Clinical Rheumatology (2019) 38:1889–1895
https://doi.org/10.1007/s10067-019-04612-3

CASE BASED REVIEW

Trauma-induced concomitant psoriatic arthritis and complex regional pain syndrome

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Received: 25 April 2019 / Revised: 12 May 2019 / Accepted: 15 May 2019 / Published online: 24 May 2019

Abstract

To report the simultaneous occurrence of psoriatic arthritis (PsA) and chronic regional pain syndrome type I (CRPS I) both triggered by intense walking in a male golfer with a history of scalp psoriasis. Sequential existence of these two conditions have been reported in the literature; however, to our knowledge, this is the first report of a simultaneous occurrence of PsA and CRPS I. This case illustrates the complex interplay between genetic predisposition and environmental risk factors with the central nervous and immune systems. As the pathogenesis of PsA has been better understood in recent years, we propose a mechanism that explains how the release of pro-inflammatory cytokines and neuropeptides following a traumatic event elicits a vicious cycle that is a common ground for the development of both PsA and CRPS I. Even unperceived trauma, such as intense walking, when directed to the synovio-entheseal complex, can precipitate the development of PsA and CRPS I in predisposed individuals.

Keywords Complex regional pain syndrome · Neurogenic inflammation · Pro-inflammatory cytokines · Psoriatic arthritis · Synovio-entheseal complex · Trauma

Introduction

The etiology and pathogenesis of psoriatic arthritis (PsA) are complex and multifactorial, and environmental, genetic, and immunologic factors appear to play important roles [1]. When considering environmental factors, the notion that physical and emotional trauma might trigger PsA in a genetically predisposed individual has been advanced many years ago [2, 3]. How trauma may predispose to PsA is not well understood, but the association of psoriasis with acro-osteolysis that occurred only at sites of previous trauma suggests the possibility of a "deep" Koebner effect [4, 5]. More recently, evidence in support of physical trauma in patients with psoriasis to be associated with PsA has been presented [6]. Pattison et al. assessed potential factors associated with the development of inflammatory arthritis in a large cohort of patients with PsA of recent onset. They found a number of environmental exposures associated with the onset of arthritis in subjects with psoriasis. But the strongest association was with trauma, which adds further support to the notion of a "deep" Koebner phenomenon in PsA [6]. The latter finding has been confirmed by Thorarensen et al. [7], who evaluated the risk of PsA among patients with psoriasis exposed to physical trauma. In their study, a matched cohort study was performed using data from The Health Improvement Network (THIN). Patients with psoriasis exposed to trauma were randomly matched to up to five unexposed psoriasis controls based on gender, age, duration of psoriasis, and the date of entry into THIN. Adjusting to for potential confounders, patients with psoriasis exposed to trauma had an increased risk of PsA compared with controls.

On the other hand, complex regional pain syndrome (CRPS) was first described for the first time in 1864 by Silas Weir Mitchell, and its pathophysiology remains to be elucidated [8]. However, among the many triggering factors, trauma is well recognized as being the most common precipitating factor. In this report, we described the co-existence occurrence of PsA and CRPS following trauma in a patient with psoriasis and discussed the potential pathophysiology of this association.

Case presentation

A 55-year-old white male golfer with scalp psoriasis of long duration presented to the clinic with new onset pain, swelling, erythema, and warmth of his left foot. His symptoms began

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9 months prior while he was on a golf tour. For about 6 months prior to his current presenting symptoms, he had noticed episodic achy pain in the bottom of his left foot and toes after prolonged walking, but he did not seek any medical care at that time. He denied sustaining any injuries except for extensive walking. The pain was located in the ball of the left foot. The pain was dull in nature and associated with swelling and exacerbated with activity. Similar symptoms of erythema, heat, and stiffness developed in his toes to the extent that he was unable to bend them. He rapidly developed left hallux varus deformity of the great toe. Severe foot pain frequently woke him up from sleep. Two different sets of X-rays of his left foot were obtained within the first 2 months which revealed no abnormalities except slight degenerative changes at first metatarsophalangeal (MTP) joint.

Subsequent X-rays were notable for new onset of periarticular osteopenia. Magnetic resonance imaging (MRI) of his left foot then showed bone marrow edema within the second through fifth metatarsal heads, subchondral low T1 signal lines (interpreted as stress fractures), soft tissue edema throughout the forefoot, and small joint effusions in the second through fourth MTP joints. Following the MRI, he was treated with a walking boot and crutches for stress fractures. Bone densitometry (DEXA) scan was normal. At that time, he had a normal complete blood count (CBC), uric acid, and erythrocyte sedimentation rate (ESR) but c-reactive protein (CRP) was elevated at 14.4 (0–8.2 mg/L). He was referred to physical therapy, which improved the pain. He was seen by an orthopedist who prescribed a steroid taper for presumed diagnosis of PsA, which helped with the swelling but the pain persisted.

In the meantime, he developed pain and swelling of his right foot, right shoulder, right ankle, and right knee. He reported increased perspiration, decreased hair on his left leg, which was cooler to touch compared with the right one. He had no constitutional symptoms or any other symptoms of connective tissue diseases. He also had 2+ edema in his left foot up to the lower tibia and tenderness and erythema of his left foot and toes, but no active synovitis. Right knee arthrocentesis was performed, and findings were compatible with inflammatory arthritis with no evidence of infection or presence of crystals. A three-phase bone scan was obtained revealing moderate hyperemia with periarticular uptake in several small joints of the left foot (Fig. 1). The diagnosis of CRPS I was made and alendronate and gabapentin were chosen for therapy. Due to worsening of symptoms, he was referred to our rheumatology service.

Upon our assessment, his left-sided toes and entire foot revealed erythema and coolness to the touch. His left lower leg had lost its hair. He had tender dactylitis from second through fourth left toes (Fig. 2). He was also tender to palpation at the insertions of left plantar fascia. Active synovitis of the right shoulder, right elbow, and right knee was evident on examination as well. His inflammatory markers remained elevated but HLA-B27 was negative. IL-6 level was 15.06 pg/mL (0–12.2). Bilateral foot X-ray showed diffuse demineralization of left foot compared with the right. Concomitant diagnoses of PsA and CRPS I were confirmed and immunosuppression was initiated with prednisone and methotrexate. At 2-months follow-up, his symptoms ameliorated to some extent but he still had pain in the ball of the left foot and occasionally shooting pain in his toes. He found himself limping intermittently. On examination, his left second through fourth toes and right great toe were still mildly swollen and painful. He had mild persistent left plantar fasciitis and left heel enthesitis. Besides persistent hair loss in left lower extremity, his erythema and cool sensation to the touch resolved. After a year, he is now off corticosteroids and is on apremilast, methotrexate, and gabapentin. His vasomotor and sudomotor symptoms are resolved and he remains pain free.

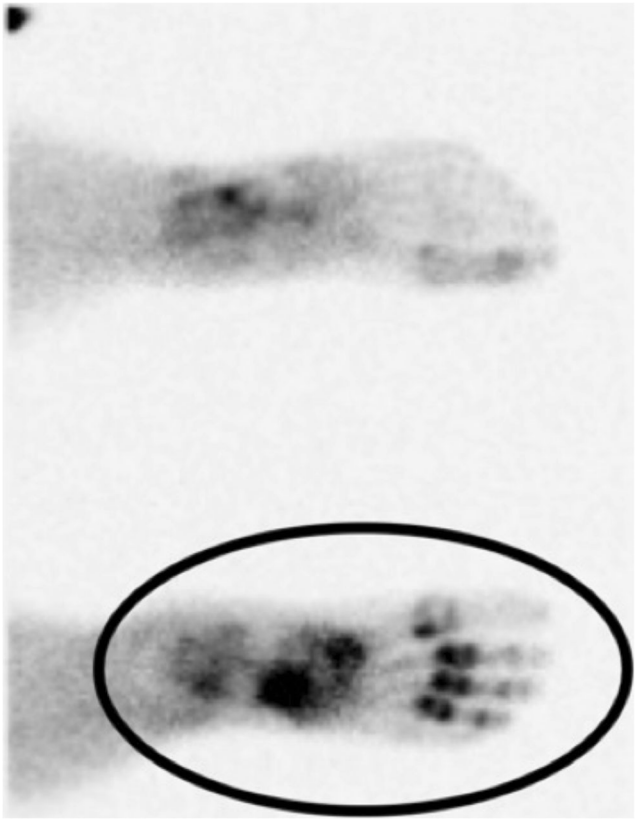

Fig. 1 Three-phase bone scan revealing moderate hyperemia with periarticular uptake in several small joints of the left foot (red circle)

The patient's full consent for publication was obtained prior to submission for publication.

Discussion

We present a patient with a known diagnosis of psoriasis in whom excessive walking and golfing served as a trigger for

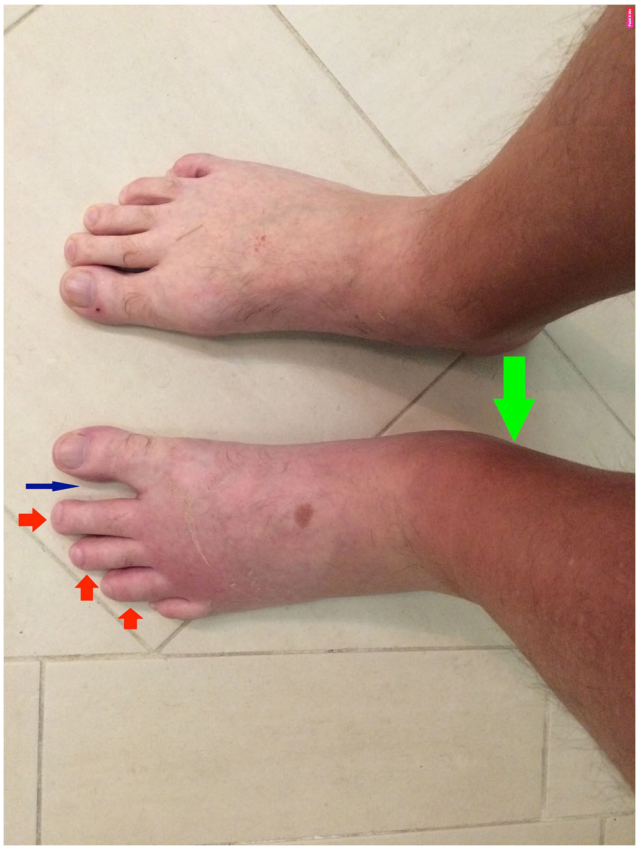

Fig. 2 (a) Edematous and erythematous of left toes and entire left foot. (b) Dactylitis from second through fourth toes (red arrows). (c) Hair loss of left lower leg (green arrow). (d) Hallux varus deformity

both CRPS I and PsA. The relationship between CRPS I and PsA has been described in the literature [1, 2], and either one of them can be the inciting etiology preceding the other one. Both CRPS and PsA can be triggered by trauma or physical activity of any degree of intensity [9–12], and some of their clinical characteristics are superimposed, thus making a diagnosis very difficult.

CRPS in general is a rare, challenging condition with little consensus in its etiology, clinical presentation, diagnosis, and treatment for which physicians must have a high index of suspicion. CRPS is a severely disabling regional pain syndrome, usually disproportionate in time or degree to the initial injury, that has a distal predominance of abnormal vasomotor edema, sudomotor, sensory, motor, or trophic findings [13]. Trauma is the most common precipitating factor and fractures have the highest rates, but other precipitating events are sprains, contusions, crushes, or strokes [14, 15]. CRPS can also be triggered by surgery, especially hand, foot, or ankle orthopedic surgery [16, 17], and has even been described following herpes zoster infection [18]. Musculoskeletal conditions and rheumatoid arthritis are known risk factors [19]. It can occur spontaneously [13] and up to 10% of patients do not recall the inciting event [20].

The key symptom though is allodynia or hyperalgesia that can be undulating, continuous, or episodic, frequently described as burning, and most commonly in the distal parts of the limbs [13]. There are two subtypes of CRPS: type I (90%) occurs after an event without nerve damage, is usually regional and does not pertain to dermatome. Type II follows a specific nerve injury [13]. Our patient has CRPS I.

CRPS can be divided into three stages of progression based on duration of symptoms but does not necessarily always evolve through these stages in a sequential manner [21]: stage I (acute): burning pain, edema, erythema, or dermatitis (last up to 3 months); stage II (dystrophic): worsening edema, skin thickening, and muscle wasting (last from 3 to 12 months); stage III (atrophic): skin atrophy, muscle atrophy, contractions, decreased range of motion, and demineralization of the bone (> 12 months) [13, 20]. Some patients develop severe symptoms from the beginning but some others remain in stage I throughout the entire disease process and overlapping of different stages occurs often [13, 21], being the course of the disease unpredictable and variable between patients [13].

CRPS I is more common in females, with a ratio over 3 to 1, and usually occurs between the fourth and sixth decades of life, and upper extremities are more commonly affected in both types of CRPS [14, 15]. CRPS I most commonly affect only one limb but can spread to other limbs [15]. Incidence and prevalence have been extremely difficult to calculate due to significant differences in study populations, different nomenclatures used, and lack of a gold standard test for diagnosis. The most common clinical manifestations are vasomotor (swelling, color, and temperature asymmetry). The most recently revised diagnostic criteria for CRPS are the Budapest Criteria, with a sensitivity of 70% and specificity of 94% [22]. They are modified from 1994 International Association for the study of Pain (IASP) [23].

The most useful ancillary test to support the diagnosis of CRPS is the three-phase bone scan, with a sensitivity of 85% [15, 24] when used in the acute phase (stage I). Plain X-ray typically shows soft tissue swelling and regional patchy osteopenia but only in 30% of the cases or less [24]. This technique is more useful when both hands are compared and included together. MRI is useful to exclude other etiologies, but does not help in the diagnosis of CRPS [24].

The pathogenesis of CRPS yet needs to be better understood, but it is certainly multifactorial with interplay of genetic, inflammatory, vasomotor, neurologic, and even psychosocial factors and tends to change as the disease course progresses [24]. But, what is the link that connects both CRPS and PsA in our patient?

There is evidence to support a genetic predisposition of CRPS, and links to human leukocyte antigen (HLA) loci have been identified [24]. CRPS has been linked to HLA-DR13, HLA-DR15, and HLA-DQ1, and the last two loci predispose to autoimmune disorders [24]. In acute stages, trauma triggers

the release of pro-inflammatory cytokines, such as TNF-α, IL-1, IL-6, IL-8, and IL-12. It also sensitizes and activates cutaneous nociceptors [23, 24], which in turn release neuropeptides—substance P (SP), calcium gene-related peptide (CGRP), and bradykinin—from sensory terminals in the skin [25]. CGRP is a potent vasodilator inducing a long-lasting increase in superficial blood flow whereas SP induces a brief vasodilation but a significant plasma extravasation [24, 25], which results in the so called neurogenic inflammation [25]. SP induces keratinocytes to produce cytokines, and as it has been demonstrated in CRPS, there is a proliferation of keratinocytes and mast cells [24, 25]. This creates a vicious cycle of constant production of pro-inflammatory cytokines and neuropeptides. These substances not only act locally in the affected limb but also act in the spinal cord probably by lowering the excitability threshold of the synapses, making them hyper-excitable [25]. Most inflammatory markers being normal point to aberrant inflammatory response in CRPS, which is not a cell-mediated immune response [26]. Experimental animal models of peripheral nerve injury, and a lesser extent in human, have shown that peripherally derived neurotrophins are involved in the induction of sympathetic sprouting in the dorsal root ganglia (DRG) and neuropathic pain [27–29]. Further support is provided by studies in animal and humans indicating that electrical stimulation of DRG neurons may modulate neuropathic pain signals [30].

Psoriatic arthritis is a hereditary polygenic condition, strongly associated with class I major histocompatibility complex (MHC) alleles, most importantly HLA-B*08, HLA-B*27, HLA-B*38, and HLA-B*39 [31, 32]. Enthesitis, dactylitis, and symmetric sacroiliitis are notably associated with HLA-B*27:05:02, whereas joint fusion, deformities, dactylitis, and asymmetric sacroiliitis are commonly associated with HLA-B*08:01:01 and HLA-C*07:01:01 [32]. IL-23R is the most strongly associated non-HLA gene to PsA, and it has been implicated in the activation and maintenance of CD-8 T cells and Th-17 cells [32]. Others include genes that regulate nuclear factor κB (NF-κB) expression (TNIP1) and signaling (TNFAIP3), RUNX1 (transcription factor that promotes Th-17 cell differentiation), and IL-12B (essential inducer of T-helper-1 cell development), among others [31, 32]. In PsA, severe psoriasis, infection, stress, obesity, smoking, and trauma can trigger inflammatory responses in multiple places in

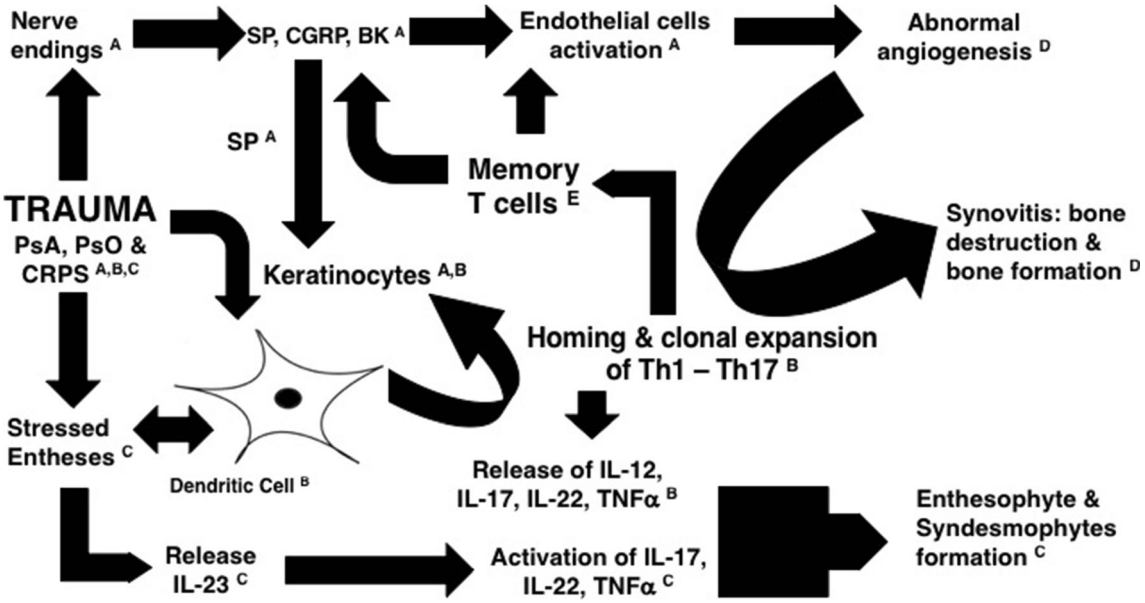

Fig. 3 (a) In CRPS (*yellow arrows*), trauma sensitizes and activates cutaneous nociceptors which release neuropeptides such as substance P (SP), calcium gene-related peptide (CGRP), and bradykinin (BK), resulting in neurogenic inflammation. Substance P directly induces stressed keratinocytes to produce cytokines. Trauma also triggers the release of pro-inflammatory cytokines directly. (b) In psoriasis (*orange arrows*), trauma activates plasmacytoid dendritic cells (DC) which in turn activate dermal DC. These DC migrate to peripheral lymph nodes and stimulate the differentiation of Th1 and Th-17 cells. These lymphocytes home to the dermis and release pro-inflammatory cytokines such as IL-12, IL-17, IL-22, and TNF-α, which in turn results in keratinocyte proliferation. (c) Biomechanical stress in the enthesis (*blue arrows*) induces the release of IL-23, which in turn stimulates the production of IL-17, IL-22, and TNF-α with resultant enthesophyte formation in peripheral enthesis and syndesmophytes in the spine. (d) In PsA, the same traumatic event produces a neurogenic inflammation similar to the one seen in CRPS, which coupled with cascade of immunologic processes, induce abnormal angiogenesis. This aberrant vasculature is responsible for the inflammatory process reaching the joint (*dark-green arrows*). There, increased expression of RANKL together IL-17 and TNF-α, and IL-22 is responsible for the synovitis and bone destruction and bone formation, respectively. The memory cells (*light-green arrows*) resulting from these processes result in a self-perpetuating cycle of chronic inflammation, SP production, and abnormal angiogenesis

susceptible individuals. This can happen in different organs such as the skin, bone marrow, small bowel, entheses, and joints [1, 4] but in which organ the disease begins is variable [31]. Trauma, particularly among patients with psoriasis, has been shown to be one of the most important risk factors to develop PsA [6, 7], especially when directed or near the synovio-entheseal complex (joints and bones) recreating a deep Koebner phenomenon [11, 26, 31, 32], whereas more superficial trauma (nerve endings and skin) is not [33].

The participation of both innate and adaptive immune systems in PsA and psoriasis is well established [26, 32, 34]. There is a prominent role of dendritic cells (DC), predominantly of an immature phenotype, in which the expression of Toll-like receptor 2 is upregulated, resulting in a Th-1 cell response with an increased production of TNF-α, IFN-γ, and IL-12. Moreover, the dendritic cell–derived IL-23, as well as the IL-12, results in the differentiation of distinct Th-17 and Th-1 subsets, respectively. T cells have an essential role in PsA and psoriasis as well, particularly CD8+ T cells. Type 17 cells, such as CD4+ Th-17 cells, mast cells, mucosal-associated invariant T cells, and type 3 innate lymphocytes, are also increased in psoriatic synovium [1, 31, 32].

In the gut, dysregulation of microbiota leads to IL-23 overproduction and its relationship with the immunological dysfunction in the pathogenesis of PsA and other spondyloarthropathies is becoming more evident [33, 34].

In the skin, expression of interferon by plasmacytoid DC activates dermal DC which migrate to lymph nodes and trigger differentiation of Th-1 and Th-17 cells. Then, these lymphocytes home to the dermis and release IL-12, IL-17, IL-22, and TNF-α. Additional IL-17 secreting cells in the dermis include type 3 innate lymphocytes and CD8+ T cells. These cytokines induce keratinocyte proliferation [31].

Alternatively, the enthesis is proposed to be the initial site of musculoskeletal disease. IL-23 release in response to biomechanical stress activates type 17 cells and other cytokines, such as IL-22 and TNF-α, with resultant inflammation, bone erosions, and pathologic bone formation. IL-22 can activate fibroblast-like synoviocytes and induce osteoclastogenesis leading to bone destruction [32]. Nonetheless, it also promotes the differentiation of mesenchymal cells into osteoblasts by the upregulation of the pro-osteogenic factors Wnt-3a, Wnt-10b, and bone morphogenetic protein (BMP)-4, resulting in enthesophyte formation in peripheral enthesis and joints and syndesmophytes in the spine [31, 32]. Ultimately, the type 17 cells, osteoclast precursors, and DC reach the joint from adjacent enthesis or the bloodstream. Increased expression of the receptor activator of NF-κB ligand (RANKL) by synoviocytes, together with increased levels of TNF-α and IL-17, drives the differentiation of osteoclast precursors into osteoclasts, with synovitis and bone resorption. Overproduction of angiogenic growth factors, chemokines, and adhesion molecules derived from fibroblast-like synoviocytes, in combination with a decrease in endothelial apoptosis, induces an aberrant angiogenesis characterized by immature vessels, facilitating the homing and clonal expansion of Th1 and Th17 cells in the inflamed synovium [32].

Simultaneously, the same trauma activates the nerve endings releasing neuropeptides, such as SP, which are overexpressed in psoriatic skin and PsA synovium [35]. SP may also activate endothelial cells, also resulting in abnormal angiogenesis. Lastly, the memory cells resulting from these processes induce a self-perpetuating cycle of chronic inflammation, SP production, and abnormal angiogenesis [32, 36]. Consequently, the trauma leading to pro-inflammatory cytokine production and neuropeptide release, which end up becoming a vicious cycle, is a common ground for the development of either CRPS or PsA, or both simultaneously, as illustrated in our case (Fig. 3).

The treatment of CRPS is usually multidisciplinary. Therapeutic modalities include behavioral or cognitive-behavioral therapy, sympathetic blocks, spinal cord stimulation, dorsal root ganglion stimulation, and physical and occupational therapy. In addition, medications used are

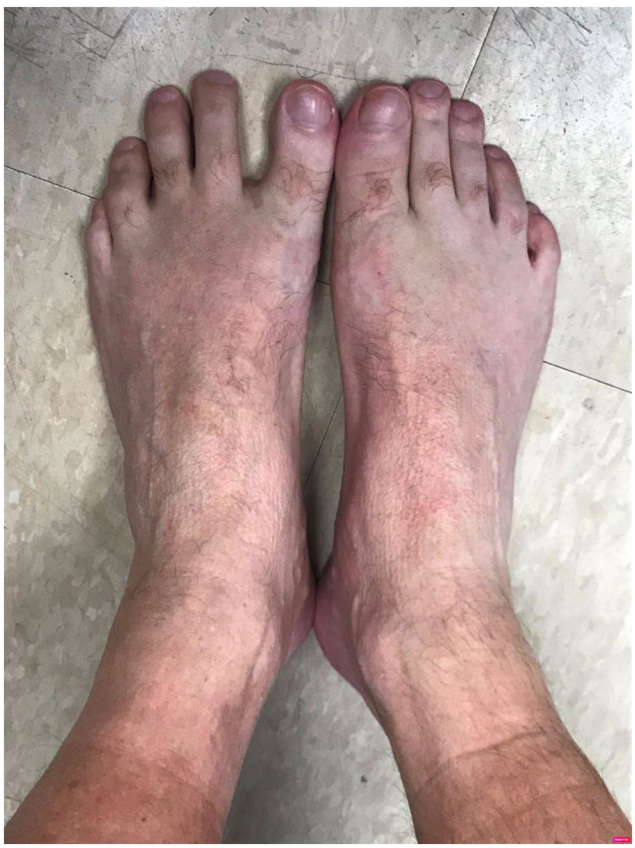

Fig. 4 (a) Resolution of left foot discoloration and edema. (b) Significant improvement in left second through fourth toe dactylitis. (c) Hair loss of left lower extremity and left hallux varus persist

bisphosphonates, analgesics, anticonvulsants, antidepressants, and corticosteroids [37]. Most cases of CRPS are mild and transient with an overall high rate of spontaneous improvement. The rest tends to respond well to physical therapy and achieves good functional recovery. Nonetheless, early recognition and treatment are crucial for better outcomes [37].

In conclusion, the presented case illustrates the coexistence of CRPS and PsA triggered by trauma and the complex interplay between genetic predisposition and environmental triggers with the central nervous and immune systems. Our patient is currently in remission of both CRPS and PsA, off of prednisone, and treated with methotrexate, apremilast, and gabapentin (Fig. 4).

Compliance with ethical standards

Disclosures None.

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