass, indicating disease progression.

- Chest CT revealed stable disease after chemotherapy (Figure 5).

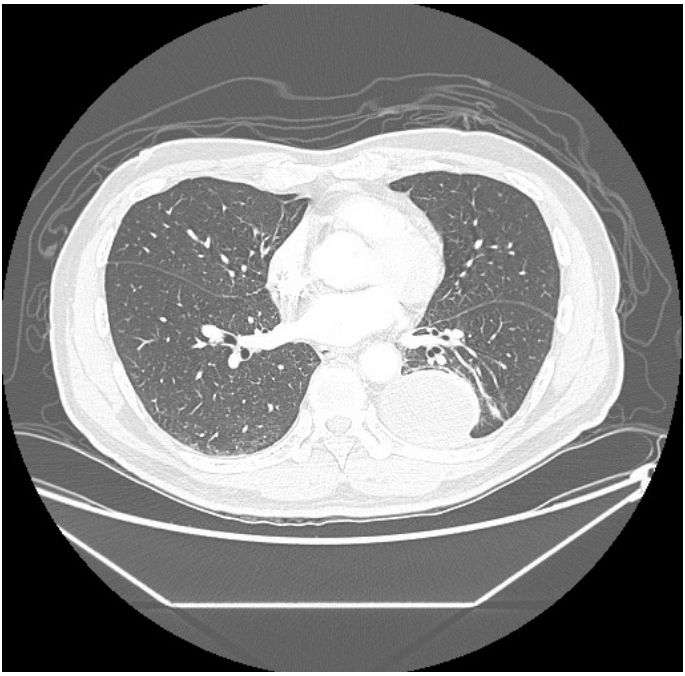
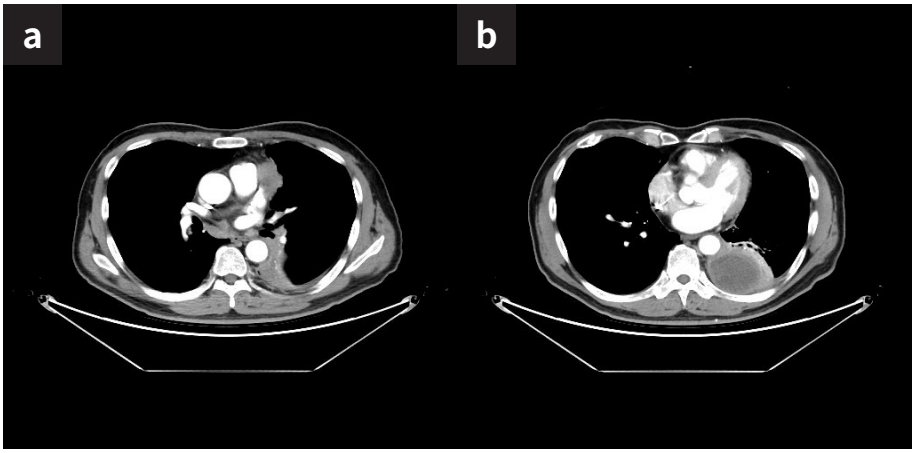


Figure 5: Computed tomography revealed stable disease after second-line chemotherapy.

- Four years later, chest CT revealed progressive disease (Figures 6a & 6b).
- CT-guided re-biopsy was performed; however, the tumor showed no PD-L1 expression (TPS < 1%) (Figure 7).




Figures 6a & 6b: Four years later, computed tomography revealed progressive disease.

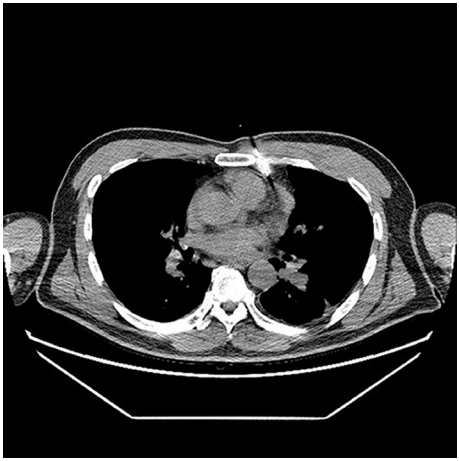


Figure 7: Re-biopsy guided by computed tomography scan was performed.

- Nivolumab 3 mg/kg and oral vinorelbine 60 mg/m2 on days 1 and 15 every 2 weeks for 8 cycles.
- Bone scan showed bone metastasis (Figure 8).
- Atezilizumab 1200 mg every 3 weeks until now.

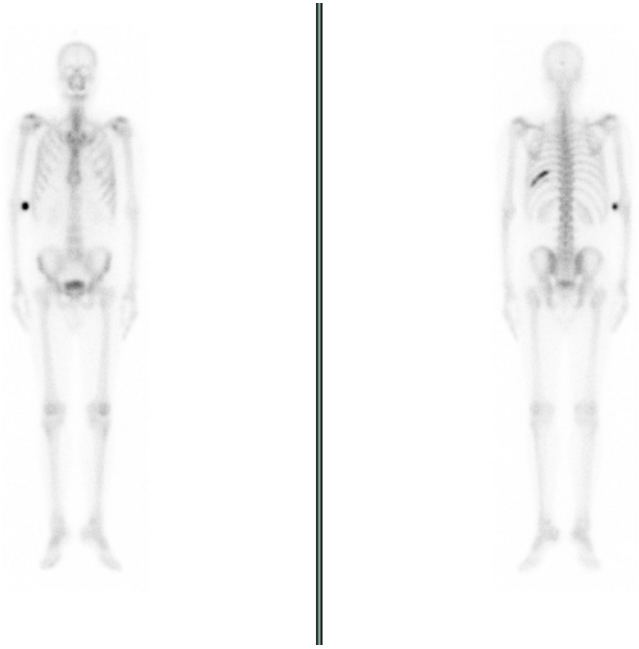


Figure 8: The bone scan showed bone metastasis.

## *Clinical Pearls*

- The success of drugs targeting the immune-checkpoint pathways, such as immune checkpoint inhibitors (ICI) targeting PD-1 and programmed cell death ligand 1 (PD-L1), have led them to become part of the standard-of-care treatment option for patients with advanced stage non-small cell lung cancer (NSCLC)[1].
- As this field continues to grow, clinical physicians should be aware of the immune related-adverse events associated with ICIs.
- There are a few reports of rapid induction of late onset autoimmune diabetes mellitus in patients receiving ICIs[2,3].
- T1DM may occur after 1 week to 12 months of nivolumab therapy and after 4 years of pembrolizumab therapy. Immunological activation derived from PD-1 receptor blockade of T lymphocytes has been proposed as a pathogenic mechanism, which would be accompanied by production of anti-GAD and anti-IA2 antibodies alongside infiltration of T lymphocytes into pancreatic islets[4].
- A study found no correlation between insulin antibody levels and development of autoimmune diabetes: some mice developed diabetes with no antibodies and others developed antibodies but did not develop diabetes[5].
- The main therapy for patients with late onset autoimmune diabetes mellitus is hormone replacement with insulin, whereas the role of corticosteroids in the evolution of T1DM induced by immunotherapy is unknown.

***References***


1. Velcheti V *et al*. Basic overview of current immunotherapy approaches in cancer. Am Soc Clin Oncol Educ Book 2016;35:298–308.
2. Hughes J *et al.* Precipitation of autoimmune diabetes with anti-PD-1 immunotherapy. Diabetes Care 2015;38:e55–7.
3. Okamoto M *et al.* Fulminant type 1 diabetes mellitus with anti-programmed cell death-1 therapy. J Diabetes Investing 2016;7:915–8.
4. Chae YK *et al*. A case of pembrolizumabinduced type-1 diabetesmellitus and discussion of immune checkpoint inhibitor-induced type 1 diabetes. Cancer Immunol Immunother 2017;66:25–32.
5. Ansari MJ *et al.* The programmed death-1 (PD-1) pathway regulates autoimmune diabetes in nonobese diabetic (NOD) mice. J Exp Med 2003;198:63–9.

# A case report - immune-related cardiomyopathy

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## *Patient profile*

Case presentation

- A 75-year-old woman with a medical history of hypertension and hyperlipidemia was diagnosed with right lower lobe lung cancer, adenocarcinoma, cT2a3M1b, stage IV (AJCC 7th), with mediastinal, LN, and liver metastases (07-21-2016) (Figure 1).
  - *EGFR* mutation: not detected
  - *ALK* (Ventana anti-ALK D5F3 IHC assay): negative
  - PD-L1 (Dako anti-PD-L1 22C3 IHC assay):TPS 95%, high expression

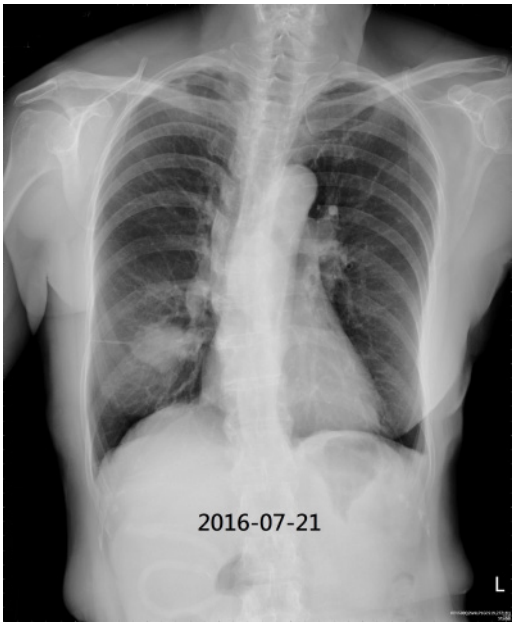


Figure 1: Chest radiography (01-11-2017). A case of right lower lobe lung cancer, adenocarcinoma, cT2a3M1b, stage IV (AJCC 7th), with mediastinal, LN, and liver metastases (07-21-2016).

Clinical course

- Initially, gemcitabine and cisplatin with right lower lobe lung lesion radiotherapy (CCRT) were administered from 08-01-2016 to 01-05-2017.
- Progression in the right lower lobe lung lesion was noted on 04-20-2017 (Figure 2).

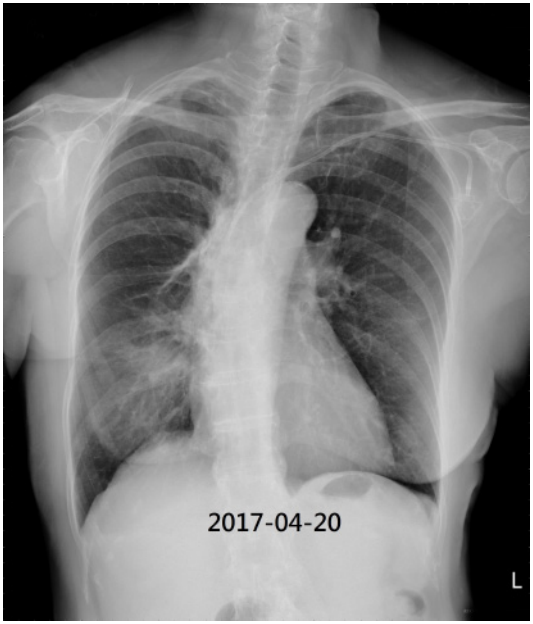


Figure 2: Chest radiography (04-20-2017). Progression of the right lower lobe lung lesion was noted on 04-20-2017.

- Pembrolizumab administration started on 04-24-2017 (Cycle 1, 04-24-2017 and Cycle 2, 05-15-2017).

- After two cycles of pembrolizumab, the clinical symptoms and images had improved (Figure 3).

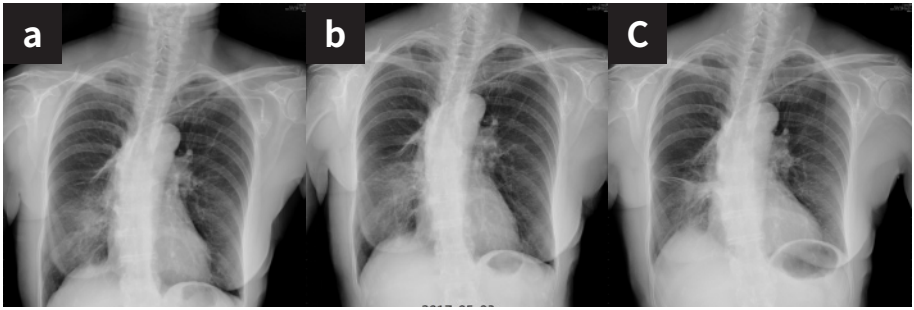


Figure 3: Chest radiography (04-25-2017, 05-03-2017, and 05-31-2017). After two cycles of pembrolizumab, the clinical symptoms and images were improved.

- Unfortunately, she developed exertional dyspnea and generalized soreness on 06-12-2017. Elevated troponin-I (6.334 ng/mL,Table 1) was noted, and EKG showed VPCs. Echocardiography revealed dilated LA, moderate TR, mild AR, diffuse LV hypokinesis with impaired LVP (EF 45%), adequate RVP, elevated LA pressure, and LV diastolic dysfunction (Table 2). Immunotherapy-related cardiomyopathy was suspected.
- Prednisolone was administered starting on 06-12-2017.
- After prednisolone administration, the clinical symptoms and cardiac enzymes were improved (Table 1 and Table 2).

Table 1: The serial changes in cardiac enzymes.

| | 06-19-2017 | 06-22-2017 | 06-26-2017 | 06-28-2017 | 07-02-2017 | 07-31-2017 |
|---|---|---|---|---|---|---|
| Myoglobin (14.3-65.8 ng/mL) | 492 | | | 124.6 | | |
| CK-MB (0.6-6.3 ng/mL) | 176.6 | | 44.3 | 55.3 | 76.8 | 25.1 |
| CK (43-165 U/L) | 781 | | | 140 | | |
| LDH (135-214 U/L) | 588 | | | 307 | | |
| Troponin-I (<0.3 ng/mL) | 6.334 | 1.920 | 0.759 | 0.462 | 0.304 | 0.046 |

CK-MB: Creatine Kinase- MB;CK: Creatine Kinase; LDH: Lactate Dehydrogenase

Table 2: Data of echocardiography

| | 06-19-2017 | 06-27-2017 | 08-02-2017 |
|---|---|---|---|
| Aorta/LA (23-37/18-38 mm) | 32/41 | 30/38 | 30/38 |
| IVS/LVPW (6-12/5-11 mm) | 8/8 | 8/8 | 13/9 |
| LV-Diameter Dias/Sys (36-52/20-36 mm) | 44/34 | 47/32 | 43/30 |
| LVEDD/LVESD volume (46-108/10-54 mL) | 87/47 | 102/41 | 83/35 |
| LV SV/EF (32-95 mL/49-76%) | 49/45 | 61/60 | 48/60 |

LA: Left Atrium;IVS: Intact Ventricular Septum;
LVPW: Left Ventricular Posterior Wall;
LVEDD: Left Ventricular End-Diastolic Diameter;
LVESD:Left Ventricular End-Systolic Diameter;LV SV: Left Ventricular Single Ventricle;EF: Ejection Fraction

## *Clinical Pearls*

- The patient developed cardiomyopathy complications after two cycles of immunotherapy (pembrolizumab). After prednisolone (10 mg TID), the cardiomyopathy improved, and the patient survived.
- The first generation of novel immunotherapies consists of antagonistic antibodies that block the specific immune checkpoint molecules cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein (PD-1) and its ligand PD-L1. Targeting these checkpoints in cancer patients has led to long-lasting tumor responses.
  However, by creating imbalances in the immune system, these new immunotherapies also generate dysimmune toxicities, called immune-related adverse events (IRAEs), that mainly involve the gut, skin, endocrine glands, liver, and lung, but can potentially affect any tissue.
- IRAEs can develop at any time during treatment: at the beginning, during treatment, and after immunotherapy termination.

- Select treatment-related AEs occur in 49% of patients and are most commonly observed in the skin (34%) and GI tract (13%); select grade 3 to 4 treatment-related AEs have been reported in 4% of patients.
- Before the initiation of corticosteroids or other immunosuppressive drugs, it is necessary to rule out any associated infection. Antibiotic prophylaxis with oral trimethoprim/sulfamethoxazole (400 mg qd) should be considered in order to prevent opportunistic infections in patients under long-termexposure to immunosuppressive drugs.

***References***


1. Michot JM *et al.* Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer. 2016 Feb;54:139-148.
2. Champiat S *et al.* Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. Ann Oncol. 2016 Apr;27(4):559-574.
3. Geisler BP *et al.* Apical ballooning and cardiomyopathy in a melanoma patient treated with ipilimumab: a case of takotsubo-like syndrome. J Immunother Cancer. 2015 Feb 17;3:4.
4. Postow MA *et al.* Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med. 2018 Jan 11;378(2):158-168.
5. Weber JS *et al.* Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. J Clin Oncol. 2017 Mar;35(7):785-792.
6. Spain L *et al.* Management of toxicities of immune checkpoint inhibitors. Cancer Treat Rev. 2016 Mar;44:51-60.
7. Raghu G *et al.* Am J Respir Crit Care Med. 2011;183(6):788-824.
8. Travis WD *et al.* Am J Respir Crit Care Med. 2013;188(6):733-748.
9. Ohshimo S *et al.* Eur Respir Rev. 2017;26(145). pii: 170012.
10. Kupeli E *et al.* Can Respir J. 2010;17(5):e102-105.

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