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Abstract.
Atrophoderma of Pasini and Pierini is a rare, considered benign, skin disease characterized by single or multiple asymptomatic atrophic plaques. Lesions can occur everywhere on the body with the trunk being the most often reported affected site. It appears in the second or third decade of life and affects mostly the female population, with male to female ratio of 1:6, commonly of white European descent.

Different risk factors were described in the literature – genetic predisposition, infections with Epstein-Barr virus, varicella zoster and Borrelia burgdorferi, vaccinations, local trauma and more. Since the pandemic with COVID-19, skin manifestations after the viral infection with COVID-19 were reported. After a thorough search of the existing medical literature, we believe, we present the first case of a rapid progression of Atrophoderma of Pasini and Pierini after COVID-19 infection.

Due to its similarity to morphea in some aspects, the condition is often misdiagnosed, and the proper treatment is often delayed. Sometimes the dilemma “Is it atrophoderma Pasini-Pierini or is it in fact morphea?” stays, but the exact histopathological verification and the “diagnostic clues” which can be used during the examination stage, are usually enough to diagnose the condition.

We present a 63-year-old female with a rapid progression of atrophoderma of Pasini and Pierini after a COVID-19 infection.

The lesion that she presented with was single, asymptomatic, with central hypopigmentation and slight atrophy, with a smooth, shiny surface and ivory color, and peripheral hyperpigmentation, measured 18x5cm, without the presence of perilesional erythema.

The patient was initially diagnosed clinically with localized scleroderma (morphea) and treated with hydroxychloroquine 200 mg once daily for a 5-year period without improvement.

Years later two biopsies from different lesional sites were taken, resulting in absence of sclerosis and dermal atrophy, but - reduction in the thickness of the dermis with fragmentation and hyalinization of collagen fibers forming a parallel orientation, dilated vascular vessels of small caliber and reduced number of skin appendages, confirming the diagnosis of atrophoderma Pasini-Pierini.

The patient’s therapy was switched to methotrexate with good therapeutic response.

Often, the two conditions – morphea and atrophoderma of Pasini and Pierini can be mistaken due to its clinical similarity and sometimes coexistence. Therefore, we will shortly review the existing literature with key points on the similarities and differences.

Key words. Atrophoderma of Pasini-Pierini, morphea, COVID-19, hydroxychloroquine, methotrexate.

Introduction.
Atrophoderma of Pasini and Pierini (APP) is a rare cutaneous disease characterized by single or multiple asymptomatic atrophic plaques with violaceous to brown pigmented patches [1]. Its independent nosological entity is highly controversial among clinicians [1]. According to Amano et al. [1] APP could even coexist with the condition - morphea.

Morphea, also called localized scleroderma, is a rare autoimmune disorder characterized by inflammation and sclerosis of the skin and the subcutaneous structures [2]. Typical for the condition are the active periods of inflammation and fibrosis, followed by irreversible damage to different structures – hair loss; cutaneous, soft tissue and bone atrophy, as well as joint contractures and growth restrictions of the affected site [2].

APP sometimes may be challenging to differentiate due to its similarity to other conditions [3]. Since morphea can lead to permanent damage to the affected tissues [2], it is important to have an early diagnosis and treatment.

Different risk factors can contribute to the morphea development, with Borrelia burgdorferi infection being a real possibility [4]. Only a small percentage (26.6%) of the patients with atrophoderma of Pasini and Pierini were found positive for the Borrelia spirochete [5].

Since the pandemic with SARS-CoV-2, the COVID-19 infection has been linked to numerous systemic complications, including the largest organ in the human body – the skin [6]. A rapid progression of localized morphea to disseminated plaque-type morphea following COVID-19 infection has been reported by Rahimi et al. [6].

To our knowledge, there is not a single case in the existing literature describing the development and/or progression of atrophoderma of Pasini-Pierini after a COVID-19 infection.

Hydroxychloroquine is a medication used for morphea due to its high response rate and low adverse drug events [7].

Methotrexate and corticosteroids can be used for localized scleroderma as well [8]. Methotrexate has been reported to be an effective treatment also for APP [9].

Our aim in the article will be a thorough review of the existing literature regarding both conditions and further diagnosing our patient based on the clinical and histopathological findings– is it morphea or atrophoderma of Pasini-Pierini?.
Case report.

A 63-year-old female came to the dermatology department with primary complaints of a transient pain in the distal phalanges, accompanied by thickening of the skin in the same area. She also reports an increase in the diameter of a painless plaque, dating from 1985, in the left lumbar region of the back, diagnosed over the years as localized scleroderma and treated with hydroxychloroquine 200 mg once daily for a period of 5 years till now. She reported using local medications, each used separately for different periods of time twice daily: methylprednisolone aceponate 0.1% 30gr cream and clobetasol propionate 0.5 mg cream. According to the patient's data, in 2019 during a regular dermatological examination, the lesion was measured 16 cm x 4 cm in size, and she noticed a visible increase in the lesions diameter after a covid infection in 2022.

Several comorbidities were reported as followed: second degree arterial hypertension, ischemic heart disease – rhythmic form; condition after pericardial effusion; Hashimoto's thyroiditis; multiple disc herniations of the cervical and lumbar region, with cervical osteochondrosis and spondyloarthritic changes; peripheral vertigo; organic mood disorders; myopia, keratoglobus and astigmatism. No reported allergies.

The patient is on systemic therapy with Candesartan cilexetil 8mg administrated once at noon, Nebivolol 1,25mg once in the morning, Rosuvastatin 5mg once at noon, Acetylsalicylic acid 75mg once in the evening, Levothyroxine sodium 12,5 mg once daily, Pregabalin 75mg once in the morning, Paroxetine 10 mg in the morning, Hydroxychloroquine 200mg once in the morning and vitamin D: 8 to 10 drops a day for the concomitant diseases.

Routine laboratory tests including a complete blood test and liver function were ordered resulting without abnormalities. ANA profile subtyping was performed: 1:320 (positive), with no increase in the subtraction values, C3 (negative), C4 (negative), as well as IgM and IgG serology for Borrelia Burgdorferi (negative). The anti-dsDNA resulted as 6 (with reference range 6-10 as grey zone).

Consultations with a cardiologist, an ophthalmologist and a rheumatologist were scheduled in order to rule out a possible systemic autoimmune disease and clarify the patient’s status, due to the past pericarditis, long-term systemic hydroxychloroquine intake, eye pathology and changes in the distal phalanges.

The dermatological examination showed in the left lumbar region, a single, clearly demarcated from the surrounding skin, elliptical-striped plaque with 18 cm x 5 cm in size, central - with hypopigmentation and slight atrophy, with a smooth, shiny surface and ivory color, and peripheral hyperpigmentation (Figures 1a,b). Separately, in the area of the distal phalanges, bilaterally thickened skin and subcutaneous tissue is observed, in places with limited mobility. Enlarged lymph nodes were not palpable.

Two biopsies from different parts of the lesion were taken. The first one exhibits interface scars for lichenoid dermatitis. The second one showed marked hyperkeratosis of "woven basket" type, intact epidermis, reduction in the thickness of the dermis with fragmentation and hyalinization of collagen fibers forming a parallel orientation, dilated vascular vessels of small caliber and reduced number of skin appendages (Figures 2a,b). The histological constellation is represented by dermal atrophy, which corresponds to atrophoderma Pasini-Pierini.

The patient was recommended serological tests for hepatitis B (HBsAg) and hepatitis C (anti HCV antibodies) before starting systemic therapy for the disease with methotrexate 15 mg weekly. A control examination every 4 weeks was recommended in order to supervise the disease and manage the dose regimen of the medications.

Discussion.

Atrophoderma is a rare skin condition first described by Pasini [10] in 1923 as “progressive idiopathic atrophoderma” and further connected to morphea by Pierini and Vivoli [11] in 1936.

Later in 1958, Canizares et al. [12] suggests “idiopathic atrophoderma Pasini – Pierini” to be acknowledged as a nosologic entity due to its differences to morphea. Results from Yokoyama et al. [13] implied that glycosaminoglycans metabolism in APP (atrophoderma of Pasini-Pierini) differs from those in morphea.
Idiopathic APP is a rare cutaneous disease, usually benign, characterized as single or multiple asymptomatic hypo- or hyperpigmented well-defined areas of depressed (atrophic) plaques, violaceous to brownish in color, and unlike morphea - without surrounding inflammation in the form of erythema [14].

The hyperpigmented atrophic lesions appear to have no definitive etiology or pathogenesis [14]. They can increase in size over the course of life [14]. Our patient first discovered her lesion in 1985 (when she was 25 years old) and over the years she noticed an increase in size. It occurs in the second or third decade of life with less than 100 cases being reported in the literature [15].

It is usually seen in white Europeans with female predominance, male-female ratio of 1:6 [15]. The lesions can be found for the first time on the trunk and with the disease progressing – later-on on the chest, arms, and abdomen [15]. According to some authors the well-defined depressed (atrophic) lesions with cliff-drop borders are a “diagnostic clue” for the disease [16].

As the name suggests, morphea or localized scleroderma, is a rare autoimmune inflammatory and sclerosing skin condition which affects the skin and the underlying subcutaneous structures [17]. The lesions can be described as active - with signs of inflammation (in the form of erythema), pain and pruritus; and as inactive – with sclerosis and atrophy involving the epidermis, dermis, and the subcutaneous structures [17].

It is primarily seen in children [18] and in women [19]. The inflammatory patches or fibrotic skin are often located on different anatomical sites – the head, neck, trunk, and upper/lower limb areas [20,21]. Despite being considered a skin-limited condition, certain subtypes can exhibit extracutaneous manifestations [21], for example fatigue, arthralgias and myalgias [22]. In some cases, the disease can progress to severe hyperpigmentation and skin atrophy, joint contractures and complications in the neuro-ophthalmological specter [21].

Positive autoantibody serologies are presented in morphea [22].

According to Wojas-Pelc et al. [23] 47% to 76% of the patients with scleroderma had antinuclear antibodies (ANA) and antibodies to the B. burgdorferi spirochete. The study included 50 patients with circumscribed sclerosis (plaque, deep linear, atrophoderma Pasini-Pierini) and the antinuclear antibodies were detected in 18% of the patients (in titer of 1:40 to 1:320) [23].

Although the patient we present had several comorbidities, including ophthalmological disorders, her laboratory tests were normal, without present antibodies to the spirochete. Her ANA profile subtyping was 1:320 (positive), with no increase in the subfraction values. This result alone could not exclude either of the conditions.

In genetically predisposed patients, certain trigger factors can contribute to the disease - different infections with Epstein-Barr virus, varicella zoster and Borrelia burgdorferi, medications, vaccinations, surgical interventions, or local trauma [21]. Our patient did not recall any certain medication intake or past event involving infection or local trauma in her adulthood.

Infection with Borrelia burgdorferi spirochete has been described as a potential triggering factor also for atrophoderma of Pasini and Pierini [24]. 38% of the patients in the study done by Buechner et al. [24] had elevated serum antibodies to B. burgdorferi. In our case presented, the IgM and IgG serology for B. burgdorferi was negative and therefore the infectious agent was ruled out as a possible disease inductor for both morphea and APP, excluding the antibiotic therapy as a possible therapeutic option.

COVID-related diseases have become a hot and interesting topic for many clinicians worldwide. Skin manifestations after a COVID-19 infection are already described in the literature -exanthematous rashes, urticarial rashes, and mucosal lesions [25]. A case presented by Lotfi et al. [25] showed a 57-year-old woman with pan sclerotic morphea that rapidly progressed after a COVID-19 infection. The laboratory tests that were conducted showed high elevations in ANA, anti-ds DNA and CRP and the skin biopsy – sclerodermoid changes [25].

After a thorough search of the medical literature, we could not find any relationship between APP and Covid-19 infection. If so, this could be the first case reported in the scientific literature of a rapid progression of atrophoderma Pasini-Pierini after a Covid-19 infection.

When the clinical findings and laboratory tests are indecisive, the diagnosis is often made with the help of histopathology. Different parts from the morphea lesion are showing different histological patterns [26]. A skin biopsy taken from the erythematous border of an inflammatory lesion will present with inflammatory cell infiltrate (lymphocytes, macrophages, plasma cells, eosinophils, and mast cells) and a biopsy from the atrophic site will present with loss of the inflammatory infiltrate, less sclerosis and missing appendageal structures [26].

Three different patterns of vascular changes in morphea are described by Kobayasi et al. [27]: the first, mostly found in unaffected skin, is presented with stimulated endothelial cells and thickened vascular wall with infiltration of mast cells and macrophages; the second, found in inflammatory and sclerotic lesion sites, described with pericytes with thick basal lamina and the third pattern, found also in inflammatory and sclerotic areas, described with activated pericytes with infiltration of plasma cells and lymphocytes [27]. Activated pericytes were concluded to be the most important vascular change in morphea [27].

The different types of collagen in the cellular and fibrotic stages of localized and systemic scleroderma were studied by Fleischmajer et al. [28]. The cellular stage is presented by perivascular or diffuse cellular infiltration consisting mainly of lymphocytes, plasma cells and macrophages and type III collagen (which can be seen also in the lower dermis) [28]. In the fibrotic stage, the type III collagen in the papillary layer can be reduced or agglutinated in contrast to the normal skin’s architecture [28]. Compact collagen consisting of type I or of type I&III collagen, can be seen in the adipose tissue or the lower dermis [28]. Collagen bundles surrounding the eccrine glands and blood vessels can be seen extending into the reticular dermis in older sclerotic morphea lesions [29].

In APP, a decrease in thickness of the dermis and absence of sclerosis can be found with additional interstitial edema, mild perivascular infiltrate and normal-looking sweat glands and skin appendages [30,31]. Macrophages and lymphocytes were present around vessels and in the dermis – between the fibers [32]. Although the presence of inflammatory infiltrate has been
described in both conditions (morphea and APP), the absence of inflammation in our histology might be due to the years of local therapy with clobetasol propionate and long-standing systemic immunosuppressive therapy with hydroxychloroquine. The atrophic appearance of the lesions results from changes in the organization of collagen and elastic fibers and not from the tissue content [31]. The same study concluded that horizontal collagen fiber organization in the lesional biopsy was increased in the lower dermis and the elastic fibers had greater disorganization in the upper dermis [31]. Normal to severe reduction and fragmentation of elastic fibers were described by Saleh et al [33]. Dermal atrophy with hyalinized, horizontally-oriented collagen bundles were present in our patient’s biopsy (Figure 2b).

Patients presenting with asymptomatic atrophic skin lesions should be considered on the differential diagnosis with atrophoderma Pasini-Pierini [30]. Clinical features and tissue biopsy can help differentiate the condition from morphea and other skin diseases [30]. Taking into consideration the given information above and the histological constellation made in our case report, a diagnosis of Atrophoderma Pasini-Pierini was made.

In terms of treatment options, hydroxychloroquine is a great option for plaque morphea with high response rate and low adverse drug events [7]. The medication is a first-line drug option for many rheumatologic and/or dermatologic conditions [34]. During the COVID-19 pandemic it was also used for the treatment of viral infection due to its immunomodulatory, anti-inflammatory, antibacterial and antiviral properties [34]. The retrospective study performed by Kumar et al. [7] showed complete response greater than 40% and partial response rate of nearly 50% to the drug [34]. The patient presented to us was diagnosed over the years as localized scleroderma and treated with hydroxychloroquine 200 mg once daily for a period of 5 years till the second consultation was made.

Lupus-associated APP can be also treated with a hydroxychloroquine [35].

In the case of Lyme disease (infection with Borrelia burgdorferi spirochete), antibiotics can be optioned for a treatment [24]. Topical and systemic steroids, antimalarials, antibiotics and phototherapy can be found effective for the atrophoderma Pasini-Pierini treatment [36]. Clinical improvement of hyperpigmentation can be seen with the Q-switched alexandrite laser [37].

Methotrexate is a widely used medication in the dermatology field due to its antiproliferative and anti-inflammatory properties [38]. Morphea can also be treated with methotrexate [39]. It is considered a drug with overall mild and reversible drug adverse events [39]. Positive response to methotrexate was found in patients with APP after 3 months of initial therapy with the drug [16]. She was initiated with methotrexate at a dose of 20 mg/wk and topical treatments for her psoriatic areas on the body [16]. Major improvements in the atrophic skin sites on her back and shoulders were administered [16].

Conclusions.

Atrophoderma of Pasini and Pierini (APP) is a rare cutaneous condition which alters the collagen organization in the dermal layer of the skin resulting in depressed (atrophic) changes. APP can sometimes exhibit similar characteristics to other skin conditions, such as morphea.

Thorough clinical examination followed by histopathological verification has proven its efficiency during the diagnostic stages of the disease.

Several key points in the case report were crucial for the diagnosis of atrophoderma of Pasini and Pierini:

1) The patient was presented with a single asymptomatic plaque characterized by central hypopigmentation and slight atrophy, with a smooth, shiny surface and ivory color, and peripheral hyperpigmentation.

2) Surrounding inflammation in the form of erythema was not observed, unlike in morphea lesions. However, the absence of inflammation in our histology might be due to the years of local therapy with clobetasol propionate and immunosuppressive systemic therapy with hydroxychloroquine.

3) Absence of sclerosis and dermal atrophy with hyalinized, horizontally oriented collagen bundles, which are specific for atrophoderma of Pasini and Pierini.

It is important to differentiate the disease since the therapeutic approach may sometimes be different even for similar skin conditions. Choosing the right therapy for every patient must be a number one priority for not only every dermatologist but also for every clinician. In such cases, when the clinical picture is very similar, a drug of choice for both morphea and APP can be methotrexate.

REFERENCES


