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Case Report

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Paraneoplastic Pemphigus Mimicking Stevens–Johnson Syndrome in a Patient with Multiple Myeloma: A Rare and Clinically Challenging Presentation

Zahra Keshavarz[1], Alireza Zangooie[2,3], Elias Sadooghi Rad[3], Roya Bojaran[4], Zahra Salehi[2,5]

[1]Department of Dermatology, Rasool Akram Medical Complex Clinical Research Development Center, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[2]Cell Therapy and Hematopoietic Stem Cell Transplantation Research Center, Research Institute for Oncology, Hematology and Cell Therapy, Tehran University of Medical Sciences, Tehran, Iran
[3]Student Research Committee, Birjand University of Medical Sciences, Birjand, Iran
[4]Department of Pathology, Vali-Asr Hospital, Birjand University of Medical Sciences, Birjand, Iran
[5]Hematology, Oncology and Stem Cell Transplantation Research Center, Research Institute for Oncology, Hematology and Cell Therapy, Tehran University of Medical Sciences, Tehran, Iran

Corresponding Author: Zahra Salehi, Cell Therapy and Hematopoietic Stem Cell Transplantation Research Center, Research Institute for Oncology, Hematology and Cell Therapy, Tehran University of Medical Sciences, Tehran, Iran
E-mail: zsalehi@sina.tums.ac.ir

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ABSTRACT

Paraneoplastic pemphigus (PNP) is a rare, severe autoimmune mucocutaneous disorder most commonly associated with lymphoproliferative malignancies. Here, we report the first documented case of PNP as a paraneoplastic manifestation of multiple myeloma (MM). A 61-year-old male with MM developed widespread mucocutaneous ulcerations shortly after his eleventh chemotherapy cycle, initially suspected to represent Stevens–Johnson syndrome. Clinical examination revealed diffuse skin peeling, mucosal involvement of the eyes, oral cavity, and genital region, and a positive Nikolsky sign. Laboratory evaluation demonstrated acute kidney injury requiring hemodialysis. Despite initial treatment with high-dose intravenous immunoglobulin, lesions persisted. Skin biopsy revealed lichenoid lymphocytic infiltration, basal vacuolar changes, subcorneal and suprabasal acantholysis, and keratinocyte dyskeratosis, confirming PNP. Viral serologies were negative, supporting the autoimmune etiology. The patient was subsequently treated with rituximab, resulting in significant improvement of cutaneous lesions over three months, with residual post-inflammatory hyperpigmentation. This case emphasizes the importance of early recognition and accurate differentiation of PNP from other blistering disorders in patients with underlying hematologic malignancies. Importantly, this represents the first reported instance of PNP presenting as a paraneoplastic manifestation of MM, highlighting the need for awareness of atypical autoimmune syndromes in this population.

Keywords: Paraneoplastic pemphigus (PNP); Multiple myeloma (MM); Stevens–Johnson syndrome (SJS); Paraneoplastic syndrome; Rituximab therapy; Case report

INTRODUCTION

Paraneoplastic pemphigus (PNP) is a rare and severe autoimmune mucocutaneous blistering disorder most frequently associated with lymphoproliferative malignancies, particularly non-Hodgkin lymphoma and chronic lymphocytic leukemia[1]. Multiple Myeloma (MM) accounts for 10–15% of hematological malignancies and 1–2% of all cancers. Although rare, it is associated with various atypical paraneoplastic manifestations, which may

present before or after the diagnosis of MM. These include vascular, neurological, dermatological, physiological, and other uncommon conditions. The clinical presentation can vary widely, making diagnosis challenging, and these rare manifestations often require careful differential diagnosis. Most information about these paraneoplastic conditions is derived from case reports, highlighting the need for more comprehensive scientific studies to better understand and manage these atypical presentations[2]. Importantly, however, despite cutaneous-paraneoplastic syndromes being described in MM, PNP has so far not been definitively reported as a paraneoplastic manifestation in MM. Cutaneous involvement in PNP is typically diffuse and varies in appearance, often presenting after mucosal symptoms. The skin manifestations can include pruritic red-purple papules, targetoid erythematous plaques, diffuse erythema, flaccid erosive blisters, and widespread exfoliative erythroderma. Due to the wide range of autoantibodies involved, PNP can mimic several other skin diseases such as lichen planus, erythema multiforme, bullous pemphigoid, pemphigus vulgaris, and graft-versus-host disease. Differential diagnoses for PNP include Stevens-Johnson syndrome, toxic epidermal necrolysis, drug-induced pemphigus, mucous membrane pemphigoid, herpes simplex virus, and others. A correct diagnosis depends on clinical presentation, histopathology, direct and indirect immunofluorescence, and immunoblot or immunoprecipitation studies[1,3-5]. Here, we report a 61-year-old male with MM who developed extensive mucocutaneous ulcerations initially suspected to represent Stevens–Johnson syndrome but ultimately diagnosed as PNP. This case highlights the importance of early recognition, accurate differentiation from other blistering disorders, and the need for coordinated multidisciplinary management in patients with underlying hematologic malignancies (Figure 1).

Figure 1. Timeline of clinical course and treatment progression in a patient with paraneoplastic pemphigus. The timeline illustrates the key stages of the patient's clinical presentation and management from January 23 to April 15. Initial presentation on January 23 included a severe mucocutaneous eruption following chemotherapy. Dermatology consultation on January 24 suggested Stevens–Johnson syndrome, and intravenous immunoglobulin (IVIG) therapy was initiated. On January 26, there was no substantial improvement, leading to a suggestion for cyclophosphamide, which was withheld due to renal concerns. A skin biopsy on January 29 revised the diagnosis to paraneoplastic pemphigus. Cardiological clearance was obtained on February 2, allowing the initiation of rituximab therapy. Significant improvement in the patient's skin condition was noted by April 15, with post-discharge monitoring showing only mild persistent features of postinflammatory hyperpigmentation (PIH).

Case presentation

On 23 January 2025, a 61-year-old man with known multiple myeloma presented to the hematology–oncology ward with a severe mucocutaneous eruption that had developed shortly after chemotherapy. His myeloma had been diagnosed in autumn 2024, and he was undergoing a planned thirteen-cycle chemotherapy regimen at weekly intervals. By the time of admission, he had completed eleven cycles, with three remaining.

Four days after receiving his eleventh chemotherapy cycle he developed multiple, widespread areas of skin peeling. Two days before admission he noticed the appearance of multiple painful, bleeding ulcers over his body. He denied fever, chills, malaise, loss of consciousness, seizures, nausea, vomiting, diarrhea, or constipation, but reported a marked loss of appetite. In the weeks prior to admission, he had taken several analgesic medications for symptom relief. Because of the temporal relationship between chemotherapy, analgesic use and the onset of diffuse skin and mucosal lesions, he was admitted with a presumed severe drug-induced mucocutaneous reaction.

His past medical history was notable for multiple myeloma, hypothyroidism, a previous episode of acute kidney injury, and aortic valve replacement with a prosthetic valve in about 2015. His regular medications at the time of admission included warfarin 5 mg (half a tablet daily, with a full tablet taken on Thursdays), acetylsalicylic acid 80 mg daily, levothyroxine 50 µg (a quarter tablet daily), thalidomide 100 mg daily, acyclovir 400 mg daily and an oral iron preparation (Ferrofort) once daily. He reported a previous allergy to an Indian brand of warfarin and to bortezomib (3.5 mg), a chemotherapy agent. His social history was unremarkable and there was no significant family history.

On admission his vital signs were stable, with a blood pressure of 131/60 mmHg, heart rate of 82 beats per minute, oxygen saturation of 100% on room air, and an oral temperature of 37.5 °C. He appeared systemically ill, primarily because of extensive skin and mucosal involvement. Examination of the skin revealed diffuse peeling and multiple ulcers over the body. The eyes were injected, and mucosal involvement of the eyes, mouth and genital region was later documented in dermatology notes. There was no jugular venous distension and no palpable lymphadenopathy. Chest examination showed clear lung fields and normal S1 and S2 heart sounds, with an audible diastolic click consistent with a mechanical aortic valve. Peripheral pulses were strong and symmetrical, and digital clubbing was present.

Initial laboratory investigations on the day of admission showed marked renal dysfunction, with a urea level of 163 and a creatinine level of 4.3, consistent with significant acute kidney injury in the context of his prior renal history. In view of this, a nephrology consultation was obtained on the day of admission. Nephrology recommended placement of a temporary Shaldon catheter and initiation of hemodialysis for two hours. They advised against the use of normal saline and instead recommended intravenous half-saline (0.45% sodium chloride) at 1000 cc every eight hours with 50 cc of bicarbonate added to each liter. A daily nephrotonic tablet was prescribed, and daily monitoring of complete blood count, venous blood gas, urea, creatinine, sodium and potassium was requested.

On 24 January 2025, dermatology was consulted because of the severity and distribution of the skin lesions (Figure 2A). The dermatologist documented generalized skin lesions of about one week's duration and mucosal lesions of approximately two days' duration. The Nikolsky sign was positive, and mucosal involvement of the eyes, oral cavity and genitals was present. There was also a history of multiple analgesic medications taken in recent weeks. In the context of underlying malignancy and the extensive mucocutaneous detachment, the working diagnosis at that stage was Stevens–Johnson syndrome. A SCORTEN score was calculated as 4, corresponding to an estimated mortality of roughly 60%. Dermatology recommended a thorough review and listing of all possible culprit medications, daily monitoring of urea, creatinine, liver function tests, electrolytes, blood sugar, venous blood gas and complete blood count, as well as a daily peripheral blood smear to assess for eosinophilia and atypical granulocytes. Intravenous

immunoglobulin (IVIG) was initiated at a dose of 2 g/kg/day.

Despite these measures, the patient's condition had not significantly improved by 26 January 2025, when a second dermatology consultation was performed. The dermatologist noted the lack of substantial clinical improvement and advised continuing intravenous immunoglobulin, specifying a dose of 50 g per day. They suggested adding intravenous cyclophosphamide 300 mg per day if approved by the hematology team. However, cyclophosphamide was ultimately not administered because of the markedly elevated urea and creatinine levels and the presence of pancytopenia. There was also a note regarding a topical medication for the oral cavity to be used three times daily, although this detail was not clearly legible in the records. Dermatology advised repeating their assessment in two days and requested an Infectious diseases consultation to help optimize antimicrobial therapy.

On 29 January 2025, a third dermatology review was undertaken. At that time, the skin lesions were described as slightly improved, but the patient remained unable to eat because of severe oral involvement. A skin biopsy was taken from a chest lesion. The differential diagnosis accompanying the biopsy request included Stevens–Johnson syndrome, toxic epidermal necrolysis, paraneoplastic pemphigus, staphylococcal scalded skin syndrome and toxic shock syndrome. Dermatology recommended close follow-up of the pathology results, continuation of intravenous immunoglobulin, and a repeat Infectious diseases consultation to decide whether to switch from the current antimicrobials (meropenem and vancomycin) to linezolid and clindamycin.

On 30 January 2025, the pathology report from the skin biopsy became available (Figure 2B). The specimen consisted of a small piece of skin measuring 3 × 2 × 1 mm. Microscopic examination revealed mild irregular acanthosis and hyperparakeratosis, with severe spongiosis and vesiculation. There was lichenoid lymphocytic infiltration with basal vacuolar interface change, dyskeratotic epidermal cells, subcorneal acantholysis, focal suprabasal acantholysis and clefting, and lymphocytic exocytosis with scattered eosinophils. In view of these findings, the pathologist concluded that the histological picture was compatible with paraneoplastic pemphigus and a lichenoid drug reaction. On the same date, serologic tests for HIV antigen/antibody, HBsAg, HBc IgM and HCV antibody were all negative, helping to exclude major viral infections before intensifying immunosuppression.

In early February 2025, as the disease remained severe and the biopsy supported paraneoplastic pemphigus in the context of multiple myeloma, dermatology decided to escalate therapy to rituximab. They recommended rituximab 500 mg intravenously once weekly. Given the patient's history of aortic valve replacement with a mechanical prosthesis, a cardiology consultation was requested before starting rituximab. Echocardiography showed a left ventricular ejection fraction of about 50% and a well-functioning mechanical aortic valve with good motion. The cardiologist considered the patient to be at moderate to high risk for rituximab therapy and advised repeat echocardiography after initiation of treatment. Before administering rituximab, the team rechecked the hemoglobin and repeated HIV, HBsAg and HCV antibody tests, all of which were again negative. Rituximab 500 mg weekly was then commenced. At approximately three months of follow-up, the patient demonstrated significant cutaneous improvement, with residual findings limited to post-inflammatory hyperpigmentation (PIH) from prior lesions.

Renal management continued in parallel. On 4 February 2025, a repeat nephrology consultation was sought. After reviewing the laboratory results from that day, nephrology recommended administration of 500 cc half-saline with 10 cc potassium chloride infused over two hours, followed by a three-hour session of hemodialysis. They also advised adding 100 cc potassium chloride to the dialysis solution, reflecting the need for careful potassium replacement in the setting of ongoing dialysis and previous restrictions on intravenous fluids.

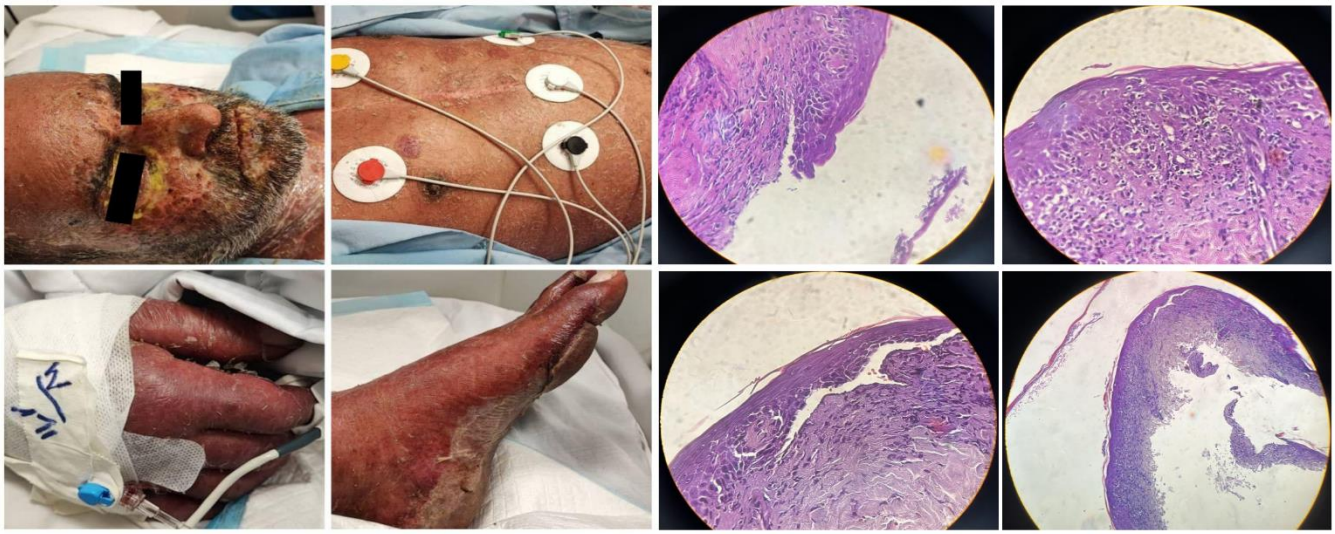

Figure 2. Clinical presentation and histopathologic features of the patient's skin lesions. **(A)** Skin lesions of the patient. **(B)** Skin biopsy reveals epidermal changes characterized by mild irregular acanthosis, hyperparakeratosis, marked spongiosis with vesicle formation, and a lichenoid lymphocytic infiltrate accompanied by basal vacuolar alteration. Dyskeratotic keratinocytes and areas of subcorneal acantholysis are present. Focal suprabasal acantholysis with cleft formation, along with lymphocytic exocytosis and scattered eosinophils, is also observed.

DISCUSSION

We describe a case of a 61-year-old man with MM who developed rapidly progressive and severe mucocutaneous ulcerations shortly after chemotherapy, initially mimicking Stevens–Johnson syndrome. The lack of clinical improvement despite appropriate supportive measures, together with the profound mucosal involvement and the subsequent histopathologic findings, ultimately led to the diagnosis of paraneoplastic pemphigus. A review of the available literature revealed no previously documented cases of PNP occurring as a paraneoplastic manifestation of multiple myeloma. Therefore, to the best of our knowledge, this case represents the first reported instance in which PNP has been identified as a paraneoplastic manifestation of multiple myeloma, highlighting the exceptional rarity and clinical importance of this presentation.

The patient initially developed extensive cutaneous involvement characterized by widespread epidermal peeling and numerous painful ulcerative lesions distributed over the trunk, upper and lower extremities, and other body surfaces, creating a picture of diffuse and progressive skin detachment. Despite receiving early supportive management and high-dose IVIG, his condition did not show meaningful improvement, and the severe oral ulcerations remained refractory, preventing adequate oral intake.

PNP is characterized by early and prominent mucosal involvement, often beginning with vesicles or bullae that rapidly evolve into painful erosions and intense stomatitis—features that can closely resemble pemphigus vulgaris [1]. In some cases, persistent and treatment-resistant oral mucositis may be the sole initial manifestation like our case. Lesions within the oral cavity can extend to the vermilion border, the tongue, the oropharynx, the nasopharynx, and even the esophagus. Other mucosal sites, including the conjunctiva and anogenital areas, may also become involved. When erosions, crusting, and ulcerations are severe—particularly on the tongue, lips, and palate—the clinical picture may mimic Stevens–Johnson syndrome or erythema multiforme [6-9].

As far as we are aware, this case is the first to document PNP as a paraneoplastic manifestation associated with multiple myeloma. Previous study demonstrated that lymphoproliferative disorders are the most frequently reported underlying conditions in the development of PNP, accounting

for as many as 84% of cases. Roughly two-thirds of PNP cases are linked to non-Hodgkin lymphoma and chronic lymphocytic leukemia. In adults, non-Hodgkin lymphoma is the most common associated neoplasm (38.6%), followed by chronic lymphocytic leukemia (18.4%) and Castleman disease (18.4%). Non-hematologic tumors make up about 16% of cases. In children and adolescents, PNP often first manifests as a sign of Castleman disease[1]. Recent studies have shown that individuals carrying the HLA Class II Drb1*03 and HLA-Cw*14 alleles have a higher susceptibility to developing PNP; these alleles are more prevalent in Caucasian and Chinese populations, respectively. By contrast, HLA-DR4 and HLA-DR1-14 are associated with pemphigus vulgaris and pemphigus foliaceus but do not appear to influence PNP risk [5, 10, 11].

Given the lack of response and the subsequent confirmation of paraneoplastic pemphigus on skin biopsy, targeted immunotherapy with rituximab was initiated. Following the start of rituximab, progression of the skin lesions gradually halted and healing began, ultimately leaving only areas of PIH as residual cutaneous changes. The management of PNP remains controversial and not well-defined. Early identification and treatment of the underlying malignancy are crucial. For solid tumors, surgical resection with minimal manipulation and efforts to block tumor blood supply is recommended, and high-dose IV immunoglobulin before and after surgery may reduce the risk of bronchiolitis obliterans[5,12,13]. Medical therapy focuses on controlling inflammation, suppressing the immune response, and wound care. High-dose corticosteroids are first-line, with additional immunosuppressants (e.g., azathioprine, mycophenolate mofetil) used if needed. Targeted therapies against IgG autoantibodies or B-cells, such as rituximab and alemtuzumab, have shown efficacy in PNP associated with lymphoproliferative malignancies. Other options include cyclosporine, cyclophosphamide, plasmapheresis, IV immunoglobulin, and biosynthetic dressings. Skin lesions may improve within 12 weeks, but mucosal lesions are often refractory, and PNP severity does not always correlate with the response of the underlying malignancy[1].

CONCLUSION

This case represents the first reported instance of paraneoplastic pemphigus (PNP) presenting as a paraneoplastic manifestation of multiple myeloma (MM). The clinical presentation mimicked Stevens–Johnson syndrome, highlighting the diagnostic challenges posed by PNP in patients with hematologic malignancies. Accurate and timely diagnosis, supported by histopathology and immunologic testing, is essential to guide appropriate therapy. Rituximab proved effective in achieving significant clinical improvement in this patient. Awareness of such atypical presentations is critical for early recognition and management, improving patient outcomes in similar scenarios.

Abbreviations

AKI	Acute kidney injury
EF	Ejection fraction
HCV	Hepatitis C virus
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
IVIG	Intravenous immunoglobulin
MM	Multiple myeloma
NHL	non-Hodgkin lymphoma
PNP	Paraneoplastic pemphigus
SCORTEN	Severity-of-illness score for toxic epidermal necrolysis
SJS	Stevens–Johnson syndrome
TEN	Toxic epidermal necrolysis

Declarations

Ethics declarations

This case report was approved by the Ethics Committee of Birjand University of Medical Sciences under the ethical approval code IR.BUMS.REC.1404.265.

Data availability

All clinical information and images included in this case report are presented within the manuscript and its supplementary materials in fully de-identified form. Due to patient privacy and ethical considerations, additional raw data cannot be publicly shared but are available from the corresponding author upon reasonable request.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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