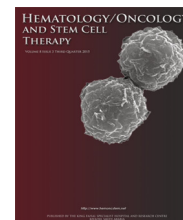




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## CASE REPORT

# Paraneoplastic pemphigus as a presentation of acute myeloid leukemia: Early diagnosis and remission

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## KEYWORDS

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Criteria;  
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## Abstract

Skin lesions are frequently encountered in clinical practice which can be a presentation of systemic diseases not excluding an occult malignancy. Commonly reported paraneoplastic dermatologic manifestations include acanthosis nigricans, dermatomyositis, erythroderma, hypertrophic osteoarthropathy, Sweet syndrome, and paraneoplastic pemphigus (PNP).

PNP is a rare autoimmune mucocutaneous disease characterized by severe stomatitis, polymorphic skin eruptions, and associated underlying neoplasms most commonly non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and Castleman disease. PNP is characterized on histopathology as dyskeratotic epithelial cells with acantholysis with a typical immunofluorescence staining pattern of direct and/or indirect staining of intercellular, basement membrane, and dermoepidermal junction with immunoglobulin-G and C3. PNP has been described to have poor prognosis with a mortality range of 75–90% and a mean survival of less than 1 year.

We describe a previously unreported case of PNP associated with acute myeloid leukemia (AML) where the patient presented with a nonhealing ulcer and hemorrhagic crusting on the face that did not respond to antimicrobials and steroids. Investigations revealed leukocytosis with peripherally circulating blasts. Skin biopsy revealed an evolving PNP and bone marrow biopsy confirmed evidence of AML. The patient underwent induction, consolidation, and then successful allogeneic bone marrow transplantation with complete remission. The skin lesion, which was initially refractory to treatments, surprisingly resolved within 7 days of starting induction chemotherapy.

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In this case, the skin lesion was a key factor in early diagnosis and instituting treatment for the underlying AML. Early intervention gave our patient a better outcome with an ongoing survival of 18 months since diagnosis, maintaining complete remission.

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## Introduction

Skin lesions are most commonly seen secondary to an infectious, autoimmune or allergic etiology. In some instances, skin lesions can be a manifestation of the myriad of systemic diseases including malignancies. The dermatologic involvement of the neoplasia can either be a primary tumor of the integumentary system, metastasis to the skin as in chloroma, or a paraneoplastic phenomenon. Commonly reported paraneoplastic skin manifestations include acanthosis nigricans, dermatomyositis, erythroderma, hypertrophic osteoarthropathy, Sweet syndrome, and paraneoplastic pemphigus (PNP) [1].

PNP presents as polymorphic cutaneous eruptions in the form of either bullous, erythematous, or verrucous papules or plaques, with or without intraoral mucosal involvement in the form of stomatitis, erosions, or ulcerations. It can also involve other mucosal regions, often the conjunctiva.

The incidence of PNP does not follow any geographic distribution or gender preponderance with a mean age at diagnosis of 51 years [2]. It has been associated with non-Hodgkin lymphoma, chronic lymphocytic leukemia, Castleman disease, thymoma, and rarely with Waldenstrom macroglobulinemia, Hodgkins lymphoma, and monoclonal gammopathy [3,4]. It has also been reported with solid tumor malignancies like adenocarcinoma of the pancreas, colon, breast, and prostate, as well as mesenchymal sarcomas [5]. Occasionally, medications like fludrabine and interferon- $\alpha$  have been shown to cause a flare up of PNP lesions in known patients [6].

We report a case of PNP associated with acute myeloid leukemia (AML) previously unreported in medical literature. This atypical presentation of AML as PNP led to the early diagnosis, treatment, and complete remission of the patient.

## Case report

A 59-year-old man, with no significant past medical history, presented to his primary care physician with a lesion on his face. He had a recent molar tooth extraction 1 month previous with no associated complications. He was a current smoker with a 20-pack-year smoking history. He had a family history of lung cancer, colon cancer, and uterine cancer, and no personal or family history of any autoimmune disease.

The lesion was just limited to his lower face around the perioral area. The patient denied any recent infection, rashes, swollen lymph nodes, fever, night sweats, bleeding, or any pain. He had no recent history of travel, trauma, insect, tick or animal bite, or any exposure to sick contacts. He did complain of stomatitis but without any oral ulcers.

On physical examination, the lesions were black, indurated, and ulcerated, with hemorrhagic crusting involving the entire lower lip along the vermilion border and infranasal area (Fig. 1). No other skin lesions were identified. There was no palpable cervical or peripheral lymphadenopathy, petechial rash, buccal lesions, or oral ulceration.

Considering the lesion to be a bacterial infection, he was initially treated with oral antimicrobials as an outpatient. With no clinical improvement, routine investigations were done that revealed leukocytosis with peripherally circulating blasts (Fig. 2) raising concern for a hematological malignancy, for which he was referred to our inpatient hematology service.

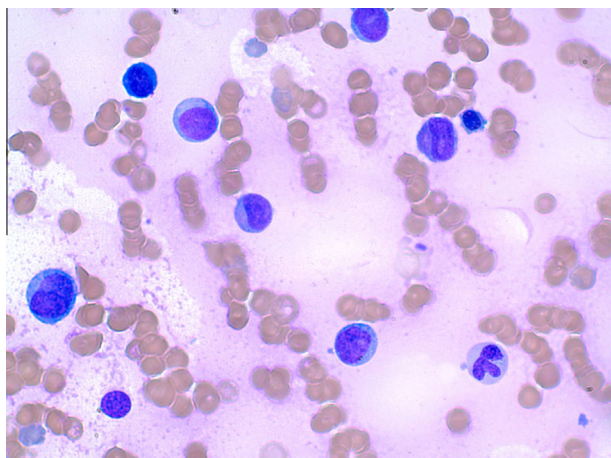
Complete blood count revealed a white cell count of 24,300/uL with 29% blasts and no bandemia, platelet count of 33,000/uL, hemoglobin of 9.1 g/dL, and hematocrit of 27. Other investigations revealed elevated lactate dehydrogenase of 664 mg/dL (normal: 140–280 mg/dL) and normal uric acid of 6.4 mg/dL (normal: 3.4–7.0 mg/dL). There was no evidence of disseminated intravascular coagulation and other laboratory tests including serum sodium, potassium, blood urea nitrogen, creatinine, and liver function tests were normal. Serum protein electrophoresis also did not reveal any monoclonal bands.

The patient was initially started on empiric antimicrobial coverage with valacyclovir, vancomycin, cefepime, and micafungin, along with dexamethasone, due to concerns of being in an immunocompromised state. A bone marrow biopsy along with a biopsy of the skin lesion was then pursued.

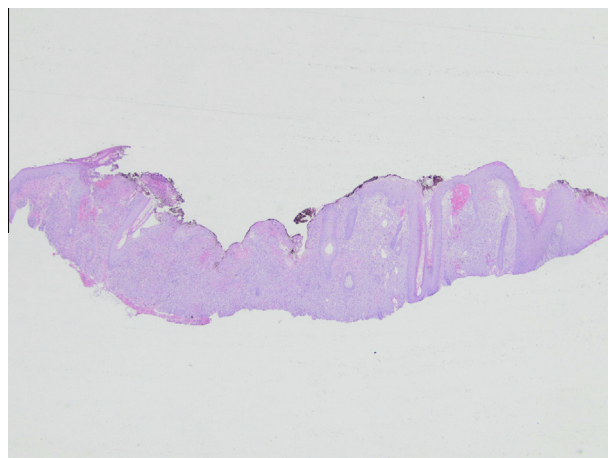
Microbiological analysis of the skin biopsy showed no evidence of herpes simplex virus in tissue culture, absence of viral cytopathic changes, or any fungal elements. Epstein-Barr virus DNA polymerase chain reaction was also negative. Wound cultures grew mixed oropharyngeal bacterial flora with few *Candida albicans*. Skin lesions remained



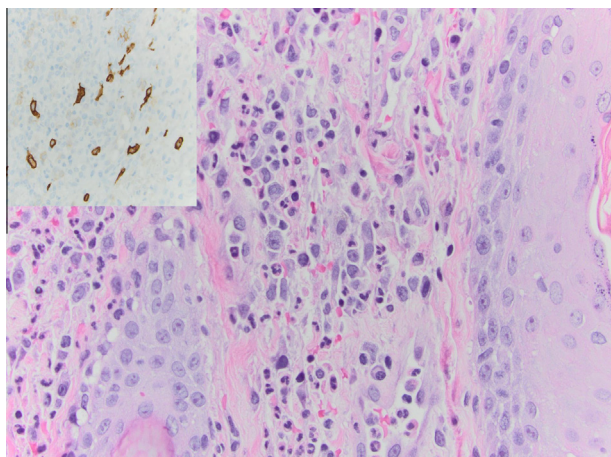
Fig. 1 Gross appearance of the skin lesion.



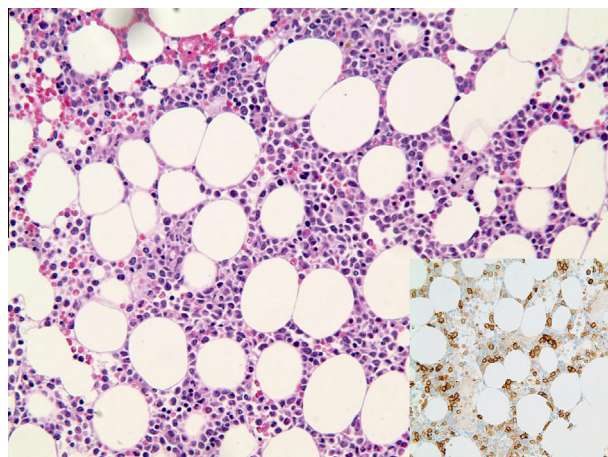
**Fig. 2** Peripheral blood smear at 60× magnification showing abundance of immature myeloid cells.



**Fig. 4** Skin biopsy at 20× magnification showing ulceration and focal adjacent acantholysis.



**Fig. 3** Skin biopsy at 400× magnification showing mixed inflammatory infiltrates deep to the ulcer. Largely neutrophilic with occasional larger leukemic cells (high nuclear to cytoplasmic ratio, scant cytoplasm, and immature chromatin with prominent nucleoli). Inset: cells positive for CD117, similar to ones seen in bone marrow (Fig. 5).



**Fig. 5** Bone marrow biopsy at 20× magnification: increased number of large, immature myeloid cells (nuclei are eccentric, hypossegmented, high nucleus-to-cytoplasm ratio, scant cytoplasm, fine chromatin, distinct nucleoli). Inset shows immature cells positive for CD117.

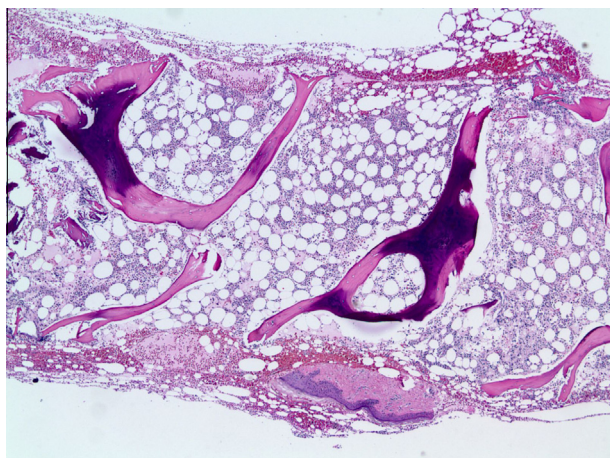
unchanged despite the patient being on broad-spectrum antimicrobial therapy as well as corticosteroids. The skin biopsy showed focal basal vacuolar change with dyskeratotic keratinocytes, adjacent focal acantholysis (Figs. 3 and 4), and direct immunofluorescence (DIF) showed positive immunoreactivity for complement C3 in a linear pattern along the dermoepidermal junction but negative for immunoglobulin (Ig)G, IgA, IgM; consistent with an evolving PNP.

Bone marrow studies revealed hypercellularity of 60%, dysmyelopoiesis, erythroid–megaloblastoid change with immunohistochemistry and flow cytometry showing predominant myeloperoxidase-positive myeloid immature cells with 47% myeloblasts, 50% CD117-positive immature cells, and 20% CD34-positive blasts, suggestive of AML. Human leukocyte antigen-antigen D related and CD11c was present excluding acute promyelocytic leukemia (Figs. 5 and 6).

The patient was started on induction therapy with cytarabine and idarubicin with rapid first complete remission. Surprisingly, the skin lesions, which were refractory to the above-mentioned treatments, resolved within 7 days of starting induction chemotherapy.

Further AML risk stratification studies showed intermediate risk normal cytogenetics and high risk “*fms-like tyrosine kinase 3* gene internal tandem duplication” positivity. After three cycles of high dose cytarabine consolidation, he underwent successful matched unrelated donor allogeneic stem cell transplantation with complete remission and subsequent recovery of his hematological cell counts. Post-transplant chimerism studies revealed 100% donor status in all his three cellular compartments. His post-transplant course did get complicated with limited graft versus host disease (GVHD) of the skin, which was successfully treated with topical steroids, and BK-virus hemorrhagic cystitis, which has also resolved.





**Fig. 6** Bone marrow biopsy at 4× magnification showing hypercellularity.

Eighteen months after diagnosis and seven months post-transplantation the patient is doing well with stable hematological cell counts.

## Discussion

PNP was first described in 1990 by Anhalt et al. [7] in a case series of five patients with ulcerative, blistering mucocutaneous disease, and pemphigus-like autoantibodies. The polymorphic cutaneous lesions of PNP have been described as bullae, erythematous, and verrucous papules or plaques, which vary from features of pemphigus, pemphigoid, erythema multiforme, GVHD, and lichen planus. Often it has multiple overlapping features from this spectrum [6,8]. Intraoral mucosal involvement from intractable stomatitis to multiple diffuse erosions and shallow ulcerations are also seen, with occasional bloody crusts on the vermilion border of lip as seen in this case (Fig. 1) [3,6]. Mucosal involvement is varied which could include the oral, laryngeal, pharyngeal, esophageal, lingual, gingival, labial, gastrointestinal, vaginal, or penile mucosa [3,9]. Conjunctiva is also very frequently involved in the form of pseudomembranous conjunctivitis which later evolves to scarring [3,10].

Camisa and Helm [9] proposed the PNP diagnostic criteria which are modified criteria from Anhalt et al. [7]. According to the diagnostic criteria PNP can be diagnosed by the presence of either all three major or two major with two minor criteria as described in Table 1 [9].

In their article, Camisa and Helm [9] described the common histologic findings such as acantholysis, keratinocyte necrosis, lichen-like inflammatory infiltrates, and dermoepidermal blisters. They also described DIF showing C3 and/or IgG deposits on epithelial cell surfaces and dermoepidermal junctions or both, and indirect immunofluorescence (IIF), which is commonly done on monkey esophagus or rat bladder epithelium, with intercellular staining and/or dermoepidermal staining [9]. This case had two major criteria of polymorphic skin eruption and concurrent neoplasia along with two minor criteria of histological signs of acantholysis and DIF showing staining of C3 immunoreac-

tivity at dermoepidermal junctions. PNP antibodies that have been implicated are most commonly anti-envoplakin and anti-periplakin antibodies. Other antibodies include bullous pemphigoid antigen 1, desmoplakin I and II, desmoglein-1 and desmoglein-3 [6,11,12]. Recent research has reported the association of PNP with alpha-2-macroglobulin-like protein 1 and anti-desmocollin antibodies as well [13].

Joly et al. [14] reviewed the various criteria for PNP in their study. They reported that high sensitivity and specificity was associated with factors such as lymphoproliferative disorders, IIF positivity on rat bladder, and immunoblotting of antibodies against envoplakin and periplakin. While low sensitivity and high specificity was associated with factors like polymorphic eruption, typical histology, DIF, or immunoblotting of antibodies against desmoplakin and bullous pemphigoid antigen 1 [3,14].

Besides the cancers, PNP is also associated with diseases like myasthenia gravis (MG) and bronchiolitis obliterans (BO) [3,11,12]. BO is an irreversible and fatal disease that occurs in lung transplant recipients and in chronic GVHD patients after allogeneic hematopoietic stem cell transplantation, with an incidence of 30–40% PNP patients progressing to BO [15,16]. Respiratory compromise in BO occurs due to the intraluminal shedding of respiratory mucosal epithelium after an immunological attack due to the preponderance of desmoplakins [3]. Such patients present with worsening exertional dyspnea that culminates to severe dyspnea, disproportionate to the chest x-ray and arterial blood gas findings [10]. Most of the PNP-associated BO is fatal, except for those with Castleman disease [15,16]. In a study of 104 patients, BO developed in 20 patients with 16 of them resulting in death [13]. This study also reported the deaths of 40 PNP patients with infectious causes, mainly pneumonia, which can be attributed to the impaired immunity with their lymphoproliferative disorder. With regards to the association with MG, a study on 58 PNP patients where 39% of them complained of muscle weakness, 35% were diagnosed with MG with positive antiacetylcholine receptor and antiacetylcholinesterase antibodies [12]. The antiacetylcholine receptor and antiacetylcholinesterase antibodies levels were significantly elevated in patients who had dyspnea. Even though PNP and MG have both been associated with thymoma, this study found no significant differences in positivity and levels of these autoantibodies between PNP with Castleman disease and thymoma [12]. This reflects that MG can be independent sequelae of PNP irrespective of the underlying thymoma. Thus, patients with PNP who develop muscle weakness or dyspnea warrant additional workup for ruling out BO and MG and patients need to be educated on these complications.

The most effective treatment for PNP is the resection or resolution of the underlying neoplasm which has shown success in patients with Castleman disease as well as reported in this case of AML [17]. High-dose systemic corticosteroids and immunosuppression with azathioprine and mycophenolate for treatment have been also recommended [6]. Rituximab is also proposed for the treatment which acts by reducing B cells that produce the PNP antibodies that may have caused the skin lesions to develop [15,18]. Intravenous Igs have also been tried as a treatment [17]. Although our patient was given dexamethasone, which was

**Table 1** Paraneoplastic pemphigus (PNP) diagnostic criteria as described by Camisa and Helm [9].

PNP diagnostic criteria (presence of either all three major or two major with two minor criteria)
Major
Polymorphic mucocutaneous eruption
Concurrent internal neoplasia
Serum antibodies
Minor
Histological signs of acantholysis in biopsy specimen from at least one anatomic site of involvement
DIF staining of perilesional tissue showing intercellular and basement membrane zone immunoreactants
IIF positive cytoplasmic staining of rat bladder epithelium
DIF = direct immunofluorescence; IIF = indirect immunofluorescence.

ineffective, the skin lesions dramatically responded to the successful induction regimen which supports the fact that treatment of the underlying neoplasm leads to its resolution in patients with AML. Different types of PNP respond variably to treatment regimens as rituximab has been proposed to be very effective in patients with follicular lymphoma.

PNP can be categorized as being severe if having extensive skin involvement (with a minimum of 20 skin lesions) with or without mucosal lesions or if there is involvement of at least two mucosal areas or oral mucosa only causing dysphagia or weight loss [9].

Patients with PNP have a poor prognosis with a reported mortality rate of 75–90% and a mean survival of less than 1 year [6]. According to one multicenter study on 53 patients; the 1-year, 3-year, and 5-year survival rates were 49%, 41%, and 38%, respectively, with the main causes of death being infections, progression of cancer, and respiratory failure due to suspected BO [6]. This study also listed the poor prognostic factors such as the presence of erythema multiforme-like skin lesions and histological evidence of keratinocyte necrosis especially when associated with severe skin or mucosal involvement [6]. Castleman disease was associated with better survival while non-Hodgkin lymphoma had a shorter survival with age, gender, or presence of PNP antibodies having no association with prognosis. Our case had a better outcome likely due to early diagnosis and treatment, with complete remission of AML. It can be proposed that AML-associated PNP may have a better survival rate than other ones, similar to Castleman disease. Similar to previously reported PNP in Castleman disease, where treatment of primary malignancy resulted in resolution of the skin disease, this case also demonstrated the effective resolution of skin lesions with treatment of primary malignancy [19].

Our case met the diagnosis criteria by Camisa and Helm [9] but further testing for autoantibodies and IIF would have been more confirmatory. The typical histopathology and IIF pattern of PNP may take several months to completely develop, so even in suspected cases where the skin biopsy does not fully meet the criteria stated above, it may still signify that the PNP is in the process of evolving [6]. In such cases it is prudent to consider it as an evolving PNP and proceed with screening for related neoplasms.

Skin lesions are commonly seen in practice, which besides being a common garden variety skin infection or autoimmune disease, can also be a manifestation of an underlying systemic disease. Some lesions may be resilient

to conventional treatment like antimicrobials or immunosuppressants, as seen in our case, which should be followed with a skin biopsy. Clinicians should remember that skin lesions, as a paraneoplastic phenomenon, could be a sign of an occult malignancy where early diagnosis and intervention are crucial. Thus, any unexplained or treatment refractory skin lesions should invoke a suspicion of paraneoplastic phenomenon followed by immediate screening for age, sex, and risk-factor appropriate neoplasms.

### Conflicts of interest

The authors declare no conflicts of interest in relation to this manuscript.

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