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Delayed effort-induced swelling with myofasciitis and systemic manifestations: A so far unrecognized type of pressure-induced urticaria

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Abstract

Diseases characterized by recurrent symptoms with prolonged intervals without any clinical manifestations can pose diagnostic difficulties. Some diagnoses will be obvious but other situations can be very challenging.

To nosologically delineate a new entity characterized by recurrent flares of induration of the forearms and legs with swelling of the extremities accompanied by intense fatigue and variable other symptoms.

Retrospective observational study of patients recorded from 2000 to 2015. All patients included were seen during a consultation at the Dermatology Department of the University Hospital of Strasbourg, France. We retrieved the medical records from patients seen and recorded over the last 16 years having induration of the extremities, the forearm and the legs occurring between 4 and 12 hours after a physical effort accompanied by systemic signs that lasted for a few days. We analyzed in detail the clinical and biological features, evolution, and treatments of these patients.

We included 6 males, with a mean age of 47 years; mean age at disease onset was 42. All patients were initially misdiagnosed as having rheumatic disorders. The mean delay before diagnosis was 5 years. The main complaint was painful induration or muscle soreness of the forearms and the legs associated with transient functional impairment and prolonged asthenia for a mean duration of 3.5 days. Induration of the deep soft tissues was very suggestive of myofasciitis. The delay between the triggering physical effort and the swelling was between 6 and 12 hours. Physical effort as triggering factor was never spontaneously mentioned. Two patients had partial response to high dose antihistamines and 2 other patients to the interleukin-1 inhibitor anakinra. One patient responded to hydroxychloroquine.

The very stereotypical presentation in those 6 patients suggests that this is a recognizable entity characterized by effort-induced induration of forearms and/or legs, due to deep edematous myofascial involvement, occurring a few hours after a physical effort. We suggest to name this entity delayed effort-induced swelling with myofasciitis and systemic manifestations.

Abbreviations: BMI = body mass index, DESMS = delayed effort-induced swelling with myofasciitis and systemic manifestations, DPU = delayed pressure urticaria, IgIV = intravenous immunoglobulins, IL = interleukin, MRI = magnetic resonance imaging, TRAPS = tumor necrosis factor associated periodic syndrome.

Keywords: autoinflammatory syndrome, delayed pressure urticaria, myofasciitis, systemic symptoms

1. Introduction

Diseases characterized by recurrent symptoms with prolonged intervals without any clinical manifestations can pose diagnostic difficulties. Some diagnoses will be obvious on clinical examination, such as the grouped vesicles of recurrent herpes simplex infection for example. The search of a triggering factor is always mandatory and often the key to diagnosis, since some toxins and/or allergens or some specific environments can also trigger a variety of symptoms that recur only upon exposure. Other situations can be very challenging, and establishing diagnosis will only be possible with a careful analysis of the history of the patient and of his family, for example, the case with the hereditary fever syndromes.[1]

The objective of this study was to describe a new entity of patients who developed recurrent flares with induration and swelling of the extremities, the legs and the forearms accompanied by intense fatigue and variable other symptoms triggered by physical activity and lasting several days. There was absolutely no anomaly between the acute flares, which recurred upon intervals of variable duration. These patients might constitute a subgroup of delayed-pressure urticaria (DPU).

2. Patients and methods

2.1. Design and setting

In the late nineties, one of the coauthors (DL) noticed that a few patients had a very stereotypical presentation with induration of

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ACB and DL contributed equally to this work.

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the extremities and the limbs after a physical effort accompanied by systemic signs that could last for a few days. He then systemically recorded those patient files. For the purpose of this study, these patients seen in the dermatology department between 2000 and 2015 were now retrieved and analyzed in detail.

2.2. Inclusion criteria

In order to include a very homogenous group of patient, they had to fulfill the following criteria:

(1) pain and/or burning sensation with swelling of the extremities and the forearm and/or the legs
(2) occurring after 4 to 12 hours after a physical effort
(3) lasting for at least 24 hours
(4) with concomitant systemic symptoms (ie, fever, asthenia)

2.3. Data collection

We analyzed in detail the clinical and biological features, evolution, treatments, and their effects as well as associated conditions. For each patient, demographical data (sex, age, age at beginning of the flares, weight, and height) were collected, as well as clinical data; special attention was paid to the following: main complaint, presence or absence of acral edema, other localizations of swelling, triggering factor(s), identification of this factor by the patient, delay between this factor and the flare, presence or absence of a refractory period, pruritus, systemic symptoms, characteristics of the flares, that is, duration, frequency, pressure test, biological analyses during and outside the flares, cutaneous histology, treatments, and their effects.

Under the French law, this type of retrospective study relying only on examination of patients' files does not need approval of an ethics committee.

3. Results

Between 2000 and 2015, 7 patients were recorded and 6 of them fulfilled the above-mentioned criteria. The reason of exclusion of 1 patient was that the triggering factor could not be unequivocally established (Fig. 1).

All patients were males, with a mean age of 47 years (38–56). Their principal characteristics are summarized in Table 1. Two of them were previously published.[2]

All patients were initially evaluated in rheumatology or internal medicine departments with complaints of muscle and/or joint pain. The suspected initial diagnoses were: dermatomyositis, "auto-inflammatory syndrome," carcinoid syndrome, rheumatism, angioedema, and DPU in only 1 case. The average delay before diagnosis was 5 years (4 months to 13 years). The mean age at onset of the disease was 42 years (35–45). Four of the patients were obese (body mass index [BMI] ≥30) and 2 were overweight (BMI ≥ 24.5).

3.1. Clinical features

3.1.1. Main complaint: recurrent induration and swelling of forearms and/or legs. A painful induration and swelling of the forearms and/or the legs, with a very unpleasant sensation of constriction was the most characteristic and the main complaint of most patients. It occurred in 4 of 6 patients and it lasted from several hours to a few days. The remaining patients reported muscle soreness of the forearms and/or the legs that also lasted from several hours to a few days.

This swelling was firm, without a godet sign and responsible for a limitation of mobility and a transient "prayer sign," initially wrongly interpreted in all of them as articular stiffness. During an acute flare, the skin could not be mobilized over the hypodermis, and the hypodermis seemed adherent to the underlying muscles, thus pointing the involvement of the fascia and the muscle. Intensity of the swelling was not compatible with normal daily

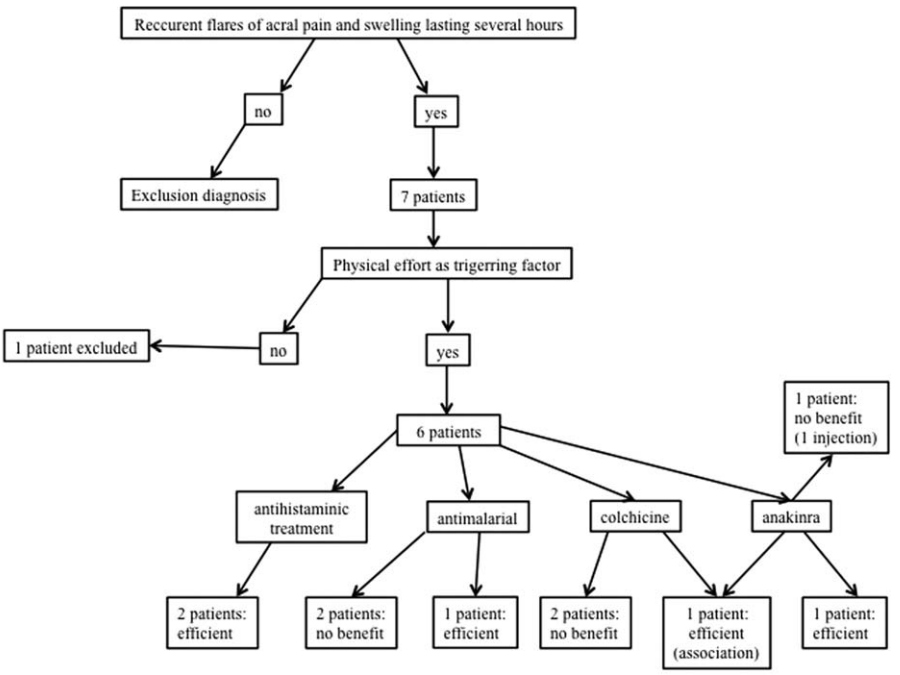

Figure 1. Flowchart of patients.

Table 1

Main clinical characteristics of the patients.

Sex	Age	Past medical history	Main features	Delay after effort	Flair duration	Systemic and other symptoms	Biology during acute flare	Cutaneous test	Delay before diagnosis	Previous suspected diagnosis	Treatment and effect
M	56	Atopy; TIA at 46 y; 3 flairs of acute urticaria	Acral swelling, burning and painful feeling, extending to forearm and legs	12 h	2 d	Asthenia	NA		13 y	Delayed pressure urticaria not confirmed	High doses anti-H1: efficient
M	48	TIA at 38 y; sicca syndrome	Painful acral swelling, extending to forearm and legs	NK	3 d	Fever, chills, arthromyalgia, asthenia, abdominal pain, and diarrhea; associated urticarial wheals	CBC N; CRP, ESR N; CPK N; AST, ALT N	Nonpruriginous dermographism; −pressure test (under steroids)	3 y	Autoinflammatory syndrome, carcinoid syndrome	Salazopyrine, NSAID, colchicine: inefficient; MTX and CS: partially efficient
M	51	Sicca syndrome	Invalidating acral swelling, extending to the face, genitals, and the legs	NK	3–4 d	Arthromyalgia, asthenia; associated urticarial wheals	CBC N; CRP N; ESR = 19, AST = 52 (1.5N), aldolase = 11 (1.5N)	Nonpruriginous dermographism	9 y	Chronic urticaria and angioedema	Combination of 4 ant-H1: efficient, recurrence if medication stopped
M	38	Renal lithiasis migraine	Painful swelling of the extremities, extending to the legs, thighs and face	6–8 h	2–3 d	Fever, asthenia, diarrhea, polypnea; associated urticarial wheals	CBC N; CRP, ESR N; AST = 41 (1.3N), ALT = 62 (1.2N)	Nonpruriginous dermographism	3 y	None	Anti-H1, colchicine, NSAID, chloroquine, montelukast, dapsone, cyclosporine: inefficient; corticosteroid: efficient but adverse effect; anakinra: efficient but escape; hydroxychloroquine: efficient
M	43		Painful swelling of the extremities, extending to legs, thighs, forearm, shoulder, trunk	6–12 h	7 d	Abdominal pain, diarrhea, fever	CBC N; CRP, ESR N; Aldolase = 7.5 (<7.6); CPK = 210 (1.25N); ALT = 138 (3N); AST N	Nonpruriginous dermographism; +pressure test	4 m	Dermatomyositis	Colchicine; +intravenous immunoglobulin + anakinra: efficient
M	45	Arterial hypertension; hypercholesterolemia	Immediate painful swelling of the extremities after effort lasting 1–2 h; free interval (6–12 h) Painful acral swelling extending to legs and thighs	6–12 h	2–3 d	Asthenia, arthromyalgias	NA	Nonpruriginous dermographism	3 y	Inflammatory rheumatism	Anti-H1, steroids, colchicine: inefficient; intravenous immunoglobulins: efficient but bad tolerance; anakinra: efficient, relapse after 9 m; hydroxychloroquine: inefficient

ALT = alanine transaminase, AST = aspartate transaminase, CBC = cell blood count, CPK = creatine phosphokinase, CRP = c reactive protein, CS = corticosteroids, d = day, ESR = erythrocyte sedimentation rate, h = hours, IL = interleukin, M = male, m = month, MTX = methotrexate, N = normal, NA = not available, NK = not known, NSAID = nonsteroidal antiinflammatory drug, TIA = transient ischemic attack, y = years.

personal or professional activities. This substantially reduced mobility probably led the patients to be explored first in the Department of Rheumatology.

These painful complaints had substantial socio-professional impact, as patients were unable to move during the flares.

3.1.2. Swelling of the extremities. All patients suffered from associated palmar and/or plantar symmetrical swelling with a burning sensation. Three patients had a more diffuse swelling involving the face (2 patients), genitals (1, this patient had also facial swelling), and shoulders and trunk (1 patient). Of note, the facial swelling was not associated with dyspnea or dysphonia.

3.1.3. Triggering effort, frequency, and duration of the flare. Physical activity was the triggering factor in all patients, though 2 of the patients did not spontaneously establish this relationship.

The delay between physical effort or pressure and the beginning of the swelling was estimated between 6 and 12 hours. The swelling lasted between 24 hours and 7 days, 3.5 days, on average. It is this long delay and the long duration of the crisis that probably explain that 2 of the 6 patients did not spontaneously establish a relationship between the physical activity and the swelling. But even the 4 patients who noticed this relationship did not mention it spontaneously and only specific questioning allowed establishing this relationship. Intensity of triggering physical activity was varying. It could be important at the beginning of the disease and then become less important as years passed, thus the disease becoming more and more incapacitating. One patient had an immediate flare after a physical effort that resolved within 2 hours. Then, 6 to 12 hours later, this patient had a 2nd flare that lasted 2 days. Few patients noticed other factors that could lower the threshold that would trigger a flare: infections (2 patients), isradipine administered for hypertension (1 patient), and warm environment (1 patient).

Four patients had 1 to 2 flares per week. One of them specified that initially he had about 2 flares per month. In 2 patients, the exact frequency of flares was not specified.

3.1.4. Systemic symptoms. All patients suffered from substantial asthenia during and after the swelling, lasting 2 to 7 days. Three patients had fever and chills, and 3 had arthromyalgias accompanying the swelling. Arthralgias were located on the extremities, extending to the knees for one of them and were not associated with joint swelling. Two patients had abdominal pain and diarrhea during the flares. None of the patient had any complaint between the flares.

3.1.5. Other signs. Three patients had urticaria, that is, erythematous transient pruriginous wheals simultaneously or just before the swelling. The urticarial wheals were mostly located on pressure areas, namely the extremities. Another patient reported 3 flares of acute urticaria 4 years after delayed effort induced swelling begun but independently from it. Acute urticaria never relapsed thereafter. During a severe flare, 1 patient noticed, labial paresthesia, sore throat, palate swelling, thoracic oppression, and polypnea without dyspnea or wheezing.

3.2. Biological assays and other investigations

Four patients had a blood sample drawn during a flare. Complete blood count was normal in 4, as was the C reactive protein. The erythrocyte sedimentation rate was normal in 3 patients and it was slightly increased at 19 at the 1st hour in 1 patient. A moderate elevation of the hepatic enzymes was noticed during acute flares in 3 patients, whereas hepatic enzymes were normal in the remaining patient. Two of them had slight increased aspartate transaminase (<1.5 N), associated with moderate increased alanine transaminase (<1.5 N) in 1 case. One patient had moderate increased alanine transaminase (3N). Aldolase was measured twice. These were moderately increased (1.5 N) once and at the higher normal limit (7.5, N < 7.6) in the other case. The creatine phosphokinase was measured twice; it was slightly increased once (1.25 N) and normal in the other case.

Outside of a flare period, patients had normal complete blood count, normal erythrocyte sedimentation rate, normal C reactive protein, and normal liver function tests. None of the patient had autoantibodies. A tumor necrosis factor associated periodic syndrome (TRAPS) was excluded in the absence of a genomic mutation of the tumor necrosis factor receptor super family (*TNFRS*) gene in 1 patient. For one of the patient with facial swelling, hereditary angioedema was ruled out; tryptase dosage was in normal range and allergological tests were negative. Dermatomyositis was excluded in the patient with predominant muscle soreness. Inflammatory rheumatism was excluded in the patient with predominant arthralgias.

The 3 patients with urticaria had a cutaneous biopsy. Histological examination revealed a mostly perivascular lymphocytic infiltrate, in the superficial dermis. Edema of the dermis was present in one, dilated vessels were observed once.

3.3. Dermographism and pressure challenge testing

A pressure test was performed in 2 patients and it was positive in one; but the patient with a negative test was under steroids when being tested. Six hours after carrying a bag of 6 kg during 20 minutes on the shoulder, a white, firm, and tense edema of the shoulder was noticed. The patient had a painful sensation located on the pressure area. The cutaneous lesion was still present 12 hours later. The night after the test, he had diarrhea. The flare spontaneously resolved thereafter. Another patient reported swelling of the shoulder few hours after carrying a bag.

Most of the patients (5/6) had a nonpruriginous dermographism.

3.4. Treatment

3.4.1. Antihistamines. Two patients were relieved from all symptoms with antihistamines, but only with high dose (4 drugs). Indeed, a double dose of antihistamines was totally inefficient. A triple dose diminished the frequency (from 2 to 1 per week) and the intensity of the flares. A quadruple standard dose of antihistamines diminished the frequency of flares to 1 or 2 per month. Intensity became bearable, that is, the patient had occasional swelling without systemic symptoms, and he reported leg pain after prolonged walking. Each attempt to decrease the antihistamines dose resulted in immediate recurrence of flares and asthenia. Another patient was treated with 4 antihistamines at once. Six months later, he was symptom-free.

3.4.2. Antimalarials. Two patients had no benefit from antimalarials. The former was only treated 2 weeks due to digestive intolerance. The 2nd patient reported no positive effect after 6 months of hydroxychloroquine treatment.

One patient was efficiently treated with hydroxychloroquine. He tried chloroquine (300 mg/day) 14 months after the symptoms begun. The treatment reduced intensity of pain and swelling, but the symptoms persisted and the patient stopped the treatment after 4 months. Twelve years later, during which the affection

became worse, another trial was done with hydroxychloroquine at 400 mg/day. Three months later, the patient was free of symptoms and the dosage was tapered down to 200 mg/day. One year later, the patient is still free of symptoms.

3.4.3. Colchicine. Colchicine alone was inefficient in 2 patients. One patient was efficiently treated with continuous colchicine (1 mg/day) and anakinra (100 mg/day) on demand at the beginning of a new flare.

3.4.4. Intravenous immunoglobulins (IgIV). IgIV were used twice. In one case, IgIV were rapidly efficient with fewer pains but persistence of moderate swelling. Unfortunately, the treatment was poorly tolerated: the patient had headache and vomiting during and after the perfusion. In the other case, an association of colchicine and IgIV could notably diminish the muscle soreness and articular stiffness, but the patient still had flares.

3.4.5. Anakinra. Anakinra was used in 3 patients. One patient only had one injection of 100 mg anakinra. He did not feel immediate benefit and therefore did not continue the treatment. One patient had initial benefit from this treatment on all the features but then progressively escaped after 9 months. Another patient had anakinra associated with colchicine and IgIV. Initially a daily dose was proposed, and then tapered down to injection on demand at the beginning of the flares. Anakinra was efficient on the frequency and intensity of the flares and IgIV could be suspended.

3.5. Associated disorders

Two patients had a previous history of a transient ischemic attack at 46 and 38 years of age, respectively. The patient aged 46 years was overweight (BMI = 24) and smoked 32 packs/year; the 2nd patient was obese (BMI = 32.9). Two patients had sicca syndrome.

4. Discussion

We report a series of 6 patients who developed recurrent flares of induration and painful swelling of the extremities, the legs and the forearms, with intense fatigue and/or fever, a few hours after a physical effort. Signs persisted between 2 and 7 days. All patients were initially misdiagnosed as having rheumatic disorders.

We suggest delineating this entity within the group of DPU, and naming it "delayed effort-induced swelling with myofasciitis and systemic manifestations" (DESMS). It is a variety of pressure-induced urticaria and corresponds probably to an autoinflammatory syndrome.

Physical urticarias are defined as urticaria occurring after specific physical stimulus. DPU is a variety of physical urticaria; flares are triggered by pressure or effort.[3–7] Typically, a few hours after pressure, swelling and/or urticarial wheals appear on the area subjected to pressure, especially palms and soles; and the symptoms usually last for several hours to a day. The patients presented here share the triggering factor (pressure), a delay of a few hours between the pressure/physical activity and the swelling and the initial acral location of the swelling with DPU.[3–7] Systemic symptoms are usually associated with severe attacks of DPU.[3–5,7–17] But these patients differ notably from typical DPU as swelling was not only restricted to the areas where pressure was applied, but it extended on the legs and/or forearms; the presence of an induration of the deep soft tissues, very suggestive of myofasciitis; the painful character of the swelling, which was the main complaint of the patients, explaining in part the delay to diagnosis; and subsequent asthenia which persisted for several days.

The patients presented here shared some features with TRAPS.[18] There are of course important distinguishing factors such as the absence of pressure as repeated and only triggering factor, the usually younger age of onset, the much longer duration of the flares, and the autosomal dominant mode of transmission in TRAPS.[19] In both entities, patients have flares with swelling, systemic symptoms, digestive features, and myofasciitis. Indeed, a myofasciitis can strongly be hypothesized in the patients described here as they presented swelling of the forearms with a transient prayer sign and myalgias with a burning sensation. Unfortunately, no magnetic resonance imaging or deep biopsy was performed during a flare to definitely confirm this assumption. However, we observed a slight and transient increase of aspartate aminotransferase, creatine phosphokinase, and/or aldolase during the flares that reflects muscle involvement. The acuteness of the flares, the type of associated systemic symptoms, the absence of marker of autoimmunity, the absence of sequels, the physical activity as triggering factor, and the complete absence of symptoms between the flares are strongly suggestive of an autoinflammatory syndrome, even though no biological inflammation is clearly demonstrated and no familial case was present in this series.

Although the clinical presentation of these patients is quite stereotypical and recognizable, there are possibly different underlying pathomechanisms that could lead to a similar clinical phenotype. Indeed, in regard to response to treatment, this could be a relatively heterogeneous disorder. Response or partial response of 2 patients to colchicine and/or the interleukin (IL)-1 receptor antagonist anakinra is compatible with IL-1 mediated autoinflammatory mechanisms contributing to pathogenesis. Two other patients were efficiently treated with high doses of antihistamines, though the delay of a few hours between pressure and swelling is not typical of a histamine-mediated mechanism. Moreover, other clinical features are neither suggestive for histamine nor for bradykinine-mediated symptoms. Histaminic angioedema are often associated with simultaneous urticarial wheals, whereas only 3 patients in this series had simultaneous urticarial wheals, specifically located on pressure area. Bradykinic angioedema is usually not associated with systemic symptoms such as fever, arthralgia, or myalgia. It is not symmetrical, while the swelling was symmetrical in all the patients reported here. It is most often in central and not peripheral location, involving preferentially the face. If acral, angioedema is mostly located on the dorsum of the hands, whereas acral swelling induced by pressure can be localized both on the palm and dorsum of the extremities, predominating on palms.[20] Recently, Boyden et al[21] discovered a mutation in a gene encoding a G-protein-coupled-receptor, adhesion G protein-coupled receptor E2 (*ADGRE2*), in a few families with vibratory urticaria. This receptor is constituted by 2 subunits: the alpha-subunit that is extracellular and inhibits the transmembrane beta-subunit, by a noncovalent binding. This receptor seems to be a mechano-sensor receptor. A vibratory stimulus induces dissociation of the 2 subunits and degranulation of the mast cells and subsequently clinical features (ie, localized swelling and urticarial wheals). The mast cells degranulation was increased in case of mutation of the *ADGRE2* gene, affecting the beta-subunit, suggesting that the causal mutation is a gain of function mutation and induces an exaggeration of a normal cellular pathway. One can hypothesize that another mechano-sensor sensitive to

pressure stimulus could be affected in patients with DESMS, inducing an exaggerate response to this type of stimulus.

To conclude, we delineate, within the group of DPU, a characteristic entity, which we suggest naming "DESMS," to help clinicians recognizing it. Its typical presentation led us define the following diagnostic criteria: bilateral and symmetrical firm and painful swelling of the extremities, beginning on the site of pressure and secondarily extending mostly on the forearm and/or legs, occurring few hours after effort, lasting several hours to days, with substantial functional impairment, and associated with prolonged systemic symptoms, mostly fatigue, that can last up to 1 week. It is important to recognize this entity, since it is responsible of substantial alteration in quality of life, and since all the patients reported here were initially misdiagnosed as having rheumatic disorders. According to our experience, we propose to first treat these patients with high doses of antihistamines. If inefficient, the next step could be either antimalarials and/or colchicine. In case of resistance, especially in those patients who have fever during the flares, the IL-1 receptor antagonist anakinra should be tested and/or IgIV.

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