

A Case of Cutaneous Leukocytoclastic Vasculitis associated with Gabapentin

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ABSTRACT

Gabapentin was approved for use in the USA in 1994 as an add-on drug in adults who have partial seizures either alone or with secondary generalised seizures. Its use has been expanded to include treatment for other conditions such as neuropathic pain and paraesthesiae. Gabapentin was prescribed for our patient who had persistent left-sided hemi-paraesthesiae consequential of a previous thalamic infarct. One week after commencement of gabapentin, she developed an adverse reaction in the form of a purpuric rash over bilateral lower limbs. Skin biopsy revealed histological features of cutaneous leukocytoclastic vasculitis. This rash completely resolved with withdrawal of gabapentin and steroidal treatment. This cutaneous adverse reaction to gabapentin has not been reported in the medical literature.

Keywords: gabapentin, partial seizures, neuropathic pain, paraesthesiae, leukocytoclastic vasculitis

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INTRODUCTION

Gabapentin was approved for use in the United States in 1994 as an add-on drug in adults who have partial seizures either alone or with secondary generalised seizures. Indications for its use has since expanded to include treatment of neuropathic pain such as trigeminal and post-herpetic neuralgia, essential tremor and ciguatera poisoning. The more common side effects associated with gabapentin are somnolence, fatigue, ataxia, dizziness and gastrointestinal upset.

CASE REPORT

Our patient was a 72-year-old Chinese lady with diabetes mellitus and had a right thalamic infarct three years prior to presentation with current problem. She was taking tolbutamide and aspirin for the last three years and was tolerating them well.

She suffered from left hemi-paraesthesiae as a result of the right thalamic infarct. Her attending neurologist prescribed gabapentin in an attempt to

alleviate this symptom. One week after she started gabapentin, she noticed a purplish rash developing over her ankles and feet. This was associated with increasing pain and swelling. She stopped taking gabapentin about two days after the onset of the rash, having taken this drug for the last nine days. She became febrile three days after the appearance of the rash. One week after onset of the rash and five days after discontinuing gabapentin, the rash has circumferentially progressed above the ankles with blistering. She was admitted after attending the emergency department.

On examination she had a low-grade fever but was non-toxic. Abnormal findings were limited to the lower



Fig. 1a This is the appearance of rash nine days after onset with extent of rash marked out. Palpable purpura is present on the medial aspect of the ankles together with prominent vesicles, bullae and haemorrhagic blisters on the dorsum of the feet.



Fig. 1b Close-up view of vesicles, bullae and haemorrhagic blisters on background of pedal oedema.

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limbs (Fig. 1a). There was a symmetrical palpable purpuric rash with multiple bullae formation over the dorsum of both feet and ankles (Fig. 1b). There were no physical signs suggesting the presence of a primary systemic illness. Nine days after onset, there was no further progression of the rash in terms of new bullae formation or extension.

Blood investigations showed increased levels of acute phase reactants – raised C-reactive protein (CRP) at 194 mg/l, erythrocyte sedimentation rate (ESR) of 80 mm/h, leukocytosis of $16.11 \times 10^9/l$, and serum ferritin at 303 ng/ml but eosinophilia was not present. Investigations done to exclude other causes of this rash include hepatitis B surface antigen, hepatitis C IgG antibody, presence of cryoglobulin and anti-neutrophil cytoplasmic antibody (ANCA); all were negative. Anti-nuclear antibody was borderline positive at a titre of 1 in 200 (homogeneous pattern). There was no evidence of microscopic haematuria or casts on microscopic examination of the urine. Blood cultures, sputum acid-fast bacilli smears, wound swab cultures and Gram stain smears for infective causes were negative. X-rays of the ankles and feet did not reveal any bony or soft tissue abnormality.

Skin biopsy showed that small vessels in the dermis were surrounded by neutrophils and nuclear debris. Red cell extravasate was present. There were no eosinophils and few lymphocytes were seen. Immunofluorescence was negative for antibodies or immune-complexes. The pathological diagnosis is leukocytoclastic vasculitis.

The patient was treated with corticosteroids 10 days after onset of rash and the rash rapidly subsided. Leukocyte count, ESR and CRP normalised and she was discharged with complete resolution of the purpuric rash a week after admission.

DISCUSSION

Overall, gabapentin has been well tolerated with a low incidence of adverse reactions⁽¹⁾. Reports of movement disorders, ataxia, mania and even stuttering associated with gabapentin are idiosyncratic, non-dose dependent side effects. Massive overdoses of gabapentin have occurred without serious health consequences⁽²⁾. The lack of potential interaction with traditional antiepileptics has enhanced its role as an adjunctive treatment agent⁽¹⁾. Gabapentin is not previously known to be associated with cutaneous vasculitis although there is a solitary report of gabapentin causing skin vesicular eruption in a patient after repeated phenytoin and carbamazepine induced Stevens-Johnson's syndrome⁽³⁾.

Predominantly cutaneous vasculitides is probably more common than the systemic necrotising vasculitides.

It can occur at any age and in both sexes. But there may be special predominance in age or sex in certain subsets of cutaneous vasculitis. It is presumed to be a hypersensitivity reaction associated with either exogenous or endogenous antigens.

Cutaneous vasculitis may be associated with various underlying primary diseases⁽⁴⁾ particularly systemic lupus erythematosus, rheumatoid arthritis, and Sjögren's syndrome. Essential mixed cryoglobulinemia associated with hepatitis C infection may present as predominantly cutaneous vasculitis. Malignancies can also be associated with cutaneous vasculitis, particularly of the lymphoid or reticuloendothelial variety.

Vasculitis associated with drug reaction⁽⁵⁾, as reported in our patient, usually presents as palpable purpura mostly occurring in the lower limbs of ambulant patients. Urticarial lesions, ulcers and haemorrhagic blisters may also occur. Signs and symptoms are usually limited to the skin, but systemic manifestations such as fever as experienced by our patient may occur. Drugs frequently implicated in vasculitis include allopurinol, thiazides, gold, sulphonamides, phenytoin, and penicillin⁽⁶⁾. In our patient, gabapentin is the most likely agent triggering the hypersensitivity reaction that manifested as cutaneous leukocytoclastic vasculitis. Aspirin and tolbutamide have not been reported to be specifically associated with such a reaction. The fact that our patient was taking aspirin and tolbutamide for the last three years, renders it highly improbable that they are the causative agents. She continued with these medications upon discharge and was well on follow up.

Once diagnosis is confirmed on biopsy and the vasculitis persists despite removal of causative agent as in our patient's case, treatment with glucocorticoid is indicated. Fortunately in her case, a rapidly tapering course of glucocorticoid was possible as her condition improved dramatically. Trial of a cytotoxic agent such as cyclophosphamide is rarely needed, unless progression to irreversible organ system dysfunction is assessed to be likely. In patients with chronic persistent isolated cutaneous vasculitis, no therapeutic regimen is dramatically effective. Plasmapheresis and dapsone have been used in such cases with limited success.

In conclusion, gabapentin was implicated in the case of our patient as a novel cause of cutaneous leukocytoclastic vasculitis.

REFERENCES

1. Beydoun A, Uthman BM, Sackellares JC. Gabapentin: pharmacokinetics, efficacy and safety. *Clin Neuropharmacol* 1995 Dec; 18(6):469-81.
2. Verma A, Radtke RA. A case of sustained massive gabapentin overdose without serious side effects. *Ther Drug Monit* 1999 Dec; 21(6):615-7.

3. Detoledo JC, Minager A, Lowe MR. Skin eruption with gabapentin in a patient with repeated anti-epileptic drug induced Stevens-Johnson s Syndrome. *Ther Drug Monit* 1999 Feb; 21(1):137-8.
4. Hautmann G, Campanile G, Lotti Tm. The many faces of cutaneous vasculitis. *Clin Dermatol* 1999; 17(5):515-31.
5. Callen J.P., Cutaneous vasculitis — what have we learned in the past 20 years? *Arch Dermatol* 1998; 134(3):355-7.
6. Garcia-Porrúa C, Gonzalez-Gay MA, Lopez-Lazaro L. Drug associated cutaneous vasculitis in adults in northwestern Spain. *J Rheumatol* 1999; 26(9):1942-4.