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Drug Induced Periungual and Subungual Pyogenic Granulomas: Report of Five Cases

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Abstract

Pyogenic granuloma (PG) is a benign, rapidly growing, eruptive hemangioma that often bleeds and ulcerates. Common causes are mechanical trauma and cast immobilization. Drugs such as retinoids and antineoplastic agents are sometimes involved. We report here five cases of pyogenic granuloma probabely associated with either antipsychotic or antiepileptic drugs.

Keywords: Pyogenic granuloma • Drug induced • Ungueal

Introduction

Pyogenic granulomas (PG) are benign rapidly growing vascular lesions. Various factors are involved in its etiopathogenesis such as, mechanical trauma, cast immobilization and hormonal factors. Drugs are also involved in the PG development. To our knowledge antipsychotic drugs have never been associated with PG. The effect with anticonvulsive drugs is exceptional. We describe five cases of PG probably associated with antipsychotic or antiepileptic drugs.

Case Reports

Case 1

A 16-year-old boy suffering from epilepsy and psychomotor retardation presented with multiple bilateral periungual and subungual painful granulomas of four toes. Lesions occurred three months after initiation of treatment with levomepromazine 100 mg/day on January 2014. The patient was also receiving propericiazine and bipyridine since 10 years. Examination revealed erythematous dome-shaped friable tumor localized to the lateral and distal subungual surface of four toes (Figure 1). Levomepromazine was suspected but not stopped (mother refusal). The patient was treated with cryotherapy and electrocoagulation with improvement. This case was notified to the Tunisian National Centre of Pharmacovigilance (TNCP) in February 2013 and valued 6 according to the Naranjo scale.

Case 2

A 16-year-old boy presented on March 2014 with rapidly growing lesions in his nail beds (ring, and middle fingers of the right hand; index and ring fingers of the left hand). The patient had been receiving phenytoin for two months for epilepsy and psychomotor retardation. He was also treated with sodium valproate and clonazepam since five years. There was no local trauma. Examination revealed oedema, erythema and tenderness in the paronychium of the affected fingers associated to granulation tissue of the proximal nail that had invaded beneath the nail plates, covering more than 20% of the nail beds in four fingernails (Figure 2). The histopathologic findings revealed superficial ulceration, proliferation of capillary-sized vessels, edematous stroma, and inflammatory cell infiltrations that were consistent with pyogenic granulomas.

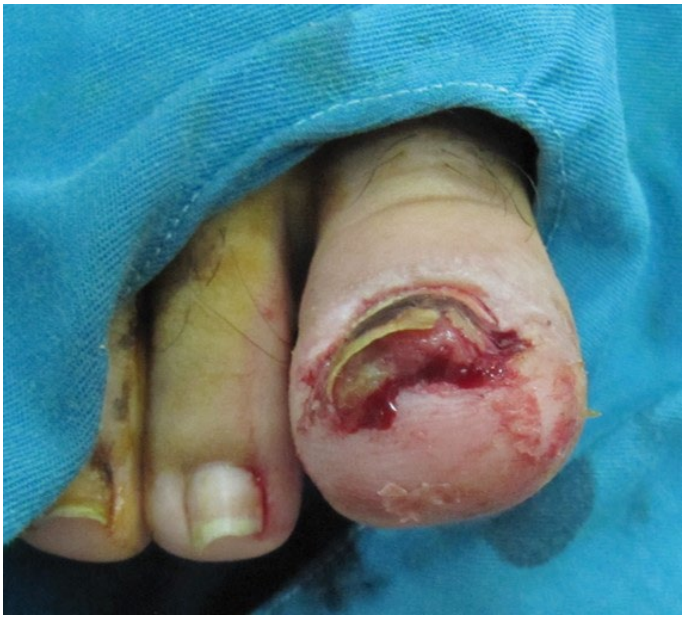

Figure 1. Dome-shaped friable tumor localized to the lateral and distal subungual surface of toes.

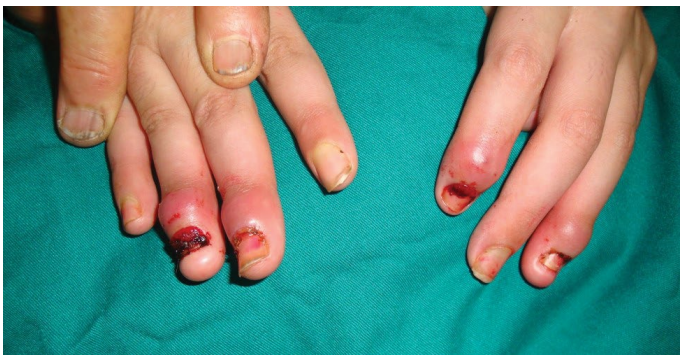

Figure 2. Pyogenic granulomas of the nail beds.

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Phenytoin administration was interrupted. We performed cryotherapy and electrocoagulation. A clinical improvement was obtained. The Naranjo scale according to the TNCP was 7 for phenytoin and 2 for sodium valproate and clonazepam

Case 3

A 30-year-old man suffering from epilepsy and psychomotor retardation developed in 2015 multiple easily bleeding periungual and subungual granulomas of the toes. The patient was receiving valpromide, amisulpride since 11 years and levomepromazine was initiated three months before. There was neither a specific episode of trauma to feet nor a past history of paronychia or PG. Clinical examination revealed fleshy, hemorrhagic papules, sized from 2 to 6 mm arising bilaterally from the periungual and subungual region with a total destruction of the big toes nails (Figure 3). Surgical excision of PG and a partial nail avulsion was performed. Histopathological features showed a lobulated proliferation of capillary vessels circumscribed in edematous stroma and a dense mixed perivascular cellular infiltrate, thus confirming the clinical diagnosis of PG. Levomepromazine was stopped and the other drugs were continued. The Naranjo scale was 6 for levomepromazine and 2 for valpromide, and amisulpride.

Case 4

An 18-year-old boy presented in 2017 with rapidly growing lesions in his nail beds. The patient had been taking carbamazepine for three months for epilepsy and psychomotor retardation. There was no local trauma. Examination revealed red nodules that had invaded beneath the nail plates, covering more than 80% of the nail beds in four toes (Figure 4). Carbamazepin administration was interrupted. Cryotherapy and electrocoagulation were performed with no reccurence of the lesion. The Naranjo scale was 7 for carbamazepine.

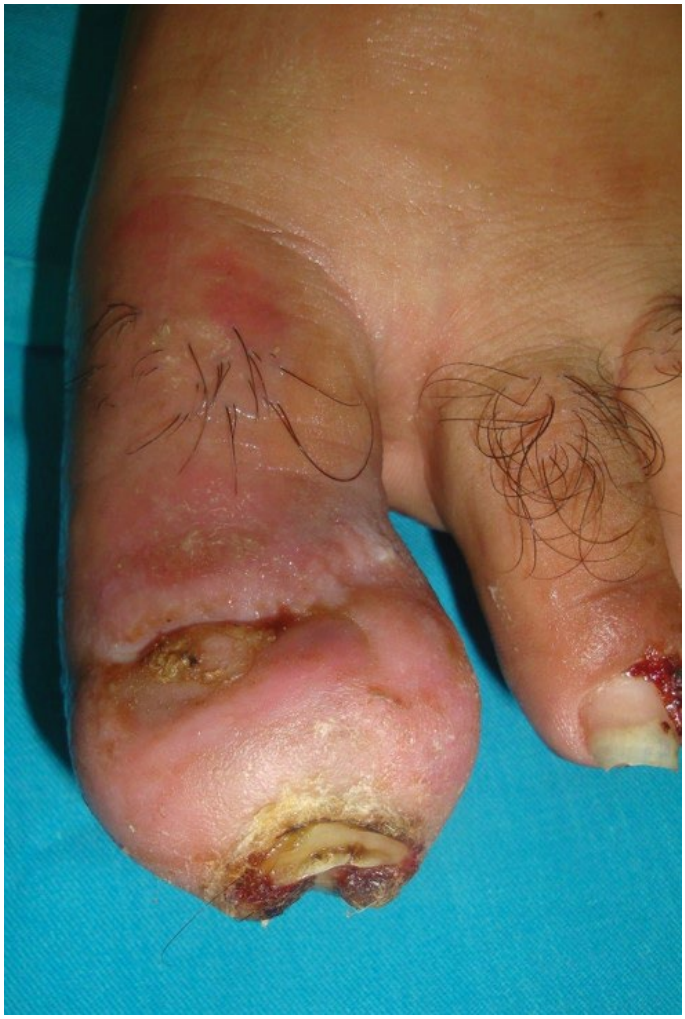

Figure 3. Periungual and subungual granulomas of the toes with a total destruction of the big toes nails.

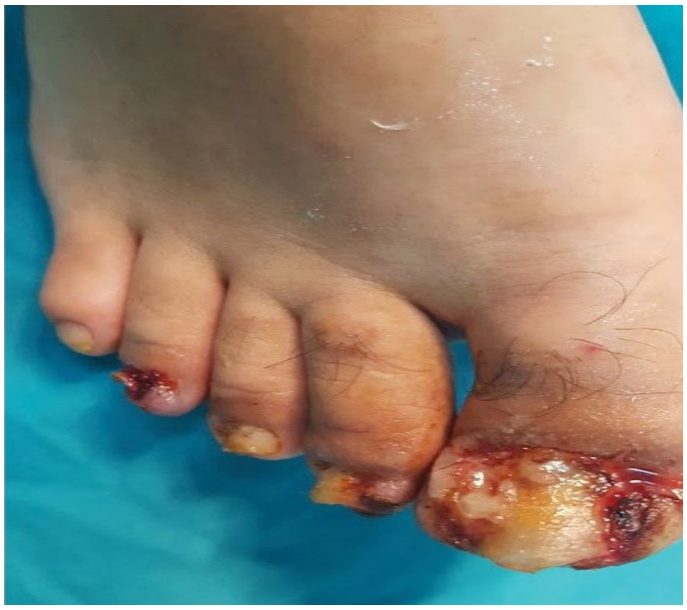

Figure 4. Pyogenic granulomas beneath the nail plates.

Case 5

A 20-year-old male patient presented in 2020 with a 2-week history of rapidly growing, painful, bleeding granulation tissue, localized on the dorsum of the toenail of the right feet. The patient had been receiving biperiden, propericiazine and levomepromazine since one year. A surgical excision and many sessions of cryotherapy were performed with mild improvement. Biperiden, propericiazine and levomepromazine were withdrawn and treatment with Trihexyphenidyl was initiated by the neurologist with regression of PG. This case was also notified to the TNCP and The Naranjo scale for these drugs was 7.

Result and Discussion

We reported five cases with psychomotor retardation and epilepsy, treated with carbamazepine, phenytoin or levomepromazine, developing pyogenic granuloma over the course of the treatment. Clinical history for other frequent causes of this vascular lesion, such as cast immobilization, mechanical trauma, psoriasis, cutaneous sarcoidosis, seronegative spondyloarthritis, antiretroviral and antineoplastic drugs, and tumor necrosis factor-α inhibitors was negative in all cases.

According to the Naranjo algorithm, the likelihood of carbamazepin, phenytoin and levomepromazin as the incriminating agents in the different cases was probable [1]. The persistance of the symptomatology at the continuation of levomepromazin in one case and mainly the favorable outcome after the drugs were withdrawn in the other cases is a major chronological argument in favor of the imputability of these molecules.

Drugs are a well-known cause of PG development [2,3]. Drug-induced PGs are mostly related to the use of retinoids, antiretroviral agents, tumor necrosis factor alpha inhibitors, rituximab, mammalian target of rapamycin (mTOR) inhibitors, epidermal growth factor receptor (EGFR) inhibitors, and anti-tumoral drugs [2,3]. Anticonvulsive induced PGs are exceptional, however, it seems not reported so far such effect with antipsychotics.

In a study of PG among patients, receiving carbamazepine up to April 2012, two patients (0.02%) developed PG [4]. A case reported in 2003, mentioned that PG was a possible carbamazepine side effect in a 15-year-old boy (Table 1 and Table 2) [5]. P Ghalayani et al described a case of extragingival PG occurring on the tongue with unusual presentation occuring after carbamazepin and phenytoin intake. Considering no relapse after switching carbamazepine by Gabapentine, reinforces the hypothesis in this case that PG may be associated with long-term carbamazepine intake [6].

Table 1. Clinical data of patients with pyogenic granulomas.

Our cases Number	Culpurit drug Naranjo scale	Delay	Outcome	Localisation	Age	Gender
1	Levomepromazine [6]	3 months	Persistence of the symptomatology after the continuation of the levomepromazine	Lateral and distal subungual surface of four toes	16 ans	Male
2	Phenytoin [7]	2 months	clinical improvement after Phenytoin withdrawl	nail beds (ring, and middle fingers of the right hand; index and ring fingers of the left hand	16 ans	Male
3	Levomepromazine [7]	3 months	No noticeable improvement after Levomepromazine withrawl	periungual and subungual region with a total destruction of the big toes nails'	30	Male
4	Carbamazepine [7]	3 months	No reccurence after the drug withdrawl	the nail beds in four toes	30	Male
5	levomepromazine biperiden, propericiazine [7]	1 year	Regression after the drugs withdrawl	the dorsum of the toenail of the right feet.	20	Male

Table 2. Reported cases of pyogenic granulomas caused by carbamazepine.

Case report number	Year of publication	Reference	Age	Culpurit drug	Delay	Localization	Outcome
1	2014	6	45	Carbamazepine	32 years	The dorsal surface of tongue	No relapse after replacing carbamazepine by Gabapentine
2	2009	5	15	Carbamazepine	3 months and a week	Bright red, sessile papules on his neck, trunk, and extremities	PG were removed by shave excision with electrodessication

The average interval between the initiation of the drug and the appearance of pyogenic granuloma was three months in most cases. In previous reports on drug-induced PGs, it was shown that the onset of PG was less than 16 months after initiation of the presumed causal drug [7].

A main characteristic of drug-induced PGs is the involvement of several nails of both the fingers and the toes, although toenail localization is more prevalent, probably because the toenails are subjected to chronic friction caused by shoes and related to body weight. Drug-induced PGs usually affect the lateral nail folds, but the rapid and massive growth of granulation tissue often invades the subungual space and the nail bed [8,9]. All these characteristics fit our cases showing that the most possible etiology is the drugs. Drug induced subungueal PG usually regresses after discontinuation of the causal drug. High-potency topical steroids, topical β-blocking medications may lead to improvement. If ineffective, cryotherapy and surgical curettage have been investigated in the treatment of drug-induced PG [10].

The occurrence of pyogenic granulomas without conventional predisposing factors suggests a mechanism driven by these antiepileptic and neuroleptic drugs. Histologic examination is necessary to rule out malignancy such as squamous cell carcinoma or amelanotic melanoma. It has been suggested that carbamazepine induced PG through the mechanism of a hypersensitivity reaction related to the release of angiogenic factors stimulated by the inflammatory process and impairment of liver functions [5].

The precise pathogenesis of PG is unclear. There have been some pathophysiological mechanisms reported previously to explain the development of drug-induced PG [7]. All of the drugs have the common mechanism of increased vascular proliferation via microtrauma or a direct effect on vascular cells [11].

Conclusion

Pyogenic granulomas may be considered as an adverse effect of antiepileptic and neuroleptic drugs. Further observations describing this cutaneous phenomenon under the treatment are needed to confirm this correlation.

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