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Spontaneous remission of chronic lymphocytic leucemia in a patient with SARS-CoV2

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ABSTRACT

Although novel therapies have improved the treatment outcome of patients, chronic lymphocytic leukaemia (CLL) is still considered incurable. Recently, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), causing coronavirus disease 2019 (Covid 19), emerged in late 2019, and it has posed a global health threat. In a limited number of cases, it has been shown that some lymphoma types spontaneously regress after SARS-CoV2 infection suggesting that the infection can trigger de immune system against the tumour cell. Cross-reactivity of pathogen-specific T cells with tumour antigens and natural killer cell activation can be the possible mechanism of this hypothesis.

1. Introduction

Chronic lymphocytic leukaemia (CLL) is a very frequent B cell malignancy of the elderly characterized by the accumulation of mature CD5, CD19, CD20, CD23, and kappa and lambda immunoglobulin light chain double-positive B cells in peripheral blood and lymphoid organs [1]. SARS-CoV2, like most of the cytopathic viruses, has the ability to induce injury and death of infected cells and tissues as part of the viral replication cycle. The main effects of the virus are attributed to a heightened inflammatory response and hyperactivation of T cells and increased production of inflammatory cytokines including interleukins (IL-6, IL-1), tumour necrosis factor-α (TNF-α) and interferon-γ (INF-γ), which triggers an inflammatory cascade [2]. Here we present an unusual case of spontaneous remission after SARS-CoV2 infection in a patient with chronic lymphocytic leukaemia who did not receive any previous treatment.

2. Case

A 67-year old male with a history of asymtomatic untreated Rai stage 1 CLL for 8 years, hypertension and diabetes, presented to the emergency department with a 2-day history of shortness of breath and fever. The patient didn't have the typical cytogenetics characteristics of CLL, such as trisomy 12 and the deletions of 11q22.3, 13q14 and 17p13. Physical examination revealed multiple lymphadenopathies, the largest of which was 20 × 10 mm, in bilateral neck and axillary regions. Rhonchi and fine crackles were heard in the middle and lower zones of the lungs. Laboratory investigations showed white blood cell count of 30,4 × 10^3/μL (Reference: 4,2–10,6 10^3/μL), neutrophil 2 × 10^3/μL (Reference: 2,6–9 10^3/μL) lymphocyte 26,5 × 10^3/μL (Reference: 0,6–3,4 10^3/μL) haemoglobin of 13.4 g/dL (Reference: 14,1–18,1 g/dL) and platelet of 237 × 10^3/μL (Reference: 140–400 10^3/μL).

In peripheral blood flow cytometry, proliferation of monotypic B lymphocytes, which constitute 89% of lymphocytes and display CD19+, CD 20+, CD22+, CD5+, CD23+, HLA DR+ immunophenotypes, was detected (Fig.1a). Thorax computer tomogrophy (CT) revealed that multiple enlarged lymphadenopathies, the largest of which was 30 × 17 mm in mediastinal, bilateral hilar, subcarinal regions and bilateral pleural effusion reaching approximately 10 mm in thickness and ground-glass opacities associated with bilateral and multilobar consolidation foci, predominantly peripheral, some with a rounded aspect. Mediastinal lymphadenopathies are shown in Fig. 2a. Diagnosis of Covid 19 was confirmed via polymerase chain reaction (PCR) of a nasopharyngeal (NP) swab. The patient was not previously vaccinated against

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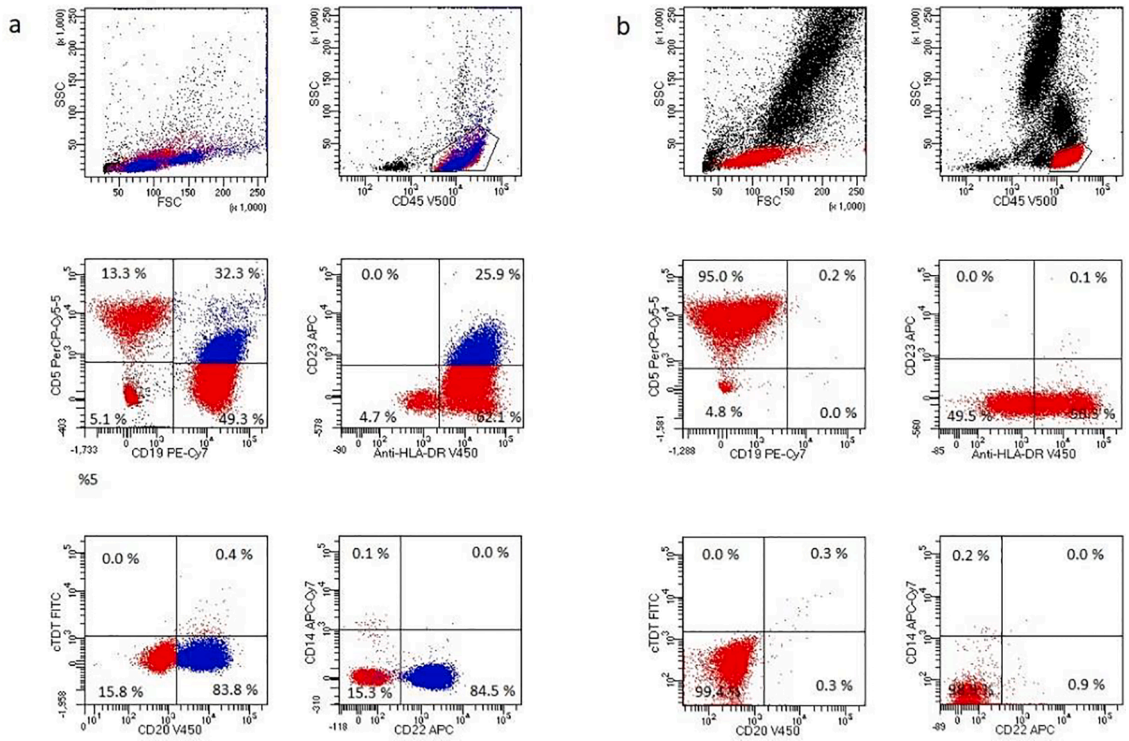

Fig. 1. **(a)** shows the flow cytometry at the time of admission. Proliferation of monotypic B lymphocytes, which constitute 89% of lymphocytes and display CD19+, CD 20+, CD22+, CD5+, CD23+, HLA DR+, immunophenotypes, was detected. **(b)** shows the flow cytometry 1 year after discharge. Proliferation of monotypic B lymphocytes which compatible with CLL, was not detected.

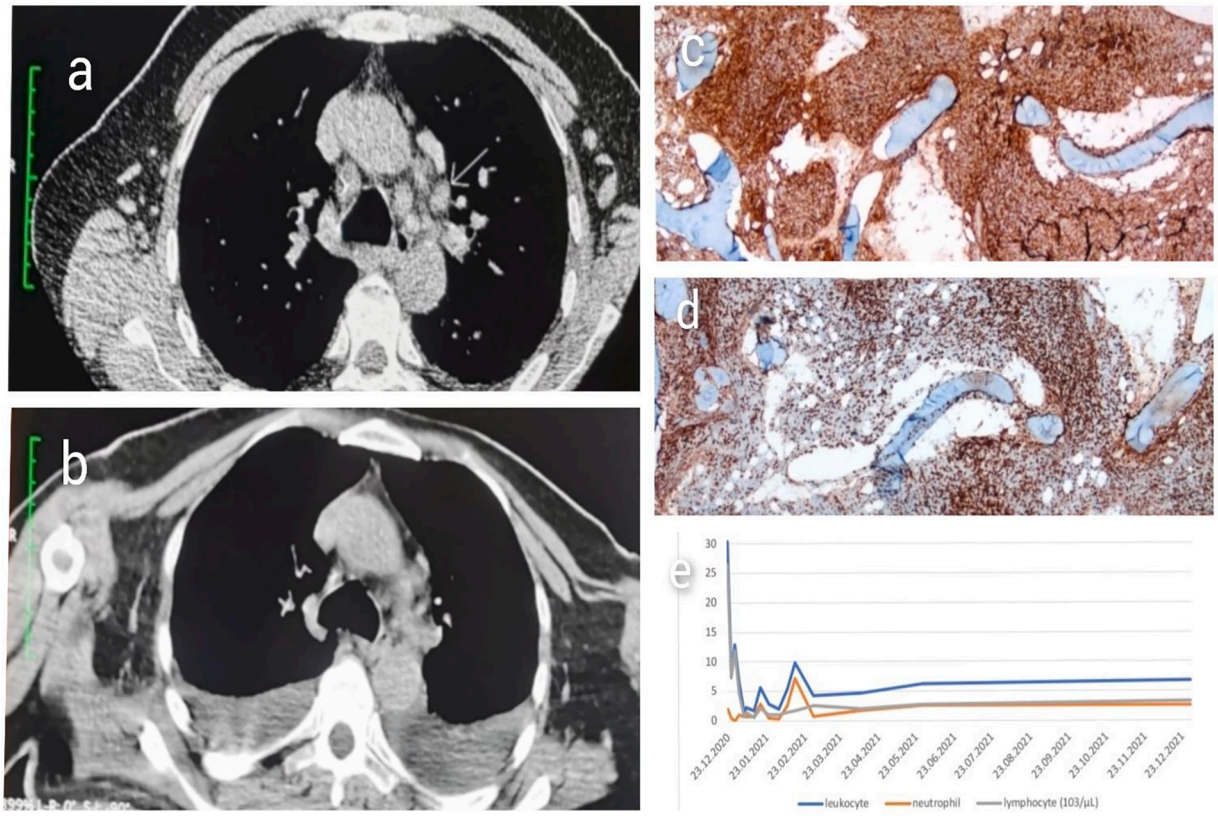

Fig. 2. **(a)** Multiple enlarged lymphadenopathies, the largest of which was 30 × 17 mm in mediastinum. **(b)** PET CT revealed regression of mediastinal lymphadenopathies, after recovery of Covid 19. **(c)** CD4+ T lymphocyte infiltration in bone marrow. **(d)** CD8+ T lymphocyte infiltration in bone marrow. **(e)** leukocyte graph.

Covid 19. On the 7th day of admission, the patient developed pancytopenia and high fever. Laboratory investigations showed white blood cell count of 1,5 × 10^3/μL, neutrophil 0,8 × 10^3/μL, lymphocyte 0,2 × 10^3/μL, haemoglobin of 9.9 g/dL and platelet of 27 × 10^3/μL. The patient was treated with favipiravir for ten days and remained hemodynamically stable. Two weeks after admission, the patient had tested negative for SARS-CoV2 but no improvement was observed in cytopenias and prolonged fevers >38 °C. No secondary infections were documented. Due to etiology of fever is unknown, multiple treatments including intravenous immunoglobulin and broad-spectrum antibiotics were used for febrile neutropenia. Fever didn't respond to any medication and last longer than a month. To evaluate the etiological cause of pancytopenia bone marrow biopsy was performed. Bone marrow cellularity was 80%. Erythroid and myeloid series cells in a normal distribution were observed. Lymphocyte phagocytosis was observed in a few megakaryocytes. Lymphoid cell infiltration with T lymphocyte phenotype was noted in the bone marrow biopsy. Lymphoid cells were negative for CD10, CD20, CD23, siklin D1, SOX-11, Tdt, perforin and PD-1. Bone marrow biopsy showed diffuse infiltration of both CD4+ and CD8+ T lymphocytes. CD4+ T lymphocyte infiltration was approximately two times greater than CD8+ T lymphocyte infiltration (Fig. 2c and 2d). Two months after admission, fever dropped and the patient was discharged to home. Three months after discharge, it was observed that the cytopenias of patient improved. To evaluate disease status, bone marrow aspiration biopsy, positron emission tomography (PET-CT) and flow cytometry were performed. Bone marrow biopsy was normocellular and infiltration was not distinguished. On PET CT, normal uptake of fluoro-2-deoxy-D-glucose (FDG) occurs in whole body and no characteristic hypermetabolic focus that could be compatible with malignancy was detected. PET CT revealed regression of mediastinal lymphadenopathies (Fig. 2b) In peripheral blood flow cytometry, proliferation of monotypic B lymphocytes which compatible with CLL, was not detected (Fig. 1b). Lymphocytosis and clinical presentations including lymphadenopathy, hepatomegaly and splenomegaly were not observed in the long-term follow-up of patient. leucocyte graph is shown in Fig. 2e. The patient is still in complete remission 12 months after recovery of Covid 19.

3. Discussion

CLL is characterized by clonal proliferation and accumulation of mature B-lymphocytes [1]. We considered spontaneous remission after Covid 19 infection in our case due to absence of monotypic B cell proliferation. The immune response against SARS-CoV2 begins with the process of introducing viral antigens with the help of antigen-presenting cells played by major tissue histocompatibility complex (MHC), which then presents the virus antigens to CD8+ cytotoxic T lymphocytes [3].

Cytotoxic T lymphocytes are a specialized population of immune cells capable of selectively killing infected cells and consequently eliminate viruses. Usually, CD8+ T lymphocytes mediate adaptive cytotoxic T cell responses [3]. SARS-CoV2 infection is associated with a reduction in CD8+ and CD4+ T lymphocytes. One prominent cause of lymphopenia may be an enhanced migration of T cells into infected compartments [4]. Despite the lymphopenia, expanded virus-specific CD8+ and CD4+ T cells can be detected in Covid 19 patients [5]. Similarly, in our case, concurrent infiltration by CD8+ T cells and CD4+ T cells infiltration was observed in the bone marrow assessment while there was lymphopenia in the peripheral blood.

CD4+ T cells play a central role in orchestrating the immune response to cancer. Essentially, CD4+ T cells recognize peptides presented on MHC class II molecules expressed primarily on antigen-presenting cells. Although most tumour cells do not express MHC class II molecules, CD4+ T cells can effect an antitumour response in the absence of CD8+ T cells by secreting cytokines, such as interferon-γ or by activation and recruitment of effector cells such as macrophages and eosinophils [6]. However, the main role of CD4+ T cells in the immune response to cancer is to prime CD8+ cells and maintain their proliferation.

The main effects of the virus are attributed to a heightened inflammatory response and hyperactivation of T cells and increased production of inflammatory cytokines including interleukins IL-6, IL-1, TNF-α and INF-γ [2]. In one study, it has been shown that cytokine levels at the tumour site were several fold higher than in the circulation, suggesting their important role in the maintenance of tumour infiltrating lymphocytes in an activated state against the tumour [7]. Based on these datas we can say that the anti-tumour effects of proinflammatory cytokines may explain the spontaneous remission in our patient with CLL. In addition, prolonged fever in our case can be attributed to excessive production of proinflammatory cytokines. On the other hand, if we had used tocilizumab, anakinra or another anticytokine agent to suppress the excessive immune response, spontaneous remission might not be achieved.

Tumour immunogenicity is determined by the mechanism of cell death that can be apoptotic or necrotic. Apoptosis is a major means of killing tumour cells by the immune system that involves T and NK cells. Thus, if the inherent property of tumour cell killing by apoptosis could somehow be accelerated, it would provide great therapeutic potential. NK cells do not require processing and presentation of antigen along with MHC molecules. In consequence, NK cells kill targets that have managed to escape T-cell mediated killing. There have been some studies demonstrating the sensitivity of tumours to lysis by NK cells in vitro and in vivo [7].

Although cross-reactivity to self-antigens or poly-reactivity is strongly selected against during T- and B-cell development, T cell receptors (TCRs) have a tendency to be cross-reactive to different peptide-MHC complexes. T-cell cross-reactivity can be either beneficial, by increasing the chances that any given pathogen- or tumour-derived peptide is recognized by a T cell. This issue of cross-reactivity is relevant given the data indicating that spontaneous regression of tumours is often associated with bacterial, fungal, viral or protozoal infections [8].

In a limited number of studies, it has been shown that some lymphoma types spontaneously regress after Covid 19 infection [9–10]. However, spontaneous remission was not reported in CLL.

4. Conclusion

Based on our case and the literature the possible mechanisms of action include cross-reactivity of pathogen-specific T cells with tumour antigens and natural killer cell activation by inflammatory cytokines produced in response to SARS-CoV2. As the number of such cases increase, we will need more research to better understand the mechanism of oncolytic effect of Covid 19.

Informed consent

The patient signed a written informed consent form for his medical data to be used in medical articles and journals.

CRediT authorship contribution statement

Hale Bülbül: Writing – review & editing, Conceptualization. **Hamza Ekmel Nazlı:** Investigation, Data curation. **Aybüke Olgun:** Supervision, Visualization. **Alper Togay:** Investigation, Data curation. **Dudu Solakoğlu Kahraman:** Project administration, Conceptualization.

Declaration of Competing Interest

The authors declare no conflicts of interest

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