CASE REPORT

Dapsone hypersensitivity syndrome not related to G6PD deficiency

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SUMMARY

Dapsone hypersensitivity syndrome (DHS) is a rare, but potentially life-threatening reaction to dapsone. We describe a 55-year-old Caucasian woman with normal glucose-6-phosphate dehydrogenase levels presenting with an extensive skin eruption, high-grade fever, pneumonitis and hepatitis, which occurred within 3 weeks after initiation of dapsone. In addition to supportive care, the patient was successfully treated with high-dose corticosteroids and antibiotics. The combination of high-grade fever, skin rash, lung and liver involvement made a dapsone hypersensitivity syndrome very likely.

BACKGROUND

This clinical case illustrates the challenges of the potentially lethal dapsone hypersensitivity reaction. 4,4'-Diaminodiphenylsulfone (dapsone) is a widely used drug. It has antimicrobial effects as well as anti-inflammatory effects. It is the drug of choice for the

treatment of leprosy, but is also used in a variety of immune-mediated disorders, including IgA vasculitis.¹

CASE PRESENTATION

A 55-year-old Caucasian woman presented to our emergency department, with fever, coughing and a rash. She was previously (2008) diagnosed with idiopathic small vessel vasculitis for which she was prescribed dapsone (100 mg four times a day) 4 weeks prior to hospitalisation. Before starting dapsone therapy, she had told her prescribing physician that she liked to eat fava beans without experiencing any problems. In addition, glucose-6-phosphate dehydrogenase was determined and found to be within the normal range.

On admission, the patient reported a 7–10-day history of progressive fever, headache, rash, dyspnoea and cough. She had been advised to stop dapsone 4 days prior to hospitalisation, because the drug was suspected to be the cause of her symptoms.

Figure 1 (A) Results of laboratory testing on admission. (B) Chest X-ray on admission. (C and D) High-resolution CT of the thorax showing infiltration and ground glass located in the upper lobes and subpleural.

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Figure 2 (A and B) Skin lesions, mostly blanching maculopapular exanthema, over the back, abdomen, arms and legs; (C) H&E stain (magnification $\times 200$) showing intraepidermal pustule formation. (D) H&E stain (magnification $\times 400$) showing fibrinoid necrosis of the small vessels and nuclear dust in the background, signifying a leucocytoclastic vasculitis. (E) H&E stain (magnification $\times 200$) showing widespread extravasation of red blood cells and surrounding involvement of capillaries.

Her medical history included hypertension, for which she had been using amlodipine for several years.

Clinical examination revealed an ill, tachypnoeic (34 breaths per minute) patient with an oxygen saturation of 82% while on four litres of oxygen. Her blood pressure was 137/86 mm Hg and pulse rate was 115 bpm. Her body temperature was 41.9°C. Auscultation of the lungs revealed bilateral basal pleural crackles. She had an erythematous, maculopapular rash over her abdomen, back, arms and legs. Her lower legs showed focal purpuric lesions, while her abdomen and back showed very subtle vesicular and pustular lesions. Mucosal areas were not affected (figure 1A, B).

INVESTIGATIONS

Laboratory testing revealed anaemia, eosinophilia, an elevated C reactive protein level and elevated transaminases (figure 2A). A chest X-ray revealed a consolidation in the left upper lung and a smaller consolidation in the right upper lobe (figure 2B). The patient was admitted to the intensive care unit because of respiratory insufficiency, and antibiotic therapy was promptly started (a combination of vancomycin and ciproxin because of the potential cross-reactivity with dapsone) under the provisional diagnosis of a pulmonary infection.

A high-resolution CT-scan showed bilateral infiltration with ground glass in the upper lobes and subpleural space (figure 2C,D).

A skin biopsy showed a leucocytoclastic vasculitis, and also collections of neutrophils in the epidermis (figure 1C). Immunofluorescence of the skin was negative for immunoglobulins and complement.

DIFFERENTIAL DIAGNOSIS

The combination of high-grade fever, skin rash, lung and liver involvement made a dapsone hypersensitivity syndrome very likely. The differential diagnosis included a systemic vasculitis with pulmonary involvement or pneumonia with an exacerbation of the patient's vasculitis.

TREATMENT

Following the antibiotics, on day 3, systemic corticosteroids were started (prednisone 1 mg/kg/day).

OUTCOME AND FOLLOW-UP

Our patient showed a remarkable recovery. After 1 week she did not need supplemental oxygen. Her skin lesions faded and her liver enzymes normalised. After 10 days, she was discharged home and treatment with steroids was tapered over a period of 4 weeks.

DISCUSSION

Our patient suffered from a life-threatening complication of dapsone therapy: dapsone hypersensitivity syndrome (DHS).^{2 3}

DHS was first described in 1950 and the incidence ranges from 0.5% to 4%.^{2 3} Known risk factors for developing DHS are: glucose-6-phosphate dehydrogenase (G6PD) deficiency, sulfone hypersensitivity, haemolytic anaemia, porphyria, personal or family history of cyanosis, use of concurrent medications metabolised by CYP3A4 and CYP2C9, rapid hydroxylators and slow acetylators.² Recent studies called attention to the association of DHS with HLA×B13:01 (affecting amino acids residues 94, 95 and 145) in Chinese patients.⁴ The exact mechanism of DHS remains unclear, but in Chinese leprosy patients, there is a 21-fold relative risk of HLA×B13:01 and DHS. This supports an underlying T-cell mediated process.^{4 5}

DHS typically presents with a triad of fever, skin eruption and involvement of an internal organ, starting weeks to months after the initiation of dapsone. The diagnosis is based on its clinical presentation.

Our patient was advised to stop dapsone and was initially treated with antibiotics. Based on the negative cultures, the multiorgan involvement and the progression of the disease, the diagnosis of DHS was soon made and steroids were started. Owing to the remarkable recovery, we can exclude the contention that a systemic vasculitis with pulmonary involvement was responsible for the progressive multiorgan involvement.

Treatment of DHS involves prompt discontinuation of dapsone, administering high-dose systemic steroids (prednisolone 1 mg/kg/day) and supportive care. Slow steroid tapering is recommended since dapsone may persist in the body for up to 35 days as a result of protein binding and enterohepatic circulation. As a late complication, hypothyroidism can occur, therefore thyroid function should be assessed during follow-up.²

Dapsone is prescribed worldwide by various disciplines. Physicians must be aware that DHS is a life-threatening idiosyncratic reaction with high mortality rates if not recognised immediately.² According to the recent literature, testing of Chinese patients for HLA×B13: 01 is recommended before starting dapsone.⁴ Whether HLA testing will be useful in Caucasian patients, however, remains to be seen.

CONCLUSION

Awareness of DHS is extremely important since early recognition and prompt treatment of this rare, but potentially fatal complication, are essential. In the past, it was thought that DHS mainly occurred in G6PD deficiency. Recently, in Chinese

patients, a strong association with HLA×B13:01 was discovered suggesting that a T-cell mediated process may be instrumental.⁴

Learning points

- Use of dapsone may be associated with adverse effects thought to be associated with glucose-6-phosphate dehydrogenase (G6PD) deficiency, including life-threatening dapsone hypersensitivity syndrome (DHS), which can present with fever, rash and multiorgan failure.
- We present an illustrative case of DHS in the absence of G6PD deficiency. It is important to consider this diagnosis, since early recognition and treatment are of utmost importance.
- All patients starting dapsone should be informed about the possibility of this severe adverse drug reaction and should be monitored closely for early recognition of symptoms and signs suggestive of DHS.

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