RÉSUMÉ DE CAS: Un homme de 76 ans avec une histoire d'accident cérébrovasculaire (ACV) et une hémiparésie droite depuis 30 ans a été transféré d'un autre hôpital quatre jours après le développement d'un nouvel ACV. Ce dernier implique une occlusion de l'artère cérébellaire postéro-inférieure et un flot sanguin distal diminué, se manifestant par de la faiblesse et de l'hypotension traitée avec des fluides et la dopamine. La phényléphrine fut substituée à la dopamine avec l'objectif de maintenir la pression artérielle systolique >80 mm Hg. La fludrocortisone 0.3 mg administrée une fois par jour ainsi que le port de bas-supports furent débutés pour le traitement de l'hypotension orthostatique. L'éphédrine 25 mg administré trois fois par jour fut ajouté et même augmenté à 50 mg trois fois par jour. La yohimbine fut débutée à 5.4 mg administrée aux huit heures puis titrée jusqu'à 10.8 mg trois fois par jour sans être capable de cesser la phényléphrine intraveineuse. La fludrocortisone fut diminuée à 0.1 mg administrée trois fois par jour et ensuite la phényléphrine fut cessée. Le patient développa une infection urinaire à *Escherichia coli* traitée au cotrimoxazole. Par la suite, une sténose sous-clavière gauche de 80% fut détectée; la yohimbine, et les bas-supports furent cessés. L'éphédrine oral fut diminué puis cessé sur deux jours et la fludrocortisone diminuée à 0.1 mg administré deux fois par jour. Le patient fut transféré à une unité de réadaptation dans une condition stable. La fludrocortisone fut discontinuée en l'absence d'hypotension ou de symptômes orthostatiques.

DISCUSSION: L'hypotension orthostatique associée à une dysfonction autonomique fut traitée avec succès à l'aide d'une combinaison de vasopresseurs intraveineux, de fluides, de bas supports, de minéralocorticoïdes oraux, et de vasopresseurs oraux. Ces deux derniers agents sont des options de traitement efficaces dans le traitement du patient dépendant de vasopresseurs intraveineux. Chez notre patient, les effets secondaires furent bien tolérés. Éventuellement, les vasopresseurs oraux furent cessés en l'absence de symptômes orthostatiques.

CONCLUSIONS: L'hypotension orthostatique secondaire à une dysfonction autonomique peut être traitée efficacement à l'aide d'un traitement initial au vasopresseur intraveineux suivi d'une thérapie orale combinée.

MARC M PERREAULT

Severe Multisystemic Hypersensitivity Reaction to Carbamazepine Including Dyserythropoietic Anemia

Sara M Lombardi, Domenico G Girelli, and Roberto Corrocher

OBJECTIVE: To report a case of multisystemic hypersensitivity reaction to carbamazepine.

CASE SUMMARY: An 81-year-old white man was admitted to our hospital because of fever, morbilliform pruritic rash, and jaundice. Fifty days before admission he had taken carbamazepine 200 mg po tid because of seizures. During the first few days following admission, a maculopapular rash progressed to generalized erythroderma with subsequent extensive skin exfoliation. After discontinuing carbamazepine the fever disappeared within 72 hours and hepatic function tests returned to normal within four days. Moreover, after admission the hemoglobin values gradually fell to 6.7 g/100 mL. A bone marrow aspirate showed hypercellularity with marked dyserythropoietic abnormalities, and the bone marrow biopsy showed large and diffused infiltration due to the presence of a low-grade small lymphocytic lymphoma. No specific therapy for the lymphoma was undertaken. The biochemical follow-up showed a total improvement of hemoglobin values. Eight months after drug discontinuation, the patient was asymptomatic; peripheral blood cell count and hemoglobin concentrations were persistently normal.

DISCUSSION: To the best of our knowledge, this is the first published case report implicating carbamazepine as the cause of anemia associated with bone marrow hypercellularity and dyserythropoietic changes, instead of hypocellularity and reduction of erythroid precursors. An interesting point raised by our observation is the possible relation between carbamazepine intake and actual lymphoproliferative disease. The development of non-Hodgkin's lymphoma following carbamazepine treatment has been reported, with regression after the drug was discontinued. However, in our case, a bone marrow biopsy repeated eight months after drug discontinuation confirmed the diagnosis of low-grade lymphoma.

CONCLUSIONS: This case report describes a severe multisystemic reaction, characterized by generalized erythroderma; and renal, hepatic, and bone marrow failure in a patient who started carbamazepine therapy 50 days beforehand.

KEY WORDS: carbamazepine, erythroderma, hepatotoxicity.

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Carbamazepine is an iminostilbene derivative chemically related to tricyclic antidepressant drugs. It has been used to treat seizures as well as trigeminal neuralgia and painful paresthesia associated with peripheral neuropathies. Carbamazepine is generally well tolerated, but several adverse reactions are described, such as skin rash, blood dyscrasias, lymphadenopathy, endocrine-metabolic effects, hepatotoxicity, nephrotoxicity, and ocular and respiratory adverse effects. We describe a patient with some of these features, in addition to anemia associated with bone marrow hypercellularity and dyserythropoietic changes.

CASE REPORT

An 81-year-old white man was admitted to our hospital in August 1995 because of fever, morbilliform pruritic rash, and jaundice. The medical history revealed that he had been taking methyldopa, amiloride, and hydrochlorothiazide because of hypertension for about 20 years and indobufen (an antiplatelet drug) for several years. He also had a six-year history of partial complex seizures with secondary generalization, for which he was initially treated with barbexaclone. Fifty days before admission, he had had two episodes of epileptic seizures. A neurologist had substituted the anticonvulsant with carbamazepine 200 mg po tid. Two weeks before admission, the patient noticed pruritus. Three days before admission, he experienced general weakness, asthenia, anorexia, and fever (up to 38.5 °C). The day before admission, a generalized rash and jaundice with dark urine and acholic feces also appeared. There was no history of chills; insect bites; animal scratches; ingestion of suspicious food (e.g., nonpasteurized milk); recent trips outside Northern Italy; or previous renal, hepatic, skin, and blood disease. Three months before the introduction of carbamazepine, a routine blood examination was normal (Table 1).

On admission, his temperature was 38.4 ˚C and blood pressure was 135/65 mm Hg. The patient was noted to have scleral icterus and a severe morbilliform cutaneous rash extending over much of the skin surface; however, lymphadenopathy was not significant. The margin of the liver was 4 cm below the right costal margin but the spleen was not palpable. A neurologic examination was normal. The routine biochemical profile at admission is reported in Table 1. Bacterial cultures and serologic screening for viruses and bacteria (hepatitis A, B, and C; Epstein–Barr; cytomegalovirus; leishmania; borrelia; Widal–Wright; and Weil–Felix) were negative, as well as antinuclear antibody. The serum concentration of carbamazepine was 2 mg/L (usual adult therapeutic range 4–12 mg/L). Skin rash and eosinophilia (550/mm³) suggested an allergic reaction. All drugs were discontinued, including carbamazepine. Rehydration with intravenous fluids (NaCl 0.9% 1000 mL/d) was started. The chest X-ray was normal. Abdominal ultrasound and computed tomography scans showed an enlarged liver with echostructural inhomogeneities, a mildly enlarged spleen (14 cm of major diameter) and no evidence of intraabdominal lymphadenopathy. Over the following days, the maculopapular rash progressed to generalized erythroderma with subsequent extensive skin exfoliation (Figure 1). Typical signs of toxic epidermal necrolysis (multiple large bullae) and/or Stevens–Johnson syndrome (erythema multiforme, involvement of the oral mucosa) were absent. After discontinuing carbamazepine, the fever disappeared within 72 hours and hepatic function tests returned to normal within four days.

Three days after admission, the patient developed oliguria with 3+ proteinuria at urinalysis. Blood urea nitrogen increased to 70 mg/dL and serum creatinine increased to 1.83 mg/dL. Urinary sodium was 5.1 mEq/L and chlorine urinary was not measurable; serum sodium was 134 mEq/L and serum chlorine was 98 mEq/L. Rehydration with NaCl 0.9% (2000 mL/d iv) was increased and diuretic therapy (furosemide 20 mg iv) was started, though diuresis only began with betamethasone 4 mg iv. The serum biochemical profile improved over several days. Moreover, after admission the leukocyte count gradually fell to 2400/mm³ (5 d after admission) and hemoglobin gradually fell to 6.7–8 g/dL (within 9–30 d). Hemolytic anemia was excluded because Coombs' tests were negative and bilirubin and reticulocyte counts were normal. A bone marrow aspirate showed hypercellularity with marked dyserythropoietic abnormalities, including dissociation between nuclear and cytoplasmic maturation, binuclearity, and nuclear bridging (Figure 2). A cytogenetic study of the marrow was performed and did not reveal abnormalities. Also, there was no evidence of hemophagocytosis. However, the bone marrow biopsy showed a large and diffuse infiltration due to the presence of a low-grade small lymphocytic lymphoma, confirmed by immunophenotype (CD20+, CD5+) and molecular evidence of a B-monoclonal population by polymerase chain reaction.

Nine days after admission, a further generalized seizure occurred. One tablet of carbamazepine 200 mg was inadvertently administered by a neurologist; within two to three hours, severe cutaneous pruritus, a further cutaneous rash, and hyperthermia (38.3 ˚C) occurred. Two days later, hemoglobin fell to 6.7 g/100 mL and the leukocyte count to 2150/mm³. Prednisone was begun and continued for 11 days, with gradual improvement of the skin reaction and of the blood biochemical profile. After 20 days, the CD4/CD8 ratio in the peripheral blood was altered (0.8, normal 2.1 ± 1) due to raised concentrations of CD8+ cells (41.2%, normal 26 ± 6%).

The patient was discharged after 44 days with only small fissures present on the soles of his feet and no tender areas. The biochemical profile at discharge is reported in Table 1. No specific therapy for the lymphoma was undertaken. Fifty days after discharge, a further bone marrow biopsy showed an apparent increase of the lymphomatous infiltration with complete regression of the dyserythropoietic abnormalities. Nevertheless, the biochemical follow-up showed a total improvement of the hemoglobin values within four months and, after six months, hemoglobin was 14.2 g/dL; hemoglobin values are reported in Figure 3. Eight months after drug discontinuation, the

Table 1. Hematologic Laboratory Values

Variable (normal value)	3 Months Before	On Admission	On Hospital Day 11	On Discharge	6 Months After
Erythrocyte sedimentation rate mm/h (<20)		11	17	28	2
CRP mg/L (<6)		121		64	4.2
Fibrinogen g/dL 0.15–0.40		15.8	7.2	18.7	7.1
Hematocrit % (36–53)		32.4	20.3	22.4	41.7
Hemoglobin g/dL (12–17)	14.5	11	6.9	7.4	14.2
White cell count per mm³ (4300–10 000)	4100	5260	3050	3900	4450
Blood urea nitrogen mg/dL (7.8–21.8)	26.4	19.8	40.5	14.5	
Creatinine mg/dL (53–115) (0.60–1.30)	54.9		128.9	90	79.3
Bilirubin mg/dL (3.42–18.81) (0.2–1.1)	14	73.4	15	8.5	
Alkaline phosphatase units/L (30–130)		294			78
Aspartate aminotransferase units/L (8–50)		42	11	22	22
Alanine aminotransferase units/L (8–45)		88		27	16
γ-glutamyl-transferase units/L (<50)		751	199		39
Lactate dehydrogenase units/L (80–200)		262	178		154

CRP = C-reactive protein.

patient was asymptomatic and without signs of lymphadenopathy on physical examination. Peripheral blood cells count and hemoglobin concentrations were persistently normal. A bone marrow biopsy confirmed the diagnosis of low-grade non-Hodgkin's lymphoma and the absence of myelodysplastic changes.

Discussion

This case report describes a multisystemic reaction, characterized by generalized erythroderma and renal, hepatic, and bone marrow failure in a patient who had started carbamazepine 50 days beforehand. A positive provocation test strongly implicated carbamazepine as the causative agent of this multisystemic reaction.

Several dermatologic reactions have been associated with carbamazepine, occurring in about 4% of treated patients.[1,2] They generally occur within a few months of therapy (range 2–20 wk), as in our patient. Reactions include rashes with or without edema, whereas dermatomyositis, erythema multiforme, lichenoid eruptions, mycosis fungoide-like lesions, and Stevens–Johnson syndrome rarely occur. Frequently, these patients have been successfully treated with steroids after carbamazepine is discontinued and a complete recovery follows within three weeks. A hypersensitivity reaction to carbamazepine characterized by generalized erythroderma, leukemoid reaction, eosinophilia, hyponatremia, and renal failure was previously described by Ray-Chaudhuri et al.[3]

Carbamazepine is also known to determine a number of hematologic abnormalities including mild leukopenia, eosinophilia, thrombocytopenia, and, rarely, leukocytosis, agranulocytosis, or aplastic anemia.[4] Carbamazepine-induced leukopenia occurs in up to 10% of patients, usually within the first three months of treatment.[5] The reaction is mild and transient,[6] although a few cases (2%) of persistent neutropenia have been described.[4,5] In some patients, the reaction appears to be dose-related.[6] Younger patients have a lower prevalence of transient leukopenia (4%) than older patients.[4,6] Usually, after discontinuation of the drug, the white cell count returns to normal values within one week.[7] De Marco and Melchiori[8] studied 653 patients taking carbamazepine from four to 48 months and reported a 5% incidence of eosinophilia with normal leukocyte count. Eosinophilia during carbamazepine therapy generally occurs as part of a hypersensitivity reaction.[3] Mild anemia has also been reported in patients on long-term carbamazepine therapy.[9] Aplastic anemia or pure red cell aplasia has rarely been described during carbamazepine therapy,[10] but it occurs five to eight times more frequently in patients treated with carbamazepine than in the general population.[11] The pathophysiology of anticonvulsant-induced aplastic

Figure 1. Generalized erythroderma and skin exfoliation.

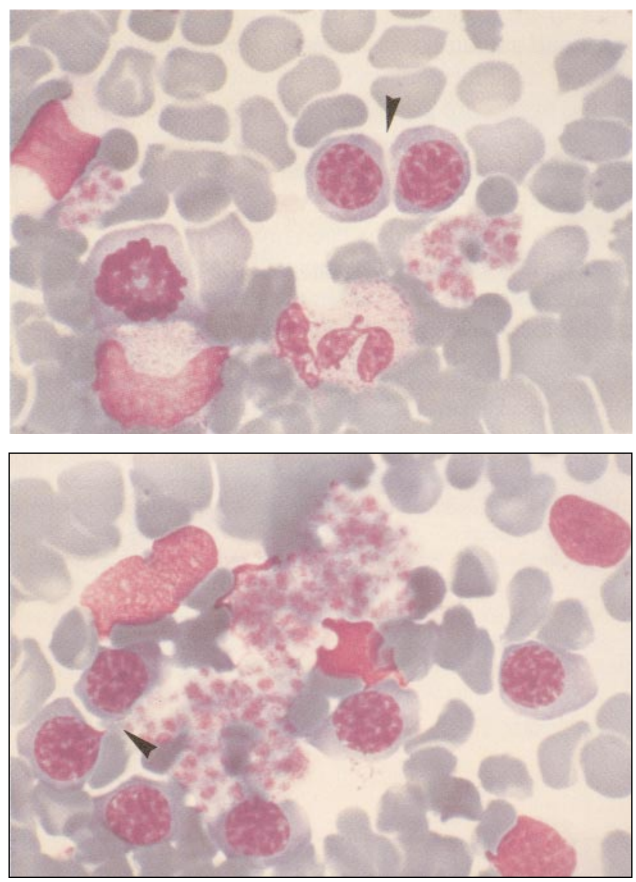

Figure 2. Peripheral blood smear showing dyserythropoietic abnormalities. A mitotic figure (top). Marked shift to the left in erythroid maturation and a nuclear bridge (bottom).

anemia remains obscure, although it has been attributed to oxidized metabolities of the drug.[12]

To our knowledge, this is the first report of carbamazepine-related anemia associated with bone marrow hypercellularity and dyserythropoietic changes instead of hypocellularity and reduction of erythroid precursors. Dyserythropoietic anemia is defined by ineffective erythropoiesis, intense bone marrow erythroid hyperplasia, and normal absolute reticulocyte counts. Reversible myelodysplastic changes are possible adverse effects of several drugs (e.g., isoniazid and other antituberculosis drugs, chloramphenicol, ethanol), but they have not been reported during treatment with anticonvulsants. Notably, hemoglobin concentrations spontaneously returned to normal after drug withdrawal (Figure 3), also excluding a possible role of the underlying non-Hodgkin's lymphoma in the development of anemia.

Hepatotoxicity is generally a mild, infrequent complication of carbamazepine therapy, whereas rare cases of serious reactions have been reported. The incidence of abnormal liver function tests (i.e., raised concentrations of transaminases) ranged from 2.4% to 8.3%[6,13] and was usually not meaningful from a clinical point of view. Nevertheless, several types of severe hepatic injury have been reported during carbamazepine treatment, including cholestatic jaundice, hepatic necrosis, and granulomatous hepatitis.[14,15] The reaction appears within the first month of therapy and improves with drug withdrawal. Soffer et al.[14] suggest two types of mechanisms: an idiosyncratic hypersensitivity type[16] and a toxin-induced reaction secondary to accumulation of toxic metabolites,[17] particularly when enzyme-inducing agents are given concurrently. Carbamazepine is structurally related to the tricyclic antidepressant imipramine, which has been an occasional cause of cholestatic liver injury.[18]

Acute renal failure has been reported[19] to occur in patients treated with carbamazepine; however, a direct relationship was not established in our patient, as prerenal failure due to hypovolemia probably occurred.

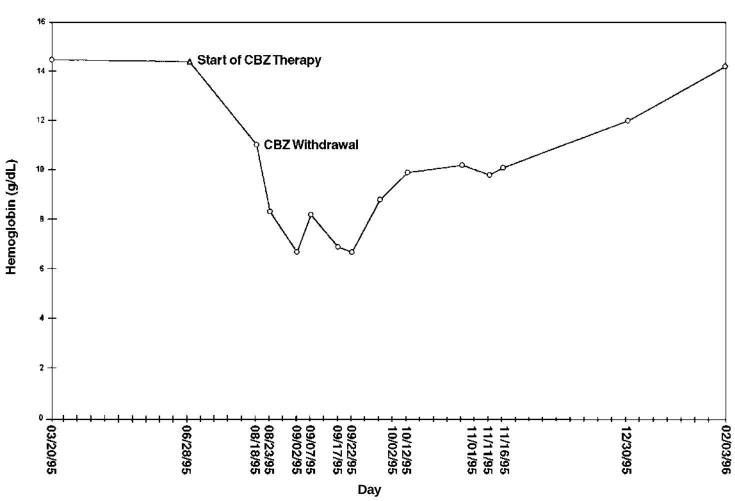

Figure 3. Follow-up hemoglobin value in a patient treated with carbamazepine.

Several immunologic alterations have been reported during carbamazepine treatment and are related to some extent to its adverse effects. The drug is known to induce disturbance of T cell subset distribution by stimulating a reversible proliferation and activation of the T suppressor cytotoxic cells. A blastogenic response to the drug has been described[20,21] in peripheral blood lymphocytes of patients with carbamazepine hypersensitivity, suggesting the presence of drug receptors on some T cells, the stimulation of which may lead to in vivo cell proliferation and activation. Indeed, in our patient we documented an inversion of peripheral blood CD4/CD8 ratio, mainly due to raised concentrations of T suppressor cells.

Carbamazepine might also induce a change in the membrane phenotype of a subset of autologous cells, leading to an autoimmune cytotoxic response. Whatever the underlying mechanism, the carbamazepine-induced immune dysregulation is thought to be caused by morphologic changes in the lymph nodes mimicking malignant lymphoma, or pseudolymphoma.[22,23] The latter has been associated not only with carbamazepine, but also with other anticonvulsants.[22] An interesting point raised by our observation is the possible relation between carbamazepine and actual lymphoproliferative disease. The development of non-Hodgkin's lymphoma following carbamazepine treatment has been reported, with regression after the drug was discontinued.[24] However, a cause–effect relationship has been questioned.[25] In our case, the presence of a low-grade small lymphocytic lymphoma was demonstrated by bone marrow morphology, immunophenotype, and molecular evidence of a B monoclonal population by polymerase chain reaction. As there was no baseline bone marrow examination, it is very difficult to speculate whether the lymphoma was induced by carbamazepine or if it was an underlying state. However, it should be stressed that a bone marrow biopsy repeated eight months after drug discontinuation (with persistent normalization of peripheral blood cell count and hemoglobin concentrations) confirmed the diagnosis of low-grade lymphoma. In this case, the persistent disease argues against a direct role of carbamazepine in the development of non-Hodgkin's lymphoma. On the other hand, it seems reasonable to postulate a role of the underlying lymphoproliferative disease in favoring the severe drug-induced reaction.

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EXTRACTO

OBJETIVO: Informar el caso de una reacción de hipersensitividad sistémica asociada al uso de carbamazepina.

RESUMEN DE CASO: Un hombre de 81 años de edad fue admitido a nuestro hospital con fiebre, erupción pruritica morbiliforme, e ictericia. Cincuenta días antes de la admisión había tomado carbamazepina 200 mg po tid para convulsiones. Durante los primeros días de la hospitalización, la erupción maculopapular progresó a una eritroderma generalizada con exfoliación extensiva de la piel. La fiebre desapareció 72 horas después de descontinuar la carbamazepina y las pruebas de función hepática regresaron a los límites normales en cuatro días. Después de la admisión los niveles de hemoglobina disminuyeron gradualmente a 6.7 g/100 mL. La aspiracón de médula ósea realizada reveló hipercelularidad con anormalidades discritropoyéticas marcadas y una biopsia de médula demostró infiltración amplia y difusa causada por la presencia de un linfoma linfocitico pequeño de grado bajo. No se instrumento ninguna terapia específica para el linfoma. El seguimiento bioquimico demostró mejoría total de los valores de hemoglobina. Ocho meses después de descontinuar el medicamento, el paciente estaba asintomático y el recuento de células sanguíneas periferales y los niveles de hemoglobina permanecían normales

DISCUSIÓN: A nuestro saber, este es el primer informe de caso reportado en el que la carbamazepina está implicada como causa de anemia con hipercelularidad de la médula ósea y de cambios diseritropoyéticos, en lugar de hipocelularidad, y reducción de los precursores entroideos. Nuestra observación trajo un punto de interés en la posible relación entre la ingestión de carbamazepina y a una enfermedad linfoproliferativa real. Se ha reportado previamente, el desarrollo de un linfoma de no Hodgkin después de un tratamiento con carbamazepina y la regresión después de descontinuarse el medicamento. Sin embargo, en nuestro caso una biopsia de médula realizada ocho meses después de descontinuar el medicamento confirmó el diagnostico de un linfoma de menor grado.

CONCLUSIONES: Este reporte de caso describe una reacción multisistémica severa, caracterizada por eritroderma generalizada, disfunción renal, hepática y de médula en un paciente en terapia con carbamazepina durante cincuenta días.

RAFAELA MENA DE GIRALDI

RÉSUMÉ

OBJECTIF: Présenter un cas de réaction d'hypersensibilité multisystémique à la carbamazépine.

RÉSUMÉ DU CAS: Un homme de 81 ans a été admis à l'hôpital en raison d'une fièvre, d'une éruption cutanée prurigineuse morbilliforme et d'une jaunisse. Cinquante jours avant son admission, le patient a débuté de la carbamazépine 200 mg po tid pour le traitement de convulsions. Dans les premiers jours de l'hospitalisation, le rash maculopapulaire a progressé vers une érythrodermie généralisée et par la suite, vers une exfoliation cutanée étendue. Après l'arrêt de la carbamazépine, la fièvre a disparu en 72 heures et les tests de la fonction hépatique sont retournés dans les limites normales en quatre jours. De plus, après l'admission à l'hôpital, les valeurs d'hémoglobine ont chuté à 6.7 g/100 mL. Une ponction de moelle a démontré une hypercellularité avec des anomalies dysérythropoiétiques et la biopsie de moelle a démontré une infiltration diffuse par un lymphome lymphocytaire. Aucun traitement n'a été amorcé pour ce lymphome. Le suivi des paramètres biochimiques a démontré une normalisation complète de l'hémoglobine. Huit mois après l'arrêt du médicament, le patient demeurait symptomatique, et les paramètres hématologiques demeuraient normaux.

DISCUSSION: Au meilleur de notre connaissance, ceci est le premier cas publié d'anémie impliquant la carbamazépine et associé à une hypercellularité cellulaire et à des modifications dysérythropoiétiques par opposition à une dépression des précurseurs des érythrocytes et une hypocellularité. Une particularité de ce cas est la possible association entre la carbamazépine et une maladie lymphoproliférative. Le développement d'un lymphome non-hodgkinien, réversible à l'arrêt du médicament, a été décrit avec la carbamazépine. Cependant, dans ce cas, la biopsie de moelle réalisée huit mois après l'arrêt de la carbamazépine, a confirmé le diagnostic de lymphome.

CONCLUSIONS: Ce cas décrit une réaction multisystémique sévère caractérisée par une érythrodermie généralisée, une insuffisance rénale et hépatique, et une dépression de la moelle chez un patient ayatn débuté un traitement à la carbamazépine 50 jours auparavant.

MARC PARENT