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CASE REPORT

Scleroderma and chronic myeloid leukemia: a sheer coincidence, a consequence of long lasting D-penicillamine therapy or a plausible relationship of both diseases?

Timuçin Kaşifoğlu · Cengiz Korkmaz · Şule Yaşar · Zafer Gülbaş

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Abstract Systemic sclerosis is a chronic multisystem disorder of unknown etiology characterized by the involvement of skin and visceral organs caused by an accumulation of collagen. It has been reported that the incidence of solid and hematological malignancy increased in systemic sclerosis. Multiple myeloma and chronic lymphocytic leukemia are the most common hematological malignancies seen in patients with systemic sclerosis. Chronic myeloid leukemia (CML) has only rarely been reported so far. We here report a case with CREST (calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactly, telangiectasia) who developed CML 7 years after the onset of CREST. Ours is the second case with CML developing after the onset of CREST in the literature. We also briefly discuss the possible tendency to hematological malignancy in systemic sclerosis.

Keywords Chronic myeloid leukemia · Scleroderma · CREST

T. Kaşifoğlu · C. Korkmaz (✉)
Division of Rheumatology, Department of Internal Medicine, Eskişehir Osmangazi University Medical Faculty, Vişnelik Mah. Alifuat Güven C. Akasya Sok. 11/11, 26020 Eskişehir, Turkey
e-mail: ckorkmaz@ogu.edu.tr

Ş. Yaşar
Deparment of Internal Medicine, Osmangazi University Medical Faculty, Eskişehir, Turkey

Z. Gülbaş
Division of Hematology, Department of Internal Medicine, Eskişehir Osmangazi University Medical Faculty, Eskişehir, Turkey

Introduction

Systemic sclerosis is a chronic multisystem disorder of unknown etiology characterized by the involvement of the skin and visceral organs caused by the accumulation of collagen. A few cases of hematological malignancies have been documented in patients with systemic sclerosis, and the mechanism by which the two may be linked is unknown [1]. The question is whether or not the connection between hematological malignancies and scleroderma is accidental, or do they share a common pathogenesis? We here report a case with CREST who developed chronic myeloid leukemia (CML) while on D-penicillamine. We also briefly discuss the possible tendency to hematological malignancy in systemic sclerosis.

Case report

A 50-year-old woman was referred to our clinic with weakness and weight loss in April 2004. She suffered from scleroderma, for which she had been received D-penicillamine for 7 years, before her admission to our clinic. On physical examination, we detected diffuse telangiectasies on her face and hands, hardness of the skin, decreased mouth wideness, sclerodactily, bilateral ralles in the median and basal zones of lungs. In complete blood count, the number of white blood cells was 164,400 mm^{-3}, (152,100 mm^{-3} of absolute neutrophils, 10,600 mm^{-3} of absolute lymphocyte), and hemoglobin was 10.8 g/dl. The immune globulin A level was 224 mg/dl (normal 82–453 mg/dl). Her bone marrow aspiration examination showed that there was myeloid hyperplasia (myeloid/erythroid ratio was

30/1), and blasts were less than 5%. Phyladelphia chromosome t (9,22) was positive on her cytogenetic and FISH analyses of the bone marrow. Rheumatological serological findings were as follows: antinuclear antibody positive in 1/80 titers, Scl-70 295.8 U/ml (normal 0–180 U/ml), SSA 232.9 U/ml (normal 0–1–180 U/ml), anti-DNA negative. The patient was diagnosed as having CML and CREST. She was given hydroxyurea while D-penicillamine was discontinued. Her leukocyte count decreased to a normal range within 3 months. Three months later, methotrexate was added to her treatment due to her polyarthritis being resistant to non-steroidal anti-inflammatory drugs. She has been in a remission period for both CML and polyarthritis for 6 months. Her last leukocyte count was 11,400 mm^{-3}. After 15 months of withdrawal of D-penicillamine, Phyladelphia chromosome was still positive.

Discussion

We believe that the concurrent existence of the disorders of CML and CREST in our case could be explained in three possible ways. To begin with, it could be a sheer coincidence. The second speculation could be the effect of D-penicillamine in the development of CML. D-penicillamine therapy is known to sometimes cause agranulocytosis, aplastic anemia and thrombocytopenia [2]. Besides this, the case reports exist in the literature about hematological malignancies possibly secondary to D-penicillamine usage. It has been reported that D-penicillamine may trigger leukemia, including acute lymphoblastic leukemia and chronic lymphocytic leukemia (CLL) [3, 4]. Penicillamine causes alterations in cellular and humoral immunity. It also causes severe Ig A deficiency and helper T-cell activity inhibition. That immunoglobulins decrease and changes occur in the cellular immunity in patients who use D-penicillamine are known and these changes may contribute to the development of the hematological malignancies. The presence of the Philadelphia chromosome in CML is the consequence of the chromosomal rearrangement. It is tempting to speculate that the long-term use of D-penicillamine may be responsible for this chromosomal change. However, the persistence of the Philadelphia chromosome after withdrawal of D-penicillamine makes this possibility very slim.

As to the third speculation, there could be a relationship between hematological malignancies and scleroderma. There are known to be reports showing hematological malignancy accompanying scleroderma in the literature. Some of these would be multiple myeloma [5], CLL [6], Hodgkin lymphoma [7], non-Hodgkin lymphoma [8], hairy cell leukemia [9]. The case we report is the second of its kind having CREST and CML simultaneously [10, 11].

Several speculations have been made in the literature to explain the relationship between cancer and scleroderma. In patients with scleroderma, the ratio of genetic abnormalities, such as deletion or fragmentation of chromosomes, was found high [12, 13]. Also, the chromosomal fragmentation rate is high in the first-degree relatives of the patients with scleroderma [14]. It is well known that the hallmark of CML is the presence of the Philadelphia chromosome, a t (9; 22) translocation, which results in the production of a Bcr–Abl fusion protein [15]. The fragile genome and the genetic damage could both cause predisposition to scleroderma and hematological malignancies. Besides these speculations, cytokines released from early neoplastic clones may have a role in the development of scleroderma. In addition to these factors, a decline in the number of natural killer-T cells in patients with scleroderma may result in the development of malignancies [16], because these cells have unique effector functions in antineoplastic immunity and in regulating the balance between tolerance and autoimmunity [17]. It is interesting to note that alpha-interferon may help improve both scleroderma and CML [18, 19]. The use of alpha-interferon in both diseases may prompt us to think of a common pathogenesis between CML and scleroderma.

Although we believe that CML accompanying scleroderma in our case could be a sheer coincidence, we still think that it could be related to the same pathogenetic mechanisms of scleroderma and CML. We also think that D-penicillamine could have played a role in the development of the CML as a provocative factor. We suggest that further studies should be made to shed light upon this possible relationship.

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