Advances in treatment for Lipoid Proteinosis (Urbach-Wiethe disease): A systematic review

Running head: Advances in treatment for Lipoid Proteinosis

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Learning points

- Lipoid proteinosis is characterized by dysphonia, hyperkeratosis, and warty plaques on elbows, knees, and knuckles, as well as moniliform blepharosis.
- Characteristic histology involves the presence of eosinophilic amorphous material in dermis, which is PAS positive, diastase resistant and negative for congo red.
- Acitretin at a dose of 0.5 mg/kg/day is the drug with the strongest evidence of efficacy and the least reported side effects in the literature.
- The use of standardized tools for reporting clinical cases is crucial, especially in the case of rare diseases, where they constitute the main source of knowledge.

Abstract

Lipoid proteinosis, also known as Urbach-Wiethe disease, is a rare autosomal recessive genodermatosis, caused by mutations in the ECM1 gene. This results in the deposition of PAS-positive, hyaline-like material on the skin, mucosae, and internal organs. Here, we present a case report of a 48-year-old man with lipoid proteinosis who exhibited significant improvement after oral acitretin therapy. To address the lack of large case-control studies on lipoid proteinosis treatment, we performed a systematic review of the literature following the PRISMA 2020 criteria. The search was conducted in PubMed, Web of Science, Cochrane, and Scopus databases from inception until June 2023. To assess the methodological quality of case reports and case series, we used the critical appraisal tool JBI. We included 25 studies that met eligibility criteria. An overall sample of 44 patients with a histopathologically confirmed diagnosis was analyzed. Treatment ranged from systemic therapies (acitretin, etretinate, dimethyl sulfoxide, corticosteroids, D-penicillamine) to surgical or laser procedures. Regarding methodological quality, the main discrepancies arose in the reporting of participant characteristics and treatment interventions. Apparently, low-dose oral acitretin could have potential in managing lipoid proteinosis, exhibiting fewer side effects compared to other therapeutic agents. Further research is needed to establish more comprehensive and evidence-based treatment guidelines.

Introduction

Lipoid proteinosis (LP), also known as Urbach-Wiethe disease or hyalinosis cutis et mucosae, is a rare autosomal recessive genodermatosis with approximately 400

cases described worldwide[1]. It is caused by loss-of-function mutations in the extracellular matrix protein 1 gene (ECM1) on chromosome 1q21[1] (OMIM 602,201), which results in the deposition of positive hyaline-like periodic acid-shift (PAS) material in the skin, mucosa, and central nervous system[1,2]. Classically, onset occurs in babyhood with hoarse cry, while skin lesions can manifest in early childhood or years later[3]. Skin manifestation consist of thickening of the skin, yellowish infiltrated papules, as well as verrucous hyperkeratosis of the elbows, knees, and knuckles. In addition, skin fragility can occur during childhood, resulting in trauma-induced blisters. One of the most typical cutaneous signs of the disease is moniliform blepharosis, which consists of the presence of beaded papules on the eyelids[3].

Although LP generally follows a benign course with a normal life expectancy, patients often experience embarrassment from skin lesions, which could significantly impact their mental health. Due to the potential to cause unesthetic scars, early treatment should be attempted to prevent future consequences in the psychosocial sphere[4]. In the current scientific literature, oral treatment as well as different surgical and laser interventions have been reported in single case reports with diverse outcomes. Due to the rarity of this disorder, there is no standard evidence-based treatment available[5]. For this reason, in this study, we present a case report and a systematic review to synthesize the scientific literature and to propose the bases of treatment of this uncommon and frequently missed diagnosis.

Material and methods

Protocol and registration

Before the start of the study, the case report and systematic review protocol was prospectively registered in the Open Science Framework (OSF) with the registration DOI: https://doi.org/10.17605/OSF.IO/WUVZ2. For the case report we followed the Case report (CARE) checklist[6] and for the systematic review the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[7]. Informed consent was obtained for the publication of images and clinical data.

Protocol deviations:

Studies using laser interventions as treatment for LP were also considered.

Data sources and search strategy:

Two independent reviewers (RB-M and J-CH-R) performed a systematic search in PubMed, Web of Science, Cochrane Library, and Scopus from the inception of the databases up to June 2023. No language or date filters were employed. Specific search terms for lipoid proteinosis ("lipoid proteinosis", "Urbach-Wiethe") and treatment ("treatment", "acitretin", "etretinate", "dimethylsulfoxide" "penicillamine") were combined using the Boolean operators "AND" and "OR".

Eligibility criteria and outcomes of interest

We developed the eligibility criteria following the PIO framework (population, intervention, and outcome).

Inclusion criteria:

- P: Patients with histopathologically confirmed diagnosis of LP (gold standard) and/or genetic test.
- I: Systemic, laser or surgery treatment of cutaneous manifestations of LP.
- O: Studies reporting skin manifestations as the main outcome. Voice status would be assessed as a secondary outcome if studies report it.

Exclusion criteria:

- Any study design that was not written in English, Spanish, French, or German.

Data management and selection process:

Mendeley Desktop (version 1.19.8) was used to assess duplicates and perform the screening process. This step was manually double-checked. Subsequently, two independent reviewers (RB-M and J-CH-R) screened records by title and abstract, and then carried out a complete read of the studies to select those that met the mentioned criteria. Any disagreement on study inclusion was considered with a third reviewer (J-JP-J).

Assessment of methodological quality:

Two independent reviewers (RB-M and J-CH-R) used the Joanna Briggs Collaboration (JBI) checklist[8,9] to assess the methodological quality of the case reports and case series included in the systematic review. JBI tools evaluate the methodological quality through eight and ten items for case reports and case

series, respectively. The overall judgment is assorted as 'Yes', 'No', 'Unclear' and 'Not applicable'. The inter-rater agreement rate was calculated.

Data extraction and qualitative synthesis:

The following data were extracted: authors, year of publication, patient characteristics, clinical presentation, ancillary diagnostic test, treatment and dosage, side effects, cutaneous and voice outcomes. In case the information of interest was not reported, the corresponding authors of the studies were contacted by J-CH-R via email. One corresponding author was contacted, but without response[10].

Case report

A 47-year-old man, child of consanguineous parents (cousins), was referred to our dermatology department of Virgen del Rocío University Hospital (Seville, Spain) with worsening of multiple cutaneous and otorhinolaryngological manifestations in June 2022. There was no family history of similar lesions.

Our patient has suffered from severe hoarseness and weak cry since birth. At the age of 10 years old, trauma-induced vesicles started to appear on his face and upper body. Progressively, the skin of the knuckles and elbows thickened as infiltrated and verrucous papules appeared (Figure 1a,1b). Physical examination revealed very dry skin. Extensive atrophic scars and waxy, infiltrated yellow papules were present on his face. A total of 4.5% body surface area (BSA) was affected. There was no history of photosensitivity, and the lesions did not show in

any predominant sun-exposed areas. On the margins of the upper and lower /eyelids, multiple beaded papules could be found (Figure 1c). Additionally, his lips and tongue were slightly thickened with reduced mobility, but without speech impairment or dysphagia. He related episodes of oral ulcers and xerostomia. He was otherwise healthy and never manifested epilepsy or other neurological signs. Haematological and biochemical examinations did not show any abnormalities.

Given the clinical examination, lipoid proteinosis, erythropoietic protoporphyria, and epidermolysis bullosa were considered potential diagnostic options. For this reason, a laryngoscopy, a cerebral computed tomography (CT) scan, and a skin biopsy were performed. Laryngoscopy revealed thickening of the vocal cords with uneven surface. Furthermore, CT revealed bilateral symmetrical calcifications located in the temporal lobes, affecting the hippocampal (Figure 1d). A skin biopsy (Figure 2) of the hyperkeratotic plaque in the left elbow revealed epidermal hyperkeratosis, hyaline infiltrate throughout the dermis, and thickening of the basement membrane. The infiltrate was positive for periodic acid-Schiff (PAS) stains, but diastase-resistant and negative for Congo red. An oropharynx and larynx biopsies were also carried out. The genetic test for the ECM1 gene is not currently available. Altogether, the diagnosis of LP was established.

In 2016, at the age of 41 years old, he required a permanent tracheostomy due to chronic dyspnoea. Regarding cutaneous manifestations, for several years, he has undergone treatment with emollient and keratolytic creams, without any improvement. In June 2022, at the age of 47 years old, our patient started oral acitretin treatment at a dose of 0.5 mg/kg/day, resulting in a significant

improvement in skin thickening and verrucous lesions, already evident after 3 months, with another noticeable improvement after one year (Figure 3). There was slight improvement in moniliform blepharosis and a notable decrease in laryngeal mucosa thickness observed by laryngoscopy. Despite this reduction, the permanent tracheostomy was retained following consensus between otorhinolaryngologists and the patient. No new skin and mucosal lesions were observed throughout the treatment period. Furthermore, no hematological or cutaneous side effects were reported.

Results

Study selection

The electronic search in the databases retrieved a total of 251 studies. Consecutively, an electronic and manual duplicate removal was carried out. After removing duplicates, the screening process, and complete reading of those potential records that could meet eligibility criteria, 25 studies[1-4,10-30] were included. One of the final selected studies[25] was identified by citation searching. Figure S1 shows the PRISMA flow chart. The list of studies excluded (N = 53) and its reasons can be found in the Supplementary Material (Table S1).

Study design and population characteristics

A sample of 44 patients with histopathologically confirmed diagnosis of LP was analyzed. There were 20 males and 24 females with a mean age of 16.9 years, ranging from 2 to 41 years. In 26 of the cases (59%) there was second grade

consanguinity[1,2,10,11,13,16,17,24,26,28]. Genetic tests were performed in 9 patients[1-3,15,22,30]. Table 1 summarizes the mutations identified.

Hoarseness and weak cry (42/44, 95.4%) was the most common symptom, present at birth in 14 of the patients[1,4,11,14,17,18,20,22,26]. A history of trauma-induced blistering and acneiform scarring was present in 32 of the 44 patients (73%)[1-4,10,13,14,16-22,24-26,30]. Cutaneous examination revealed atrophic and hypochromic scars, along with yellowish waxy papules and verrucous skin plaques, predominantly affecting the facial region, upper-trunk and extremities (40/44, 90.9%)[1-4,10-24,26-30]. Multiple beaded papules (moniliform blepharosis) were present throughout the eyelid margins in 61.4% (27/44) of the cases[1-3,10,11,14,15,17,18,21-30]. In 32 out of 44 subjects (73%) the tongue was slightly enlarged with a short, thick frenulum that significantly limited mobility [1-3,10,12,13,15-18,21,22,24,25,27,28,30]. Neurological manifestations were relatively infrequent, observed in only five patients of the total sample (5/44, 11.4%)[11,16,17,26].

Table 2 summarizes the characteristics of the patients included in our study. Supplementary material (Table S2) shows a detailed description of each case.

Systemic treatments

Oral retinoids

A total of 27 patients treated with acitretin have been reported in the included literature[1-4,10,11,13,15,18,21,22,24,25]. Most of the cases received a dose of 0.5 mg/kg[1,3,4,10,13,18,22] and the duration of treatment ranged from 3 to 24 months. Only two studies did not report the dose and/or duration of treatment[24,25]. Details of

alternative treatment regimens can be found in the Supplementary Material (Table S3). Of those 27 patients, 17 subjects (62.9%) showed improvement in skin, being especially notable in 12 (44.4%) of them[2,3,10,13], while ten patients (37%) did not show any improvement[1,10,11,22,24]. Regarding voice, 17 patients (62.9%) showed improvement in hoarseness[2-4,10,13,18,21,22,25] and 9 (33.3%) did not[1,2,10,11,24]. Only in one case did not report about voice outcome[15]. Side effects, such as xerosis and xerostomia, appeared only in 2 patients[22]. Treatment had to be stopped in one case due to the appearance of multiple painful pyogenic granulomas[3].

Five patients were treated with etretinate using a dose of 1 mg/kg/day for 2 months followed by 0.5 mg/kg/day for 4 months[17,24,28]. Treatment had to be discontinued in two cases due to gastric discomfort[28]. Of the remaining three patients, two showed notable improvement[17], while the remaining one did not improve at all[24].

Dimethyl sulfoxide:

Dimethyl sulfoxide was used in five patients with a dose of 60 mg/kg/day for 3 years[12,26,29]. Only in one patient was a significant overall improvement described[29]. Regarding the remaining patients, dimethyl sulfoxide showed no efficacy in three cases[26], and one patient's report lacked documentation on cutaneous or vocal outcomes[12]. Bad breath was observed in four patients[26,29].

Corticosteroids:

One patient was treated with corticosteroids[30]. Specifically, submucosal oral injections were administered for one year, followed by oral and topical

corticosteroids for two years, with notable results. No side effects or analytical changes were observed.

For the management of the initial stage of the disease, characterized by spontaneously occurring or trauma-induced vesicles, bullae, and scars, Kaya et al.[20] employed an oral prednisolone regimen at a daily dose of 15 mg (1 mg/kg) for ten days. Additionally, the topical application of 0.1% diflucortolone-2-valerate and 1% chlorquinaldol cream was administered twice daily. This therapeutic approach accelerated the healing process and improved the cosmetic appearance of the scars.

D-penicillamine:

One patient was treated with 600 mg/day oral D-penicillamine for two years with modest improvement in skin texture and hoarseness[19]. No side effects were observed.

Human placental extract:

Srivalli et al.[28] attempt treatment with etretinate in two siblings. Since it was not tolerated due to gastric irritation, both patients received intramuscular injections of human placental extract on alternate days with topical application of placental extract gel. After two months of treatment there was a significant improvement in the appearance of the skin and in the quality of voice.

Other therapeutic alternatives

Laser

Fractional ablative CO_2 laser therapy has shown favorable results in the treatment of eyelid papules[11] and facial scars[23]. Specifically, for facial scar treatment, a regimen of four sessions of ablative laser resurfacing spaced by six weeks was employed. The laser was operated at a pulse energy of 40mJ and a spot density of 100 spots/cm^2. Subsequently, nonablative radiofrequency sessions were conducted every two weeks for a total of six sessions.

Surgical procedures:

The primary complications of LP are mainly related to the psychological impact of unsightly scars. To improve their appearance, dermabrasion[14,16] and chemical peels, such as 80% phenol[14], Jessner's solution[16], or 35% trichloroacetic acid[16] have been used.

In addition, alternative treatments, such as surgical removal[16], curettage, or cryosurgery[27], have shown promising results in the treatment of papules and hyperkeratotic plaques.

Methodological quality assessment (JBI):

The included studies were assessed using the standard JBI Critical Appraisal Checklist for Case Series and Case Reports[8,9]. Specific results for each study can be found in Tables S4 and S5. The inter-rater reliability was 95.5% (212/222).

Most of the case reports provided complete descriptions of the demographic characteristics and clinical history of the patients, except five of them[4,12,18,19,29]. Most reports included detailed explanations of diagnostic tests, some even incorporating histopathological or CT scan images, as well as genetic test results. However, a significant proportion of the cases did not adequately address the differential diagnosis[4,18,19,23,27,29,30]. Almost all studies included a detailed description of treatment procedures, except for two case reports[12,25]. Excluding one case report[12], the remaining described post-intervention outcomes, although they did not include pre and post-intervention images[19,20,25]. Only some of the authors[3,14,21,27,29,30] reported the possible adverse events.

Detailed clinical information from the patients was provided in all case series, except for five cases[13,15,17,28], which did not include demographic characteristics. Almost all studies clearly reported intervention outcomes, but only Bakry OA. et al.[13], Dertlioglu SB. et al.[10] and Ozkaya-Bayazit E. et al.[26] incorporated images before and after intervention.

Discussion

LP is a rare progressive autosomal recessive disorder with infiltration of hyaline material in the skin, mucosa, and internal organs[31].

In 20% of cases, consanguinity of the parents is observed[31], although in our systematic review the consanguinity rate reached 59%. The age of diagnosis is

highly variable, but the clinical manifestations begin in childhood and affects both sexes equally.

The diagnosis is usually suspected based on clinical findings, but the gold standard technique is histopathological study. Skin biopsy highlights epidermal hyperkeratosis and the presence of eosinophilic amorphous material in the papillary dermis, the basement membrane, and around the capillaries. The material is PAS positive and diastase resistant. It is differentiated from amyloid by its negative staining with Congo red stain[2].

Currently, there is no curative intervention for LP. Despite its characteristic indolent progression and the absence of a demonstrable impact on life expectancy, the unsightly scarring can cause a profound impact in the psychological sphere. Therefore, it is important to explore therapeutic alternatives to relieve its symptoms.

In vitro studies indicated that oral retinoids modulate the metabolism of the connective tissue matrix of the basement membranes[22]. Administration of acitretin at doses of 0.5 mg/kg/day has been reported to result in a variable improvement in cutaneous papules and plaques, reduction of blistering, and a concurrent improvement in mucosal lesions and hoarseness. Some authors declare that acitretin is more effective in treating mucosal lesions compared to skin lesions[3], but in our systematic review we found similar improvement. In our case report, there was notable improvement in skin, with a remarkable disappearance of verrucous plaques on the elbows and knuckles and softening of the skin. Improvement in

hoarseness was difficult to assess as the patient had a permanent tracheostomy, but decreased pharyngeal mucosal thickness was observed on laryngoscopy.

Acitretin represents the treatment with the most substantial evidence within the primary included studies, with approximately 63% of the patients experiencing overall improvement in both skin and voice. In most of the reviewed cases, acitretin was well tolerated, with only mild side effects recorded, such as xerosis or xerostomia in two cases. It was discontinued in one case due to the onset of multiple painful pyogenic granulomas. Despite these positive aspects, the absence of a standardized and objective measurement tool, alongside with the low methodological quality of the studies, makes it difficult to provide a strong recommendation.

Only one case report discussed the management of the initial stage of the disease with systemic corticosteroids[20]. Although the development of new lesions ceased with the treatment and the cosmetic outcome was ameliorated, it remains unclear whether the improvement was a result of the treatment or the natural course of the disease.

As previously stated, the main limitation to draw conclusions is the lack of accuracy in documenting both patient's clinical characteristics and treatment protocols. Several reports merely mentioned the kind of intervention, omitting essential information such as dosage, duration, or frequency, making it difficult to reproduce the results.

Most of the cases inadequately reported assessments of voice and skin outcomes. This is particularly notorious in voice assessment, where the evaluation was limited to the presence or absence of hoarseness and weak cry. Moreover, in the evaluation of skin manifestations, none of the studies incorporated objective measures such as BSA or any patient-reported outcome measures[32]. For this reason, we consider of crucial importance the performance of pre and postintervention images.

Methodological considerations

Considering the principal limitation of this systematic review to be the low methodological quality of the available clinical cases, and that this is a frequently encountered issue in rare disease research, we would like to emphasize the importance of implementing standardized tools for the comprehensive documentation of case reports. In particular, the utilization of frameworks like the CARE checklist[6], as applied in our study, ensures uniform and meticulous case report descriptions.

Limitations

One of the main limitations of our systematic review is inherent to the rarity of this genodermatosis. As there are no large case-control studies or clinical trials, we included case reports and case series. On the other hand, only studies written in English, Spanish, French or German were considered, so potential records could have been missed. In addition, the major limitation of our case report is the absence of genetic testing.

Conclusions

LP is an uncommon genodermatosis, with limited cases reported. In this study we add a new case report of LP to the current literature, and we perform the first systematic review for managing the clinical skin manifestations of this disease. The absence of case-control studies or clinical trials reported in the literature emphasizes the importance of accurate documentation of clinical characteristics and treatment protocols in case reports and case series, as they constitute the main source of information for rare diseases. Our principal motivation for conducting this systematic review is providing a better healthcare and treatment for these patients and aiding healthcare professionals in making clinical decisions. However, the diversity of treatments and the absence of standardized consensus in measuring clinical outcomes, precluded us to make sound clinical recommendations.

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Figure legends

Figure 1. Patient's clinical and imaging features. (a,b) Skin thickening, hyperkeratosis and multiples verrucous papules on the elbows and knuckles. (c) Moniliform blepharosis: multiple beaded papules on the upper and lower eyelids. (d) Cerebral computed tomography scan showing bilateral symmetrical calcifications of the temporal lobes (marked in red as *).

Figure 2. Histopathology. (a) Deposits of amorphous hyaline material in the papillary dermis, basement membrane, and around the capillaries (H-E, 2x). (b) Positive Periodic Acid-Schiff (PAS) staining.

Figure 3. Remarkable improvement of hyperkeratotic plaques over elbows (a) and papules over the dorsum of the knuckles (b) after acitretin therapy.

Table 1: Mutations identified in the articles reviewed.

	Position	Sequence change	Mutation type	Predicted protein change	Location
Akoglu G. et al. (2011)[2]	Exon 3	NA	Nonsense	p.R53X	Turkey
Carnevale C. et al. (2017)[3]	Exon7/Exon 10	c.735_736delTG/ c.1446_1450delCCCTG	Nonsense/Frameshift	p.C245X/p.A484LfsX9	Italy
Chelvan H. et al (2011)[15]	Exon 2	c.94C>T	Nonsense	p.Q32X	India
Ghazawi F. et al (2019)[1]	Exon 9	c.1387G>T	Nonsense	p.Glu463X	Pakistan
Luo X. et al. (2016)[22]	Exon 10 Exon 7/10	c.1522C>T c.841C>T/c.1596delG	Nonsense Nonsense/frame-shif	p.R508X p.R281X/p.R532RfsX3	China China
Zhang R. et al (2014)[30]	Exon 6	c.658T>G	Missense	p.C220G	China

NA: Not available.

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Demographic characteristics	Gender:	Male: 20 of 44
		Female: 24 of 44
	Mean age, years (SD): 16.9 (11.77)	
	Consanguinity: 26 of 44 (NA = 9)	
Clinical presentation	Hoarseness: 42 of 44 (NA = 1) History of vesicles and scarring after trauma: 32 of 44 (NA = 5) Eyelid papules: 27 of 44 (NA = 2) Limitation of oral movement: 32 of 44 (NA = 3) Acneiform scars+ Warty papules + Hyperkeratotic plaques: 40 of 44 (NA = 0) Neurological symptoms: 5 of 44 (NA = 6)	
Diagnostic test	Skin biopsy: 43 of 44 (NA = 0)	
	Cranial CT scan: 30 of 44 (NA = 0)	No abnormalities: 23 of 30
		Bilateral temporal calcifications: 7 of 30
	Skull X-ray: 5 of 44	No abnormalities: 1 of 5
		Calcifications in the sella turca: 4 of 5
	MRI: 1 of 44	No abnormalities: 0 of 1
		Bilateral temporal calcifications: 1 of 1
	Genetic test: 9 of 44 (NA = 0)	
	Indirect laryngoscopy: 36 of 44 (NA = 0)	No abnormalities: 6 of 36
		Thickened vocal cords: 30 of 36

Therapy	Acitretin: 27 of 44 Etretinate: 4 of 44 Dimethyl sulphoxide: 5 of 44 Systemic corticosteroids: 2 of 44 D-penicillamine: 1 of 44 Human placental extract: 1 of 44 Topical treatment: 2 of 44 Laser: 4 of 44

Table 2: Demographic characteristics, clinical presentations, diagnostic tests and therapies of the patients included in the review:

SD: Standard deviation. NA: Not available. CT: computed tomography. MRI: Magnetic resonance imaging

CPD Questions

Question 1. In which of the following genes is the mutation that causes lipoid proteinosis located?

(a) CFTR
(b) DMD
(c) EMC1
(d) HTT
(e) FMR1

Question 2. What is the term for the presence of multiple beaded papules on the eyelids, characteristic of lipoid proteinosis?

(a) Blepharitis marginalis
(b) Moniliform blepharosis
(c) Distichiasis
(d) Congenital trichiasis
(e) Blepharochalasis

Question 3. For which of the following drugs is there no published evidence of its efficacy in the treatment of lipoid proteinosis?

(a) Dimethylsulfoxide
(b) Penicillamine
(c) Etretinate
(d) Human placental extract
(e) Methotrexate

Question 4. What is the right dose of acitretin to treat lipoid proteinosis symptoms?

(a) 0.25 mg/kg/day
(b) 0.5 mg/kg/day
(c) 1 mg/kg/day
(d) 5 mg/kg/day

(e) 0.05 mg/kg/day

Question 5. For which of the following stains is the histological study of lipoid proteinosis positive?

(a) Congo Red stain
(b) Giemsa
(c) Toluidine blue stain
(d) Periodic acid-Schiff stain
(e) Wright's stain

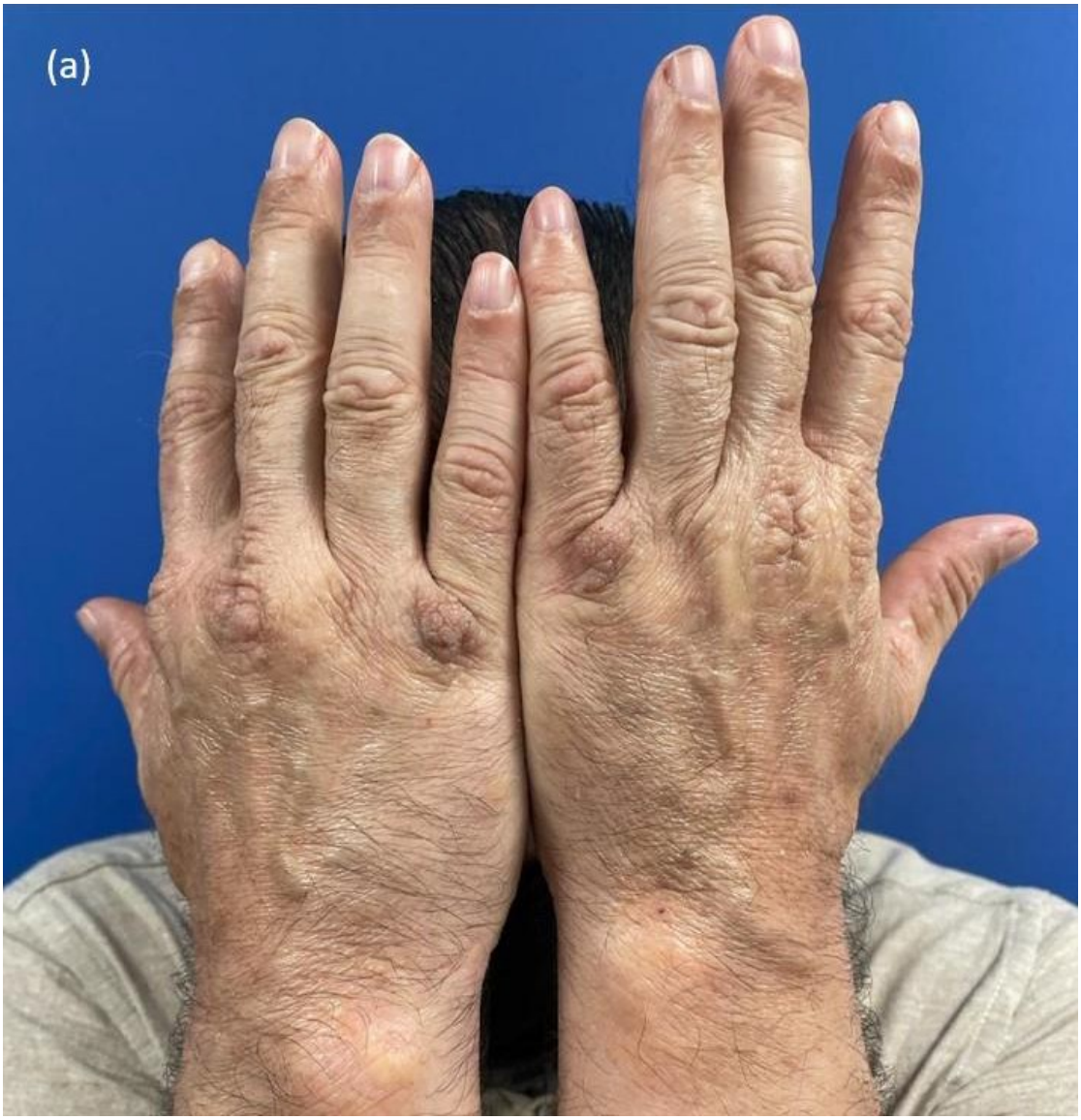


Figure 1a
151x156 mm (DPI)

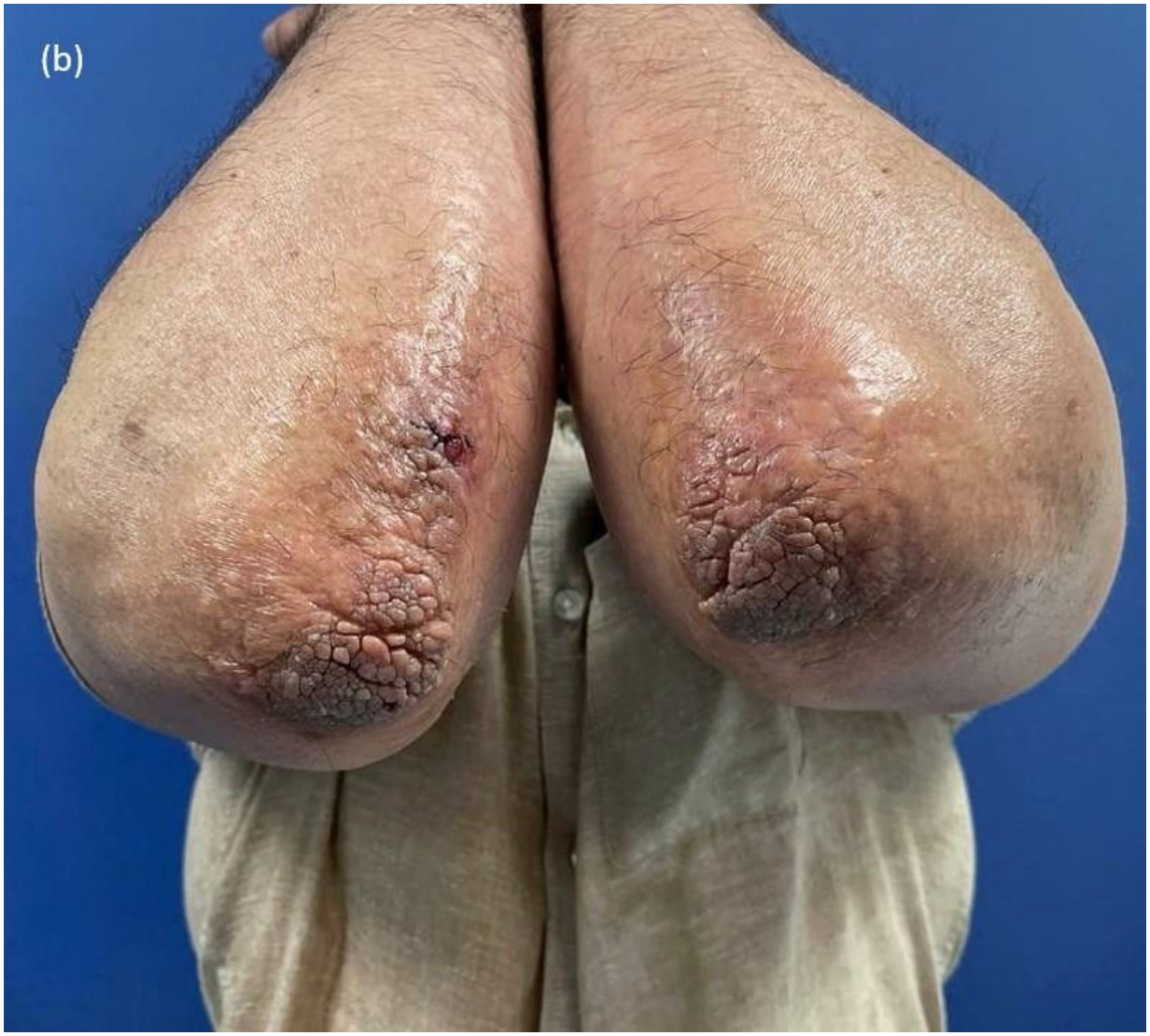


Figure 1b
173x156 mm (DPI)

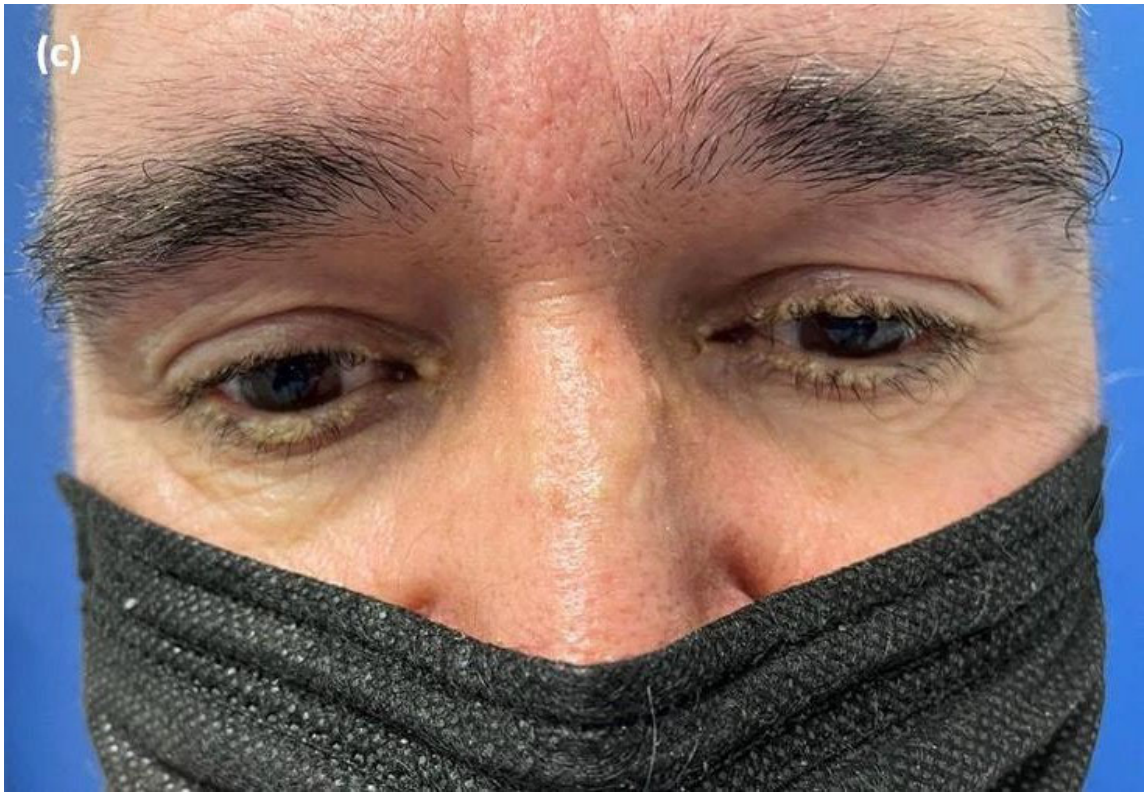


Figure 1c
155x107 mm (DPI)

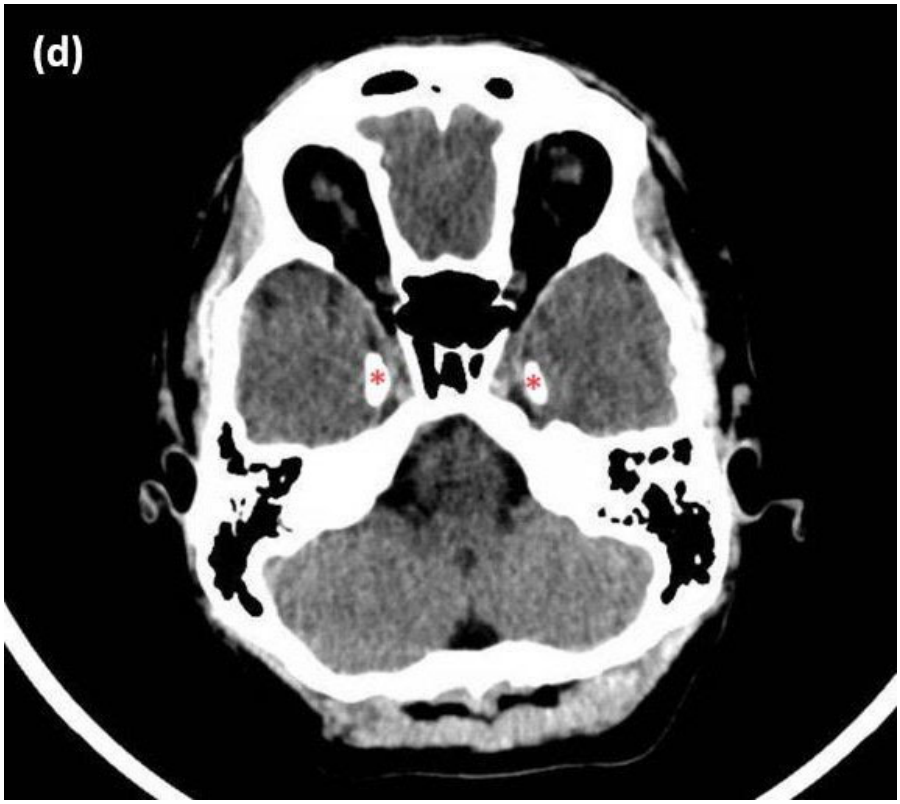


Figure 1d
121x108 mm (DPI)

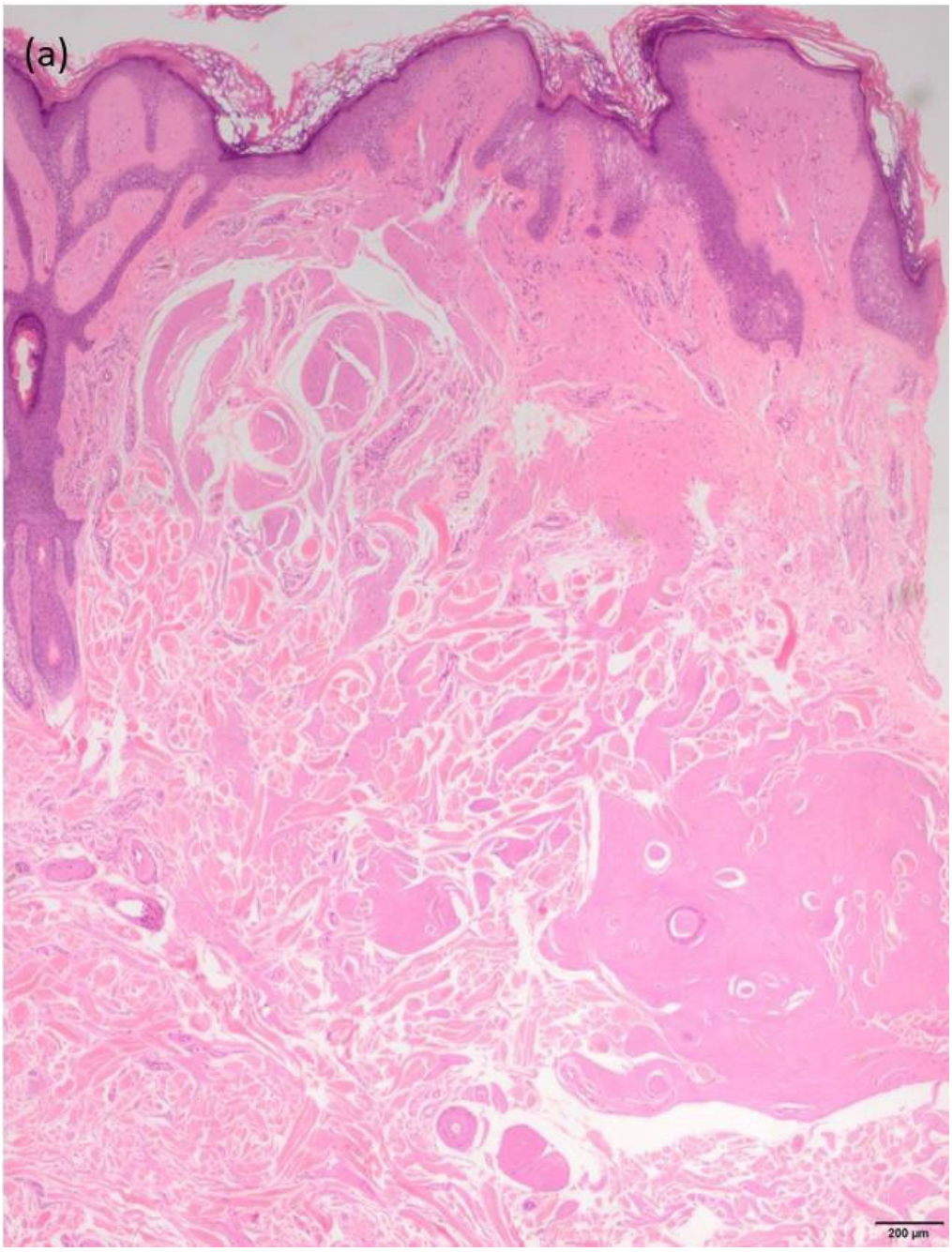


Figure 2a
137x181 mm (DPI)

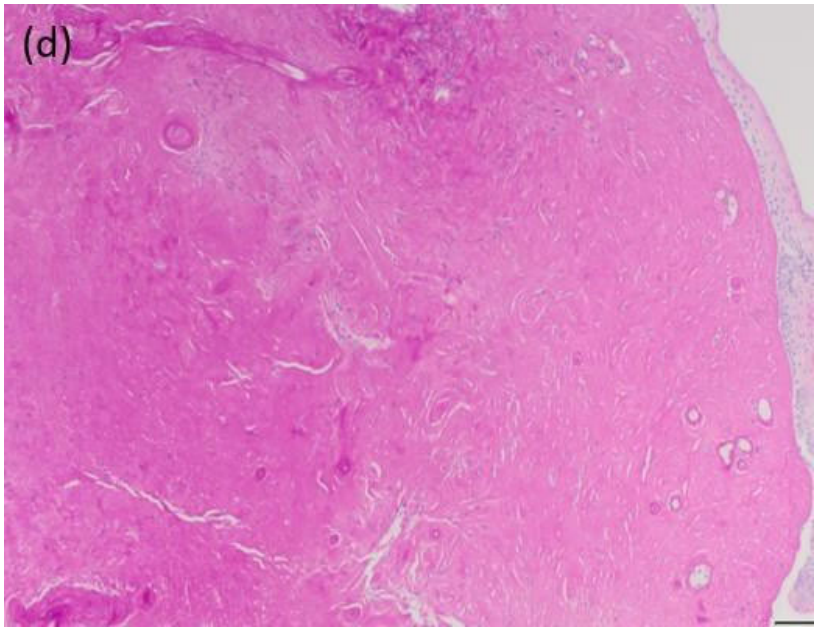


Figure 2b
110x85 mm (DPI)

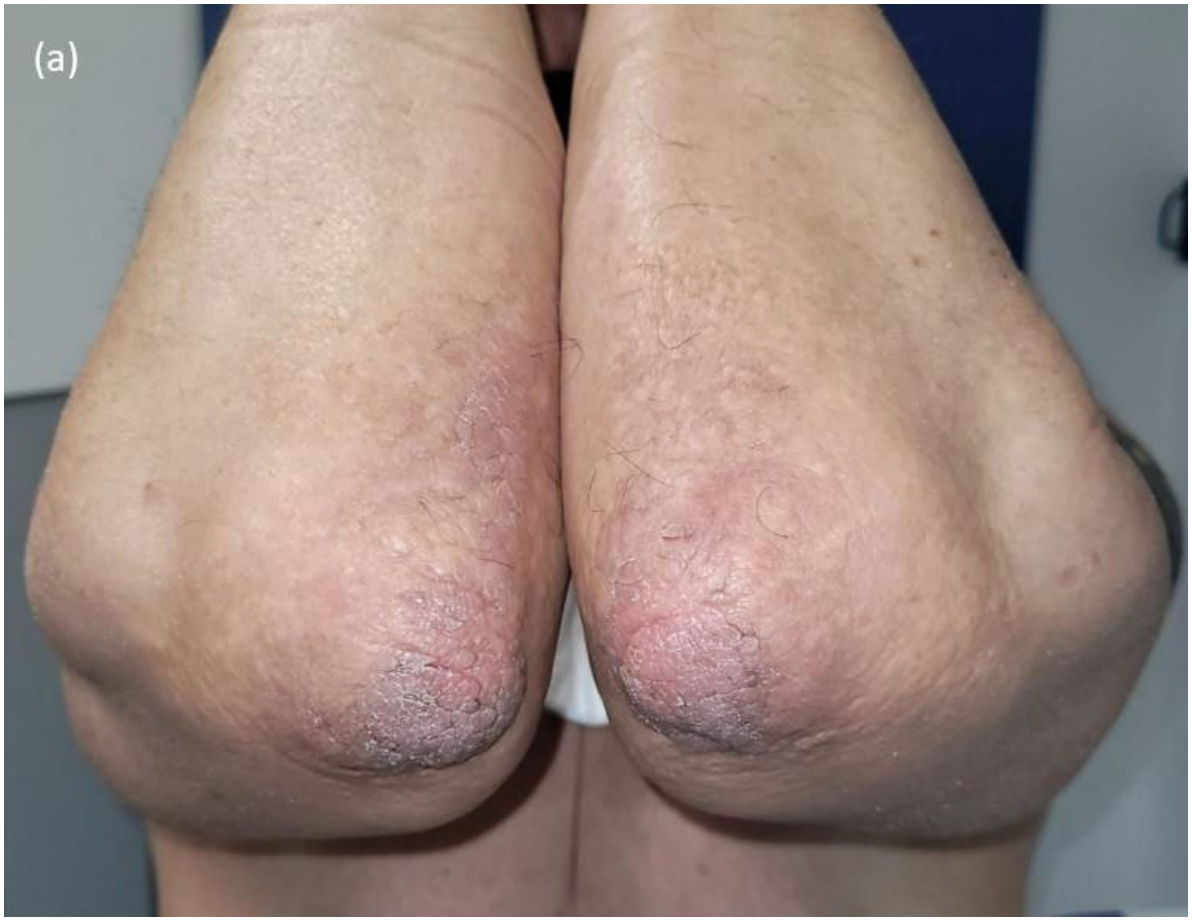


Figure 3a
161x124 mm (DPI)

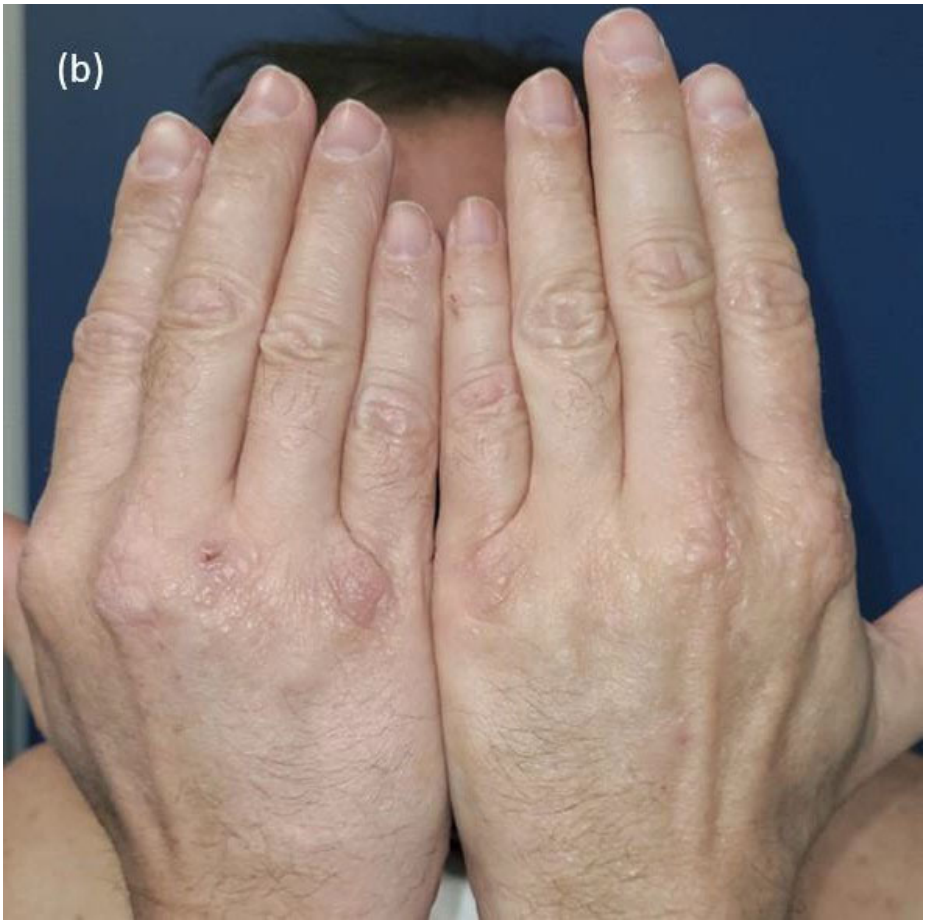
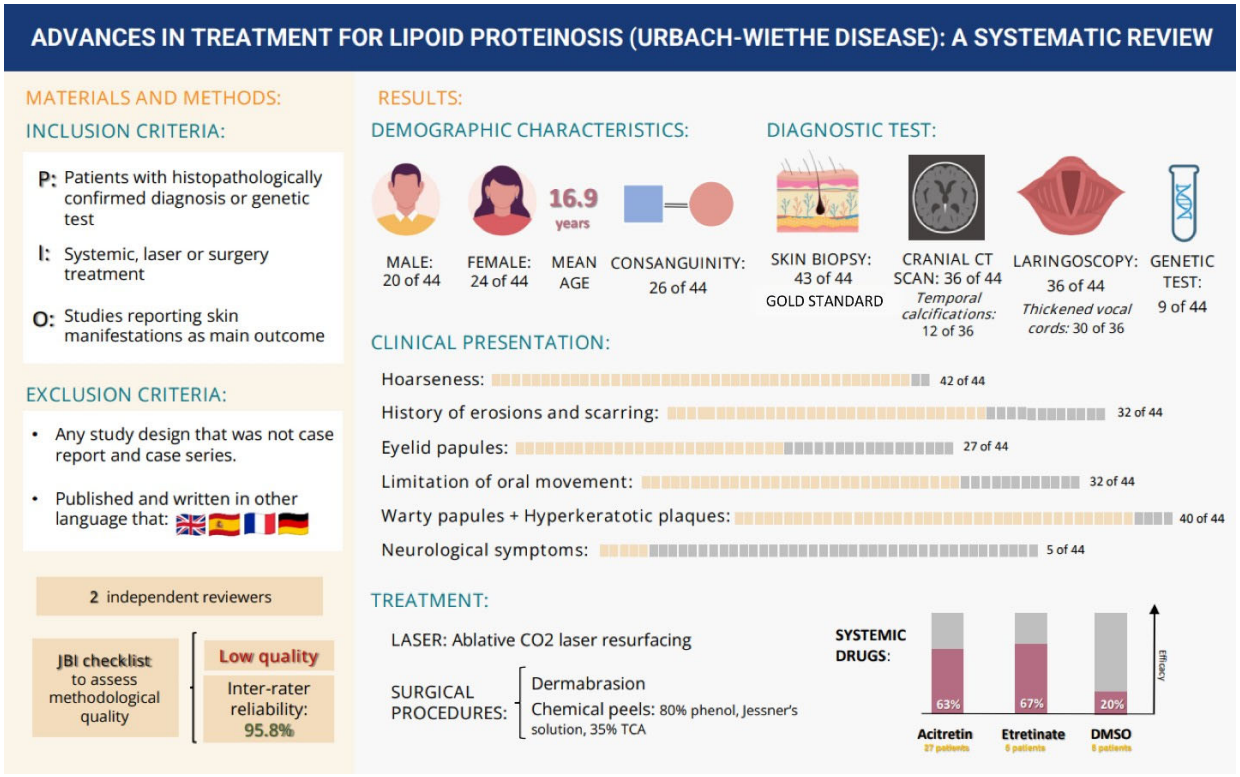


Figure 3b
125x124 mm (DPI)



Graphical Absract