Hypoxia Induced By Sulfasalazine Toxicity

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**Initial Presentation**
- 67 year old man came to ER with non-productive cough, SOB, chest pain, diffuse maculopapular rash and hypoxemia for 3 weeks.
- History of ulcerative colitis.
- He had received several courses of antibiotics for presumed lung infection without a clinical response.

**Past Medical History**
- Ulcerative colitis for which he took sulfasalazine from 1969 to 2000. Sulfasalazine was restarted in February 2014.

**Physical Examination**
- Non-productive cough induced by speaking.
- O2 sat of 89 % room air at rest.
- Chest auscultation: bibasilar inspiratory crackles.
- Skin exam: diffuse maculopapular rash.

**Hospital Course**
- Chest radiograph: diffuse ground glass opacities / bilateral patchy consolidation (Fig. 1).
- Chest CT : bilateral GGO (Fig. 2).
- PFT: mid to moderate restriction (Table 1).
- CBC: HgB 9.3 WBC 7.6 Eos 6.6 %.
- ABG: Ph 7.46 PO2 73, PCO2 37 on 2 L NC.
- ESR 26, CRP 8.06, C-ANCA < 1:20, P-ANCA <1:20.
- The time course of his symptoms plus his abnormal spirometry and chest imaging plus the lack of evidence for infection/vasculitis suggested a diagnosis of sulfasalazine pulmonary toxicity.
- Sulfasalazine was discontinued.
- Over next five days, the patient reported progressive improvement of all pulmonary symptoms.
- Patient was discharged home with supplemental oxygen.
- Chest radiograph three weeks later (Figure 3): near resolution of initial changes.
- At 2 month follow-up, his pulmonary symptoms had resolved, O2 sats were 98 % and his PFTs improved (Table 2).
- Naranjo Score (1) (assessment for probability for adverse drug reaction) = 5 to 7 (probable).

**Data:**

**Table 1. PFTs at presentation**

<table>
<thead>
<tr>
<th></th>
<th>Actual</th>
<th>% predicted</th>
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</thead>
<tbody>
<tr>
<td>FVC</td>
<td>2.9</td>
<td>61</td>
</tr>
<tr>
<td>FEV1</td>
<td>2.3</td>
<td>63</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>79</td>
<td>103</td>
</tr>
</tbody>
</table>

**Table 2. PFTs at 3 week follow up**

<table>
<thead>
<tr>
<th></th>
<th>Actual</th>
<th>% predicted</th>
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</thead>
<tbody>
<tr>
<td>FVC</td>
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<td>81.9</td>
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<tr>
<td>FEV1</td>
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<tr>
<td>FEV1/FVC</td>
<td>73</td>
<td>95</td>
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**Table 3. Clinical signs and laboratory findings in sulfasalazine toxicity**

1. Absent CXR
2. Hypoxia
3. Breathlessness
4. Fever
5. Restrictive lung function
6. Cough
7. Peripheral eosinophilia
8. Crepitations/rales/crackles
9. Rash
10. Obstructive lung function
11. Weight loss
12. Chest pain

Red denotes presence in our pt.

**Discussion**
- Sulfasalazine is a compound of 5-aminosalicylic acid (5-ASA) and sulfapyridine joined by an azo bond. However, the component of the drug that causes adverse pulmonary drug reactions and the mechanisms involved are not known.
- 50 cases of sulfasalazine-associated pulmonary toxicity have been reported. Table 3 displays the frequency of various symptoms and clinical findings, and our patient all 9 of the most common findings that all occur in more than 50% of cases. A chest radiographic abnormality appears essential to make this diagnosis (found in 50/50 cases). The mean age is 48 yrs (range 12–88). The average duration of exposure to sulfasalazine was 17.8 months with a range of 0.5–120 months. BAL and lung biopsy are non-specific, and helpful only in exclusion of other conditions. The time course for resolution of this syndrome is variable.
- Of the 50 (8%) cases have been fatal. The cause of death is respiratory failure.
- **DIFFERENTIAL DIAGNOSIS:** Infection, ARDS, Vasculitis/toxic lung injury. Two specific entities in the differential dx to consider are pulmonary manifestations of the underlying disease for which sulfasalazine was used including pulm manifestations of IBD and rheumatoid arthritis.
- **TREATMENT/OUTCOME:** 1. withdrawal of drug (94 %), often with 2. addition of corticosteroids (40%). 96 % of pts treated with withdrawal of drug alone improved, with 67 % having symptom improvement in 2 months. 80 % of pts prescribed corticosteroids improved with 65 % having symptom resolution in 2 months. Therefore, role of corticosteroids influencing outcome of patients with suspected pulmonary toxicity is not strong (2).

**Conclusions**
- Sulfasalazine pulmonary toxicity manifests as an acute or sub-acute form of respiratory failure with diffuse pulmonary opacities. The presence of rash and peripheral eosinophilia each occur in approximately half of the cases and are a clue to the diagnosis.