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Case Report: B-cell Acute Lymphoblastic Leukemia/Lymphoma Following Castleman Disease

Meng Zhao[1]†, Qirui Li[2]†, Tao Jiang[3]*, Dafei Xu[4,5], Qian Ma[3], Lunfei Tao[3], Ziwei Miao[5]

[1]Department of Epidemiology and Health Statistics, School of Public Health, Southeast University, Nanjing 210000, Jiangsu Province, China

[2]Experimental Teaching Center of Basic Medical Science, School of Medicine, Nanjing University of Chinese Medicine, Nanjing 210000, Jiangsu Province, China

[3]Jiangsu Provincial Second Chinese Medicine Hospital, The Second Affiliated Hospital of Nanjing University of Chinese Medicine Nanjing, Nanjing 210000, Jiangsu Province, China

[4]Tiankang Hospital, Chuzhou 239300, Anhui Province, China

[5]Department of Neurology, Tianyou Hospital of Tongji University, Shanghai 200000, China

†These authors contributed equally to this work and share the first authorship.

***Corresponding author:** Tao Jiang, kiangtao@njucm.edu.cn

Abstract: Castleman disease (CD) is a rare nonmalignant lymphoproliferative disorder presenting systemic symptoms such as fever, night sweats, fatigue, anemia, effusions, and multifocal lymphadenopathy. The etiology of CD has not been clarified to date. The coexistence of CD with B-cell acute lymphoblastic leukemia/lymphoma (B-ALL/LBL) has been rarely reported. Although the pathogenesis remains unclear, this association probably reflects an incidental and fortuitous finding rather than the alteration of a common pluripotent stem cell precursor. Herein, the study reports on one case of CD coexisting with B-ALL/LBL and elucidates the underlying mechanism of pathology in some aspects.

Keywords: Castleman disease; B-cell acute lymphoblastic leukemia; Case report

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1. Introduction

Castleman disease (CD) is a rare lymphoproliferative disorder first described 60 years ago by Dr. Benjamin Castleman [1]. It is a group of clinicopathologic disorders with similarities in histopathology and clinical features found in hematology, oncology, rheumatology, and virology [2]. A large number of case reports and reviews have examined the clinical manifestations [3], pathologic features [4], and treatment [5] of this complicated condition in recent decades. One of the key characteristics of CD is its heterogeneous nature, making diagnosis and treatment challenging. It can present as either a localized or systemic disease, and its symptoms can range from mild to severe. CD is also known to be linked to other underlying medical conditions, such as human immunodeficiency

virus (HIV) infection, and certain forms of cancer. Treatment options for CD depend on the specific form and severity of the disease and may involve the use of immunosuppressive drugs, biological agents, and in some cases, surgical intervention [6]. The management of CD often involves a multidisciplinary approach, with collaboration between specialists in different fields to provide the best possible care for patients [7–9].

B-cell acute lymphoblastic leukemia/lymphoma (B-ALL/LBL) is a common type of blood cancer [10,11]. It is primarily a childhood disease, but relapsed pediatric and adult patients have poor prognoses [12]. It is characterized by the rapid overproduction of malignant immature hematopoietic cells that inhibit normal hematopoiesis in the bone marrow and invade peripheral organs [13,14]. Studies have shown that CD patients have a significantly higher risk of severe allogeneic cytopenia, multi-organ failure, and lymphoma [15]. There are still 10% of patients who fail to respond to initial treatment and 40% to 70% who relapse despite improvements in treatment over the past 30 years [16].

It is quite a rare event for CD to progress to B-ALL/LBL, which belongs to different pathogenic cell types. This case report first reports a case of a CD patient who progressed to B-ALL/LBL and was treated with thalidomide and retinoic acid, respectively.

2. Case report

2.1. Case description

The patient, a female, presented with abdominal distension, loss of appetite, general weakness, and palpitations in 2002 with no obvious cause. She was treated for hepatitis and gastritis at local hospitals (Tianchang Hospital, Anhui Province, and Tiankang Hospital, Tianchang City, Anhui Province) without obvious abnormalities. Blood pressure was 160/100 mmHg, the abdominal circumference was 83 cm, blood tests were normal, and an MRI image of the upper abdomen showed “enlarged liver and spleen with signs of ascites in the abdominal cavity; MRV of the upper abdomen showed that the inferior vena cava was slightly distorted and flattened in the hepatoportal region, suggesting cirrhosis with massive ascites.” The diagnosis of Buga syndrome was considered, and he was admitted to Jiangsu Provincial People’s Hospital, where he was proposed to undergo vascular dissection. The lymph node biopsy was performed because of the enlarged lymph nodes in the neck found 2 d before the operation, and the pathology on April 6, 2004, showed that the vascular giant follicular lymphoid tissue was hyperplastic, further immunotyping confirmed the diagnosis of CD. 2 courses of chemotherapy were given to the CHOP regimen, and the lymph nodes subsided, and the patient was transferred back to Tiankang Hospital for further chemotherapy. After the 3rd course of CHOP, the patient was discharged from the hospital on August 1st, 2004, and switched to immunotherapy: alpha-interferon (300 U subcutaneous injection) twice a week for 6 months. However, the patient’s condition was unstable during immunotherapy, and ascites persisted and worsened from time to time. 6 months later, following 7 courses of the CHOP regimen, hypoproteinemia developed. At the same time, human albumin was given for long-term maintenance (20 g each time), but the results were poor, and ascites still existed as well as a drug reaction - peripheral neuritis. The above conditions made the treatment difficult to carry out.

On March 25, 2006, this patient was treated with a trial of thalidomide (no CHOP-related treatment). After one month of treatment, the patient’s ascites had significantly decreased, the spleen and liver had significantly decreased in size, and the patient’s condition had improved steadily. During thalidomide administration, the patient complained of weakness, loss of appetite, and occasional manifestations of peripheral neuritis, but they were relatively mild, and no special treatment was given. The patient’s cumulative chemotherapy drug dosage: total immunosuppressant (CTX) 7.4 g, total vincristine (VCR) 14.0 mg, total vincristine 90 mg, total human albumin 3000 g. On March 25, 2006, he was given 300 mg daily (100 mg tid) of Response Stop. Along 47 months, total

dose of Reactive Discontinuation: 391,500 mg. (After stabilization of the disease, the patient missed and refused doses due to side effects associated with thalidomide: malaise, peripheral neuritis, and constipation, which decreased after education).

Table 1. Patient treatment time points

Date	Patient's condition
Early 2002	Onset of disease
2004	CHOP-based regimen 10 times
March 25, 2006	Thalidomide 300 mg/d
July 2009	Thalidomide dosage reduced to 150 mg/d
February 2010	Discontinue thalidomide

After 7 years of discontinuation, on April 22, 2017, the patient had recurrent leukopenia, during which he was treated with recombinant human granulocyte-stimulating factor injection for leukocyte elevation. On February 6th, 2023, the patient was diagnosed with B-ALL/LBL by bone marrow cytology (2.3), bone marrow biopsy (2.4), immunohistochemical markers, immunophenotyping (2.5), and pathology (2.6). Patients were treated using GM-CSF+All-trans retinoic acid (ATRA) with more favorable results. In addition, after treatment with translational medicine, the patient's condition improved and persisted for 2 two years.

Table 2. Changes in patients' leukocyte concentrations during treatment

Test date	Leukocyte concentration (*10^9/L)	Main diagnosis	Main treatment methods
September 24, 2017	3.00		
April 25, 2018	3.10		
October 15, 2018	2.00		
March 13, 2019	2.00		
December 06, 2020	3.24		
December 08, 2020	2.27		
December 10, 2020	1.82	Leukopenia + CD	
December 16, 2020	2.33		Thalidomide
December 17, 2020	1.79		
December 19, 2020	2.93		
December 21, 2020	5.20		
December 25, 2020	1.75		
December 29, 2020	1.79		
January 02, 2021	1.15		
February 01, 2021	2.73		
February 02, 2021	10.07	B-ALL/LBL	
February 05, 2021	8.42		GM-CSF+All-trans retinoic acid (ATRA)
September 18, 2022	3.56		

2.2. Bone marrow cytology

The patient underwent bone marrow cytology (**Figure 1**). On December 14, 2020, the results showed active nucleated cell proliferation and detected a class of morphologically similar atypical lymphocytes (nature to be determined) in 32.5% of the cases as well as altered granulomatous morphology. On May 3, 2021, and on October 8 of the same year, bone marrow cytology results indicated active nucleated cell proliferation and occasional atypical lymphocytes. However, On September 21, 2022, bone marrow cytology results indicated that nucleated cell proliferation was markedly active, and abnormal cells were detected in approximately 60% of cases.

On October 2, 2022, the patient underwent bone marrow histopathology (**Figure 2**) and the diagnosis was that the patient had characteristics of leukemia. Hematopoietic tissue hyperplasia is active, with a volume of about 50–60%, and adipose tissue hyperplasia is reduced. Granular, red, megakaryocyte proliferation is reduced, rare; naïve cell proliferation, medium cytosol, cytoplasm is less, the nucleus is round or slightly irregular, diffuse or focal distribution; a little fibrous tissue proliferation is seen scattered.

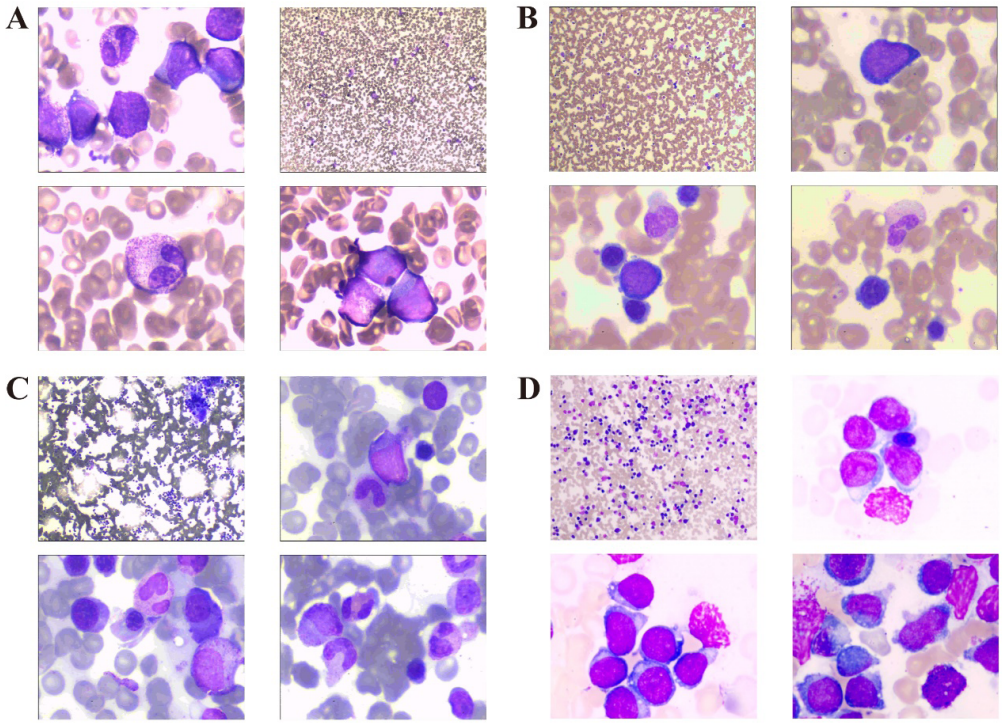

Figure 1. Bone marrow cytology results on different dates. (A) December 14, 2020; (B) May 3, 2021; (C) October 8, 2021; (D) September 21.

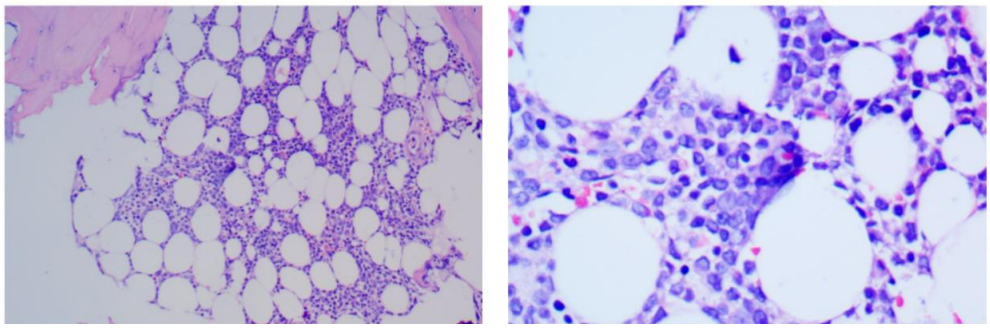

Figure 2. Bone marrow biopsy.

2.3. Immunophenotyping

On October 4, 2022, the patient was immunophenotyped by flow cytometry (**Figure 3**). Gate analysis was set up on a CD45/SSC dot plot, and a population of abnormal cells was visible in the distribution area of the primitive extension towards CD45-negative, not demarcated from nucleated erythrocytes, totaling approximately 83% of the nucleated cells, which positively expressed HLA-DR, CD10, CD19 (dim), CD33, CD34, CD58, CD123, cCD79a, and TdT. Myeloid proliferation was markedly suppressed. The results showed that the patient was compatible with the immunophenotype of B-ALL/LBL. On February 8, 2023, the patient was again immunophenotyped by flow cytometry and the diagnosis remained B-ALL (**Figure 4**).

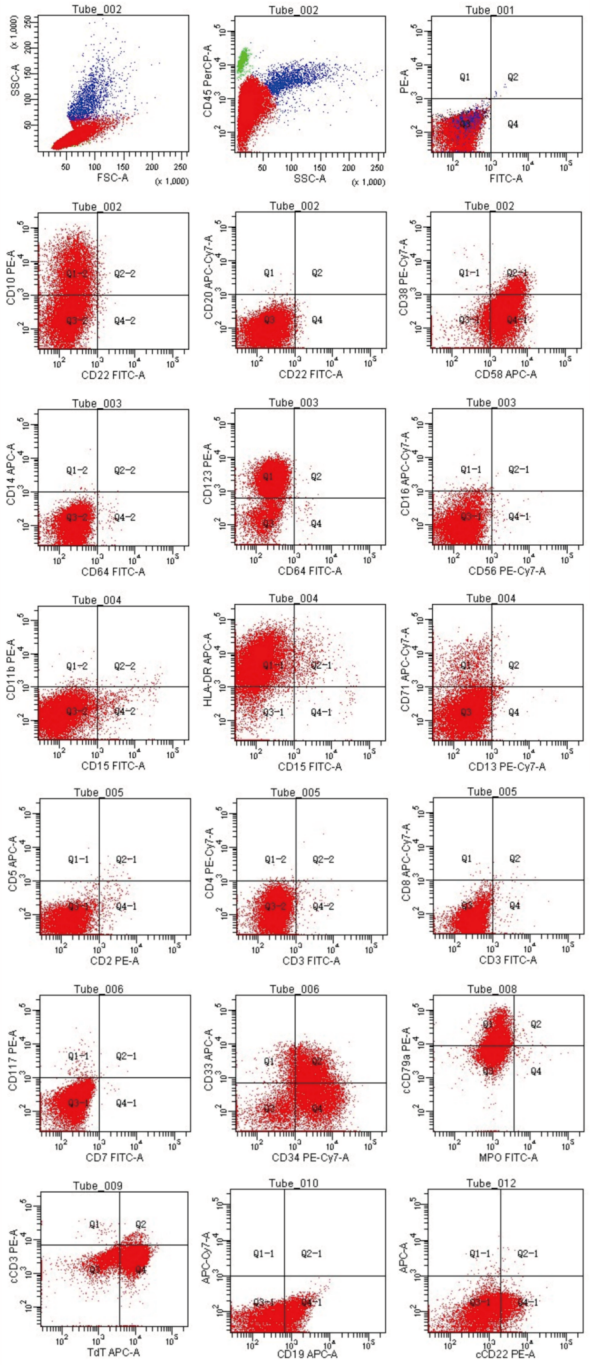

Figure 3. Immunophenotyping (October 4, 2022).

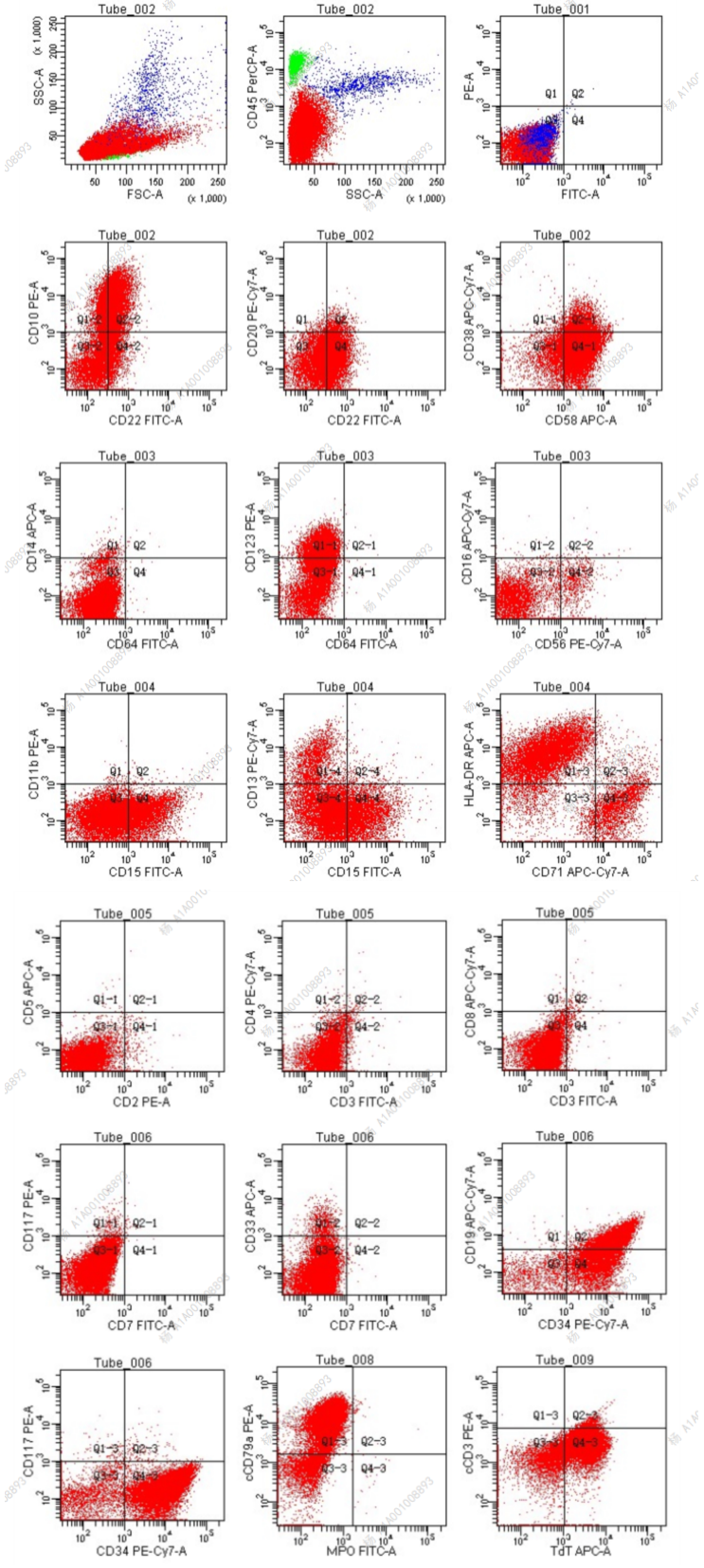

Figure 4. Immunophenotyping (February 8, 2023).

2.4. Pathology

On February 6, 2023, the patient underwent a bone marrow biopsy for pathology (**Figure 5**). The results showed that the patient had a tumor of the lymphohematopoietic system, which was considered to be B-ALL.

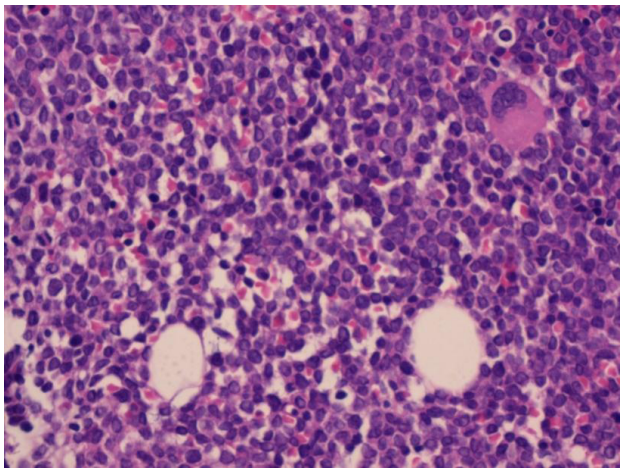

Figure 5. Bone marrow biopsy for pathology.

3. Discussion

The pathogenesis of CD is unknown and can affect the growth of B lymphocytes across multiple medical disciplines, including hematology, oncology, rheumatology, and virology. Patients with CD may present with symptoms such as fever, night sweats, fatigue, anemia, and lymphadenopathy, which are caused by elevated levels of IL-6 and other pro-inflammatory cytokines. Three main therapeutic approaches have been used to manage CD, including anti-inflammatory and immunosuppressive therapies, elimination of cytotoxic treatments that cause hypercellularemia, and blocking of IL-6 signaling with mAbs [17]. Glucocorticoids are also commonly used, but their effects are often limited and temporary, with symptoms frequently reappearing as the dose is reduced. In severe cases, autologous stem cell transplantation has shown good results [18]. Recent studies have shown that multicentricity, histopathological type, and anemia are important risk factors for reducing progression-free survival [19]. In 2004, there was no established treatment protocol for CD, and treatment was performed concerning that of lymphoma, with a brief period of stabilization after CHOP and add-on therapy, followed by persistent and progressive decreasing hypoproteinemia, and thoracoabdominal fluid.

Thalidomide is an effective immunomodulator that inhibits the production of a variety of cytokines, including IL1, IL6, IL12, tumor necrosis factor-α, and VEGF. It has been shown that thalidomide is effective in relieving CD [20–22]. Meanwhile, in the year 2004, considering that there was no readily available reference treatment protocol here, after full communication with the family, the study used thalidomide for treatment. After the use of thalidomide, the dose of albumin was reduced, and after half a month, ascites were reduced, and for about a month ascites disappeared, and the treatment achieved good results. There is no treatment-related side effects occurred, and the patient showed sustained clinical improvement.

Autoimmune diseases are a recognized risk factor for malignant lymphoma. It has been shown that autoimmune diseases such as dry syndrome, systemic lupus erythematosus, rheumatoid arthritis, autoimmune thyroiditis, celiac disease, and herpes-like dermatitis are associated with an increased risk of malignant lymphoma [23-24]. However,

the exact mechanism has not been clarified and may be due to immune dysregulation with abnormal immune responses and reduced tumor immune surveillance. It has been suggested that CD has an intrinsic tendency to progress to lymphoma, but the molecular mechanisms involved in its transformation remain unclear [25]. The autoimmune manifestations of CD patients and the discovery of auto-reactive T cells and pathogenic auto-antibodies would support its being an autoimmune disease [26]. From these results, Castleman's disease is likely the underlying disease that triggers B-ALL. The association between it and B-ALL/LBL is complex and the relationship between CD and macrophages is still unknown. Several studies have speculated that Castleman disease is likely to be the disease underlying the immune factors that trigger B-ALL. Through the lens of translational medicine, the patient transformed from CD to B-ALL. After patients were diagnosed with B-ALL, the study first treated them based on the CHOP regimen, however, the results were not satisfactory. At the same time, the high cost of CHOP-based treatment options makes it difficult for patients' families to afford the high cost of treatment. After full communication with the patient's family and also in conjunction with some cases of translational medicine [27], the treatment plan was switched.

Macrophages are one of the important effector cells that perform immunosurveillance functions in the body and can kill tumor cells extracellularly by secreting and releasing soluble cytotoxic factors. Macrophages are highly versatile and heterogeneous cells that play a key role in both innate and adaptive immunity. In response to environmental stimuli, macrophages can differentiate into two subpopulations, classical (M1) or alternative (M2) activated macrophages. M1 polarization is characterized by the ability of macrophages to produce high levels of pro-inflammatory cytokines, increased expression of co-stimulatory molecules, and increased efficiency of antigen presentation, which supports its function of clearing tumor cells. In contrast, M2 macrophages mediate immunomodulatory functions through the production of anti-inflammatory cytokines and higher levels of scavenger mannose receptors and mainly exhibit immunosuppressive properties [28–30]. On the one hand, the M1/M2 polarization state can disrupt the balance of lymphocyte subpopulation differentiation or alter their tolerogenic clearance [21–33], leading to the pathogenesis of autoimmune diseases [34–36], and immune defects of genetic, iatrogenic or infectious origin may play an important role in CD development [37]. Burrer *et al.* (2016) found that Kaposi's sarcoma-associated herpesvirus (KSHV) is associated with CD, while Bhaskaran *et al.* (2017) found that KSHV infection induces M2 polarization [38,39], which suggested M2 polarization may contribute to the occurrence and development of CD. On the other hand, accumulating evidence suggests that M2 polarization may contribute to a variety of cancers, including lung cancer, pancreatic cancer, breast cancer, etc. and may promote cancer metastasis [40–42]. In addition, *in vitro* experiments have also confirmed that promoting M1 polarization can induce B-ALL cells apoptosis [43]. Although there is currently a lack of convincing *in vivo* experiments and the role of tumor microenvironment (TME) in B-ALL is still poorly understood, the above research can still make polarization become a potential research direction for the connection between CD and B-ALL.

M1 macrophages exhibit good anti-tumor properties by antigen presentation to T cell receptors and recruiting $CD8^+$T and NK cells to the TME, while M2 macrophages are associated with poor prognosis in many tumors. In the early stages of tumors, due to the chronic inflammatory environment in TME, the proportion of M1 macrophages is relatively high. But as tumor cells secrete a large amount of M2-like cytokines (such as IL-10, CCL-2/3/4/5/7/8, CXCL12, VEGF, etc.), M2 macrophages begin to rapidly increase [44]. Although most M2 macrophages can secrete anti-inflammatory cytokines such as IL-10, but to its ability to divert cytotoxic T cells to kill malignant cells, the pro-inflammatory nature of the TME has not impacted [45]. However, when the transformation between M1 and M2 phenotypes occurs whether macrophages have an antitumoral ability to

eradicate aberrant malignant cells before the formation of tumor still remains unclear [46]. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is an autocrine and a paracrine cytokine. It stimulates the growth, differentiation, and function of normal and leukemic myeloid progenitors, which activate immune system cells [47–49]. GM-CSF augments both innate and adaptive immunity by facilitating the growth and function of neutrophils, macrophages, monocytes, and dendritic cells [50,51]. GM-CSF can induce macrophage polarization toward M1. GM-CSF has also been implicated in leukemogenesis, although altered regulation of GM-CSF expression in myeloproliferative disorders is complex. In this case, significant efficacy was observed by using GM-CSF to increase leukocyte levels.

In the recent years, many malignant tumors are associated with autoimmune diseases. This is usually believed to be related to chronic inflammation caused by autoimmune diseases [52]. Chronic inflammation can lead to tissue and cell damage, accompanied by a certain degree of repair and fibrosis. In this cycle of destruction and regeneration, the stability of genes is disrupted, ultimately leading to malignant cell mutations. Subsequently, immune cells will recruit to malignant cells and lead to new inflammation, further leading to tumor invasion and metastasis. All-trans retinoic acid (ATRA) is a bioactive derivative of vitamin A. In general, it promotes cell maturation differentiation and apoptosis by binding to specific nuclear receptors and can be mediated by non-genomic signal pathways, such as MAPK and PKA [53]. It can reverse certain pre-cancerous cells and even cancerous cells into normal cells [54]. It has been successfully used in precancerous lesions and cutaneous T-cell lymphomas. Acute promyelocytic leukemia, promotes the maturation of primitive cells, thereby alleviating the severe bleeding associated with the disease. Hung et al. (2008) found that ATRA could exert its anti-inflammatory effects by inhibiting the production of macrophage inflammatory cytokines such as JNK-AP-1 signaling pathway expression minus iNOS, NO, and COX-2, thereby protecting against LPS-induced organismal injury [55]. Zhang *et al.* (2019) found that ATRA could also inhibit LPS-stimulated macrophage pro-inflammatory factors IL-1β, TNF-α, and iNOS production through direct activation of protein kinase, TNF-α, and iNOS production [56]. Moreover, there have been many reports regarding the cell biological effects of ATRA on human myeloma cells and a few clinical trials. Most of these reports have revealed growth inhibition by ATRA mediated by down-regulation of the IL-6/IL-6R auto/paracrine loop and upregulation of p21/Cip1[57]. However, He *et al.* (2022) found that ATRA can promote M2 polarization of macrophages in an inflammatory environment [58], so it was combined with GM-CSF to enhance its therapeutic effect.

Studies have shown a synergistic effect between ATRA and GM-CSF [59]. Treatment of human myeloblastic leukemia with ATRA in combination with GM-CSF enhances granulocytic differentiation. The study used GM-CSF to increase leukocyte levels in patients with significant efficacy. First, recent study showed that during *in vitro* ATRA and GM-CSF treatment of healthy bone marrow progenitor cells, stimulation of normal granulocytes was observed [60], possibly due to increased sensitivity to growth factors. Secondly, in bone marrow tissue cultures of patients with chronic granulocytic leukemia, ATRA inhibits the clonal expansion of stem cells. In the present case, the patient was in ineffective remission with GM-CSF and ATRA. The relapse of the disease in the middle of the process may be related to the infection with COVID-19, which made the treatment disturbed.

In addition to GM-CSF, in the subsequent analysis and reference of the case, it was found that IL-2, another immunostimulant, may also play its biological functions by inducing polarization [61] and its γ chain subunit can be well combined with FERM domains of JAK1 and JAK3, which is a hot spot for hematologic malignancies [62]. Besides, it was also found that IL-2 exerts its therapeutic value in other types of tumors by activating, stimulating the proliferation and affecting the phenotype of other immune cells, such as NK cells, DC cells and T cells [63–69].

However, related studies are mainly animal or cell experiments. Due to the species specificity of biological therapeutic agents, more studies are needed to verify their clinical value. Therefore, future research can also explore its therapeutic value in similar diseases.

To summarize the present paper, a few highlights will be listed:

(1) CD is a benign and rare lympholiferative disease;

(2) Treatment of CD with thalidomide is first reported in China;

(3) Long-term, stable control ofCD with thalidomide treatment;

(4) CD can turn into B-ALL/LBL;

(5) Treatment of B-ALL/LBL by translational medicine protocols through ATRA and GM-CSF.

4. Conclusion

In conclusion, the study reports a rare case of CD that was later found to have B-ALL/LBL, and it treated CD with thalidomide and B-ALL/LBL with retinoic acid. Future studies can not only confirm the hypothesis proposed in this case through *in vivo* and *in vitro* experiments, but also focus on the relationship between CD and macrophage polarization and the dynamic polarization of macrophages in TME. In addition, the target molecules affecting macrophage function in the disease can be analyzed by bioinformatics methods to further explore the detailed molecular mechanism of the disease and its treatment strategies.

Authors' contributions

Conceptualization – Tao Jiang, Qian Ma,

Data curation – Qirui Li, Meng Zhao

Manuscript writing – Tao Jiang, Qirui Li, Meng Zhao

Manuscript revision – Dafei Xu, Lunfei Tao, Ziwei Miao

Disclosure statement

The authors declare no conflict of interest.

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