sciendo

FCO • 13(1) • 2022 •26–29
DOI: 10.2478/fco-2022-0002

Forum of Clinical **Oncology**

Paraneoplastic pemphigus associated with squamous cell carcinoma of the cervix

Case Report

Fiste O.[1]*, Liontos M.[1], Svarna A.[1], Gagari E.[2], Zagouri F.[1], Dimopoulos M.A.[1]

[1]*Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Alexandra Hospital 80 Vasilissis Sophias, 11528 Athens, Greece*
[2]*A. Syngros Hospital for Dermatologic and Venereal Diseases, Department of Dermatology, University of Athens School of Medicine, Athens, Greece*

Received 1 April 2022; Accepted 18 May 2022

Abstract: **Background:** Paraneoplastic pemphigus is an autoimmune skin and mucosal disorder, rarely associated with solid malignancies, with devastating impact. **Patients and methods:** Herein, we report the case of a middle-aged patient who presented with recalcitrant stomatitis and was ultimately diagnosed with advanced-stage cervical cancer. **Results:** Despite the prompt initiation of immunosuppressive medications, in parallel with systemic therapy for her underlying neoplasm, she eventually died within 10 months. **Conclusions:** Considering its heterogeneous clinicopathological and immunological manifestations, paraneoplastic pemphigus remains a genuine diagnostic challenge, whereas its abysmal prognosis highlights the need of additional effective immunosuppressants.

Keywords: *paraneoplastic pemphigus • paraneoplastic syndromes • cervical cancer • gynaecological cancer*

1. Introduction

Paraneoplastic pemphigus (PNP), which accounts for approximately 5% of the annual total number of pemphigus cases[1], represents a rather rare autoimmune bullous mucocutaneous disorder, mostly related to lymphoproliferative neoplasms and Castleman disease[2]. Indeed, underlying solid malignancies can be found in less than 15% of PNP patients[3]. We report the uncommon case of PNP associated with de novo metastatic squamous cervical cancer.

2. Patients and Methods

A 46-year-old Caucasian female with an unremarkable medical history presented with painful stomatitis, of 2-months duration, which persisted despite the use of antiseptic mouthwash, antifungal oral gel, and topical corticosteroid. She declined the use of any tobacco products or drugs, and she did not drink alcohol on a regular basis. Her family history was negative for autoimmune, skin, and malignant diseases. Physical examination revealed both erythematous blisters and erosions of the oropharynx, while it was notable for bilateral inguinal lymphadenopathy. Upon seeking a more detailed gynaecological history, the patient recalled three episodes of perimenopausal vaginal bleeding within the last year.

Laboratory blood tests yielded normal values, except for iron deficiency anaemia (haemoglobin = 7.8 g/dL, Mean Corpuscular Volume = 67 fl, ferritin = 6 mcg/L) and increased C-reactive protein levels (22.6 mg/dL, normal <6). Histological examination of an oral lesion demonstrated apoptotic keratinocytes, interface dermatitis, and moderate lymphocytic perivascular infiltration, and the use of Enzyme-Linked ImmunoSorbent Assay detected serum immunoglobulin G antibodies against desmoglein3 (anti-Dsg3). We also performed a colposcopy, which indicated the presence of cervical cancer; The subsequent cervical biopsy confirmed the presence of medium-grade squamous cell carcinoma in the cervix. Magnetic resonance imaging (MRI) of the abdomen revealed the presence of a 7.8 x 3.6 cm

* *E-mail: ofiste@med.uoa.gr*

Open Access. © 2022 Fiste O. *et al.*, published by Sciendo. BY-NC-ND This work is licensed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 License.

bulky mass in the cervix (its locoregional extended to the parametrium and rectum) enlarged internal iliac and inguinal lymph nodes, peritoneal disease, and adrenal metastasis. Computed tomography (CT) of the thorax showed a single macronodular lesion in the middle lobe of the right lung.

3. Results

According to the aforementioned clinical (severe and persistent stomatitis in a patient with an underlying neoplasm), histopathological (interface dermatitis), and immunopathological (circulating anti-Dsg3) findings, a diagnosis of PNP associated with FIGO Stage IVB cervical cancer was made. Thus, the patient started first-line platinum-based chemotherapy combined with oral prednisone at a dose of 1 mg/kg daily. Initially, her mucosal lesions gradually improved, yet flared during corticosteroids tapering. Besides, disease restaging revealed new peritoneal metastases, so second-line treatment with the combination of cisplatin and topotecan every 3 weeks, along with 50 mg prednisolone and 200 mg azathioprine per day had been initiated. Given the remarkable clinical improvement of PNP within a few weeks, oral azathioprine was discontinued, and corticosteroid was used in lower doses (20 mg/day). Unfortunately, 3 months later, stomatitis not only worsened but the patient also developed haemorrhagic cheilitis and dysphagia. Re-evaluation with CT scans confirmed that the disease had progressed. Due to both shortage of available chemotherapy options in this case of recurrent metastatic cervical cancer and the increased Programmed Death-Ligand 1 expression (Combined Positive Score = 2), immunotherapy represented an attractive treatment option. Prednisolone oral solution instead of tablets, at a daily dosage of 50 mg, and third-line pembrolizumab were commenced, however, she died of multi-organ disease progression within 17 days, only 10 months after the initial diagnosis.

4. Discussion

The idea that several skin manifestations, including pemphigus, could indicate the presence of an occult malignancy was first proposed in 1868 by the Austrian dermatologist Ferdinand von Hebra[4]. Two centuries later, Anhalt et al. not only described the distinct and rare entity of PNP but also proposed its diagnostic criteria[5], which have been revised by various research groups[2, 3, 6]. The presence of (i) persisting and severe stomatitis, with or without polymorphic mucocutaneous eruptions, (ii) serum autoantibodies of a specific immunoprecipitation pattern, and (iii) underlying neoplasm, appear to correspond to the essential features for the diagnosis of PNP (7). Only a small fraction of PNP cases is associated with non-haematological malignancies. There seems to be no gender correlation, though the disease usually develops in middle-aged (45-70 years of age) patients and precedes the diagnosis of cancer in 30% of cases[1, 3, 8].

Regarding its clinical manifestation, painful and intractable stomatitis represents the earliest presenting, most consistent, and persisting sign. Mucositis, though, could also extend to the upper airways (including the pharynx and larynx) and to the upper gastrointestinal tract[2, 7]. The complex pathogenetic mechanisms of PNP have not yet been fully elucidated. The current literature suggests the involvement of both cellular (natural killer cells, activated cytotoxic CD8+ T-lymphocytes, macrophages) and humoral (autoantibodies' repertoire against the plakin family proteins, including bullous pemphigoid antigen 230, plectin, envoplakin, periplakin, desmoplakin, and desmoglein types 1 and 3) autoimmune responses[8, 9]. As mentioned above, biopsy of an early lesion, especially from the perilesional erythema, direct and indirect immunofluorescence microscopy, immunoprecipitation for the serologic detection of antibodies, and additional evaluation for an underlying malignant disease are mandatory to confirm the presence of PNP[7].

PNP's prompt diagnosis will enable the initiation of an adequate treatment by a multidisciplinary team. Systemic corticosteroids either alone or with other immunosuppressive agents, like azathioprine, cyclosporine, cyclophosphamide, and mycophenolate mofetil are used as first-line therapy[1, 8]. Additionally, prednisolone used with intravenous immunoglobulin or plasmapheresis may also result in good responses[1, 8, 10, 11]. Both the chimeric anti-CD20 monoclonal antibody rituximab, which has already been approved by the European Medicines Agency for the treatment of patients with moderate to severe pemphigus vulgaris, and the novel Bruton tyrosine kinase inhibitor ibrutinib have demonstrated efficacy in B-cell lymphoma patients[12-14]. Furthermore, the humanized anti-CD52 monoclonal antibody alemtuzumab and the interleukin-6 blocker tocilizumab have shown promising activity against mucositis in refractory PNP cases associated with haematologic malignancies[15, 16]. Still, the prognosis remains extremely poor; the vast majority of deaths occur within the first year of PNP diagnosis[1, 8], mainly due to the neoplasm's progression and infections such as bronchiolitis obliterans leading to progressive respiratory failure[17].

Abbreviations

anti-Dsg3: antibodies against desmoglein3; CT: computed tomography; MRI: magnetic resonance imaging; PNP: paraneoplastic pemphigus.

Author Contributions

Conceptualization, M.L.; Data curation, O.F., A.S.; Supervision, M.L, and M.A.D.; Writing—original draft, O.F.; Writing—review & editing, M.L, A.S., E.G., F.Z., and M.A.D. All authors have read and agreed to the published version of the manuscript.

Funding

This case-report article received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

All data generated or analysed during this study are included in this published article

Conflicts of Interest

The authors declare no conflict of interest.

References

[1] Paolino G, Didona D, Magliulo G, Iannella G, Didona B, Mercuri SR, et al. Paraneoplastic emphigus: insight into the autoimmune pathogenesis, clinical features and therapy. Int J Mol Sci. 2017; 18(12): 2532. DOI: 10.3390/ijms18122532

[2] Anhalt GJ. Paraneoplastic pemphigus. J Investig Dermatol Symp Proc. 2004; 9(1): 29-33. DOI: 10.1111/j.1087-0024.2004.00832.x

[3] Zimmermann J, Bahmer F, Rose C, Zillikens D, Schmidt E. Clinical and immunopathological spectrum of paraneoplastic pemphigus. J Dtsch Dermatol Ges. 2010; 8(8): 598-606. DOI: 10.1111/j.1610-0387.2010.07380.x

[4] Miyashiro D, Sanches JA. Paraneoplastic skin disorders: a review. G Ital Dermatol Venereol. 2016; 151(1): 55-76.

[5] Anhalt GJ, Kim SC, Stanley JR, Korman NJ, Jabs DA, Kory M, et al. Paraneoplastic pemphigus. An autoimmune mucocutaneous disease associated with neoplasia. N Engl J Med. 1990; 323(25): 1729-35. DOI: 10.1056/NEJM199012203232503

[6] Joly P, Richard C, Gilbert D, Courville P, Chosidow O, Roujeau JC, et al. Sensitivity and specificity of clinical, histologic, and immunologic features in the diagnosis of paraneoplastic pemphigus. J Am Acad Dermatol. 2000; 43(4): 619-26. DOI: 10.1067/mjd.2000.107488

[7] Frew JW, Murrell DF. Paraneoplastic pemphigus (paraneoplastic autoimmune multiorgan syndrome): clinical presentations and pathogenesis. Dermatol Clin. 2011; 29(3): 419-25, viii. DOI: 10.1016/j.det.2011.03.018

[8] Kim JH, Kim SC. Paraneoplastic pemphigus: paraneoplastic autoimmune disease of the skin and mucosa. Front Immunol. 2019 ; 10: 1259. DOI: 10.3389/fimmu.2019.01259

[9] Amber KT, Valdebran M, Grando SA. Paraneoplastic autoimmune multiorgan syndrome (PAMS): Beyond the single phenotype of paraneoplastic pemphigus. Autoimmun Rev. 2018; 17(10): 1002-1010. DOI: 10.1016/j.autrev.2018.04.008

[10] Nanda M, Nanda A, Al-Sabah H, Dvorak R, Alsaleh QA. Paraneoplastic pemphigus in association with B-cell lymphocytic leukemia and hepatitis C: favorable response to intravenous immunoglobulins and prednisolone. Int J Dermatol. 2007; 46(7): 767-9. DOI: 10.1111/j.1365-4632.2007.03225.x

[11] Izaki S, Yoshizawa Y, Kitamura K, Kato H, Hashimoto H, Korman NJ, et al. Paraneoplastic pemphigus: potential therapeutic effect of plasmapheresis. Br J Dermatol. 1996; 134(5): 987-9. DOI: 10.1111/j.1365-2133.1996.tb06349.x

[12] Lee A, Sandhu S, Imlay-Gillespie L, Mulligan S, Shumack S. Successful use of Bruton's kinase

inhibitor, ibrutinib, to control paraneoplastic pemphigus in a patient with paraneoplastic autoimmune multiorgan syndrome and chronic lymphocytic leukaemia. Australas J Dermatol. 2017; 58(4): e240-e242. DOI: 10.1111/ajd.12615

[13] Ito Y, Makita S, Maeshima AM, Hatta S, Suzuki T, Yuda S, et al. Paraneoplastic pemphigus associated with b-cell chronic lymphocytic leukemia treated with ibrutinib and rituximab. Intern Med. 2018 ; 57(16): 2395-2398. DOI: 10.2169/internalmedicine.0578-17

[14] Vezzoli P, Berti E, Marzano AV. Rationale and efficacy for the use of rituximab in paraneoplastic pemphigus. Expert Rev Clin Immunol. 2008; 4(3): 351-63. DOI: 10.1586/1744666X.4.3.351

[15] Bech R, Baumgartner-Nielsen J, Peterslund NA, Steiniche T, Deleuran M, d'Amore F. Alemtuzumab is effective against severe chronic lymphocytic leukaemia-associated paraneoplastic pemphigus. Br J Dermatol. 2013; 169(2): 469-72. DOI: 10.1111/bjd.12324

[16] Gu L, Ye S. Tocilizumab cannot prevent the development of bronchiolitis obliterans in patients with castleman disease-associated paraneoplastic pemphigus. J Clin Rheumatol. 2019; 25(5): e77-e78. DOI: 10.1097/RHU.0000000000000675

[17] Lee J, Bloom R, Amber KT. A systematic review of patients with mucocutaneous and respiratory complications in paraneoplastic autoimmune multiorgan syndrome: Castleman's disease is the predominant malignancy. Lung. 2015; 193(4): 593-6. DOI: 10.1007/s00408-015-9732-8