# Murphy's law in force: sequential adverse events encountered during the treatment of Pneumocystis pneumonia (cotrimoxazole-induced acute peripheral neuropathy and primaquine-induced methemoglobinemia)

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## ABSTRACT

Methotrexate monotherapy is a common management strategy in rheumatoid arthritis (RA). Treatment with immunosuppression can lead to opportunistic infections such as *Pneumocystis jirovecii* pneumonia (PJP). The treatment options for PJP include cotrimoxazole, clindamycin-primaquine and dapsone. Though these drugs are generally well tolerated, they can result in potentially severe adverse effects. Sometimes several undesired events may occur in a single patient, reminding us of Murphy's law. Herein, we report a case which exemplifies this adage. A 50-year-old female developed PJP, while on methotrexate therapy for RA and was treated with cotrimoxazole. The latter resulted in painful peripheral neuropathy, which improved after cotrimoxazole was stopped. Salvage therapy for PJP with primaquine-clindamycin, lead to another serious adverse event, methemoglobinemia. Withdrawing the offending drug resulted in dramatic improvement.


A 50-year old woman with rheumatoid arthritis (RA) on methotrexate therapy (15mg per week) for the preceding two years presented with fever, dry cough and breathlessness of one-week duration. She had a heart rate of 110 beats/minute, blood pressure 110/60mmHg, respiratory rate 34 breaths/minute and oxygen saturation by pulse oximetry (SpO2) of 74%. Chest radiograph suggested the presence of bilateral symmetrical and basal predominant perihilar infiltrates with peripheral sparing (Figure 1A). Computed tomogram (CT) of thorax revealed bilateral diffuse ground glass opacities and areas of consolidation (Figure 2A). There was no mediastinal lymphadenopathy or effusion. Hemoglobin was 10.3g/dL; total leukocyte and platelet counts were 11,400/mm$^3$, and 224,000/mm$^3$, respectively. Echocardiography, renal function and liver function tests were normal. A possibility of *Pneumocystis jirovecii* pneumonia (PJP) was considered. She was unfit for bronchoscopy, and induced sputum examination did not identify any organism, including *Pneumocystis*. Empiric treatment with cotrimoxazole (trimethoprim 960mg and sulphamethoxazole 4,800mg/day in three divided doses) and prednisolone was started. She improved, and was


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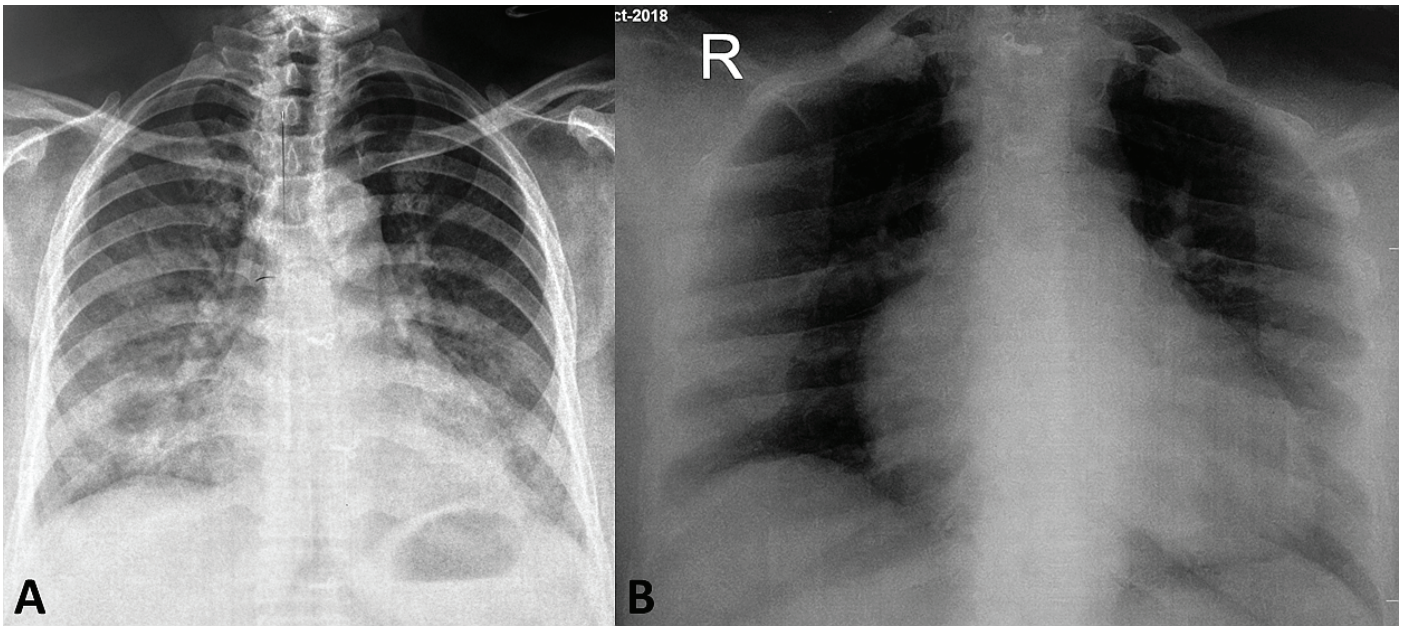
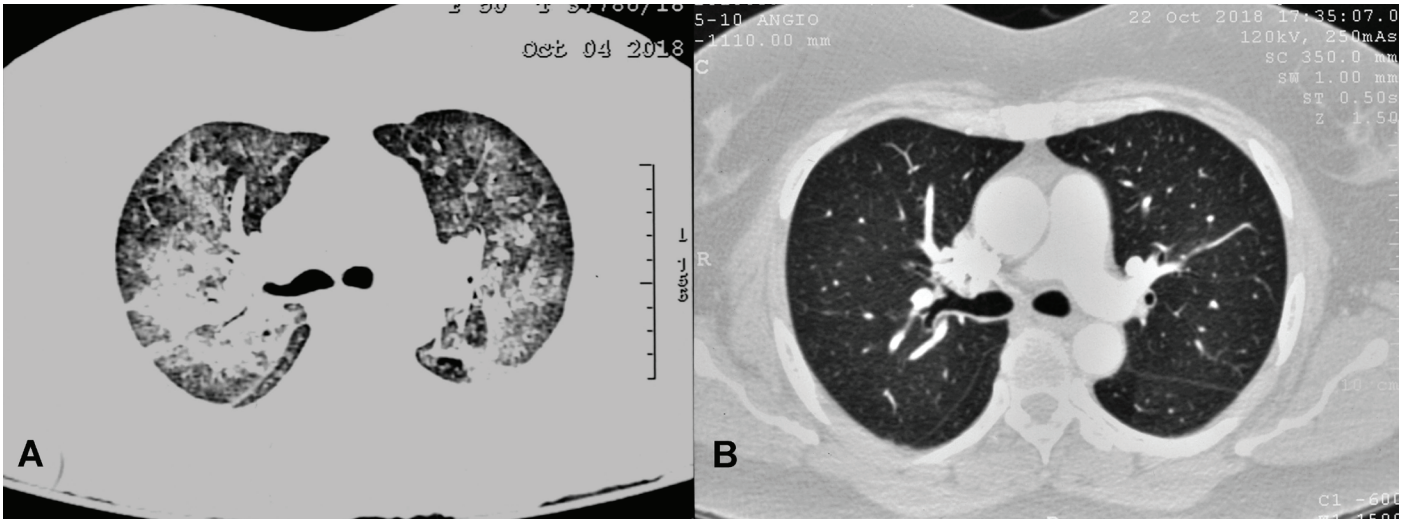
**Figure 1:** Chest radiograph (A) at presentation showing diffuse bilateral symmetrical basal predominant infiltrates, with peripheral sparing. (B) Unremarkable chest radiograph obtained during the second hospitalisation for breathlessness.




discharged after seven days. Three days later, she noted "needle and pin" sensations, along with weakness involving both her hands and legs. A nerve conduction study suggested axonal sensorimotor neuropathy. Antinuclear antibodies, antineutrophil cytoplasmic antibody, hepatitis B surface antigen, hepatitis C virus and human-immunodeficiency virus antibodies were not detected in the serum. Cotrimoxazole-induced peripheral neuropathy was suspected and the drug was stopped. Neuropathic symptoms resolved and she regained full muscle power in five days. Clindamycin-primaquine (primaquine 30mg base orally once/day and clindamycin 600mg orally thrice/day) was initiated for PJP. Six days later, she reported to the emergency with dyspnea. There was no fever, cough, chest pain, palpitation or orthopnea. Her SpO2 on room air was 90%, BP was 120/90mmHg, respiratory rate was 30 breaths/minute and heart rate was 110 beats/minute. Chest radiograph did not show any lung parenchymal opacities (Figure 1B). CT pulmonary angiography did not reveal acute pulmonary embolism and the

**Figure 2:** (A) Computed tomography (CT) of the thorax, performed at the initial presentation showing bilateral diffuse ground glass opacities and consolidation. There was no mediastinal lymphadenopathy or effusions. (B) CT scan performed during the second admission, which was normal.



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lung parenchyma was unremarkable (Figure 2B). On arterial blood gas analysis (on inspired oxygen fraction of 0.3), the partial pressure of arterial oxygen (PaO2) and the estimated arterial oxygen saturation (SaO2) were 100mmHg and 98%, respectively. The "saturation gap" (SaO2-SpO2 gap) suggested methemoglobinemia (primaquine-induced), which was confirmed by co-oximetry (14.8%). She improved after stopping clindamycin-primaquine and is currently doing well at six months of follow-up.

# Discussion

PJP is a rare complication of methotrexate monotherapy.[1] The treatment options include cotrimoxazole, clindamycin-primaquine and dapsone. Also, cotrimoxazole, dapsone, atovaquone and rarely pentamidine are the drugs recommended for prophylaxis (either primary or secondary) against PJP in immunosuppressed individuals.[2] The use of these drugs may sometimes cause serious adverse events including cytopenias, neuropathy, renal failure and rarely methemoglobinemia. The index patient experienced several rare adverse events sequentially, highlighting the epigram "Murphy's law"—when things can go wrong, they will.[3] Cotrimoxazole is generally well tolerated and adverse effects are mild. Painful peripheral neuritis is unusual with sulfonamides,[4–6] and generally attributed to the sulpha component.[5] Polyneuritis usually presents as painful paresthesias, followed by distal muscle weakness occurring within 1–2 weeks of therapy (range, two days after starting treatment to one month after discontinuation of therapy). The lower limbs are more frequently affected than upper limbs, and the symptoms can re-occur on reintroducing the sulpha drugs. The symptoms usually improve after the culprit drug is withdrawn, though residual weakness may persist in some. In the index case, painful paresthesias occurred after 10 days of therapy, followed by muscle weakness, and she recovered completely after withdrawing the offending drug.

Salvage therapy with clindamycin-primaquine resulted in another uncommon complication, methemoglobinemia, suspected on the basis of the 'saturation gap'. Methemoglobin absorbs both the wavelengths used in pulse oximetry (660nm and 940nm, usually absorbed by deoxyhemoglobin and oxyhemoglobin, respectively), leading to an erroneous estimation of oxygen saturation. Co-oximetry is a spectrophotometric analysis of blood, where absorbance at multiple wavelengths is measured to give an estimate of oxyhemoglobin, deoxyhemoglobin and various dyshemoglobins (including carboxyhemoglobin and methemoglobin).[7] This technique is employed whenever there is a discrepancy between pulse oximetry and the estimated oxygen saturation obtained from blood gas analysis (saturation gap). More accurate determination of methemoglobin levels is possible with the use of Drabkin's agent and the method of Evelyn-Malloy.[8,9] In most cases of methemoglobinemia, withdrawal of the offending drug is sufficient. Supportive therapy (oxygen supplementation or assisted ventilation) or specific therapy with (methylene blue) may be required in some.[10]

Peripheral neuropathy is a rare complication of cotrimoxazole therapy. Primaquine-clindamycin is an alternative for treating PJP, but can cause methemoglobinemia in susceptible individuals. A high index of suspicion and withdrawal of the offending drug usually results in improvement.

## Learning points

- The commonly used treatment of PJP can result in unusual complications (cotrimoxazole-induced painful neuropathy) and a high index of suspicion is required to recognise these rare adverse events.
- Drug-induced methemoglobinemia is an important differential diagnosis to be considered in unexplained hypoxemia.
- Timely recognition and withdrawal of the offending drug is essential in managing this potentially life-threatening condition.

**Competing interests:**
Nil.

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