Telitacicept for systemic lupus erythematosus with post-surgical papillary thyroid carcinoma: A case report

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Abstract. Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a complex etiology primarily linked to abnormalities in B lymphocytes within the human body, resulting in the production of numerous pathogenic autoantibodies. Telitacicept is a relatively novel humanized, recombinant transmembrane activator, calcium modulator and cyclophilin ligand interactor fused with the Fc portion (TACI-Fc). It works by competitively inhibiting the TACI site, neutralizing the activity of B-cell lymphocyte stimulator and A proliferation-inducing ligand. This, in turn, inhibits the development and survival of plasma cells and mature B cells. A 28-year-old female was admitted to the Department of Rheumatology and Immunology (People's Hospital of Longhua; Shenzhen, China) in June 2021 due to systemic edema for more than a month and hair loss lasting for a week. After comprehensive examination, the patient was diagnosed with SLE with hematological system involvement, serositis, lupus nephritis and secondary antiphospholipid syndrome. After receiving medications including glucocorticoids, mycophenolate mofetil and cyclosporine, the patient's white blood cells, platelets, hemoglobin, urinary protein and multiple serositis returned to normal. However, the levels of complement 3 (C3) and C4 did not significantly improve. Subsequently, the patient underwent thyroid ultrasound examination, which suggested thyroid nodules. After thyroid puncture biopsy, the patient was diagnosed with papillary thyroid carcinoma (PTC). After surgical resection, the patient was confirmed to have PTC by pathological biopsy, with no lymph node metastasis. At two months after surgery, the patient was treated with telitacicept, and the complement levels not only returned to normal but also remained stable for a long time. The present case was the first to report the use of telitacicept for the successful treatment of a patient with SLE with post-surgical PTC, providing a potential therapeutic option for SLE with a prior history of carcinoma. The role of telitacept in this field requires further research and attention.

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder that features the generation of numerous autoantibodies and immune complexes, potentially compromising diverse bodily systems. B cells are purportedly pivotal in the etiology of SLE (1), since the abnormal proliferation, differentiation and maturation of these cells lead to the secretion of autoantibodies that inflict harm on various bodily systems. The cytokines B-lymphocyte stimulator (BLyS) and A proliferation-inducing ligand (APRIL) occupy pivotal positions in the intricate process of B-cell maturation and differentiation (2).

Telitacicept is an important biological agent that can effectively suppress the proliferation and differentiation of B cells and plasma cells, by specifically targeting both BLyS and APRIL. Furthermore, it exhibits the potential to dampen the activity of long-lived plasma cells (3). Telitacicept was approved in March 2021 in China for the treatment of SLE (4), but it has not been widely accepted due to its high cost.

Thyroid carcinoma is the most common malignancy of the endocrine system, exhibiting a gradual increase in its incidence rate in high-income countries to certain middle-income countries. Globally, in 2020, the estimated number of new cases of thyroid cancer was ~449,000 in women and ~137,000 in men, corresponding to age-standardised incidence rates of ~10.1 per 100,000 women and ~3.1 per 100,000 men. In each sex, incidence rates are five times greater in high and very high Human Development Index countries than in low and medium Human Development Index countries (5). Previous meta-analyses and observational studies have shown that the risk of thyroid carcinoma is increased in patients with SLE (6-8). The present case documents a 28-year-old female patient who developed papillary thyroid carcinoma (PTC) 1 year after being diagnosed with SLE. Following surgical removal of the tumor, the

patient was administered with telitacicept for treatment. To the best our knowledge, the present case was the first reporting the instance of a patient suffering from both SLE and PTC undergoing postoperative telitacicept treatment.

Case report

The patient, a 28-year-old female, was diagnosed with SLE at Department of Rheumatology and Immunology, People's Hospital of Longhua (Shenzhen, China) in June 2021, having experienced systemic edema for >1 month and hair loss for a week. After undergoing comprehensive examinations, the patient was diagnosed with lupus-related hematological damage, which was evidenced by leukopenia, thrombocytopenia, autoimmune hemolytic anemia and polyserositis accompanied by pericardial and pleural effusion. Additional complications included lupus nephritis and secondary antiphospholipid syndrome. After treatment with high-dose steroids, mycophenolate mofetil (MMF) and cyclosporine A (CsA) (Fig. 1), the patient's white blood cells, platelets, hemoglobin, urinary protein and polyserositis normalized (Fig. 2). Complement 3 (C3) levels improved but could not be maintained within the normal range for a prolonged period, whilst C4 levels remained unchanged (Fig. 1). During the course of treatment (Fig. 1), the patient developed herpes zoster, which improved after reducing the dosage of MMF and CsA and administering antiviral treatment with famciclovir. The dosage of MMF was adjusted from twice a day, 0.75 g each time to once a day, 0.5 g. The dosage of CsA has also been adjusted from twice a day (bid), 0.05 g each time to once a day (qd), 0.05 g. Famciclovir is administered three times a day, with 0.25 grams per administration.

On December, 2022, a thyroid ultrasound (Fig. S1) revealed a solid nodule near the isthmus of the left lobe of the thyroid gland, classified as American College of Radiology Thyroid Imaging Reporting and Data System (ACRTI-RADS) (9) grade 4, along with a mixed cystic-solid nodule in the right lobe, classified as ACRTI-RADS grade 2. Thyroid puncture pathology confirmed the diagnosis of PTC in the left lobe (data not shown). In May 2023, a total left thyroidectomy, isthmectomy, subtotal right thyroidectomy and lymph node dissection in the central region of the left neck were performed at Department of Thyroid and Breast Surgery, People's Hospital of Longhua (Shenzhen, China). The specimens were sectioned into book-leaf-like shapes every 3 mm, and all suspected lesions visible to the naked eye were sampled. All specimens were fixed with 4% neutral formaldehyde, routinely embedded in paraffin, sliced at 4 μm, stained with H&E according to standard procedures and observed under a light microscope. Fig. 3A shows that the thyroid follicular epithelium exhibits papillary and branching proliferation, featuring a fibrovascular core. The surface is lined with a single layer of tumor cells. The cell nuclei are large, oval, densely packed and exhibit a ground-glass appearance. Nuclear grooves and small clear nucleoli can be seen (red rectangular shape). Left thyroid and isthmus are consistent with PTC. The final diagnosis was small PTC in the left lobe (pT1N0M0, stage I; Fig. 3) (10). Postoperative blood examination revealed a significant decrease in thyroid-stimulating hormone levels, therefore, oral administration of levothyroxine sodium tablets at a dose of 100 μg qd was required. Owing to the failure of conventional drug therapy to successfully restore the patient's complement levels, the treatment plan has been adjusted accordingly since July 2023. Next, CsA was discontinued, and treatment with prednisone at a dosage of 10 mg qd, MMF at 0.75 g bid and hydroxychloroquine (HCQ) at 0.2 g qd was continued. In addition, the patient also received a subcutaneous injection of 160 mg of telitacicept once a week (4). After 1 month, the C3 and C4 levels returned to normal. Due to the recovery of the patient's C3 and C4 levels and the relatively high price of telitacicept, the dosage of telitacicept for subcutaneous injection was reduced to 80 mg once a week starting from September 2023 (Fig. 1).

During the medication period, regular follow-up visits were made to the Department of Thyroid and Breast Surgery, People's Hospital of Longhua (Shenzhen, China), where thyroid function and ultrasound examinations were conducted at half-year intervals. Thyroid stimulating hormone gradually normalized (data not shown) and no thyroid nodules or enlarged lymph nodes were observed.

In December 2023, there was one episode of cough, nasal congestion and yellow nasal discharge, suggestive of acute upper respiratory tract infection. Cefuroxime was administered twice daily, with 0.5 g each time, and compound pseudoephedrine hydrochloride was administered twice daily, with one tablet each time. After administering both orally for 3 days, the aforementioned symptoms improved. In late December 2023, a urine nitrite test yielded positive results (data not shown), but there were no symptoms of frequent urination, urgency or pain. A complete urine culture test indicated the presence of *Klebsiella pneumoniae* (data not shown). After taking levofloxacin tablets for 14 days, once a day at a dosage of 0.5 g each time, the urine nitrite test became negative.

Discussion

The reasons for the comorbidity of SLE and thyroid carcinoma remain elusive. Antonelli *et al* (11) previously found that the incidence of thyroid carcinoma in patients with SLE is significantly elevated compared with that in age-matched normal controls, particularly in those with evidence of thyroid autoimmunity. In another study, Okosieme *et al* (12) discovered that patients with autoimmune thyroid disease and thyroid carcinoma exhibit similar yet distinct thyroid globulin antigen epitopes compared with those with positive anti-thyroid globulin antibodies, suggesting that autoimmune mechanisms may serve a role in the development of thyroid carcinoma. In addition, SLE and thyroid carcinoma are more prevalent in women. Previous studies indicate a significant increase in estrogen receptor expression within thyroid carcinoma tissues and in the peripheral blood of patients with SLE (13-15). Estrogen may exert a significant role in the pathogenesis of both conditions, though the exact mechanism remains elusive. Therefore, further research is necessary to determine whether there is an association between the comorbidity of these two conditions.

Although inheritance, hormones and the environment have been identified as risk factors for developing SLE (16,17), abnormal activation of the immune system is the core mechanism, characterized by excessive B-cell responses and the

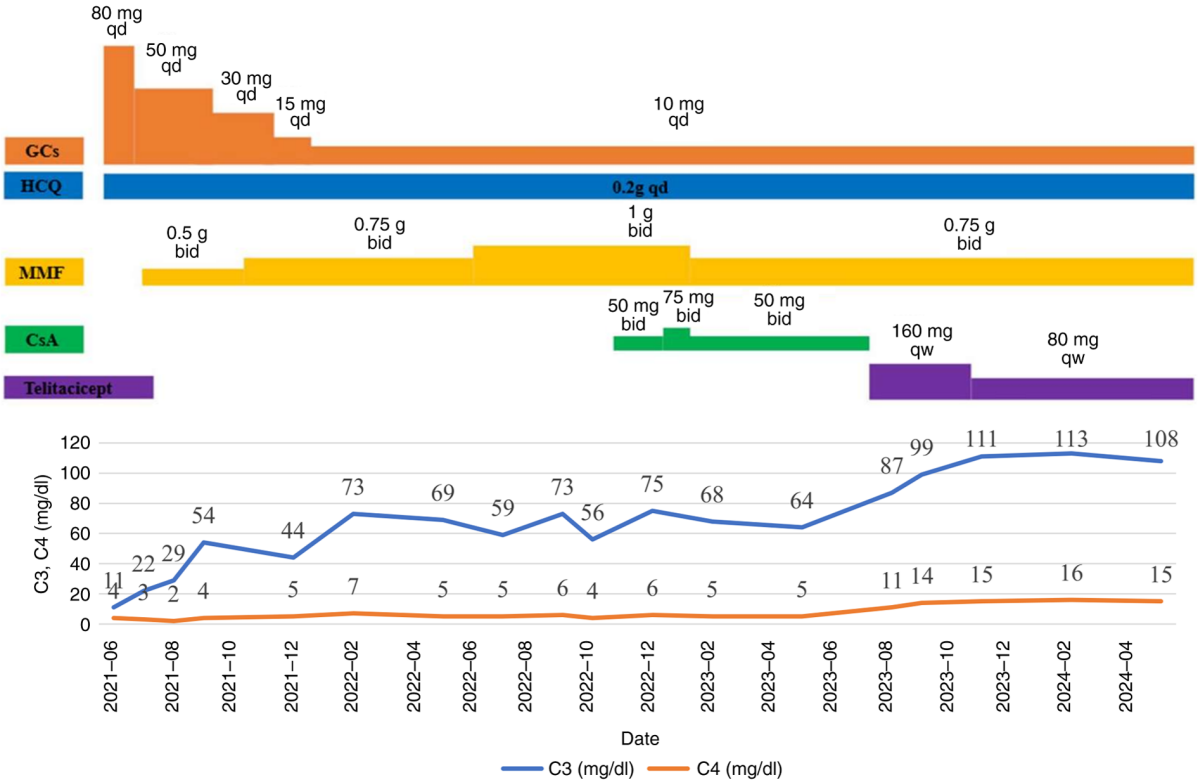

Figure 1. Treatment medication process and laboratory indicators. GCs, glucocorticoids; HCQ, hydroxychlorogyine; MMF, mycophenolate mofetil; CsA, cyclosporine A; C3, complement 3; C4, complement 4; bid, twice daily; qd, once a day; qw, once a week.

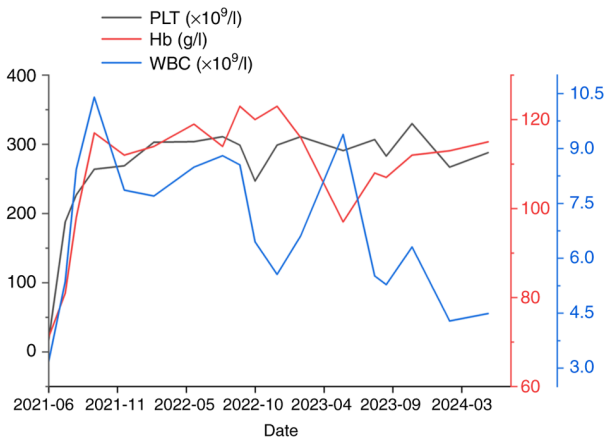

Figure 2. Trends in levels of PLT (black line), Hb (red line) and WBC (blue line). The reference values for PLT, Hb and WBC are 125 to 350x10^9/l, 115 to 150 g/l and 3.5 to 9.5x10^9/l, respectively. PLT, platelets; Hb, hemoglobin; WBC, white blood cells.

production of autoantibodies (18). Telitacicept is a TACI-Fc fusion protein that, by competitively inhibiting the TACI site, neutralizes the activity of BLyS and APRIL, thereby inhibiting the development and survival of plasma cells and mature B cells. It not only inhibits the transformation of immature B lymphocytes into mature B lymphocytes, but can also prevent the transition of mature B cells into plasma cells. In addition, it can affect the secretion of autoantibodies from abnormal plasma cells, thereby controlling disease progression (19). BLyS binds to B-cell activating factor receptor 3 and functions through the alternative/noncanonical NF-κB signaling pathway, effectively blocking its activity (3). The application of telitacicept in the treatment of SLE has resulted in a higher response rate of the Systemic Lupus Erythematosus Disease Activity Index, significantly reducing immunoglobulin levels and increasing complement levels (20).

To date, only two biological agents have been approved for the treatment of SLE, namely belimumab (21) and telitacicept (4). There have been multiple reports (20,22-28) whereby patients with SLE without a history of carcinoma have significantly elevated complement levels after treatment with telitacicept. The present case showed a significant increase in complement levels after the addition of telitacicept, similar to the treatment effects observed in previously reported cases of patients with SLE without concurrent cancer treated with telitacicept (20,22-28).

To the best of our knowledge, no previous study has documented the use of these agents in patients with a history of carcinoma who also suffer from SLE. However, biological agents used to treat other rheumatic diseases, such as rheumatoid arthritis (RA), psoriasis (PS), inflammatory bowel disease (IBD) and ankylosing spondylitis (AS) have been marketed earlier (29). In addition, there have been reports on the use of biological agents in patients with a history of carcinoma who also suffer from these rheumatic diseases. A Danish population-based cohort study previously showed that among patients with RA with a history of carcinoma, treatment with biological disease-modifying antirheumatic drugs was not associated with an increased risk of a second malignant neoplasm (30). Furthermore, two large prospective studies, one originating from the British Society for Rheumatology Biologics (31) and the other from the German RA Observation of Biologic

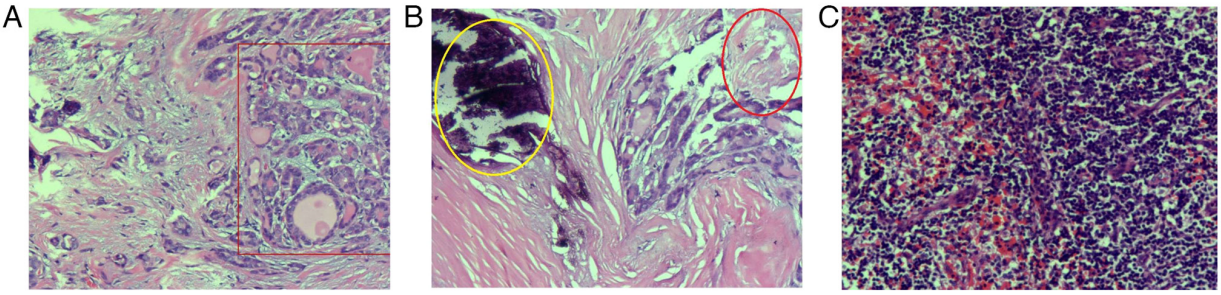

Figure 3. Thyroid pathology results. (A) It is evident that the thyroid follicular epithelium exhibits papillary and branching proliferation, featuring a fibrovascular core. The surface is lined with a single layer of tumor cells. The cell nuclei are large, oval, densely packed and exhibit a ground-glass appearance. Nuclear grooves and small clear nucleoli can be seen (red rectangular shape). Left thyroid and isthmus are consistent with papillary thyroid carcinoma. (B) In the left thyroid and isthmus, calcification (yellow ellipses) and punctured lesion tissue (red ellipses) are visible. One lymph node is present in the capsular region, without evidence of carcinoma metastasis (0/1). (C) Examination of lymph nodes in the central region of the left neck revealed five lymph nodes, all without metastasis (0/5) (hematoxylin and eosin staining; magnification, x50).

Therapy registry (32), have been conducted to investigate the utilization of biological drugs in patients diagnosed with RA. However, neither studies reported any increases in carcinoma recurrence in patients with a previous history of malignancy and under biological treatments. Another recent study has suggested that the administration of biologics targeting TNF-α, IL-17, IL-23 and IL-12 for the treatment of PS in patients with a prior history of carcinoma appears to be a safe approach (33). A multicenter real-life experience added evidence to the safety of secukinumab in patients with PS with a personal history of carcinoma (34). Secukinumab, as the world's first approved fully human IL-17A inhibitor, can specifically neutralize IL-17A from multiple sources and inhibit its pro-inflammatory activity (35). Initially, secukinumab was approved by the United States Food and Drug Administration (FDA) for the treatment of patients with moderate to severe plaque psoriasis, AS, and active psoriatic arthritis (PsA) (36). A previous meta-analysis included 34 studies (17 IBD, 14 RA, 2 PS and 1 AS), consisting of 24,328 patients and 85,784 person-years of follow-up. Rates of carcinoma recurrence were found to be similar among individuals not on immunosuppression, receiving anti-TNFs, immunomodulators and combination immunosuppression (37).

Whilst several existing guidelines recommend avoiding immunosuppression for 5 years after index carcinoma (38-42), a number of studies have indicated it may be safe to initiate these agents earlier than 5 years in certain patients (37,43). The majority of thyroid carcinoma mortality cases are from the non-papillary histological subtypes, whereas PTC has a 5-year survival rate of >90% (44). In addition, thyroid carcinoma deaths have fallen by 50% in women and by 33% in men over the past 40 years (45). Considering the present SLE case with hypocomplementemia and PTC who underwent surgery, after the treatment with MMF and CsA failed to achieve satisfactory results, the patient was effectively treated with telitacicept. During the postoperative follow-up, no tumor recurrence or lymph node metastasis was observed. Furthermore, the safety data derived from patients suffering from RA, PS, IBD and AS cannot be universally applied to patients with SLE due to various reasons, primarily because each disease exhibits a unique pathogenic mechanism.

In conclusion, to the best of our knowledge, the present case was the first to report the use of telitacicept for the successful treatment of a patient with SLE with post-surgical PTC, providing a potential therapeutic option for SLE with a prior history of carcinoma. However, the present case is only based on a single case and therefore the conclusion drawn may not be broadly representative and cannot be directly generalized to a broader patient population. Therefore, further research, particularly prospective randomized controlled trials, are warranted to verify the present findings and ensure patient safety.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

JT and BL designed and supervised the study. JT, HH and LT performed data collection and analysis. HH and LT performed data analysis and interpretation. All authors confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of People's Hospital of Longhua (Shenzhen, China; approval no. 059A[2024]). The patient provided written informed consent for the case study to be published.

Patient consent for publication

The patient who participated in the study provided written informed consent for the publication of any associated data and images.

Competing interests

The authors declare that they have no competing interests.

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