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Case Report

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Ecthyma Gangrenosum in Three Unrelated Patients with Combined Immunodeficiency

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Abstract

Background: *Ecthyma Gangrenosum (EG) is a necrotizing vasculitis characterized by cutaneous manifestation ranging from a nodule or papule to necrotic ulceration with surrounding erythema, especially with black eschar or central crust. The most common pathogen that causes EG is Pseudomonas aeruginosa (PA). PA is an opportunistic pathogen with predominance incidence among patients with primary immunodeficiency with hypo or agammaglobulinemic, malignancies, and acquired immune deficiency.*

Case Presentation: *In this case study, we present three unrelated patients (three male toddlers, mean age: 0.75 years) with the primary manifestation of EG, who underwent immunological assessment and were diagnosed with combined immunodeficiency. All patients were alive although EG has a high mortality rate, the prognosis depends on the host and the degree of immunosuppression. A history of Persistent fever followed by skin lesions was common in our cases. Surprisingly, the initial immunological assessment reported different cellular and humoral immune deficiencies with the overall diagnosis of combined immunodeficiency based on the ESID criteria. For patients suspected of EG, early diagnosis and administration of appropriate systemic antibiotic therapy can considerably reduce morbidity and potential mortality.*

Conclusions: *This case report illustrates the importance of immunodeficiency evaluation in patients with a skin lesion and considers pseudomonas aeruginosa culture for initiating appropriate antipseudomonal antibiotic therapy. Although recent studies show high EG-related mortality with predisposing factors, hopefully, due to appropriate intravenous antibiotics and immunoglobulin therapy, all patients remained alive.*

Keywords: Ecthyma Gangrenosum, Combined Immunodeficiency, Immunoglobulins

Introduction

Ecthyma gangrenous (EG) is a rare skin disorder that usually starts as an erythematous macule, which developed into a vesicle. These Lesions can rapidly indurate and develop pustules or bullae, which slough and leave an eschar [1]. The first case of EG was reported by L Borker. Hitschman and Kreibichin, which accompany Pseudomonas septicemia [2]. Although several studies show more pathogens associated with EG, Pseudomonas Aeruginosa (PA) is the most reported cause [3]. PA as an opportunistic bacterium can detect from the skin, nose, throat, and stool [4]. The most common

site for superinfection of the skin with Pa includes the gluteal and anogenital region, the extremities, the trunk, and the face [5]. The pathogenesis of skin lesions due to Pa is mainly dependent on the vessel walls invasion interfering with the toxin followed by ischemic necrosis resulting in necrotic ulcer with a black/gray eschar surrounded by an erythematous halo [6]. Since the first report of EG, several studies show the EG incidence among patients with predisposing risk factors like pre-existent viral infections, weak mechanical skin barriers, especially immunocompromised individuals, and even previously healthy patients. In addition, malignancies like leukemia and primary immunodeficiency disorders like leukocyte adhesion deficiency-1 (LAD), and X-linked agammaglobulinemic (XLA) are reported related to EG [7-9].

However, skin necrosis is a symptom of a broad range of pathologies, the diagnoses of EG are based on clinical findings that are confirmed by the skin and blood culture [1,2]. Besides, early appropriate treatment e.g., antibiotics, and surgical debride reduce EG-related mortality rates, also understanding the patient's immunological status and underlying disease affect the prognosis, and initiation of appropriate treatment can reduce mortality rates [3]. This manuscript summarizes three cases of EG who were admitted to a tertiary hospital with pursuing chief complaints, initial evaluation, and treatment.

Case Reports

Case 1

A 16-month-old male was admitted to the hospital with a one-week history of fever and lesions on his left groin, neck, and left axilla. His fever started 3 days after influenza vaccine and did not respond to initial treatment (Acetaminophen). He hospitalized due to persistent fever and then Bullae lesions began 2 days after admission and progressed to a necrotic lesion with infectious secretion with a positive lesions culture which showed pseudomonas aeruginosa, he received appropriate antibiotics (Amikacin and Imipenem) based on the culture and G-CSF due to leukopenia with no response. He had a diarrhea history due to milk powder allergy when he was 2 months. His vaccination was upon the routine plan. His parents were relative and did not report any recent travel and allergic reaction. The physical examination showed vesicular dark lesions on his left leg, axillary region, and neck. His lower extremities were swollen and tender, especially on left foot. The left foot was warmer than the right and had more lesions compared to other sites. The liver enlarged up to 3 cm below the right costal margin, and the spleen was impalpable. In chest examination, coarse crackles at both lungs and the right lung consolidation on the chest X-ray (CXR) found. The laboratory findings summarized in Table. In the first days of admission, neutropenia and thrombocytopenia detected which improving during hospitalization.

Table: Laboratory Data

A. Complete Blood Count

CBC / Case number	WBC 1000/ul	Neutrophils 1000/µl	Lymphocyte 1000/µl	HB g/dl	Platlet cell/ul
1	2700	1215	1405	10.7	306000
2	7980	1516	5426	9	381000
3	7900	5925	1422	11.9	219000

CBC: Complete Blood Count

B. Lymphocyte Transformation Test

LTT / Case	PHA (normal range≥3)	BCG (normal range≥2.5)	Candidia (normal range≥2.5)
1	4	2.2	4.4
2	3.2	3.1	2.2
3	4.3	3.1	1

LTT: Lymphocyte Transformation Test, **PHA:** Phytohemagglutinin

C. Flow Cytometry

CD markers / Case	$CD3^+$	$CD4^+$	$CD3^+/CD4^+$	$CD8^+$	$CD3^+/CD8^+$	CD16	CD19	CD56
1	88% Absolut=1236×10^3/µl (range=1400-8000)	58%	1.51 (range=0.9-5.5)	31%	2.84 (range=0.4-2.3)	4%	7% Absolut=98×10^3/µl (range=600-3100)	4%

2	70.1% Absolut=3798 (range=2400-6900)	55.2%	1.27 (range=1.4-5.1)	18.2%	3.84 (range=0.6-2.2)	-	14.2% Absolut=770 (range=700-2500)	-
3	68% Absolut=967 (range=2400-6900)	62%	1.09 (range=1.4-5.1)	6%	11.37 (range=0.6-2.2)	1.5%	14% Absolut=199 (range=700-2500)	3%

CD3: T-cells (general), CD4: T helper, CD8: T cytotoxic, CD16: Granulocytes/natural killer cells (NK), CD19: B-cells, CD56: NK

D. Immunoglobulins

Igs / Case	IgG mg/dl	IgM mg/dl	IgA mg/dl	IgE mg/dl
1	110 Normal range for age:(666-1340)	18 Normal range for age:(76-233)	<3 Normal range for age:(24-116)	1 Normal range for age: ()
2	820 Normal range for age:(377-774)	65 Normal range for age:(40-141)	<37 Normal range for age:(13-56)	3 Normal range for age:()
3	698 Normal range for age:(363-1690	86 Normal range for age:(48-249)	7 Normal range for age:(7-78)	0.7 Normal range: 70-400)

E. Immunoglobulin Response

Case	Anti-Tetanus IgG	Anti-Diphtheria IgG
1	1.5	0.26
2	2.12	>1
3	-	-

NBT: Nitro blue Tetrazolium Test

On the second day of administration, he admitted to the intensive care unit (ICU) due to his unstable condition. He suffered extensive ulcerative lesion with necrotic center on his left foot, which was more tender and warmer than the opposite site. Following surgery consultation, Doppler sonography and X-ray of lower extremities were performed, which showed subcutaneous and intermuscular adenoma, which suspected to myositis and necrotizing fasciitis, was ruled out. In this center, bacterial blood culture was negative. We started antibiotics therapy with Meropenem, Vancomycin, and Clindamycin, and then changed the regimen to Ceftazidime and Clindamycin after 22 days of administration. In addition, human serum albumin and calcium with heart monitoring, prescribed and because of low hemoglobin, packed red blood cells was infused. He received Ribavirin suspected for Crimean Congo Hemorrhagic Fever. On hospital day 3, the necrotic lesion was debrided and drained surgically. Finally, based on immunology consultation, he started receiving 5-gram intravenous immunoglobulin (IVIG). He was continued on antibiotics and finally discharged from the hospital in a stable condition with receiving monthly IVIG.

Case 2

A 5-month year's old male admitted to this center with four days' history of fever and chilling, which did not respond to medical treatment with cephalexin. The fever was complicated with several lesions on the face after one day. Erythematous plaques without pus seen on the cheek, under the right eye, and genitalia Picture 1. His vaccination was upon the routine plan. His parent were not relatives and did not report any recent travel or contact with the ill person. His sibling was healthy. In his physical examination, multiple hemorrhagic plaques were observed on the right leg and left thigh. Lower extremities and scalp swallowed. He did not have organomegaly on the abdominal examination. The chest examination was normal. He was under observation in the pediatric intensive care unit and received 2-gr intravenous immunoglobulin (IVIG) because of his severe edema (suspicious of Kawasaki disease) on the first day of admission. He started on abroad-spectrum systematic antibiotic regimen (Meropenem, Vancomycin, and Amikacin) after admission. On hospital day 5, his fever reduced and skin lesions improved, while his wound culture grew Pseudomonas aeruginosa. Because of the immunodeficiency suspicion, bone marrow aspiration (BMA) performed, which reported maturation arrest in the myeloid series. For agammaglobulinemic assessment, immunologic workup was performed which yielded in Table and compare with other cases.

Picture 1
Case 2: Initial Lesions

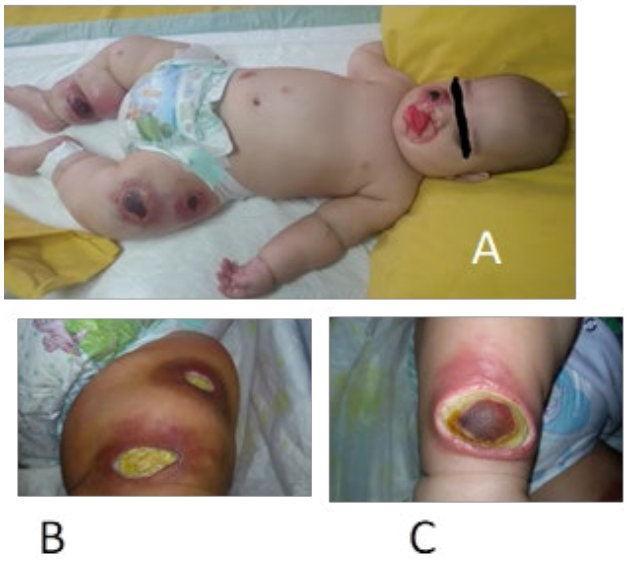

Figure 1: Ecthyma Gangrenosum (A) His lower extremities were swollen and tender, especially on left foot. The left foot was warmer than the right and had more lesions compared to other sites; (B) vesicular dark lesions on his left leg; (C) a necrotic lesion with infectious secretion with a positive lesions culture which showed pseudomonas aeruginosa

Case 2: Recent

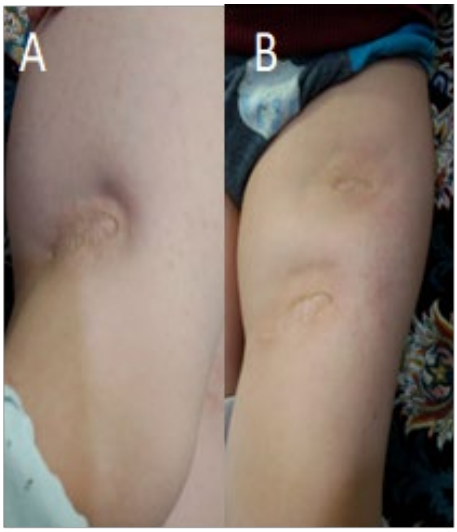

Figure 2: Multiple scars were observed on the right leg (A) and left (B) thigh

Further Flow Cytometry Information

Case 2: Flow Cytometry Lymph Phenotyping Analysis, Gate: Lymph (21.0%), Viability: >90%

CD1	0.1	CD34	2.3
CD2	69.6	CD11	2.5
CD3	70.1	CD9	0.3
CD4	55.2	CD10	0.1
CD5	68.2	CD19	14.2

CD7	69.2	CD20	13.5
CD8	18.2	CD22	12.9
CD13	0.1	CD45	95.1
CD33	2.5	CD18	90 rang(60-90)
CD14	1.3	CD11a	99 rang(Total=50-90,Lymph=50-90)
CD15	97 rang(60-90)	CD11b	90 rang(Total=40-85,Lymph=5-20)
		CD11c	97 Rang (Total=10-30%, Lymph=2-8%)

With Ecthyma Gangrenosum impression, he received intravenous methylprednisolone 1 mg/kg/BD and Mometasone ointment twice a day. He continued on antibiotics and underwent surgical debridement of the necrotic lesion and skin graft. His temperature gradually returned to normal after surgical and medical treatment on hospital day 15, he discharged from the hospital in stable condition with prophylactic antibiotic (Cotrimoxazole) and repeating complete blood count every 2 weeks.

Case 3

A 6 months old male admitted to this center with a history of a two-week fever. The fever accompanied by erythematous papule, which transformed into necrotic, bullous, gangrene lesions, spread through his thigh, posterior conjunctiva, and left flunk Picture 2. One week before referral to this center, he hospitalized and received antibiotics (Meropenem, Vancomycin, and Ciprofloxacin) upon a positive pseudomonas wound culture and positive Klebsiella cerebrospinal fluid (CSF) culture. He had a history of alcoholic defecation two days before hospitalization. His parents were not relatives and his older siblings were healthy. He did not have a history of recent travel or contact with a contiguous disease. In the physical examination, a few gangrenous 2*3 mm lesions with surrounding blisters were scattered on his left flank, thigh, and posterior conjunctiva. The right testis was larger than normal and bilateral hydroceles noted. The sclera was icteric. Pulmonary and heart examinations were normal. The abdomen distended with a bilateral erythematous lesion, without tenderness, rebound, or guarding. The liver enlarged to 3 Cm below the right costal margin and the spleen was impalpable.

The broad-spectrum antibiotic (Amikacin, Meropenem, and Vancomycin) administrated as well as two doses of IVIG to provide passive antimicrobial coverage. In addition, abdominal sonography and surgical debridement performed. Sonography showed mild pulmonary edema, cellulitis, myositis, and hydrocele. On hospital day 2 regarding the abnormal liver function test (LFT), he received Ursobil, and LFT checked two times every week. Vitamins and fresh frozen plasma (FFP) prescribed to correct international normalized ratio (INR). The immunologic function was tested. The lymphocyte subtypes detail notice in the Table and compared with others. The T CD8+ cells reduced and the lymphocyte transformation test (LTT) was dysfunctional Table, further confirming the diagnosis of combined Immunodeficiency. He discharged with 5 mg IVIG, antibiotics, and antifungal prophylaxis

Picture 2
Case 3: Initial Lesions

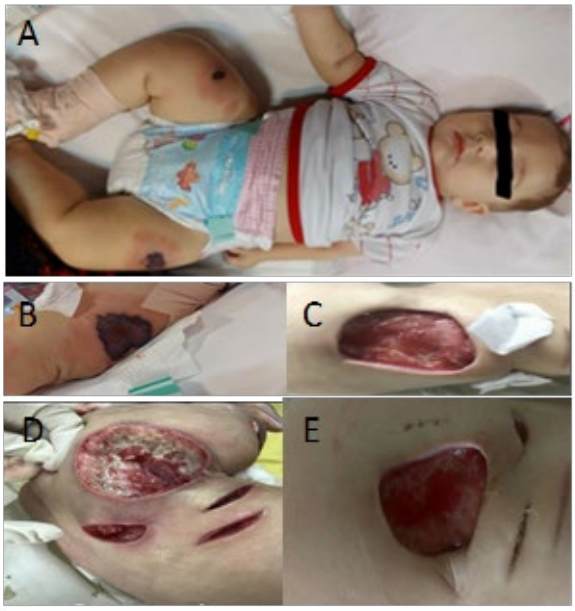

Figure 3: Erythematous papule which transformed to necrotic, bullous, and gangrene lesions and spread through his thigh

Case 3: Recent

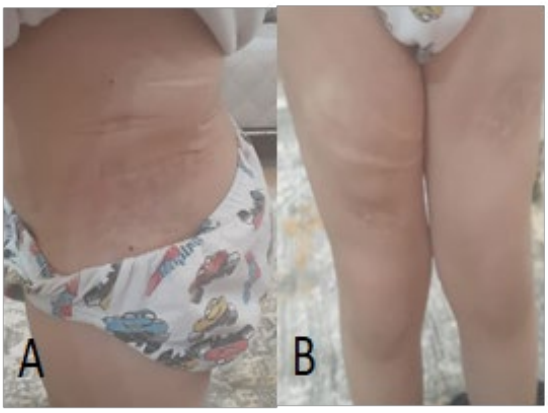

Figure 4: A few scars were scattered on his left flank and thigh

The first step of Biochemical diagnosis of CID suspected patients is complete blood count, which gives clues of immunological alteration. Despite, the assessment of absolute neutrophil and lymphocyte count of our cases influenced by Pa toxin, after human immunodeficiency virus (HIV) ruled out the specific evaluation of immunological parameters performed. This evaluation included:

• Measurement of immunoglobulins (IgA/IgG/IgM/IgE) which summarized in Table-D. Except for generalized hypogammaglobinemia in Case one, reduced IgE and IgA seen in Cases 2 and 3.

• Vaccinal response which done when maternal antibodies transferred via placenta decrease (6 month years old) Table-E. Based on our data we detected less than 1 Iu/mL Anti-Diphtheria IgG in Case 2.

• Measurement of leukocyte subtypes by flow cytometry (Immunophenotyping of CD3/CD4/CD8/CD19 and NK) summarized at Table-C. $CD3^+$ as a general lymphocyte and $CD19^+$ as a B lymphocyte marker reduced in Case 1 and 3. Reduced $CD3^+/CD4^+$ in Case 2 and 3 shows lymphocyte impairment, and high $CD3^+/CD8^+$ indicate low CD8+ in all cases. More CD information provide in Table-F.

• Lymphocyte function assessment by Lymphocyte Transformation Test (LTT) measured by lymph proliferation after stimulation with phytohemagglutinin (PHA). Table-B. In our study, all patients had normal PHA level, however cell proliferation against BCG in Case 1 was slightly low and cell proliferation against Candida in Case 2 and 3 were reduced.

Case 3: Flow Cytometry Lymph Phenotyping Analysis, Gate: Lymph (39%), Viability: 90%, Specimen: Pb

CD2	77.4	CD20	21.3	CD56	0.3
CD3	84.3	CD38	0.1		
CD4	67.2	CD4/CD8(dual)	0.4		
CD8	7.9	CD2/CD19(dual)	0.2		
CD10	1	CD3/HLADR(dual)	2.1		
CD19	19.1	CD16	1.5		

Discussion and Conclusion

Ecthyma Gangrenosum is a rare skin disorder, which is an ulcerative variant of septic vasculitis. EG characterized by sharply circumscribed "pinched out" deep ulceration. These lesions usually start as an erythematous macule, which subsequently forms a vesicle, pustules, bullae with debris, and necrotic material within the ulcer [1]. Since the first case report of EG, several studies show different causative pathogens [2]. In a study of 164 patients diagnosed with EG from 1974 to 2014, PA was detected in 73.65% of cases, whereas other bacteria and even Candida albicans, were detected in only 17.35% and 9% of cases respectively [3]. Although in Case 3 we isolated Klebsiella from CSF culture, Pa detected from all lesions culture. However, Klebsiella can cause EG [4]. A case report from Isezuo K.O in 2018 shows different isolated organisms from CSF (S.aureus) and lesions (E.coli) culture in the concept of co-infection at EG pathogenesis [5]. Pa species are a normal part of the skin flora and usually found in the anogenital, axillae, and external ear canal [6]. Clinical manifestations related to PA are mainly due to the vessels walls invasion mediated by the toxin, and usually affects the lower extremities, especially gluteal and genital areas [7]. Fever, diarrhea, pneumonia, shock are the most relevant associated symptoms especially in PA sepsis [5]. As CCHF suspected in Case two, several studies show infections that can mimic EG, like mycobacterial ulcer, cutaneous leishmaniosis cutaneous tuberculosis, and even deep fungal infections thus, EG must be considered in any necrotic lesions that are unresponsive to

prolonged antibiotics [8]. Another important differential diagnosis is necrotizing fasciitis, which ruled by MRI in Case 3 [9].

Despite, EG usually described in immunocompromised patients, it also seen in patients suffering from malnutrition, underlying (hematological) malignancy, and even previously healthy individuals [10]. A literature review by Danel J Lewis et al in 2019 shows cutaneous manifestations of primary immune deficiency disorders (PID) [11]. Several studies show EG in patients who suffer from X-linked agammaglobulinemic (XLA) (Burton hypogammaglobinemia), which is characterized by the complete absence of circulating B-cells and plasma cells, with decreased(IgG) or absent (IgA and IgM) levels of immunoglobulins [12]. Leukocyte Adhesion Deficiency (LAD) reported with EG. These disorders involve an absence of ß2-integrin subunit (CD18), which prevents neutrophils aggregation [11]. Neutrophils are a vital part of the cellular host defense against bacterial infections, whereby neutrophil count bellow 500/mm3 cause the greatest risk of bacterial infections [13]. Two cases of our study (Case 1 and 2) had neutropenia on the first days of admission, which resolved after treatment. In addition to several case reports of neutropenia with EG, PA toxins can produce neutropenia through bone marrow suppression and inhibition of granulocyte migration [2]. In 2003, Maria Baro, ET, al. reported X-linked agammaglobulinemic with EG, that neutropenia with bone marrow granulocyte arrest resolved when infection was treated. They also postulated that neutropenia could result from a neutrophil-altered response to stress due to mutations in the Btk gene that expressed in myeloid series [14].

Unlike other cases, case 3 had neutrophil predominance. In a case report at a tertiary hospital in Sokoto, the index patients also had neutrophil predominance as usual neutropenia associated with PA. However, our patient's immunological comparison did not show obvious differences, this might explained by their relatively good immunity [8]. Another primary immune disease that leads to neutrophil dysfunctions is chronic granulomatous disease (CGD), it is caused by gene mutations encoding essential subunits of NADPH oxidase complex subsequently neutrophils fail to increase oxygen consumption for the destruction of phagocytes bacteria (e.g.; Klebsiella, Pseudomonas, Candida) and fungi [15]. Nitro blue tetrazolium Blood Test (NBT) was normal (100%) in all our cases, thus we rollout CGDs. Besides underlying immunodeficiency diseases, some studies suggest that the immunoglobulin level and B cell percentage decreased in the disease process and are transient [10]. However, hypogammaglobinemia and reduced B cell observed in our cases, CID applied based on other flow cytometry data and ESID criteria. However, it should be considered molecular diagnosis such as next-generation sequencing (NGS) is the exact diagnostic modality [16].

Combined immunodeficiency (CID) is an Inborn Error of Immunities (IEIs) characterized by defects in both humoral and cellular limbs of the immune system. The main clinical manifestations of IEIs are susceptible to unusual or recurrent infections that are difficult to treat [17]. Previous studies show variable skin manifestations in CID patients with syndromic features (e.g.: atopic dermatitis in Wiskott-Aldrich syndrome, bulbar telangiectasia and ataxia in Ataxia-telangiectasia, Café au lait macules and telangiectasia in sun-exposed are in Bloom syndrome, dermatitis, prominent papulopustular eruption and recurrent staphylococcal infections with abscess formation in Hyper-IgE syndrome (Job syndrome) [18-21].

The first step of Biochemical diagnosis of CID-suspected patients is a complete blood count, which gives clues of immunological alteration [22]. Despite, the assessment of absolute neutrophil and lymphocyte count of our cases being influenced by Pa toxin after HIV was ruled out the specific evaluation of immunological parameters was performed. This evaluation included in our study all patients were alive [23,24]. Although EG has a high mortality rate, prognosis depends on the host and the degree of immunosuppression. In patients with EG and septicemia secondary to pseudomonas it ranged from 38% - 77%, and in patients without sepsis is about 15% [25]. Notably, neutropenia below 500 cells can predispose a patient to severe PA infection and this seems to be associated with a higher mortality rate even in a previously healthy child [13]. EG's high mortality rate emphasizes the importance of early suspicion and proper treatment even when the diagnosis has not been confirmed. While awaiting culture results, empirical antimicrobial therapy with anti-pseudomonas penicillin and aminoglycoside should be started, and adjusted based on culture results. Administration of GCSF along with antibiotics should be considered to shorten the duration of neutropenia, to help resolve the EG, and to minimize the risk of septicemia in immunocompromised patients.

In conclusion, EG is a rare skin disorder, usually caused by PA, and commonly occurs in immunocompromised individuals. Despite, the previously healthy and immunocompetent individuals, may become affected; we must consider an immune assessment for all patients, especially in early childhood. Furthermore, early diagnosis of an underlying illness, notably primary immunodeficiency, leads to using the appropriate treatment and preventing EG-related mortality.

Ethical Approval and Consent

Written informed consent for publication obtained from the patient and parents of the patient prior to being included in the study.

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