Small lymphocytic lymphoma in a patient with CREST syndrome

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We report a case of a 61-year-old man with a history of CREST syndrome (calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) who presented for evaluation of thrombocytopenia. He had evident cervical adenopathy and lymph node biopsy showed small lymphocytic lymphoma (SLL) with evident systemic adenopathy and bone marrow involvement. The patient achieved a complete remission with FCR (fludarabine/cyclophosphamide/rituximab) chemotherapy. About 30 cases of lymphomas are reported in the literature in association with systemic sclerosis. To our knowledge, there are no reports of a small lymphocytic lymphoma (SLL) in association with limited cutaneous systemic sclerosis with classic features of the CREST syndrome.

Systemic sclerosis (SSc) is an autoimmune systemic disease characterized by systemic inflammation, vascular abnormalities, and fibrosis of the skin and internal organs. Two forms of SS have been described: diffuse cutaneous systemic sclerosis (DcSSc) and limited cutaneous systemic sclerosis (LcSSc). Patients with LcSSc may display features of the CREST syndrome (calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia). An increased risk of cancer in SSc patients had been reported in retrospective studies, with reports of lung and breast cancers being dominant. Around 30 cases of non-Hodgkin lymphomas (NHL) were reported in association with SSc, in both DcSSc and LcSSc subsets. To our knowledge, there has been no report of small lymphocytic lymphoma (SLL) in association with LcSSc/CREST syndrome.

CASE
A 61-year-old white man was referred to our clinic for evaluation of thrombocytopenia. He had had Raynaud disease and thickening on the skin of his hands along with telangiectatic changes on his face for the past 30 years, yet he was diagnosed with CREST syndrome only 1 year before being referred to us. At that time, he presented with worsening exertional dyspnea and was found to have evidence of interstitial lung disease and severe pulmonary hypertension. He underwent a transbronchial lung biopsy that showed pulmonary endothelialitis. He also reported acid reflux symptoms and had an upper endoscopy that showed Barrett esophagus (with high-grade dysplasia). His ANA titer was 1:160 with a centromeric pattern yet he had a negative anticentromere antibody, negative ENA screen and a negative Scl-70 antibody. He was started on mycophenolate mofetil along with sildenafil. Because of worsening pulmonary functions, mycophenolate mofetil was changed to cyclophosphamide. We held his cyclophosphamide and his platelet count did not improve significantly. We also noted that the patient had a few small cervical lymph nodes. The patient denied B symptoms. Biopsy of these nodes revealed small lymphocytic lymphoma (SLL) (Figure 1). The neoplastic cells were positive for CD5, CD19, CD20(dim), CD23(partial), surface kappa light chains, and negative for cyclin D1. Lactate dehydrogenase was not elevated. Total body CT scan showed small mediastinal, hilar, axillary, retroperitoneal, and inguinal adenopathy (Figure 2). Additionally, fatty hepatomegaly, no splenomegaly, and inflammatory changes were noted in the lungs. Bone marrow biopsy revealed 40% cellular marrow with 5% to 10% involvement with lymphoid aggregates (Figure 3), and
with clonal lymphocytes expressing the same immunophenotype seen on lymph node biopsy. About 55% of the CD5+/CD19+ clonal population also expressed CD38. Megakaryocytes were adequate numerically and morphologically within normal limits. Cytogenetic/ FISH analysis revealed deletion of 13q14 (5%) and deletions of 11q22.3 and 17p13.1 (4%) of the interphase cells from the bone marrow specimen. After treatment with 3 cycles of fludarabine (25 mg/m² on day 1-3), cyclophosphamide (200 mg/m² on day 1-3), and rituximab (375 mg/m² on day 1), the patient achieved a complete remission yet no further chemotherapy could be given because of protracted thrombocytopenia. Repeat bone marrow biopsy after chemotherapy showed a hypocellular marrow (10%), only 0.2% clonal B-cells (only seen on flow cytometry), and decreased megakaryocytes (with normal distribution).

**DISCUSSION**

Small lymphocytic lymphoma is an indolent form of B-cell NHL. Historically, B-SLL was considered a different disease from B-chronic lymphocytic leukemia (CLL). They are now considered as different manifestations of the same disease and are grouped together in the World Health Organization (WHO) classification of NHL. The median survival of patients with SLL/CLL is 10 years and most patients are asymptomatic at diagnosis. Most patients with SLL/CLL do not require treatment at presentation unless they have a cytopenia or organ dysfunction. By definition, an absolute lymphocyte count of <5 x 10^9/L has been used to distinguish SLL from CLL, but this is now considered an artificial distinction. Other differences include lower rates of cytogenetic abnormalities, higher rates of CD38 expression, and mutated IgVH gene status with SLL compared to CLL. Both diseases are treated with the same type of chemotherapy regimen using rituximab and nucleoside analogues with FCR (fludarabine, cyclophosphamide, rituximab) being the most popular regimen used in the US. Based on 1985-2005 cumulative data from M.D. Anderson Cancer Center, the response rate, survival, event-free survival, and adverse prognostic features are comparable between SLL and CLL.

Some autoimmune diseases seem to increase the risk of developing NHL. Although this association is established for rheumatoid arthritis and Sjögren syndrome, it is still debated in other diseases like SSc.
On a recent systematic review, risk factors for malignancy in patients with SSc were old age, female gender, and diffuse skin involvement (DcSSc). Vettori et al. recently published a systematic review of all cases of NHL reported in association with SSC; 20 cases were identified by searching MEDLINE from 1959-2009. Of those 20 cases, only 5 suffered from LcSSc. Different manifestations of the full-blown CREST syndrome were described in these cases and occasional overlap with other systemic manifestations of scleroderma were also reported, like scleroderma renal crisis. The subtypes of NHL reported were all of the B-cell type and included histiocytic lymphoma of the colon, the Pinkus variant of skin and muscle, SLL, mucosa-associated lymphoid tissue (MALT) lymphoma of the salivary gland and Helicobacter pylori-associated gastric MALT lymphoma. The duration between the presentation of SSC and NHL was as little as 1.5 years up to 11 years and some occurred simultaneously raising the possibility that SSC could be considered a “paraneoplastic” manifestation of NHL. T-cell NHL cases were reported in association with DcSSc but not with LcSSc. The association between SSc and NHL may be incidental or secondary to an emergence of a malignant clone from a pool of polyclonal chronically stimulated B-cells, deficiency of T- and NK-cells, or common genetic backgrounds that predispose to both disorders, like the HLA-DRB5 haplotype.

To our knowledge, there have been no reports of a small lymphocytic lymphoma (SLL) in association with LcSSc/CREST syndrome. The other peculiar features of this case were the development of SLL while the patient was receiving cyclophosphamide. The remarkable complete response rate to nucleoside analogue-based chemotherapy despite the presence of the 17p deletion (indicative of activation of the p53 tumor-suppressor gene and potential resistance of nucleoside analogues), and the presence of all the classic features of the CREST syndrome. The stabilization of lung function after chemotherapy, and rituximab, suggests that the malignant lymphocyte clone could be instrumental in the pathogenesis of lung injury through the production of autoantibodies or through presentation of auto-antigens to T-cells.

A series of recent studies of rituximab in a few patients with scleroderma showed improvement in dermal hyalinized collagen content, dermal myofibroblast numbers, and pulmonary function. Treatment with rituximab was well tolerated in these studies. Reactivation of the JC virus leading to progressive multifocal leukoencephalopathy (PML) is a rare but devastating complication that has been reported in patients with B-cell NHLs after treatment with rituximab. Rituximab is usually combined with chemotherapy and its role in JC virus reactivation, independent of the immune suppressive effect of chemotherapy, is unclear. In December 2006, the US Food and Drug Administration released an alert for rituximab after 2 patients with SLE developed PML and died after off-label treatment with rituximab. The role of JC virus reactivation, and development of PML, after rituximab treatment for rheumatologic condition is also unclear as these patients had usually received multiple immune suppressive agents in the past.

The authors declare no conflict of interest.
REFERENCES

32. Boselli S, De Santis M, Lane S, Speno C, Angelucci C, Tolusso B, Sica G, Ferreccio C. B-cell depletion in diffuse progressive systemic sclerosis: safety, skin score modification and IL-6 modulation in an up to thirty-six months follow-up open-label trial. Arthritis Rheum. 2010; 62 (2) 1384-1392