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PLEVA: Spreading Information in the Age of Misinformation

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PLEVA: Spreading Information in the Age of Misinformation

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Abstract: Pityriasis lichenoides (PL) is an uncommon cutaneous rash of uncertain etiology. PL is typically characterized by small, raised reddish-brown spots that sometimes come together in groups. The spots typically evolve into hemorrhagic crusts and ulcers. PL has an acute form named pityriasis lichenoides et varioliformis acuta (PLEVA) and a chronic form named pityriasis lichenoides chronica (PLC) and is difficult to diagnose, categorize, and treat. The exact cause of PL is unknown. There are a few hypotheses that the causes of PL could be a hypersensitivity reaction to an infection such as a virus, bacteria, parasites, an inflammatory reaction to medication, or a low-grade lymphoproliferative disorder. PLEVA usually presents suddenly and progresses rapidly. PLEVA shows up mainly on the trunk of the body and the proximal extremities. Many of the cutaneous lesions heal with transient or persistent hyper- or hypo- pigmentation. Many treatments have been tested to resolve the forms of PL such as Narrowband UVB phototherapy, anti-inflammatory antibiotics, corticosteroids, and TNF-alpha inhibitors. There are a few potentially deadly variants of PL. Due to PL being such a rare disorder, only having an incidence of 0.05%, there is not much research on the disorder. Specifically, there is not much compiled research on the disorder. Data from published works and patient experiences were collected to formulate this project. Discussions on PL can help create interest in pursuing new research on the topic. New research can then potentially lead to new answers and treatments for the various forms of PL.

Keywords and Phrases: Pityriasis lichenoides, Pityriasis lichenoides et varioliformis acuta, Pityriasis lichenoides chronica, Dermatology, Rare skin disorders, Medicine, Vaccine, Antibiotic, Honors thesis, Undergraduate research

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Acknowledgments

I would first like to thank Professor Sabrina Moore for helping me navigate the thesis process and for all the time that she has sacrificed to be my mentor throughout this journey. I would also like to thank the Eastern Kentucky University Honors Program for giving me the opportunity to formulate my own research project during my undergraduate studies. Lastly, I would like to thank my family and all the other people in my life who have supported my educational goals throughout my journey at Eastern Kentucky University.

Introduction

Pityriasis lichenoides (PL) is an uncommon cutaneous rash of uncertain etiology.[1] PL is usually characterized by small, raised reddish-brown spots that sometimes come together in groups.[2] PL is characterized as an auto immune disease.[3] PL is difficult to diagnose, categorize, and treat.[1] There is an acute form, pityriasis lichenoides et varioliformis acuta (PLEVA), and a chronic form, pityriasis lichenoides chronica (PLC). Many patients show overlapping features between each of the forms of PL.[4] The exact incidence of PL is not known and the disease is rare. PL is most common in children and young adults under the age of 30, although PL can present at any age. There is a slight male predominance, and all races can be affected by PL. The diagnosis of PLEVA is usually confirmed with a skin biopsy which can help to exclude other differential diagnoses. Some of the histological features of PLEVA include a wedge shaped deep dermal and superficial lymphohistiocytic infiltrate, parakeratotic scale and crust with thinning of the granular layer, interface dermatitis with basal cell necrosis and vacuolation, epidermal spongiosis and necrosis in developed lesions, and extravasated erythrocytes.[4] PL is not thought to be hereditary.[5] PL is also typically relatively benign.[6] Various cases will be analyzed in this research.

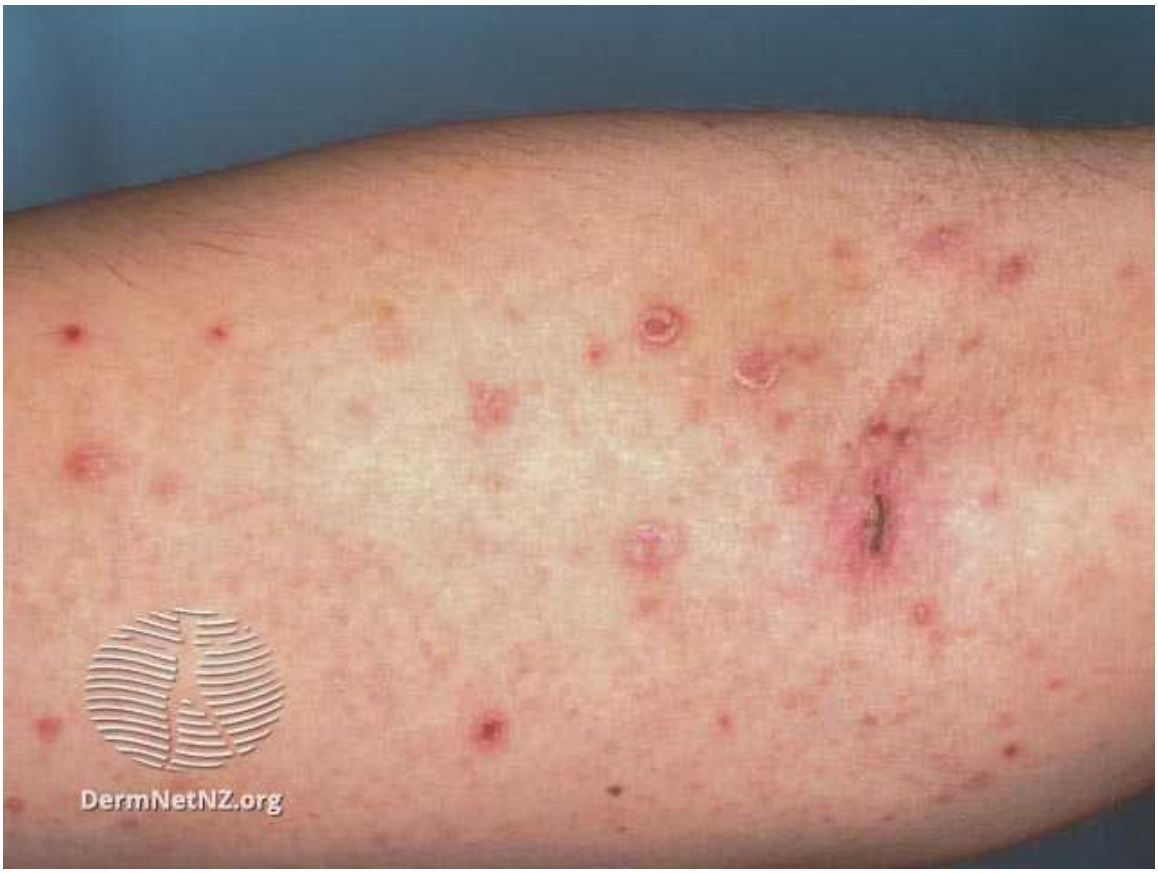

Figure 1. Pityriasis lichenoides acuta on the arm.[4]

Causes

The exact cause of PL is unknown. There are a few hypotheses that the causes of PL could be a hypersensitivity reaction to an infection such as a virus (Epstein-Barr Virus, cytomegalovirus, human immunodeficiency virus), bacteria (Staphylococcus, Streptococcus), parasites (Toxoplasma gondil), an inflammatory reaction to medication (anti-TNF agents, statins, antidepressants, vaccines, and radiocontrast dye), or a low-grade lymphoproliferative disorder.[4] According to the National Institutes of Health, lymphoproliferative disorders comprise a heterogeneous group of diseases characterized by uncontrolled production of lymphocytes that cause monoclonal lymphocytosis,

lymphadenopathy and bone marrow infiltration.[7] Lymphocytes are forms of leukocytes which are white blood cells. In other words, a lymphoproliferative disorder is characterized by an uncontrolled production of white blood cells.

In a certain case, a six-year-old male was presented to the dermatology department of JSS Medical College with a history of reddish raised lesions over the trunk and extremities for eight days. The measles, mumps, and rubella (MMR) vaccine had been administered seven days prior to the onset of lesions. The patient was not on any medications and previous vaccinations were uneventful. Based on the clinical and histopathological features, a diagnosis of PLEVA following the MMR vaccination was made.[8]

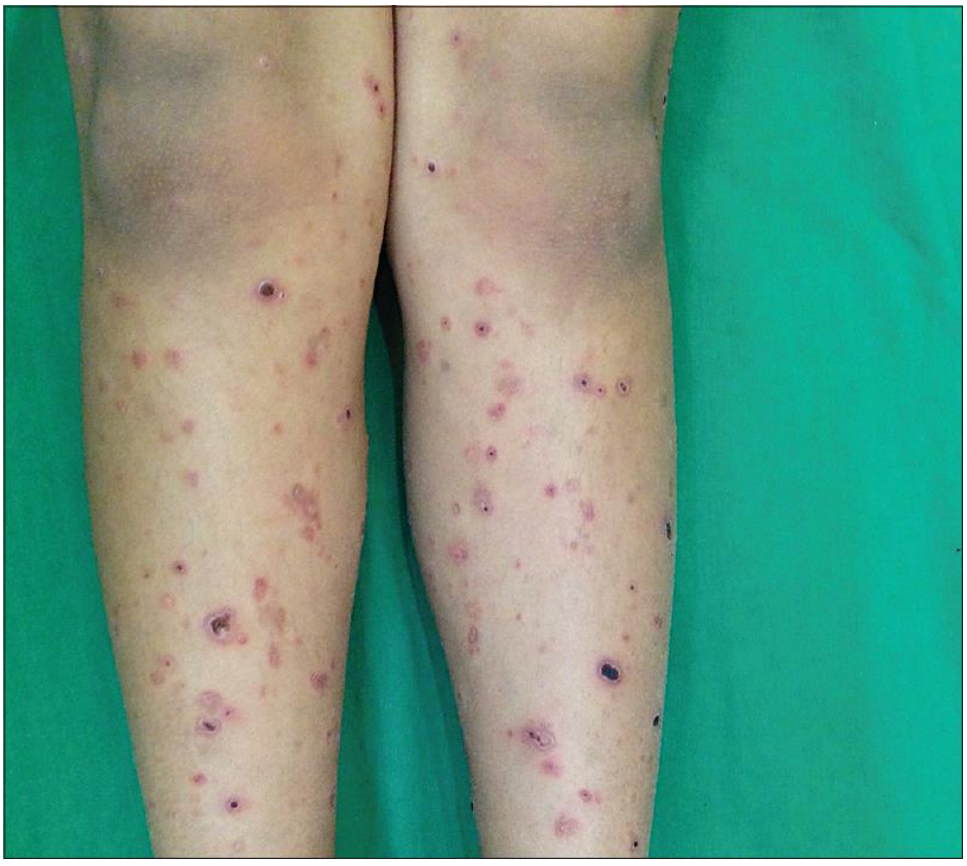

Figure 2. Multiple erythematous papules with central crusting over the legs.[8]

In another case, an eight-year-old female went to an emergency dermatology clinic with a rash that had been ongoing for about four days. The patient received her first dose of the MMR vaccine 10 days prior to the onset of the rash. This case was diagnosed as PLEVA. PLEVA has a rare association with vaccination, but professionals still find it important to add the reaction to the list of possible side effects of vaccination.[9]

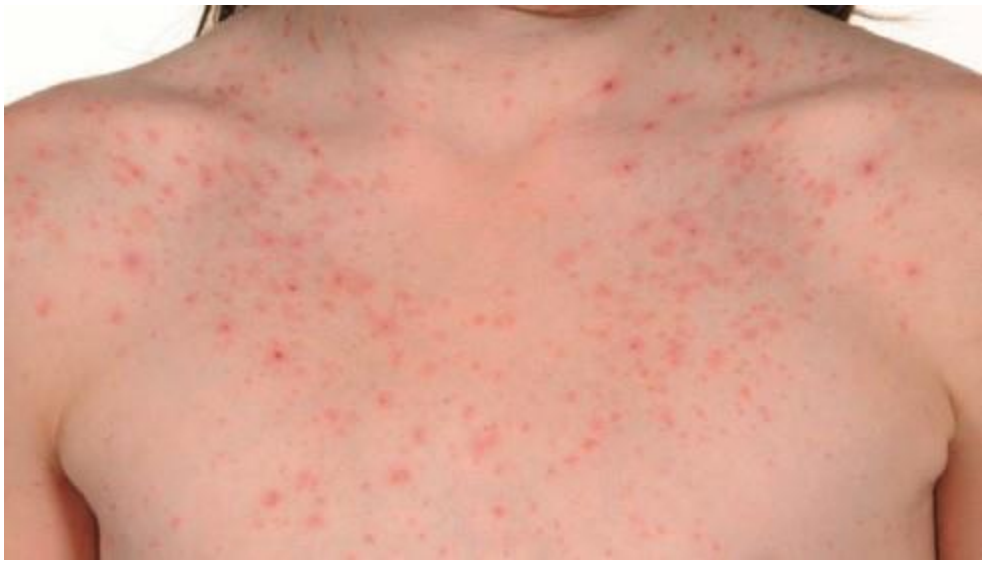

Figure 3. Erythematous, scaly papules and papulnecrotic lesions on trunk and limbs.[9]

As stated, a widely accepted theory is that PL is an inflammatory response to extrinsic antigens such as infectious agents, drugs, and vaccines. Historically, only the MMR vaccine was connected to the occurrence of PL. In a new case, a twelve-year-old healthy male developed erythematous papules on the trunk, abdomen, and limbs five days after the Influenza vaccination. Histopathological examination and clinical data lead to the diagnosis of PLEVA. This is one of the first cases of PLEVA associated with the Influenza vaccine.[10]

A forty-five-year-old female presented an itchy skin rash four days after radiocontrast iodide injection for a parathyroid scan. The patient underwent physical examinations and laboratory tests, and was later diagnosed with PLEVA. Unlike the other cases, this woman developed symptoms later in life. Iodide may cause a variety of skin eruptions and there are some other reports of provocation of PLEVA. In this case the occurrence of PLEVA lesions after the radioactive iodide injection could be attributed to the provocation of the particular lesions by iodide. This is an example of drug induced PLEVA.[11]

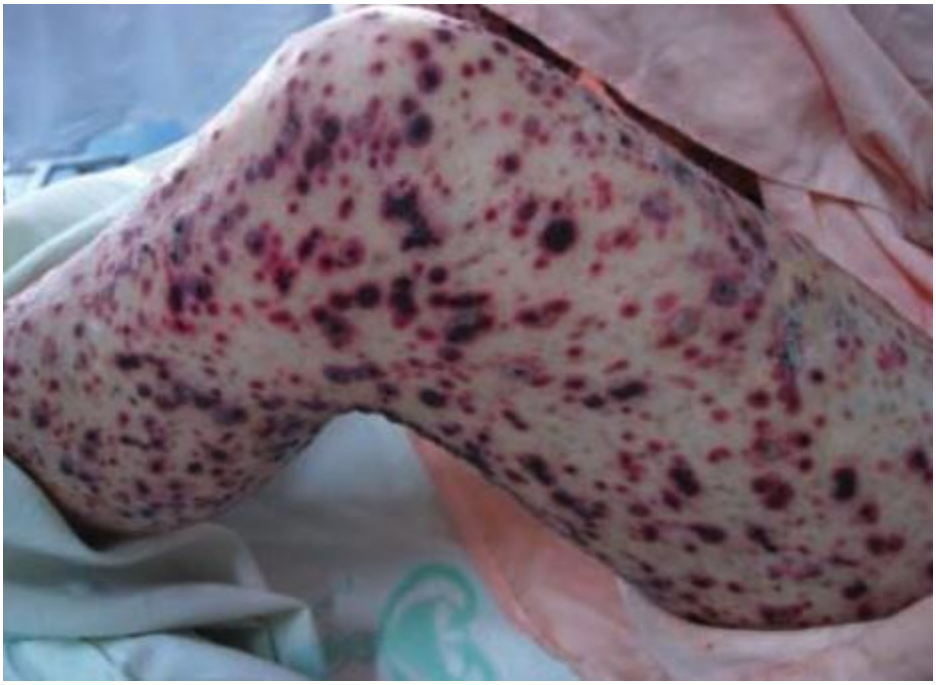

Figure 4. PLEVA lesions on the left leg.[11]

Tumor necrosis factor alpha (TNF-α) inhibitors improve inflammatory diseases like Crohn's disease (CD). TNF-α may induce infections, neoplasms, or auto-immune diseases. In a particular case, a thirty-five-year-old male who was dealing with CD for about 10 years began taking adalimumab, which is a TNF inhibitor. After the second

injection of adalimumab, the patient developed popular lesions on the trunk, buttocks, and extremities. Microscopic examination of a skin biopsy presented findings that were consistent with PLC. Due to an increased risk of lymphoma under anti-TNF-α treatments, patients with PLC need to be closely monitored.[12]

From the author's experience, Streptococcus was thought to be a trigger of PLEVA in two related cases. Shortly after exposure to a certain strain of Streptococcus bacteria, two eight-year-old male patients who attended the same school began to show signs and symptoms of PLEVA. One of the patients ceased to show symptoms after a few weeks with the help of antibiotics, while the other patient continued to show symptoms for years, despite taking antibiotics. Both patients were professionally diagnosed with PLEVA, with the chronic case being diagnosed through a biopsy. This unknown strain of Streptococcus bacteria is thought to be the cause of onset of PLEVA in these cases. There could have been additional cases of PLEVA from this unknown strain of Streptococcus at the school that were not reported.

Effects

PLEVA usually presents suddenly and progresses rapidly. PLEVA shows up mainly on the trunk of the body and the proximal extremities. There can be between 10 to 50 reddish-brown erythematous papules of about 5 to 15 millimeters in diameter. The spots typically evolve into hemorrhagic crusts and ulcers. Many of the cutaneous lesions heal with transient or persistent hyper- or hypo- pigmentation. PLEVA may evolve into PLC and many patients show features of both PLEVA and PLC.[4] It is not fully known why PLEVA has the possibility to progress into PLC. PLEVA begins abruptly and may cause itching or burning while PLC may develop over days, is less irritating, and

typically lasts longer than PLEVA. The spots connected with PLC usually fade within three to four weeks, but new spots may appear. There is no clear answer on how long each form of PL lasts, but many cases resolve on their own within a few months. PL is not contagious.[2]

PL affects roughly 1 in 2000 people per year.[13] If looking at the population of the United States at about 336 million and dividing that number by 2000, about 168,000 people per year are affected by PL. This comes in at less than 1% of the population. More specifically, the incidence of PL is thought to be 0.05%.[14] Taking into consideration that PL has multiple forms, PLEVA cases specifically are even less prevalent than the number presented, making PLEVA an extremely rare disorder. PLC is thought to be the most common form of PL.[15]

The forms of PL can occur at any age, but most cases are seen in the first three decades of life and are more common in males than in females. Another way to describe how PLC presents itself is as widespread, small, scaly papules with the most characteristic feature being a circular scale attached centrally and loose at the periphery which comes away intact on easy scratching. Even though there is no clear indicator of how long a certain form of PL lasts, most lesions erupt over a period of months or years.[16]

In a study of 124 patients who were diagnosed with PL, PLC was recorded 37% of the time while PLEVA was recorded 57.3% of the time. Clinical features of both disorders were seen simultaneously in the remaining patients. The median age of PL onset was 60 months, but the median age of onset for PLEVA was younger than the median age of onset for PLC. A history of infection or drug intake preceded the diagnosis

in 30% and 11.2% of patients with PLC and PLEVA, with onset being more common during the fall (30%) or winter (35%). The median duration of the disease was 20 months for PLC and 18 months for PLEVA. The disease was recurrent in 77% of patients, with 59% exhibiting pruritus and 32% showing no symptoms. The remainder of the patients experienced fever, arthralgia, or both.[17]

PLEVA has certain effects concerning histology. The disease presents as sharply delimited, moderately dense, lymphocytic infiltrate involving the superficial vascular plexus, which goes into a wedge-shaped pattern to involve the lower dermis (Figure 5). The superficial dermis presents a dense lichenoid infiltrate and impressive exocytosis of lymphocytes into the epidermis. The stratum corneum shows parakeratosis, which may be confluent and contain collections of neutrophils (Figure 6). The epidermis shows pronounced hydropic change and foci of keratinocyte necrosis. Various scattered extravasated erythrocytes are also seen (Figure 7).[18]

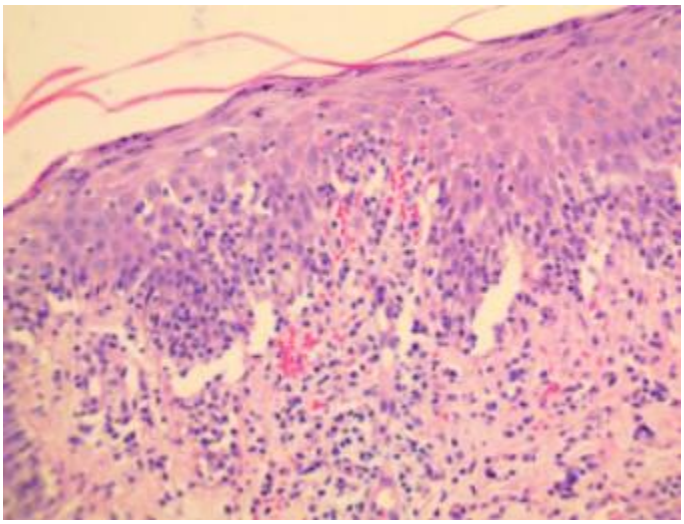

Figure 5. Wedge shaped pattern PLEVA histology.[18]

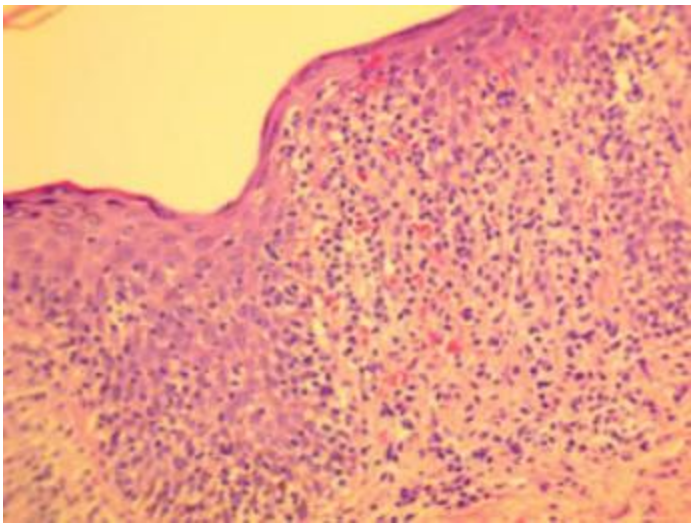

Figure 6. Parakeratosis PLEVA Histology.[18]

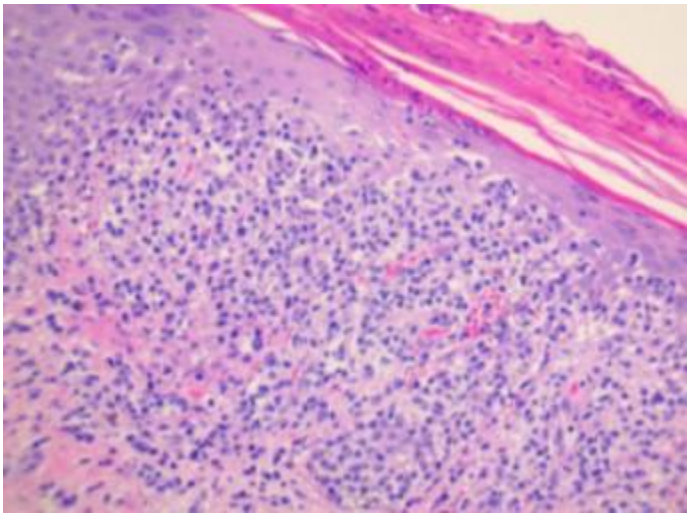

Figure 7. Extravasated erythrocytes PLEVA histology.[18]

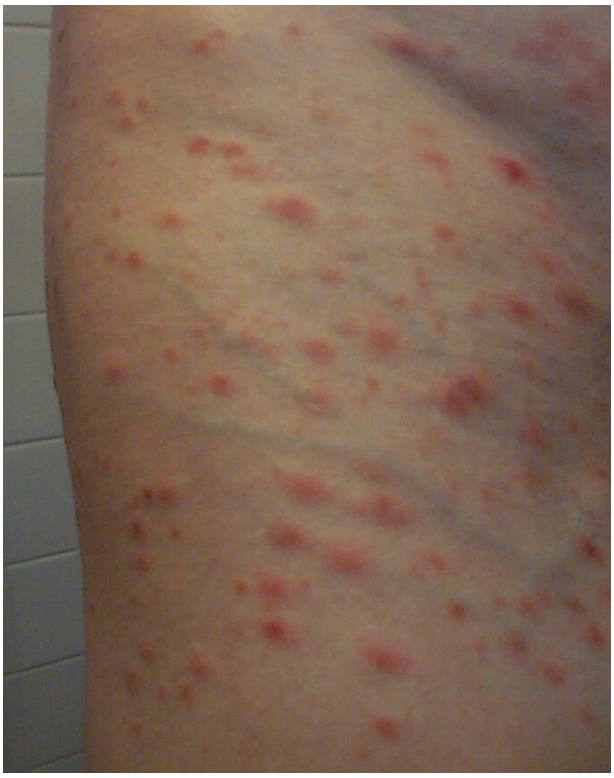

Figure 8. Pityriasis Lichenoides et Varioliformis Acuta.[19]

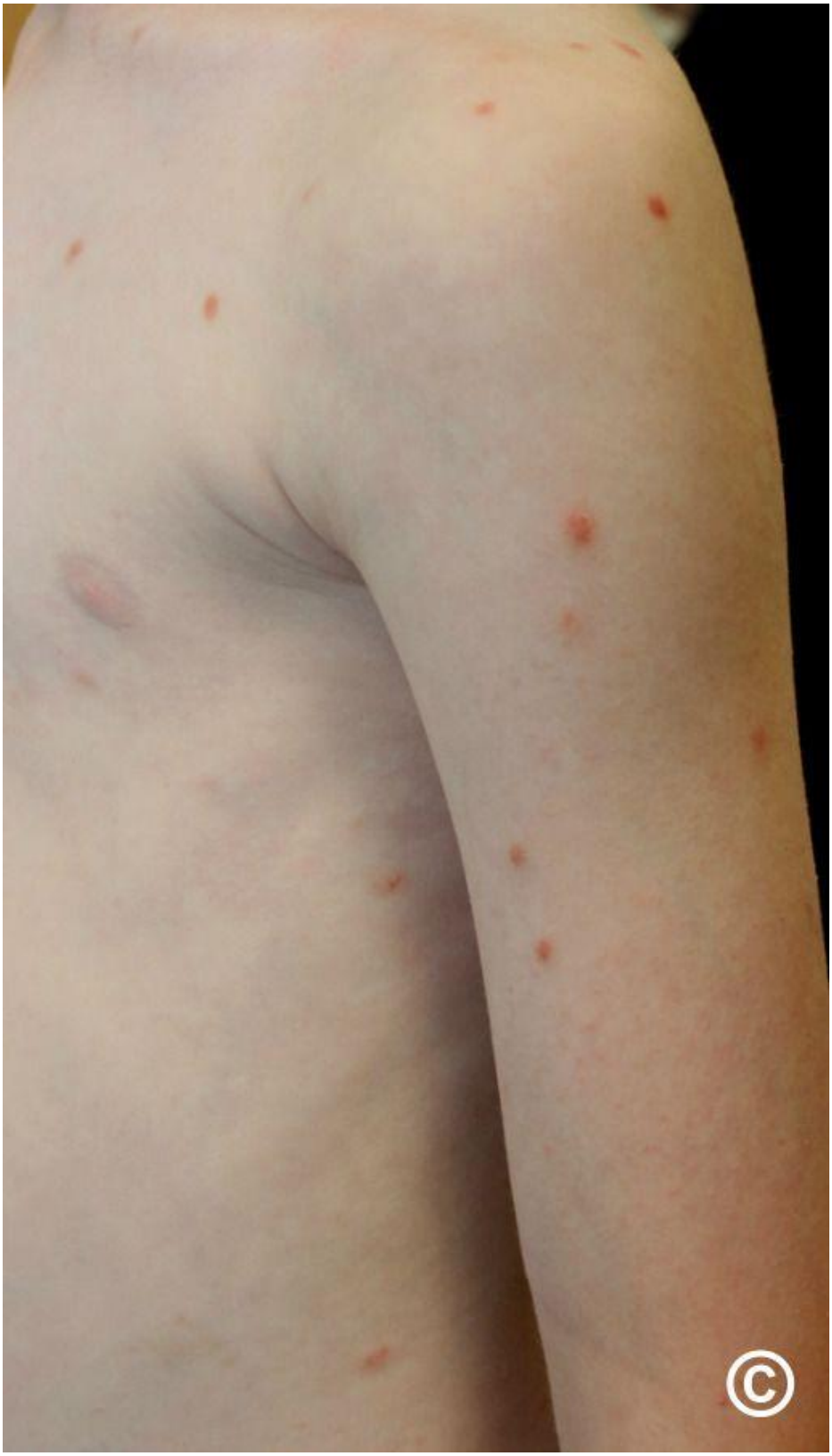

Figure 9. Pityriasis lichenoides.[20]

Treatments

There are a multitude of treatments that have been tested to resolve the many forms of PL such as Narrowband UVB phototherapy, anti-inflammatory antibiotics, corticosteroids, and TNF-alpha inhibitors.[21] Due to patients having different responses to the same therapeutic approaches, there is no gold standard of treatment for the different forms of PL. Most treatment is symptomatic and doesn't have a major effect on the progress of the disease.[16] All forms of PL are very difficult to treat and the best-case scenario is usually the form of PL resolving on its own.

In a specific study, 31 PL patients with a mean age of 42.6 years were given treatment. Twenty-three patients had PLEVA and eight patients had PLC. The patients were given treatment with Narrowband UVB (311 nm) three to four times weekly in a Daavlin cabinet that was equipped with Philips TL-01/100 W fluorescent lamps. Narrowband UVB phototherapy was administered for a maximum of 60 sessions, and if a patient had more than 90% clearance of clinical lesions before 50 to 60 sessions, the phototherapy was stopped. Narrowband UVB treatment led to a complete response of at least 90% clearing of skin lesions in 65.2% of PLEVA patients and 87.5% of PLC patients. Two PLEVA patients and two PLC patients relapsed after successful treatment in a mean time period of six months. Based on the data, Narrowband UVB phototherapy seems to be an effective treatment option for management of PLEVA and PLC. Further study is needed to learn the long term complications of Narrowband UVB treatment for forms of PL such as PLEVA and PLC.[22]

A thirty-year-old patient was referred to the Department of Dermatology and Venereology due to some skin changes that were accompanied by itching that persisted

for one and a half months. Red papules were located on the trunk, upper and lower limbs, but more severely affecting the trunk. A biopsy of skin lesions confirmed a diagnosis of pityriasis lichenoides et varioliformis acuta. Doxycycline treatment and continuing treatment with betamethasone and gentamicin were recommended to the patient. Upon competition of the doxycycline treatment, skin changes were in regression and urate levels decreased. Based on the regression of symptoms in this case after the doxycycline treatment, it can be thought that doxycycline can be an effective treatment option for PLEVA.[23]

Bromelain is a crude aqueous extract of the stems and immature fruit of pineapple. In this study, eight patients (three males and five females) who had been diagnosed with PLC were treated for three months with oral bromelain. The dosage was 40mg three times per day for one month, 40mg twice a day for 1 month, and 40mg per day for one month. The results showed complete clinical recovery after the treatment. A follow up was conducted 12 months after treatment which showed two patients experiencing a relapse five to six months after the suspension of therapy, but the patients responded to another brief cycle of therapy. There were no side effects encountered during therapy. Bromelain can be considered an effective therapeutic option to treat PLC and its effectiveness could be related to its anti-inflammatory, immunomodulatory and/or anti-viral properties.[24]

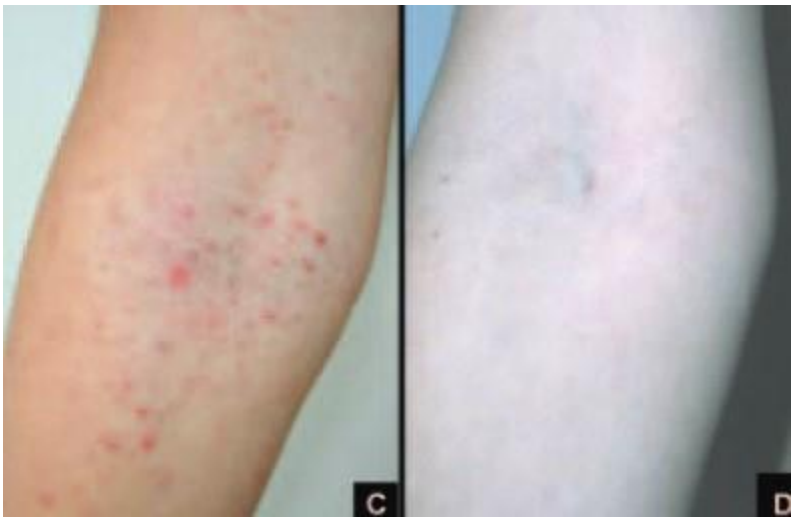

Figure 10. Patient number 7: Detail of upper limb before (C) and after 35 days of therapy with bromelain (D).[24]

From June 2018 to January 2020, 16 children diagnosed with PL (eight with PLC and eight with PLEVA) at Beijing Children Hospital, Capital Medical University, and National Center for Children's Health were observed. Oral erythromycin was applied at fifteen to thirty mg kg^{-1} d^{-1}, divided into twice daily. A complete response was defined as greater than 90% resolution in lesions; partial response was defined as 50% to 90% resolution; no response was defined as less than 50% response. Complete response and partial response were considered as a good response. Relapse was defined as the reappearance of more than ten lesions when the disease reached complete or partial response. Out of the patients, there were four girls and 12 boys with ages ranging from 1.6-10 years old. The oral erythromycin had a treatment duration range of 1-6 months. Out of the 16 patients, complete response was observed in four patients, partial response was observed in five patients, and no response was observed in seven patients. Erythromycin was seen to be more effective in the PLEVA group with seven out of eight

patients having a good response compared to two out of eight patients in the PLC group having a good response. In the children with a good response, the median response time was two weeks. There is a possibility of a slight recurrence of symptoms after stopping treatment. The dose of erythromycin given could influence treatment response. Based on the findings, erythromycin is effective and safe in treating pediatric PL.[25]

A forty-one-year-old Caucasian female had an eight-year history of refractory PLC. Many treatment methods were tested such as clobetasol propionate, oral erythromycin, ultraviolet b (UVB), and psoralen-ultraviolet A (PUVA) phototherapy. These treatment methods had no significant benefits over the course of treatment. Twice daily topical tacrolimus ointment (0.1% Protopic®, Fujisawa, Middlesex, UK) was used for lesions on the left side of the patient's body. Diprobase® (Schering-Plough, Middlesex, UK) emollient was applied to the right side of the patient's body. Within two weeks, the lesions on the side treated with topical tacrolimus began to resolve and by four weeks the lesions were almost completely resolved on the left arm, and no new lesions appeared on the left leg. By this stage, the patient had used approximately 20g of Protopic®. No burning, irritation, or other adverse effects were noticed from the Protopic®. After discontinuing the Protopic®, new lesions occurred after one to two weeks but were fewer in number. Treatment was continued to treat the areas with new lesions as needed. In this case topical tacrolimus was used because of its inhibitory effect on T cells. At the time of this study, it was believed that this was the first report of the use of topical tacrolimus in PLC. As can be seen, topical tacrolimus was successful in treating this patient who was diagnosed with PLC.[26]

Variants

Occasionally, PLEVA can present rare variants. Variants of PLEVA are very serious and sometimes life-threatening. PL has the potential to progress to cutaneous lymphoma or an ulceronecrotic presentation, which both carry a high risk of mortality.[1] According to the Mayo Clinic, Cutaneous T-cell lymphoma (CTCL) is a rare type of cancer that begins in white blood cells called T cells (T lymphocytes). These cells normally help the body's germ-fighting immune system. In cutaneous T-cell lymphoma, the T cells develop abnormalities that cause them to attack the skin.[27] In other words, the T cells that are supposed to help the body fight germs end up attacking the skin. PLEVA and PLC were mentioned previously, but PL can also present itself as febrile ulceronecrotic Mucha-Habermann disease (FUMHD), which is also known as pityriasis lichenoides with ulceronecrosis and hyperthermia (PLUH). FUMHD is a rare and severe form of pityriasis lichenoides which has effects that rapidly progress to large destructive ulcers. This form can also cause fever, extensive loss of skin tissue, and infection. More specifically, FUMHD represents a fulminant and sometimes lethal variant of PLEVA that may also affect other body systems. FUMHD occurs most commonly in children and young adults where males tend to be more affected. FUMHD starts out as a normal PLEVA case but then develops into widespread ulceronecrotic lesions. A diagnosis of FUMHD can be confirmed by biopsy of skin lesions. In 2010, there were only 31 cases of FUMHD that had been reported in English literature.[1]

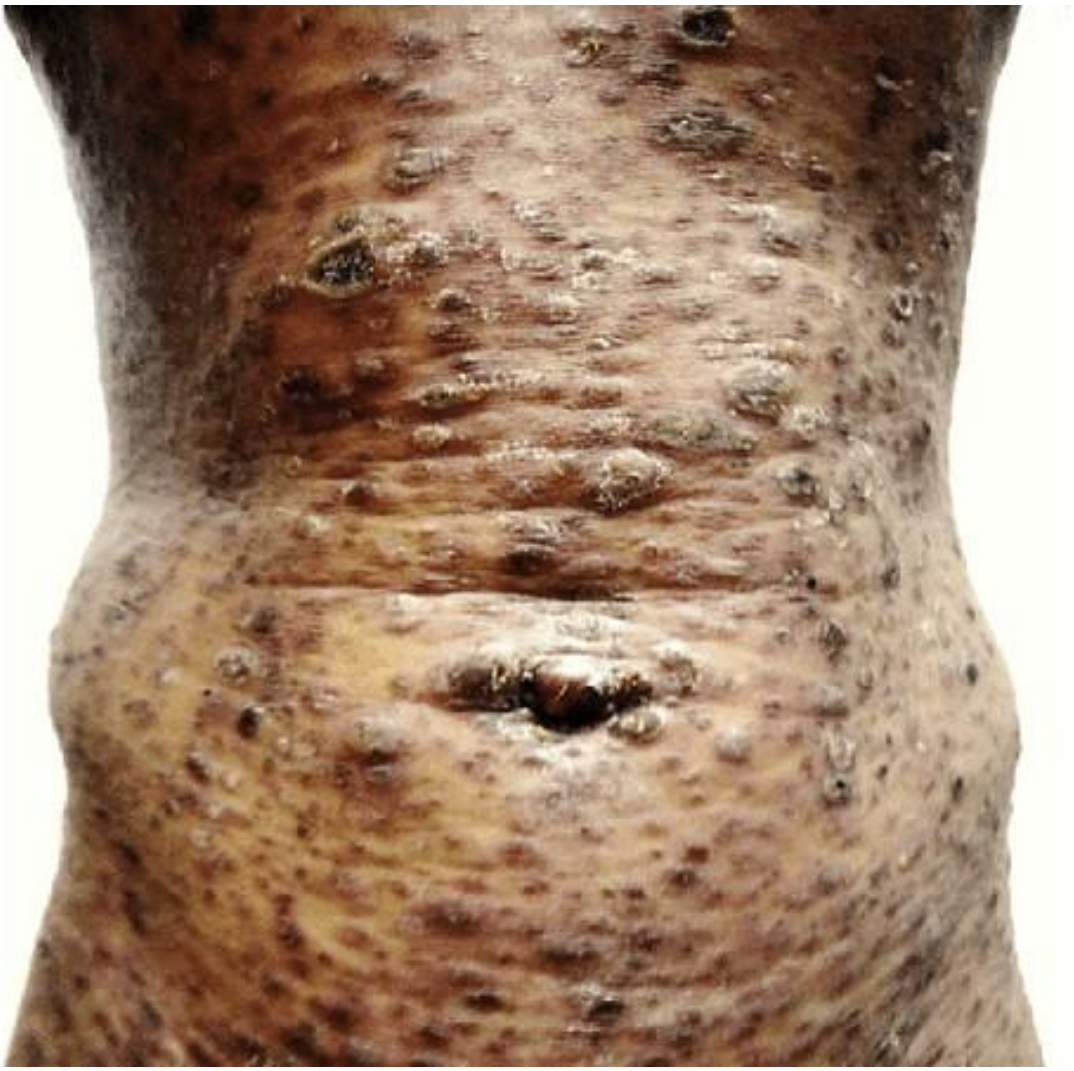

Figure 11. Febrile ulceronecrotic Mucha-Habermann disease. Generalized ulceronecrotic papules and plaques covering the whole trunk.[28]

In a specific case, a forty-nine-year-old male presented with erythematous papules and crusted plaques all over the body. The illness was accompanied by a high-grade fever of 101° F with tachycardia. Around 25-30% of body surface area was involved with symmetrical distribution of the lesions on the upper limbs, lower limbs, and trunk. The palms and soles showed multiple erythematous maculopapular and pustular lesions. The nails were also discolored with longitudinal ridging. Based on the presentation and clinico-pathological correlation, the diagnosis of ulceronecrotic variant of PLEVA was made. The patient was treated with antibiotics, oral corticosteroids, and symptomatic treatment which resulted in mild improvement. The patient showed exacerbation of the disease around six weeks later as new lesions continued to develop. Intravenous antibiotics and pulse therapy was implemented, but the patient succumbed to the illness secondary to acute respiratory distress syndrome and multisystem failure.[1]

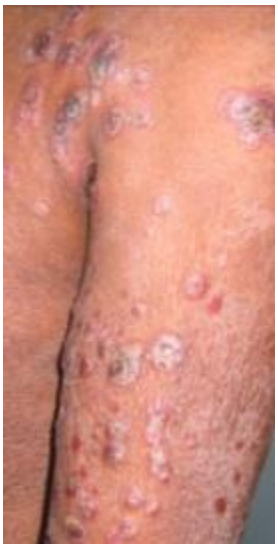

Figure 12. Multiple erythematous crusted papulo-plaque lesions on left upper limb.[1]

More recently, there are 41 cases described to date of FUMHD. In one case, a twenty-three-year-old man had clinical and histological findings that suggested a diagnosis of FUMHD. The patient attempted prednisone 1mg/kg daily without improvement. Steroid therapy was implemented and progressively tapered to 5mg on alternating days, and treatment with intravenous immunoglobulins (IVIG) at 400mg/kg/die for 5 days monthly was put into place, associated with methotrexate (MTX) 10mg/m^2. Progressive improvement of cutaneous lesions was observed and a complete remission with mild residual sclero-atrophic lesions and hyper-pigmentation was obtained after five courses of treatment. Extracorporeal photochemotherapy (ECP) was started as a maintenance treatment and six months after beginning ECP the patient was still in remission. After MTX and steroids were discontinued, new lesions developed and reintroduction of low dose MTX gained a rapid improvement with complete clearing of the cutaneous lesions. Only one case of FUMHD treated by IVIG had been reported in literature at the time of this study. IVIG proved to be effective in inducing a major improvement of ulceration and in arresting the appearance of new lesions in this case.[29]

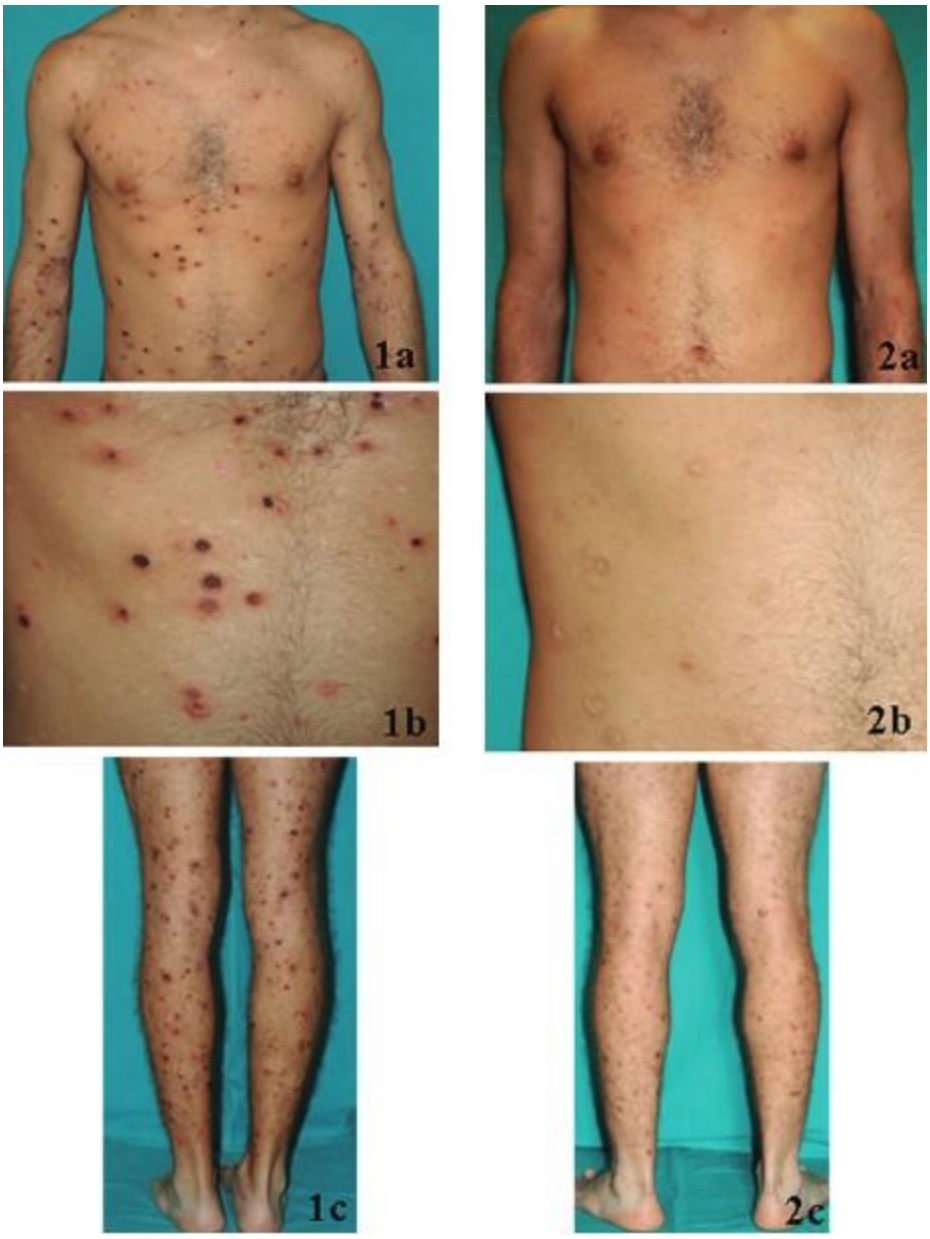

Figure 13. 1a, 1b, and 1c represent clinical status prior to treatment. 2a, 2b, 2c represent clinical status after five IVIG courses.[29]

The exact etiology of FUMHD is unknown, but multiple reports have shown the possibility of hypersensitivity to an infectious agent. Elevation of microbe-specific antibody titers, deposition of immune complexes in dermal vessels, familial outbreaks and associated constitutional symptoms have been offered as evidence for infectious casualty. Reported etiologic pathogens of PLUH include EBV, HIV, parvovirus B19, adenovirus, *staphylococcus aureus* and group A Streptococcus on throat cultures, *Mycoplasma pneumoniae* and *Toxoplasma gondii.* In a particular patient, the transition of PLEVA to PLUH has been associated with increased levels of TNF-α in one patient. Many therapies such as systemic corticosteroids, antibiotics, acyclovir, dapsone, methotrexate, psoralen plus ultraviolet A, and TNF-α inhibitors (such as infliximab and etanercept) have been used. No improvement was seen in the patient when the previous therapies were tried.[1]

A six-year-old male presented with a two-month history of pruritic skin eruptions on the neck and upper trunk. Based on the clinical and histopathological findings, the patient was diagnosed with PLEVA. Systemic prednisolone (0.5 mg/kg daily) and erythromycin (30 mg/kg/d) were used for therapy. Initial improvement was seen two weeks later but the patient had developed tense bullae on the trunk and legs. Erythromycin was discontinued and low-dose oral dapsone (0.5 mg/kg daily) was put in place. Oral prednisolone was tapered slowly. There was rapid improvement with dapsone and the lesions resolved, leaving only hypopigmented macules. Bullae are not usually part of the clinical spectrum of PLEVA. At the time of this study, there were only two other cases of PLEVA with bullae in children that could be located. The term PLEVA pemphigoides was suggested for this rare clinical variant of PLEVA with bullae.[30]

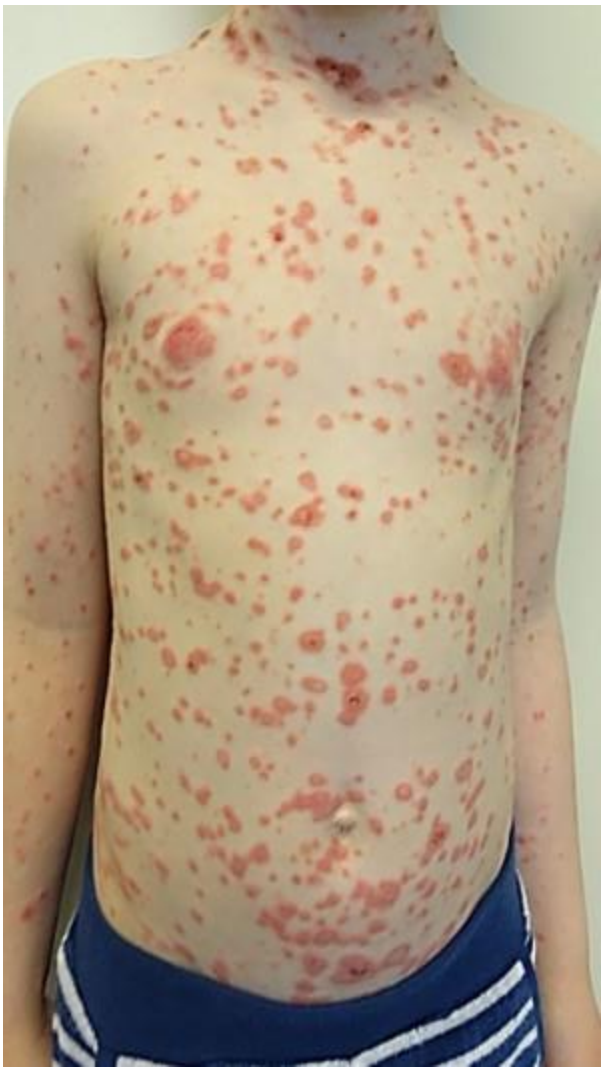

Figure 14. Initial presentation with erythematous macules, papules, and papulovesicles as well as erosions, crusts, and scaling.[30]

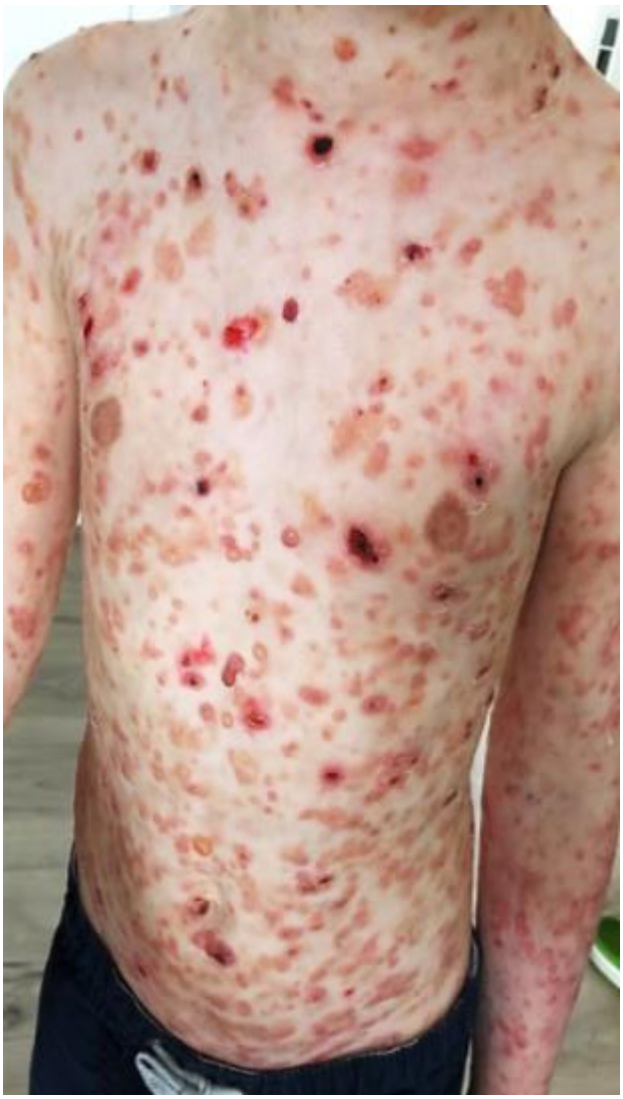

Figure 15. Development of tense blisters on the trunk and legs.[30]

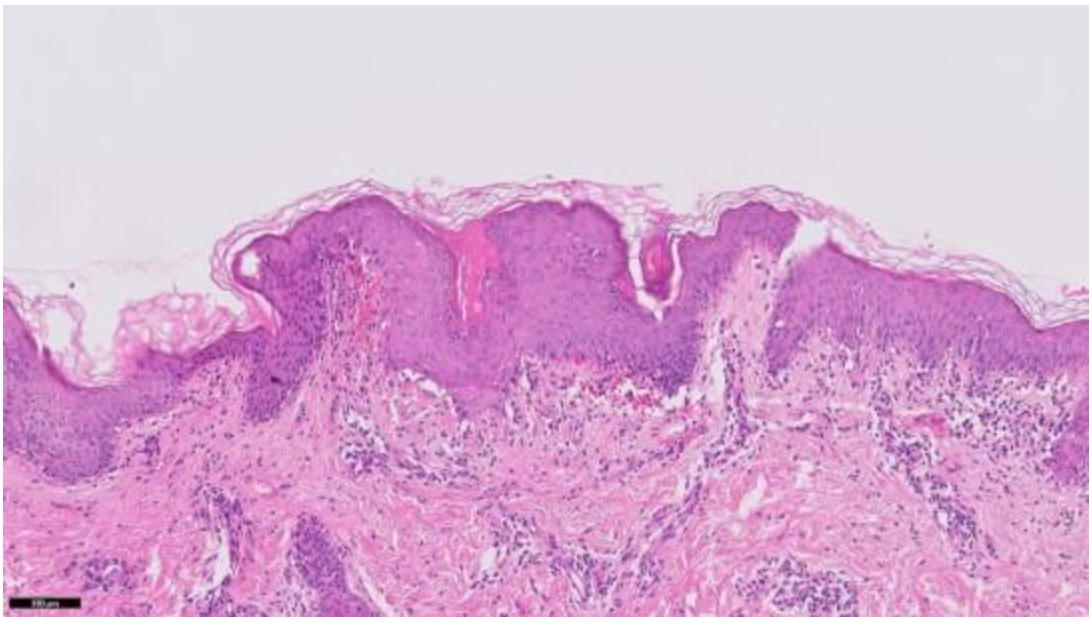

Figure 16. Histopathology (hematoxylin and eosin stain) of lesional skin showing interface dermatitis with necrosis of the epidermal basal layer with no intra- or subepidermal blistering (magnification x10).[30]

Methods

Data from published works and patient experiences were collected to formulate this project. Examples include information from patient case studies, scholarly journals, and patient experiences. The data was refined and combined into a singular sequential project. The results were analyzed in context of the goals of the research paper.

Purpose

The aim of this research paper was to spread awareness on a subject that is difficult to research, such as a rare disorder. Awareness might help prevent an untreated case of PL, PLEVA, or PLC in the future. Preventing misinformation surrounding the different forms of PL is of utmost importance in this work. Compiling various studies

into one source also increases efficiency when looking for information and answers to questions about this topic. Helping providers and patients understand what to look for and questions to ask can help ease the burden on those dealing with any form of PL. Hopefully this material will spark discussions in the field of dermatology concerning PLEVA and other rare disorders. These discussions can help create interest in pursuing new research on the topic of PL, PLEVA, or PLC. New research can potentially lead to new answers and treatments for the various forms of PL.

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