Oncology emergencies:

Dr Dainik Patel
Medical Oncologist
Lyell McEwin Hospital
Adelaide Cancer Centre (Tennyson Centre, 480 specialist centre)
Agenda:

- Background
- Cancer related emergencies
- Chemotherapy related emergencies
- Immunotherapy related emergencies
Background:

Cancer patients present to the ED with poorly managed symptoms or treatment related toxicities

- Most common: fever, infection, GI toxicity, pain, respiratory illness

Some particular syndrome need to be promptly recognized to avoid long term consequences

- Multidisciplinary approach is necessary
GP’s role:

**Early**
- Recognize red flags
- Prevention
  - Education
  - Close monitoring

**presentation**
- Assessment and initial treatment
- Communication with team and ED

**Post**
- Follow up visits and investigations
Agenda:

- Background
- Cancer related emergencies
- Spinal cord compression
- Superior ven-cava syndrome
Cancer related emergencies: spinal cord compression

5% of all cancer patients

- Common problem in prostate, lung, breast and RCC. Other includes Hodgkin’s lymphoma, myeloma as well.

Thoracic: 60%, lumber: 25% and cervical 15%

- Always image whole spine MRI as third of the cases have multi-level metastasis

Survival is limited in patients with multiple spinal metastasis with cord compression
Cancer related emergencies: spinal cord compression

- Commonly, presenting symptoms is pain
- Muscle weakness (60-86%)
- 2/3 not ambulatory at time of diagnosis
- Sensory loss is less common
- Bladder and bowel dysfunction: late
- Functional capacity is the single most predictor of outcome
spinal cord compression; CT vs MRI
Cancer related emergencies: spinal cord compression (ESMO guidelines)

Recognize and expedite
Start early treatment

Suspicious symptoms
- High suspicion for SCC
- Low threshold for MRI

Multidisciplinary evaluation
- Intravenous glucocorticoids

Decompressive surgery followed by radiotherapy

YES
- Radioresistant tumour
- Displacement of SC on MRI
- Single area of SCC
- <48 hours symptomatic interval
- >3 months expected survival

NO
Radiotherapy

Figure 1 Algorithm for the management of SCC.

MRI, Magnetic resonance imaging; SC, spinal cord; SCC, spinal cord compression.
Cancer related emergencies: Superior Vencava Syndrome

![Diagram showing the distribution of malignancies causing SVC syndrome. Non-small-cell lung cancer is the largest category at 50%, followed by small-cell lung cancer at 22%. Lymphoma contributes 12%, germ-cell cancer 3%, metastatic cancer 9%, mesothelioma 1%, thymoma 2%, and other cancers 4%.]

Cancer related emergencies: Superior Vencava Syndrome
Cancer related emergencies: Superior Vencava Syndrome

Radiographic evidence of mediastinal mass (lymphoma) with pleural effusion

Fig. 5 Superior vena cava syndrome with blood returning via collateral veins draining to the azygos vein. White open arrows pointing to collaterals. White solid arrow pointing to azygos vein.
Cancer related emergencies: Superior Vencava Syndrome (ESMO guideline)

Malignant SVC syndrome

Investigate: brain metastases? Airway or cardiac compression?

Grade 1, 2, 3 symptoms

Tissue biopsy, staging evaluation Multidisciplinary discussion

Develop stage- and tumour-specific definitive treatment plan

Surgically managed tumour (e.g. thymoma, residual germ cell mass)

Preop chemo → Surgery (resection/reconstruction)

Definitive treatment (same as without SVC syndrome)

Chemo/radiosensitive tumour (e.g. SCLC, lymphoma, germ cell)

Definitive treatment (same as without SVC syndrome)

Intermediate tumour (e.g. NSCLC)

Definitive treatment (same as without SVC syndrome)

Poor treatment options (e.g. malignant pleural mesothelioma)

Persistent/recurrent Grade 2-4 symptoms

Grade 1, 2

Grade 3

Consider stent, early radiotherapy

Radiotherapy, supportive care

Grade 3

Stent (rarely surgical bypass)

Venogram, urgent stent, direct thrombolytics if thrombus

Grade 4 symptoms
Chemotherapy related emergencies

Background

cancer related emergencies

Chemotherapy related emergencies

Febrile neutropenia

Diarrhea
Chemotherapy related emergencies: Febrile neutropenia

10%–50% of patients with solid tumours and >80% of those with hematological malignancies

- The degree and duration of neutropenia closely correlate with the risk of serious infectious complications.

Clinically documented infections occur in 20%–30% of febrile episodes.

GCSF has reduced significantly rate of FN
Chemotherapy related emergencies: Febrile neutropenia

Responsible for fungal and viral infection after prolong duration

Figure 1 | Neutrophils crosstalk with immune and non-immune cells in inflamed tissues and lymph nodes.

Chemotherapy related emergencies: Febrile neutropenia

<table>
<thead>
<tr>
<th>Empirical antibiotic therapy for Febrile Neutropenia</th>
<th>Moderate risk penicillin allergy</th>
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<tbody>
<tr>
<td>No Penicillin / Cephalosporin Allergy</td>
<td>History suggestive of moderate/low risk (delayed rash which is NOT urticarial or DRESS/SJS/TEN)*</td>
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<tr>
<td>&gt; Piperacillin/tazobactam 4.5g IV every six hours</td>
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<tr>
<td>Note: Continue piperacillin/tazobactam as mono-therapy in stable patients</td>
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<tr>
<td>See additional information below for patients with known or suspected MRSA infection/colonisation</td>
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<tr>
<td>&gt; Cefepime 2g IV every eight hours</td>
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<tr>
<td>Note: Continue cefepime as mono-therapy in stable patients</td>
<td></td>
</tr>
<tr>
<td>See additional information below for patients with known or suspected MRSA infection/colonisation</td>
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<tr>
<td>&gt; Vancomycin 25mg/kg IV (Actual Body Weight) up to a maximum of 3g for initial dose</td>
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<tr>
<td>(See Table 2 in the Statewide Vancomycin Dosing Guidelines for subsequent doses)</td>
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<tr>
<td>PLUS</td>
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<tr>
<td>&gt; Ciprofloxacin 400mg IV every twelve hours</td>
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<tr>
<td>Note: Continue vancomycin and ciprofloxacin as dual-therapy in stable patients.</td>
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<tr>
<td>ADD</td>
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<tr>
<td>&gt; Metronidazole 500mg IV every twelve hours</td>
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<tr>
<td>in patients with features of intra-abdominal infection (e.g. diverticulitis/typhilitis or perineal abscess/collection</td>
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</table>

**NOTE:** Unless specifically stated antibiotic doses in this guideline reflect recommendations for patients with NORMAL RENAL FUNCTION. Refer to Therapeutic Guidelines or AMH for dose adjustments in patients with renal impairment.
Chemotherapy related emergencies: Diarrhea

- Common problem
- Chemotherapy: many but not all
- TKI: any (sunitinib, pazopanib)
- Preventable and treatable
- Could lead to ICU admission

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Proportion with grade 3-4 diarrhea (%)</th>
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<tr>
<td>Saltz et al, 2001</td>
<td>6%</td>
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<tr>
<td>Irinotecan with infused fluorouracil or folinic acid</td>
<td>15%</td>
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<tr>
<td>O’Shaughnessy et al, 2002</td>
<td>5%</td>
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<tr>
<td>Docetaxel</td>
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<tr>
<td>Docetaxel with capecitabine</td>
<td>14%</td>
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<tr>
<td>Chau et al, 2005</td>
<td>16%</td>
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<tr>
<td>Bolus fluorouracil with folinic acid</td>
<td></td>
</tr>
<tr>
<td>Infused fluorouracil</td>
<td>5%</td>
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<tr>
<td>Falcone et al, 2007</td>
<td>20%</td>
</tr>
<tr>
<td>FOLFOXIRI</td>
<td></td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>12%</td>
</tr>
<tr>
<td>Fuchs et al, 2007</td>
<td>14%</td>
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<tr>
<td>FOLFIRI</td>
<td>19%</td>
</tr>
<tr>
<td>mF72 capelIRI</td>
<td>47%</td>
</tr>
<tr>
<td>Van Cutsem et al, 2011</td>
<td>11%</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td></td>
</tr>
<tr>
<td>FOLFIRI with cetuximab</td>
<td>16%</td>
</tr>
<tr>
<td>Tveit et al, 2012</td>
<td>10%</td>
</tr>
<tr>
<td>FLOX</td>
<td></td>
</tr>
<tr>
<td>FLOX with cetuximab</td>
<td>17%</td>
</tr>
</tbody>
</table>

FOLFOXIRI = oxaliplatin, irinotecan, fluorouracil, and folinic acid (leucovorin). FOLFIRI = folinic acid (leucovorin), fluorouracil, and irinotecan. mF72 = irinotecan with bolus fluorouracil. capelIRI = capecitabine and irinotecan. FLOX = folinic acid (leucovorin), oxaliplatin, and bolus fluorouracil.

Table 1: Randomised trial data of the frequency of grade 3-4 diarrhoea with different chemotherapy regimens.
Chemotherapy related emergencies : Diarrhoea

Mechanism of diarrhoea

- Decrease surface area (secretory)
- Increase motility (like irinotecan)
- Decreased enzyme activity (osmotic)
- Bacterial overgrowth
- Increase mucous secretions
- Over-treated constipation
Chemotherapy related emergencies: Diarrhoea

- Patient has chemotherapy with or without radiotherapy
  - Grade 1 diarrhoea
    - Start self-medicating with 4 mg loperamide followed by 2 mg up to every 2 h
      - Improvement or resolution
      - No acute intervention required
  - Grade 2 diarrhoea
    - Inform cancer unit
  - Grade 3 and 4 diarrhoea
    - And
    - No improvement after 12 h or eight doses of loperamide
    - Urgent clinical assessment
Chemotherapy related emergencies: Diarrhoea management

**Flow diagram of action required for managing chemotherapy-induced diarrhoea**

- **Urgent clinical assessment**
  - **Low risk**
    - Well hydrated, no vomiting
    - Outpatient management
  - **High risk**
    - Dehydrated, vomiting, neutropenic, abdominal pain
    - Admit to hospital
    - Resuscitate and continue loperamide at least every 2 h with or without prophylactic quinolones and consider adding octreotide
    - Recovery
    - Urgent multidisciplinary involvement and investigations

*Source: Guidance on the management of diarrhoea during cancer chemotherapy* (Lancet Oncol 2014; 15: e447–60)
Immunotherapy side effects: background

James Allison, of the University of Texas MD Anderson Cancer Centre, and Kyoto University's Tasuku Honjo
Immunotherapy related emergencies: Background

The Renaissance of Immunotherapy

Enthusiasm Phase 1978-1985
- 1976: 1st study with adoptive T-cell transfer in CA
- 1978: Discovery of tumor specific mABs
- 1985: 1st study with BCG in bladder CA

Skepticism Phase 1985-1997
- 1986: IFN-α (cytokine) approved for CA
- 1990s: Discovery of checkpoint inhibitor (Allison)

Renaissance Phase 1997-
- 1997: 1st mAB approved for CA
- 2000: 1st checkpoint inhibitor approved for CA
- 2011: IL-2 (cytokine) approved for CA


https://grandroundsinurology.com/immunotherapy-for-prostate-cancer/
Immunotherapy: current landscape

Immuno-Oncology PD-1 and PD-L1 Inhibitor Uptake in the United States

Source: U.S. FDA, IQVIA, National Sales Perspectives, Feb 2018; IQVIA Institute, Apr 2018
Notes: Met – metastatic; rec/met – recurrent/metastatic; 1L+ – 1st line; 2L+ – 2nd line; HCC – hepatocellular carcinoma.
Report: Global Oncology Trends 2018: Innovation, Expansion and Disruption. IQVIA Institute for Human Data Science, May 2018
Immunotherapy related emergencies: striking differences from chemotherapy

- Minimal infusion related reaction
- Patients stay on these treatment longer
- **Side effects:**
  - Fewer than chemotherapy
  - Not predictable
  - Not dose dependent (no dose reduction)
  - Can arise at any time (even after stopping)
  - Any system of body get involved
  - Could be life threatening
  - Need a team to manage side effects
Possible Mechanisms Underlying Immune-Related Adverse Events.
Immunotherapy related emergencies: Spectrum of organ involvement

Any system of body get involved!

The Immune Checkpoint Inhibitors Unleashed to Fight Cancer
May 17, 2017 • By Dana Direnzo, MD, Ami A. Shah, MD, MHS, Clifton O. Bingham III, MD, & Laura C. Cappelli, MD, MHS
Immunotherapy: timeline for side effects

Even after completion of treatment!

Management of toxicities from immunotherapy: ESMO Clinical Practice and follow-up†
Society for Medical Oncology.)
### Table 4. Typical management of irAEs

<table>
<thead>
<tr>
<th>Severity—CTCAE grade</th>
<th>Ambulatory versus inpatient care</th>
<th>Corticosteroids</th>
<th>Other immunosuppressive drugs</th>
<th>Immuno therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ambulatory</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Continue</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory</td>
<td>Topical steroids or Systemic steroids oral 0.5–1 mg/kg/day</td>
<td>Not recommended</td>
<td>Suspend temporarily&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>Hospitalization</td>
<td>Systemic steroids Oral or i.v. 1–2 mg/kg/day for 3 days then reduce to 1 mg/kg/day</td>
<td>To be considered for patients with unresolved symptoms after 3–5 days of steroid course</td>
<td>Suspend and discuss resumption based on risk/benefit ratio with patient</td>
</tr>
<tr>
<td>4</td>
<td>Hospitalization Glass and consider intensive care unit</td>
<td>Systemic steroids i.v. methylprednisolone 1–2 mg/kg/day for 3 days then reduce to 1 mg/kg/day</td>
<td>To be considered for patients with unresolved symptoms after 3–5 days of steroid course</td>
<td>Discontinue permanently</td>
</tr>
</tbody>
</table>

Some dysimmune toxicities may follow a specific management: this has to be discussed with the organ specialist.

<sup>a</sup>Outside skin or endocrine disorders where immunotherapy can be maintained.

- Steroid sparing agent in refractory cases: Infliximab, mycophenolate, azathioprine
Immunotherapy: flow of management

Phone call from patient or carer
Need to have 24 hour hot line

Establish background and treatment regimen
Recognise red flags
Urgent vs semi-urgent
Arrange blood test (if patient has non-specific mild symptoms)

Initiate therapy (remotely located patient)
Urgent contact with physician

- Endocrinopathies
- Rest of the system
Immunotherapy related emergencies

- Pituitary gland
  - Hypophysitis
  - Corticotropin (ACTH) decrease
  - Secondary adrenal insufficiency

- Thyroid gland
  - Hyperthyroidism
  - Hypothyroidism
  - TSH increase or decrease
  - Thyroiditis
  - Free thyroxine increase or decrease
  - Autoimmune thyroiditis

- Adrenal glands
  - Primary adrenal insufficiency

- Pancreas
  - Diabetes mellitus
# Immunotherapy related emergencies

<table>
<thead>
<tr>
<th>Gland</th>
<th>Event(s)</th>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>Pituitary</td>
<td>Hypophysitis</td>
<td>Blood tests: ACTH, FSH, LH, TSH, cortisol level&lt;sup&gt;c&lt;/sup&gt;, FT4, stimulation or dynamic testing, brain imaging, vision tests</td>
</tr>
<tr>
<td></td>
<td>Secondary adrenal insufficiency&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>Hyperthyroidism</td>
<td>Medical history and physical exam, blood tests (TSH, T3/T4), radioactive iodine uptake test, thyroid scan, presence of thyroid autoantibodies (thyroid peroxidase Ab, thyroglobulin Ab, thyroid-stimulating immunoglobulins)</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
<td></td>
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<td></td>
<td>Thyroiditis&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Adrenal</td>
<td>Primary adrenal insufficiency&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Blood tests (ACTH, cortisol level&lt;sup&gt;c&lt;/sup&gt;, blood sugar, serum potassium, serum sodium, serum pH), ACTH stimulation test, insulin-induced hypoglycemia test, imaging tests</td>
</tr>
<tr>
<td></td>
<td>Corticotropin (ACTH) insufficiency</td>
<td></td>
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</table>
Immunotherapy case 1: Hepatitis (only 3 doses of drug)

58yr old ECOG 1 Metastatic RCC Hx of Psoriasis (local Rx)
On clinical trial with Nivolumab and cabozantinib

Tolerated well During 2nd cycle
Abnormal LFTs
On routine bloods
Started on 1 mg/kg prednisolone

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<th>24/04/2018 13:26</th>
<th>26/04/2018 17:17</th>
<th>27/04/2018 00:00</th>
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<td><strong>Total Protein</strong></td>
<td>(60 - 80) g/L</td>
<td>72</td>
<td>76</td>
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<tr>
<td><strong>Bilirubin</strong></td>
<td>(2 - 24) umol/L</td>
<td>5</td>
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<td><strong>Globulins</strong></td>
<td>(21 - 41) g/L</td>
<td>42</td>
<td>39</td>
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<tr>
<td><strong>Alkaline phosphatase</strong></td>
<td>(30 - 110) U/L</td>
<td>88</td>
<td>125</td>
<td>136</td>
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<td><strong>Alanine Aminotransferase</strong></td>
<td>(0 - 55) U/L</td>
<td>46</td>
<td>457</td>
<td>593</td>
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<tr>
<td><strong>Aspartate aminotransferase</strong></td>
<td>(0 - 45) U/L</td>
<td>34</td>
<td>236</td>
<td>336</td>
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<tr>
<td><strong>Gamma Glutamyl Transpeptidase</strong></td>
<td>(0 - 60) U/L</td>
<td>72</td>
<td>76</td>
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<tr>
<td><strong>Lactate dehydrogenase</strong></td>
<td>(120 - 250) U/L</td>
<td>200</td>
<td>159</td>
<td>189</td>
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<tr>
<td><strong>Urate</strong></td>
<td>(0.15 - 0.45) mmol/L</td>
<td><strong>0.69</strong></td>
<td><strong>0.79</strong></td>
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</tr>
</tbody>
</table>
Immunotherapy case 1: Hepatitis (only 3 doses of drug)

- 58yr old ECOG 1
- Metastatic RCC
- Hx of Psoriasis (local Rx)
- On clinical trial with Nivolumab and cabozantinib

- Tolerated well
- During 2nd cycle
- Abnormal LFTs
- On routine bloods
- Started on 1 mg/kg prednisolone
No new symptoms
On routine bloods
Started on 1 mg/kg prednisolone

Did not have re-challenge due to severe psoriasis flare
CT shows excellent response

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Immunotherapy case 2: Diabetes and hypothyroidism

70-Y F, ECOG 1, with metastatic lung cancer, >50% PD-L1 expression
3-weekly pembrolizumab (C1 1/5/18).

Presenting complaint: Polyuria, polydipsia and dry mouth

Examination: Unremarkable, stable vitals

Investigations: BGL 42, Ketones 6.8 mmol/L
HbA1c 8% TSH 97.6; fT4 <5

Diagnoses:
Diabetes (DKA) and hypothyroidism due to Pembrolizumab
Pembrolizumab was held
DKA protocol, started on levothyroxine 75 mcg
Diabetes education
Basal-bolus insulin regimen (insulin adjustment via phone clinic)
Immunotherapy case 3: hypopituitarism

42 yr old lady with resected high risk melanoma On nivolumab for 4 months

Presenting complaint: lethargy and hypotension in chemo suite

Examination: Unremarkable, hypotensive

Investigations: Cortisol <3 ACTH:3

Diagnoses: hypopituitarism nivolumab was held On corticosteroid replacement Resumed Nivolumab
Immunotherapy case 4: Vasculitis and Pneumonitis

71 man, metastatic melanoma
On second line of treatment with
Combination of Ipilimumab and Nivolumab

Presented with cough, SOB and fever associated with cold hands after 2 weeks of first infusion.

O/E: Crackles on both lower lobes
Immunotherapy case 4: Vasculitis and Pneumonitis
Immunotherapy case 4: Vasculitis and Pneumonitis

Commenced on Prednisolone 1.5mg/Kg with improvement in cough, SOB and fever after 2 days. Septic screen was negative

Hands got worse!
Immunotherapy case 4: Vasculitis and Pneumonitis

IV methylprednisolone for 3 days
Reviewed by vascular and rheumatology team
vasculitis screen and angiogram of UL was normal
Immunotherapy case 4: Vasculitis and Pneumonitis

steroids were weaned over 4 months. Not any complication except local infection.
Immunotherapy case 4: Vasculitis and Pneumonitis

- After a year without any treatment!
- FDG PET scan negative for any melanoma.
Figure 1. The five pillars of immunotherapy toxicity management.
only possible with team approach!

- Emergency department
- General Practitioner
- Medical oncologist
- Patient on immunotherapy
- Allied health staff
- Nurse practtioner
Take home message:

- More cancer patients will be on treatment and need team approach for management
- Emergencies could be identified early and treat effectively
- Communication with other team members is crucial
- Steroids remained useful drug in many oncology emergencies
- Immune related side effects need to be considered with patient on immunotherapy until proved otherwise.
Thank You!