

No statistical differences were found in serum VEGF levels between the other angiosarcoma patients (cases 3–11) in whom the *p53* gene point mutation was not detected; these patients include those without metastasis ($153 \pm 70 \text{ pg ml}^{-1}$, range 65–223, $n=4$), those with metastasis to parotid lymph nodes ($166 \pm 70 \text{ pg ml}^{-1}$, range 62–244, $n=6$), and those with remote metastasis ($119 \pm 101 \text{ pg ml}^{-1}$, range 7–269, $n=7$) (Fig. 1).

Because of serious heart failure, the patient who had detectable *p53* gene point mutation (case 1) was treated with local radiation therapy alone. The other patients were treated with surgery, radiation therapy, local or systemic administration of recombinant interleukin-2 (IL-2), and immunotherapy using IL-2 and IL-2-activated lymphocytes. The effect of these treatments may have contributed to the serum VEGF levels. Therefore, serum VEGF levels may not be correlated with clinical course in most cases of angiosarcomas without *p53* gene mutation.

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Generalized Pustulosis and Severe Tubulointerstitial Nephropathy as Manifestations of Carbamazepine Hypersensitivity Syndrome

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Sir,

Anticonvulsant hypersensitivity syndrome (AHS) is a multisystemic disorder with cutaneous changes and typical blood abnormalities that may be triggered by any of the aromatic antiepileptic drugs (1, 2). We present the case of a patient who, following carbamazepine treatment, developed AHS with major cutaneous and systemic manifestations that are not common in the context of this syndrome.

CASE REPORT

A 26-year-old woman was referred to our department for evaluation of a 10-day history of malaise, fever of up to 40°C and a generalized exanthem. The patient had been on carbamazepine therapy (400 mg daily) for 1 month because of temporal epileptic seizures. She reported no previous history of drug allergies.

Examination revealed a red-violet exanthem involving the trunk, extremities, palms and soles; the face was

severely affected, accompanied by mild oedema. A large number of pinhead-sized pustules were observed on her face and upper back with an intensely erythematous skin (Fig. 1). A biopsy taken from these pustular lesions revealed follicular and non-follicular intraepidermic spongiform pustules, with a perivascular infiltration of lymph cells and eosinophils in the upper dermis. Vasculitis was absent. These histological changes were consistent with an acute generalized exanthematous pustulosis.

Systemic examination revealed a deteriorated overall condition of the patient, fever, hepatomegaly and swollen bilateral inguinal lymph nodes. The first laboratory tests disclosed eosinophilia (13.5%) and elevated liver function tests: aspartate aminotransferase 63 U/l (0–37 U/l), alanine aminotransferase 262 U/l (0–40 U/l) and gamma glutamyltranspeptidase 335 U/l (11–49 U/l).

In view of the clinical and histological changes, we considered the case to be related to carbamazepine, so



Fig. 1. Mild facial oedema with pustules, erythema and desquamation.

the treatment was discontinued and the patient was admitted for observation. The disease did not evolve favourably, renal impairment developing into severe renal failure within a few days: creatinine 12.1 mg/dl (0.7–1.4 mg/dl) and urea 121 mg/dl (18–38 mg/dl). Urinalysis showed proteinuria (100 mg/dl), leucocyturia and microhematuria. Serologic tests for ANA, antiDNA and ANCA antibodies were all negative. A renal biopsy disclosed an acute tubulointerstitial nephritis with no involvement of glomeruli or vascular structures, and with no immune deposits on direct immuno-fluorescence. Therapy with oral prednisone followed by intravenous methylprednisolone was administered, but oliguric renal failure was severe enough to require hemodialysis. Renal function gradually improved, allowing discontinuation of dialysis treatment. Her recovery was complete 4 weeks later.

The liver and cutaneous symptoms resolved more satisfactorily, with complete remission 10 days after admission. Nevertheless, the patient developed a widespread exfoliation in the final stage of the cutaneous disease, and numerous micropurpuric lesions on her fingertips. A biopsy specimen taken from these micropurpuric lesions revealed non-specific perivascular dermatitis with no deposits on direct immuno-fluorescence. These non-specific lesions spontaneously faded and the

patient was finally discharged from hospital 30 days after admission.

Once completely recovered, the patient was patch-tested with carbamazepine 0.1%, 1% and 10% in petrolatum, showing positive results. Seven months later, she developed a morbiliform exanthem after 4 weeks of treatment with phenytoin, but on this occasion the eruption disappeared with no systemic involvement after withdrawal of the drug.

DISCUSSION

Differential diagnosis of generalized pustular eruptions in adults includes subcorneal pustular dermatosis, eosinophilic pustular folliculitis, pustular psoriasis and acute generalized exanthematous pustulosis, among others.

AHS is one of the adverse effects of aromatic antiepileptic drugs such as phenytoin, carbamazepine, phenobarbital and primidone. Most cases have been related to phenytoin and carbamazepine because they are more widely used (1, 2). The true incidence of this syndrome is not well established because of the lack of reliable diagnostic criteria. Nevertheless, among patients on carbamazepine treatment the incidence may range from 1:1000 to 1:10000.

Although the pathogenesis is not well understood, the most accepted hypotheses suggest the inability of these patients to detoxify certain oxides, which are formed from the metabolism of anticonvulsants. Constitutional factors, HHV-6 infection and a specific T-cell response, are also being discussed as possible pathogenic mechanisms (3).

AHS clinical manifestations usually start 2 to 8 weeks after the initiation of anticonvulsant therapy and consist of fever, skin rash, lymphadenopathy, hepatopathy and eosinophilia (4, 5). Cutaneous changes are present in up to 87% of the patients with AHS, and usually consist of a morbiliform exanthem, although some cases of exanthematous pustulosis have been reported (1, 4). Fever is the most common systemic complaint and the liver is the internal organ most frequently affected in this syndrome, with an incidence of 100% and 51%, respectively. Hepatic changes range from transitory high transaminase levels to fulminant hepatic failure. This patient showed the mildest form of liver impairment. Renal involvement is not common, but when it is present a prerenal failure secondary to hypovolaemia is the most frequent clinical feature. Our patient developed severe parenchymatous renal failure which, although not common, has been described in isolated cases of AHS (1, 2, 6).

Treatment consists of discontinuing the suspected drug, regulation of nutritional and fluid imbalance and the management of possible complications, which in this patient even required haemodialysis. Unlike our case, the prognosis is good for most patients, with

spontaneous healing a few weeks after withdrawal of the drug (1, 2).

An essential issue to take into account in these patients is the high prevalence of cross-reactivity between the different aromatic anticonvulsants, which in some reports is up to 80% and makes the choice of an alternative drug for these patients difficult. Although valproic acid, lamotrigine and vigabatrine are considered the safest antiepileptic drugs for these patients, some cases of hypersensitivity anticonvulsant syndrome have been reported to be triggered by them (1, 2).

In conclusion, we present an extremely unusual case of AHS, since both pustular exanthem and severe tubulointerstitial nephropathy are exceptional in the context of this syndrome, especially if we consider their combined appearance.

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A Four-Year History of Pruriginous Erythroderma Leading to the Diagnosis of Idiopathic Hypereosinophilic Syndrome

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Sir,

Idiopathic hypereosinophilic syndrome (IHS) is characterized by persistent eosinophilia (above $1.5 \times 10^9/l$ for more than 6 months) of unknown origin in association with dysfunction of one or more organs due to tissue infiltration by eosinophils (1). Cutaneous, cardiac, neurologic and/or pulmonary manifestations are often observed. Among the skin lesions, erythroderma is a rare complication of IHS and has only been reported in a few cases (2–6).

CASE REPORT

In December 1994, a 67-year-old man with no history of atopy or current medication was referred due to severely itching erythroderma of a few weeks' duration (Fig. 1), small bullae on the upper limbs (Fig. 2), a palmo-plantar keratoderma and slight edema of the skin. White cell count was $12.2 \times 10^9/l$ with 9% eosinophils ($1.1 \times 10^9/l$, normal range 0–0.5). A skin biopsy showed non-specific, mild vasculitis with eosinophils. Topical treatment was not sufficiently effective but prednisone (1 mg/kg daily) relieved the skin lesions and pruritus, with normalization of blood eosinophilia. Between April 1996 and March 1997 the patient's symptoms relapsed, with blood eosinophilia ranging between $1.5 \times 10^9/l$ and $4.0 \times 10^9/l$. Short courses of prednisone temporarily improved the skin lesions.

In June 1997 the patient was admitted to our



Fig. 1. Erythroderma with papulous and eczematous lesions. In 1942 the patient had a plate in his right femur following a fracture. Removal of the plate did not improve his skin condition.