Case report

Cutaneous paraneoplastic pemphigus syndrome associated with undifferentiated uterine sarcoma

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ABSTRACT

Pemphigus is a group of autoimmune intraepidermal blistering diseases caused by immunoglobulins directed against keratinocyte cell surface components. In this case report, we identify a non-classical paraneoplastic pemphigus (PNP) foliaceous related to an undifferentiated uterine sarcoma.

The patient is a 54-year-old Chinese female with a past medical history of arthritis who presented with worsening fatigue in November 2017 and an itchy, blistering, erythematous annular plaque that first appeared on her chest in February 2018. Given high suspicion for primary immunobullous disease despite negative immunofluorescence and lack of subepidermal split on initial biopsy, a repeat biopsy was performed from the right thigh showing positive intraepidermal “net-like” staining for C3 and IgG, but was negative for IgA, IgM, and fibrinogen. IgG antibodies against desmoglein 1 were elevated at 280u (reference range < 18), but none resulted against desmoglein 3, consistent with pemphigus foliaceus. This patient’s PNP was resistant to treatment with azathioprine, dapsone, mupirocin cream, or betamethasone ointment, but responded to prednisone and rituximab per lymphoma protocol at 375 mg/m² weekly for one month in December 2018.

In February 2019, the patient had 2–3 episodes of postmenopausal vaginal bleeding and subsequent hysteroscopy with dilation and curettage revealed an undifferentiated uterine sarcoma. The patient underwent an exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic lymph node sampling. After surgical staging, she noted significant improvement in her baseline skin lesions and had no new lesions since surgery. Repeat desmoglein antibodies showed anti-Dsg1 antibodies of 32u (reference range < 18) and anti-Dsg3 antibodies of 1u (reference range < 19), as compared to the anti-Dsg1 antibodies of 280u in June 2018. She has since completed 4 cycles of adjuvant gemcitabine and docetaxel for her stage IIb undifferentiated uterine sarcoma with no recurrence of the pemphigus lesions.

1. Introduction

Pemphigus is a group of autoimmune intraepidermal blistering diseases caused by immunoglobulins directed against keratinocyte cell surface components. It is histologically characterized by acantholysis and can be life-threatening with whole body skin and mucosal tissue involvement. Classically there are two major types of pemphigus: vulgaris (PV) and foliaceous (PF), where IgG autoantibodies recognize desmosomal components desmoglein 3 (Dsg3) and desmoglein 1 (Dsg1) respectively (Patricio et al., 2009; Porro et al., 2014). With further studies, non-classical pemphigus diseases have been described including pemphigus herpetiformis, IgA pemphigus, and paraneoplastic pemphigus (Porro et al., 2014). In Europe and North America, the incidence of PV and PF is about 1–5 new cases per 1 million inhabitants annually (Zimmermann et al., 2010). Paraneoplastic pemphigus is estimated to account for 3–5% of all pemphigus cases annually (Paolino et al., 2017).

Paraneoplastic pemphigus (PNP) was first characterized in 1990 due to the autoantibodies differences in antigenic specificity in PNP when compared to PV or PF (Anhalt et al., 1990). Anhalt et al. found that the five patients’ autoantibodies demonstrated broad tissue specificity and could react with all epithelia, possibly due to the autoantibodies binding to desmoplakin I (Anhalt et al., 1990). The underlying neoplasms in these five patients included a malignant follicular large cell lymphoma, chronic lymphocytic leukemia, diffuse mixed small and large cell (CD4+ and CD8+) malignant lymphoma, encapsulated benign thymoma, and a poorly differentiated neurogenic or reticulum-cell sarcoma of the retroperitoneum.

In this case report, we identify a non-classical paraneoplastic pemphigus foliaceous related to an undifferentiated uterine sarcoma.
notes a “massive improvement” subjectively after completing rituximab, with no new active lesions and stabilization of existing lesions. She had tapered off of prednisone and azathioprine during this time and reported no major side effects from rituximab. Follow up in February 2019 showed no new lesions with stable existing disease, approximately 4 months out from rituximab initiation. The patient’s anti-Dsg1 autoantibody levels and pictures of her disease stabilization were not obtained at this time.

Later that month, the patient had 2–3 episodes of postmenopausal vaginal bleeding. A transvaginal ultrasound showed a 14.2 × 5.9 × 9.8 cm uterus with heterogeneous, thickened endometrium measuring up to 5 cm in thickness with increased associated vascularity on Doppler. Endometrial biopsy showed blood with scant superficial strips of endocervix and endometrium with no diagnostic abnormality and pap test revealed ASCUS with negative HPV testing. Given the bleeding and suspected inadequate results during the initial biopsy, the patient was scheduled for a hysterectomy with D&C. Final pathology of the endometrial curettings revealed an undifferentiated uterine sarcoma. A broad immunohistochemical work up was positive for vimentin and demonstrated patchy positivity for EMA and CD138. A CT scan (Fig. 2) in April 2019 showed markedly abnormal endometrium with suspicious pelvic and retroperitoneal lymph nodes and probable involvement of the upper cervix. The patient underwent an exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic lymph node sampling showing cervical stroma, endometrioid, and left fallopian tube involvement by undifferentiated uterine sarcoma with lymphovascular invasion, 3/3 pelvic node involvement, and normal ovaries and right fallopian tube.

Following surgical staging, the patient noted significant improvement in her baseline skin lesions and no new lesions since surgery (Fig. 3). Repeat desmoglein antibodies at this time showed anti-Dsg1 antibodies of 32u (reference range < 18) and anti-Dsg3 antibodies of 1u (reference range < 19), as compared to the anti-Dsg1 antibodies of
During follow up to this day, the authors are concerned that the patient’s symptoms and signs of neutropenic enterocolitis have not improved. It is possible that earlier pelvic imaging would have noted changes to her uterus or a retroperitoneal mass. However, it is also possible that nothing would have been revealed through earlier imaging, especially given that the patient had no abdominal or pelvic symptoms and that over 80% of PNP are associated with hematologic neoplasms.

The large case review by Kaplan et al. examining 163 cases of PNP between 1990 and 2003 found all patients to have oral mucosal involvement, with 45% of patients having isolated oral mucosal lesions as the first sign of disease. However, of the 10 total (6.2%) sarcoma cases, only 1 was a poorly differentiated sarcoma (Kaplan et al., 2004). This represents a distinct difference between the presented patient, who only experienced cutaneous lesions without visible mucosal lesions.

Another point of difference between the described PNP cases and this case was in the autoantibodies expressed. To our knowledge, no PNP cases exist that express only anti-Dsg1 IgG, like this patient did. Studies suggest mucosal involvement arises in the setting of positive anti-Dsg3 IgG, which could explain the lack of mucosal involvement in this patient. One case report supports this by describing a patient with only mucosal lesions early on, when the patient tested positive only for anti-Dsg3 IgG, but not anti-Dsg1 IgG. After cutaneous lesions appeared, antibodies to both Dsg1 and Dsg3 were detected (Seishima et al., 2004). Although this is unique from the presented patient, who lacked mucosal lesions, further research is needed to explore the relationship between anti-Dsg3 IgG and mucosal lesions and if anti-Dsg1 IgG contributes to cutaneous skin lesions. The lack of common features present in other case reports and the unique autoantibody presentation may suggest that a different type of paraneoplastic pemphigus process was present in this patient, possibly involving autoantibodies not previously described in the literature.

Several studies have documented triggers of pemphigus disease that are not neoplastic. These triggers include viral infections, Mycobacterium tuberculosis, contact allergens, emotional stress, dietary factors, UV or ionizing radiation, electrical or chemical burns, and certain medications (Ali et al., 2016; Osipowicz et al., 2018; Ruocco et al., 2013). Although there is a possible connection between M. tuberculosis exposure and pemphigus disease, this patient’s pemphigus disease was not thought to be related to latent tuberculosis infection. This patient immigrated from China, so it is possible that the latent tuberculosis infection was present for many years. Furthermore, the symptomatic improvement of her PNP after treatment of her sarcoma stands out.

Given the strong association with hematologic neoplasms and the often rapid and fatal course of PNP, surgical resection is usually not an option for patients experiencing PNP. Nevertheless, the overall patient course and significant response to rituximab coupled with surgical resection of the tumor and subsequent chemotherapy provides some hope for patients with severe PNP from solid neoplasms.

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.

4. Contributions of each author

Bijan Morshedi drafted the initial manuscript, reviewed changes made by Dr. Kari Ring, formatted the manuscript for submission, made changes based on the reviewers feedback, and submitted the final formatted manuscript.

Dr. Kari Ring reviewed the initial manuscript making significant edits and approved the formatted manuscript for submission.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests.
interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Ali, R.A., Elsherif, R.H., Saleh, M.A., Ismail, M.H., 2016. Evaluation of exposure of pemphigus vulgaris patients to Mycobacterium tuberculosis and Aspergillus fumigatus. Eur. J. Clin. Microbiol. Infect. Dis. 35, 1749-1752. https://doi.org/10.1007/s10096-016-2721-x.

Anhalt, G.J., 2004. Paraneoplastic pemphigus. J. Invest. Dermatol. Symp. Proc. 9, 29-33. https://doi.org/10.1111/J.1087-0024.2004.00832.X.

Anhalt, G.J., Kim, S., Stanley, J.R., Korman, N.J., Jabs, D.A., Kory, M., Izumi, H., Ratnie, H., Mutasim, D., Aris-Abd, L., Labib, R.S., 1990. Paraneoplastic pemphigus. N. Engl. J. Med. 323, 1729-1735. https://doi.org/10.1056/NEJM199012203232503.

Kaplan, I., Hodak, E., Ackerman, L., Mimouni, D., Anhalt, G.J., Calderon, S., 2004. Neoplasms associated with paraneoplastic pemphigus: a review with emphasis on non-hematologic malignancy and oral mucosal manifestations. Oral Oncol. 40, 553-562. https://doi.org/10.1016/j.oraloncology.2003.09.020.

Osipowicz, K., Kowalewski, C., Woźniak, K., 2018. Mycobacterium tuberculosis and pemphigus vulgaris. Postep. dermatologii i Alergol. 35, 532-534. https://doi.org/10.5114/ada.2018.72744.

Paolino, G., Didona, D., Magliulo, G., Iannella, G., Didona, B., Mercuri, S.R., Moliterni, E., Donati, M., Ciofalo, A., Granata, G., Ranuzzi, P., Falasca, V., Calvieri, S., 2017. Paraneoplastic pemphigus: insight into the autoimmune pathogenesis, clinical features and therapy. Int. J. Mol. Sci. 18. https://doi.org/10.3390/ijms1812532.

Patricio, P., Ferreira, C., Gomes, M.M., Filipe, P., 2009. Autoimmune bullous dermatoses: a review. Ann. N. Y. Acad. Sci. 1173, 203-210. https://doi.org/10.1111/j.1749-6632.2009.04717.x.

Porro, A.M., Caetano, L. de V.N., Maehara, L. de S.N., Enokihara, M.M. dos S., 2014. Non-classical forms of pemphigus: pemphigus herpetiformis, IgA pemphigus, paraneoplastic pemphigus and IgG/IgA pemphigus. An. Bras. Dermatol. 89, 96-106. https://doi.org/10.1590/abd1806-4841.20142459.

Ruocco, V., Ruocco, E., Lo Schiavo, A., Brunetti, G., Guerrera, L.P., Wolf, R., 2013. Pemphigus: etiology, pathogenesis, and inducing or triggering factors: facts and controversies. Clin. Dermatol. 31, 374-381. https://doi.org/10.1016/j.clindermatol.2013.01.004.

Seishima, M., Oda, M., Oyama, Z., Yoshimura, T., Yamazaki, F., Aoki, T., Nei, M., Hashimoto, T., 2004. Antibody titers to desmogleins 1 and 3 in a patient with paraneoplastic pemphigus associated with follicular dendritic cell sarcoma. Arch. Dermatol. 140, 1500-1503. https://doi.org/10.1010/archderm.140.12.1500.

Zimmermann, J., Bahmer, F., Rose, C., Zillikens, D., Schmidt, E., 2010. Clinical and immunopathological spectrum of paraneoplastic pemphigus. JDDG J. der Dtsch. Dermatologischen Gesellschaft 8, 598-605. https://doi.org/10.1111/j.1610-0387.2010.07380.x.