Severe Drug-induced Pneumonitis Associated with Minocycline and Nicotinamide Therapy of a Bullous Pemphigoid

Sir,

Minocycline hydrochloride, a semisynthetic tetracycline derivative, continues to be one of the most frequently used antibiotics. Long-standing familiarity with minocycline has established its relative safety (1). However, minocycline has few but severe side effects that are not widely known, but should be recognized early as drug-related (2). We describe a fatal case with probable minocycline-induced pneumonitis during the treatment of a bullous pemphigoid.

CASE REPORT

An 84-year-old man was evaluated for a purpuric, erythematous vesiculo-bullous eruption of 2 months' duration. Physical examination revealed crusted, erythematous, slightly indurated macules, vesicles on erythematous bases, and ulcers mainly on the neck, chest and flexor forearms. A chest X-ray taken at that time was normal. A skin biopsy including the results of direct immunofluorescence was interpreted as a bullous pemphigoid (BP). Therapy was initiated with nicotinamide 600 mg daily and minocycline hydrochloride 200 mg daily.

After 15 days, he suddenly developed high fever, a dry cough and dyspnea. Auscultation of the chest revealed scattered fine crackles over the upper- and mid-zones of both lungs. The leukocyte count was 14,200/mm^3 with 2% eosinophils. The C-reactive protein was 14.6 (normal = <0.3). Chest X-ray showed a bilateral interstitial pattern, which was marked in the upper- and mid-zones of both lungs. Severe hypoxemia ($paO_2 = 28.7$ mmHg) was present when the patient breathed room air. Findings of serologic testing for viral disease (cytomegalovirus, Epstein-Barr virus) and cultures from sputa and blood were negative.

As pneumonitis due to an adverse drug reaction was suspected, both nicotinamide and minocycline were discontinued. Despite treatment, the chest roentogenograms showed diffuse and confluent involvement in the bilateral fields (Fig. 1a). Lymphocyte stimulation tests for nicotinamide and minocycline were inconclusive. Nine days after onset of pneumonitis, the patient died. An autopsy was performed. The specimens obtained from the lung showed diffuse damage to the epithelium and endothelium of the alveolar walls. Macrophages, type II pneumocytes and red blood cells were conspicuous in the alveolar spaces, and lymphocytes and plasma cells were observed within the interstitial spaces. Hyaline membranes were formed along the surface of the alveolar ducts. Neither granuloma formation nor eosinophil infiltration was observed (Fig. 1b).

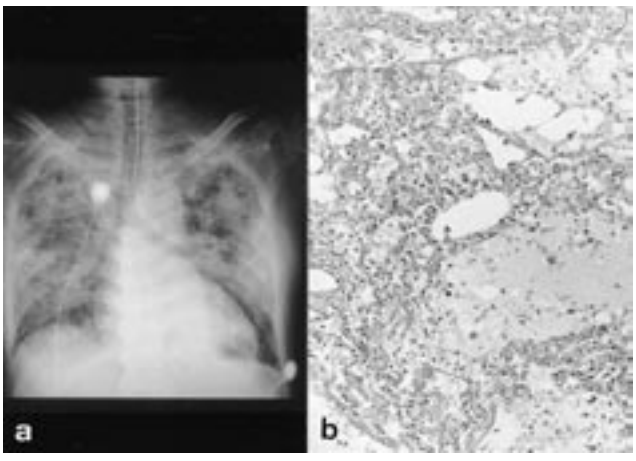

Fig. 1. (*a*) Chest roentogenogram showing diffuse and confluent infiltrates in the lungs. The patient was in respiratory distress at the time of this chest roentogenogram. (*b*) Autopsied specimens obtained from lungs showed diffuse damage of the alveolar walls and infiltration of red blood cells, lymphocytes and plasma cells.

DISCUSSION

Since 1986, the combination therapy of nicotinamide and tetracycline (or minocycline) has been reported to be effective in the treatment of BP (3). However, more serious and rare adverse effects due to minocycline have been identified, including pneumonitis, hepatotoxicity, Sweet's syndrome, drug-induced lupus, serum sickness-like reaction, and hypersensitivity syndrome (2). Single cases and a small series of patients with pneumonitis have been reported, mostly in Japan. Almost all of the published cases were characterized by high fever, dry cough, chest pain, dyspnea, and pulmonary infiltrates on the chest roentogenogram, sometimes with eosinophilia in the blood within 4 weeks after administration of the drug.

Pneumonitis due to minocycline in most cases is considered to be caused by allergic reaction (4). Thus, the outcome of minocycline-induced pneumonitis is usually favourable. Shirahama et al. (5) reported an 83-year-old man who developed pneumonitis after 12 days of treatment with minocycline at 200 mg daily for BP. The symptoms resolved after minocycline was discontinued. Whether pneumonitis in our case was caused by allergic reaction or cytotoxic reaction is unclear. However, there was a definite association between the respiratory symptoms and administration of minocycline and nicotinamide therapy. To our knowledge, this is the only reported fatal case of minocycline-associated with pneumonitis. According to the literature, 3 patients died as a result of minocycline toxicity, 1 of fulminant hepatic failure (6), 1 of myocarditis (7) and 1 of pancytopenia (8).

REFERENCES

1. Delaney TJ, Leppard BJ, MacDonald DM. Effects of long-term treatment with tetracycline. Acta Derm Venereol (Stockh) 1974; 54: 487 – 489.
2. Knowles SR, Shapiro L, Shear NH. Serious adverse reactions induced by minocycline. Arch Dermatol 1996; 132: 934 – 939.
3. Berk MA, Lorincz AL. The treatment of bullous pemphigoid with tetracycline and nicotinamide. Arch Dermatol 1986; 122: 670 – 674.
4. Bando T, Fujimura M, Noda Y, Hirose J, et al. Minocycline-induced pneumonitis with bilateral hilar lymphadenopathy and pleural effusion. Internal Medicine 1994; 33: 177 – 179.
5. Shirahama S, Furukawa F, Aoki R, Takigawa M. Drug-induced pneumonitis due to minocycline for the treatment of bullous pemphigoid. Risho Derma 1997; 51: 218 – 220.
6. Davies MG, Kersey PJW. Acute hepatitis and exfoliative dermatitis associated with minocycline. BMJ 1989; 298: 1523 – 1524.

7. Gough A, Chapman S, Wagstaff K, Emery P, et al. Minocycline induced autoimmune hepatitis and systemic lupus erythematosus-like syndrome. BMJ 1996; 312: 169 – 172.
8. Parneix-Spake A, Bastuji-Garin S, Lobut J, Erner JB, et al. Minocycline as possible cause of severe and pro-tracted hypersensitivity drug reaction. Arch Dermatol 1995; 131: 490 – 491.

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Delayed Pressure Urticaria Causing Obstruction of Urinary Flow

Sir,
Delayed pressure urticaria (DPU) is a condition in which red, itchy and sometimes painful cutaneous swellings occur at sites where prolonged pressure has been applied to the skin. Swellings occur from 30 min – 9 h after pressure application, and individual lesions resolve within 12 – 72 h.

CASE REPORT

A 51-year-old man presented to a specialist urticaria clinic with a 5-year history of pressure related weals. He gave no history of spontaneous wealing. Six to 12 hours after vigorous weight-bearing exercise, the soles of his feet would become itchy, swollen and painful. He noticed similar symptoms affecting his hands several hours after heavy lifting or manual work. Tight-fitting clothes would likewise cause swelling and wealing at underlying sites (e.g. at the waistline, socks, and shoes). In addition to these classical symptoms of pressure urticaria, he volunteered problems following sexual activity with his wife. Three to 4 hours following sexual intercourse, he would, on each occasion, suffer severe swelling and wealing of the skin over the base, shaft and prepuce of his penis. During this time, attempts at micturition resulted in dribbling and severe impediment of urinary outflow. In parallel with the swelling of penile tissue, his urinary symptoms would spontaneously resolve within 24 – 48 h and not recur if sexual contact was avoided.

Clinical examination was only possible between episodes of genital swelling. This only revealed linear areas of discrete swellings at his waistline and circumscribed weals on the soles of his feet, whilst genito-urinary examination was normal. Application of pressure to the patient's back with a calibrated, spring-loaded dermographometer at 100 g/mm^2 for 70 s resulted in the development of erythematous indurated papules at 6 h, confirming the diagnosis of delayed pressure urticaria (1).

DISCUSSION

The pathogenesis of delayed pressure urticaria has yet to be fully elucidated. However, histology of lesional skin shows an infiltrate of neutrophils in early weals, with mononuclear cells, neutrophils and eosinophils in later weals (2). Decreased number of stainable mast cells in pressure induced sites of DPU has suggested that mast cell degranulation is a factor in the development of these weals (3). Release of cytokines such as interleukin-6 from affected skin (4) into the circulation may account for the associated malaise, pyrexia and increased erythrocyte sedimentation rate in some patients with DPU.

Dyspareunia and vulvodynia have previously been described in people suffering physical urticaria, and are now being recognized in association with dermographism and delayed pressure urticaria (5 – 6). From a recent survey of urticaria patients attending our specialist clinic, we have found that obstruction of urinary flow is a rare problem amongst the male population with delayed pressure urticaria. However, a patient with hereditary angioedema did report similar swellings and urinary difficulties.

REFERENCES

1. Kobza-Black A, Lawlor F, Greaves MW. Consensus meeting on the definition of physical urticarias and urticarial vasculitis. Clin Exp Dermatol 1996; 21: 424 – 426.
2. Winkelmann RK, Kobza-Black A, Dover J, Greaves MW. Pressure urticaria – histopathological study. Clin Exp Dermatol 1986; 11: 139 – 147.
3. Barlow RJ, Ross EL, MacDonald DM, Kobza-Black A, Greaves MW. Mast cells and T lymphocytes in chronic urticaria. Clin Exp Allergy 1995; 25: 317 – 322.
4. Lawlor F, Bird C, Camp RD, Barlow RJ, Barr RM, Kobza-Black A, et al. Increased interleukin-6, but reduced interleukin-1, in delayed pressure urticaria. Br J Dermatol 1993; 128: 500 – 503.
5. McFadden JP, Newton JA, Greaves MW. Dyspareunia as a complication of delayed pressure urticaria. Br J Sexual Med 1988; 15: 61.
6. Lambiris A, Greaves MW. Dyspareunia and vulvodynia: unrecognised manifestations of symptomatic dermographism. Lancet 1997; 349: 28.

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