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Immune-Related Adverse Events

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Advances in Cancer Immunotherapy™ - Los Angeles
June 19, 2015

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Presentation Objectives

- Define Immune-Related Adverse Events (irAEs)
- Describe common irAEs including:
  - Symptoms
  - Time to onset
  - Appropriate management
- Provide patient case examples of irAEs

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Immune-Related Adverse Events (irAEs)

- irAEs include any adverse event occurring as a result of the up-regulation of the immune system causing inflammation and off-target effects of the drug.
- The suffix “itis” means inflammation, and irEAs can manifest as a variety of “itis’s” which most commonly include:
    - Hepatitis
    - Colitis
    - Dermatitis
    - Pruritus
    - Thyroiditis
    - Hypophysitis

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Colitis

- Diarrhea and/or colitis is the most common and potentially most serious complication of anti-CTLA-4 therapy.
  - –Some trials report up to 31% of patients experiencing some grade of diarrhea, with 6% experiencing severe colitis (Hodi, 2010).
  - –Bowel perforation, sepsis, and death have been reported.
- Diarrhea and/or colitis is less common with anti-PD1/PDL-1 therapy
  - Trials of anti-PD1 antibodies have reported the incidence of diarrhea to be approximately 17%, with just 1% experiencing grade 3/4 diarrhea (Hamid, 2011).

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Colitis Symptoms

•Signs and symptoms to monitor for: diarrhea, abdominal pain, nausea, inability to eat or drink, mucus or blood in the stool.
•Ask patients to report any bowel habit changes promptly and to keep good records of time of day, frequency, volume, and texture.
•Rule out other causes of diarrhea, including clostridium difficile or other infections diarrheas.

•***Clinical Pearl*** – colitis can occur without diarrhea, important to take all GI-related symptoms seriously and evaluate.

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Colitis Management

•**MILD/Gr 1** – less than 4 stools per day above baseline – manage symptomatically, i.e. bland diet, PPI, immodium/lomotil, consider delaying a dose until sx improve.
•**MODERATE/Gr 2** – increase of 4 to 6 stools per day above baseline – consider colonoscopy; treatment with steroids should be initiated. Low-dose steroids may be sufficient 0.5mg/kg per day of solumedrol or equivalent – but if no improvement within 24 hrs would consider higher dose. Hold immunotherapy.
•**SEVERE/Gr 3 or higher** – increase of 7 or more stools per day above baseline or other complications – initiate high dose steroids 1mg/kg of solumedrol or equivalent. Immunotherapy should be discontinued. For patients who do not respond to high doses steroids within 1 week or show clinical signs of worsening colitis, consider infliximab.
•Prevention – no known methods. Budesonide was tested as a way to prevent immune-related colitis and a randomized phase II trial no benefit shown (Weber, 2009).

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Hepatitis

•Less common than colitis, seen in 2 to 9% of patients and at least 1 death has been reported on anti-CLTA-4 therapy alone (Hodi, 2010).

• Incidence with anti-PD1 closer to 0.5% (Pembrolizumab PI) Hepatotoxicity appears worse when ipilimumab combined other drugs including dacarbazine (Robert, 2011), vemurafenib (Ribas, 2013), and anti-PD-1 (Wolchok, 2013) and should be used cautiously.

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Hepatitis Symptoms

- Abdominal bloating or pain, dyspepsia, jaundice and nausea.
    - Can be asymptomatic
- Hepatic function (transaminases and total bilirubin) should be monitored at baseline and prior to each dose of treatment.
- Abnormal LFT's should be monitored more frequently.

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Hepatitis Management

- Rule out other causes of liver function test abnormalities.
- Increase LFT monitoring until improvement.
- Corticosteroid treatment should be used with Gr 3 or higher elevations. Prolonged taper may be required.
- Mycophenolate may be useful in patients with persistent severe hepatotoxicity.

- ***Clinical Pearl*** – time to onset data not available, but liver function test abnormalities appear to be dose dependent.

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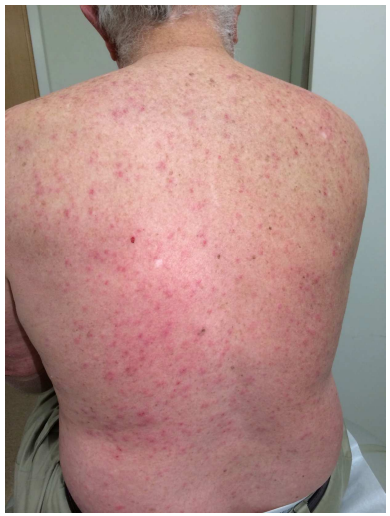
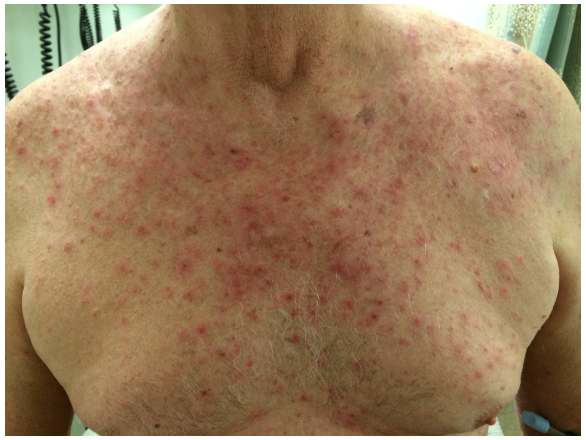
Dermatitis

•Commonly seen with anti-CTLA-4 with up to 40% of patients reporting some grade of dermatologic side effect (Hodi, 2010). Seen in approximately 30% of patients on anti-PD1(Pembrolizumab PI)

- Occasionally see severe rashes (Stevens-Johnson syndrome, toxic epidermal necrolysis, full thickness dermal ulceration)
- Median time to onset for moderate to severe dermatologic toxicity with anti-CTLA4 was 3 weeks (Hodi, 2010).





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Dermatitis Symptom Surveillence

- Symptoms most commonly include an erythematous macular rash and/or itching
- Determination of severity and treatment is driven by symptoms.
- Rule out other etiologies of rash, i.e. poison ivy, contact dermatitis, cellulitis, etc.
- Rash is generally not thought of as an infusion-related event.

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Dermatitis Management

- Mild or moderate dermatitis (rash and pruritis) can be managed symptomatically.
  - Topical non-steroidal anti-itch cream, antihistamines, oatmeal baths.
- If rash persists for more than a week or interferes with ADLs would start moderate potency steroid creams (triamcinolone 0.1%) OR moderate dose parenteral steroids at 0.5mg/kg/day of prednisone or equivalent.
- Serious rashes require discontinuation of immunotherapy and management with high dose steroids.
- Rapid tapering of steroids not advised and may results in the recurrence or worsening of symptoms.
- Antibiotics not helpful.

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Endocrinopathies

•A variety of autoimmune endocrinopathies have been reported (Corsello, 2013) with immunotherapy and can be serious to fatal if not managed correctly.
•Hypophysitis, first seen with anti-CLTA-4 therapy, presented a new form of autoimmune pituitary disease.
•Hypophysitis, thyroid disease or abnormal thyroid function tests, and primary adrenal insufficiency have all been reported.
•Mechanism of injury not fully understood.
•Hypothyroidism is the most common endocrinopathy seen with anti-PD1 and occurs in approximately 8% of patients (Pembrolizumab PI).

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Endocrinopathies Symptom Surveillance

•Monitor patient for signs and symptoms associated with pituitary, thyroid, or adrenal disease.

- Often nonspecific but my include headache, fatigue, changes in mental status, abdominal pain, hypotension.

•Check thyroid function tests at baseline and every 12 weeks while on treatment. TSH is the most sensitive test, but if symptoms would consider full panel including T3, T4, cortisol, and ACTH.

•Time to onset may be much later – median 11 weeks with anti-CTLA-4 (Hodi, 2010) and 14 weeks with anti-PD1 (Pembrolizumab PI).

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Endocrinopathies Management

- Treatment of endocrinopathies requires appropriate hormone replacement, corticosteroids, and possibly stopping ipilimumab.
  - A cosyntropin stimulation test may be helpful prior to starting steroids.
  - Many endocrinopathies can be controlled and if hormone levels stable and at less than 7.5mg of prednisone, then treatment can be continued.
  - Endocrine function may not return

- **Clinical Pearl** – Does a pre-existing thyroid disorder put patient at higher risk of developing additional endocrinopathies? Not as far as we know.

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Other irAEs

- Long list of other IMAEs
  - Ocular manifestations – conjunctivitis, uveitis and scleritis
  - Pneumonitis
  - Neurologic complications – Gillian Barre syndrome, inflammatory myopathy, aseptic meningitis, temporal arteritis, posterior reversible encephalopathy syndrome.
  - Sarcoidosis
  - Systemic vasculitis, including renal disease.
  - Autoimmune pancreatitis
  - Red cell aplasia, pancytopenia, autoimmune neutropenia, acquired hemophilia A

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Case Study

- 78 year old male with metastatic melanoma widespread to retroperitoneal lymph nodes.
- Presented to clinic in February 2012 for discussion of treatment options.
    - Initially presented to his dermatologist in December 2006 with a mole on the top of the left foot that had been there for several years.
    - Dermatologist biopsied lesion and it showed a 1.5mm melanoma. Ulceration status or mitotic rate was not reported.
    - A wide local excision was performed, but no sentinel lymph node biopsy.

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Case Study (Cont)

•He was followed for several years by his dermatologist until March of 2011 when he noted swelling in the right groin.
•A biopsy performed in May 2011 was found to be metastatic melanoma with an extensively necrotic tumor with occasional tumor cells with melanin pigment.
•A superficial lymph node dissection was done, and an additional 5 lymph nodes were removed, all negative for melanoma.
•In December 2011 a CT scan raised the concern of new adenopathy in the retroperitoneum and subsequently a PET/CT was performed later that month confirming extensive PET-avid disease in the retrocrural and retroperitoneal disease.
•A biopsy of the retroperitoneum was performed in late January 2012 confirming metastatic melanoma to that area.

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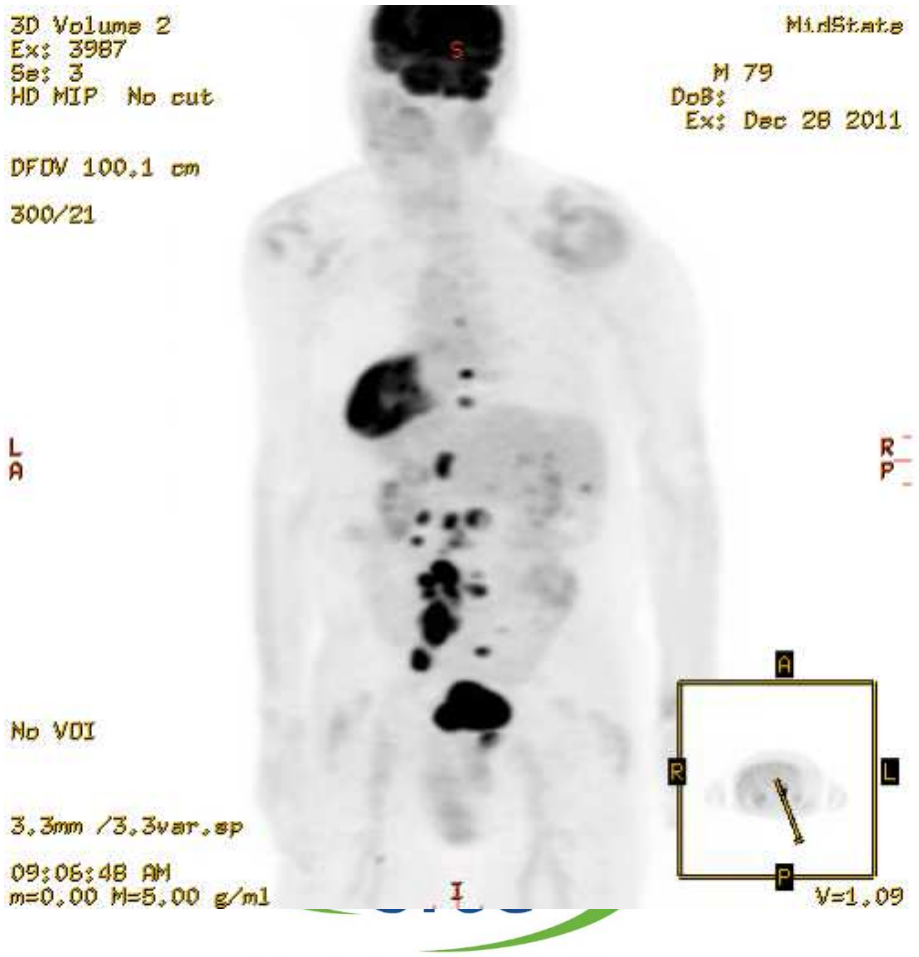
Case Study (Cont)

- PET scan showing significant metastatic disease



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Case Study (Cont)

- **PAST MEDICAL HISTORY**: Melanoma, Hypertension, Hypercholesteremia, Vitilogo (spontaneous in 2009)
- **PAST SURGICAL HISTORY**: Hernia repair and Back surgery.
- **CURRENT MEDICATIONS**: fluticasone, 1 spray, Nasal, Daily; lisinopril, 10 mg, Oral, Daily; LORazepam, 0.5 mg, Oral, Q8H PRN; simvastatin, 40 mg, Oral, Nightly, ondansetron, 8mg, oral, Q8H PRN, oxyCODONE, 5mg, Oral, 1-2 tabs ORAL Q4H PRN.
- **ALLERGIES**: Review of patient's allergies indicates no known allergies.
- **SOCIAL HISTORY**: He quit smoking about 48 years ago. His smoking use included Cigarettes. He has a 16 pack-year smoking history. He has never used smokeless tobacco. He reports that he drinks about 10.5 ounces of alcohol per week. He reports that he does not use illicit drugs. Lives with his partner of 38 years. Never married. No children. Retired telephone company employee.
- **FAMILY HISTORY**: N/A

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Case Study (Cont)

- On presentation to clinic
  - persistent nausea (on around the clock ondansetron)
  - lower abdominal pain (taking oxyCODONE 10mg orally every 6hrs)
- Labs
  - Mild anemia (Hgb 12.6)
  - LFT's normal
  - LDH 475 (normal range 118-242)
- ECOG Performance Status: 0
- Review of Systems negative other than nausea and abdominal pain.
- BRAF status negative.

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Case Study (Cont)

- He elected the clinical trial and was enrolled on CA209-004 – a phase 1 trial to receive ipilimumab 3mg/kg and nivolumab (anti-PD-1) at 1mg/kg.
- Received cycle#1 on 2/13/2012.
- On 2/20/2012 he called the office and noted a mild rash on his back, chest, and legs. The rash was erythematous and intermittently pruritic.
    - Supportive treatment with moisturizing creams and oatmeal bath recommended.
- On that same day, he noted that the pain in the abdomen and nausea had improved.

Case Study (Cont)

- On 2/26/2012 he noted changes in his vision that he described as a “sea of floaters”.
- He was seen by opthamology and diagnosed with panuveitis. He was started on Prednisone 60mg po qd.
- He was seen in clinic on 3/6/2012 and his vision had improved and a 3-week steroid taper was started.
- At that visit, his LDH was 206 – down from a peak of 586.

Case Study (Cont)

•Restaging CT C/A/P on 3/26/2012 showed interval improvement of metastatic disease but increased bilateral ground-glass opacities in the lung. He was feeling well and denied any respiratory symptoms.
•On 4/3/2012 he noted shortness of breath while walking up his steep driveway and on 4/8 he developed a dry cough when taking deep breaths. He called clinic on the morning of 4/10 to report these symptoms and was asked to come in for evaluation.
•On presentation to clinic, his resting O2 sat was 96% but he desaturated to 78% with exertion.
•CXR showed increased interstitial markings on the periphery of the lung.

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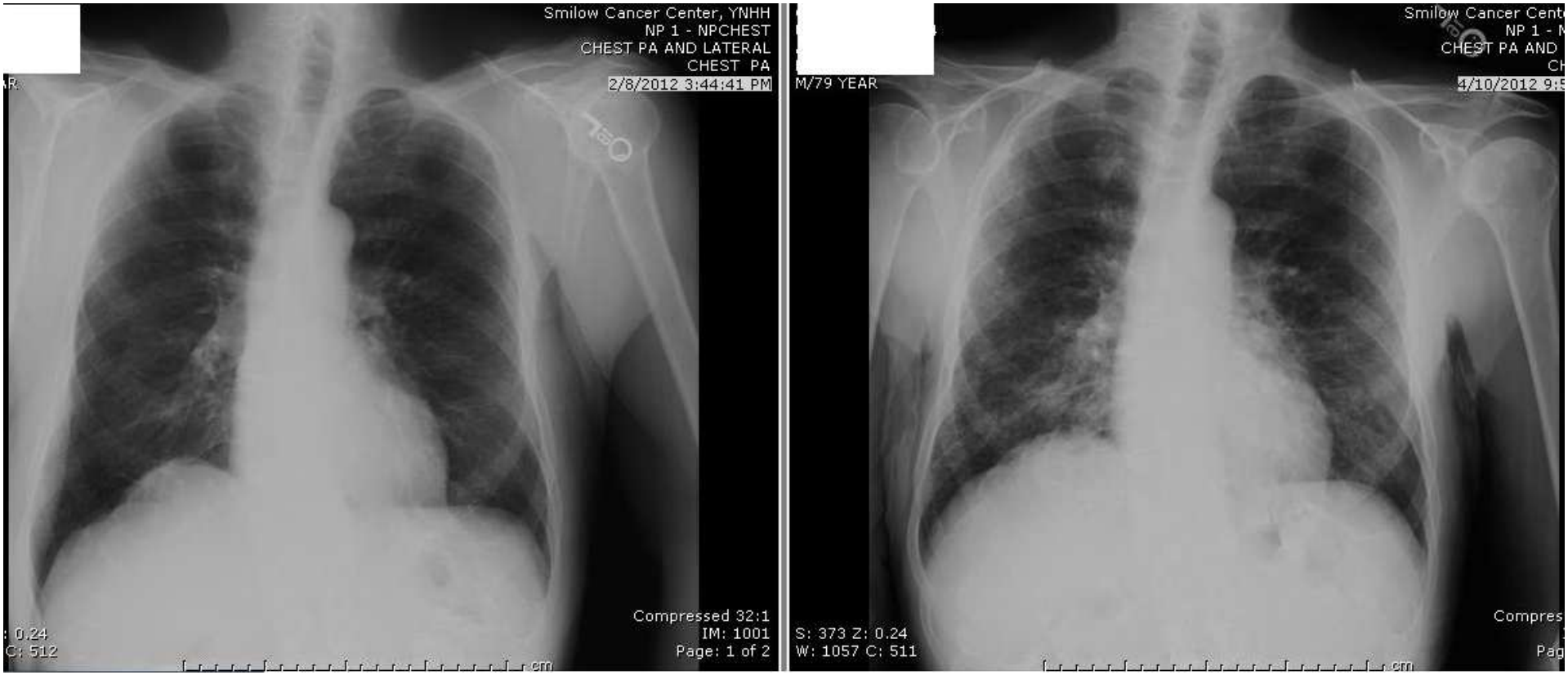
Case Study (Cont)

CXR showing increased interstitial markings compared to baseline



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Case Study (Cont)

- Admitted patient to hospital and started methylprednisolone 2mg/kg.
- A bronchoscopy was performed to rule out infection causes and to attempt to biopsy the lung.
  - Cytology was negative
  - Biopsy of lung parenchyma was consistent with mild chronic inflammation – suggestive of treatment related pneumonitis.
- O2 saturation improved and patient was discharged home after 2 days in hospital on a 4 week steroid taper.

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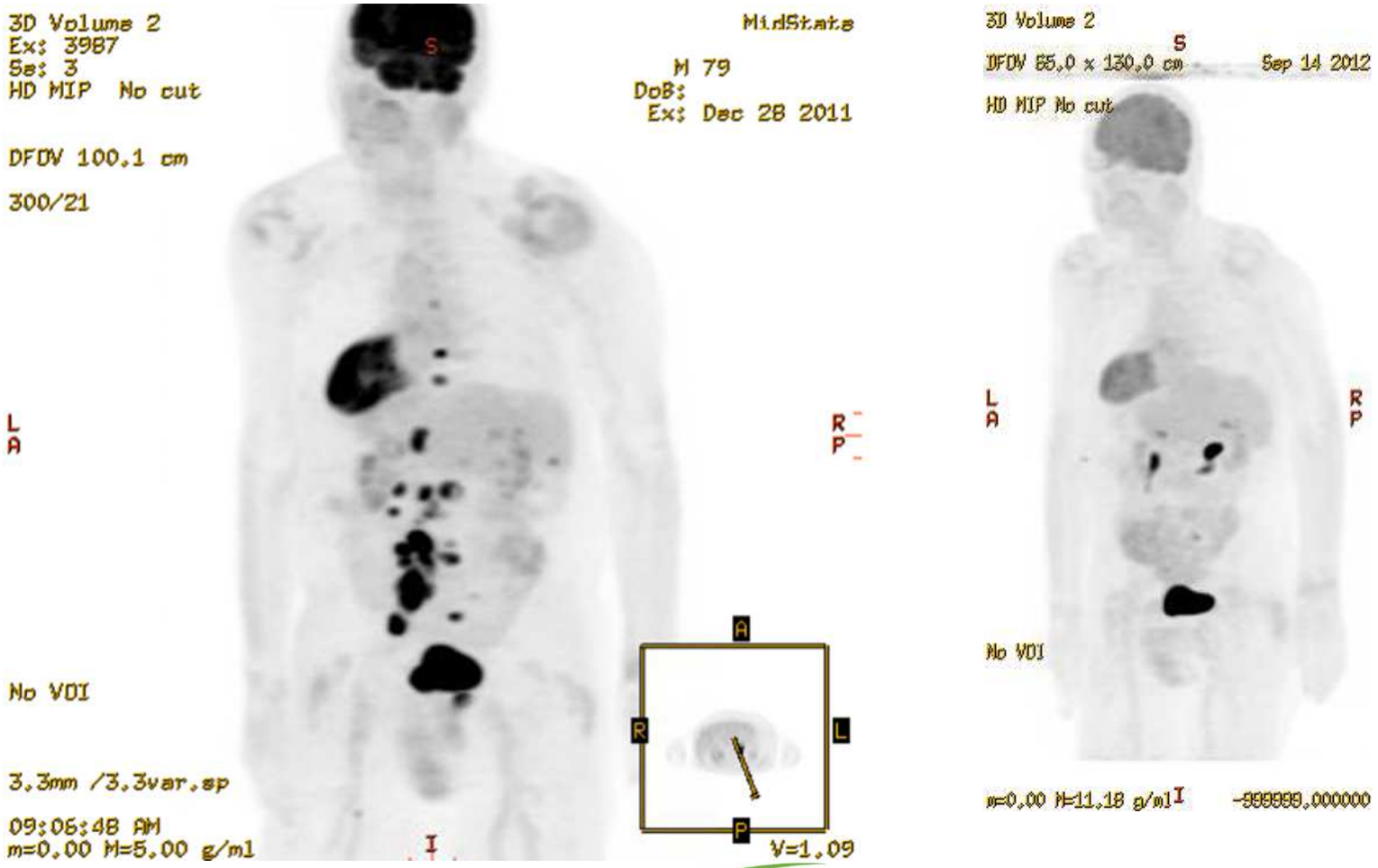
Case Study (Cont)

•A 4/17 CXR showed less confluent airspace disease in the RLL, but persistent prominence of the interstitium in both lower lung zones and in the periphery. Steroid taper continued.
•Steroid tapered over 1 month. Symptoms of SOB improved. Patient reporting overall improved energy and stamina.
•Restaging scans showed extensive regressing of disease.

Case Study (Cont)



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General Guidelines for treating irAE's

- Rule out all causes of adverse event, and if no other explanation, assume IMAE.
- Consider symptomatic care when appropriate.
- Consider holding or delaying a dose for mild toxicity.
- Use steroids when necessary – not too early, not too late.
- Moderate dose steroids for moderate toxicity, high doses for more serious toxicity. May need to add adjuvants to steroids if toxicity appear refractory, i.e infliximab or mycophenolate.
- When steroids are used for serious toxicity, taper over at least 30 days. Rapid taper may result in recurrence or toxicity and may be more severe.
- Symptom prophylaxes not appropriate!

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