CancerCare Manitoba
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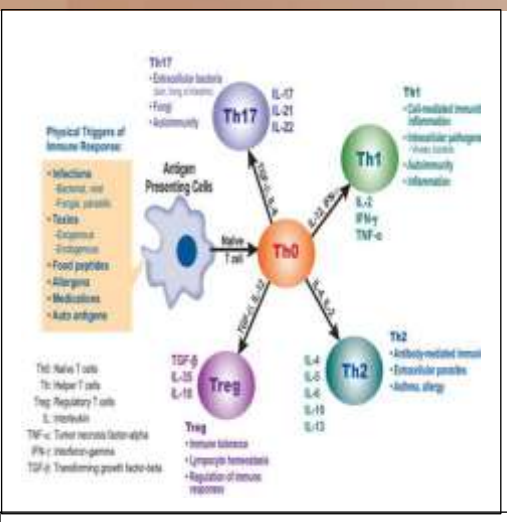
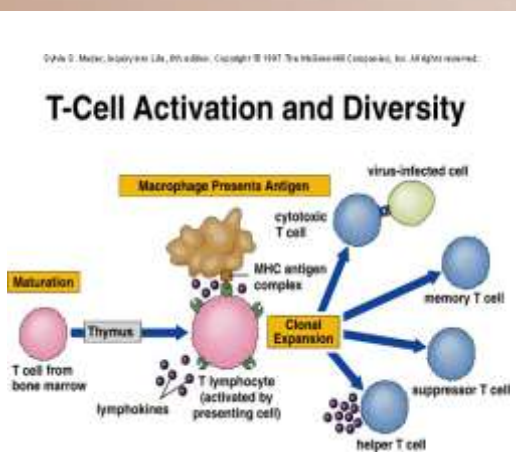
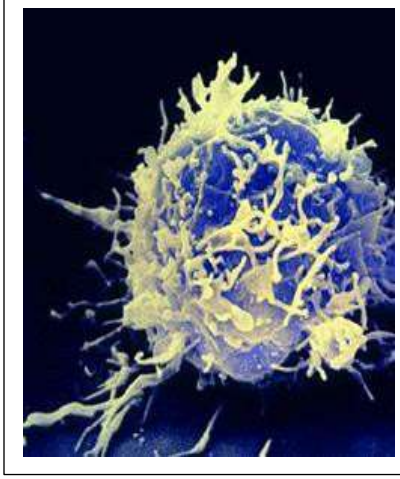
PARTICIPANT GUIDE

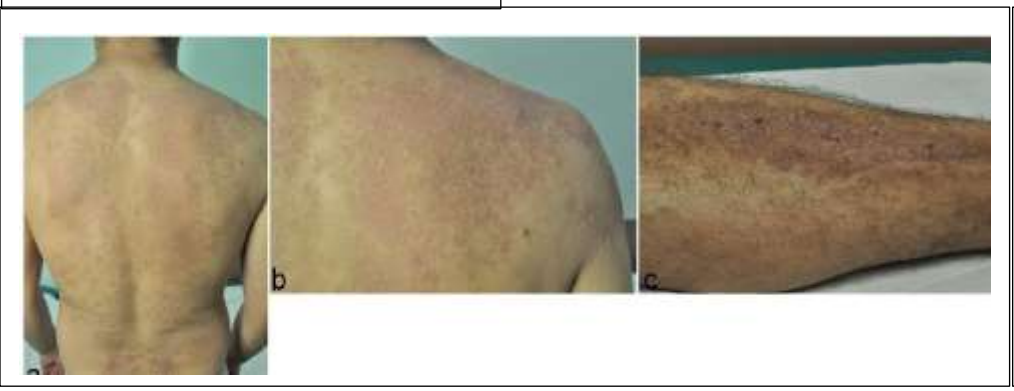
IMMUNOTHERAPY
& its complications

A module of the Early Cancer Diagnosis Workshop Series









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www.cancercare.mb.ca/diagnosis

IMMUNOTHERAPY & ITS COMPLICATIONS
EARLY DIAGNOSIS WORKSHOP ACKNOWLEDGEMENTS

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HISTORICAL BACKGROUND:

IN SIXTY, Manitoba's Cancer Patient Journey Initiative, was established in June 2011 with a mandate to get patients from suspicion of cancer, through diagnosis, and to their first treatment faster – in sixty days or less – and to do so in a way that also provides a smoother experience for patients. The Cancer Patient Journey Initiative established a partnership of Manitoba Health, CancerCare Manitoba, Diagnostic Services of Manitoba, Manitoba's regional health authorities, Family Physicians and other health care providers, and patients. While In Sixty's five-year mandate came to a close in June 2016, significant cancer journey improvements initiated during that time are still underway in areas of primary care, diagnostics, specialty care, IT support, and communication.

The Early Cancer Diagnosis series was established as a consequence of and with funding from the In Sixty initiative. Ongoing support for the continued development of new modules in the Early Cancer Diagnosis series is provided by CancerCare Manitoba's Community Oncology Program (COP). The COP was established in 2012 with the amalgamation of the Community Cancer Program Network (CCPN) and Uniting Primary Care and Oncology (UPCON). The COP also oversees the work of the Transitions Initiative and CCMB's Underserved Populations Program.

TABLE OF CONTENTS

All modules in the Early Cancer Diagnosis Workshop series are updated annually to reflect current standards of practice.

Cover pictures sourced from: MS Word ClipArt

IMMUNOTHERAPY WORKSHOP OUTLINE

WORKSHOP INTRODUCTION

Since the approval of ipilimumab by regulatory agencies in Europe and North America for the treatment of advanced melanoma, monoclonal antibodies directed against immune checkpoints have become standard of care in the first line or relapsed setting for a rapidly expanding list of indications. The introduction of immune checkpoint inhibitors into our therapeutic armamentarium has been attended by stories of spectacular success in treating, and sometimes inducing a durable response (possibly curing) in a number of malignancies. Their use has also been marked by the emergence of a wide range of immune-related adverse events (irAEs) affecting nearly every organ system in the body. Insofar as those irAEs may emerge a full year or more after the completion of therapy, and might present with subtle, undifferentiated symptoms and signs, primary care clinicians need to be aware of and vigilant for such immune-related complications. The timely diagnosis and treatment of irAEs can spare patients considerable morbidity, and in some instances can be life-saving.

Critical to the body's defense against infection is the "immune synapse". The ability of T cells to participate in immunologic surveillance depends on the ability of T lymphocytes to distinguish self- versus non-self-antigens which are presented by antigen-presenting cells (APCs) such as dendritic cells. The ability of a T cell to attack cells (such as bacteria or cancer cells) bearing "non-self" antigens is regulated by a set of stimulatory and inhibitory receptors whose expression is regulated by a complex system involving a variety of cytokines. Collectively this system of receptors, cytokines, and the cell-to-cell interactions they regulate are referred to as the "immune synapse".

The participation of CD4+ and CD8+ cells in the process of recognizing and attacking cells which bear "non-self" antigens begins with the presentation of an antigen* by the major histocompatibility complex (MHC) of an APC and the concurrent interaction of so-called co-stimulatory molecules (such as CD28) which are embedded in the T-cell membrane with their corresponding ligands (such as CD80 or CD86) in the APC cell membrane. In biochemistry, a ligand is a molecule that binds to another molecule. Such interactions initiate intracellular signaling which "ramps up" the immune response. This augmentation of immune activation by co-stimulatory molecules would eventually lead to the destruction of normal tissue were it not for the so-called immune checkpoints, which also consist of transmembrane molecules of the T-cell surface membrane and their corresponding ligands. These immune-checkpoint molecules include, among others, the cytotoxic T-lymphocyte antigen-4 (CTLA-4) and the programmed cell death protein-1 (PD-1) and its ligand (PD-L1). Malignant tumor cells are able to exploit such immune checkpoints to their own advantage, disabling cytotoxic T-cells which infiltrate the tumor and which might otherwise attack and destroy the tumor cells. Monoclonal antibodies directed against these proteins, known collectively as **immune checkpoint inhibitors (ICPi)** effectively **take the brakes off the immune system** and allow T-cells to attack and destroy malignant cells. Further explication of the molecular biology of the immune synapse and the mechanism of action of ICPis can be found in the addenda to this module. The field of immunotherapy is constantly evolving. As such, we anticipate our knowledge of the immune complications of ICPis and the list of specific indications for their use will continue to grow for the foreseeable future. *see illustration on page 38*

WORKSHOP OBJECTIVES

- Recognize the constellation of signs and symptoms for which immune-related adverse events (irAE) should be considered in the differential diagnosis
- Describe those circumstances in which the primary care clinician should initiate urgent communication with the medical oncologist of a patient who is being or has been treated with an immune checkpoint inhibitor
- Explain the work up of suspected irAEs of the endocrine system, skin, GI tract, lung and liver
- Describe the role of steroids and other immune suppressant drugs in the management of irAEs

PRE-READINGS (FOUND IN SUPPLEMENTAL MATERIALS)

1. ESMO Immunotherapy Toxicities Clinical Practice Guidelines

   DOI: https://doi.org/10.1093/annonc/mdx225

2. ASCO Immunotherapy Guidelines

   DOI: https://doi.org/10.1200/JCO.2017.77.6385

CASES

CASE 1: FLORIDA BOTTOMS, AGE 71

Florida Bottoms is visiting you today because she has developed diffuse, crampy abdominal pain in association with the increasingly frequent passage of loose-to-watery stools. Mrs. Bottoms was diagnosed with a Stage IV melanoma twelve weeks ago. She was seen by a medical oncologist shortly thereafter; a metastatic work up including a PET/CT showed a lung lesion. Mrs. Bottoms consented to treatment with an immune checkpoint inhibitor, pembrolizumab, for first-line treatment of metastatic melanoma, which she started eight weeks ago. Five weeks ago (three weeks into her treatment) she was seen at a walk-in clinic complaining of a diffuse itching, and was prescribed hydroxyzine 10 mg TID and hydrocortisone 1% cream, with partial benefit. At that visit she also received a script for cloxacillin for a paronychia. Seven weeks into her course of pembrolizumab, she noticed an increase in the frequency of her stools, which became loose and watery three days ago.

QUESTION #1: WHAT ARE SOME POSSIBLE DIAGNOSES? WHAT QUESTIONS DO YOU HAVE FOR MRS. BOTTOMS?

QUESTION #2: HOW IS GASTROINTESTINAL TOXICITY GRADED?

Question #3: What are you looking for on physical exam?

Case 1 continued: You note that Mrs. Bottoms looks generally well, with HR 92, RR 14, T 36.3 C, BP 122/78 and O_2 saturations of 96% on room air. Inspection of the oral cavity reveals normal gingiva and normal buccal mucosa bilaterally. Her lungs are clear and heart sounds are normal.

Abdominal examination discloses moderately increased bowel sounds, mild tenderness in the suprapubic area and the left lower quadrant, but no mass or organomegaly.

Skin exam is unremarkable.

Question #4: What grade of gastrointestinal irAE does Mrs. Bottoms have? How should her irAE be treated?

CASE 2: MUSTAFA "MUSTY" AZMEH, AGE 61

You have an office practice in Manitoba's Interlake district, and you admit to the local hospital. Mustafa ("Musty" to his Canadian friends) became your patient at the time of his family's immigration from Syria in 2015. In 2016 you referred him for counseling regarding complaints of sleep disturbance and labile moods that emerged just when Musty and his family seemed to be settling into a regular routine in their new life as Canadians. Several months later Musty was diagnosed with a urothelial bladder cancer after presenting with hematuria and cystitis-like symptoms. Musty initially had an attempt at surgical cure with a transurethral resection of a bladder tumor (TURBT), but he was found to have muscle invasive disease, for which he subsequently underwent a cystectomy and pelvic node dissection. He was enrolled thereafter in a study involving the adjuvant use of a PD-L1 inhibitor, atezolizumab. Musty experienced several weeks of Grade I – II diarrhea while on the study drug, but this eventually settled on steroids, and he completed the study. He was deemed disease-free at a follow up visit with his medical oncologist three months ago, nine-months after receipt of the final dose of atezolizumab. Musty presents to your office today complaining of progressive fatigue which began within a few weeks of that visit to the oncologist.

QUESTION #1: WHAT ARE THE MOST COMMON CAUSES OF FATIGUE IN A GENERAL PRACTICE OUTPATIENT POPULATION? WHAT ADDITIONAL DIAGNOSTIC CONSIDERATIONS ARE IMPLICIT IN MUSTY'S PRESENTATION?

Case 2 continued: As Musty tells the story of acute-on-chronic tiredness, he endorses a history of mood symptoms, but says that his irritability and sadness are much better than they were in 2016, and the sleep disturbance that attended the mood symptoms has largely resolved. On a detailed review of symptoms, you learn that Musty has developed progressive limitation of exertional capacity over the past few weeks. Climbing stairs, for example, precipitates acute, global weakness. He gets light headed when rising from a bed or chair, and he has fainted on a couple of occasions in the past week. Musty denies having had a problem with syncope or presyncope prior to this. He feels cold a lot. Musty complains of headaches which emerged in the past 10 days. He denies any change in his bowel habit. He finds himself thirstier than normal, but he only gets up to void once overnight.

QUESTION #2: WHAT WILL YOU LOOK FOR ON PHYSICAL EXAMINATION?

Case 2 continued: Musty's complete physical examination is largely unremarkable, except that he has mild pallor and a marked postural drop in blood pressure, his sitting pressure and pulse recorded at 104/64 and 100, respectively; his standing blood pressure is 86/48, HR 120. Cranial nerve examination is normal except for the loss of the temporal extremes of his visual fields.

QUESTION #3: WHAT IS ON YOUR DIFFERENTIAL DIAGNOSIS NOW?

Case 2 continued: Concerned about Musty's postural hypotension and the possibility of an endocrine irAE, you admit Musty to hospital with a view to IV fluid resuscitation, and you make urgent telephone calls to your favorite endocrinologist and to Musty's medical oncologist. You have Musty seen initially in the Emergency Department for the administration of 2L of normal saline. On advice from the endocrinologist, you send off a random ACTH and cortisol, CBC, TSH, T3 & T4, testosterone and a biochemistry panel, and order IV dexamethasone 4 mg as a stress-dose corticosteroid (because the diagnosis is not clear and stimulation testing might be needed; otherwise hydrocortisone 100 mg IV could have been used).

QUESTION #4: WHAT TESTS SHOULD BE PERFORMED IN PATIENTS WITH SUSPECTED HYPOPHYSITIS?

Case 2 continued: **Musty feels much better after the IV fluids and dexamethasone, and his vital signs normalize. Cortisol and ACTH levels come back depressed, in keeping with a diagnosis of hypophysitis. TSH, T4, blood glucose, electrolytes, and renal and liver function tests are all normal. An MRI is pending.**

QUESTION #5: WHAT ELSE IS REQUIRED IN THE MANAGEMENT OF MUSTY'S HYPOPHYSITIS?

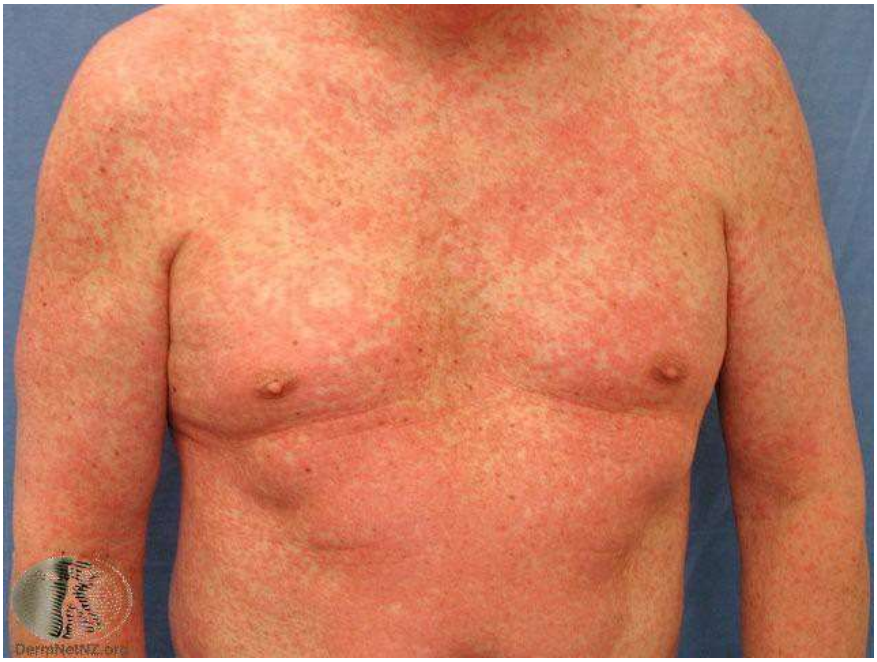
Case 3: Leanne Tull, age 54

Leanne was diagnosed with metastatic melanoma six weeks ago. Four weeks ago Leanne was started on a combination of two immune checkpoint inhibitors: nivolumab (a PD-1 inhibitor) and ipilimumab (a CTLA-4 inhibitor). Leanne presents to your office complaining of an itchy, bumpy and red rash of the neck, anterior chest and upper back that started about a week ago. In the past two days Leanne has noticed the emergence of similar lesions more diffusely across the chest, back, waist and extremities, in a centripetal distribution. The rash is getting itchier. She is having some difficulty sleeping and is having difficulty concentrating at work. Leanne denies a history of allergies of any kind. She has not been around anyone with a similar rash.

QUESTION #1: WHAT DERMATOLOGIC IRAES CAN COMPLICATE THE USE OF IMMUNE CHECKPOINT INHIBITORS?

Case 3 continued: On examination the majority of the patient's skin is affected by an erythematous maculopapular morbilliform rash. Heaviest on the upper chest, upper back, waist and proximal extremities, the rash is also present to a lesser degree over the abdomen and distal extremities. You estimate it covers 70 – 80% of her skin surface. No pustules are seen. No lip or tongue swelling is noted, no vesicles or bullae are seen, and the oral mucosa and conjunctiva look normal. No lesions of the palms or soles are seen.

Leanne's rash was similar to that of the man in the photograph below:



QUESTION #2: HOW ARE DERMATOLOGIC IRAES OF THE IMMUNE CHECKPOINT INHIBITORS GRADED? WHAT GRADE IS LEANNE'S REACTION?

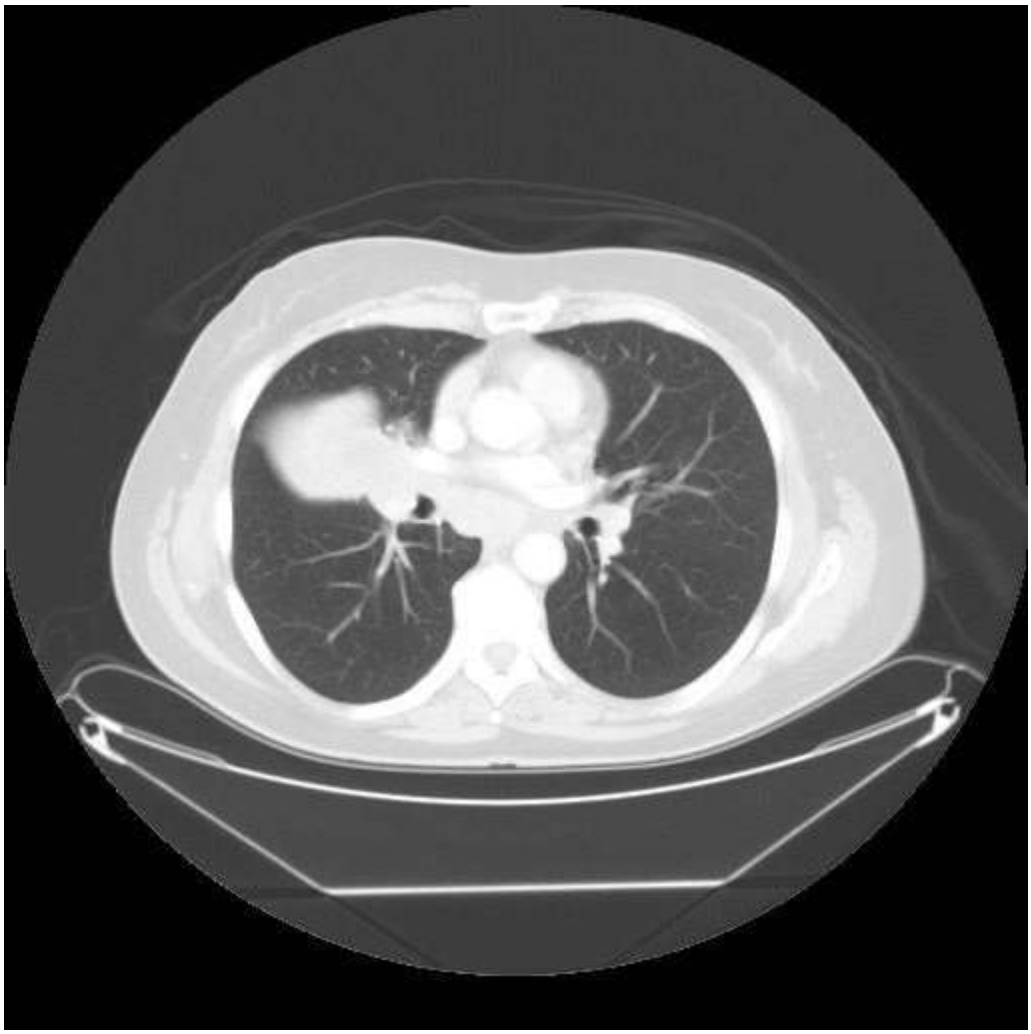
For more information on the grading of toxicities, click on this link to the CTCAE grading tools (Version 5):

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

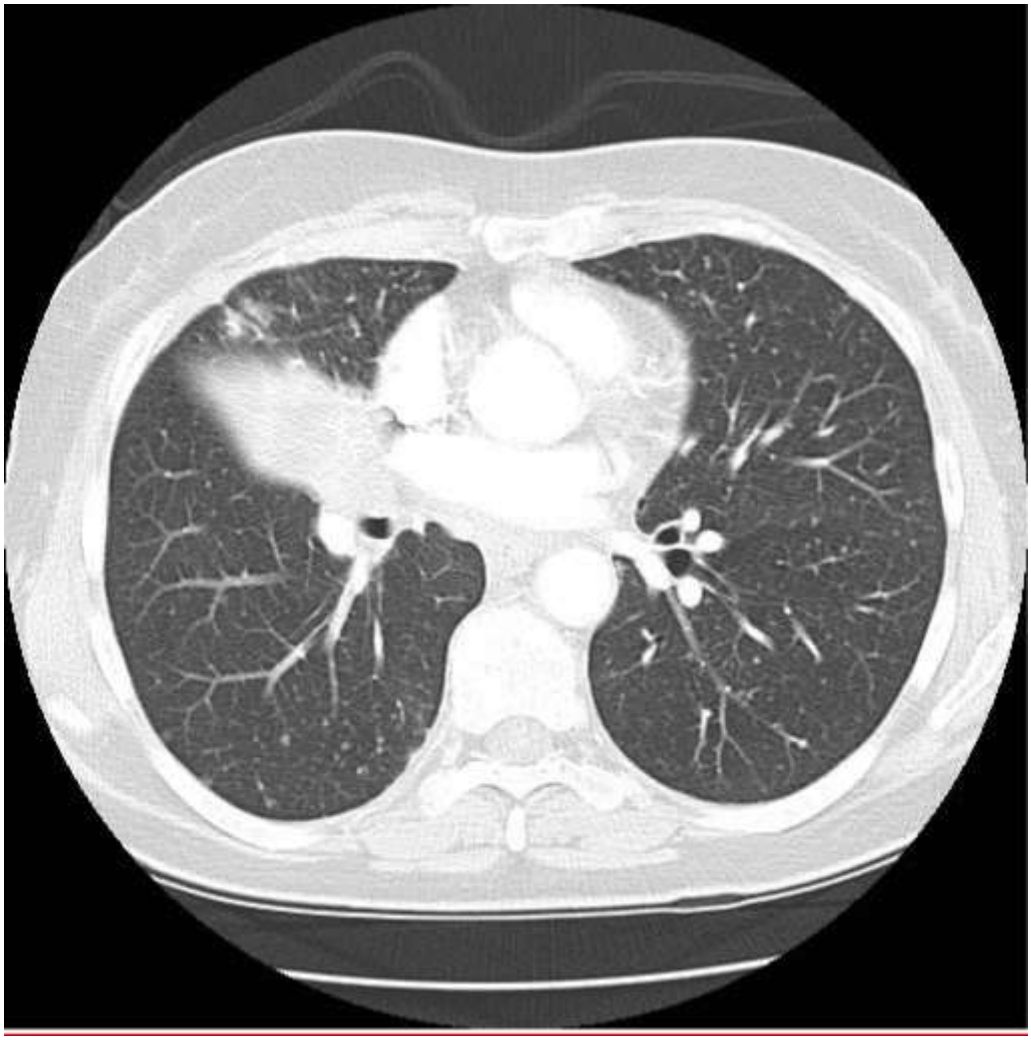
QUESTION #3: WHAT ARE THE NEXT STEPS IN THE MANAGEMENT OF LEANNE'S RASH?

CASE 4: AL VEOLAR, AGE 66

Al is a 66-year-old man diagnosed with T3 N3 M0 Stage IIIB adenocarcinoma of the right lung in May of last year. Al smoked ½ pack/day for 50 years, and quit shortly after a right hilar mass was found on CT.



His ECOG was 0 at time of diagnosis, at which time he had mild shortness of breath. His mutation status was ALK negative, EGFR negative (these are mutations which can play a role in the malignant transformation of lung tissue, and which, if present, also render the cancer susceptible to treatment with targeted agents). The tumor PD-L1 status was unknown. Initial CT showed a right hilar lobar mass with obstruction of the right middle lobe bronchus, with pretracheal, subcarinal, and right hilar lymphadenopathy. Left supraclavicular and lower neck lymph nodes were positive on PET scan. It was felt to be borderline between Stage IIIB and Stage IV, but Al was offered curative intent radiotherapy (to a dose of 60 Gray) with carboplatin and paclitaxel due to his excellent functional status and ability to include the left sided nodes in the RT field. Al received 54 of a planned 60 Gy course of radiation. His last cycle of chemotherapy was discontinued due to esophagitis and febrile illness requiring admission. A follow up CT in October last year showed a decrease in the right hilar mass, with progression of the right pretracheal lymph node.

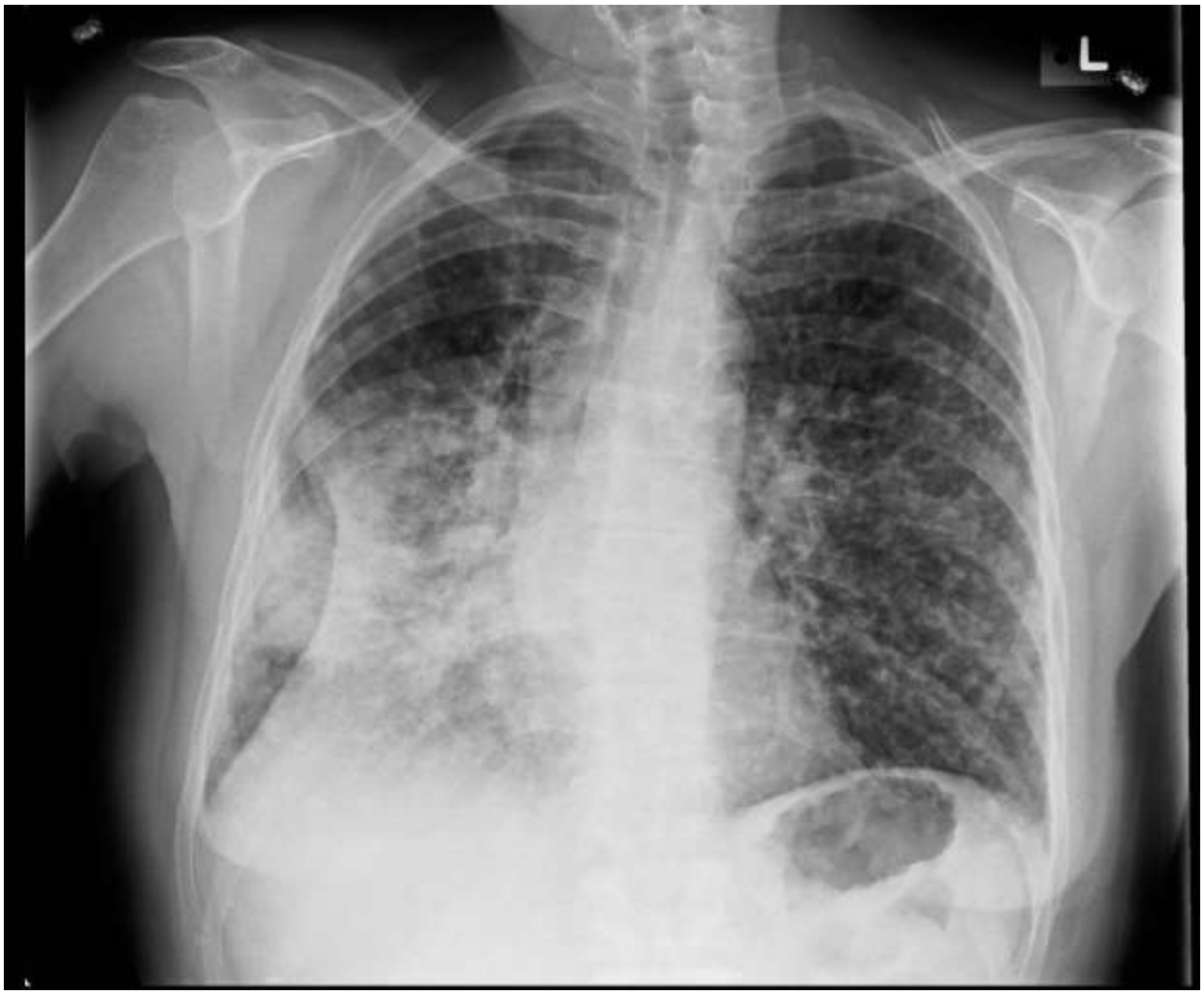


On a more recent repeat study innumerable new tiny pulmonary nodules had developed.

Second line treatment with nivolumab was offered on a q14 day schedule. Potential side effects were discussed including nausea, fatigue, vomiting, and autoimmune type reactions including colitis, pneumonitis, thyroiditis, hepatitis, rash, or other allergic type reactions. Plans were made for four cycles with a follow up CT upon completion.

On day 12 of the first cycle of nivolumab, the patient presented to ER with a non-productive cough, chest pain with deep breaths, and increasing shortness of breath, progressive since onset 5 days prior (nivolumab Cycle 1, Day 7). In the ER, at 09:20 am: BP 94/61, HR 134, RR 24, temp 36.6 C, SpO2 88% on room air. Al was visibly dyspneic, with increased work of breathing, sitting in a tripod posture. His lungs were clear, with no adventitia. Serum chemistry was

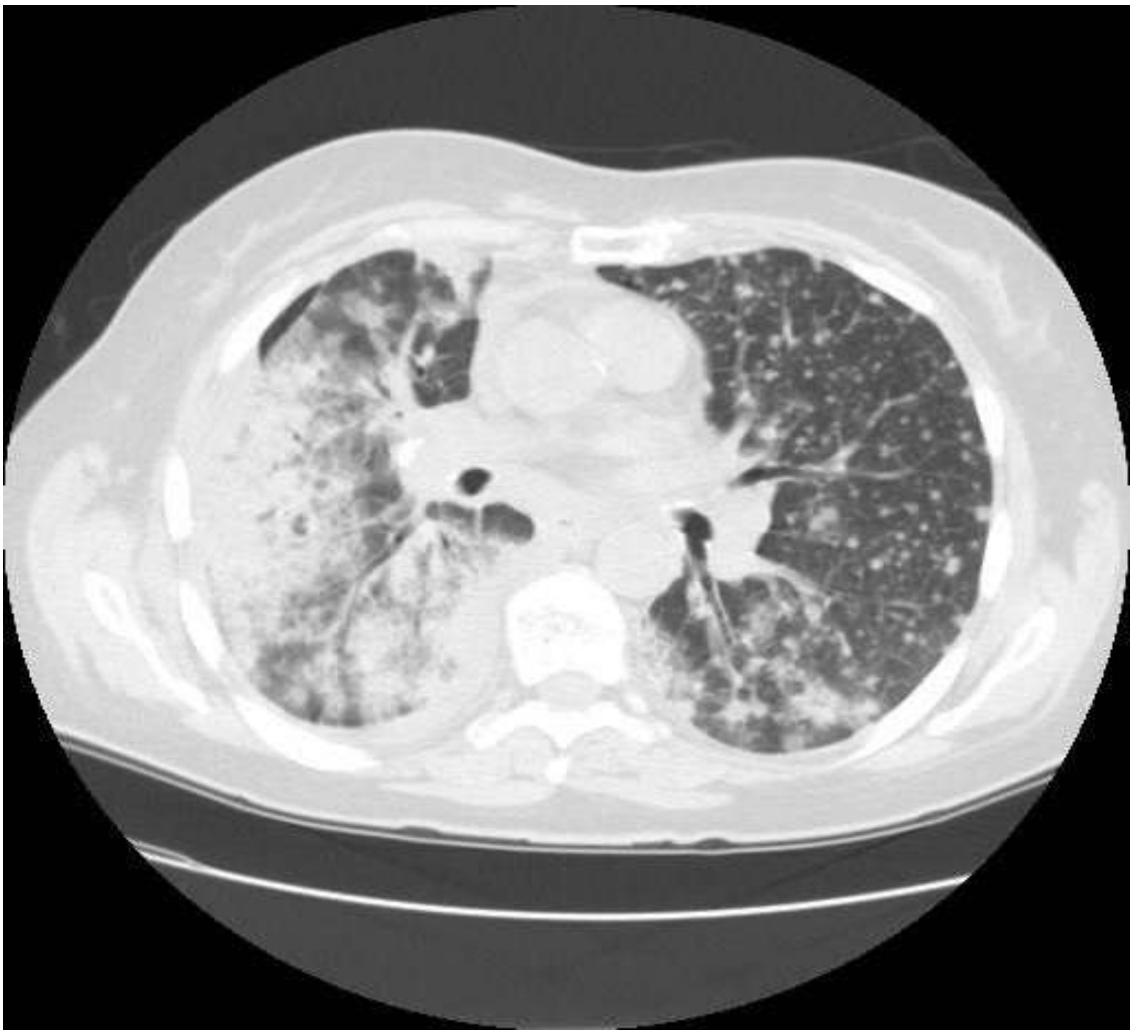
normal, WBC 12, Hb 125, Plt 376. The chest radiograph showed marked deterioration compared with a chest radiograph from three months prior, with the suggestion of acute pneumonic consolidation in right mid lung zone.



QUESTION #1: What is on your differential diagnosis? What action would you take next?

Case 4 continued: Al was admitted to hospital with a working diagnosis of pneumonia and placed on oral levofloxacin, supplemental O2, IV fluids, and prophylactic dalteparin.

The next day, (Cycle Day 13) Al looked about the same, possibly slightly better. At 12:30 pm his BP was 102/58, HR 114, RR 22, temp 37.8 C. However, his SpO2 on 4 L nasal prongs was only 90%, and he had crepitations and decreased air entry to the RLL. His WBC was 12.2, Hgb 123, Plt 361, normal chemistry. A repeat CT showed no PE, multiple mediastinal and hilar lymph nodes, new small right pleural effusion, extensive pulmonary nodules through the hemithoraces and confluent areas of airspace opacity within the right lower lobe. The working diagnosis remained that of pneumonia.



QUESTION #2: WHO YA GONNA CALL?

Case 4 continued: Al's case was discussed with the oncologist. The differential considered included pneumonia, progression of malignancy, and pneumonitis. The plan at this point was to continue antibiotics with close monitoring, and if not improving, or worsening, to start a trial of prednisone 1 mg/kg* with a slow taper over weeks in case of pneumonitis.

QUESTION #3: ASSUMING THIS TO BE AN IMMUNE PNEUMONITIS, WHAT GRADE IS IT? DO YOU AGREE WITH THE CHOICE OF STEROID?

That evening (still Day 13 of the first cycle of nivolumab), Al was feeling worse, and restless with increased shortness of breath and fever. His BP was 83/55, HR 157, RR 40, SpO2 81% on 4L/min nasal prongs, temp 38.4 C. On lung auscultation there was poor air entry to the right lower lobe. Lab: WBC 12.2; chemistry unchanged. Venous gas: pH 7.42; pCO2 32; HCO3 21; lactate 1.03.

A bolus of IV crystalloid was administered and Al's levofloxacin was discontinued in favor of vancomycin and piperacillin/tazobactam. In the wee hours of Day 14, Al's BP was 91/56, HR 124, RR 32, T 37.8 C, SpO2 89% on 6L per face mask. By the morning, his BP had risen slightly to 103/60, HR 124, T 38.3 C, RR 36, SpO2 95% 6L FM. Venous gas: pH 7.47; pCO2 33; HCO3 24; lactate 1.25 mmol/L.

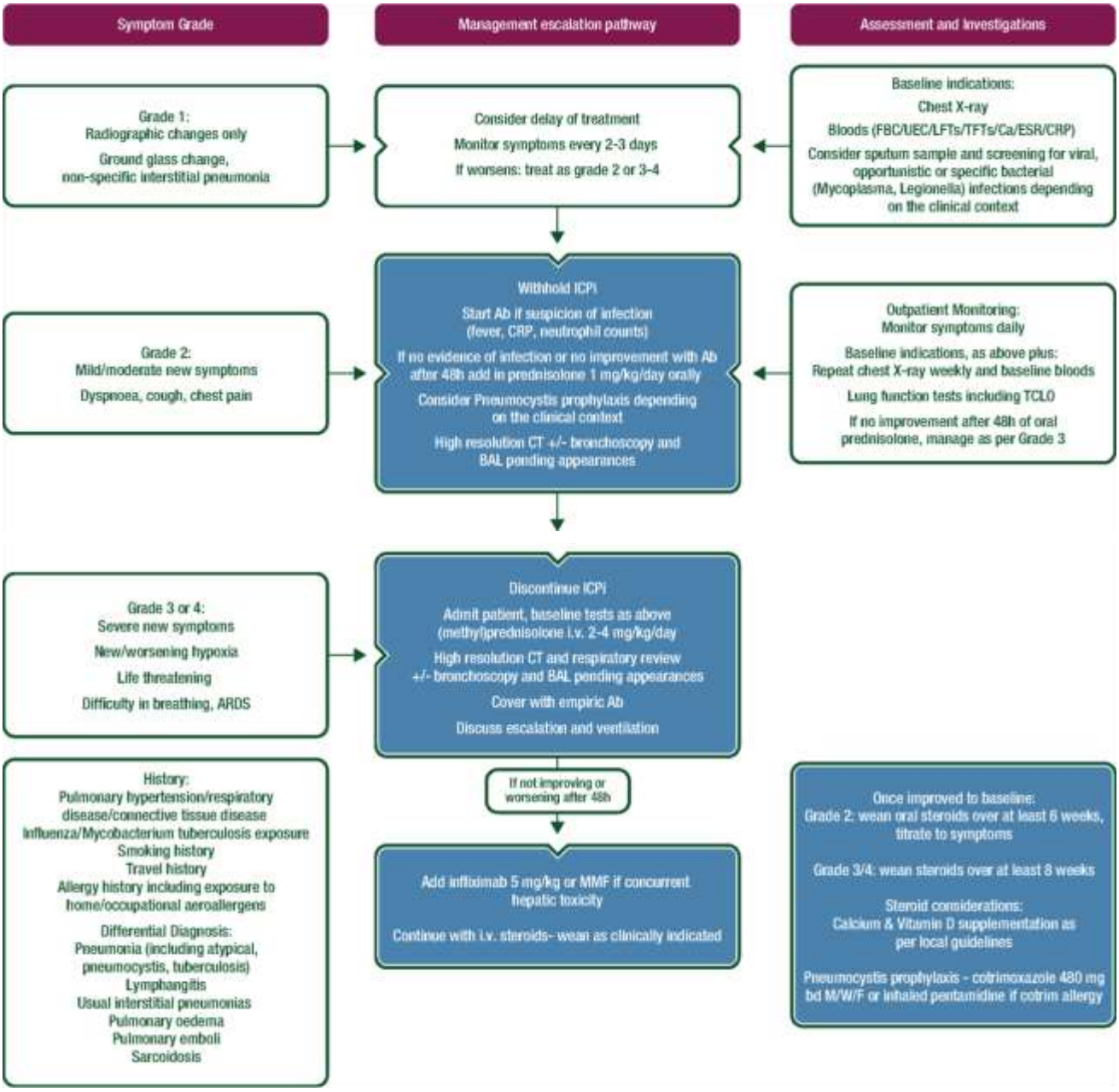
At 08:00 that morning, azithromycin was added to the antibiotic regimen and Al was started on IV methylprednisolone, 100 mg q24 hours.

By noon he was deteriorating, with decreased air entry to both lower lobes and fine crepitations throughout on inspiration. BP 115/70, HR 120, RR 40, T 37.2 C, SpO2 87 % on 9 L non-rebreathe FM.

QUESTION #4: HOW MIGHT YOU PREVENT AL FROM CRASHING AT THIS POINT?

Case 4 continued: Al was transferred to ICU, and BiPap was initiated. BP 94/55, HR 111, RR 41, SpO2 96%, FiO2 90%. Al was mentating normally, and was able to eat with the mask off for brief periods.
Lab: WBC 16; Hb 115; Plt 359.
Venous gas: pH 7.39 pCO2 38 HCO3 23 lactate 1.89 Discussed with oncologist. Plan: to consider short term intubation and bronchoscopy; and if further deterioration to perform bronchoaveolar lavage (BAL).

QUESTION #4: HOW COMMONLY DOES AN IRAE PRESENT AS A PNEUMONITIS?



Haanen J.B.A.G. et al. (August 2017) Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 28 (Supplement 4): iv119-iv142, 2017

DOI: 10.1093/annonc/mdx225

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[1] Haanen J.B.A.G. et al. (August 2017) Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 28 (Supplement 4): iv119-iv142, 2017 DOI: 10.1093/annonc/mdx225

[2]*Symptom to Diagnosis: An Evidence-Based Guide, 3e* Eds. Scott D.C. Stern, et al. New York, NY: McGraw-Hill, 2014,

[3]Weis, 2011. Weis J.: Cancer-related fatigue: prevalence, assessment, and treatment strategies. Expert. Rev. Pharmacoecon Outcomes Res. 2011; 11: pp. 441-446

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[6]https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

[7]Naidoo J, Wang X, Koo KM et al. Pneumonitis in patients treated with anti-programmed death-1/programed death Igand therapy. J Clin Oncol 2017; 35: 709-717

LINKS AND RESOURCES

Haanen J.B.A.G. et al. (August 2017) *Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.* Annals of Oncology 28 (Supplement 4): iv119-iv142, 2017

ESMO Immunotherapy Toxicities Clinical Practice Guideline 2017

Brahmer Julie R et al. (Feb 2018) *Management of Immune-Related Adverse Event in Patients Treated with Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline.* J Clin Oncol 36 © 2018 American Society of Clinical Oncology and National Comprehensive Cancer Network

Brahmer JR, Abu-Sbeih H, Ascierto PA, et al. *Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events.* Journal for ImmunoTherapy of Cancer 2021;9: e002435. doi:10.1136/jitc-2021-002435

ASCO Immunotherapy Guidelines

Navigation Services: https://www.cancercare.mb.ca/Patient-Family/support-services/cancer-navigation-services

Follow-up and Management of Checkpoint Inhibitor Related Toxicities in Cancer Patients July, 2020 Clinical Practice Guideline SUPP-018 – Version 1 (www.ahs.ca/guru)

Video link: https://www.youtube.com/watch?v=5AXApBbj1ps

Facilitator Guidelines adapted from the Breast Cancer Workshop, Cancer Care Outreach Program on Education, BC Cancer Agency and University of British Columbia, Continuing Professional Development.

SUPPLEMENTAL INFORMATION INCLUDED

Immune checkpoint inhibitors currently in use or under study at CancerCare MB

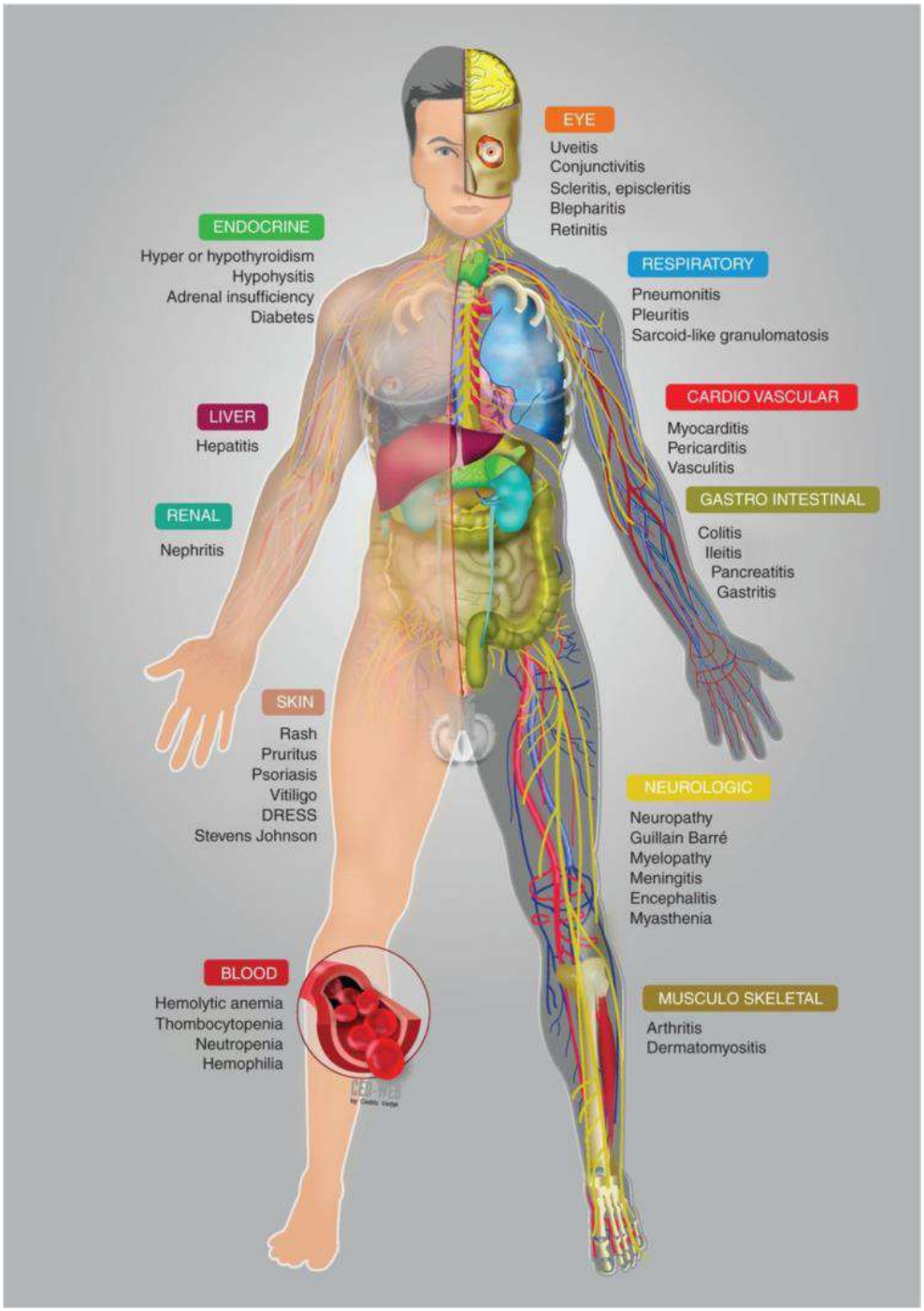
Generic name (Trade name)	Class of immune checkpoint inhibitors	Indications for use
Atezolizumab (Tecentriq®)	PD-L1 inhibitor	• Locally advanced or metastatic non-small cell lung cancer with progression on or after platinum-based chemotherapy. • First line unresectable or metastatic hepatocellular carcinoma (in combination with bevacizumab)
Avelumab (Bavencio®)	PD-L1 inhibitor	• Metastatic Merkel Cell Carcinoma • Unresectable locally advanced or metastatic urothelial cancer whose disease has not progressed following first-line platinum-based chemotherapy (maintenance)
Cemiplimab (Libtayo®)	PD-1 inhibitor	• Metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or radiation
Durvalumab (Imfinzi®)	PD-L1 inhibitor	• Locally advanced, unresectable, Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following platinum-based chemoradiation • Extensive-stage small cell lung cancer (in combination with etoposide and either carboplatin or cisplatin)
Ipilimumab (Yervoy®)	CTLA-4 inhibitor	• Unresectable or metastatic melanoma (single agent) • Unresectable or metastatic melanoma (in combination with nivolumab) • Renal Cell Carcinoma; Intermediate/Poor-Risk; 1st Line (in combination with nivolumab) • Metastatic non-small cell lung cancer (in combination with nivolumab and platinum-doublet chemotherapy) • Unresectable pleural mesothelioma (in combination with nivolumab)
Nivolumab (Opdivo®)	PD-1 inhibitor	• Relapsed Hodgkin Lymphoma • Unresectable or metastatic melanoma (single agent or in combination with ipilimumab)

		• Adjuvant melanoma • Locally advanced or metastatic non-small cell lung cancer with progression on or after platinum-based chemotherapy. • Metastatic non-small cell lung cancer (in combination with ipilimumab and platinum-doublet chemotherapy) • Unresectable pleural mesothelioma (in combination with ipilimumab) • Advanced or metastatic renal cell carcinoma who have received prior anti-angiogenic therapy. • Intermediate or poor risk metastatic renal cell carcinoma (in combination with ipilimumab) • Recurrent or metastatic squamous cell cancer of the head and neck progressing on or after platinum-based therapy. • Adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer in patients who have residual pathologic disease following prior neoadjuvant chemoradiotherapy.
Pembrolizumab (Keytruda®)	PD-1 inhibitor	• Relapsed Hodgkin lymphoma • Refractory primary mediastinal B-cell lymphoma • Metastatic Colorectal Cancer (1st line MSI-H) • Unresectable or metastatic melanoma • Adjuvant melanoma • Metastatic non-small cell lung cancer • Metastatic non-small cell lung cancer who have disease progression on or after platinum-containing chemotherapy. • Locally advanced or metastatic urothelial cancer who have disease progression during or following platinum-containing chemotherapy • Advanced or metastatic renal cell cancer (in combination with axitinib) • Metastatic or unresectable recurrent head and neck squamous cell carcinoma • Locally advanced unresectable or metastatic carcinoma of the esophagus or esophagogastric junction.

NOTE: MANY OF THESE AGENTS ARE CURRENTLY BEING STUDIED IN SOLID TUMORS AND HEMATOLOGICAL MALIGNANCIES. TREMILIMUMAB, A CTLA-4 INHIBITOR IS ALSO BEING INVESTIGATED IN CLINICAL TRIALS.

THE SPECTRUM OF IRAES SEEN WITH IMMUNE CHECKPOINT INHIBITORS

Immune related Adverse Events can affect nearly every tissue in the human body. The following is a brief summary of the range of possible irAEs, with particular focus on the irAEs not covered in the cases of this module.



From: Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper
Ann Oncol. 2015;27(4):559-574. doi:10.1093/annonc/mdv623

I. DERMATOLOGIC REACTIONS

There are four basic histopathologic patterns seen in the skin reactions to immune checkpoint inhibitors:

A. **The commonest pattern is that of inflammation, which can be acute, subacute or chronic. Epidermal changes might be psoriasiform or lichenoid reactions. A generalized maculopapular rash (see Case 3) is the commonest skin reaction. A lichenoid interface chronic dermatitis such as lichen planus is also a common reaction.**

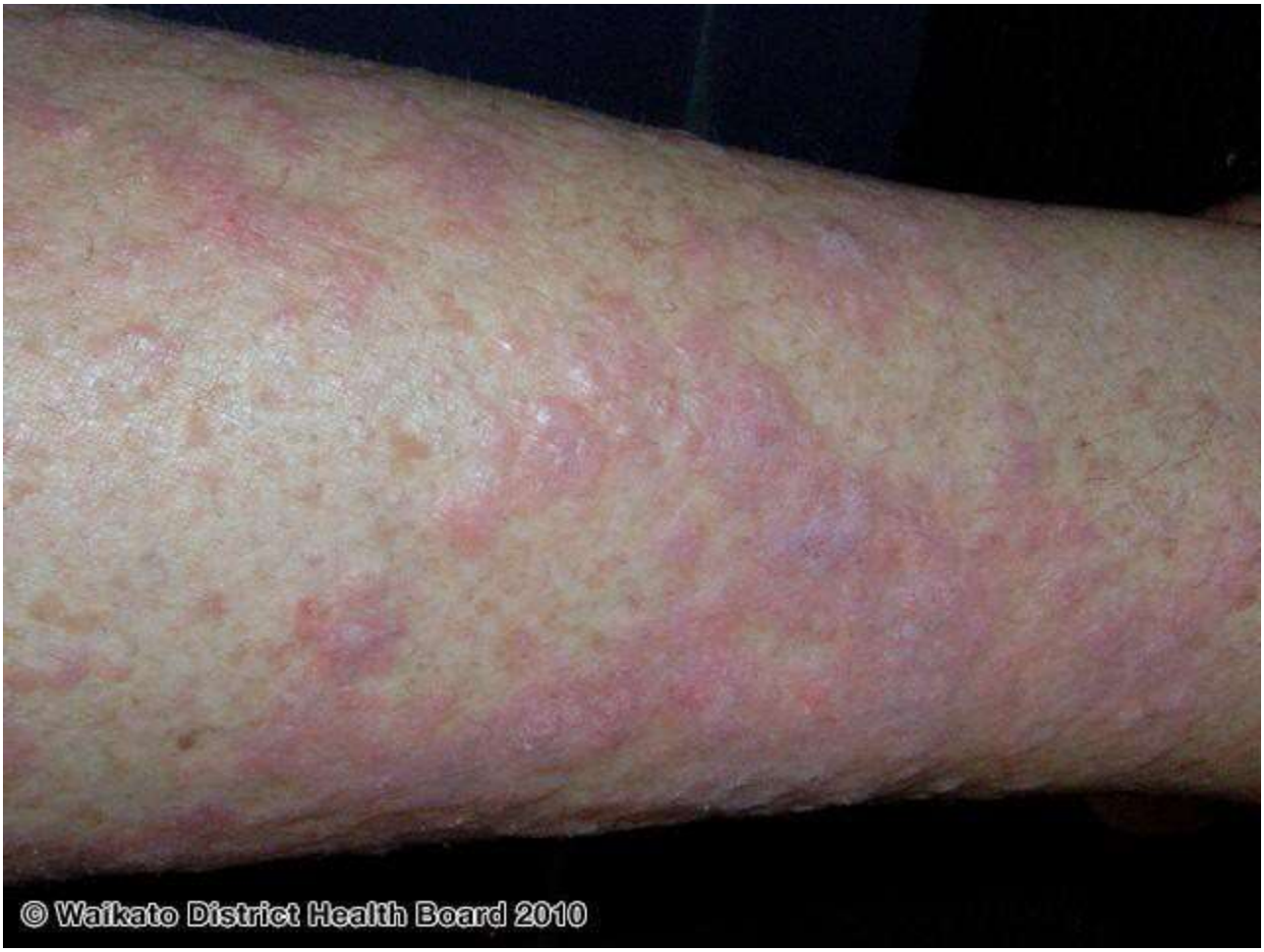


Figure 1: Lichenoid dermatitis. From DermNet NZ. See link to Creative Commons Attribution-NonCommercial-No Derivs 3.0 (New Zealand)

https://creativecommons.org/licenses/by-nc-nd/3.0/nz/legalcode

B. Immunobullous skin lesions resembling bullous pemphigoid or dermatitis herpetiformis;

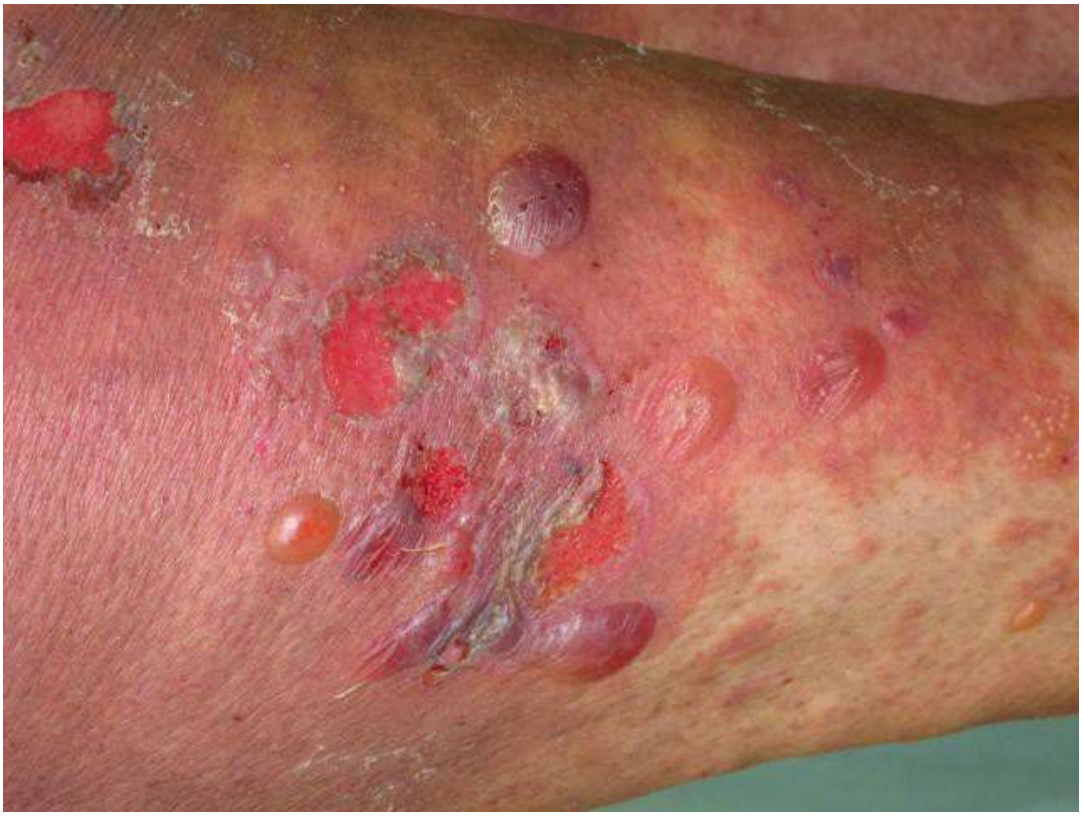


Figure 2: Bullous Pemphigoid. From DermNet NZ. See link to Creative Commons Attribution-NonCommercial-No Derivs 3.0 (New Zealand)

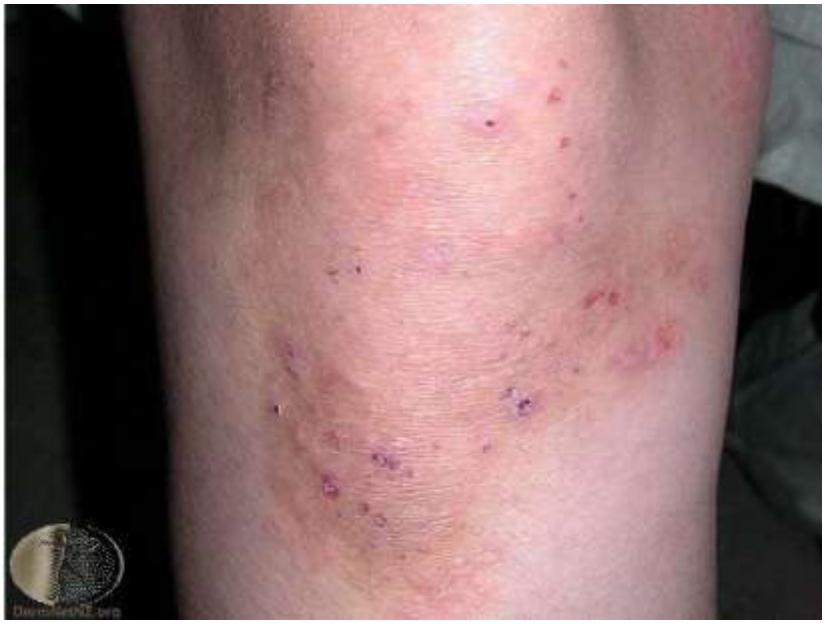


Figure 3: Dematitis Herpetiformis. from DermNet NZ. See link to Creative Commons Attribution-NonCommercial-No Derivs 3.0 (New Zealand)

C. **Keratinocyte alteration—acantholytic dyskeratosis (Grover's disease);**

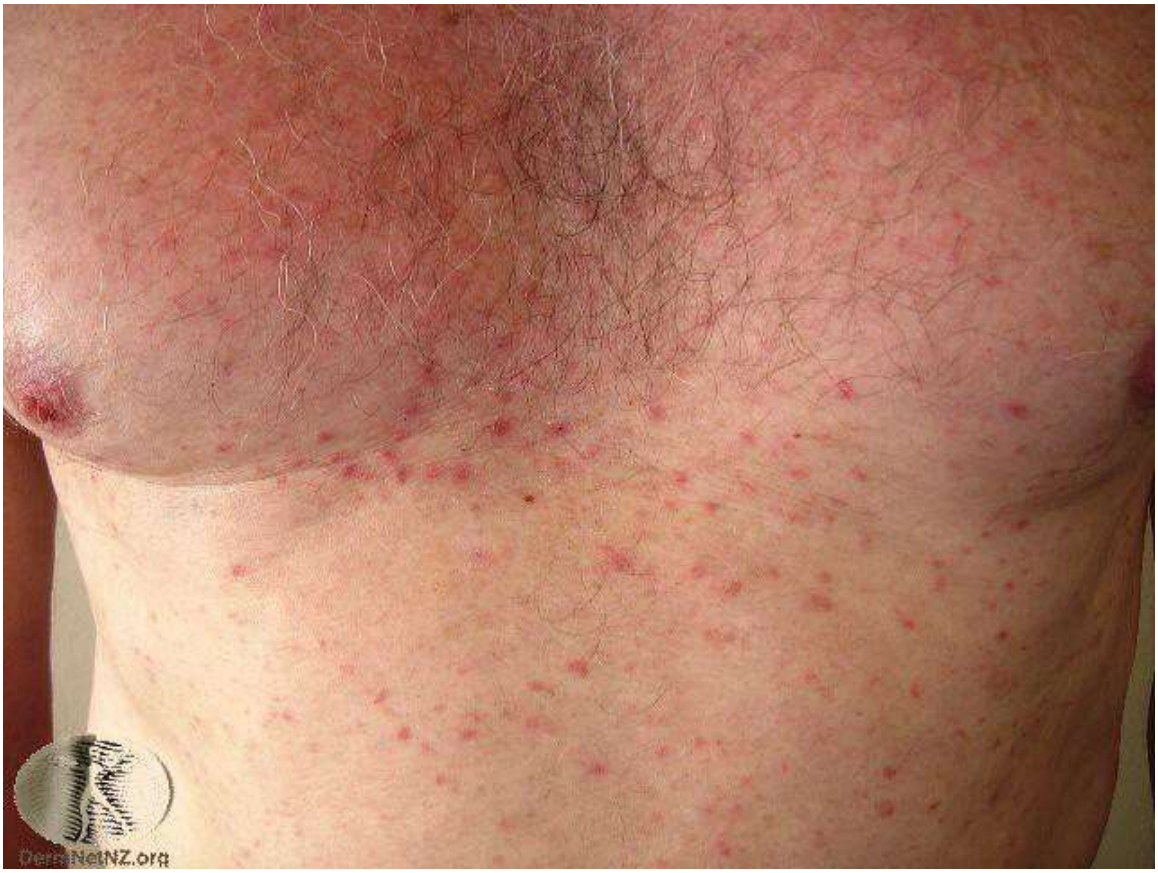


Figure 4: Grover's disease. From DermNet NZ. See link to Creative Commons Attribution-NonCommercial-No Derivs 3.0 (New Zealand)

D. **Immunologic attack on melanocytes (halo nevi, regression of nevi, tumoural melanosis and vitiligo**

Figure 5: Vitiligo. From DermNet NZ. See link to Creative Commons Attribution-NonCommercial-No Derivs 3.0 (New Zealand)

The more common skin reactions can usually be managed with topical steroids and emollients, and sometimes require the discontinuation of the ICPi. The commonest skin irAEs are:

- **Rash. The most common skin irAE is a morbilliform maculopapular exanthem.**
- **Pruritus – also very common; often with no visible rash.**
- **Vitiligo (in melanoma patients). Vitiligo has been noted to be associated with good clinical responses to anti-PD-1 MoAbs in patients treated for melanoma**

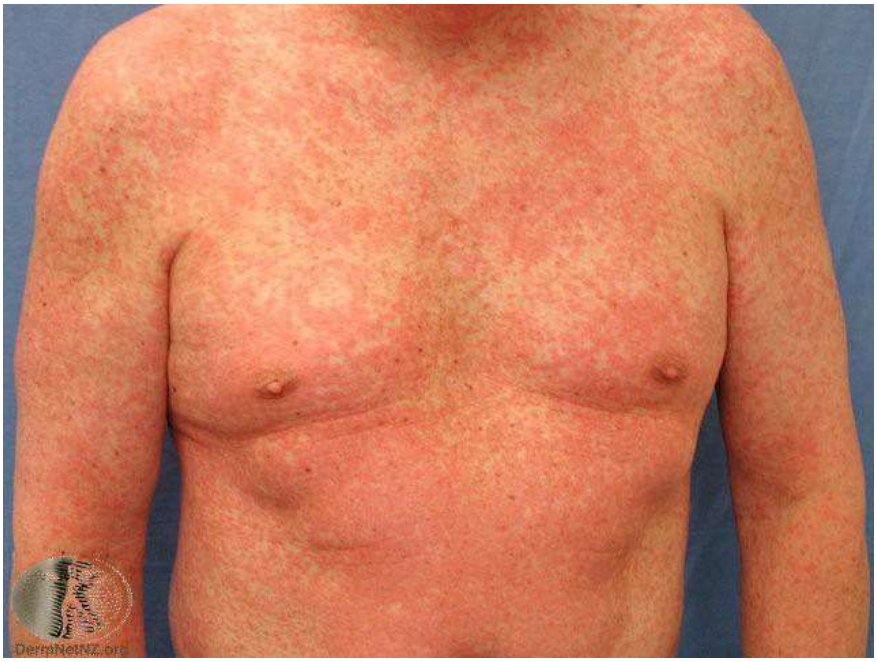


Figure 6: Morbilliform Drug Rash. From DermNet NZ. See link to Creative Commons Attribution-NonCommercial-No Derivs 3.0 (New Zealand)

For the most serious skin reactions, which are rare but have been fatal in some cases, the patient should be hospitalized for intravenous steroids, and might require ICU admission. Their care should be actively supervised by a dermatologist as well. Such severe skin reactions include:

- **drug rash with eosinophilia and systemic symptoms (DRESS)**
- **acute febrile neutrophilic dermatosis (Sweet syndrome)**
- **Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN)**

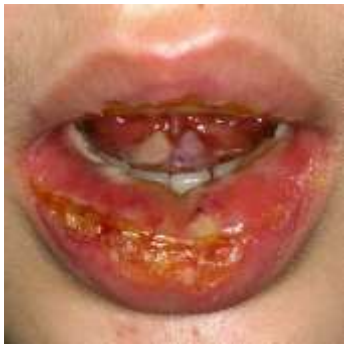


Figure : Mucosal SJS. From DermNet NZ. See link to Creative Commons Attribution-NonCommercial-No Derivs 3.0 (New Zealand)

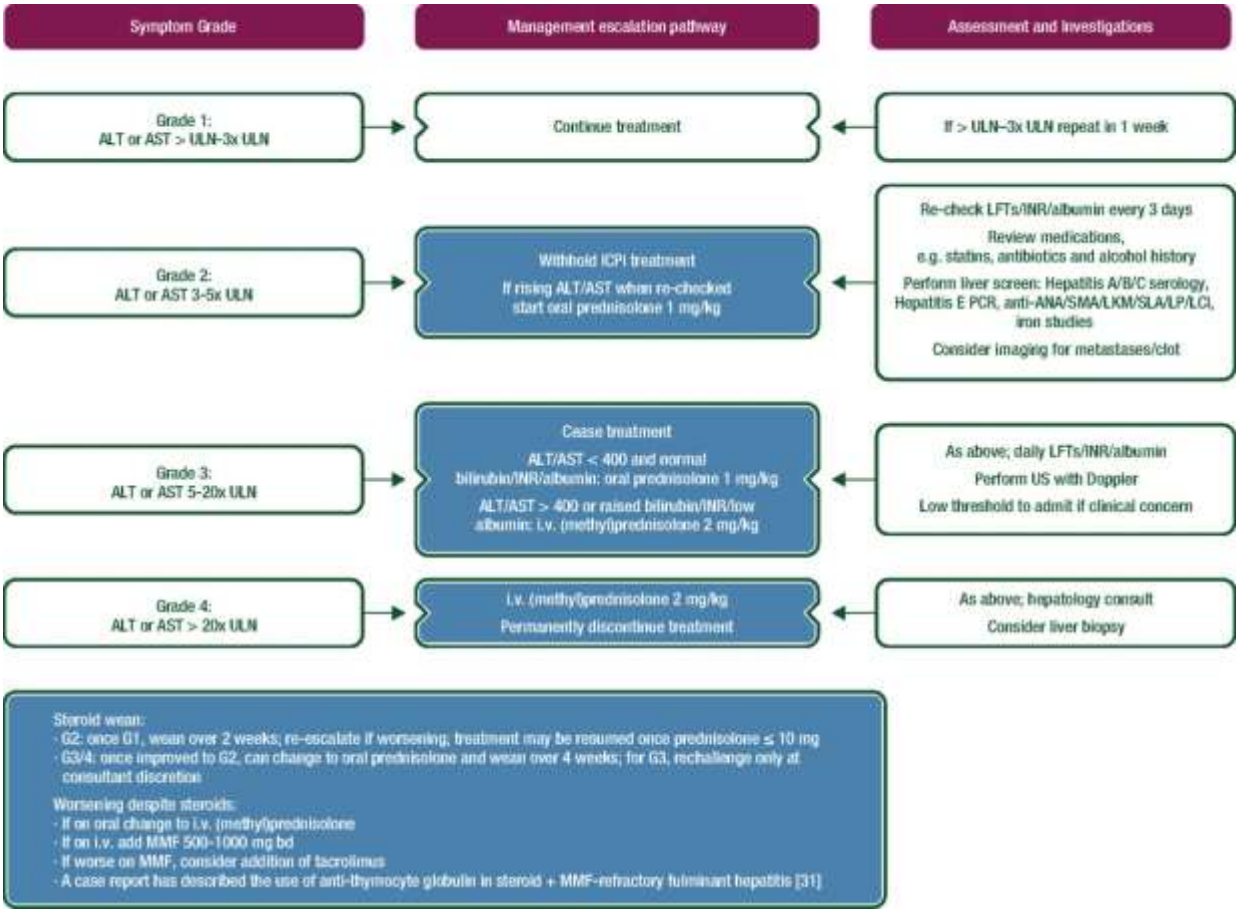
II. HEPATOTOXICITY

Elevations of AST and ALT occur in up to 10% of patients on CTLA-4 inhibitors and up to 5% with PD-1 and PD-L1 inhibitors.

Grade 3-4 hepatotoxity occurs in 1-2% of patients on ICPis.

Hepatotoxicity is more likely to occur in: patients on combinations of ICPis; patients on an ICPi for hepatocellular carcinoma; patients with renal carcinoma who are also on a tyrosine kinase inhibitor; and patients receiving concomitant cytotoxic chemotherapy.

Note that infliximab, which itself carries a risk of hepatotoxicity, is not usually used for hepatotoxicity from immune checkpoint inhibitors. Typically, steroids are used initially; mycophenylate mofetil is added on if additional immune suppression is indicated.



Haanen J.B.A.G. et al. (August 2017) Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 28 (Supplement 4): iv119-iv142, 2017

DOI: 10.1093/annonc/mdx225

III. Gastrointestinal Toxicity

Although diarrhea and enterocolitis are the most common gastrointestinal irAEs (see Case 1), upper GI pathology can also complicate ICPi use. Epigastric pain and other upper GI symptoms can signify an auto-immune pancreatitis, esophagitis, gastritis or duodenitis.

IV. Endocrine Toxicity

The most common endocrine irAEs are hypo- and hyperthyroidism (which, when it occurs, usually evolves into a hypothyroid state). Such irAEs probably have a pathogenesis similar to other autoimmune thyroid disorders.[1] Ipilimumab administered at a dose of 3 mg/k is associated with a risk of thyroid autoimmune disease of 1-5%. PD-1/PD-L1 MoAb use has a 5-10% associated rate of thyroid disorders. The combination of ipilimumab and a PD-1 or PD-L1 blocking agent has a 20% incidence of thyroid dysfunction. Not all cases progress to the point of requiring replacement therapy, but those who do will probably require life-long treatment. The literature recommends that TSH & T4 be checked at least monthly while patients are receiving immune checkpoint inhibitors.

Immune checkpoint inhibitor use can be complicated by autoimmune hypophysitis, presenting most commonly as hypocortisolism (see Case 2), which can also be a sign of primary adrenal failure of autoimmune origin.

Type I diabetes emerges as an irAE in <1% of patients treated with immune checkpoint inhibitors. Even so, blood sugars should be monitored regularly in patients on ICPis. Even patients with Type II diabetes are potentially at risk for diabetic ketoacidosis if they become hyperglycemic in association with ICPi use. Patients with hyperglycemia should have C-peptide and Abs against glutamic acid decarboxylase (GAD) and islet cells (ICA) measured to distinguish between Type I and Type II DM.

V. Renal Toxicity

Renal toxicity with ICPis is rare, but the incidence of renal dysfunction of autoimmune origin is approximately 5% for combination (or sequential) CTLA-4 – PD-1/PD-L1 therapy.

VI. Neurotoxicity

Although relatively uncommon, a wide range of neurologic irAEs have been documented; they need to be distinguished from neurologic manifestations of malignant disease progression, infection, or seizure disorder. See the ESMO clinical practice guideline[1] or the ASCO guideline for further details.

VII. Other Immune Toxicities

The reader is referred to the ESMO and ASCO clinical practice guidelines for information on ocular, cardiac, musculoskeletal and hematologic irAEs, and for a discussion of the risk of allograft rejection in patients who have had liver, kidney, or heart transplantation.

THE IMMUNE SYNAPSE:

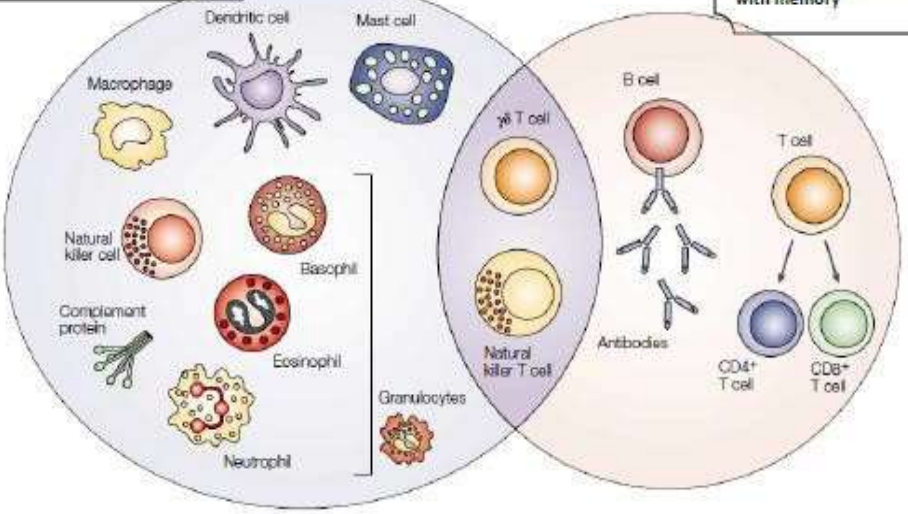
The immune system is comprised of two "arms": Innate and Adaptive[1]

Innate Immunity[2,3]

First line of immune defense;
response is immediate, but not antigen-specific

Adaptive Immunity

Slow, Antigen-specific response, with memory



The immune system comprises our defense against infection with bacteria, viruses, parasites and protozoa, and toxins, as well as against cancer.

1

Tumours express a multitude of proteins, known as tumour-associated antigens[4,5,6,7]

2

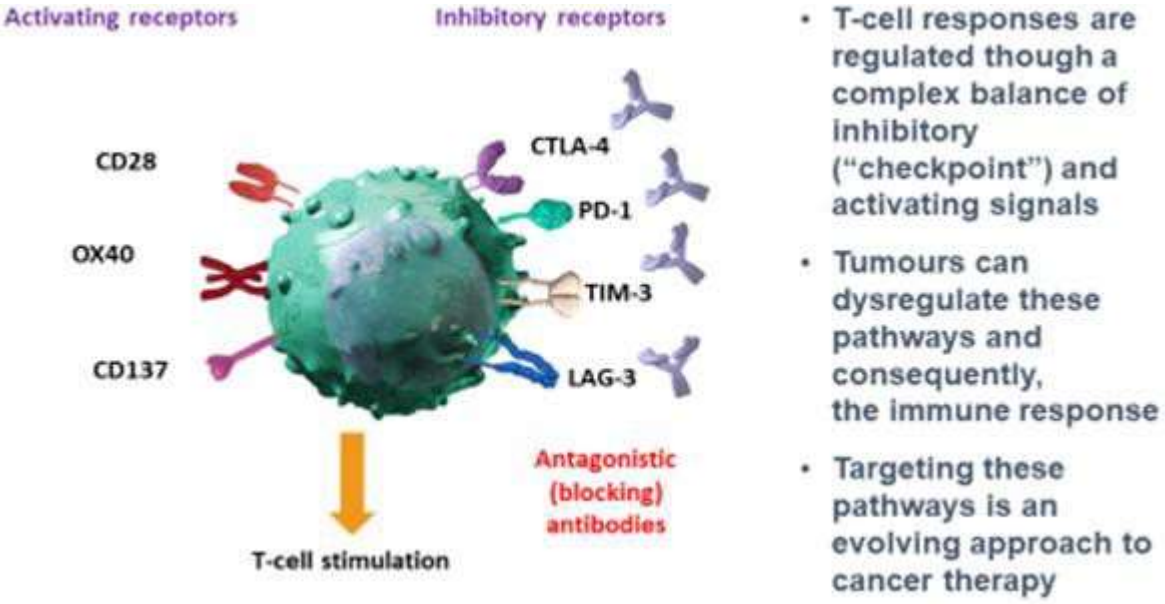
Antigen presenting cell (APC) captures tumour-associated antigens[5]

3

APC matures

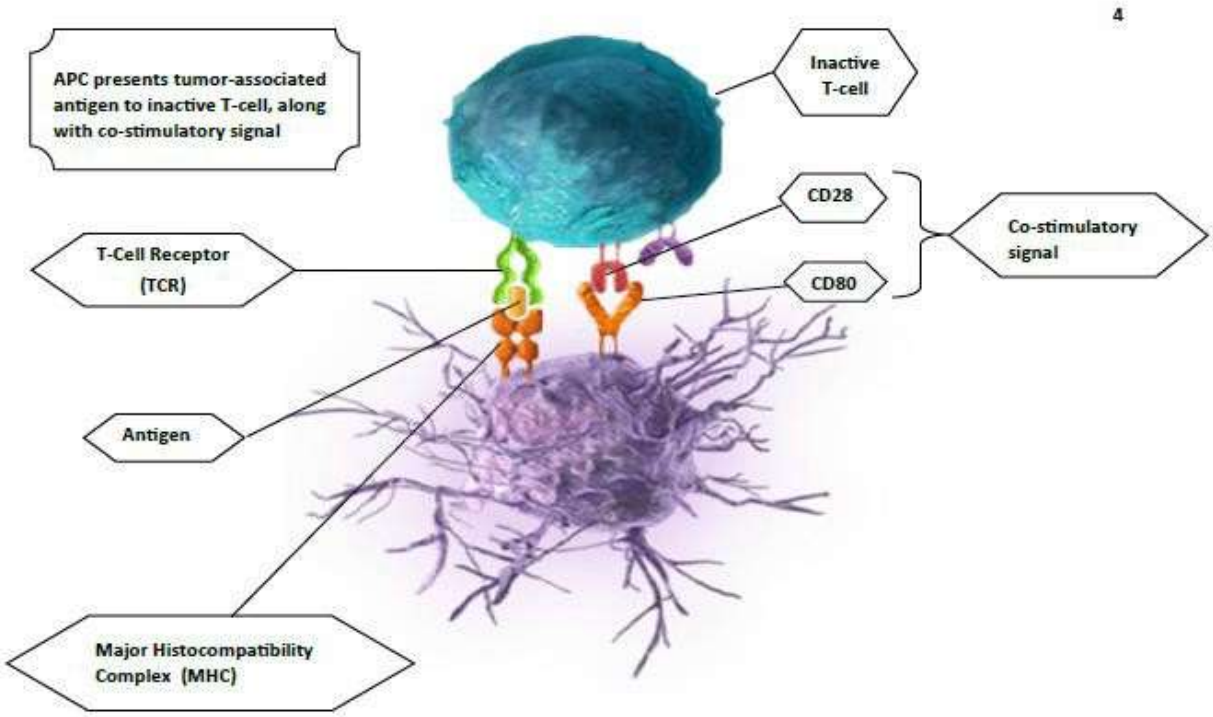
When an antigen presenting cell (APC), such as the dendritic cell depicted above, presents antigen with its major histocompatibility complex (MHC) to a T-cell receptor (TCR, such as CD4 or CD8) a co-stimulatory signal augments the T-cell activation against that antigen. This co-stimulatory signal is established when the T-cell's CD28 binds to the APC's CD80 or CD86. In resting (inactive) T-cells, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is an intracellular protein. After a T-cell receptor engages an antigen borne by the MHC of an APC, and a co-stimulatory single through CD28 is established, CTLA-4 migrates to the T-cell surface membrane, where it out-competes with CD28 to bind with CD80 and CD86, thereby initiating intracellular signaling that suppresses T-cell activation. Blocking CTLA-4 at the surface membrane with an anti-CTLA-4 monoclonal antibody (MoAb) (such as ipilimumab) allows continued activation of the T-cell against the antigen.

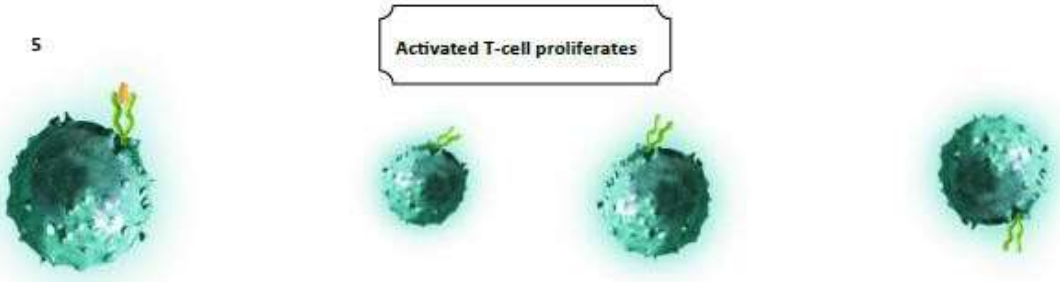
T-CELL REGULATION

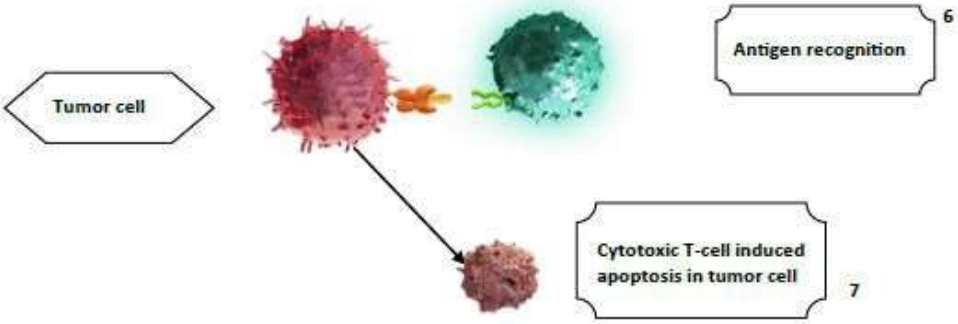


When an activated T-cell encounters on the MHC of a tumor cell the very same antigen against which the T-cell has been activated, the T-cell will destroy the tumor cell – unless the T-cell's PD-1 encounters on the tumor cell surface the ligand to PD-1, viz., PD-L1, which announces to the T-cell that the tumor is "self" (rather than "non-self") tissue. In that case, the T-cell is deactivated, a process known as T-cell exhaustion. MoAb directed against PD-1 or against PD-L1 can prevent T-cell exhaustion, permitting the T-cell to proceed with its attack on the tumor cell.

Adapted from Mellman I, *et al*. *Nature* 2011; 480(7378):480-9; Pardoll DM. *Nat Rev Cancer* 2012; 12(4):252-64


4
APC presents tumor-associated antigen to inactive T-cell, along with co-stimulatory signal
Inactive T-cell
CD28
CD80
Co-stimulatory signal
T-Cell Receptor (TCR)
Antigen
Major Histocompatibility Complex (MHC)


5
Activated T-cell proliferates


Tumor cell
6
Antigen recognition
Cytotoxic T-cell induced apoptosis in tumor cell
7

Immune Synapse and T-cell regulation images sourced from:

1. Abbas AK, et al. Cellular and Molecular Immunology. 7th ed. Philadelphia, PA: Elsevier Saunders; 2012.
2. Figure reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Cancer. Dranoff G. Nat Rev Cancer. 2004; 4:11-22.
3. Vesely MD, et al. Annu Rev Immunol. 2011; 29:235-271.
4. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012; 11:252-264.
5. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature. 2011; 480:480-489.
6. Heemskerk B, Kvistborg P, Schumacher TNM. The cancer antigenome. EMBO J. 2013;32(2):194-203.
7. Boudreau JE, Bonehill A, Thielemans K, Wan Y. Engineering dendritic cells to enhance cancer immunotherapy. Mol Ther. 2011;19(5);841-8.

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