

Case presentation

Periungual pyogenic granuloma formation in a patient with complex regional pain syndrome

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Abstract

Peripheral nerve injury has been associated with the development of periungual pyogenic granulomas (PGs). We present the case of a 39-year-old woman with an eight-month history of periungual PGs in the setting of a four-to-five year history of a traumatic inciting event that produced symptoms consistent with complex regional pain syndrome (CRPS). Although recurrent, these periungual PGs have remitted after treatment with topical timolol maleate. This case exhibits an underappreciated association between peripheral neurologic abnormalities, which include CRPS, and cutaneous abnormalities. It also presents evidence that supports the concept that PGs that are not appropriate for surgical treatments may be treated with topical timolol maleate.

Case synopsis

History: A 39-year-old woman presented to the NYU Dermatologic Associates with recurrent, periungual lesions. Since July, 2014, she had developed rapidly-growing, red, periungual papules on the halluces and the third finger of the right hand. The papules were painful, tender, friable, and intermittently were associated with purulent drainage. The patient denied change in medications or overall health prior to the onset of the periungual papules. She treated the sites with hydrogen peroxide daily without improvement.

Past medical history included obesity, anxiety, plantar fasciitis, arthralgias of the knees, migraine headaches, asthma, gastroesophageal reflux disease, and obstructive sleep apnea. The patient was in an automobile accident in September, 2009, and has had multiple herniated discs and has suffered from complex regional pain syndrome/reflex sympathetic dystrophy (CRPS/RSD), cervical and lumbar radiculopathy, fibromyalgia, myofascial pain syndrome, chronic fatigue syndrome, and autonomic dysregulation, which presented with allodynia, hyperalgesia, muscle spasticity/contractures, intermittent neurogenic edema, changes in hair growth patterns, skin erythema, nail trophic changes, oro-mandibular dyskinesia dystonia, cervical and lower leg dystonias, blepharospasms, and hyper/hypohidrosis. The pain has improved with the use of pregabalin, naltrexone, nerve blocks, botulinum toxin injections, and multiple traditional medications and nutraceuticals, although none had been changed in the few months prior to presentation.

Biopsy and excision were deferred to avoid generating pain and furthering the progression of her CRPS/RSD. She was started on topical timolol maleate drops with improvement, but topical timolol maleate gel 0.5%, which was applied once to twice daily under occlusion, was more effective. Mupirocin was applied as needed. Initial lesions resolved over weeks to months. New lesions subsequently formed and resolved with the application of timolol maleate. All of the fingers have been affected except the fifth digits. Lesions often recur on halluces.

Physical examination: On the halluces and right third finger were periungual, friable, red papules.

Laboratory data: None.

Histopathology: None.



Figures 1-7. Periungual erythematous friable papules showing improvement with topical timolol treatment

Discussion

Diagnosis: Periungual pyogenic granuloma formation in a patient with complex regional pain syndrome

Comment: Pyogenic granuloma (PG) is a common, acquired, benign, vascular neoplasm of the skin and mucous membranes [1]. PGs were initially thought to result from the production of granulation tissue in response to a pyogenic agent but were later determined to occur independently of infectious agents and without a granulomatous appearance histopathologically [2]. They often appear as solitary, red, friable, pedunculated papules or nodules that bleed easily [3]. Although their pathogenesis has not been elucidated, PGs have features that are consistent with reactive neovascularization [1] and are thought to form in the setting of trauma, hormonal changes of pregnancy, and specific medications [4]. Periungual PGs may form in the setting of trauma, such as ingrown toenails, retronychia, and frictional trauma. In addition, retinoids, antiretroviral therapies, epidermal growth factor receptor inhibitors, chemotherapeutic agents, cyclosporine, and inflammatory systemic diseases have been associated [5].

There are reports that associate the development of PGs with peripheral nerve injury, which includes reflex sympathetic dystrophy (RSD). RSD is a type of complex regional pain syndrome (CRPS), which is a term that is used to describe disorders in which there is spontaneous or induced pain which is out of proportion to the inciting stimulus in the setting of an array of autonomic and motor abnormalities. There are multiple published diagnostic criteria for CRPS, which has made the definition of the disease, its pathogenic mechanisms, and optimal treatments difficult to determine. In general, subtypes of CRPS involve nerve injury, burning pain, allodynia, hyperalgesia, edema, alterations in sweating, blood flow, skin color or skin temperature changes, decreased range of motion, motor dysfunction, and trophic changes in the absence of a disease that may cause these findings [6].

A report of skin diseases in patients with RSD noted the development of vascular reactivity, superficial ulcers, erythematous papules, xerosis, reticulate erythema, and post-inflammatory pigmentation [7]. It was reported that after hand trauma, a patient developed periungual lesions that appeared to be consistent with a bacterial whitlow with histopathologic features that included proliferation of ectatic capillaries in an edematous loose stroma with a mixed inflammatory cell infiltrate [8]. Nine patients were identified who developed onychomadesis and proximal nail fold periungual PGs after removal of a cast placed in the setting of hand fracture. The patients had suffered from paresthesias and pain prior to removal of the cast, which suggested peripheral nerve injury [9]. A retrospective, observational study was published that associated histories of periungual and subungual PGs that were identified during a five-year period. Three out of 58 patients with periungual PGs had associated peripheral nerve injury, which was related to bone fracture and cast immobilization. One of these patients also had a diagnosis of reflex sympathetic dystrophy [10]. PGs also have been reported to develop in a patient with Guillain-Barre syndrome [11]. These reports suggest that peripheral nerve injury is associated with the development of PGs. Although our patient has evidence of peripheral nerve injury and severe clinical symptoms, she also is on a complex regimen of traditional and nutraceutical medications. An association of these medications with the development of PGs has not been ruled out.

Treatment of PGs includes the application of topical silver nitrate, imiquimod 5%, electrocautery, curettage, cryotherapy, laser, sclerotherapy, and surgical excision [3, 12]. Surgical excision is recommended since it has the lowest recurrence rate [12]. Topical and systemic beta-blockers, such as timolol maleate and propranolol, have been utilized to treat infantile hemangiomas, which generated interest in their role in the treatment of other benign vascular lesions. Although their mechanism in this setting has not been elucidated, beta-blockers may act to soften lesions by promoting peripheral vasoconstriction and support regression by promoting apoptosis and blocking pro-angiogenic factors [13]. Twice daily treatment with topical timolol maleate of PG on a child's finger led to resolution of the lesion in three weeks without recurrence [14]. Topical timolol maleate treatment over one month also led to the resolution of a PG on the cheek of a five-month old girl [15]. A larger study of six patients with PGs that tested the efficacy of topical timolol maleate and oral propranolol, found that all of the lesions responded, at least partially, after two months of treatment with resolution of bleeding [13].

Considering our patient's underlying CRPS, surgical excision was deferred. Topical imiquimod was deferred as it may be associated with extensive inflammation and pain that exceeds that resulting from surgical techniques [14]. Topical timolol maleate treatment produced effective regression of the periungual PGs. This result adds support for the use of topical timolol for the treatment of PGs in sensitive sites, in young patients with concern for scars, and in patients that have been refractory to prior treatments.

References

1. North PE, Kincannon J. Vascular neoplasms and neoplastic-like proliferations. In: Bologna JL, et al Dermatology eds. 3rd Edition. London: Mosby 2012;114:1922
2. Park YH, et al. Subcutaneous and superficial granuloma pyogenicum. *Int J Dermatol* 1996; 35:205
3. Walsh JJt, Eady JL. Vascular tumors. *Hand Clin* 2004; 20:261
4. Requena L, Sanguenza OP. Cutaneous vascular proliferation. Part II. Hyperplasias and benign neoplasms. *J Am Acad Dermatol* 1997; 37:887
5. Richert B, et al. Nail tumors. *Clin Dermatol* 2013; 31:602

6. Borchers AT, Gershwin ME. Complex regional pain syndrome: a comprehensive and critical review. *Autoimmun Rev* 2013; 13:242
7. Webster GF, et al. Reflex sympathetic dystrophy: occurrence of inflammatory skin lesions in patients with stages II and III disease. *Arch Dermatol* 1991; 127:1541
8. Tosti A, et al. Reflex sympathetic dystrophy with prominent involvement of the apparatus. *J Am Acad Dermatol* 1993; 29:865
9. Tosti A, et al. Onychomadesis and pyogenic granuloma following cast immobilization. *Arch Dermatol* 2001; 137:231
10. Piraccini BM, et al. Periungual and subungual pyogenic granuloma. *Br J Dermatol* 2010; 163:941
11. Mazereeuw-Hautier J, Bonafe JL. Bilateral Beau's lines and pyogenic granulomas following Guillain-Barre syndrome. *Dermatology* 2004; 209:237
12. Lee J, et al. Treatment options for cutaneous pyogenic granulomas: a review. *J Plast Reconstr Aesthet Surg* 2011; 64:1216
13. Wine Lee L, et al. Treatment of pediatric pyogenic granulomas using beta-adrenergic receptor antagonists. *Pediatr Dermatol* 2014; 31:203
14. Malik M, Murphy R. A pyogenic granuloma treated with topical timolol. *Br J Dermatol* 2014; 171:1537
15. Khorsand K, et al. Pyogenic granuloma in a 5-month-old treated with topical timolol. *Pediatr Dermatol* 2014; 32:150