Dermatology Practical & Conceptual

Acquired Perforating Dermatosis: Clinical and Histopathological Analysis of 95 Patients From One Center

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ABSTRACT

Introduction: Acquired perforating dermatosis (APD) is a disease group characterized by transepidermal elimination of dermal connective tissue materials such as collagen, elastic fibers, and keratin through the epidermis and observed with pruritic skin lesions.

Objectives: In this study, we aim to clarify the clinical, histopathological, and dermoscopic characteristics of APD, identify the associated systemic disease, and figure out treatment options.

Methods: This study was designed as a single-center retrospective, observational, cross-sectional study. We evaluated all accessible APD cases between January 2004 and June 2022 in a tertiary care hospital.

Results: A total of 95 patients with confirmed APD were included in the study. Sixty percent of the patients were women and 40% were men. The median age at diagnosis was 63.1 years (35-85 years). The most common site of lesions was the lower extremities which were detected in 86.31% of the patients. The concomitant systemic disease was identified in 84.21% of the patients. The most common systemic disease was type 2 diabetes mellitus (65.26%). Antihistamines and topical corticosteroids were the most commonly prescribed treatment agents.

Conclusions: Transepidermal elimination of dermal connective tissue components is a feature of APD and the disease usually presents with pruritic papules and nodules with central keratotic crust or plug. The diagnosis of APD requires a clinical examination and histological investigation. APD is usually accompanied by systemic comorbidities. There are several topical and systemic medications available for APD, however, sometimes the therapy might be challenging.

Introduction

Acquired perforating dermatosis (APD) is a disease group characterized by transepidermal elimination of dermal connective tissue materials such as collagen, elastic fibers, and keratin through the epidermis and observed with pruritic skin lesions. The disease can be divided into 4 different groups: reactive perforating collagenosis (RPC), elastosis perforans serpiginosa (EPS), perforating folliculitis (PF), and Kyrle disease (KD).

The type of dermal connective tissue material is important for classifying diseases. RPC is characterized by the transepidermal elimination of collagen fibers, EPS with elastic fibers, and KD with abnormal keratin. The characteristic lesions of the disease are pruritic umbilicated papules and nodules with a central keratotic crust or plug which often appear on the extensor surfaces of the extremities. Numerous pathways have been identified for APD, but the pathogenesis of transepidermal elimination is still unclear. APD is usually accompanied by systemic diseases like diabetes mellitus, and chronic kidney disease [1-3].

Objectives

In this study, 95 patients with APD who had been diagnosed through clinical and histological investigation were examined. With this investigation, we aim to clarify the clinical, histopathological, and dermoscopic characteristics of APD, identify the associated systemic disease, and figure out treatment options.

Methods

This study was designed as a single-center retrospective, observational, cross-sectional study. We evaluated all accessible APD cases between January 2004 and June 2022 at Gazi University Faculty of Medicine, Department of Dermatology, Ankara, Turkey. The inclusion criteria were being compatible with the APD in the histopathological analysis and clinical examination.

The Gazi University Faculty of Medicine Local Ethical Committee approved the study. The Helsinki Declaration and Guidelines for Good Clinical Practice were used to perform the study, which was done by its most recent revisions. Patients fully informed consent was obtained.

Medical records of patients were retrospectively reviewed and demographic characteristics (gender, age at diagnosis, disease duration), clinical characteristics (disease subtype, distribution of skin lesions, characteristics of lesions, symptoms of patients, Koebner phenomenon, triggering factor of the disease, associated systemic comorbidities, distribution of associated systemic comorbidities by years), histopathological characteristics (analysis of the biopsy specimen, the type of disease, pre-diagnosis of the biopsy specimen), dermoscopic characteristics, and treatment characteristics (topical treatments, phototherapy, systemic treatments) of patients was obtained from dermatopathology records and our hospital database.

Patients were divided into three groups according to treatment response, good response (complete remission of skin lesions and clinical symptoms); partial response (partial disappearance of skin lesions and clinical symptoms); and no response.

Statistical Analysis

IBM SPSS Statistics Version 24.0 was used to perform the statistical analysis (Statistical Package for Social Sciences, SPSS Inc.). Descriptive statistics were used to examine demographic data and disease features. Continuous variables were shown as mean standard deviation (SD), and categorical variables were shown as frequency counts and percentages.

Results

Demographic and Clinical Characteristics

A total of 95 patients with confirmed APD were included in the study. Sixty percente (N = 57) of the patients were women and 40% (N = 38) were men. The median age at diagnosis was 63.1 years (35 - 85 years). The median duration of the disease was 21 months (ranging from 9 days to 30 years). The most common APD type was RPC, 83.15% (N = 79) of the patients, followed by 11.57% (N = 11) with EPC, 3.15% (N = 3) with KD, 2.10% (N = 2) with PF. The most common site of lesions was the lower extremities and was detected in 86.31% (N = 82) of the patients, trunk lesions in 78.94% (N = 75), upper extremity lesions in 68.42% (N = 65), head lesions in 3.15% (N = 3) of the patients. Multiple site involvement was present in 80% (N = 76) of the patients. Hyperkeratotic papules (48.42%, N = 46) and excoriated papules (36.84%, N = 35) were the frequently seen lesions; plaques and nodules were also observed (Figure 1). All patients had symptoms of pruritus, and 6.31% (N = 6) of the patients additionally suffered from pain. Koebner phenomenon was present in 25.26% (N = 24) of the patients.

Investigations for triggering factors revealed scabies history in 7 patients (7.36%), medicines in 5 (5.26%), SARS-CoV-2 vaccines in 2 (2.10%), pregnancy, and SARS-CoV-2 infection in 1 (1.05%) patient for each.

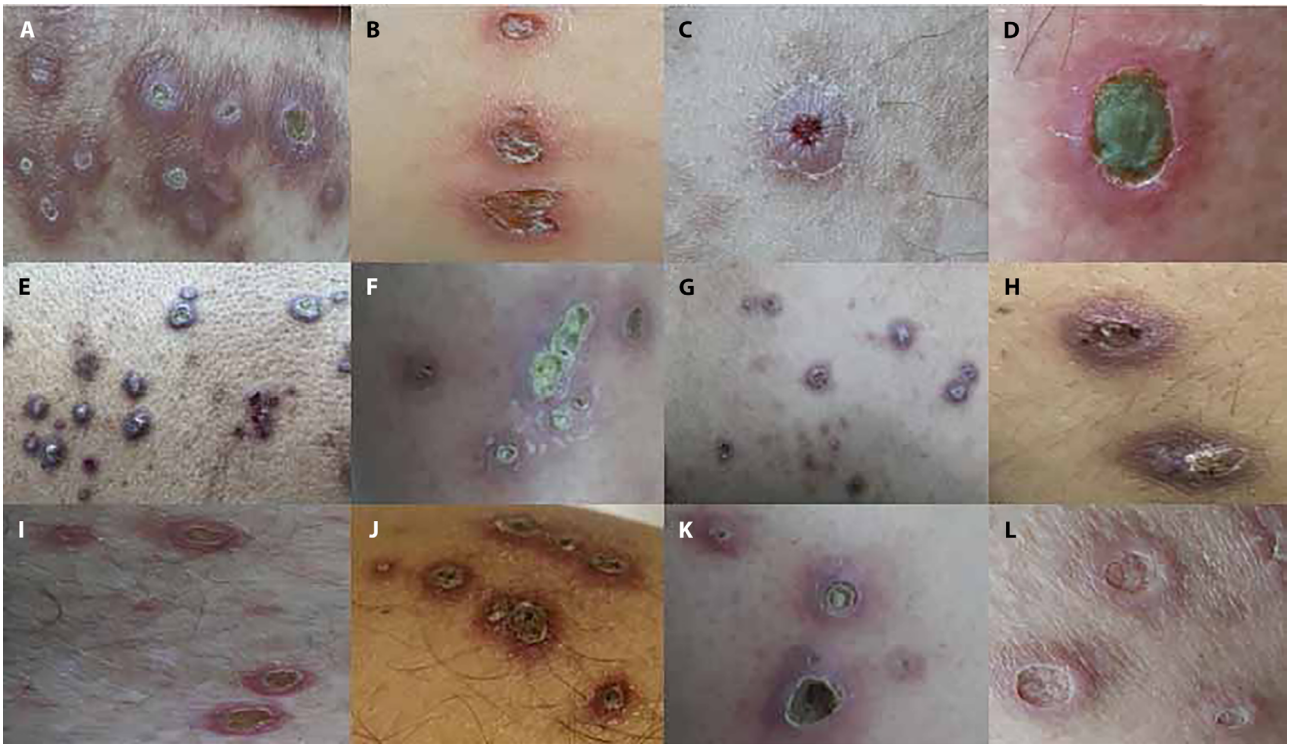

Figure 1. Clinical pictures from different acquired perforating dermatosis cases characteristic with umbilicated papules and nodules with central keratotic plug.

Concomitant Systemic Diseases

The concomitant systemic disease was identified in 84.21% (N = 80) of the patients. The patients associated systemic disorders are listed in Tables 1 and 2. The most common systemic disease was type 2 diabetes mellitus (65.26%, N = 62). 50% (N = 31) of patients with diabetes had been taking insulin, and 38.70% (N = 24) of patients had diabetes-related complications.

Hypertension was the second most common comorbidity and was found in 56.84% (N = 54) of the patients, 45.26% (N = 39) had a cardiovascular disease history, 23.15% (N = 22) of patients had at least one concurrent hepato-biliary disease, 17.89% (N = 17) of the patients had chronic kidney disease, 64.70% (N = 11) received renal replacement therapy (hemodialysis), none of the patients had renal transplantation., 16.84% (N = 16) of the patients had one or more malignancy history, and 25% (N = 4) of these malignancy patients were under active chemotherapy.

The other coexisting diseases included hypothyroidism (7.36%, N = 7), rheumatoid arthritis (3.15%, N = 3), familial Mediterranean fever (2.10%, N = 2), ankylosing spondylitis (1.05%, N = 1), dermatomyositis (1.05%, N = 1), and Gaucher disease (1.05%, N = 1).

Also, we analyzed the distribution of associated systemic comorbidities by years (Figure 2).

Table 1. Associated systemic diseases of patients

Comorbidities	% (N)
Diabetes Mellitus	65.26% (62)
Hypertension	56.84% (54)
Cardiovascular disease	45.26% (39)
Hepato-biliary disease	23.15% (22)
• Hepatitis B infection history	13.68% (13)
• Cholelithiasis	6.31% (6)
• Hepatosteatosis	3.65% (3)
• Cirrhosis	3.65% (3)
• Hepatitis C infection history	3.65% (3)
• Wilson disease	1.05% (1)
Pulmonary Disease	18.94% (18)
• Asthma	9.47% (9)
• COLD	6.31% (6)
• Interstitial lung disease	3.15% (3)
Chronic kidney disease	17.89% (17)
Malignancy history	16.84% (16)
• Colorectal cancer	5.26% (5)
• Hematological malignancy	4.21% (4)
• Hepatocellular cancer	3.15% (3)
• Bladder cancer	1.05% (1)
• Cutaneous malignancy	1.05% (1)
• Breast cancer	1.05% (1)
• Prostate cancer	1.05% (1)
• Schwannoma	1.05% (1)
Hypothyroidism	7.36%, (7)
Rheumatological disease	7.36%, (7)

Table 2. Comparison of concomitant systemic diseases of RPC, EPS, KD, and PF

Disease (N)	RPC (79 - 83.15%)	EPS (11 – 11.57%)	KD (3 – 3.15%)	PF (2 – 2.10%)
Diabetes Mellitus (62)	52 (83.87%)	6 (9.67%)	3 (4.83%)	1 (1.61%)
Hypertension (54)	46 (85.18%)	5 (9.25%)	2 (3.70%)	1 (1.85%)
Cardivascular Disease (39)	31 (79.48%)	4 (10.25%)	3 (7.69%)	1 (2.56%)
Hepato-Biliary Disease (22)	15 (68.18%)	5 (22.72%)	1 (4.54%)	1 (4.54%)
Pulmonary Disease (18)	13 (72.22%)	4 (22.22%)	1 (5.55%)	-
Chronic Kidney Disease (17)	14 (82.35%)	-	2 (11.76%)	1 (5.88%)
Malignancy (16)	11 (68.75%)	3 (18.75%)	2 (12.5%)	-
Hypothyroidism (7)	5 (71.42%)	2 (28.57%)	-	-

EPS = elastosis perforans serpiginosa; KD Kyrle disease; PF = perforating folliculitis; RPC = reactive perforating collagenosis.

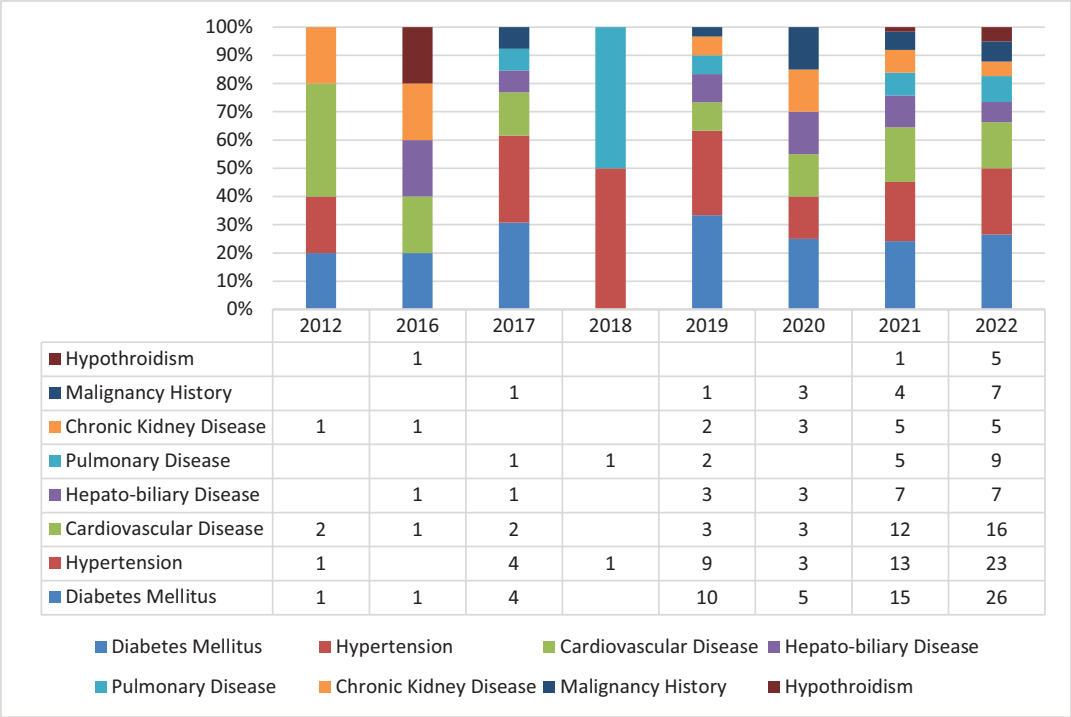

Figure 2. Distribution of associated systemic comorbidities by years.

Histopathological Characteristics

All patients (100%, N 95) had histopathological findings compatible with diagnosis of APD. In the histopathological analysis, basophilic debris was observed in all of the biopsy specimens. 78.94% of the biopsy specimens transepidermal collagen fiber elimination, 11.57% of the biopsy specimens transepidermal elastic fiber elimination, and 3.15% of the biopsy specimens transepidermal both collagen and elastic fiber elimination was detected (Figure 3).

After evaluating the pre-diagnosis of the biopsy specimen, in 69.74% (N = 66) of the biopsy specimens, where APD was suspected, other common pre-diagnosis was dermatitis herpetiformis (25.26%, n = 24), scabies (18.94%, N = 18), bullous pemphigoid pre-bullous stage (17.89%, N = 17), pityriasis lichenoides et varioliformis acuta (PLEVA) (16.84%, N = 16), neurotic excoriation (14.73%, N = 14) and prurigo nodularis (13.68%, N = 13).

Dermoscopic Characteristics

Dermoscopic analysis of 41 lesions from 18 patients was obtained (Table 3). Central keratotic plug was the common finding (100%), also white irregular halo (60.97%), peripheral erythematous zone (60.97%), thin scale ring surrounding the lesion (51.21%), and altered hair shaft (41.46%) were among the commonly seen characteristic. Dotted-linear (26.82%), hairpin (26.82%), and glomerular (4.87%) vessels were detected in the dermoscopic analysis of APD lesions (Figure 4).

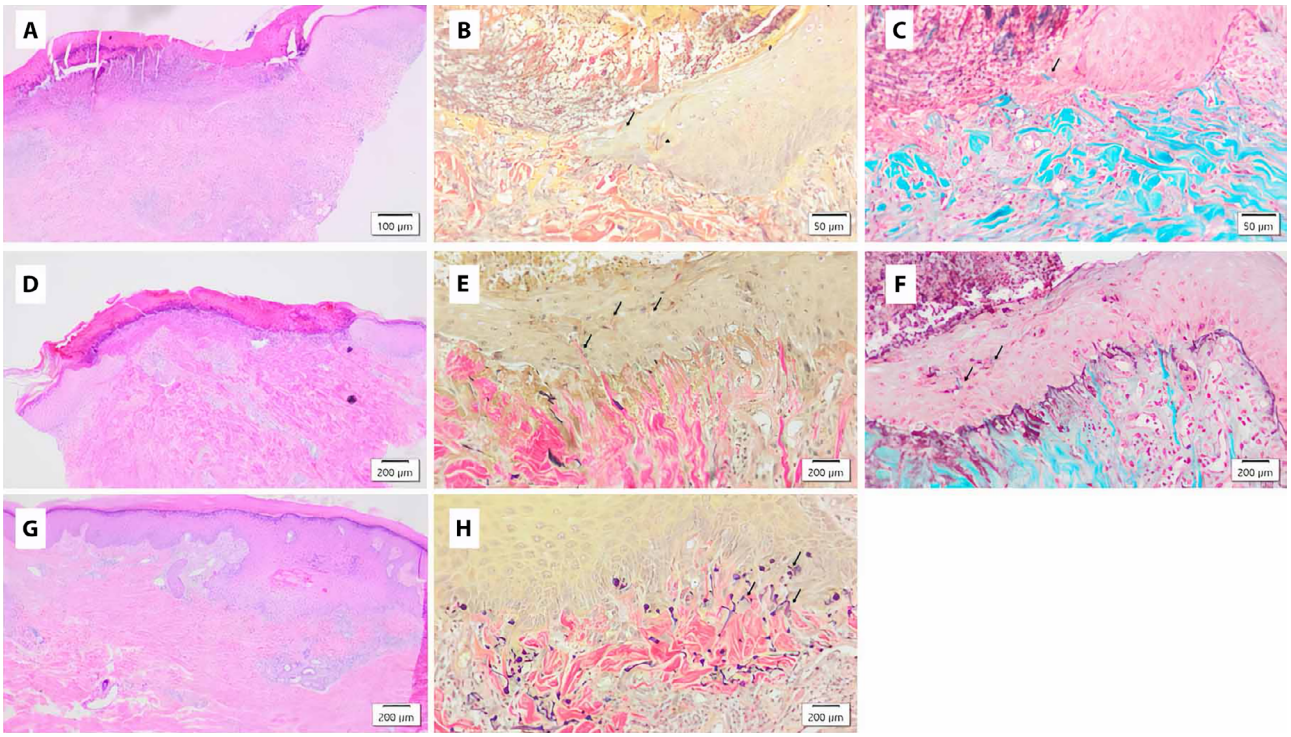

Figure 3. (A-C) A case with elastic and collagen fiber alteration from the epidermis. (A) Epidermal ulceration and basophilic inflammatory debris are observed (H&E stain). (B) Collagen fiber penetration into the epidermis was observed as red (arrow) and elastic fiber penetration was observed as black fiber (arrowhead) with Elastic Von Gieson (EVG) staining. (C) With Masson trichrome stain, green-colored (arrow) collagen fiber alteration was observed from the epidermis to the dermis perpendicularly. (D-F) In a case with only collagen fiber alteration from the epidermis (D). Ulceration and basophilic debris were observed (H&E stain). (E) Fibers altered from the epidermis in EVG stain are red (arrows), f. Green is traced in Masson trichrome stain (arrows). (G) In a case with only elastic fiber altered from the epidermis. (H) Epidermal hyperplasia (H&E stain). Fibers altered from the epidermis in the EVG stain were observed in black, perpendicular to the dermis (arrows).

Table 3. Dermoscopic analysis of acquired perforating dermatosis patients in our study

Dermoscopic Feature	N	%
Central keratotic plug	41	100%
White halo surrounding the lesion	25	60.97%
Peripheral erythematous zone	25	60.97%
Thin scale ring surrounding the lesion	21	51.21%
Altered hair shaft	17	41.46%
Dotted and linear vessels distribution radially	11	26.82%
Peripheral hairpin vessels	11	26.82%
Peripheral striation	11	26.82%
Peripheral hyperpigmentation	10	24.39%
Focal red dots/globules	6	14.63%
Peripheral glomerular vessels	2	4.87%
Pigment network-like area	2	4.87%
Peripheral pigment network	1	2.43%
Hemorrhage	1	2.43%
Red background	1	2.43%

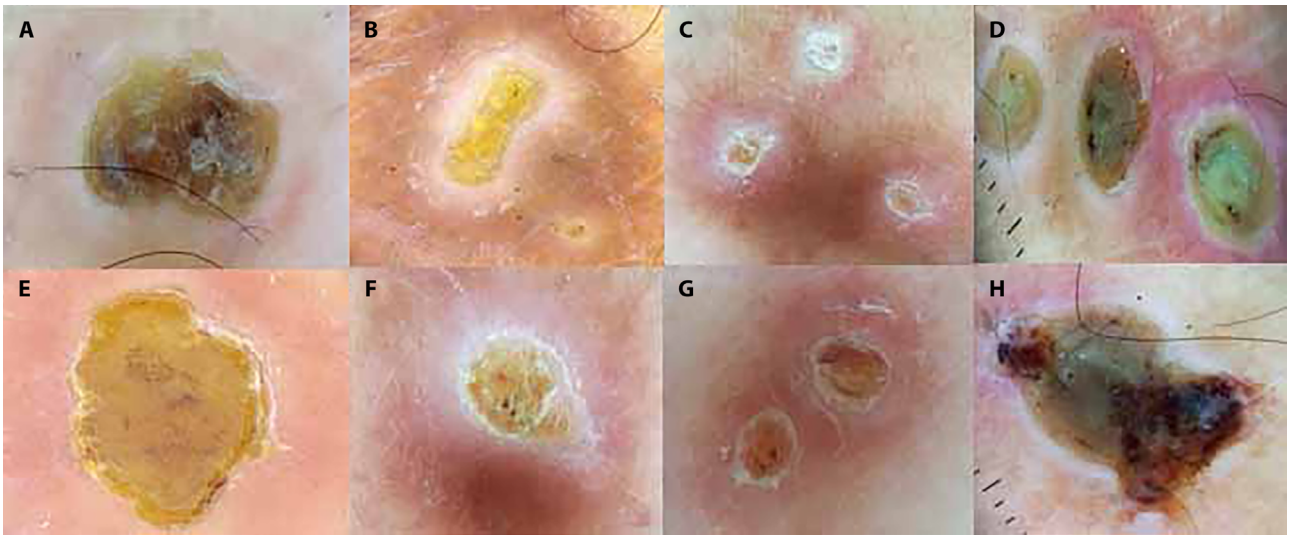

Figure 4. Dermoscopic pictures from different APD lesions. (A) Central keratotic plug, white irregular halo surrounding the lesion, peripheral erythematous zone; (B) Central keratotic plug, white irregular halo surrounding the lesion, altered hair shaft, peripheral hyperpigmentation, peripheral pigment network; (C) Central keratotic plug, white irregular halo surrounding the lesion, peripheral erythematous zone, peripheral hyperpigmentation, peripheral striation, peripheral hairpin vessels, dotted and linear vessels, thin scale ring surrounding the lesion; (D) Central keratotic plug, white irregular halo surrounding the lesion, peripheral erythematous, altered hair shaft; (E) Central keratotic plug, thin scale ring surrounding the lesion, Peripheral erythematous zone, dotted and linear vessels; (F) Central keratotic plug, white irregular halo surrounding the lesion, peripheral erythematous, altered hair shaft, dotted and linear vessels; (G) Central keratotic plug, thin scale ring surrounding the lesion, peripheral erythematous zone, dotted and linear vessels; (H) central keratotic plug, white irregular halo surrounding the lesion, pigment network-like area, altered hair shaft.

Treatment and Outcome Characteristics

Antihistamines and topical corticosteroids were the most commonly prescribed treatment agents (both 83.15%, N = 79) also, topical dapsone 2.10% (N = 2), topical retinoids 2.10% (N = 2), and topical calcineurin inhibitors 1.05% (N = 1) were used for treatment.

Systemic steroid treatment was applied in 31.57% (N = 30) of the patients, systemic retinoids (4.21%, N = 4), omalizumab (2.10%, N = 2), methotrexate (1.05%, N = 1), allopurinol (1.05%, N = 1) were also prescribed to patients. Photodynamic therapy was another treatment option and was used in 24.21% (N = 23) of the patients.

After treatment 35.78% (N = 34) of the patients had a complete response, 50.52% (N = 48) of the patients showed partial response and 10.52% (N = 10) of the patients had no response. Also, 5 patients (6.09%) died during the follow-up due to underlying systemic disease.

Conclusions

In this study we describe a case series of APD which involved 95 patients. In our patient cohort, RPC was the most common form of APD and occurred in 83.15% of the patients. We also observed cases of EPS (11.57%), KD (3.15%), and PF (2.10%).

Clinical examination plus histopathological analysis are gold-standard methods for the diagnosis of APD [1-3]. Characteristic lesions are umbilicated papules and nodules with central keratotic crust or plug. The most common lesions in our study were excoriated and hyperkeratotic papules, also with plaques and nodules. The lower extremity was the most commonly affected area in our study (86.31%) and it was similar to the literature [4,6,7,9-11]. Koebnerization such as linear localized lesions in the excoriated skin are observed in the APD and were detected in 25.26% of our patients. Other studies have reported different frequencies for the Koebner phenomenon (31% - 56%) [4,6]. Similar to the complaints of our patients, pruritus is the most common reported symptom of APD. However, pain which was experienced by 6.31% of our patients is also a reported symptom.

The pre-diagnosis of biopsy specimens in our study showed that APD was suspected in 68.28% (N = 56) of the patients, and dermatitis herpetiformis, scabies, bullous pemphigoid pre-bullous stage, PLEVA, neurotic excoriation, and prurigo nodularis were among the other common suspected diseases. APD is characterized by hyperkeratosis of stratum corneum, hyperplasia of the epidermis, central basophilic plug, basophilic debris, and transepidermal elimination of connective tissue materials, these features help to

differentiate it from prurigo nodularis, granuloma annulare, sarcoidosis, and infections [1,2,4].

Recently, Wang et al published a study on dermoscopic analysis of APD lesions in 39 patients and determined central homogeneous structureless area, dotted and linear vessels, and white halo periphery at the lesion among the most common characteristics of APD lesions [12]. In our study central keratotic plug, white halo surrounding the lesion, and peripheral erythematous zone were the most commonly observed dermoscopic features, also dotted, linear, hairpin, and glomerular vessels were detected. Elmas et al evaluated 60 lesions from 7 patients and identified the histopathologic counterpart of the dermoscopic analysis [13]. The central yellow-brown structureless area corresponded to the central keratin crust, peripheral white rim to invaginating epidermal hyperplasia, white structureless area to fibrotic collagen accumulation in the dermis, peripheral dotted vessels to superficial dilated vessels, and brown reticular lines to hyperpigmented basal keratinocytes [13]. Dermoscopy may be an alternative diagnostic tool in APD patients.

The pathogenesis of the disease is still unclear, and several factors have been identified. Vasculopathy, hypoxic conditions, and superficial trauma in genetically susceptible individuals can trigger necrobiosis of collagen fibers in the dermis and result in transepidermal elimination of these fibers, which is the main component of the disease. Additionally, increased toxic metabolites, oxidative stress, and advanced glycation end products may cause collagen cross-linking and abnormal collagen formation. Akoğlu et al investigated receptors of advanced glycation end products in the biopsy materials from APD patients and compared them with the healthy control group, and observed overexpression of receptors in endothelial cells, fibroblasts, and inflammatory cells of the dermis in APD patients [8]. Also, to understand the molecular pathogenesis of the disease, Gambichler et al analyzed lesional and perilesional CD34, matrix metalloproteinase-1 (MMP-1), tissue inhibitor of metalloproteinases-1 (TIMP-1), transforming growth factor-ß3 (TGF-ß3) levels [14]. Compared to perilesional skin, endothelial cells showed decreased CD34 immunoreactivity that indicates vascularization defect of lesions and also increased TGF-ß3, MMP-1, and TIMP-1 activity that can be associated with altered extracellular matrix metabolism has been detected in the lesional skin [14]. TGF-ß overexpression also has roles in fibrosis, case reports of concomitant APD and diseases characterized by fibrosis have been published. TGF-ß may be effective both on tissue fibrosis and tissue remodeling on APD [17]. In this study, we detected one APD patient with pulmonary fibrosis.

Because APD is frequently associated with systemic comorbidities such as diabetes mellitus, chronic kidney diseases, malignancies, and endocrinological diseases, it is important to consider and question patients in terms of concomitant systemic diseases (Table 4) [15,16,33-35]. In our study, 84.21% of the patients had at least one concurrent systemic disease; the most common diseases include diabetes mellitus, hypertension, and cardiovascular diseases.

Kawakami et al reported that diabetic microangiopathy may be a triggering factor for APD and theorized that a combination of trauma and dermal necrosis due to decreased blood flow secondary to diabetic microangiopathy may be an important factor in the pathogenesis of APD [15]. Diabetic complications such as neuropathy, nephropathy, and retinopathy are suggestive of diabetic microangiopathy [15]. All these point to the need to evaluate diabetic patients with APD in terms of diabetic complications. In this study, we observed 62 patients with type 2 diabetes mellitus, 38.70% of whom had diabetes-related complications. The mean HbA1c level was 7.70% (4.4% - 16.4%). Our findings also support the diabetic microangiopathy theory.

Morton et al observed APD patients with chronic kidney disease and theoretically explained skin changes secondary to renal failure, such as calcium microdeposition in the dermis, may lead to inflammatory response and connective tissue degradation, which can be observed in the APD pathogenesis [16]. In our study 17.89% of the patients had chronic kidney disease, and 64.70% of these patients were on hemodialysis.

Malignancies are one of the commonly detected comorbidities in APD patients [32,33]. In our study, 16.84% of the patients had a history of malignancy; colorectal cancer (31.25%), hematologic malignancies (25%), and hepatocellular cancer (18.75%) were the most common accompanying malignancies. Singh et al published a patient with APD associated with mediastinal synovial sarcoma [32]. Increased TGF-ß3 has been shown in APD skin specimens, and mesenchymal stem cells secrete growth factors such as TGF-ß3. It is theorized that cytokines such as TGF-ß3 may be a connection between APD and mesenchymal tumors [32].

Similar to our observation in our patient cohort, patients with APD may also have concurrent conditions such as hypothyroidism, infections, and pulmonary, hepatobiliary, and rheumatological diseases, all of which are thought to have a role in the pathogenesis of the disease [33,35].

Various factors are believed to trigger APD, including medicines, pregnancy, trauma, and scabies [18,26]. APD cases secondary to the use of tyrosine kinase inhibitors, tumor necrosis factor-α (TNF-α) inhibitors, VEGF inhibitors, and epidermal growth factor receptor (EGFR) inhibitors have been published [18,24-26]. Gilaberte et al reported a PF after TNF-α inhibitors (infliximab) treatment in a patient with rheumatoid arthritis [25]. There are several theories about how TNF-α inhibitors contribute to the pathophysiology of APD, including the idea of blocking TNF-α may

Table 4. Review of published clinical studies of acquired perforating dermatosis patients in the literature

Study	Country – Year	Patient Number (Female/ Male)	Mean Age at Onset (years)	Mean Duration of Disease (month)	Most Common Localication	Positive Koebner Phenomen (N-%)	Concurrent Systemic Disease (N-%)	Comorbidities (N)
Saray et al [4]	Turkey – 2006	22 (6/16)	48	6.2	Lower Extremity (16 - 72.7%)	7 – 31.8%	19 – 86.4%	CKD (16), DM (11), Hepatitis (6), Hypothyroidism (2), Renal Transplant Recipients (2), Tuberculosis Lymphadenitis (1)
Satti et al [5]	Saudi Arabia – 2010	15 (12/3)	54	6	Extremities (12 – 80%)	-	15 – 100%	DM (12), CKD (12), Hypertension (11), Hepatitis (3), Pulmonary Disease (1), Hyperlipidemia (1), Malignancy (1), Cardiovascular Disease (1), Rheumatoid arthritis (1)
Akoglu et al [6]	Turkey – 2013	25 (11/14)	51.8	3	Lower Extremity (22 – 88%)	14 – 56%	21 – 84%	DM (12), Cardiovascular Disease (9), HT (8), CKD (5), Hepato-biliary Disease (5), Thyroid Disease (3), Pulmonary Disease (2), Hyperlipidemia (2), Psychiatric Disorder (2), Malignancy (1), Polycytemia Vera (1)
Kim et al [7]	Korea - 2014	30 (18/12)	55.5	7.8	Lower Extremity (22 – 73.3%)	11 – 36.6%	19 – 63.3%	DM (17), CKD (10), Dermatitis (9), Hypertension (6), Hepatitis (2), Hypothyroidism (1), Pulmonary Disease (1)
Akoglu et al [8]	Turkey – 2016	41 (25/16)	51	5.3	-	-	-	DM (22), Hypertension (17), Cardiovascular Disease (12), COPD (7), Hyperlipidemia (3), CKD (2)
García-Malinis et al [9]	Spain – 2017	31 (19/12)	54	7	Lower Extremity (22 – 66%)	-	30 – 90%	Hypertension (10), Chronic venous insufficiency (9), Cardiac disease (8), DM (7), Pulmonary Disease (7), Hepatic Disease (6), Rheumatic disease (6), CKD (5), Thyroid Disease (3), Psychiatric Disorder (3), Malignancy (3), Dermatologic Disorder (3), Hyperlipidemia (3), Hyperuricaemia (2), Ulcerative Colitis (1)
Garrido et al [10]	Portugal – 2019	57 (28/29)	61.3	-	Lower Extremity (40 – 70.2%)	-	53 – 93%	DM (28), CKD (16), Psychiatric Disorder (12), Malignancy (9), Infectious diseases (8), Hypothyroidism (5), Gastroenterological Disease (5), Rheumatological Disease (5), Neurological Disease (4)
Gore Karaali et al [11]	Turkey- 2020	80 (49/31)	58.4	17.6	Lower Extremity (64 – 80%)	35 – 43.7%	71 – 88.8%	DM (66), CKD (28), Malignancy (4), Hepatitis (3), Hypothyroidism (2), Vitiligo (1), Psoriasis (1), Scabies (1)
Edek et al (this study)	Turkey – 2022	95 (57/38)	63.1	21	Lower Extremity (82 – 86.31%)	24 – 25.26%	80 – 84.21%	DM (62), Hypertension (48), Cardiovascular Disease (43), Hepato-biliary disease (22), Pulmonary Diseases (18), CKD (17), Malignancy (16), Hypothyroidism (7), Rheumatoid Arthritis (3), Familial Mediterranean Fever (2), Dermatomyositis (1), Gaucher Disease (1), Ankylosing Spondylitis (1)

cause fibronectin accumulation, which may contribute by stimulating epithelial migration and proliferation [25]. In our study, we observed one patient under etanercept treatment for ankylosing spondylitis presenting with generalized pruritic lesions and diagnosed with APD after histopathologic analysis.

Healy et al and Eriyagama et al. reported pregnant patients with pruritic skin lesions with APD diagnoses [19,20]. We observed a patient who developed APD after pregnancy. APD should be considered among the pruritic pregnancy dermatosis.

Various APS case reports following scabies have been published. Intense scratching during scabies infection can cause superficial skin microtrauma and transepidermal elimination of dermal materials [22,23]. In addition to case reports of APD occurring following scabies, 7.36% of the patients in our study had scabies history of previous scabies infection.

One of our patients with hypothyroidism and coronary artery disease developed RPC one month after the second dose of CoronaVac (Sinovac) vaccine. Another patient with known coronary artery disease, hypertension, and diabetes mellitus had RPC two months after the second dose of CoronaVac (Sinovac) vaccine. SARS-CoV-2 vaccines have been linked to various cutaneous manifestations such as lichen planus, bullous pemphigoid, psoriasis, and cutaneous vasculitis [27-30]. So far, no cases of APD have been reported after SARS-CoV-2 vaccines. Considering the comorbidities of these patients it is difficult to build such a relationship between APD and SARS-CoV-2 vaccines. Immune dysregulation and increased cytokine levels triggered by viral components and adjuvants of SARS-CoV-2 vaccines may take part in the pathogenesis of APD.

Treatment of APD may be challenging, sometimes it may require a combination of therapies. Treatment modalities include topical-intralesional-systemic steroids, antihistamines, topical-oral retinoids, and phototherapy [36]. While choosing treatment the accompanying systemic diseases should be considered. Additionally, new medicines such as allopurinol, and dupilumab should be considered for the treatment of resistant patients. As in other reports in the literature, topical steroid and antihistamine combination was the most common treatment in our study (Table 5) [10].

In the literature and treatment guidelines, phototherapy has been recognized as one of the effective treatment options for APD [37,38]. Mechanisms of antipruritic effects of phototherapy include mast cell suppression, and reduced epidermal nerves decreasing TGF-β expression, which is important in APD pathogenesis. UV light may exert its effects by inhibiting neutrophil infiltration, which is characteristic in the early stage of APD, or neutrophils secretion of MMP that is involved in APD by digesting the extracellular matrix and destroying the basement membrane [37].

Systemic retinoids are one of the options in APD treatment, in our study acitretin was used in four patients, one of them (25%) had a complete response, however, three patients had a partial response.

Allopurinol recently has shown success in APD treatment in the case reports. Allopurinol may be effective in APD treatment via decreasing oxygen-free radicals, crosslinking of collagen fibers secondary to advanced glycation, and skin necrosis by inhibition of the xanthine-oxidase enzyme [39-43]. In our study, allopurinol was used in one patient with chronic kidney disease, congestive heart failure, hyperuricemia, and diabetes mellitus after treatment complete regression of APD lesions was observed.

The limitation of this study is its retrospective design. To the best of our knowledge, this study is the longest-term and largest case series in the literature.

Transepidermal elimination of dermal connective tissue components is a feature of APD and the disease usually presents with pruritic papules and nodules with central keratotic crust or plug. Various factors like medicines, trauma, pregnancy, and scabies can be the etiological agent of the disease.

Table 5. Treatments and outcomes of the patients

Treatment (N)	Complete Response	Partial Response	No Response
Topical Corticosteroids and Antihistamines (79)	25.31%	43.03%	31.64%
Systemic Steroids (30)	23.33%	36.66%	30%
Phototherapy (23)	26.08%	56.52%	17.39%
Systemic Retinoids (4)	25%	75%	-
Omalizumab (2)	-	100%	-
Topical Dapsone (2)	-	-	100%
Topical Retinoids (2)	-	100%	-
Topical Calcineurin Inhibitors (2)	-	50%	50%
Methotrexate (1)	-	100%	-
Allopurinol (1)	100%	-	-

Although the etiology of the disease is still unclear, several theories such as vasculopathy, hypoxia, superficial trauma, and oxidative stress have been put out to explain it. The diagnosis of APD requires a clinical examination, histological investigation, and dermoscopic analysis, which may also be useful. APD is usually accompanied by systemic comorbidities. There are several topical and systemic medications available for APD, however, sometimes the therapy might be challenging. The clinical, histopathological, dermoscopic, and therapeutic features of 95 patients were examined in this study. Future case reports and studies can help us in identifying the characteristics of APD.

References

1. Rapini RP, Herbert AA, Drucker CR. Acquired perforating dermatosis. Evidence for combined transepidermal elimination of both collagen and elastic fibers. *Arch Dermatol.* 1989;125(8): 1074-1078. PMID: 2757403.
2. Patterson JW. The perforating disorders. *J Am Acad Dermatol.* 1984;10(4):561-581. DOI:10.1016/s0190-9622(84)80259-5. PMID: 6371074.
3. Lynde CB, Pratt MD. Clinical Images: Acquired perforating dermatosis: association with diabetes and renal failure. *CMAJ.* 2009;181(9):615.. DOI: 10.1503/cmaj.082013. PMID: 19687103. PMCID: PMC2764758.
4. Saray Y, Seçkin D, Bilezikçi B. Acquired perforating dermatosis: clinicopathological features in twenty-two cases. *J Eur Acad Dermatol Venereol.* 2006;20(6):679-688. DOI:10.1111/j.1468-3083.2006.01571.x. PMID: 16836495.
5. Satti MB, Aref AH, Raddadi AA, Al-Ghamdi FA. Acquired reactive perforating collagenosis: a clinicopathologic study of 15 cases from Saudi Arabia. *J Eur Acad Dermatol Venereol.* 2010;24(2):223-227. DOI:10.1111/j.1468-3083.2009.03333.x. PMID: 20205317.
6. Akoglu G, Emre S, Sungu N, Kurtoglu G, Metin A. Clinicopathological features of 25 patients with acquired perforating dermatosis. *Eur J Dermatol.* 2013;23(6):864-871. DOI:10.1684/ejd.2013.2237. PMID: 24446068.
7. Kim SW, Kim MS, Lee JH, et al. A clinicopathologic study of thirty cases of acquired perforating dermatosis in Korea. *Ann Dermatol.* 2014;26(2):162-171. DOI:10.5021/ad.2014.26.2.162. PMID: 24882969. PMCID: PMC4037667.
8. Akoglu G, Sungu N, Karaismailoglu E, Aktas A. Expression of the receptor for advanced glycation end products in acquired reactive perforating collagenosis. *Indian J Dermatol Venereol Leprol.* 2017;83(4):432-435. DOI:10.4103/ijdvl.IJDVL_113_16. PMID: 28474638.
9. García-Malinis AJ, Del Valle Sánchez E, Sánchez-Salas MP, Del Prado E, Coscojuela C, Gilaberte Y. Acquired perforating dermatosis: clinicopathological study of 31 cases, emphasizing pathogenesis and treatment. *J Eur Acad Dermatol Venereol.* 2017;31(10): 1757-1763. DOI:10.1111/jdv.14220. PMID: 28300323.
10. Garrido PM, Queirós C, Borges-Costa J, Soares-Almeida L, Filipe P. Acquired perforating dermatosis: clinicopathologic study of a 10-year period at a tertiary teaching hospital. *Int J Dermatol.* 2020;59(4):445-450. DOI:10.1111/ijd.14760. PMID: 31876297.
11. Gore Karaali M, Erdil D, Erdemir VA, Gurel MS, Koku Aksu AE, Leblebici C. Evaluation of clinicopathological and treatment characteristics of 80 patients with acquired perforating dermatosis. *Dermatol Ther.* 2020;33(6):e14465. DOI:10.1111/dth.14465. PMID: 33112028.
12. Wang W, Liao Y, Fu L, Kan B, Peng X, Lu Y. Dermoscopy Features of Acquired Perforating Dermatosis Among 39 Patients. *Front Med (Lausanne).* 2021;8:631642. DOI:10.3389/fmed.2021.631642. PMID: 33898479. PMCID: PMC8060433.
13. Elmas ÖF, Kilitci A, Uyar B. Dermoscopic Patterns of Acquired Reactive Perforating Collagenosis. *Dermatol Pract Concept.* 2020;11(1):e2020085. DOI:10.5826/dpc.1101a85. PMID: 33354399. PMCID: PMC7735399.
14. Gambichler T, Birkner L, Stücker M, Othlinghaus N, Altmeyer P, Kreuter A. Up-regulation of transforming growth factor-beta3 and extracellular matrix proteins in acquired reactive perforating collagenosis. *J Am Acad Dermatol.* 2009;60(3):463-469. DOI:10.1016/j.jaad.2008.06.006. PMID: 19231643.
15. Kawakami T, Saito R. Acquired reactive perforating collagenosis associated with diabetes mellitus: eight cases that meet Faver's criteria. *Br J Dermatol.* 1999;140(3):521-524. DOI:10.1046/j.1365-2133.1999.02722.x. PMID: 10233279.
16. Morton CA, Henderson IS, Jones MC, Lowe JG. Acquired perforating dermatosis in a British dialysis population. *Br J Dermatol.* 1996;135(5):671-677. PMID: 8977664.
17. Tsuboi H, Mukuno A, Sato N, Katsuoka K, Yanase N. Acquired reactive perforating collagenosis in a patient with lung fibrosis. *J Dermatol.* 2004;31(11):916-919. DOI:10.1111/j.1346-8138.2004.tb00626.x. PMID: 15729865.
18. Tsutsui K, Namikawa K, Mori T, et al. Case of acquired reactive perforating collagenosis induced by panitumumab for colon cancer. *J Dermatol.* 2021;48(2):e114-e115. DOI:10.1111/1346-8138.15718. PMID: 33264448.
19. Healy R, Cerio R, Hollingsworth A, Bewley A. Acquired perforating dermatosis associated with pregnancy. *Clin Exp Dermatol.* 2010;35(6):621-623. DOI:10.1111/j.1365-2230.2009.03763.x. PMID: 20015283.
20. Eriyagama S, Wee JS, Ho B, Natkunarajah J. Acquired reactive perforating collagenosis associated with urticarial vasculitis in pregnancy. *Clin Exp Dermatol.* 2014;39(1):81-83. DOI:10.1111/ced.12169. PMID: 23730710.
21. Gontijo JRV, Júnior FF, Pereira LB, Pedrosa MS. Trauma-induced acquired reactive perforating collagenosis. *An Bras Dermatol.* 2021;96(3):392-393. DOI:10.1016/j.abd.2020.06.022. PMID: 33840572. PMCID: PMC8178551.
22. Brinkmeier T, Herbst RA, Frosch PJ. Reactive perforating collagenosis associated with scabies in a diabetic. *J Eur Acad Dermatol Venereol.* 2004;18(5):588-590. DOI:10.1111/j.1468-3083.2004.00978.x. PMID: 15324402.
23. Hinrichs W, Breuckmann F, Altmeyer P, Kreuter A. Acquired perforating dermatosis: a report on 4 cases associated with scabies infection. *J Am Acad Dermatol.* 2004;51(4):665-667. DOI:10.1016/j.jaad.2004.02.025. PMID: 15389212.
24. Vano-Galvan S, Moreno C, Medina J, Pérez-García B, García-López JL, Jaén P. Perforating dermatosis in a patient receiving bevacizumab. *J Eur Acad Dermatol Venereol.* 2009;23(8):972-974. DOI:10.1111/j.1468-3083.2008.03078.x. PMID: 19470057.

25. Gilaberte Y, Coscojuela C, Vázquez C, Roselló R, Vera J. Perforating folliculitis associated with tumour necrosis factor-alpha inhibitors administered for rheumatoid arthritis. *Br J Dermatol*. 2007;156(2):368-371. DOI:10.1111/j.1365-2133.2006.07598.x. PMID: 17223880.
26. Severino-Freire M, Sibaud V, Tournier E, et al. Acquired perforating dermatosis associated with sorafenib therapy. *J Eur Acad Dermatol Venereol*. 2016;30(2):328-330. DOI:10.1111/jdv .12720. PMID: 25209374.
27. Edek YC, Tamer F, Öğüt B. Lichen planus pigmentosus inversus with nail involvement following COVID-19 vaccination: A case report. *Dermatol Ther*. 2022;35(11):e15809. DOI:10.1111/dth.15809. PMID: 36086935. PMCID: PMC9538839.
28. Afacan E, Edek YC, İlter N, Gülekon A. Can Covid-19 vaccines cause or exacerbate bullous pemphigoid? A report of seven cases from one center. *Int J Dermatol*. 2022;61(5):626-627. DOI:10.1111/ijd.16086. PMID: 35080255.
29. Krajewski PK, Matusiak Ł, Szepietowski JC. Psoriasis flare-up associated with second dose of Pfizer-BioNTech BNT16B2b2 COVID-19 mRNA vaccine. *J Eur Acad Dermatol Venereol*. 2021;35(10):e632-e634. DOI:10.1111/jdv.17449. PMID: 34131967. PMCID: PMC8447171.
30. Bostan E, Gulseren D, Gokoz O. New-onset leukocytoclastic vasculitis after COVID-19 vaccine. *Int J Dermatol*. 2021;60(10):1305-1306. DOI:10.1111/ijd.15777. PMID: 34241833. PMCID: PMC8444793.
31. Chae KS, Park YM, Cho SH, Cho BK. Reactive perforating collagenosis associated with periampullary carcinoma. *Br J Dermatol*. 1998;139(3):548-550. DOI:10.1046/j.1365-2133.1998 .02435.x. PMID: 9767316.
32. Singh EN, Kumar S, Agarwal US, Meena R, Purohit S. Acquired reactive perforating collagenosis associated with mediastinal synovial sarcoma. *Clin Exp Dermatol*. 2019;44(3):325-327. DOI:10.1111/ced.13684. PMID: 29893023.
33. Huseynova L, Akdogan N, Gököz Ö, Evans SE. Acquired reactive perforating collagenosis in association with prostate adenocarcinoma, chronic lymphocytic leukemia, and Graves' disease. *An Bras Dermatol*. 2020;95(3):336-339. DOI:10.1016/j.abd.2019.09.029. PMID: 32359703. PMCID: PMC7253912.
34. Fernandes KA, Lima LA, Guedes JC, Lima RB, D'Acri AM, Martins CJ. Acquired perforating dermatosis in a patient with chronic renal failure. *An Bras Dermatol*. 2016;91(5 suppl 1):10-13. DOI:10.1590/abd1806-4841.20164619. PMID: 28300880. PMCID: PMC5324979.
35. Harbaoui S, Litaiem N. Acquired Perforating Dermatosis. 2023 Feb 13. In: *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 30969537.
36. Lukács J, Schliemann S, Elsner P. Treatment of acquired reactive perforating dermatosis - a systematic review. *J Dtsch Dermatol Ges*. 2018;16(7):825-842. DOI:10.1111/ddg.13561. PMID: 29927512.
37. Sezer E, Erkek E. Acquired perforating dermatosis successfully treated with photodynamic therapy. *Photodermatol Photoimmunol Photomed*. 2012;28(1):50-52. DOI:10.1111/j.1600 -0781.2011.00634.x. PMID: 22212004.
38. Matsui A, Nakano H, Aizu T, Sawamura D. Treatment of acquired reactive perforating collagenosis with 308-nm excimer laser. *Clin Exp Dermatol*. 2016;41(7):820-821. DOI:10.1111 /ced.12891. PMID: 27663164.
39. Hoque SR, Ameen M, Holden CA. Acquired reactive perforating collagenosis: four patients with a giant variant treated with allopurinol. *Br J Dermatol*. 2006;154(4):759-762. DOI:10.1111 /j.1365-2133.2005.07111.x. PMID: 16536825.
40. Krüger K, Tebbe B, Krengel S, Goerdt S, Orfanos CE. Erworbene reaktiv perforierende Dermatose. Erfolgreiche Behandlung mit Allopurinol in 2 Fällen [Acquired reactive perforating dermatosis. Successful treatment with allopurinol in 2 cases]. *Hautarzt*. 1999;50(2):115-120. DOI: 10.1007/s001050050874. PMID: 10097954.
41. Doehner W, Schoene N, Rauchhaus M, et al. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies. *Circulation*. 2002;105(22):2619-2624. DOI: 10.1161/01 .cir.0000017502.58595.ed. PMID: 12045167.
42. Rees R, Smith D, Li TD, et al. The role of xanthine oxidase and xanthine dehydrogenase in skin ischemia. *J Surg Res*. 1994;56(2): 162-167. DOI:10.1006/jsre.1994.1027. PMID: 8121173.
43. Hawkes JS, Young CM, Cleland LG. Ischaemia reperfusion injury in pedicle skin flaps in the pig: lack of protective effect of SOD and allopurinol. *Br J Plast Surg*. 1989;42(6):668-674. DOI: 10.1016/0007-1226(89)90079-9. PMID: 2605403.