Anticonvulsant hypersensitivity syndrome (DRESS syndrome): report of 4 cases

Sabrina Meik[1], Mariana Arias[2], Laura Fernández Mego[2], María Carolina López Santoro[2], Alejandra Abeldaño[3], Graciela Pellerano[4]

ABSTRACT

Anticonvulsant hypersensitivity syndrome is a rare and potentially fatal reaction characterized by fever, skin rash and internal organ involvement. Phenytoin, phenobarbital and carbamazepine are the most frequent aromatic anticonvulsivant drugs causing the reaction.

We report 4 adult patients, 2 males and 2 females, between 20 and 42 years old with clinical, laboratorial and histopathological findings consistent with anticonvulsant hypersensitivity syndrome started 4 and 8 weeks after the administration of the drug. The causative drugs were phenytoin, carbamazepine and the association of valproic acid and lamotrigine (Dermatol Argent 2010;16(4):272-277).

Keywords:

DRESS (Drug Rash with Eosinophilia and Systemic Symptoms), Anticonvulsant hypersensitivity syndrome.

Date Received: 6/3/2010 | **Date accepted:** 25/3/2010

Introduction

The anticonvulsant hypersensitivity syndrome (AHS) is a rare and severe syndrome characterized by skin lesions, fever, lymphadenopathy, eosinophilia and systemic symptoms , occurring between 1 and 8 weeks after administration of the antiepileptic. Its incidence is approximately of 1 in 1,000 to 1 in 10,000 patients exposed to an anticonvulsant drugs.[1,2] The mortality rate is about 10%.[3]

Bocquet et al.,[4] used in 1996 the acronym DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) to redefine the term drug hypersensitivity syndrome. The aromatic anticonvulsants such as diphenylhydantoin, phenobarbital and carbamazepine are most commonly involved in these reactions.1

We report 4 cases, 2 male and 2 female, of 20 to 42 years old, who presented an hypersensitivity syndrome secondary to anticonvulsant drugs which started after 4 to 8 weeks of drug administration. The causative drugs were diphenylhydantoin, carbamazepine and the association of valproic acid and lamotrigine.

[1] Resident physician. Participant of the SAD specialization career.

[2] Dermatologist.

[3] Section Chief of Photomedicine.

[4] Head of Dermatology Unit.

Acute General Hospital Dr. Cosme Argerich

Correspondent author: Dr. Sabrina Meik. Luis M. Fields 501 9, CABA, Argentina. Tel: 15-60939818

e-mail: sabrinameik@hotmail.com

TABLE 1. Clinical findings

Patient	Sex/Age	Associated anticonvulsants / Weeks from the beginning of the drug administration and HAS	Cutaneous manifestations	Systemic Manifestations
1	M/22	Difenilhidantoine 4 weeks	Scarlatiniform rash. Pustules on face and upper trunk. Facial edema.	Fever. Leukocytosis-eosinophilia Polyadenopathies. Hepatitis (elevated transaminases x 25-30). Alteration of coagulogram
2	M/42	Carbamazepine 6 weeks	Scarlatiniform rash. Pustules on chin and trunk. Facial edema. Violaceous macules in soles and palms. Commitment of hard palate (vesicles over an erythematous base).	Fever. Leukocytosis-eosinophilia Polyadenopathies. Hepatic compromise (hepatomegaly, slight increase of FAL and bilirubin).
3	F/22	Difenilhidantoine 6 weeks - worse when rotate by lamotrigine	Morbilliform papular rash with some bulls-eye lesions. Follicular papules. Facial and lip edema. Violaceous macules in soles and palms.	Fever. Lymphocytosis-eosinophilia Polyadenopathies. Hepatic compromise (increased transaminases, FAL and hyperbilirubinemia).
4	F/20	Valproic acid + lamotrigine 4 weeks	Erytropigmentated lichenified Rash. Follicular papules in limbs.	Fever. Leukocytosis-eosinophilia Hepatic compromise (increased transaminases and FAL).

Clinical cases

Between September 2007 and November 2008 four cases of AHS were diagnosed. Table 1 summarizes the clinical data of patients.

Case 1

Male patient aged 22 years, followed up by the Department of Neurology because of tonic-clonic seizures, under treatment for 1 month with phenytoin. He consulted our department for presenting a maculopapular rash of 4 days of evolution associated with fever and fatigue.

Physical examination: erythematous papules forming AGMIN plaques in face, trunk and limbs. Cervical axillary and inguinal adenopathies.

Complementary studies:

- Laboratory (positive data), leukocytosis (WBC 51,690 cells/mm3), eosinophils (47%), increased transaminases (GOT 849 IU/l, GPT 1123 IU/l), FAL 934 IU/l, hypoalbuminemia (2,7 g/dl), hypocholesterolemia (83 mg/dl), LDH 1507 U/l and alteration of coagulation (PT 60%, KPTT 60 sec).
- Serology HIV, HBV and HCV non-reactive.
- CT and MRI of the brain: parenchymal lesions are not observed.
- Blood cultures and urine cultures: negative.
- Skin biopsy: folliculitis and perifolliculitis suppurative. Dermal infiltrate of lymphocytes and eosinophils.

The patient evolved with a poor general condition, progression of cutaneous involvement to an erythemato-violaceous rash that spread to nearly all the integument. Pustules predominantly on upper body, meliceric scabs in beard and ear and significant facial edema **(Photos 1 and 2)**.

With a history of ingestion of anticonvulsant, the clinical conditions and histopathology data, the patient was diagnosed HAS. Medication was discontinued, and it was started treatment with meprednisona at 40 mg/day, antihistamines, vitamin K subcutaneously, ranitidine and cephalothin IV (10 days).

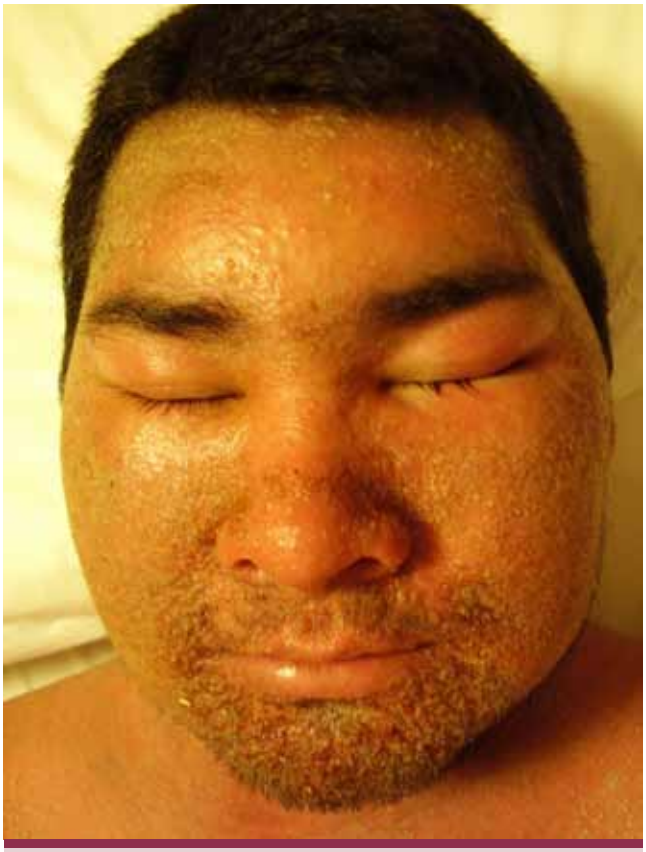

PHOTO 5. Histopathology structures inside the parasite.

After 12 days of treatment only a mild erythema was evident in the lower limbs with desquamation on the rest of the integument, improvement of general condition and normalization of laboratory parameters, so began the gradual decline of glucocorticoids until complete suspension.

Case 2

42-year-old male patient, who was hospitalized in Medical Services Clinic by rash of 10 days duration associated with fever and polyadenopathies.

Personal history: hypertension, drug addiction (heroin) and alcohol, hemorrhagic stroke with right paresis faciobraquiocrural. Polymedicated with clonazepam, paroxetine, enalapril, nimodipine, ranitidine, hydrochlorothiazide, and carbamazepine. The latter drug was initiated 6 weeks before the beginning of symptoms.

Physical examination: generalized erythemato-violaceous papular rash that leaves areas of healthy skin. Significant facial edema. Serous oozing blisters on upper limbs. Pustules located in the beard region and trunk **(Photo 3)**. Violaceous macules in support areas of soles. Commitment to hard palate with vesicles over an erythematous base. Hepatosplenomegaly. Generalized polyadenopathies.

Complementary studies:

- Laboratory (positive data), leukocytosis (WBC 31,600 cells/mm3), eosinophilia (8%), increased GPT (62 IU/l) and FAL (385 IU/l) and hypoalbuminemia (2.7 g/dl).
- Serology HIV, HBV and HCV non-reactive.
- Blood cultures and urine cultures: negative.
- Skin biopsies:
  - Erythema multiforme pharmacology (upper limb vasicle).
  - Spongiotic subacute dermatitis psoriasiform type (rash on the trunk).

Carbamazepine was discontinued and supportive measures were taken, with good results.

Case 3

22 year-old female patient. Consulted our service due to rash of 10 days duration associated with fever and diarrhea. She was diagnosed epilepsy 2 months before, which is why she was treated with diphenylhydantoin.

Personal history: lumbosacral myelomeningocele, recurrent urinary tract infections, bilateral hydronephrosis, neurogenic bladder, chronic renal failure on hemodialysis three times a week, parathyroidectomy for secondary hyperparathyroidism, epilepsy (newly diagnosed).

Physical examination: generalized papular morbilliform rash, some bull's eye lesions. Follicular erythematous papules of 1-2 mm. Facial and labial edema with desquamation. Violaceous macules on palms and soles **(Photo 4)**. Cervical and axillar adenopathies.

Complementary studies:

- Laboratory (positive data), anemia (Hto 28%), urea 126 mg/dl, leukocytosis (WBC 19,600 cells/mm3), eosinophilia (13.8%), lymphocytosis (42.9%), elevated transaminases (GOT 72 IU/l, GPT 56 IU/l), FAL 721 IU/l, total bilirubin 2.06 mg/dl and LDH 2,020 IU/l.

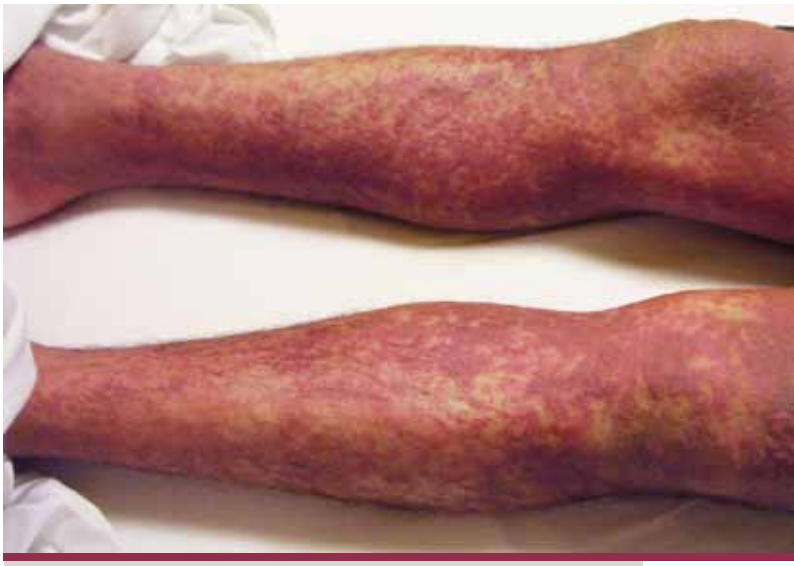

PHOTO 2. Case 1. Erythemato-violaceous rash on lower limbs.

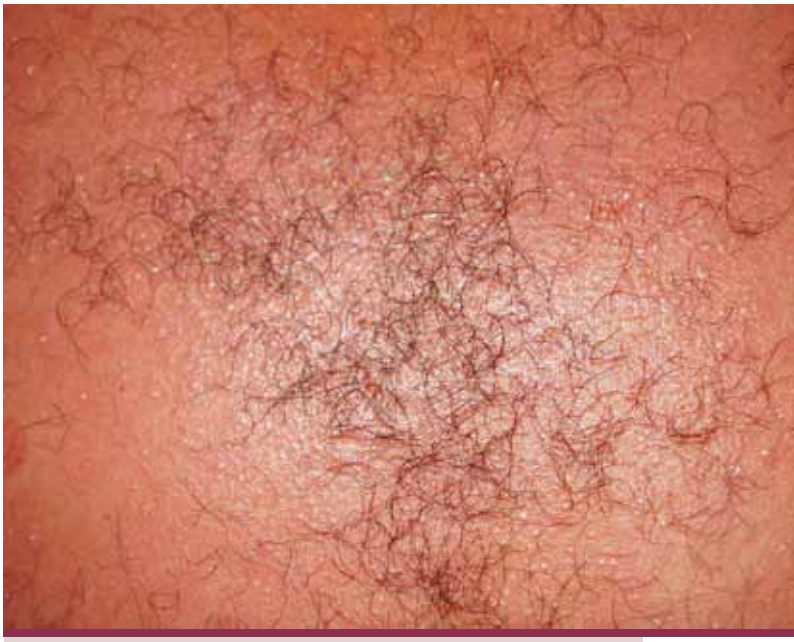

PHOTO 3. Case 2. Multiple pustules over an erythematous base.

- Serology HIV, HBV and HCV non-reactive.
- Blood cultures: negative.
- Skin biopsy compatible with farmacodermia.

It was decided the hospitalization and assessment by the Department of Neurology. Diphenylhydantoin was discontinued and lamotrigine started. Patient evolutioned unfavorably with clinical and laboratory deterioration. Lamotrigine was then discontinued and switched to phenobarbital. Measurements of support were made and the patient was administrated meprednisona 40 mg/day, with good clinical outcome and complete resolution.

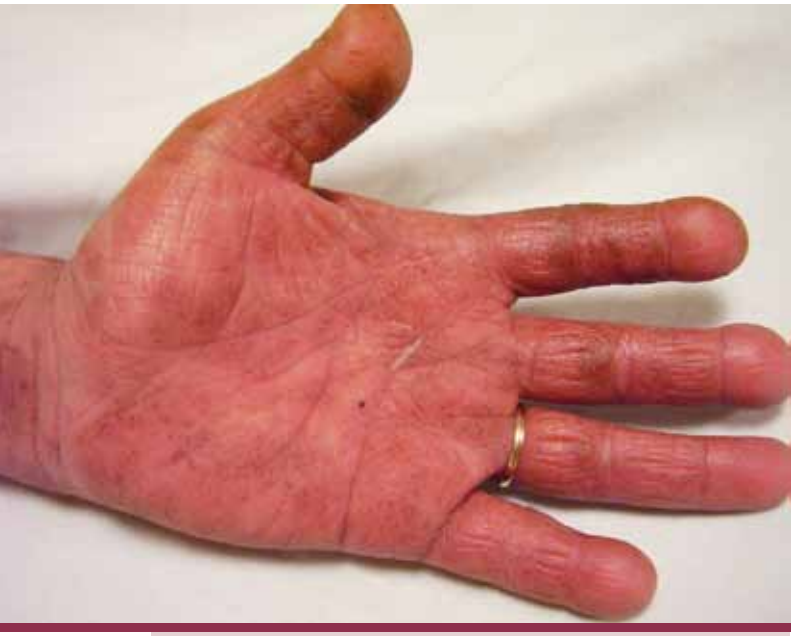

PHOTO 5. Histopathology structures inside the parasite.

Case 4

Female patient aged 20 years. She had a personal history, diagnosed epilepsy 3 months before, for which she began treatment with valproic acid and lamotrigine. After 4 weeks of initiation she developed skin lesions, with a regular general status and fever, so treatment was suspended. After 2 months consulted our department due to the persistence of pruritic skin lesions.

Physical examination: generalized cutaneous commitment with erythematous rash, pigmented and lichenified **(Photo 5)**. Follicular erythematous papules on limbs.

Complementary studies:

- Laboratory: leukocytosis (WBC 11,300 cells/mm^3), eosinophilia (8.9%), increased transaminases (GOT 54 IU / l, GPT 177 IU / l) and FAL 526 IU / l.
- Skin biopsy: subacute spongiotic dermatitis. With a history of ingestion of anticonvulsant and clinical manifestations it was interpreted as persistent HAS. Meprednisona was started at 40 mg/day and gradual decline, with complete resolution of skin lesions and normalization of laboratory results after a month of treatment. Endocrinological evaluation confirmed secondary adrenal insufficiency, for which we had to continue with hydrocortisone VO.

Discussion

Cutaneous adverse drug reactions are common and affect approximately 2-3% of hospitalized patients. Fortunately, only about 2% of them are severe, and very few are fatal.[5]

Of all the drugs, the most frequently associated to DRESS syndrome are antibiotics (41%), mainly penicillin derivates and sulfonamides derivatives and in some cases, minocycline and anti-inflammatories (11%) and anticonvulsants (10%).[6] It has also been described the association with other drugs such as allopurinol, gold salts, and dapsone.[7]

TABLE 2. Classification ofanticonvulsants

Aromatic 1st generation	Diphenylhydantoin, phenobarbital,ethosuximide, primidone.
Aromatic 2 nd generation	Carbamazepine, benzodiazepines, oxcarbazepine.
Non-aromatic	Valproic acid
New aromatic	Lamotrigine, topiramate, felbamate
New non-aromatic	Gabapentin, vigabatrin

Anti-epileptic drugs can be classified **(Table 2)** in aromatic of first generation, of second generation, new aromatic, non-aromatic and new non-aromatic.[6] It has been reported rate of cross-reactivity between them about 70%.[8]

Clinically, HAS is mainly characterized by severe skin condition, fever, lymphadenopathy, eosinophilia and internal organ involvement. Fever is present in 90-100% of patients and it usually precedes rash by several days. Localized or generalized lymphadenopathy has an incidence of 70%. The cutaneous involvement is found in approximately 90% of cases.[2] It usually appears as an erythematous eruption, papular and pruritic affecting face and trunk, and later the extremities.[2] Although rare, pustules are one possible form of presentation,[9] as well as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).[10] In 25% of cases there is periorbital facial edema,[2] finding presented in 3 of our 4 patients.

In relation to systemic involvement, the internal organ most frequently affected is the liver (50-60%). Liver disease can range from an elevation of transaminase levels to fulminant hepatic necrosis.[1] All our patients had liver commitment with elevated transaminases which in the first case was of 25 to 30 times above its normal value associated with coagulation disorders. The kidney is the second most affected organ presenting either nephritis, vasculitis or renal failure. Hematological alterations as leukocytosis with eosinophilia and atypical lymphocytosis are described in 50% of cases; it can also be found agranulocytosis, aplastic or hemolytic anemia and/or thrombocytopenia. Other possible manifestations are ulcerations in the mucosa, carditis, pneumonitis, pancreatitis, conjunctivitis and pharyngitis (10%), splenomegaly, arthralgia and myalgia.[1,2, 9-11] Commitment of the thyroid gland occurs late with hypothyroidism 3 months after initiation of the reaction, although is usually transient and disappears in most patients within 12 to 18 months.[1]

The proposed diagnostic criteria for hypersensitivity syndrome or DRESS are as follows: 11

1. Presence of drug rash;
2. Hematologic abnormalities:
   a. Increased eosinophils 1.5 per 109/L
   b. Presence of atypical lymphocytes;
3. Systemic involvement:
   a. Adenopathies larger than 2 cm in diameter or hepatitis (transaminases greater than 2 times normal values).
   b. Interstitial nephritis
   c. Interstitial pneumonitis
   d. Carditis

Classically, it appears from 1 to 8 weeks after starting the antiepileptic therapy. Re-exposure to the anticonvulsant generates rapid and severe recurrence of all symptoms, which justifies the banning of the drug for life.[1,2]

Although in most cases, resolution occurs in weeks, there are described cases of prolonged course of several months[12], as we observed in our fourth patient. A minority of patients continues to present non-specific rash and general malaise for one year after the initial reaction. These patients are at risk of subsequently developing autoimmune diseases.[13]

Diagnosis is made by a history of intake of such drugs, compatible clinical manifestations, complementary laboratory tests and the histopathological study.[11]

Differential diagnosis includes other cutaneous drug reactions, acute infections (streptococcus, Epstein Barr virus, hepatitis A and B, etc.), lymphoma or pseudolymphoma and reaction similar to serum sickness.[2]

Treatment in the acute stage is the suspension of all potentially causative drugs and administration of systemic corticosteroids at doses of 0.5 to 1 mg/kg/day, especially when presented with visceral manifestations that threaten the patient's life.[14] After evaluating the possible therapeutic alternatives, it is imperative to keep in mind the high rate of cross-reactivity between aromatic anticonvulsants. Although there are secondary cases to lamotrigine there is no evidence of cross-reactivity between this drug and the aromatic anticonvulsants, but in our third case this substitution resulted in worsening of the picture. Valproic acid appears to be a safe alternative in the election of a new and anticonvulsant as well as gabapentin, topiramate or vigabatrin.[1,15]

Other treatments are given IV immunoglobulin and plasmapheresis.[16]

Conclusion

It is important to emphasize the role of the dermatologist in the early detection of these cases, which are potentially fatal, since the cutaneous involvement is an important early semiotic element in this type of pathology.

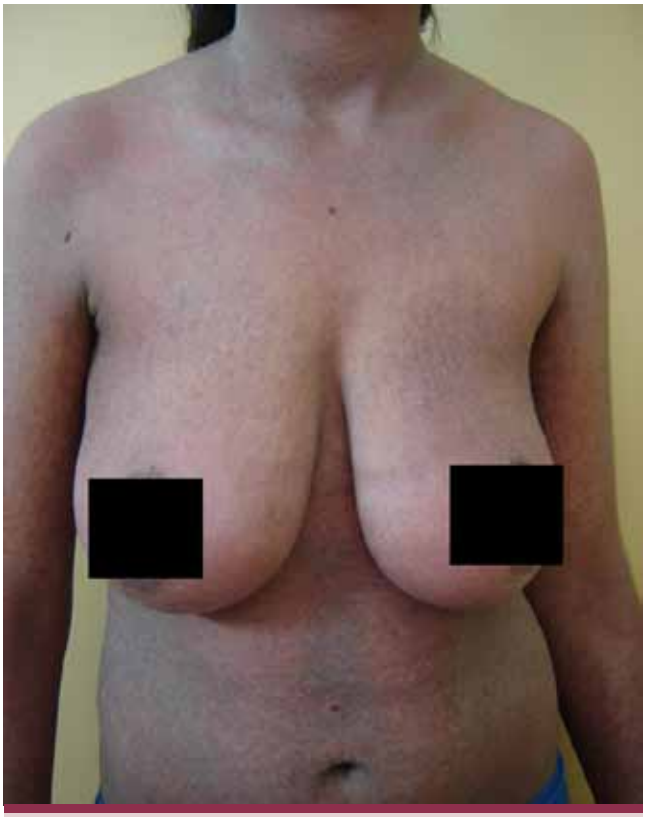

PHOTO 5. Histopathology structures inside the parasite.

References

1. Allende Bandrés MA, Izuel Rami M, Uribeta Sanz E, Villar Fernández I, et al. Cross hypersensitivity syndrome between antiepileptic drugs: report of a case. Farm Hosp 2004;28:56-58.
2. Kaminsky A, Moreno M, Díaz M, Charas V, et al. Anticonvulsant hypersensitivity syndrome. Int J Dermatol 2005;44:594-598.
3. Allam JP, Paus T, Reichel C, Bieber T, et al. DRESS syndrome associated with carbamazepine and phenytoin. Eur J Dermatol 2004;14:339-342.
4. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rush with Eosinophilia and Systemic Symptoms: DRESS). Semin Cutan Med Surg 1996;15:250-257.
5. Wolf R, Orion E, Marcos B, Matz H. Life-threatening acute adverse cutaneous drug reactions. Clin Dermatol 2005;23:171-181.
6. Aldama AB, Gorostiaga G, Rivelli V. Reacciones cutáneas por anticonvulsivantes. Espectro clínico de 39 casos. Act Terap Dermatol 2005;28:164-168.
7. Revuz J, Valeyrie-Allanore L. Reacciones medicamentosas. En: Bolognia J, Jorizzo J, Rapini R. Dermatología, versión en español de 1ra edición en inglés. Editorial Elsevier, Madrid; 2004:333-353.
8. Shear NH. Defining the drug hypersensitivity syndrome: pharmacological basis. En: Dyall-Smith D, Marks R. Dermatology at

the Milennium (800), New York: Parthenon 1999:394-395.
9. Kleier RS, Breneman DL, Boiko S. Generalized pustulation as a manifestation of the anticonvulsant hypersensitivity syndrome. Arch Dermatol. 1991;127:1361-1364.
10. Petkov T, Pehlivanov G, Grozdev I, Kanaklieva S, et al. Toxic epidermal necrolysis as a dermatological manifestation of drug hypersensitivity syndrome. Eur J Dermatol 2007;17:422-427.
11. Estrella V, Baroni E, Leroux MB, Sánchez A y cols. Síndrome de hipersensibilidad a anticonvulsivantes (SHA). Rev Argent Dermatol 2007;88:46-54.
12. Harman KE, Morris SD, Higgins EM. Persistent anticonvulsant hypersensitivity syndrome responding to ciclosporin. Clin Exp Dermatol 2003;28:364-365.
13. Moreno M, Díaz M, Dancziger E, Kaminsky A. Síndrome de hipersensibilidad. Dermatol Perú 2004;14:44-51.
14. Ghislain PD, Roujeau JC. Treatment of severe drug reactions: Stevens-Johnson syndrome, toxic epidermal necrolysis and hypersensitivity syndrome. Dermatol Online J 2002;8:5.
15. Galindo PA, Borja J, Gómez E, Mur P , et al. Anticonvulsant drug hypersensitivity. J Investig Allergol Clin Inmunol 2002;12:299-304.
16. Mostella J, Pieroni R, Jones R, Finch CK. Anticonvulsant hypersensitivity syndrome: treatment with corticosteroids and intravenous immunoglobulin. South Med J 2004;97:319-321.