VGH CTU Noon Report

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Case

34-year-old female with a history of right breast carcinoma on neoadjuvant chemotherapy and multiple sclerosis who presents to hospital with a fever.

Case

- Diagnosed with COVID a couple of weeks ago, symptoms improved initially but over the past 5 days she noted increased fatigue and weakness. She then developed a fever (38.7^{o}C) and called her medical oncologist who advised her to present to the ED
- In ED she was noted to be febrile, dyspneic, tachycardic (HR 120), and hypotensive (97/65 mmHg)
- She received 1L of plasmalyte bolus, ceftriaxone 2 g IV, and vancomycin 1g IV
- Referred to CTU

Past Medical History

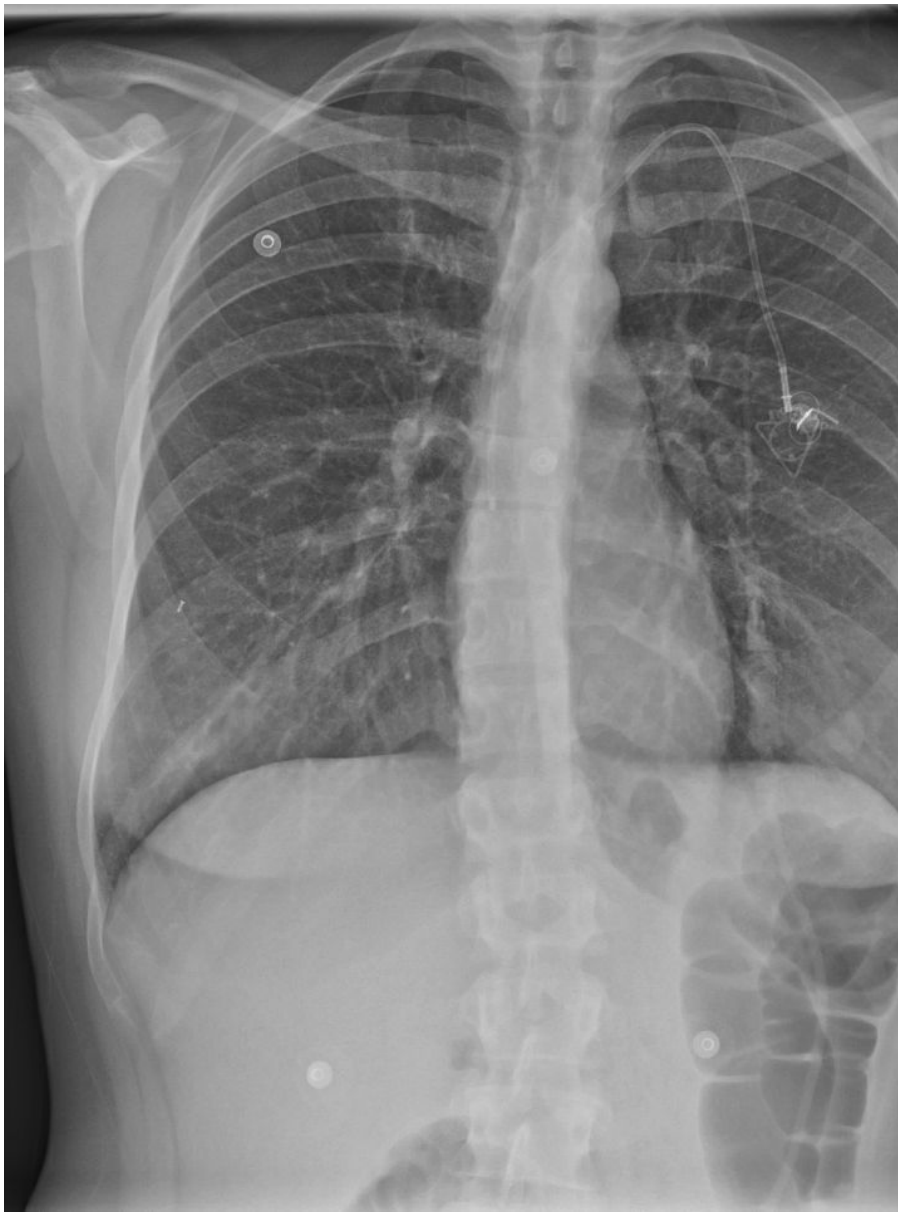
1. Right Breast Carcinoma
   - Stage II and Grade 3
   - Triple receptor negative (ER-, PR-, and HER2 -)
   - BRCA1 pathological variant
   - Started treatment with neoadjuvant chemotherapy per the KEYNOTE 522 study via a left Port-A-Cath
     - Completed 12 weeks of paclitaxel and carboplatin combination with pembrolizumab
     - Planned to start first cycle of AC (Doxorubicin + Cyclophosphamide)
     - LHRH to protect ovarian function as unable to undergo fertility treatment prior to chemotherapy
2. Multiple Sclerosis
   - Relapsing Remitting MS diagnosed in 2019
   - Treated with Ocrevus but then stopped at the time of breast cancer diagnosis per direction of her neurologist with plan to start again after cancer treatment

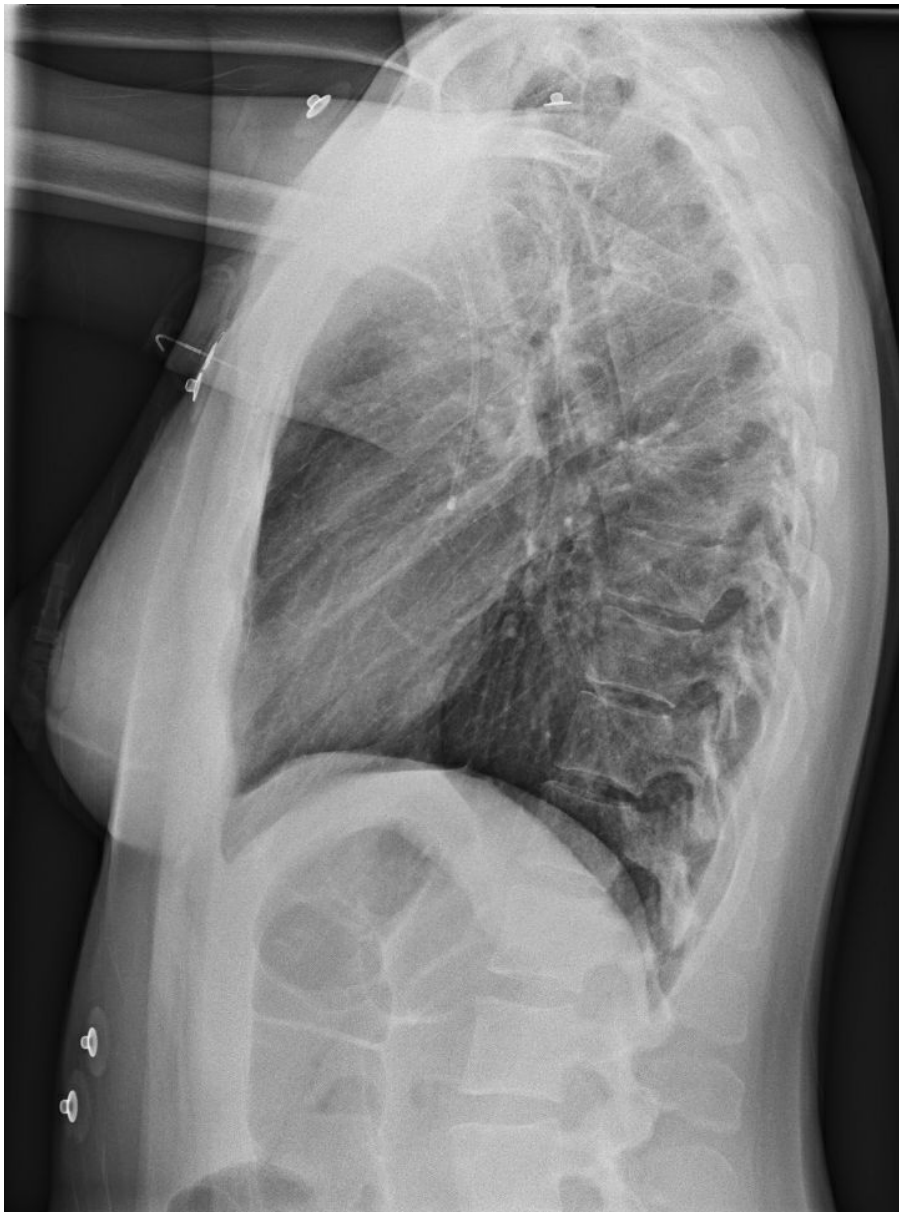
History

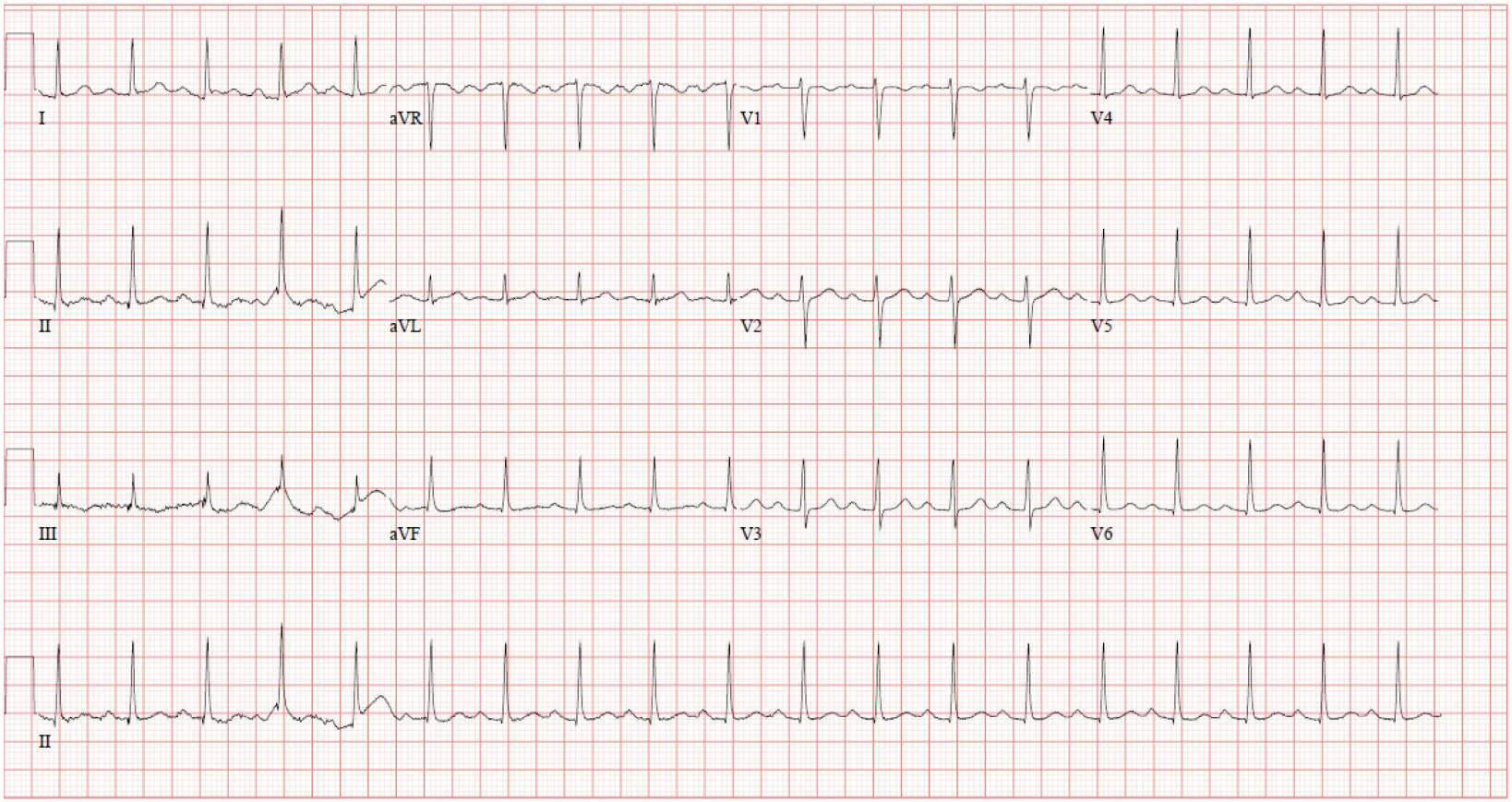
- 2-week history of a runny nose, developed a dry cough and dyspnea over the last 5 days
- Feels very fatigued since completing her 5th cycle of chemotherapy 4 days prior and is more dependent on her husband
- Spending a significant amount of time in bed
- Mild headache, but denies any urinary symptoms, abdominal pain, diarrhea, or other infectious symptoms

Physical

- TMAX: 38.3 (Temporal Artery); HR: 110 bpm (Peripheral); RR: 19; 113/66 mmHg SpO2: 99 %
- H&N: No mucositis. Patient has a Port-A-Cath for chemotherapy, on inspection of the site and on palpation there was no evidence of any erythema, redness, fluctuance, or tenderness.
  No neck stiffness.
- General: Lying down comfortably in bed, did not appear to be in any distress. Alert and oriented.
- CVS: Normal S1-S2, no murmurs, no added sounds, JVP not appear to be elevated.
- Resp: Decreased air entry bilaterally, mild bibasilar crackles. No wheezing
- GI: Abdomen nondistended, soft, nontender, bowel sounds present
- LL: No pitting edema, no evidence of soft skin tissue infection.



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MASCC Score

- Multinational Association for Supportive Care in Cancer Risk Index Score
- Risk stratify patients with febrile neutropenia to determine if low or high risk
- Low-risk
  - Can be considered for oral antibiotics and outpatient management if clinically stable
- High-risk
  - Require inpatient management with IV broad-spectrum antibiotics and close monitoring

MASCC Score Component	Score
Burden of illness: no or mild symptoms (clinically stable, minimal signs of infection)	5
Burden of illness: moderate symptoms	3
Burden of illness: severe symptoms	0
No hypotension (systolic BP ≥90 mmHg)	5
No chronic obstructive pulmonary disease (COPD)	4
Solid tumor or hematologic malignancy without prior fungal infection	4
No dehydration requiring parenteral fluids	3
Outpatient at onset of fever	3
Age <60 years	2
Maximum total score	**26**

Score	Risk Category
≥21	Low risk
<21	High risk

High Risk Patients

- ASCO/IDSA guidelines do recommend using the MASCC scoring system to risk stratify patients
- Prioritize clinical judgment over scoring system, for example patients with significant co-morbidities should not be candidate for outpatient therapy even if MASCC score ≥21
- Additionally, if discharging patients should live <1 hour from clinic or hospital and PCP or Oncologist agrees to outpatient management

- High-Risk Patients
  - Chemotherapy-related neutropenia that is expected to be prolonged (duration >7 days) and profound (ANC <0.1)
  - Significant medical co-morbid conditions (eg, hypotension, pneumonia, new-onset abdominal pain, neurologic changes)

GCSF

- IDSA/ASO 2023 guidelines do not recommend routine use of G-CSF after onset of febrile neutropenia, but can consider it in patients with:
  - Profound neutropenia (ANC <0.1) and expected prolonged neutropenia (>10 days)
  - Severe clinical presentation (sepsis, unstable)
  - Pneumonia, invasive fungal infection
  - Age >65
  - Uncontrolled infection or poor marrow reserve
- No clear reduction in overall mortality but modest reduce (~1-2 days) in hospital length of stay

Case Continued

- Discharge home with amox-clav and ciprofloxacin and follow-up with oncologist
- Two days later presents to hospital again with ongoing fevers (TMAX 39.5) and new diarrhea and nausea along with peri-anal pain
- Hemodynamically stable, received 2L of RL and covered empirically with PIP-TAZO and Vancomycin
- Referred to CTU

CT Abdomen and Pelvis w/ Contrast

1. Mild generalized edema with small volume ascites, perinephric free fluid, periportal edema and pericholecystic free fluid. This may be a result of generalized acute systemic illness or aggressive fluid resuscitation.
2. No intra-abdominal source of metastatic disease or metastatic lymphadenopathy.

Infectious Disease Consult

- Suspect fever related to a drug reaction secondary to her chemotherapy as she completed 12 weeks of paclitaxel and carboplatin combination therapy with pembrolizumab (immunotherapy)
- However, as she is immunosuppressed with persistent GI/Respiratory symptoms they can't rule out an infection and thus recommended extended respiratory virus panel, nasopharyngeal PJP PCR, and legionella urinary antigen
- Also recommend GI consult for EGD and C-scope to rule out CMV disease or other pathology
- Recommend continue PIP-TAZO and stop vancomycin, additionally recommend a 3-day course of azithromycin to cover for atypical pathogens

Gastroenterology Consult

- Suspect immune-checkpoint inhibitor colitis which is supported by her relative recent exposure to pembrolizumab but did still consider opportunistic infections including mycoplasma and CMV on the differential
- In discussion with oncology recommend starting prednisone 1 mg/kg and if she shows clinical improvement then would hold off on a scope, but will consider if persistent symptoms

Case Resolution

- She was continued on prednisone with a taper as an outpatient and did well with eventual resolution of her symptoms
- Started on Vitamin D, Ca, and PPI for prophylaxis
- She was not restarted on pembrolizumab as initially planned and instead completed neoadjuvant therapy with Doxorubicin and CYC alone
- Eventually received bilateral mastectomies and right sentinel node biopsy and breast reconstruction
- Did not require adjuvant radiotherapy as she had a completed pathological response in the breast and axilla

Immune Checkpoint Inhibitors MOA

- Cancer cells generally up-regulate suppressive signaling to T-cells via CTLA-4 and PD1/PD1-ligand, to evade the immune anti-tumor response
- Checkpoint inhibitors block these inhibitory signals, thereby re-activating the immune response to cancer cells
- Common checkpoint inhibitors:
  - PD-1 inhibitors: Nivolumab, Pembrolizumab, Cemiplimab
  - PD-Ligand (PD-L1) inhibitors: Atezolizumab, Avelumab, Durvalumab
  - CTLA-4 inhibitors: Ipilimumab, Tremelimumab
- Checkpoint inhibitors are indicated for many types of cancer and the field is rapidly expanding
  - Melanoma
  - Lung Cancer
  - RCC
  - Breast Cancer
  - H&N Cancer
  - Cervical Cancer

Immune Checkpoint Inhibitors Adverse Events

- High incidence of toxicity
- Checkpoint inhibitors lead to dysregulated, hyperactive immune responses which mimic autoimmune diseases (e.g., IBD, ILD, etc.)
- Any organ system can be involved, with the most common being the skin, colon, adrenal, lungs, and liver
  - “Like a box of chocolates, you never know what you're gonna get”
- Adverse events can occur within the first few weeks to months after treatment
- Common clinical presentations include:
  - Myocarditis
  - Colitis
  - Hepatitis
  - Nephritis
  - Endocrinopathies (e.g., thyroid disease, adrenal insufficiency)
  - GBS
  - MG

Management of Immune Checkpoint Inhibitor Adverse Events

- Varies based on the organ involved but basic principals to consider include stopping the immune checkpoint inhibitors in critically ill patients
- First line therapy is corticosteroids
  - 1 mg/kg of prednisone
  - Most patients with response to steroids within 48-72 hours
- Second line therapy
  - Consider anti-TNF inhibitors (e.g. infliximab)

Objectives

- MSI
  - Approach to febrile neutropenia including diagnosis and initial workup
- Juniors
  - Management of febrile neutropenia
  - Empiric antibiotics
  - Role of GCSF
- Seniors
  - MASCC score to triage
  - Immunotherapy toxicity (ie, recognize on differential)
  - Familiar with management of immunotherapy toxicity

THE UNIVERSITY OF BRITISH COLUMBIA

Thank you for listening!

Questions and Discussion