Acquired C1-inhibitor deficiency in chronic lymphocytic leukaemia: a case report

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Case report

Acquired C1-inhibitor deficiency is a rare disorder with varying manifestations and an estimated prevalence of 1 per 100 000 to 500 000 population.[1] We present a case of acquired angio-oedema that manifested after a diagnosis of chronic lymphocytic leukaemia (CLL).

In June 2017, a 60-year-old man who was previously healthy was found to have lymphocytosis on routine health screening. Physical examination showed multiple lymph nodes with no hepatosplenomegaly. A lymph node biopsy was consistent with small lymphocytic lymphoma. Bone marrow examination revealed small mature-looking lymphocytes with a background of smudge cells. The leukaemia cells co-expressed the CD5 antigen and B-cell surface antigens, with restricted kappa immunoglobulin light chain expression. Fluorescence in situ hybridisation analysis demonstrated a homozygous 13q14.2 gene deletion. Serum kappa and lambda free light chain (FLC) results were 99.50 mg/L (reference 6.70-22.40 mg/L) and 12.50 mg/L (reference 8.30-27.00 mg/L), respectively, with a kappa to lambda ratio of 7.96. Beta-2 microglobulin level was 4.64 mg/L (reference 1.09-2.53 mg/L). The patient screened seronegative for human immunodeficiency virus, syphilis, and hepatitis B and C. Overall findings were consistent with a diagnosis of CLL Rai stage II (Binet stage B), with Eastern Cooperative Oncology Group performance status zero. A 'wait and watch' approach was adopted initially until mid-2018 when the patient started to report fatigue and absolute lymphocyte count doubled in less than 6 months. Owing to limited resources, the patient was given weekly intravenous rituximab (500 mg) but developed herpes zoster infection after two cycles. Treatment was changed to chlorambucil (8 mg once daily) and prednisolone (20 mg once daily) for 10 days per cycle, repeating every 28 days, with acyclovir prophylaxis.

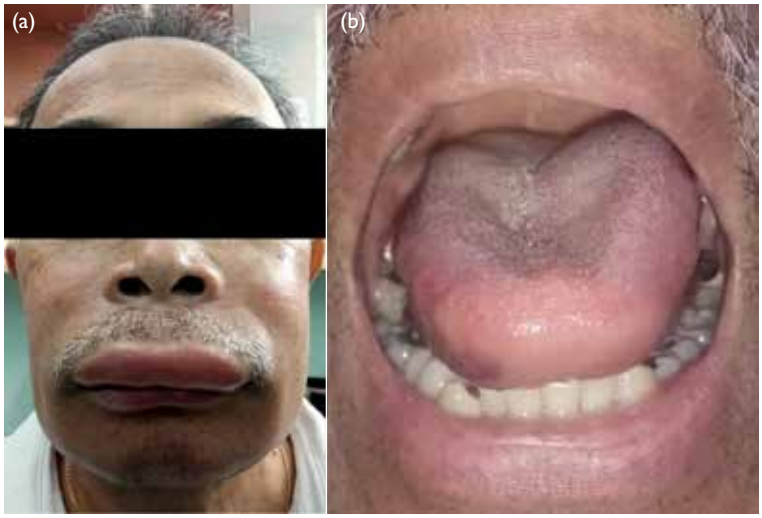

FIG 1. (a, b) Photographs showing 60-year-old man with angio-oedema of the lips and tongue

At 1 year after this treatment started, the patient presented with an acute event of angio-oedema that began as a tingling around his face and mouth similar to a bee sting and swelling of his lips and tongue (Fig 1), sparing the larynx, abdomen, extremities, and genital involvement. There were no identifiable inciting episodes. He denied intake of angiotensin-converting enzyme inhibitors, traditional medications, or over-the-counter drugs. He had no history of atopy or angio-oedema.

The patient remained well until early 2020 when he presented with similar episodes of angio-oedema that recurred on three occasions. A complete workup revealed a C1 esterase inhibitor antigen level of 4 mg/dL (reference 19-37 mg/dL) with function being 9% (reference <66%). Complement C1q level measured using radial immunodiffusion assay was undetectable with low complement 3 and 4 [0.29 g/L (reference value 0.9-1.8 g/L), <0.02 g/L (reference value 0.15-0.45 g/L), respectively]. Owing to restricted resources, anti-C1 inhibitor antibodies and monoclonal component isotypes were unavailable.

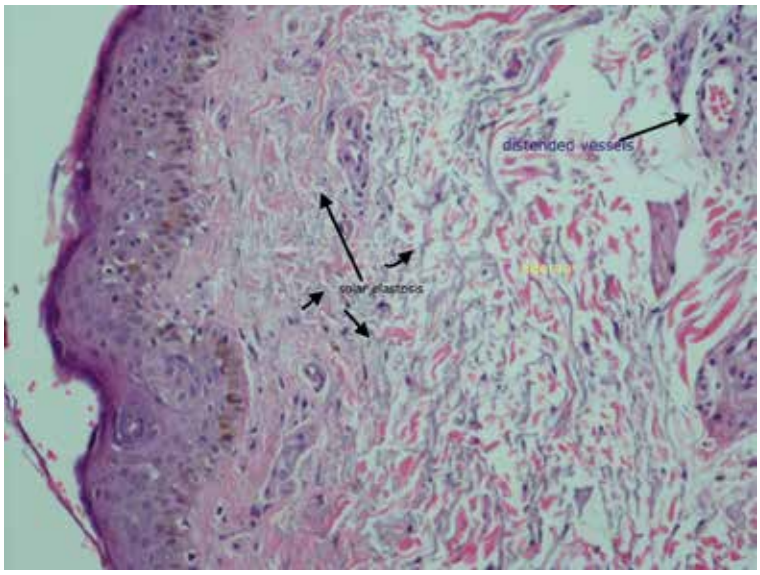

FIG 2. Skin punch biopsy showed solar elastosis in background of prominent oedema (H&E stain, ×200)

Autoimmune screening (antinuclear antibody and rheumatoid factor) and serum cryoglobulin were negative. Skin biopsy showed features of angio-oedema without atypical lymphocytes (Fig 2). During the fourth acute attack of angio-oedema, the patient was given tranexamic acid and danazol and symptoms completely resolved within 24 hours.

The overall clinical manifestations and laboratory findings were consistent with the diagnosis of acquired angio-oedema due to C1 deficiency in association with CLL. We decided to initiate chemotherapy—rituximab, cyclophosphamide, vincristine, and prednisolone. After two cycles, the patient developed urticaria vasculitis over his limbs that responded to cetirizine and resolved completely after completing six cycles of chemotherapy. C1 esterase inhibitor functional assay normalised. He remained free of any recurrent angio-oedema and urticaria during the 1-year follow-up period. He was able to resume work and could live independently.

Discussion

Angio-oedema can be hereditary or acquired. The latter often presents after the fifth decade of life with no family history.[1] Symptom onset and absence of family history led to a diagnosis of acquired angio-oedema in our patient due to C1 esterase inhibitor deficiency. The median time to diagnosis is reported to vary between 10 months and 10 years.[2] Our patient was diagnosed 9 months after symptom onset and during the third episode of angio-oedema. To the best of our knowledge, only about 20 cases of CLL have been reported to be associated with angio-oedema.[2] Many diseases are reported to be associated with acquired angio-oedema, with lymphoproliferative disorders and B-cell malignancies the most common.[3]

In acquired angio-oedema, C1 esterase inhibitor protein level is decreased due to excessive consumption, or may be dysfunctional due to the presence of antibodies against C1 inhibitor, leading to defective inhibition of the complements and kinin system. This results in exaggerated response in the classic complement pathway and production of bradykinin leading to angio-oedema, in which C1q and C4 level is low, as in our case.[2] Our patient also developed urticaria vasculitis. This was likely due to C1q depletion and low complement, as previously reported.[2] Urticaria vasculitis, which likely involves tumour-associated immune complexes, has been described as a rare association with haematological malignancy.[4] The achievement of disease remission led to resolution of both angio-oedema and urticarial vasculitis in our case.

Our patient demonstrated a kappa-restricted serum FLC with the summated FLC being 112 mg/L, confirming the monoclonal nature of serum FLC. Studies have shown that serum FLC may be elevated in almost 50% of patients with CLL. This finding is an adverse prognostic factor for time to treatment and overall survival.[5]

The mainstay of treatment for acute acquired angio-oedema includes C1 esterase inhibitor concentrate from human plasma or recombinant C1 inhibitor concentrate.[3] Nonetheless these products are not widely available in most healthcare facilities, including our centre where fresh frozen plasma is a reasonable alternative, although not without potential risks. Long-term prophylactic treatment with antifibrinolytic agents and danazol has been shown to be equally efficacious,[2] with a recommendation to avoid the former in the presence of thromboembolic risk factors.[2] It is vital to treat the underlying disease to prevent acute attacks, regardless of the treatment options.[2] Our patient has had no further attacks of angio-oedema after receiving rituximab, cyclophosphamide, vincristine, and prednisolone chemotherapy. This is in concordance with the literature that reports resolution of angio-oedema after treatment of the underlying malignancy.[4]

Our case highlights the challenge posed in managing a patient with CLL and atypical features. Clinical suspicion should be heightened in patients who present with recurrent episodes of angio-oedema. Treating the underlying malignancy often leads to complete resolution of symptoms.

Author contributions

Concept or design: ASO Tang, TS Leong, LP Chew.

Acquisition of data: ASO Tang, JTH Lee, QY Wong, ST Yeo.
Analysis or interpretation of data: JTH Lee, QY Wong, ST Yeo.
Drafting of the manuscript: ASO Tang, TS Leong, LP Chew.
Critical revision of the manuscript for important intellectual content: All authors.

Conflicts of interest

The authors declare that they have no conflict of interest or financial disclosure.

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Ethics approval

This article does contain studies with human participants and was registered via National Medical Research Register Malaysia with a Research ID of NMRR-20-1666-56020. The patient(s) provided written informed consent for all treatments and procedures and consent for publication.

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