Renal Replacement Therapy

CASE REPORT Open Access

A case of hemodialysis and steroid therapy for carbamazepine-induced eosinophilic granulomatosis with polyangiitis: a case report with literature review

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Abstract

Background: Carbamazepine-induced acute kidney injury is mainly caused by acute tubulointerstitial nephritis. Only one case of carbamazepine-induced eosinophilic granulomatosis with polyangiitis (EGPA) with acute kidney injury has been reported. But the patient's condition improved with the immediate discontinuation of carbamazepine. We present a case requiring hemodialysis and steroid therapy for carbamazepine-induced EGPA with acute kidney injury.

Case presentation: A 77-year-old man with allergic rhinitis was prescribed carbamazepine for trigeminal neuralgia 1 year ago. He developed rash and itching on the left forearm 1 month ago and was diagnosed with polymorphic exudative erythema and admitted to our hospital. Laboratory data revealed leukocytosis eosinophilia and renal failure (serum creatinine 9.2 mg/dL). Carbamazepine was discontinued, and hemodialysis was initiated because of acute uremia and oliguria. A lymphocyte stimulation test for carbamazepine was positive. Polyneuropathy in the upper and lower extremities was observed by electromyogram, and a renal biopsy indicated EGPA. The main clinical findings were allergic rhinitis, eosinophilia, and vasculitis symptoms, such as multiple mononeuritis and muscle weakness. Renal biopsy showed diffuse cellular infiltration dominated by eosinophils in the interstitium, with granulomatous changes in particular observed around the arteriole. Fibrinoid necrosis was also observed around the arteriole. We therefore made a diagnosis of carbamazepine-induced EGPA. Following steroid therapy after the discontinuation of carbamazepine, the patient was discharged from our hospital without hemodialysis. In contrast with the previous case of EGPA, the present case had the following characteristics: (1) elderly male patient, (2) hemodialysis required for acute kidney injury, and (3) improved renal function following steroid therapy after discontinuation of carbamazepine.

Conclusion: Our case report indicates that early diagnosis and appropriate therapy can improve acute kidney injury caused by carbamazepine and allow the patient to discontinue dialysis.

Keywords: Eosinophilic granulomatosis with polyangiitis, Carbamazepine, Acute kidney injury

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Background

Eosinophilic granulomatosis with polyangiitis (EGPA), also known as Churg-Strauss syndrome, is defined as an eosinophil-rich necrotizing vasculitis of small-to-medium blood vessels according to the 2012 Chapel Hill consensus conference [1]. This disease is associated with allergic mechanisms [2] and characterized by preceding asthma, allergic rhinitis, eosinophil-rich vasculitis, polyneuropathy, purpura, gastrointestinal ulcer, cerebral infarction, and myocardial infarction. The mean onset age in Japan is 55 ± 14 years (gender ratio [M to F] of 2:1) [3].

Carbamazepine is typically administered as an antiepileptic drug. Acute kidney injury caused by carbamazepine was first reported in 1972 [4]. Hogg et al. have shown that carbamazepine-induced renal failure is typically caused by acute tubulointerstitial nephritis [5].

Here, we present the case of an elderly man who required hemodialysis and steroid therapy for carbamazepine-induced EGPA with acute kidney injury.

Case presentation

A 77-year-old man was admitted to our hospital because of acute kidney injury with skin eruption. He was taking only carbamazepine (100 mg/day), which had been prescribed for trigeminal neuralgia 1 year previously. Before 9 months, serum creatinine was 1.0 mg/dL, and there was no proteinuria and hematuria. Rash and itching had appeared on his left forearm 1 month previously, and anorexia had also appeared 10 days ago. The patient had a previous history of allergic rhinitis, but no asthma. There was no family history of EGPA.

Physical examination on admission revealed erythema with a lesion of approximately 1 cm and mild infiltration on the face, trunk, and limbs, which was diagnosed as polymorphic exudative erythema (Fig. 1). Blood pressure was 126/77 mmHg, pulse rate was 93/min, and body temperature was 37.3 °C. The patient had muscle weakness of the limbs and decreased thermal nociception and tactile sense. A manual muscle test (MMT) was performed on the iliopsoas 4/4, quadriceps 4/4, and hamstring 4/4. But the vibratory sensation was normal.

Laboratory testing was performed on admission (Table 1). Arterial blood gas analysis showed a mixed anion gap metabolic acidosis and respiratory acidosis (a pH of 7.40, $PaCO_2$ of 30.8 Torr, PaO_2 of 82.8 Torr, and bicarbonate of 8.2 mmol/l). Hematocrit was 36.4%, and hemoglobin was 12.9 g/dL. The leukocyte count was 15,900 mm^3, with a differential count of 68.9% neutrophils, 16.1% eosinophils, 6.3% monocytes, and 8.2% lymphocytes, and there were no atypical lymphocytes. The platelet count was 22.4 × 10^4/μL. For serum electrolytes, the corrected calcium was 10.3 mg/dL, and phosphate was 6.4 mg/dL. Serum urea nitrogen was 87.1 mg/dL, serum creatinine 9.2 mg/dL, and uric acid 13.1 mg/dL. Total protein was 5.6 g/dL, and albumin was 2.5 g/dL. Liver function tests included lactic dehydrogenase 273 IU/L. Serological tests for antinuclear antibody, anti-glomerular basement membrane antibody, MPO-ANCA, and PR3-ANCA were all negative except for C-reactive protein, which was 15.7 mg/dL. Complement levels were within normal limits (C3

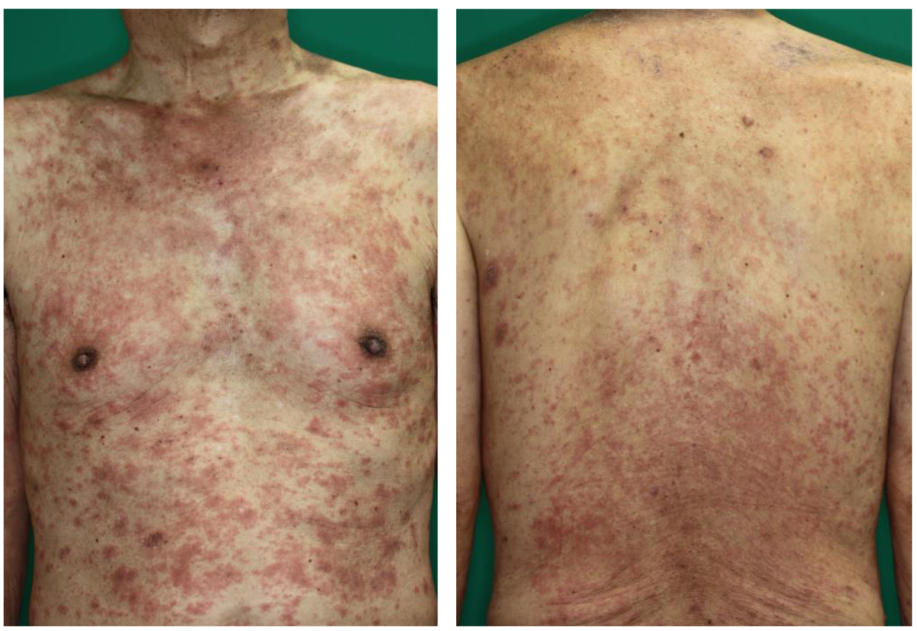

Fig. 1 Skin findings. Polymorphic exudative erythema was found in the face, trunk, and extremities

Table 1 Laboratory data

Urinalysis	
Protein	(3+)
Blood	(±)
Glucose	(–)
RBC	1–4/HPF
WBC	50–99/HPF
Urinary chemistry	
NAG	92.3 U/L
α1-MG	59.5 mg/L
β2-MG	150 μg/L
Arterial blood gas	
pH	7.399
$PaCO_2$	30.8 Torr
PaO_2	82.8 Torr
HCO_3^-	8.2 mmol/L
BE	− 5.5 mmol/L
Peripheral blood	
WBC	19800/μL
seg	68.9%
lym	8.2%
mono	6.3%
eos	16.1%
baso	0.5%
Hb	12.9 g/dL
Plt	22.4 × 104/μL
Blood chemistry	
T.P	5.6 g/dL
Alb	2.5 g/dL
T-bil	0.3 mg/dL
AST	18 IU/L
ALT	54 IU/L
LDH	273 IU/L
UN	87.1 mg/dL
Cr	9.2 mg/dL
UA	13.1 mg/dL
Na	135 mEq/L
K	4.4 mEq/L
Cl	96 mEq/L
Ca	10.3 mg/dL
P	6.4 mg/dL
Serological test	
CRP	15.7 mg/dL
IgG	887 mg/dL
IgE	84 mg/dL
C3	142 mg/dL
C4	35 mg/dL
CH50	57 mg/dL
ANA	< 1:40
MPO-ANCA	< 1.0 U/mL
PR3-ANCA	< 1.0 U/mL
Anti-GBM Ab	< 2.0 IU/mL
Anti-CL β2gpI Ab	< 1.2 U/mL
Anti-CL-igg Ab	< 8 U/mL
LA	1.18

RBC red blood cell, *WBC* white blood cell, *seg* segmented neutrophils, *lym* lymphocytes, *mono* monocytes, *eos* eosinophils, *baso* basophils, *Hb* hemoglobin, *Plt* platelet count, *NAG N*-acetyl-β-D-glucosaminidase, *T.P.* total protein, *Alb* albumin, *T-bil* total bilirubin, *UN* urea nitrogen, *Cr* creatinine, *UA* uric acid, *CRP* C-reactive protein, *MG* microglobulin, *CH50* total complement activity, *ANA* anti-nuclear antibody, *MPO–ANCA* myeloperoxidase anti-neutrophil cytoplasmic antibody, *PR3* proteinase-3, *GBM* anti-glomerular basement membrane, *Ab* antibody, *CL* cardiolipin, *GPI* glycoprotein I, *LA* lupus anticoagulant

142 mg/mL, C4 35 mg/mL, and CH50 57 mg/mL). IgG (887 mg/dL) and IgE (84 mg/mL) were normal. Urinalysis dipstick examination indicated 3+ for protein (2.6 g/day) and ± for blood, and microscopic urinalysis indicated 1–4 RBC/HPF and 50–99 WBC/HPF. N-acetyl-β-D-glucosaminidase was 92.3 U/L (0–10.9 IU/L), α-microglobulin was 59.5 mg/L (1.0–15.5 mg/L), and β-microglobulin was 150 μicr (≦ 230 μg/L). The urine bacterial culture test was negative. The parasite egg test was negative. Chest X-ray was normal, but abdominal CT scans showed bilateral renal enlargement. Echocardiography was shown that ejection fraction was 69%, and there were no asynergy and valvular disease.

Clinical course following admission

Figure 2 illustrates the patient's clinical course, renal function, and eosinophil count. Carbamazepine was discontinued immediately upon admission because of suspected drug-induced polymorphic exudative erythema. After hospitalization, oliguria (200 mL/day) and uremia appeared, and the patient required hemodialysis on days 4 and 6. A percutaneous renal biopsy was performed on day 8, and the specimen was routinely processed. A lymphocyte stimulation test for carbamazepine was positive, and polyneuropathy in the upper and lower extremities was identified by electromyogram. EGPA caused by carbamazepine was subsequently diagnosed. The patient was treated with pulse corticosteroid therapy with 500 mg methylprednisolone from days 12 to 14 followed by prednisolone 30 mg per day (0.6 mg/kg), after which eosinophilic count and renal function improved. The patient was discharged on day 29, with serum urea nitrogen of 21.5 mg/dL and serum creatinine of 1.6 mg/dL and proteinuria 0.08 g/day.

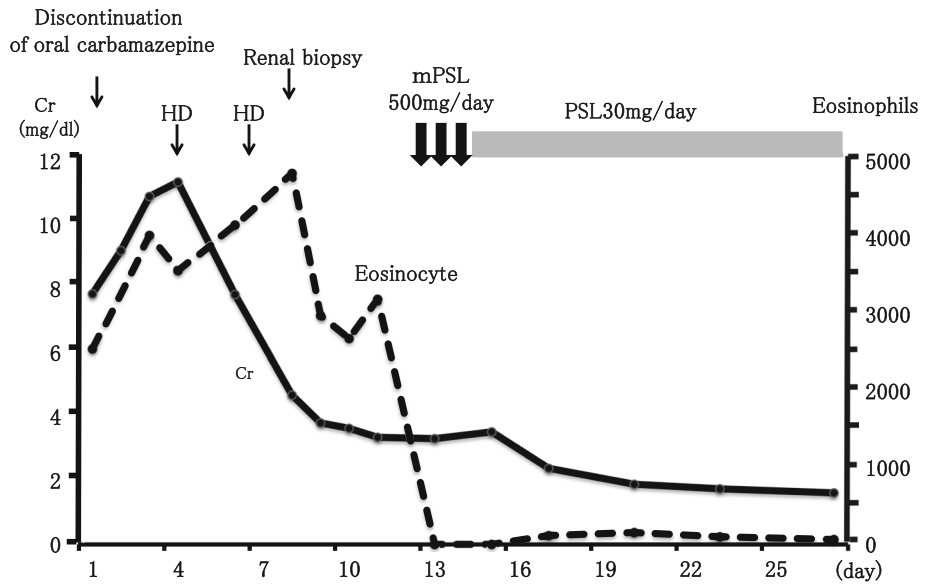

Fig. 2 Clinical course, renal function, and the count of eosinophils after admission

Kidney pathology

Renal biopsy was performed on day 8. The observed sections contained 26 glomeruli, all of which were virtually normal. Diffuse cellular infiltration dominated by eosinophils was observed in the interstitium, with granulomatous changes in particular observed around the arteriole (Fig. 3a). Fibrinoid necrosis was also observed around the arteriole by Masson trichrome staining (Fig. 3b). Immunofluorescence studies did not reveal deposits in the glomeruli. These findings were compatible with a diagnosis of granulomatous polyangiitis.

Discussion

Drugs are common causes of various type of kidney disease, especially acute tubulointerstitial nephritis, although granulomatous interstitial nephritis can also

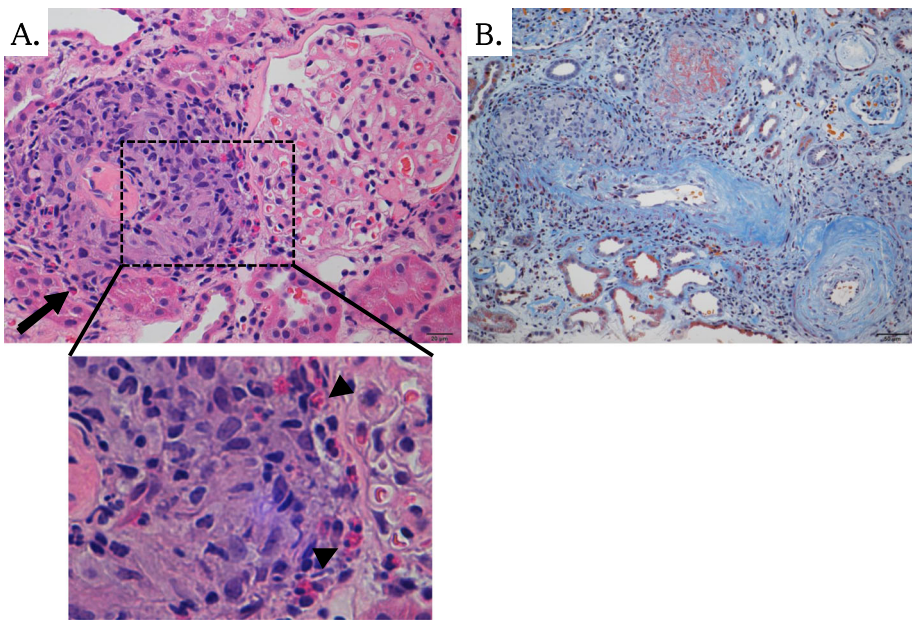

Fig. 3 Renal biopsy findings. **a** The granulomatous angitis: cellular infiltrate around from interlobular arterioles to arteriolar vein was remarkable. There was diffuse involvement of perivascular granulomatous changes (long arrow) and eosinophilic infiltration (arrowheads). Scale bar, 20 μ0 (hematoxylin and eosin staining, × 200). **b** Necrotic lesion: fibrinoid necrosis was observed around the arteriole (arrow). Scale bar, 50 μ0 (Masson stain, × 200)

Table 2 Comparison of previous and the current reports on carbamazepine-induced EGPA

Case	Age/sex	Clinical symptoms				Period from internal use to onset	Treatment		
		Fever	Skin rash	Eosinophilia	S-Cr on admission		CBZ	HD	Steroid
[6]	42/male	+	+	+	3.0 mg/dl	2 months	Withdrawal	–	–
Our case	77/male	+	+	+	9.2 mg/dl	1 year	Withdrawal	+	+

S-Cr serum creatinine, *CBZ* carbamazepine, *HD* hemodialysis

arise [4, 6–8]. EGPA has been associated with drugs such as sulfonamides, phenytoin, thiourea, antisyphilitic arsenical compounds, iodine, and leukotriene receptor antagonists [9]. In the present case, allergic drug reaction was suspected because of the patient's history of allergic rhinitis, eosinophilia, and rash. Furthermore, lymphocyte stimulation testing for carbamazepine was positive, and EGPA was subsequently diagnosed because of the patient's polyneuropathy, mild muscle weakness, and renal biopsy that revealed eosinophilic infiltration, fibrinoid necrotizing vasculitis, and extravascular granulomas.

The French Vasculitis Study group has identified a five-factor score (FFS) that predicts survival without the need for additional immunosuppression [10]. In our case, FFS was 2 (serum creatinine and proteinuria). Among patients with FFS ≥ 1, 92% have a worse renal prognosis and are typically treated with glucocorticoids and immunosuppressants [11, 12]. However, our patient was able to discontinue hemodialysis starting 500 mg methylprednisolone pulse and prednisolone 30 mg per day (0.6 mg/kg) after the discontinuation of oral carbamazepine. Given that our patient was elderly and had mild peripheral neuropathy and no other organ disorders, additional immunosuppressive therapy was not initiated. Prednisolone was gradually decreased in accordance with a previous report [13]. The patient's serum creatinine level was approximately 1 mg/dL after 2 years of steroid treatment. These data suggest that discontinuation of carbamazepine and steroid therapy may be effective in elderly patients with carbamazepine-induced EGPA.

The differential disease of our case is drug-induced hypersensitivity syndrome (DIHS). Our case was not confirmed DIHS criteria [14], because he did not have fever and lymphadenopathy. Eguchi et al. reported the case of DIHS induced by carbamazepine [15]. The case has shown diffuse interstitial infiltration of lymphocytes, not eosinophils, while our case shows characteristic findings of EGPA which were granulomas with eosinophil infiltration and fibrinoid necrotic vasculitis.

In this case, the urine output increased, while there is about 1 week until the steroid treatment started. Carbamazepine is generally difficult to remove by hemodialysis. Therefore, it is considered that tubular interstitial disorder was improved by withdrawal of carbamazepine.

Conclusion

We report the development of EGPA in an elderly male patient following the oral administration of carbamazepine for more than 1 year. The patient was subsequently able to discontinue hemodialysis. Our case highlights the importance of making a rapid diagnosis by renal biopsy and providing appropriate treatment.

Literature review

Carbamazepine causes side effects, such as skin eruption and eosinophilia, in our laboratory analyses, within 2 months of administration in 60% of cases [16]. However, carbamazepine-induced AKI may occur after several years of administration [8, 17]. Furthermore, the common cause of AKI associated with carbamazepine is acute tubulointerstitial nephritis [4, 5].

Only one case of carbamazepine-induced EGPA has been reported to date [18]. This case was a 42-year-old man who developed the condition 2 years after starting oral administration of carbamazepine. When this patient was hospitalized, serum creatinine was 3.0 mg/dL and his renal function was improved by only discontinuation of carbamazepine. On the other hand, our case highlights two key observations: (1) hemodialysis was required for acute kidney injury, although the renal function was improved by the steroid therapy after the discontinuation of carbamazepine, and (2) an elderly man treated with carbamazepine for 2 years (Table 2).

To our knowledge, our report is the first case of carbamazepine-induced EGPA which can discontinue dialysis. Although EGPA typically occurs in women aged 55 ± 14 years, our patient was a 77-year-old male [3]. The relationship between allergy and age is unclear in EGPA. However, allergies in the elderly frequently involve environmental factors, including drugs [19].

Acknowledgements

We thank Clare Cox, PhD, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

Authors' contributions

All authors read and approved the final manuscript.

Funding
Not applicable

Availability of data and materials
Not applicable.

Ethics approval and consent to participate
Not applicable

Consent for publication
Informed consent of the patients involved was provided about the publication of this article.

Competing interests
The authors declare that they have no competing interests

Received: 5 October 2019 Accepted: 17 April 2020
Published online: 05 May 2020

References

1. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, Flores-Suarez LF, Gross WL, Guillevin L, Hagen EC, Hoffman GS, Jayne DR, Kallenberg CG, Lamprecht P, Langford CA, Luqmani RA, Mahr AD, Matteson EL, Merkel PA, Ozen S, Pusey CD, Rasmussen N, Rees AJ, Scott DG, Specks U, Stone JH, Takahashi K, Watts RA. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013;65:1–11. https://doi.org/10.1002/art.37715.
2. Diny NL, Rose NR, Čiháková D. Eosinophils in autoimmune diseases. Immunol. 2017;8:484. https://doi.org/10.3389/fimmu.2017.00484.
3. Sada KE, Amano K, Uehara R, Yamamura M, Arimura Y, Nakamura Y, Makino H. A nationwide survey on the epidemiology and clinical features of eosinophilic granulomatosis with polyangiitis (Churg-Strauss) in Japan. Mod Rheumatol. 2014;24:640–4. https://doi.org/10.3109/14397595.2013.857582.
4. Nicholls DP, Yasin M. Acute renal failure from carbamazepine. Br Med J. 1972;25:490. https://doi.org/10.1136/bmj.4.5838.490.
5. Hogg RJ, Sawyer M, Hecox K, Eigenbrodt E. Carbamazepine-induced acute tubulointerstitial nephritis. Pediatr. 1981;98:830–2. https://doi.org/10.1016/s0022-3476(81)80861-x.
6. Bijol V, Mendez GP, Nose V, Rennke HG. Granulomatous interstitial nephritis: a clinicopathologic study of 46 cases from a single institution. Pathol. 2006;14:57–63. https://doi.org/10.1177/106689690601400110.
7. Ulinski T, Sellier-Leclerc AL, Tudorache E, Bensman A, Aoun B. Acute tubulointerstitial nephritis. Pediatr Nephrol. 2012;27:1051–7. https://doi.org/10.1007/s00467-011-1915-9.
8. Viani F, Claris-Appiani A, Rossi LN, Giani M, Romeo A. Severe hepatorenal failure in a child receiving carbamazepine and erythromycin. Eur J Pediatr. 1992;151:715–6.
9. Conron M, Beynon HL. Churg-Strauss syndrome. Thorax. 2000;55:870–7. https://doi.org/10.1136/thorax.55.10.870.
10. Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Le Toumelin P. Medicine. The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. Medicine (Baltimore). 2011;90:19–27. https://doi.org/10.1097/MD.0b013e318205a4c6.
11. Cohen P, Pagnoux C, Mahr A, Arène JP, Mouthon L, Le Guern V, André MH, Gayraud M, Jayne D, Blöckmans D, Cordier JF, Guillevin L. Churg-Strauss syndrome with poor-prognosis factors. Arthritis Rheum. 2007;57:686–93. https://doi.org/10.1002/art.22679.
12. Ribi C, Cohen P, Pagnoux C. Treatment of Churg-Strauss syndrome without poor-prognosis factors. Arthritis Rheum. 2008;58:586–94. https://doi.org/10.1002/art.23198.
13. Pagnoux C, Guilpain P, Guillevin L. Churg-Strauss syndrome. Curr Opin Rheumatol. 2007;19:25–32. https://doi.org/10.1097/BOR.0b013e3280119854.
14. Kano Y, Hirahara K, Mitsuyama Y, Takahashi R, Shiohara T. Utility of the lymphocyte transformation test in the diagnosis of drug sensitivity: dependence on its timing and the type of drug eruption. Allergy. 2007;62:1439–44. https://doi.org/10.1111/j.1398-9995.2007.01553.x.
15. Eguchi E, Shimazu K, Nishiguchi K, Yorifuji S, Tanaka A, Kuwahara T. Granulomatous interstitial nephritis associated with atypical drug-induced hypersensitivity syndrome induced by carbamazepine. Clin Exp Nephrol. 2012;16:168–72. https://doi.org/10.1007/s10157-011-0531-0.
16. Askmark H, Wiholm BE. Epidemiology of adverse reactions to carbamazepine as seen in a spontaneous reporting system. Acta Neurol Scand. 1990;81:131–40. https://doi.org/10.1111/j.1600-0404.1990.tb00949.x.
17. Hegbrant J, Kurkus J, Oqvist B. Carbamazepine-related acute renal failure. Neurology. 1993;43:446–7. https://doi.org/10.1212/wnl.43.2.446.
18. Imai H, Nakamoto Y, Hirokawa M, Akihama T, Miura AB. Carbamazepine-induced granulomatous nectrotizing angiitis with acute renal failure. Nephron. 1989;51:405–8. https://doi.org/10.1159/000185332.
19. De Martinis M, Sirufo MM, Ginaldi L. Allergy and aging: an old/new emerging health issue. Aging Dis. 2017;8:162–75. https://doi.org/10.14336/AD.2016.0831.

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