Severe dapsone-induced hypoalbuminemia in a case of mucous membrane pemphigoid

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INTRODUCTION
Dapsone, or 4,4'-diaminodiphenylsulfone, is commonly used in several dermatologic indications such as neutrophilic dermatoses, vasculitis, and autoimmune bullous diseases. Historically, dapsone was used for sleep disorders and then as an antibiotic to treat streptococcal infection, tuberculosis, and leprosy. Some dose-dependent adverse effects are well known, such as increased methemoglobinemia, hemolytic anemia, and neutropenia. Axonal neuropathy is a rare cumulative dose-related adverse effect attributed to direct drug toxicity, occurring after prolonged exposure. Idiosyncratic drug reactions have also been described such as dapsone hypersensitivity syndrome that appears in the few weeks after dapsone introduction, or hepatitis, which generally occurs within a few days after the start of treatment.

We report a case of severe dapsone-induced hypoalbuminemia, a long-term drug reaction that can occur after a long delay, in a patient with mucous membrane pemphigoid.

CASE REPORT
A 64-year-old woman was referred to our Department of Dermatology for episodic widespread oral erosions evolving for the past 2 years. She had no medical history and did not receive any drugs. Physical examination did not show other mucosal involvement or skin lesions. Histopathologic examination of a biopsy performed on a gingival blister showed a subepidermal blister. Direct immunofluorescence microscopy showed linear IgG and C3 deposits along the dermoepidermal junction. Serum anti-BP180 antibodies, 23 U/L (normal value < 12 U/L), were detected by enzyme-linked immunosorbent assay.

A diagnosis of mucous membrane pemphigoid was considered, based on clinical features, histologic pattern, direct immunofluorescence, and detection of serum anti-BP180 antibodies. Dapsone 75 mg once daily was started and rapidly led to complete remission with good clinical and biological tolerance.

Two years later, the patient was referred for rapidly progressive dyspnea associated with generalized edema. Chest radiograph showed a large right pleural effusion. More than half a liter of pleural liquid was removed by thoracocentesis. Biochemical analysis showed a sterile yellow-citrine transudate. A plasma electrophoresis blood test showed hypoalbuminemia, 19 g/L (normal range 35-52 g/L), with a normal gammaglobulin value, 7.5 g/L (normal range 7-15 g/L), and mild hyponatremia, 131 mM/L (normal range 135-145 mM/L). There was no evidence for a digestive loss (diarrhea or enteropathy) or proteinuria (0.62 g/24 h) that could explain the low serum albumin level. Complete blood cell count did not show thrombopenia or leucopenia, which suggested a portal hypertension (positron emission tomography—computed tomography did not show any hypermetabolic lesion). Diuretic treatment did not improve the patient’s dyspnea. A second thoracocentesis and ascites puncture removed 2.5 L of pleural fluid and 3 L of ascites, respectively.

In the absence of an obvious cause explaining the low albumin level, dapsone was suspected and the culprit drug was stopped. No other potentially dapsone-related adverse events were recorded, such as methemoglobinemia, cytopenia, hepatitis, or neuropsychiatric disorders. During the month that followed dapsone withdrawal, the patient lost 13 kg...
and albumin level returned to normal value (27 g/L) and remained stable up to 8 months of follow-up.

DISCUSSION

We report a case of severe dapsone-induced hypoalbuminemia. Despite the fact that this adverse effect is mentioned in the summary of product characteristics, it is rare. Indeed, no case of dapsone-induced hypoalbuminemia has been reported in the French pharmacovigilance database since the 1980s. Our local pharmacovigilance center performed its research in international textbooks such as *Martindale* and *Meyler’s Side Effect of Drugs*, and in an international pharmacovigilance database (via VigiLyze, which is a World Health Organization database), in which it found 4 similar reported cases of isolated dapsone-induced hypoalbuminemia.6-8 These patients were all treated with dapsone for dermatitis herpetiformis, with doses ranging from 50 mg 3 times a week to 300 mg daily. The delay from the introduction of dapsone to the first symptoms was particularly long, from 3 to 10 years. Clinical symptoms were dyspnea and edema of the lower limbs or ascites. Hypoalbuminemia was the main biological feature, ranging from 8 to 24 g/L. Of the 4 patients, 3 completely recovered after dapsone withdrawal after a variable delay from 5 weeks to 13 months, and 1 patient died from bronchopneumonia while still receiving dapsone. Table I summarizes the data for these four patients. The physiopathology of dapsone-induced hypoalbuminemia is unclear. Kingham et al8 first suspected the role of the dermatitis herpetiformis—associated enteropathy because their 2 patients had histologically proven gut villous atrophy with increased protein loss. However, gluten-free diet and resolutive protein loss did not improve the hypoalbuminemia. Our patient had mucous membrane pemphigoid, not a dermatitis herpetiformis, without digestive symptoms which argues against the hypothesis of an associated enteropathy.

It has also been hypothesized that a metabolite of dapsone, an albumin-bound molecule, might act as haptens, leading to the formation of antibodies directed against dapsone and the destruction of both dapsone and albumin.2

Hypoalbuminemia has also been reported in patients with “dapsone hypersensitivity syndrome,” which is a severe multiorgan drug reaction, close to or identical to a drug reaction with eosinophilia and systemic symptoms.2,4,9,10 However, the “dapsone syndrome” occurred within the first weeks after initiation of dapsone, whereas the 4 cases of dapsone-induced hypoalbuminemia, including the present one, occurred after a much longer delay. Additionally, these 4 patients did not have a rash, fever, lymphadenopathy, blood eosinophilia, and various organ involvement, which are characteristic of dapsone syndrome.6-8

Although rare, hypoalbuminemia is a potentially serious adverse effect of dapsone that can be observed several years after its introduction.

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| Article | First author | Patient no. | Age (years) | Time between introduction of dapsone and first symptoms, years | Dapsone dosage (mg) | Lowest albumin serum concentration (g/L) | Highest sedimentation rate (mm/h) | Evolution |
|---------|--------------|-------------|-------------|---------------------------------------------------------------|---------------------|----------------------------------------|---------------------------------|-----------|
| 1       | Kingham     | 1           | 51          | 3                                                             | 100/d               | 8                                      | 117                             | Healing in 6 wk after discontinuation |
|         |              | 2           | 26          | 11                                                            | 150/d               | 14                                    | Unknown                         | Healing in 5 wk after discontinuation |
| 2       | Young       | 3           | 56          | 10                                                            | 100—300/d           | 24                                    | 92                              | Death                              |
| 3       | Cowan       | 4           | 56          | 8                                                             | 100/wk—50/d         | 20                                    | 124                             | Healing in 13 mo after discontinuation |
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