Gynecologic Oncology Reports 32 (2020) 100534

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case report

Cutaneous paraneoplastic pemphigus syndrome associated with undifferentiated uterine sarcoma

Bijan Morshedi*, Kari Ring

University of Virginia Health System, 1215 Lee St, Charlottesville, VA 22903, United States

ARTICLE INFO

Keywords:
Paraneoplastic pemphigus
Undifferentiated uterine sarcoma
Uterine cancer pemphigus
Paraneoplastic syndrome

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/m^2 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 has 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 (Patrício 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.

* Corresponding author.
E-mail addresses: bm8wr@virginia.edu (B. Morshedi), kel7j@virginia.edu (K. Ring).

https://doi.org/10.1016/j.gore.2019.100534
Received 6 September 2019; Received in revised form 24 December 2019; Accepted 26 December 2019
Available online 18 January 2020

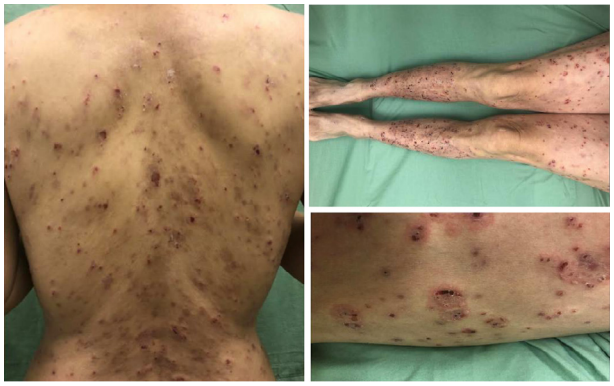

Fig. 1. Patient's dermatological findings on initial presentation in June 2018, prior to the diagnosis of undifferentiated uterine sarcoma.

2. Case report

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. Medications included Vitamin D and CoQ10. Family history was negative for any skin or autoimmune diseases, but a maternal uncle had lung and brain metastases from an unknown primary tumor. Her only allergy is dermatitis to chlorthalidone. She has never used any tobacco products or drugs and does not drink regularly. Physical exam was notable for erythematous crusted annular plaques with significant hyperpigmentation and tense bullae on the chest, abdomen, back, bilateral extremities, right temple, and right ear without intraoral or ocular lesions (Fig. 1).

Biopsy of the right abdomen in March 2018 showed pustular and eosinophilic spongiotic dermatitis with negative immunofluorescence. Biopsy of the left forearm in April 2018 showed intraepidermal pustular dermatitis with eosinophils with negative direct immunofluorescence.

Laboratory studies in May 2018 showed a normal CBC and CMP, normal TPMT metabolizer status, negative ANA, and a positive Quantiferon Gold. Chest X-Ray showed tiny calcified nodule left apex and calcification in the left hilum consistent with old granulomatous disease prompting referral to Infectious Disease for treatment of latent tuberculosis with rifampin monotherapy for 4 months, starting on June 2018.

Given high suspicion for primary immunobullous disease in spite of 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.

Given normal G6PD levels, the patient was started on dapsone in June 2018 with some improvement to existing blisters but continued developing new lesions. Her treatment at this time included betamethasone ointment daily, clobetasol solution daily for the scalp, mupirocin for open eroded areas, hydroxyzine for pruritis, and dapsone 100 mg daily. More aggressive immunosuppression was considered but withheld given her latent Tb. Given disease progression despite dapsone, it was discontinued and prednisone 40 mg daily was started along with rifampin 10 mg/kg daily.

Her lesions improved significantly on prednisone, but flared with tapering. Infectious disease recommended starting rituximab 4 weeks after initiation of Tb therapy, so rituximab was held until September 2018, when it was started per lymphoma protocol at 375 mg/m^2 weekly for one month. She received 3 doses of rituximab while taking 5 mg prednisone daily and 150 mg azathioprine daily.

In December 2018, evaluation from the patient's Dermatologist 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 hysteroscopy 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. In situ hybridization for kappa and lambda RNA were both negative. ERG, desmin, smooth muscle actin, myogenin, CD45, CD3, CD20, S100, melan-A, HMB45, cyclin-D1, CD30, alk, keratin, CD10, and p63 were all negative. Staining for SMARCA4 showed a loss in the tumor cells.

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 stromal, endomyometrium, 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

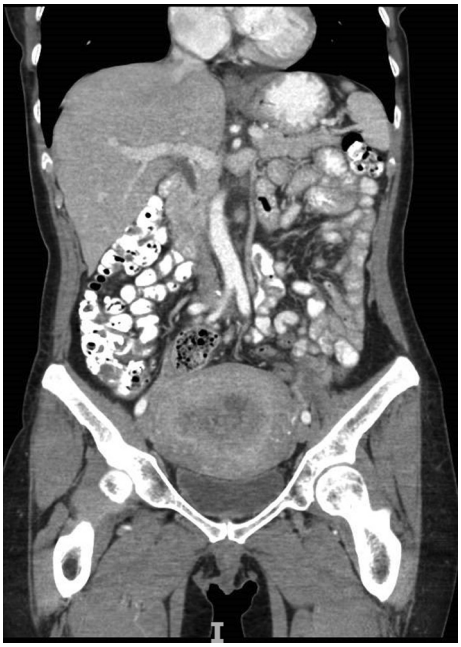

Fig. 2. CT scan in April 2019 after the patient was diagnosed with undifferentiated uterine sarcoma by hysteroscopy with dilation and curettage but prior to surgical resection of the tumor.

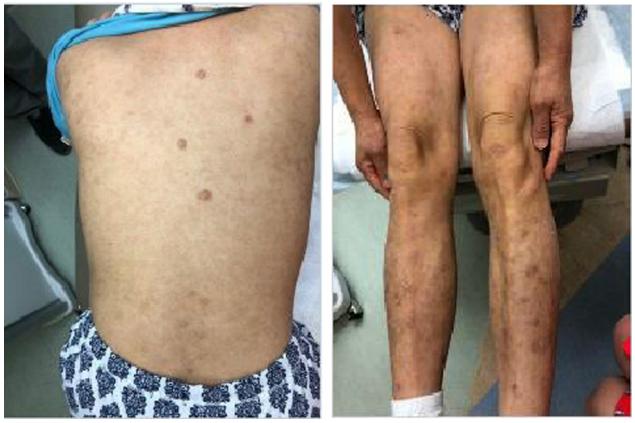

Fig. 3. Patient's dermatological findings during a follow up visit in May 2019, after surgical resection of the undifferentiated uterine sarcoma.

280u in June 2018. She started 4 cycles of adjuvant gemcitabine and docetaxel for her stage IIB undifferentiated uterine sarcoma in May 2019 and completed treatment in August 2019. A CT scan of her chest, abdomen, and pelvis in September 2019 revealed no new sites of disease in the abdomen or pelvis with stable enlarged periaortic lymph nodes concerning for metastasis, which prompted ongoing radiation to the pelvis and para-aortic nodes. Follow up through November 2019 has shown no recurrence of her pemphigus disease.

3. Discussion

In summary, this report describes the course of a patient's paraneoplastic pemphigus foliaceous related to an undifferentiated uterine sarcoma, which showed a decrease in Dsg1 antibodies from 280u to 32u in conjunction with significant improvement in dermatologic lesions. This patient's PNP was resistant to treatment with azathioprine, dapsone, mupirocin cream, or betamethasone ointment. The patient demonstrated no new lesions after surgery and "around 80% improvement from baseline" of her existing skin lesions. Significant scarring and hyperpigmentation still exist from previous lesions, but have become lighter with time.

It is important to note that this patient demonstrated no new lesions and stabilization of existing disease after completing rituximab treatment, prior to surgical intervention for the undifferentiated uterine sarcoma. It is possible, but very unlikely, that she would have continued to improve with time independent of surgery given her history of stabilization and severe relapse with tapering of high dose steroid treatment. In her postoperative visit, the patient stated that the surgery "cured her pemphigus" and that her previous treatments "helped a little but did not fix it." The patient's unprompted focus on the resolution of her pemphigus disease after the surgery, not from immunosuppressive treatment, sparked this case report. Given the patient's certainty that surgery "cured her pemphigus", the chart review only demonstrating disease stabilization without new lesions during immunosuppressive treatment, a decrease in autoantibodies and improvement of symptoms after surgery, and no recurrence of the patient's pemphigus disease during follow up to this day, the authors are confident that this patient had some type of paraneoplastic pemphigus.

Although over 180 reports exist documenting paraneoplastic pemphigus, only around 6% of these cases were caused by sarcomas. Anhalt *et al* described several neoplasms that are commonly associated with PNP including non-Hodgkin's lymphoma (42%), chronic lymphocytic leukemia (29%), Castleman's disease (10%), thymomas (6%), sarcomas (6%), and Waldenstrom's macroglobulinemia (6%) (Anhalt, 2004). With the known association between pemphigus disease and occult malignancy, patients that do not respond to routine therapy warrant further evaluation for an underlying cause, such as a neoplastic or infectious etiology. In this patient's case, the PNP started in November 2017 and her postmenopausal bleeding started in February 2019, so 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 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. Investig. 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., Ratrie, H., Mutasim, D., Ariss-Abdo, 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/ijms18122532.

Patrício, 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.1749-6632.2009.04737.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/10.1001/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.