Pemphigus vulgaris in an elderly woman diagnosed with subacute thyroiditis: A case report

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1 | INTRODUCTION

Pemphigus vulgaris (PV) affects between one and five individuals per million every year, with a high percentage of these cases reported in the fifth and sixth decade of life. The etio-pathogenesis of PV is well known and involves the generation of immunoglobulin subtype G (IgG) auto-antibodies, which are directed against desmosomal, non-desmosomal, and mitochondrial proteins on keratinocytes. The association between PV and autoimmune thyroid disease (e.g., Graves and Hashimoto’s thyroiditis) has been attributed to shared antigens as well as the genetic susceptibility of the individual. However an association between PV and non-autoimmune thyroid disease is unknown.

Subacute thyroiditis (SAT) is a viral induced thyroid disease that affects middle aged women and has a global incidence of 12.1 cases per 100,000/year. After an exhaustive PubMed English literature search, we found that this is the first case to report PV in an elderly woman with SAT.

2 | CASE HISTORY

A 70-year-old woman reported to the Department of Oral and Maxillofacial Pathology with multiple oral ulcerations. The patient gave a 2 month history of experiencing painful oral ulcers. She also complained of hair loss, malaise, fatigue, myalgia, and arthralgia.

The patient had been diagnosed with SAT, 9 years prior. Her medical records showed a fluctuation of thyroid function tests (TFTs) for a period of 12 months (i.e., November 2011 to November 2012). Given her lack of recent TFT records, the same were advised and were within normal limits (Table 1).

Her ultrasound report showed findings suggestive of multinodular goiter. The patient underwent a fine needle aspiration biopsy that revealed colloid red blood cells, follicular cells, and epithelioid cells. The cytopathological findings were suggestive of SAT.

The patient’s records showed that she was negative for anti-thyroid antibodies (i.e., anti-thyroglobulin [antiTgO] and anti-thyroid peroxidase [antiTPO]) and was not under medication for her thyroid condition. On re-testing, her negative status for anti-thyroid antibodies remained unchanged.

Besides a history of an upper respiratory tract infection prior to developing symptoms of thyroid disease, the patient had no other relevant medical history or family history of vesiculobullous lesions and thyroid disease.

When we examined the patient, we found a firm solitary nodular and tender swelling over the thyroid gland on the right side of her neck, measuring 8.5 cm x 11.2 cm in greatest dimensions.

After an exhaustive PubMed English literature search, we found that this is the first case to report PV in an elderly woman with SAT.
The patient returned after 4 months with bullae on the trunk, arms, elbows, back, legs, and groin (Figure 3). Nikolsky’s sign and Asbøe-Hansen’s sign were both positive. Her oral mucosa was covered with ulcers on the soft palate, buccal mucosa, tongue, dorsum, ventrum, and lateral borders, and floor of the mouth.

**TABLE 1** Timeline of patient’s thyroid function test values

| Month and Year | Triiodothyronine (T3) ng/ml | Tetraiodothyronine (T4) ng/ml | Thyroid stimulating hormone (TSH) μIU/ml |
|----------------|-----------------------------|-------------------------------|--------------------------------------|
| November 2011  | 2.2                         | 12.2                          | 0.37 Hyperthyroid                     |
| January 2012   | 2.5                         | 1.47                          | 1.25 Hyperthyroid                     |
| August 2012    | 2.4                         | 8.84                          | 1.55 Hyperthyroid                     |
| November 2012  | 2.2                         | 9.12                          | 0.71 Hyperthyroid                     |
| December 2012-December 2020 (No records) |               |                               |                                      |
| January 2021   | 0.57                        | 6.1                           | 1.45 Euthyroid                       |

**FIGURE 1** Oral manifestations of pemphigus vulgaris. A. Oral ulcerations seen on the ventral surface of the tongue. B. White coated tongue showing a large ulcer on the right lateral border

**FIGURE 2** Hematoxylin and eosin stained micrograph of oral pemphigus vulgaris. A. The micrograph (100x) shows a complete split between the epithelium and the connective tissue. B. At a higher magnification (400x), the split is seen to be suprabasilar with basal cells attached to the basement membrane appearing “tombstone-like.” The underlying connective tissue stroma shows a predominantly lymphocytic inflammatory infiltrate
FIGURE 3  Skin manifestations of pemphigus vulgaris (clockwise). A. Flaccid bullae, fluid filled vesicles, and lesions which showed healing by crusting and pigmentation on the right elbow. B. Multiple healing lesions which show scarring seen on the upper back. C. Large bulla seen over the umbilicus and multiple vesicles showing healing by scarring scattered over the abdomen. D. A crop of fluid filled vesicles seen around the right ankle.

FIGURE 4  The flowchart elaborates on the etiopathogenic mechanisms, which could account for the clinical presentation of pemphigus vulgaris in this patient who was earlier diagnosed with subacute thyroiditis. Cbl-b, casitas B-lineage lymphoma proto-oncogene B; CTLA-4, cytotoxic T lymphocyte associated protein 4; FcγRIIB gene, Fc fragment of IgG receptor IIb; HSP70, heat shock protein 70; IL-6, interleukin 6; PAMPs, pathogen associated molecular patterns; PD-1, programmed death-1; SMP-1, second mitochondrial elongation factor 2 like protein 1.
We referred the patient to the Department of Dermatology where she was administered dexamethasone-cyclophosphamide pulse therapy in four phases.7

We have been following the patient’s progress for the last 2 years and are happy to report that the patient is responding well to the treatment.

3 | DISCUSSION

SAT is a self-limiting painful thyroiditis caused by viral infection and accounts for 3%–6% of all thyroid diseases.8,9 A large number of viruses have been associated with SAT including severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2).8,10–13 The mechanism proposed for this association is viral damage caused to the thyroid follicular cells via angiotensin converting enzyme-2 (ACE-2) and transmembrane protease serine-2 (TMPRSS2) receptors.10,12

Major histocompatibility complex class II alleles and haplotype frequencies have been analyzed for both PV and SAT in various populations around the world. SAT associated human leucocyte antigen (HLA) haplotypes are HLA-B*35, HLA-18:01, DRB1*01, and HLA-C*04:01.13,14 The HLA haplotype complex cause destruction of the thyroid gland via cytotoxic T lymphocytes.11 The release of T4 and T3 in large quantities results in the hyperthyroidism phase of SAT.15 A transient period of increased thyroid-stimulating hormone secretion may occur (known as the hypothyroidism phase of SAT).8 Post viral infection, the inflammation subsides and normal thyroid function is resumed (known as the euthyroid phase of SAT; Figure 4). In PV, the specific HLA genotypes promote a switch from IgG1 (remission) to IgG4 autoantibodies (acute state), which attack the desmoglein adhesion proteins between keratinocytes.3,15 In addition, the presence of non-desmosomal autoantibodies, in particular, the cell membrane receptors, such as thyroperoxidase, also contribute to the phenomenon of epitope spreading.2,3 The generation of these autoantibodies results from molecular mimicry between environmental infectious agents (e.g., viral agents) and self antigens.16

The bystander activation and/ or molecular mimicry following the hyperthyroidism phase of SAT has the potential to unmask non-immunodominant Dsg3 epitopes on oral keratinocytes.17 The disruption of Dsg3 protein would expose epitopes on Dsg1 (i.e., inter-molecular epitope spreading phenomenon).16 This could explain the subsequent cutaneous involvement following oral symptoms seen in this patient (see Figure 4).

4 | CONCLUSION

The study of physiologic loss of immunological tolerance and its effect on the epitope spreading phenomenon could further elucidate autoimmune pathogenesis in elderly individuals.

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CONFICT OF INTEREST

Nothing to disclose.

AUTHOR CONTRIBUTIONS

Study concept: Carvalho and Dhupar. Design: Carvalho and Dhupar. Definition of intellectual content: Carvalho, Dhupar, Spadigam, and Naik. Literature search: Carvalho, Dhupar, Spadigam, and Naik. Clinical studies: Carvalho, Dhupar, Spadigam, and Naik. Experimental studies: Carvalho, Dhupar, Spadigam, and Naik. Manuscript preparation: Carvalho, Dhupar, Spadigam, and Naik. Manuscript editing: Carvalho, Dhupar, Spadigam, and Naik. Manuscript review: Carvalho, Dhupar, Spadigam, and Naik. Guarantor: Carvalho, Dhupar, Spadigam, and Naik.

INFORMED CONSENT

Written informed consent for publication of clinical details was obtained from the patient.

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REFERENCES

1. Popescu I, Statescu L, Vata D, et al. Pemphigus vulgaris – approach and management. Exp Ther Med. 2019;18(6):5056-5060. doi:10.3892/etm.2019.7964
2. Saleh MA, Salem H, El Azizy H. Autoantibodies other than anti-desmogleins in pemphigus vulgaris patients. Indian J Dermatol. 2017;62(1):47-51. doi:10.4103/0019-5154.198032
3. Pan M, Liu X, Zheng J. The pathogenic role of autoantibodies in pemphigus vulgaris. Clin Exp Dermatol. 2011;36(7):703-707. doi:10.1111/j.1365-2230.2011.04092.x
4. Baldini E, Odorisco T, Tuccilli C, et al. Thyroid diseases and skin autoimmune. Rev Endocr Metab Disord. 2018;19(4):311-323. doi:10.1007/s11154-018-9450-7
5. Wang H, Yang Y, Hu J, et al. Serum detection of anti thyroid peroxidase and antithyroglobulin antibodies in Chinese patients with Pemphigus Vulgaris and Pemphigus Foilaceous and literature review. Front Immunol. 2021;12:653356. doi:10.3389/fimmu.2021.653356
6. Tabassom A, Edens MA. De Quervain Thyroiditis. StatPearls. January 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK526066
7. Parshica JS. Pulse therapy as a cure for autoimmune diseases. Indian J Dermatol Venereol Leprol. 2003;69:323-328.
8. Alfadda A, Sallam R, Ellawad G, AlDhukair H, Alyahya M. Subacute thyroiditis: clinical treatment and long treatment outcome. Int J Endocrinol. 2014;2014:794943. doi:10.1155/2014/794943
9. Vural C, Paksoy N, Gok N, Yazal K. Subacute granulomatous (De Quervain’s) thyroiditis: fine-needle aspiration cytology and ultrasonographic characteristics of 21 cases. CytoJournal. 2015;12:9. doi:10.4103/1742-6413.157477
10. Rehman M, Farooq H, Ali M, et al. The association of subacute thyroiditis with COVID-19: a systematic review. SN Compr Clin Med. 2021;1:13. doi:10.1007/s42399-021-00912-5. Available from: https://pubmed.ncbi.nlm.nih.gov/33942028/
11. Stasiak M, Tymoniuk B, Adamczewski Z, et al. Sonographic pattern of Subacute thyroiditis is HLA- dependent. Front Endocrinol. 2019;10:3. doi:10.3389/fendo.2019.00003
12. Li L, Wu X, Hu B, et al. Localized subacute thyroiditis presenting as a painful hot nodule. BMC Endocr Disord. 2014;14(1):4. doi:10.1186/1472-6823-14-4

13. Gaballa S, Hlaing KM, Bos N, et al. A rare case of subacute painful thyroiditis causing thyroid storm and a successful trial of propylthiouracil. Cureus. 2020;12(7):e9461. doi:10.7759/cureus.9461

14. Kong M, Porte S. Case report: De Quervain’s thyroiditis as a long-term sequelae complication to SARS-CoV-2 infection. Case Rep Acute Med. 2021;4:64-70. doi:10.1159/000517705

15. Christopher D. Pemphigus: pathogenesis to treatment. R I Med J (2013). 2016;99(12):28-31.

16. Mak TW, Saunders ME, eds. Autoimmune disease. In: The Immune Response. Basic and Clinical principles, 1st ed. Elsevier; 2006:963-1023.

17. Nishihara E, Amino N, Kudo T, et al. Moderate frequency of anti-thyroglobulin antibodies in the early phase of subacute thyroiditis. Eur Thyroid J. 2019;8(5):268-272. doi:10.1159/000501033

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