



## CASE AND RESEARCH LETTERS

### Granuloma Annulare Possibly Secondary to Oral Treatment With Topiramate<sup>☆</sup>



### Granuloma anular posiblemente secundario a la ingesta de topiramato

To the Editor:

Granuloma annulare (GA) is a benign and typically self-limiting granulomatous disease of unknown etiology; it tends to resolve spontaneously over a period of months or years. It usually presents with annular lesions on the hands, upper limbs, trunk, or lower limbs; facial involvement is rare. It is associated with diabetes mellitus, paraneoplastic disorders, thyroid disturbances, and some drugs.<sup>1</sup>

A woman aged 38 years, with a personal history of an eating disorder for which she had been on treatment with topiramate for several months, was seen in dermatology outpatients for slightly pruritic lesions that had arisen on the dorsum of both her hands some months earlier. On physical examination, confluent papules with an annular morphology were observed on the dorsum of the fingers of both hands and over the metacarpophalangeal joints of the left hand (Figs. 1 and 2). Histology revealed focal degeneration of collagen and elastic fibers, mucin deposits, and a perivascular and interstitial lymphohistiocytic infiltrate in the upper and mid dermis, confirming the diagnosis of GA (Fig. 3). There were no significant findings in the blood tests requested. The patient was initially treated with topical tacrolimus and corticosteroids, and subsequently with oral corticosteroid therapy, with no improvement. On reviewing her medical history, we observed a chronological relationship between the introduction of topiramate and the appearance of the GA lesions. With a suspicion of GA secondary to topiramate, we decided, with the consent of the psychiatry department, to withdraw the drug, and this led to complete resolution of the lesions within a month.

Four types of drug-induced granulomatous dermatitis have been identified: interstitial granulomatous dermatitis, exacerbation of rheumatoid nodules secondary to



**Figure 1** Granuloma annulare over the metacarpophalangeal joint of the left hand.



**Figure 2** Granuloma annulare on the dorsum of the phalanges of the right hand.

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methotrexate, drug-induced sarcoidosis, and drug-induced GA.

The first case of drug-induced GA, published in 1980, was associated with gold salts for the treatment of juvenile arthritis.<sup>4</sup> Other cases have been reported since that

**Table 1** Cases of Topiramate-Induced Granuloma Annulare.

	Age	Sex	Latency Period Until the Appearance of GA	Latency Period Until the Disappearance of GA	Site
Cassone G et al. <sup>1</sup>	50	Female	1 mo	2 wk	Left lower limb
Lagier L et al. <sup>2</sup>	44	Female	3 mo	2 wk	Dorsum of the feet Lower limbs
Ruzzetti F et al. <sup>3</sup>	29	Female	6 y	2 wk	Dorsum of the hands Lower limbs
Heras S et al.	38	Female	2 mo	1 mo	Dorsum of the feet Dorsum of the hands

time, mainly involving allopurinol, calcitonin, diclofenac, anti-tumor necrosis factor drugs, calcium channel blockers, and various chemotherapeutic agents.<sup>2-7</sup> However, we have only found 3 cases involving topiramate (Table 1),<sup>1-3</sup> all with lesions affecting the lower limbs, in contrast to our patient, in whom the lesions were on her hands. As in the 3 cases described in the literature, we detected a chronological relationship between treatment with topiramate and the appearance of GA in our patient, as the lesions appeared very soon after the introduction of topiramate and disappeared within 2 to 3 weeks of withdrawal of the drug, with no subsequent recurrence.<sup>1,3</sup> Additionally, although it is widely known that GA lesions sometimes resolve after biopsy,<sup>1-3</sup> we observed no improvement in our patient after performing biopsy. However, confirmation of the reappearance of GA lesions after rechallenge with topiramate has not been performed in our patient.

Topiramate is an antiepileptic drug that has a structure based on D-fructose, a monosaccharide, and differs

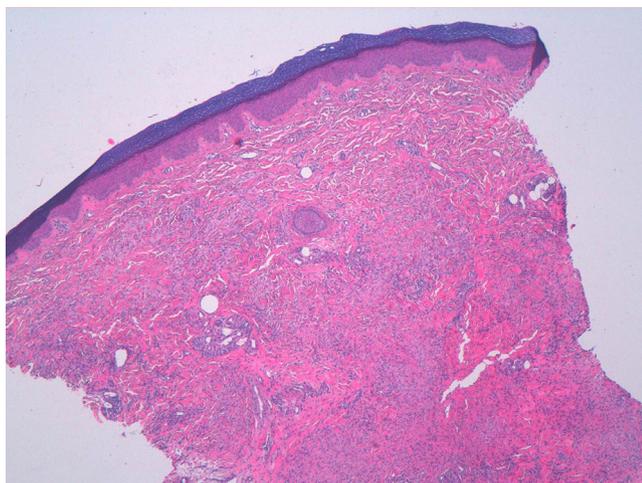
considerably from other antiepileptic drugs. It is indicated in the treatment of partial or generalized seizures, migraine prophylaxis, and in impulse control.<sup>2,3</sup> It has a multiple mechanism of action, including inactivation of the voltage-gated sodium channels and potentiation of amino-butyric acid-mediated neurotransmission, and it is a glutamate receptor antagonist.<sup>3</sup> Rare cutaneous side effects reported with topiramate include alopecia, oligohydrosis, pemphigus, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrosis<sup>2</sup>; the appearance of GA is very rare. The pathogenesis of GA secondary to topiramate is unknown, but, given the extensive use of this drug, the disorder is probably underdiagnosed. In patients with GA refractory to the usual treatments, a detailed medical history should therefore be taken to exclude the possible implication of any drug in its onset.

### Conflicts of Interest

The authors declare that they have no conflicts of interest.

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**Figure 3** Focal degeneration of collagen and elastic fibers, mucin deposits, and a perivascular and interstitial lymphohistiocytic infiltrate in the upper and mid dermis. Hematoxylin-eosin, original magnification  $\times 10$ .

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## Acquired Port-Wine Stain (Fegeler Syndrome): A Report of 3 Cases<sup>☆</sup>



### Malformación capilar adquirida (síndrome de Fegeler): 3 casos

*To the Editor:*

Capillary malformation is a condition included in the group of vascular malformations.<sup>1</sup> It is one of the most common vascular abnormalities and can affect up to 0.3% of newborns.<sup>2,3</sup> It presents clinically as a homogeneous erythematous macule with well-defined borders. It is typically unilateral and is usually present at birth. However, cases of acquired capillary malformation have been reported in patients with no previous lesions of this type.

Patient 1 was a 9-year-old girl followed-up from her first year of life for mastocytosis presenting as urticaria pigmentosa and treated with sodium cromoglycate and cetirizine. When she was 7 years old, a well-defined pink macule started to become visible, affecting segmentally the area of the first branch of the trigeminal nerve, and the superior part of the area of the second branch, with a more violaceous appearance in the periocular region. She presented no other lesions and there was no family history of interest. Skin biopsy revealed a capillary proliferation, negative for GLUT-1, consistent with a diagnosis of capillary malformation.

Patient 2 was a girl aged 8 years, with no past history of interest. She was referred to our clinic for macules on the left side of her face. The macules had first been noticed by her parents when the child was 4 years old, and they had grown progressively. Her parents stated that the macules became more evident in hot environments and after physical exertion. On examination, patchy pink macules were observed in a segmental distribution along the left body of the jaw and they were seen to become more intense after the patient performed physical exercise.

Patient 3 was a 7-year-old boy with no past history of interest. He was seen for a lesion in the right jaw region. His parents had first noticed the lesion when the child was about 4 years old. They stated that it had been asymptomatic, although its intensity increased with physical activity

and with heat. On examination, a patchy pink macule with superficial telangiectasias was observed. The macule became more intense after the child performed physical exercise.

None of the 3 patients had any family history of interest or presented other lesions. Clinically there was no thrill and the lesions were not detectable on ultrasound. Photos of the children when they were younger were requested to check that the lesions had not previously escaped the parents' attention. The children were referred to a reference center for laser treatment, which was only rejected by the third patient (Fig. 1).

The immense majority of capillary malformations are present at birth or appear in the first years of life. Cases of acquired capillary malformations are rare and were first described in 1939 in a patient who had suffered spinal cord injury.<sup>4</sup> Ten years later, Fegeler<sup>5</sup> reported a new case of post-traumatic capillary malformation, which has been named Fegeler syndrome since that time. The etiological factors that can trigger their de novo appearance have not been identified, though a history of trauma is present in up to a third of cases. Previously it has been proposed that the appearance of congenital capillary malformations could be due to a deficit of sympathetic innervation (responsible for vasoconstriction), leading to vascular ectasia that presents as this vascular malformation.<sup>6</sup> Acquired cases associated with spinal trauma conform to this hypothesis. Other possible etiologies have also been proposed, such as estrogenic impregnation, either during pregnancy or in the pubertal-adult period.<sup>7,8</sup> In some isolated cases, capillary malformations have been related with drugs, herpes zoster, sun damage, cluster headaches, and acoustic neuroma.<sup>7,8</sup> In a capillary malformation of the port wine stain type, the possibility of a postnatal mutation of the *GNAQ* gene might also be considered.<sup>9</sup> Despite these proposals, no triggering event has been discovered in many cases. The age at onset reported in the literature varies between 3 and 69 years, with a mean age of 25 years. Lesions most often arise on the face and upper limbs, and they have not been associated with other malformations or skin lesions. Typical and acquired capillary malformations are histologically and morphologically indistinguishable.

The differential diagnosis based on the type of vascular lesion is extensive. But perhaps it is most important to rule out this lesion as part of a syndromic diagnosis associated with more serious repercussions than the purely cosmetic. These include capillary malformation-arteriovenous malformation syndrome (a family history of similar lesions or of arteriovenous malformation is usually detected, the capillary malformations are multiple, with a browner color, increased local temperature, a whitish peripheral halo, and possibly with arterial flow visible on ultrasound) and

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