Immune-Related Adverse Events (irAE) Case Study

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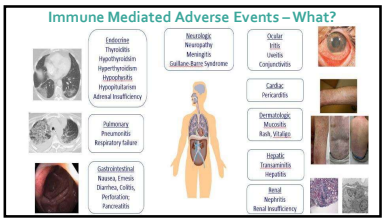
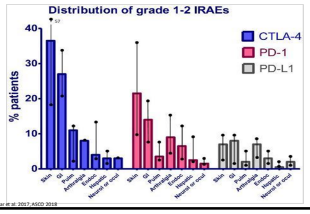
Immune Mediated Adverse Events – What?



Distribution of grade 1-2 IRAEs



IASLC 2017; Kumar et al. 2017, ASCO 2018

NCI-CTCAE Guidelines for Grading Select Adverse Reactions[1]

- The table lists NCI-CTCAE guidelines for grading the severity of select adverse reactions that may be associated with KEYTRUDA® (pembrolizumab)†

	Grade 1	Grade 2	Grade 3	Grade 4
Pneumonitis		Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; oxygen indicated	Life-threatening; ventilatory support indicated (eg, invasive mechanical ventilation or pneumonitis)
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe; abdominal pain; change in bowel habit; medical intervention indicated (eg, enteral tube)	Life-threatening consequences; urgent intervention indicated
Hyperthyroidism		Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Hypothyroidism		Symptomatic; thyroid replacement therapy indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Endocrine disorders – other	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolonging hospitalization indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
Infusion-related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	Prolonged (eg, not quickly responsive to symptomatic treatment); recurrent symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated

ADL = activities of daily living; CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; NSAIDs = nonsteroidal anti-inflammatory drugs.
†Grade 5 not applicable.

1. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Bethesda, MD: National Cancer Institute; 2009. NIH Publication 09-7473. Updated version CTCAE v4.03: June 14, 2010.

Presentation and Management of Pneumonitis

- Occurs with both CTLA-4 inhibitor and PD-1 use; higher rate of occurrence with anti-PD-1s (~3%)

Management

IASLC
Grade 1: May present without symptoms, no intervention needed. Hold if radiographic evidence. May repeat CT in 3-4 weeks.
Grade 2: Withhold therapy. Prednisone 1-2 mg/kg. Taper slowly over 1 month. Hold until Grade 1 or less. Consider bronchoscopy and empirical Abx. Monitor q 3 days with pulse oximetry.
Grade 3-4: Permanently discontinue therapy. Prednisone 1-2 mg/kg or IV methylprednisolone, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g BID or IVIG for 5 days or cyclophosphamide. Empirical Abx. Pulmonary and infectious disease consult. Bronchoscopy with BAL +/- transbronchial biopsy.

IASLC 2017; Kumar et al. 2017, ASCO 2018

Case Study

- Jerry is a 51 yo male and has stage IIIB non small cell lung cancer. He completed concurrent chemotherapy and radiation (cCXRT) (carboplatin and taxol once a week for six weeks) and thereafter started durvalumab in July 2019.

After 3 cycles, patient developed a cough.
- It lasts for a few minutes and occurs in the mornings.
- Does not affect any activities of daily living (ADL's).
- Feels an occasional wheeze a few times a week. When that occurs, he tries to cough it up, but nothing comes out.
- Dyspnea on exertion (DOE) only when walking up the stairs. Difficulty with deep breathing.
- No pain, fevers, chills.

Do you give the 4th cycle of Durvalumab?

Case Study

- May be mild beginnings of pneumonitis, but patient able to perform all ADL's still and symptoms are mild.
- OK to treat today, per attending oncologist, but low threshold to hold treatment and obtain urgent scans if symptoms worsen.
- Patient to aware to contact clinic immediately if symptoms worsen.

We proceeded with C4.

Case Study

September 18th, 2019

- Continues with loose cough and shortness of breath (SOB) if significant exertion, still able to complete ADL's without difficulty.
- Inhalers have not helped significantly.

What would be your next steps with Jerry with C5 of durvalumab?

Case Study

Visit on October, 2nd 2019

- Held C6 due to ulnar surgery on 9/30/19. Plan was to resume on 10/30/19. Symptoms stable. Still able to perform ADL's.
- Wants to return to work.

Case Study

October 30th, 2019

CT CAP from 10/22/19: Evolving post-radiation changes with increased consolidation near treated nodule as well as other regions of organizing pneumonia consistent with radiation pneumonitis.

- Doing well, no SOB, able to climb stairs. Cough has worsened, since a recent cold and has not improved.

Would you treat C6 of durvalumab?

Case Study

- Discussed in depth holding Durvalumab, but in absence of clinically meaningful symptoms (only having mild to moderate cough), patient was restarted. Close monitoring.

November 11th, 2019

- Patient writes in, stating: cough has gotten worse to the point where he cannot sleep. Denies fevers or chills. Worse in the AM and at night.
- Coughing yellow and black mucus, with some redness, but after expectorating, wheezing in the chest will stop.
- He has tried codeine syrup, it does help slightly, but it is only like a band-aid.
- Denies any SOB.

Would you treat on scheduled infusion on November 14th, 2019?

Case Study

- NP ordered a chest Xray to ensure that this was not pneumonia:
- Results stated: **Left basilar nodular consolidation and hilar opacity with fissural thickening, likely reflecting sequelae of radiation therapy to known lung cancer.**
- We held the next 2 treatments, due to patient's symptoms.

Case Study

December 11th, 2019

- Continues to have the same cough and symptoms as 2 weeks prior. Decision was made to treat patient, since there were no improvements in symptoms with holding treatment 2 weeks prior.

CT Chest from December 19th, 2019

- Interval development of a **4.1 cm cavitary mass in the LLL left hilum with fistulous connection with the left mainstem bronchus. Remainder of the left lower lobe demonstrates worsening consolidation when compared to 10/22/2019.** Scattered centrilobular nodules throughout all lobes of the lung, greatest in the right middle lobe, is consistent with **infectious disease, possibly related to aspiration of necrotic material from the cavitary lesion and bronchopulmonary fistula**. Unchanged right lower lobe partially cystic pulmonary nodule.

Case Study

Seen by Pulmonary:

- Felt unclear cause of cough, increased antacids, added fluticasone.
- Asked to begin prednisone 60 mg QD
- Continue current inhalers, add albuterol two puffs, 2 to 3 times a day for wheezing and cough.
- Now with difficulty swallowing, likely radiation esophagitis. Swallow study same day.

December 23rd, 2019

- Still coughing, produces some brownish sputum upon awakening, yellowish during the day, occasionally a scant amount of red blood.
- Denies fevers or chills, still takes guaifenesin with codeine at night. Using liquid morphine sulfate if awakening in the with coughing, 1-2 times each evening.

Case Study

December 23rd, 2019

- **Ibuprofen** 800 mg no more than once or twice a day. If increased hemoptysis, discontinue.
- Continue **with daytime cold medicine** during the day, **guaifenesin AC** at bedtime.
- May use **liquid morphine sulfate** if awakening with a cough in the night.
- **Guaifenesin oral** during the day.
- Add **Morphine IR** pills 15 mg if needed for chest wall pain or at night to help with sleeping.
- **Polyethylene glycol** daily for constipation.
- To ED for any sudden increase in pain, shortness of breath, fevers, chills or anything unusual.

Case Study

December 24th, 2019

- Antibiotics were started on patient, as sputum culture returned positive, but the sensitivities had not returned yet. Grew rare serratia marsecens.
  - Started amoxicillin and the azithromycin.
  - Once sensitivities returned, we switched to moxifloxacin. Possible serratia super infection.

December 30th, 2019

Visit with attending oncologist:

- Clinically stable, feels somewhat better after steroids.
- Cough is still an issue. Weight declining rapidly, has trouble tolerating thin liquids.
- Continue prednisone 60 mg QD, plan for 4 weeks total with repeat imaging and then taper over 1 to 2 months.
- Started PCP prophylaxis with Sulfamethoxazole / Trimethoprim DS three times weekly.

Case Study

January 10th, 2020 Seen by Otolaryngology, head and neck surgery.

- has lost 15 lbs in 3 weeks.
- difficulty swallowing liquids, and foods sticking in chest. Heartburn daily, voice quality changes.
- videofluoroscopic swallowing evaluation revealed a moderately unsafe, mildly inefficient oropharyngeal swallow, likely secondary to his h/o lung cancer and chemo-XRT.
- barium tablet was observed to briefly linger in the esophagus, around the level of the aortic arch. Some retention of liquid and solid barium was also observed in the mid to distal esophagus. Aspiration risk is moderate-high. Will refer to GI.

Case Study

Follow up visit with pulmonologist on January 20th, 2019

Radiation pneumonitis:

- Though cough is r/t pneumonitis, other factors may be contributing: postnasal drip, GERD, and asthma/COPD at last visit. He recommended starting on budesonide / formoterolcetirizine, and famotidine. Durvalumab may also be contributing to pneumonitis.
- The cavitary mass and fistulous tract may be due to radiation pneumonitis and bronchitis. Respiratory infection may be due to aspiration of necrotic material from the cavitary lesion. Patient's symptoms have improved.
- Recommend continuing prednisone, may consider decrease to 50 mg daily after 4 weeks. Would continue moxifloxacin. Await results of repeat chest CT, scheduled for 1/29/20.

Case Study

CT chest 1/29/20

1. When compared to the 12/19/2019 exam, the **left infrahilar cavitary mass with fistulous connection to the left mainstem bronchus is increased in size and associated with suspected invasion and fistulous connection to the mid esophagus.**

2. Multifocal areas of groundglass opacity and tree-in-bud nodularity, some which are increased from the prior exam and others of which are improved. Findings are concerning for recurrent aspiration.

3. Obstruction of the left lower lobe airways is associated with near complete atelectasis of the left lower lobe, new from the prior exam.

Case Study

Visit with attending oncologist on 1/29/20

- Significant decline in the past month, swallowing worse, severe back pain and weight loss. Cough continues.
- Continue with prednisone 60 mg daily, admit patient for expedited workup.

Inpatient

- **Dysphagia, cough, cavitary lung mass**: Most likely due to pneumonitis (2/2 radiation + potentially durvulumab) and new fistula leading to aspiration and recurrent respiratory infections. Per review with radiology, possible that cavitary mass may be 2/2 infection and chronic aspiration, bu cannot exclude recurrence/extension of malignancy given invasion seen on CT.

Case Study

EGD and Bronchoscopy on 2/3/20 inpatient.

- Admitted for a left lower lobe cavitary mass and tracheo/broncho-esophageal fistula. The differential diagnosis for this mass includes infection (aspiration), malignancy, or pneumonitis secondary to XRT or PD-1 inhibitor. However, given the focal nature, PD-1 toxicity seems less likely. Favor infection vs progressive malignancy vs XRT toxicity.
- EGD and bronchoscopy found a mass invading the left main bronchus, and cavity lined with purulent, mucoid secretions. The orifice to what appeared to be the left upper lobe airway was seen on the other end of the cavity. Fistula to the esophagus could not be identied. GI team performed EGD, esophageal stent and NGT placed.

Summary

- Checkpoint inhibitor therapy is becoming more widely used
- Important to recognize side effects, usually an "itis"
- Important to rule out other etiologies in differential diagnosis of symptoms where appropriate
- Treatment typically involves glucocorticoids for severe reactions, holding immune checkpoint inhibitor
- In steroid-refractory cases, may need to use infliximab or other immunosuppressants
- Consult heme/onc and subspecialty services where appropriate
- Understanding and managing immune related adverse events is taking on increasing