Case Report

ANNALS OF MEDICINE & SURGERY

OPEN

Paraneoplastic pemphigus in a patient with T-cell lymphoma: a case report

Yohannis Derbew Molla, MD[a,*], Isak Omer Answar, MD[b], Biruk Mulat Worku, MD[c], Amanuel Kassa Tadesse, MD[b], Elias manaye tefera, MD[c], Bewketu Abebe Alemu, MD[b], Gebrehiwot Lema Legese, MD[c], Samuel Addisu Abera, MD[b]

Introduction and importance: Paraneoplastic pemphigus (PNP) is an uncommon autoimmune mucocutaneous disease characterized by severe stomatitis, polymorphous skin eruptions, and the presence of underlying neoplasms. Unique histopathological features include suprabasal acantholysis and clefts with scattered necrotic keratinocytes.

Case presentation: A 27-year-old female patient presented with a 3-month history of a painless swelling, approximately the size of a pea, on the left lateral aspect of her neck and axillary area. This swelling progressively increased in size and number. Additionally, she had reddish, itchy, raised skin lesions over her elbows bilaterally, which gradually spread to involve most of her body, including her lips, tongue, and buccal mucosa. These skin lesions were associated with difficulty swallowing both liquid and solid foods. A diagnostic test, including a biopsy, confirmed the diagnosis of PNP. Subsequently, the patient was managed with chemotherapy and other supportive measures, leading to improvement and eventual discharge.

Clinical discussion: PNP is a rare blistering disorder associated with neoplasms, often presenting diagnostic and treatment challenges. Patients with PNP may develop a diverse range of lesions. It is crucial to promptly recognize and manage the underlying malignancy for improved patient outcomes.

Conclusion: This case highlights the rare association between T-cell lymphoma and PNP. Clinicians should also remain vigilant for the possibility of PNP in lymphomas that are not of B-cell lineage.

Keywords: Lymphoma, paraneoplastic, pemphigus vulgaris

Introduction

Paraneoplastic illnesses are generally caused by the distant effects of cancer rather than by the direct invasion of a primary tumour or tissue damage caused by metastasis. These effects can occur due to the release of biologically active peptides or the tumour's impact on the local immune system. Paraneoplastic pemphigus (PNP) is an example of a paraneoplastic phenomenon that arises from an autoimmune disorder associated with lymphoproliferative disorders or other malignancies[1]. It was first described in 1990 by Anhalt[2]. PNP is a rare and often fatal condition that can be linked to both benign and malignant neoplasms. Haematologic and lymphomatoid cancers such as thymoma, B-cell lymphoma, chronic lymphocytic leukaemia, Castleman's disease, Waldenstrom's macroglobulinemia, and T-cell lymphoma are commonly associated with PNP[3]. The diagnosis of PNP can be challenging due to its wide range of clinical presentations, with oral ulcerations being the most common feature. Similar conditions like Stevens–Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, and medication reactions can make diagnosis difficult. Furthermore, many cases of PNP are still not correctly diagnosed[4–6]. Diagnosis is typically made using clinical, histological, and immunofluorescent tests[7].

'This case report has been reported in line with the SCARE Criteria'[8].

HIGHLIGHTS

- Paraneoplastic pemphigus is a rare autoimmune mucocutaneous disease.
- It is associated with both benign and malignant neoplasms.
- Prompt recognition and management of the underlying malignancy is vital for improved patient outcomes.

Clinical presentation

She is a 27-year-old Ethiopian adult patient who was previously in good health 3 months ago. However, during that time, she began to notice a painless swelling about the size of a pea on the left side of her neck and in her armpit area. This swelling gradually increased in size and spread to other parts of her body over a period of two months. About a month before her current presentation, she started to develop reddish, itchy, raised skin lesions

Departments of [a]Surgery, [b]Internal Medicine and [c]Pathology, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

**Corresponding author. Address: University of Gondar College of Medicine and Health Sciences, Gonder, (None), Ethiopia. E-mail: yderbew73@gmail.com (Y. D. Molla).*

Annals of Medicine & Surgery (2024) 86:2256–2261

Received 15 December 2023; Accepted 25 February 2024

Published online 6 March 2024

http://dx.doi.org/10.1097/MS9.0000000000001920

on both of her elbows. These lesions continued to spread and eventually covered most of her body, including her lips, tongue, and the inside of her cheeks. As a result, she experienced difficulty swallowing both liquids and solid foods. In addition to these symptoms, she also had a productive cough with whitish sputum, averaging 1–2 acc per day. She experienced a pleuritic type of chest pain on both sides for the same duration. Along with these respiratory symptoms, she had a low-grade intermittent fever, night sweats, and significant but unspecified weight loss. The patient has no personal or family history of diabetes, hypertension, or asthma. She has not taken any medications in the past.

Upon examination at presentation, the patient appeared acutely ill, displaying symptoms such as a rapid pulse rate of 120 beats per min (tachycardia), a respiratory rate of 28 breaths per min (tachypnea), and an oxygen saturation level of 96% on room air. Her blood pressure was measured at 130/80, indicating normal levels, and she had a temperature of 37.8° C, indicating a fever. Physical observations revealed periorbital puffiness, pink conjunctiva, and non-yellowing sclera, suggesting no signs of jaundice. The lymphoglandular system examination revealed multiple enlarged lymph nodes in the lateral cervical, submandibular, axillary, and inguinal areas on both sides of the body. These lymph nodes were firm, non-tender, and not clumped together. During the abdominal examination, no signs of organ enlargement or fluid accumulation were observed. However, the patient did exhibit grade 2 bilateral pitting oedema in her legs. On the integumentary system, the patient displayed diffuse erythematous skin rashes with muculopapular characteristics. These rashes were accompanied by areas of exfoliation, ulceration, and hyperpigmentation throughout her body. Additionally, multiple scratch marks were present on her trunk and extremities (Figs. 1 and 2).

During the investigation, a comprehensive blood test revealed leukocytosis of 11.62 thousand with 73% neutrophilia, and the patient's haemoglobin level was 12.9 g/dl. Other tests, such as Lactate dehydrogenase and Erythrocyte sedimentation rate were within normal range, and viral markers were negative. A chest X-ray showed lymphadenopathy in the mediastinal and right hilar regions, but no signs of pneumonia or bronchiolitis obliterans. An abdominal ultrasound revealed lymphadenopathy in the intra-abdominal area. Lymph node biopsy showed effaced lymphoid architecture by diffuse proliferation of intermediate to large cells with open chromatin undergoing frequent mitotic activity infiltrating the surrounding fibroadipose tissue. Paracortical areas show increased vascularity with an arborizing pattern. The endothelial cells are prominent, and there are a significant number of eosinophils in the background (Figs. 3 and 4). Vascular proliferation is lined by high-endothelial cells with an index of high-grade non-Hodgkin lymphoma, most likely angioimmunoblastic type. Subsequent immunohistochemistry showed positivity for CD2, CD3 and CD4 with very high proliferative index (Ki67) (Figs. 5–8). Skin biopsy showed variable epidermal atrophy, parakeratosis, basal cell spongiosis, accompanied by apoptotic keratinocytes, and suprabasal clefts. Immunohistochemistry showed angioimmunoblastic T-cell lymphoma (Figs. 9 and 10).

With the diagnosis of paraneoplastic pemphigus associated with T-cell lymphoma, the patient was managed using the following treatment regimen: dexamethasone 8 mg IV tid, fusidic acid application, betamethasone ointment at night, liquid paraffin 2–3 times a day, daily wound care, and a chemotherapy-epoch regimen consisting of Etoposide (80 mg), Doxorubicin (16 mg), Vincristine (0.64 mg), Cyclophosphamide (1200 mg), and Prednisone (96 mg) (Table 1). Ultimately, the patient's condition improved and they were discharged without any complications. Subsequent follow-ups at 1 year showed persistent remission in the patient.

Figure 2. Diffuse erythematous maculopapular rash with areas of exfoliation, ulceration and hyperpigmentation.

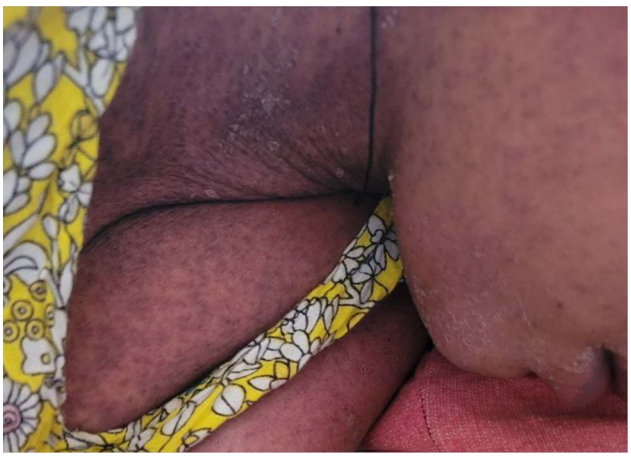

Figure 1. Shows diffuse maculopapular skin rash with areas of hyperpigmentation.

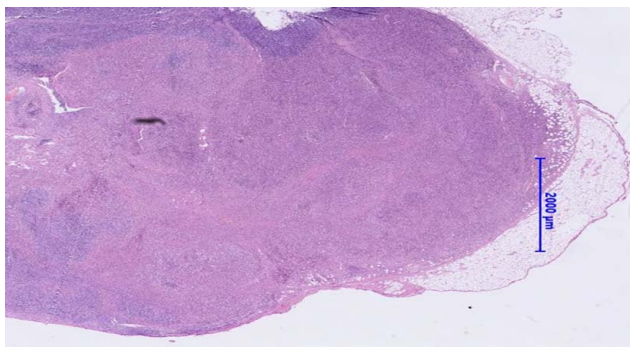

Figure 3. Lymph node biopsy showing effaced lymphoid architecture by a diffuse proliferation that shows extracapsular adipose tissue infiltration (hematoxylin and eosin).

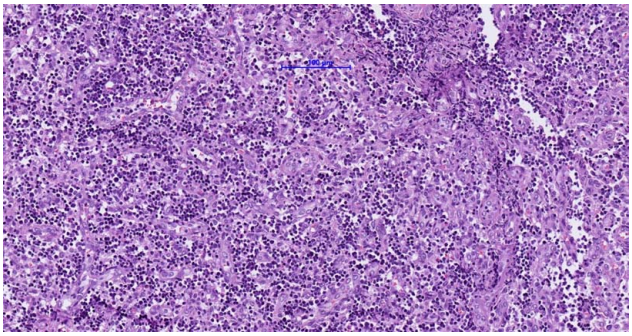

Figure 4. Lymph node biopsy showing Proliferation of atypical small to intermediate sized cells that tend to cluster around accentuated arborizing blood vessels (hematoxylin and eosin).

Discussion

T-cell lymphomas constitute less than 15% of non-Hodgkin lymphomas in the United States. These lymphomas specifically target T lymphocytes, a type of white blood cell. Although there are various types of T-cell lymphoma, they are all considered to be relatively uncommon. Among these types, angioimmunoblastic T-cell lymphoma accounts for ~4% of all lymphomas. The incidence of this lymphoma is equal between males and females. It is more frequently diagnosed in older adults, with a median age of 65–70 years. This lymphoma typically affects the lymph nodes, bone marrow, spleen, and liver, often causing enlargement of these organs. Individuals with this lymphoma commonly experience symptoms such as fever, weight loss, skin rashes, and are prone to developing infections. Furthermore, this lymphoma tends to progress rapidly. Initial treatment is often successful, but recurrence of the lymphoma is common[9,10].

PNP is an extremely rare and life-threatening autoimmune disease characterized by blistering of the skin. This condition is associated with an underlying neoplasm[11]. PNP can be defined and identified by the following features: "(1) painful stomatitis and a polymorphous cutaneous eruption with lesions that may be blistering or lichenoid or may resemble erythema multiforme or a drug eruption; (2) histologic findings that reflect the variability of the cutaneous lesions, showing acantholysis, lichenoid, or interface change; (3) direct immunofluorescence demonstrating deposition of IgG and complement in the epidermal intercellular spaces, and often granular/linear complement deposition along the epidermal basement membrane zone; (4) serum autoantibodies that bind the cell surface of skin and mucosae in a pattern typical for pemphigus; (5) the serum autoantibodies identify desmogleins 1 and 3, as well as members of the plakin family of epithelial proteins, including desmoplakins I and II, envoplakin, periplakin, bullous pemphigoid antigen 1 (BPAg1),

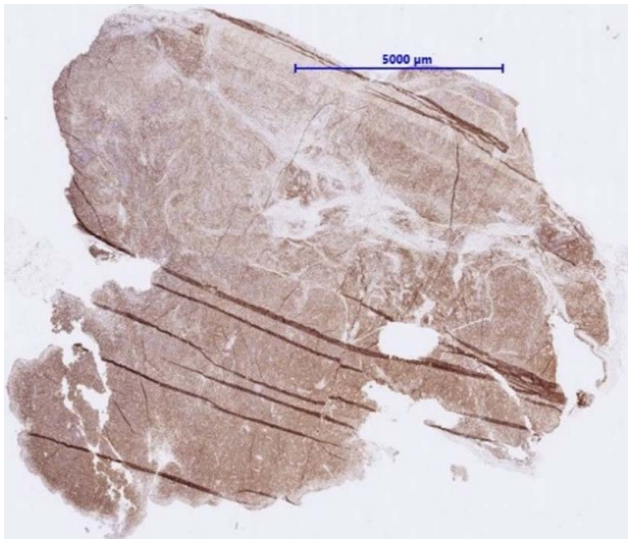

Figure 6. Skin biopsy showing interface dermatitis with vacuolar degeneration of basal keratinocytes.

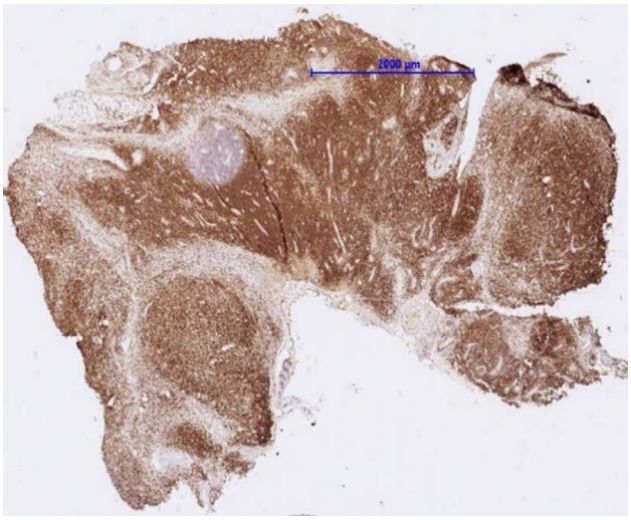

Figure 5. Skin biopsy showing intra-epidermal supra-basal separation.

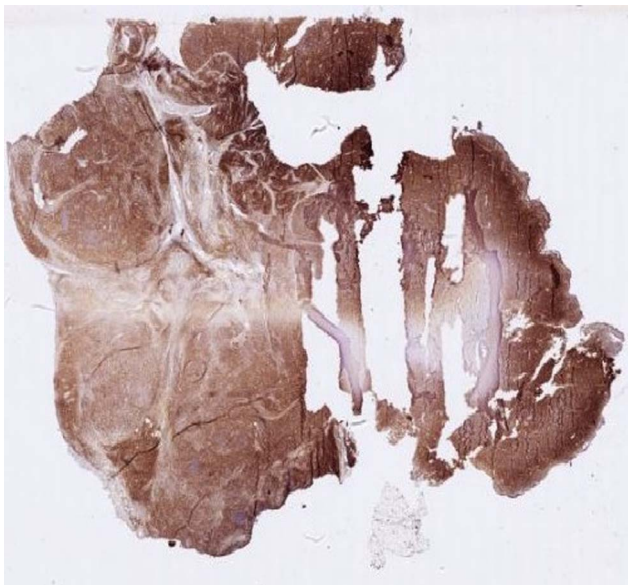

Figure 7. Immunohistochemistry of the LN biopsy showing diffuse CD2 and CD3 positivity.

Figure 8. Immunohistochemistry of the LN biopsy showing diffuse CD2 and CD3 positivity.

and plectin."[5]. Although the disease's prevalence is unknown, it is less widespread than pemphigus vulgaris (PV) or pemphigus foliaceus (PF). Stevens–Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, and medication reactions are just a few examples of conditions with similar clinical characteristics. In addition, there is considerable evidence that most instances are still not diagnosed correctly[4,6,12,13].

The etiopathogenesis of PNP remains poorly understood. It is believed that the development of skin lesions in PNP is caused by an autoimmune response triggered by antibodies that target tumour antigens but also cross-react with epithelial antigens. One example of such an antibody is Interleukin-6, a cytokine that is produced and released by tumour cells. Interleukin-6 promotes B-cell differentiation and stimulates the growth of the humoral branch of the immune system[14,15]. The development of autoantibodies in PNP can be influenced by factors such as depressed cellular immunity, which favors autoimmunity, or the expression of new antigenic determinants by the malignant tumour. These factors can lead to the production of cross-reactive autoantibodies against the skin[16]. The pathogenesis of PNP appears

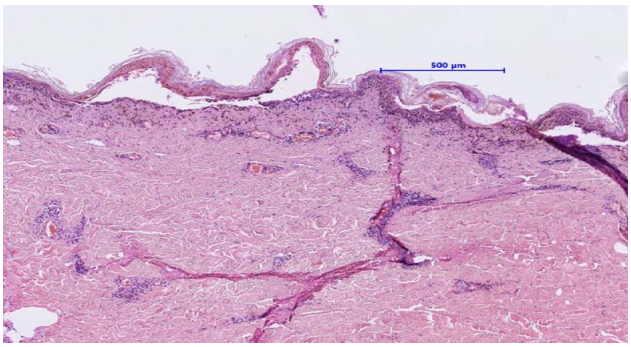

Figure 9. Immunohistochemistry of the LN biopsy showing diffuse CD4 staining and a very high Ki67 index.

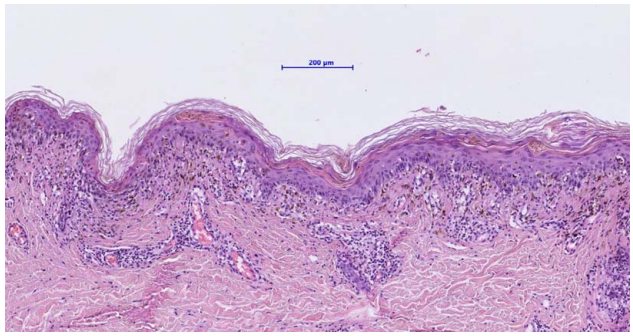

Figure 10. Immunohistochemistry of the LN biopsy showing diffuse CD4 staining and a very high Ki67 index.

to involve interactions between the immune system and a coexisting tumour, with autoantibodies targeting both desmosomal and hemidesmosomal antigens. Periplakins and envoplakins are the most commonly targeted antigens in PNP patients[17].

PNP is associated with a limited number of lymphoproliferative neoplasms. There have been only a few cases in which an underlying neoplasm could not be identified. According to one study, the approximate frequency of specific neoplasms is as follows: Non-Hodgkin's lymphoma (NHL) at 42%, chronic lymphocytic leukaemia (CLL) at 29%, Castleman's disease (giant follicular hyperplasia) at 10%, thymoma (malignant and benign) at 6%, sarcoma at 6%, and Waldenstrom's macroglobulinemia at 6%. The majority of cases are linked to CLL and NHL, but a notable finding is the disproportionate occurrence of Castleman's disease[18,19]. This suggests that the relationship between PNP and Castleman's disease may provide insight into the cause of the autoimmunity. In paediatric cases, where Castleman's disease is the underlying tumour in nearly all children, the connection is even more apparent[18].

Patients with PNP may develop a diverse range of lesions. In addition to the prominent oral mucosal lesions, lung involvement and a wide-ranging polymorphous cutaneous eruption can also occur. The initial and most common symptom is severe stomatitis, which eventually gives way to mucositis. The oral mucosal lesions are typically severe, with erosions and crusting that resemble those seen in Stevens–Johnson syndrome and erythema multiforme, particularly affecting the lateral tongue and vermilion of the lips. Erosions can occur in any part of the oropharynx, tongue, and lips, as well as in the conjunctivae, anogenital region, and other mucosal surfaces such as the nose, throat, larynx, and oesophagus. Mucosal lesions usually appear before cutaneous lesions, with the upper body being the most commonly affected area[20–23].

The involvement of other organs in PNP can have an impact on various types of epithelia, including the gastrointestinal and respiratory tracts. This sets it apart from other forms of pemphigus, which typically only affect the squamous epithelium. The first indication of pulmonary involvement is often obstructive lung illness, which can progress to bronchiolitis obliterans and ultimately lead to mortality. While earlier published series reported a pulmonary illness incidence of around 30%, more recent data suggests a significantly higher incidence ranging from 59.1 to 92.8%[24].

To make a diagnosis, clinical, histological, and immunofluorescent results are utilized. Due to the complexity of the

Table 1

The table illustrates the haematologic and renal parameters used to follow the patient's response during chemotherapy.

Parameters	Before 1st cycle	After 1st cycle	After 2nd cycle	After 3rd cycle	After 4th cycle	After 5th cycle	After 6th cycle
Haemoglobin	12.9	8.8	10.2	10.5	11.3	11	11.8
Haematocrit	37.4	24.7	30.2	31.3%	34.5%	33.7	35.4
Platelet	429 000	132 000	234 000	180 000	220 000	250 000	200 000
WBC	11 620	4230	5678	4980	6450	5690	7250
Neutrophil	73%	54%	57%	61%	66%	60%	57%
Creatinine	0.76	0.88	0.65	0.77	0.49	0.56	0.77

WBC, white blood cell.

disease, multiple biopsies are often required for an accurate diagnosis. The histology of skin lesions can vary depending on their nature. Blisters that cover the basal layer typically exhibit acantholysis, while the basal layer may also show vacuolar degeneration in conjunction with a band-like infiltrate of lymphocytes in the dermis, which is commonly observed in lesions that are both histopathologically and clinically lichenoid[2,5]. The histology results can vary, ranging from milder bullous lesions to a dense lichenoid reaction. The morphology of the clinical lesions and the histological changes typically align. In cases of non-inflammatory blisters, there is more noticeable suprabasal acantholysis, while erythematous inflammatory maculopapular lesions tend to exhibit interface and lichenoid dermatitis more prominently[6].

High-dose corticosteroids are the primary treatment option, and aggressive immunosuppressive medications are often used to manage the condition. Concurrent use of immunosuppressive medications, such as azathioprine, cyclosporine, and mycophenolate mofetil, helps reduce the required dosage of steroids and minimizes associated side effects. Additionally, any underlying malignancy should be addressed with chemotherapy. Studies have shown that a combination of prednisolone at 0.5–1.0 mg/kg/day and cyclosporine at 5 mg/kg/day or cyclophosphamide at 1–2 mg/kg/day is effective in treating the condition[5]. When initial treatment fails, the patient is critically ill, or immediate intervention is necessary, alternative therapies may be considered. Rituximab, a monoclonal antibody that targets CD20 on B cells, has shown positive results in individuals with underlying B-cell lymphoma. However, plasmapheresis and intravenous immunoglobulin have yielded poor outcomes[12,23]. In our case, the patient was treated with steroids, chemotherapy, and other supportive measures. The prognosis for patients with PNP presenting with erythema multiforme-like skin lesions and histologic keratinocyte necrosis is typically more severe and rapidly lethal. Extreme caution should be exercised in these cases. Additionally, the prognosis for patients with T-cell lymphoma remains poor due to the aggressive nature of the neoplasm and potential complications such as severe infections and bronchiolitis obliterans[26]. Ultimately, the patient expressed her utmost contentment with the level of care she received.

Conclusion

PNP is an uncommon autoimmune blistering disorder that is linked to the presence of tumours, which often presents challenges in terms of diagnosis and treatment. It is crucial to promptly identify and manage the underlying cancer in order to improve patient outcomes. Effective patient care relies on the collaborative efforts of dermatologists, oncologists, and immunologists. Further research is needed to enhance our understanding of PNP and to explore innovative targeted therapies for this intricate disease. This particular case highlights the rare connection between T-cell lymphoma and paraneoplastic pemphigus, suggesting that T cells may play a role in the development of this condition. Clinicians should also remain vigilant about the possibility of PNP in lymphomas that are not derived from B cells.

Ethical approval

The case report has been submitted for Ethical Board Review and approved as ethically sound report.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Source of funding

NA.

Author contribution

All authors contributed to the conception, writing and editing of the case report. All authors are agreed to be accountable for all aspects of it.

Conflicts of interest disclosure

No potential conflicts of interest relevant to this article was reported.

Research registration unique identifying number (UIN) (for case reports detailing a new surgical technique or new equipment/technology)

NA.

Guarantor

Yohannis Derbew Molla, and Biruk Mulat Worku.

Data availability statement

NA.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Reference

[1] Amagai M, Nishikawa T, Nousari HC, *et al*. Antibodies against desmoglein 3 (pemphigus vulgaris antigen) are present in sera from patients with paraneoplastic pemphigus and cause acantholysis in vivo in neonatal mice. J Clin Invest 1998;102:775–82.

[2] Anhalt GJ, Kim SC, Stanley JR, *et al*. Paraneoplastic pemphigus. An autoimmune mucocutaneous disease associated with neoplasia. N Engl J Med 1990;323:1729–35.

[3] Gill H, Trendell-Smith NJ, Loong F, *et al*. Paraneoplastic pemphigus due to CD8-positive cytotoxic T-cell lymphoma. Br J Haematol 2010;149: 464464.

[4] Bialy-Golan A, Brenner S, Anhalt GJ. Paraneoplastic pemphigus: oral involvement as the sole manifestation. Acta Derm Venereol 1996;76: 253–4.

[5] Anhalt GJ. Paraneoplastic pemphigus. J Investig Dermatol Symp Proc 2004;9:29–33.

[6] Anhalt GJ, Kim S, Stanley JR, *et al*. Paraneoplastic pemphigus. N Engl J Med 1990;323:1729–35.

[7] Horn TD, Anhalt GJ. Histologic features of paraneoplastic pemphigus. Arch Dermatol 1992;128:1091–5.

[8] Sohrabi C, Mathew G, Maria N, *et al*. The SCARE 2023 guideline: updating consensus Surgical CAse REport (SCARE) guidelines. Int J Surg Lond Engl 2023;109:1136–40.

[9] Samad MA, Mahboob E, Shafiq A, *et al*. Types of T-cell lymphoma-a cytogenetic perspective. Ann Med Surg 2022;84:104844. Accessed January 29, 2024. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9758356/

[10] Mugnaini EN, Ghosh N. Lymphoma. Prim Care Clin Off Pract 2016;43: 661–75.

[11] Zaheri F, Pas HH, Bremer J, *et al*. Paraneoplastic pemphigus: a detailed case series from the Netherlands revealing atypical cases. J Eur Acad Dermatol Venereol 2023;37:147–53.

[12] Borradori L, Lombardi T, Samson J, *et al*. Anti-CD20 monoclonal antibody (rituximab) for refractory erosive stomatitis secondary to CD20+ follicular lymphoma–associated paraneoplastic pemphigus. Arch Dermatol 2001;137:269–72.

[13] Allen C, Camisa C. Paraneoplastic pemphigus: a review of the literature. Oral Dis 2000;6:208–14.

[14] Kaplan I, Hodak E, Ackerman L, *et al*. Neoplasms associated with paraneoplastic pemphigus: a review with emphasis on non-hematologic malignancy and oral mucosal manifestations. Oral Oncol 2004;40: 553–62.

[15] Wolff K, Goldsmith LA, Katz SI, *et al*. Fitzpatrick's dermatology in general medicine. McGraw-Hill; 2008.

[16] Rybojad M, Leblanc T, Flageul B, *et al*. Paraneoplastic pemphigus in a child with a T-cell lymphoblastic lymphoma. Br J Dermatol 1993;128: 418–22.

[17] Czernik A, Wieczorek M. Paraneoplastic pemphigus: a short review. Clin Cosmet Investig Dermatol 2016;9:291–5.

[18] Mimouni D, Anhalt GJ, Lazarova Z, *et al*. Paraneoplastic pemphigus in children and adolescents. Br J Dermatol 2002;147:725–32.

[19] Irrera M, Bozzola E, Cardoni A, *et al*. Paraneoplastic pemphigus and Castleman's disease: a case report and a revision of the literature. Ital J Pediatr 2023;49:33.

[20] Antiga E, Bech R, Maglie R, *et al*. S2k guidelines on the management of paraneoplastic pemphigus/paraneoplastic autoimmune multiorgan syndrome initiated by the European Academy of Dermatology and Venereology (EADV). J Eur Acad Dermatol Venereol 2023;37:1118–34.

[21] Zhang J, Qiao QL, Chen XX, *et al*. Improved outcomes after complete resection of underlying tumors for patients with paraneoplastic pemphigus: a single-center experience of 22 cases. J Cancer Res Clin Oncol 2011;137:229–34.

[22] Sehgal VN, Srivastava G. Paraneoplastic pemphigus/paraneoplastic autoimmune multiorgan syndrome. Int J Dermatol 2009;48:162–9.

[23] Cervini AB, Tosi V, Kim SH, *et al*. Paraneoplastic pemphigus or paraneoplastic autoimmune multiorgan syndrome. Report of 2 cases in children and a review of the literature. Actas Dermo-Sifiliográficas Engl Ed 2010;101:879–86.

[24] Nikolskaia OV, Nousari CH, Anhalt GJ. Paraneoplastic pemphigus in association with Castleman's disease. Br J Dermatol 2003;149:1143–51.

[25] TD H. Histologic features of paraneoplastic pemphigus. Arch Dermatol 1992;128:1091–5.

[26] Leger S, Picard D, Ingen-Housz-Oro S, *et al*. Prognostic factors of paraneoplastic pemphigus. Arch Dermatol 2012;148:1165–72.