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CASE REPORT

Spontaneous regression of chronic lymphocytic leukemia

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ABSTRACT

Immune therapy and graft-versus-tumor effect seen after allogeneic hematopoietic stem cell transplantation provide proof-of-principle of the ability of human immune system to control cancer. Spontaneous regression of cancer is another dramatic evidence of the existence of powerful immune surveillance in human body. We report a 54-year-old man with 13q14 deleted chronic lymphocytic leukemia and diffuse lymphadenopathy, who had spontaneous normalization of leukocytosis and resolution of lymphadenopathy thirteen years after the diagnosis of chronic lymphocytic leukemia. Better understanding of spontaneous regression may help elucidate body's immune response against tumor cell. This may further enhance the development of immune therapies and provide insight towards tumorigenesis.

Key words: immune surveillance, chronic lymphocytic leukemia, spontaneous regression

INTRODUCTION

Host immunity plays a critical role in both -creating a microenvironment hostile for
tumorigenicity in conjunction with tumor suppressor system as well as in propagating tumor genesis.[1] One potential window to our understanding the relationship between immunity and cancers is the phenomena of spontaneous remission which has been described in a variety of human cancers.2, 3 Regressing tumors are often found to have lymphocytic infiltration in histology suggesting possible role of host immunity.[2] The effectiveness of bacillus of Calmette and Guerin (BCG) therapy as a non-specific immune stimulant in reducing the recurrence of superficial bladder tumours is a good example of the role of host immunity. The graft-versus-tumor effect seen after allogeneic hematopoietic cell transplantation for human malignancies also supports a powerful role of human immune system to eradicate cancer. Newer classes of targeted immunotherapies against programmed cell death 1 (PD-1) and cytotoxic leukocyte antigen 4 (CTLA-4) pathways on different types of T cells are believed to relieve the inhibition of immune activation against tumors.[4] The efficacy of anti-PD-1 antibody such as nivolumab and anti-CTLA-4 agents such as ipilimumab in wide variety of cancers support the role of immunity in cancer regression.[5]

Prior studies have reported spontaneous remission in chronic lymphocytic leukemia[6, 7]; however, it is considered a rare phenomenon, and most of the cases had early stage disease (Rai stage I, Binet A). We describe a case of a spontaneous remission of a more advanced case of chronic lymphocytic leukemia (Rai stage II, Binet B) and review the literature regarding potential mechanisms for spontaneous regression of cancers.

CASE REPORT

A 54-year-old man presented with a history of enlarged left axillary lymphadenopathy for a few months. He denied any fever, night sweats, weight loss, fatigue, recurrent infection or bleeding. Past medical history was significant for hypertension, hyperlipidemia and hay fever. Medications included losartan-hydrochlorothiazide, metoprolol, atorvastatin aspirin and fexofenadine. He consumed alcohol socially but did not smoke. On examination, he had diffuse lymphadenopathy including a 4 cm right supraclavicular, a 3 cm right axillary, a 3cm left axillary, and a 3 cm right inguinal lymph node. Laboratory findings included hemoglobin of 17.4 gm/dl, white blood count of 15,700/µL, absolute lymphocyte count of 9,800/µL, platelet count of 177,000/µL with normal liver and renal function tests. A computed tomography (CT) scan of chest, abdomen and pelvis revealed diffuse lymphadenopathy involving bilateral axillary, external iliac, right internal iliac and inguinal lymph nodes; spleen measured 13 cm. Excisional biopsy of left axillary lymph node was consistent with CD20

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Table 1, Clinical course of chronic lymphocytic leukemia

Clinical or laboratory findings	*At diagnosis*	*11 years after diagnosis*	*13 years after diagnosis*
Lymphadenopathy (clinical exam)	Diffuse lymphadenopathy including right supraclavicular, bilateral axillary and right inguinal lymph nodes	Resolution of inguinal lymph nodes, otherwise stable lymphadenopathy	No palpable lymphadenopathy
WBC/Absolute lymphocyte count (per µL)	15,700/9,800	16,600/11,100	7,200/2300
Hemoglobin (gm/dl)	17.4	15.2	15.2
Platelet (per µL)	177,000	133,000	131,000
LDH (IU/L)	611 (Ref: 313-618 U/L)	146 (Ref: 98-192 U/L)	137 (Ref: 98-192 U/L)

LDH lactate dehydrogenase; WBC white blood count

+, CD23+, CD5 weakly positive small lymphocytic lymphoma with cytogenetics revealing 46,XY [11] and fluorescent in situ hybridization (FISH) with deletion of 13q14. A bone marrow biopsy revealed hypercellular bone marrow (60 %) with involvement by chronic lymphocytic leukemia (25% marrow space) (CD20 +, CD23+, CD5+). The patient was placed on an active surveillance and continued to do well for several years (Table 1). A repeat FISH performed in peripheral blood five years after the diagnosis revealed deletion of 13q14 in 21.5% of the interphase cells; FISH was negative for a rearrangement of the IgH region at 14q32, trisomy 12 and for deletions of 11q22.3, 13q34 and17p13.1.

At eleven-year follow-up, he was noted to have resolution of palpable inguinal lymphadenopathy. He denied any viral illness triggering his resolution but did receive inactivated trivalent influenza vaccine on 3rd, 4th, 7th and 10th year after diagnosis. At 13 years after the initial diagnosis, he had normalization of leukocytosis (white blood count of 7,200/µL) and lymphocytosis (absolute lymphocyte count of 2,300/µL) as well as resolution of all palpable lymphadenopathy.

DISCUSSION

Complete Remission in CLL is defined as (i) absence of lymphadenopathy, splenomegaly or constitutional symptoms; (ii) peripheral lymphocytosis less than 4 X 109/l, no anemia, no thrombocytopenia; (iii) bone marrow lymphocytosis in aspirates < 30% and/or normal bone marrow histology, as defined by the absence of lymphoid infiltration for more than 2 months.[8] In the absence of repeat bone marrow biopsy, our patient did meet rest of the criteria. Spontaneous regression of cancer, a subject of many controversies in the past, is now a well-established phenomenon.[9] However the exact mechanism behind regression remains poorly understood.

In CLL cases undergoing spontaineous regression, Giudice et al reported persistence of residual neoplastic clone detected by flow cytometry in peripheral blood, negativity of Zap-70 gene expression, mutation in IgVH gene and an overexpression of B-cell antigen receptor (BCR) related genes.[6] The role of BCR has been further studied and it is now believed that BCR provides signals for growth to chronic lymphocytic leukemia (CLL) cells by intracellular activation of BCR-associated kinases including spleen tyrosine kinase (Syk), Bruton's tyrosine kinase (Btk) and phosphatidylinositol 3-kinases (PI3K). CLL has distinct BCR signaling compared with normal B cells that is characterized by low-level IgM expression (IgM is the membrane portion of BCR that binds to various extracellular antigen), variable response to antigen stimulation, and elevated expression of downstream pathways10 BCR signal transduction inhibitors (ibrutinib -inhibitor of Btk, fostamatinib-inhibitor of Syk and IPI-145, a dual PI3K p110δ and p110γ inhibitor,) are evolving as a promising new strategy for targeted CLL treatment.[11-13] .Unmutated IgVH is also considered to be an independent adverse prognostic marker in patients with CLL. Fourteen CLL patients with unmutated IgVH are believed to overexpress a protein ZAP-70 15 which is also believed to enhance BCR signaling.10 Although the IgVH gene status, Zap-70 or BCR expression was not tested in our patient, immunological modulation involving BCR signaling may contribute to spontaneous regression.

Our patient had isolated 13q deletion, which is the most common genetic abnormality in CLL.[16] Patients with a normal karyotype or deletion of 13q14 as the sole genetic abnormality have a better prognosis with up to 63% survival at the end of 5 years[16] than those with a complex karyotype or deletion of 11q23 (associated with bulky lymphadenopathy and a high incidence of residual disease following autologous transplantation) or 17p13 mutation(correlate with re-

sistance to purine analogues).[17]

Prior studies support immunological role in spontaneous regression of NHL. Abe et al described 15 reported cases of spontaneous regression in aggressive NHL where complete regression occurred as early as 14 days up to 8 months from presentation; however, 40% of patients with initial complete regression eventually relapsed. Regression was thought to be related to biopsy in 12 cases and infection with measles or Epstein Barr Virus in the remainder 3 cases. The decrease in size of remaining lymph nodes after initial biopsy was described as a possible indicator of spontaneous regression.[18] However, Horning et al studied 83 patients with low grade NHL, who were initially treated without therapy over 11 months to 17 years, and identified spontaneous regression in 22% of patients including 3 of 21 patients with small lymphocytic lymphoma. Remission was described up to 93 months after initial diagnosis and was linked to viral infection in only one patient.[19] Baraboutis et al compared 5 cases of spontaneous regression of Human Immunodeficiency Virus (HIV)-related lymphomas in pre-highly active anti-retroviral therapy (HAART) era with 18 cases in HAART era. In pre-HAART era, 60% patients eventually relapsed whereas the remainder patients who did not relapse received treatment with zidovudine. In HAART era, relapse occurred in 22% of patients. Based on the study, the reversal of immunosuppression with HAART was described as a possible mechanism for regression of lymphomas.20 Our patient did have a biopsy initially but his tumor persisted for few years before regressing slowly; he did receive influenza vaccine prior to the regression which could be a triggering event.

Human cancer cells express antigens that differentiate them from the nontransformed body cells such as mutational antigens (such as p53), overexpressed cellular antigens (such as HER-2) or viral antigens (such as human papillomavirus proteins). Tumor cells can evade host defenses by mechanisms such as reduced immune recognition (through loss of antigens), increased resistance to the cytotoxic effects of immunity (through induction of anti-apoptotic mechanisms) or the establishment of an immunosuppressive state within the tumor microenvironment mediated by various cytokines and growth factors. In process, there is also an immunoselection of tumor cells that are more capable of surviving in an immunocompetent host and the chronic inflammation that ensues may end up promoting tumorigenesis. Thus, recent evidences suggest that the host immunity should be regarded as a immune-surveillance system rather than an outright protective system, which occasionally ends up promoting tumor progression either by the selection of tumor cells that are more fit to survive in an immunocompetent host or by the establishment of conditions within the tumor micro-environment that facilitate tumor outgrowth.[1]

CONCLUSION

The spontaneous normalization of leukocytosis and resolution of lymphadenopathy thirteen years after the diagnosis of chronic lymphocytic leukemia in the reported man demonstrates the ability of body's immune response against tumor cell. Deeper understanding of the process of spontaneous regression may further enhance the development of immune therapies and provide insight towards tumorigenesis. Additionally, this case illustrates the importance of surveillance without therapy in asymptomatic patients with indolent lymphomas and lymphoproliferative disorders.

CONFLICT OF INTEREST

James O Armitage reports receiving consulting fees from Celgene, Conatus – IDMC, GlaxoSmith-Kline – IDMC, Roche, Spectrum and Ziopharm and serving on the board of directors for Tesaro bio, Inc. There are no conflicts of interest for any other authors.

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