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CASE REPORT

# 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.[1] 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.[2,3]

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.[4,5] 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.[6]

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 × 11.2 cm in greatest dimensions.

Her skin and oral examination revealed multiple, irregular shallow ulcers, which were confined to the dorsum and ventrum of tongue, left buccal mucosa, and lower labial mucosa. Her tongue also showed the presence of hypertrophied papillae with a white coat covering the entire dorsum (Figure 1).

A biopsy from the ventrum and left border of the tongue revealed denuded oral epithelium, a suprabasilar split, hyperchromatic acantholytic cells within the intra-epithelial vesicle, and chronic inflammatory infiltrate (Figure 2). Serum titers for desmoglein-1 (Dsg-1) and desmoglein-3 (Dsg-3) using enzyme linked immuno asssay technique were 43.73 and 184.03, respectively.

A diagnosis of PV was made and the patient was prescribed topical triamcinolone acetonide (0.1% w/w) and systemic predniso(lo)ne 1 mg/kg/day therapy. The patient was asked to report for a follow-up visit after 2 weeks but failed to do so. Subsequently, we lost all communication with the patient for a period of 4 months.

TABLE 1 Timeline of patient's thyroid function test values

| Month and Year | Thyroid function tests | | Thyroid status | |
|---|---|---|---|---|
| | 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 |

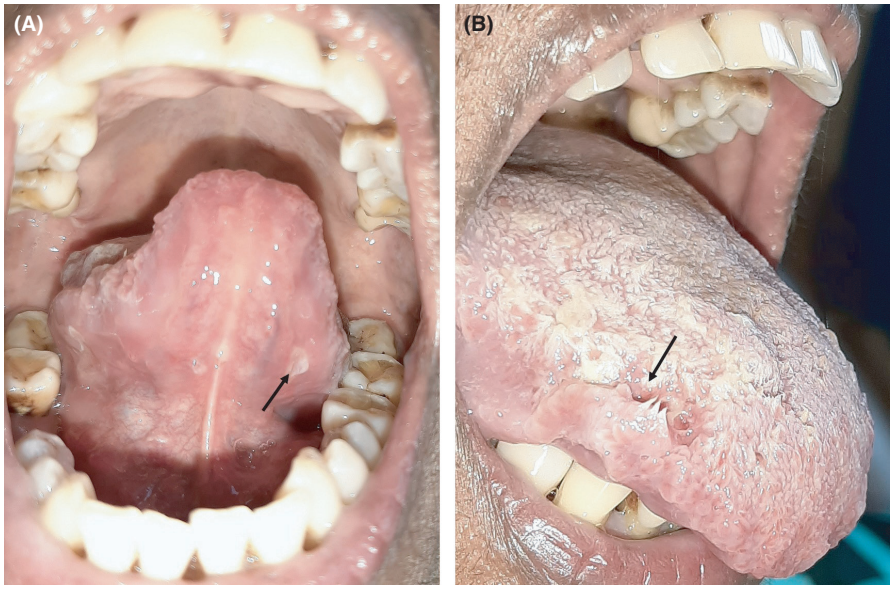


FIGURE 1 Oral manifestations of pemphigus vulgaris. A. Oral ulcerations seen on the ventral surface of the tongue. B. White coated tongue showing a large ulcer on the right lateral border

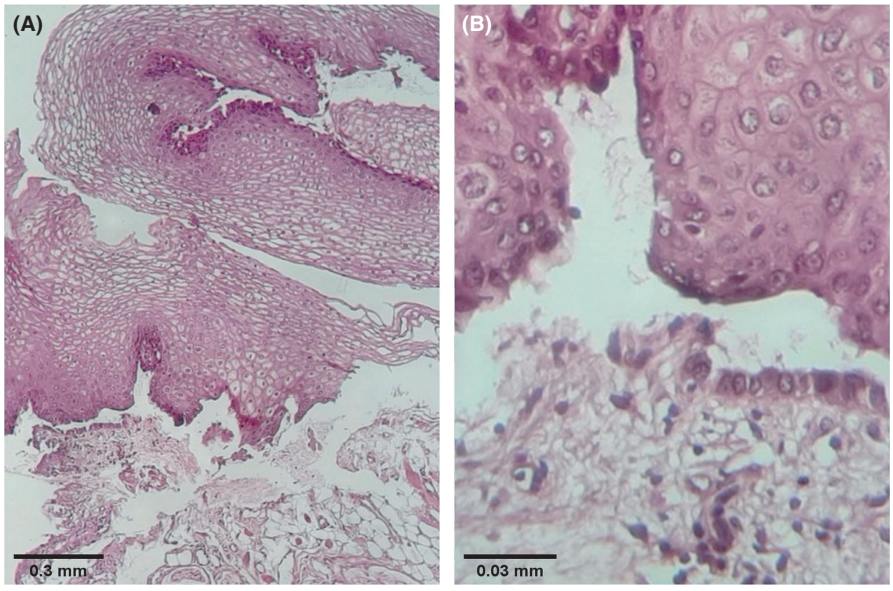


FIGURE 2 Hematoxylin and eosin stained micrograph of oral pemphigus vulgaris. A. The micrograph (100×) shows a complete split between the epithelium and the connective tissue. B. At a higher magnification (400×), the split is seen to be suprabasilar with basal cells attached to the basement membrane appearing "tombstone-like." The underlying connective tissue stroma shows a predominantly lymphocytic inflammatory infiltrate

The patient returned after 4 months with bullae on the trunk, arms, elbows, back, legs, and groin (Figure 3). Nikolsky's sign and Asböe-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.

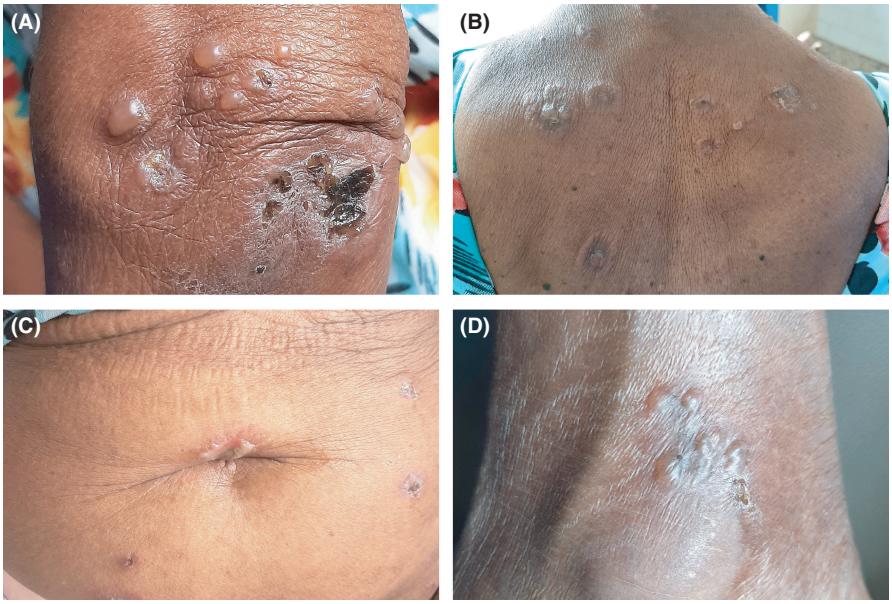


**FIGURE 3** Skin manifestations of pemphigus vulgaris (clockwise). A. Flaccid bullae, fluid filled vesicles, and lesions which showed healing by crusting and pigmentation on the right elbow. B. Multiple healing lesions which show scarring seen on the upper back. C. Large bulla seen over the umbilicus and multiple vesicles showing healing by scarring scattered over the abdomen. D. A crop of fluid filled vesicles seen around the right ankle

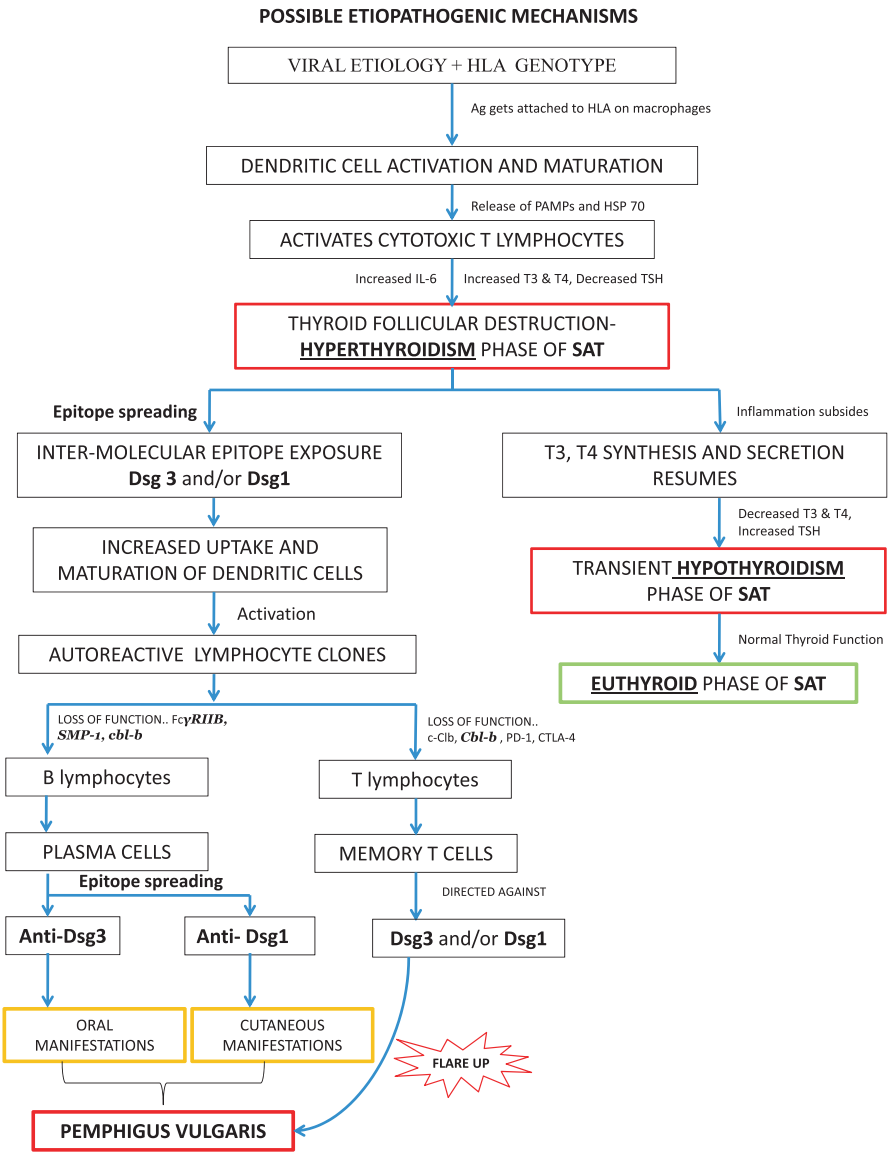


**FIGURE 4** The flowchart elaborates on the etiopathogenic mechanisms, which could account for the clinical presentation of pemphigus vulgaris in this patient who was earlier diagnosed with subacute thyroiditis. Cbl-b, casitas B-lineage lymphoma proto-oncogene B; CTLA-4, cytotoxic T lymphocyte associated 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 $T_4$ and $T_3$ in large quantities results in the hyperthyroidism phase of SAT. 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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The authors wish to thank the patient for her collaboration.

### CONFLICT 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. *Data acquisition:* Carvalho, Dhupar, Spadigam, and Naik.; *Data analysis:* 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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