A rare case of acute lymphoblastic leukemia in a patient with light chain (AL) amyloidosis treated with lenalidomide.

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Case Report

A rare case of acute lymphoblastic leukemia in a patient with light chain (AL) amyloidosis treated with lenalidomide

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Abstract: Lenalidomide belongs to a novel class of drugs called Immunomodulators which are now being used for the treatment of plasma cell dyscrasias with variable degrees of efficacy and toxicity. Though Second Primary Malignancies (SPM) have been a concern with its use, the benefits of the treatment outweigh the risks. The leukemogenic risk seems to be potentiated especially when combined with alkylating agents and the SPMs documented are predominantly myeloblastic. To date there are no reported cases of new lymphocytic leukemias in AL amyloidosis, regardless of whether undergone treatment or not. We present a case of AL amylodosis who was treated with lenalidomide and subsequently developed acute lymphoblastic leukemia.

Keywords: Second primary malignancy, acute lymphoblastic leukemia, AL amyloidosis, lenalidomide

Introduction

Plasma cell neoplasms are characterized by clonal proliferation of plasma cells in the bone marrow leading to the production of monoclonal immunoglobulins. They are sometimes accompanied by tissue deposition of monoclonal immunoglobulins or their components. Amyloidosis refers to a distinct group of tissue deposition disorders among which light-chain (AL) amyloidosis is the most common type. The introduction of lenalidomide and other immunomodulators (IMiDs) as a treatment modality for amyloidosis was a significant breakthrough in this disease. Multiple trials are ongoing with IMiDs in combination with other drugs for the treatment of AL amyloidosis [1]. There have been rare cases in which plasma cell neoplasms treated with lenalidomide develop acute leukemia post lenalidomide treatment and these cases were predominantly myeloblastic. We describe a rare incidence of B-lymphoblastic leukemia in a patient with AL amylodosis who received lenalidomide and dexamethasone for 56 months.

Case

A 73 year old female presented to our institution in the fall of 2007 with 3 month history of lower extremity edema. A routine complete blood count at the time of presentation showed hemoglobin of 11.5 g/dL, normal WBC count, and platelets 319,000/μL. Serum and urine protein electrophoresis with immunofixation detected lambda light chains. A kidney biopsy was obtained and showed multiple glomeruli with moderate to severe diffuse mesangial expansion with accumulations of acellular, weakly PAS positive material that shows red-green birefringence staining with Congo red when examined under polarized light microscopy consistent with amyloid deposition (**Figure 1**). Immunofluorescent studies demonstrated smudgy lambda light chain deposition in the interstitium and vessel walls. Kappa light chain was negative. The diagnosis of renal amyloidosis, AL lambda type involving glomeruli, interstitium and vessels was rendered. Bone marrow studies demonstrated a population of lambda light chain restricted plasma cells by flow cytometry. The bone marrow aspirate smears

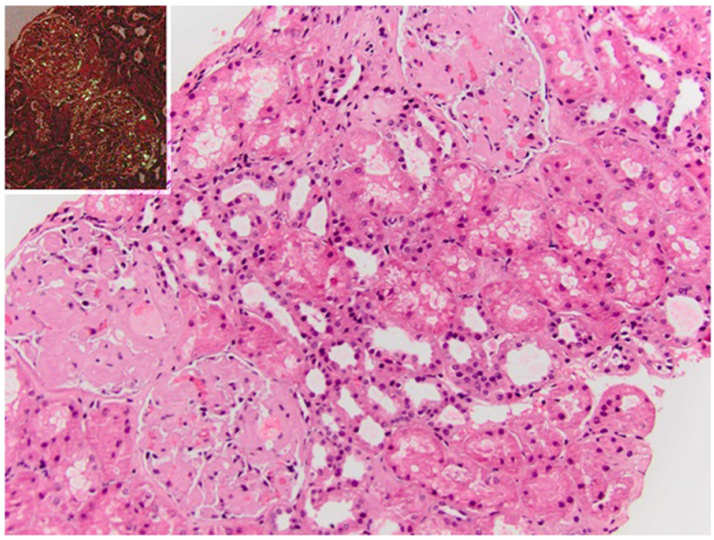

Figure 1. Renal Biopsy with insert demonstrating amyloid deposits showing birefringence on polarizing microscopy after Congo red staining.

showed trilineage hematopoiesis and with a population of plasma cells, 5-8% of the total cellularity (**Figure 2A**). Congo red stain was positive for amyloid deposition. Cytogenetic and FISH (fluorescent in-situ hybridization) panel for multiple myeloma were within normal limits. These findings were compatible with lambda light chain amyloidosis.

Lenalidomide was started at 15 mg daily for 21 days, followed by 7 days off, for a 28 day total cycle. Dexamethasone was given at a dose of 20 mg weekly. She received aspirin for thromboembolic prophylaxis. At the initiation of treatment, her serum lambda light chain level was 60 mg/dL. There was initially a flare in her lambda light chains to 101 mg/dL then the levels started to improve. The patient achieved partial hematologic response with more than 50% reduction in the level of the serum monoclonal protein in less than 2 months and a complete hematologic response with complete disappearance of the monoclonal protein in the serum in 7 months. The patient continued to be on the same regimen for a total duration of 56 months.

In November 2012, she presented with generalized weakness, lightheadedness and easy bruising. On complete blood count the patient was found to have severe thrombocytopenia at 16,000/μL. Her WBC count was normal at 5,600 cells/μL and the hemoglobin was 12.0 g/dL. Review of peripheral blood smear showed numerous blasts. Bone marrow studies demonstrated a markedly hypercellular marrow with sheets of medium sized blast (**Figure 2B**). Flow cytometric studies showed an expanded B-lymphoblast population with dim CD45+, bright CD38, dim-moderate CD19, CD20, CD10, dim TdT, moderate CD34, variable CD33 and moderate-bright HLA-DR expression, all consistent with a diagnosis of B-lymphoblastic leukemia. FISH analysis showed copy gain of MYC and IGH in 13% of the nuclei, deletion of p53 gene in 76% of the cells, deletion of ABL gene in 79% of the cells and low levels of copy gain for BCR (6.5%) and MLL genes (9%), monosomy 7 (79.5% of the cells), deletion of 20q (79.5% of the cells), tetrasomy 8 and copy gains for 5p/5q. There were no rearrangements for any studied probe set. Cytogenetic studies demonstrated a normal karyotype: 46 XX.

The patient began induction chemotherapy with daunorubicin, vincristine and prednisone and achieved a complete remission. Phase 2 of induction chemotherapy included cytoxan, cytarabine, 6-mercaptopurine and intrathecal methotrexate [2]. Consolidation chemotherapy with high dose methotrexate was administered and was complicated by an admission for infection and bleeding. A few months after the completion of consolidation chemotherapy, the patient unfortunately relapsed. Salvage chemotherapy was attempted with vincristine and dexamethasone. Due to complications of her disease and treatment, she eventually developed multi-organ failure and was put on comfort measures.

Discussion

It is estimated that more than 12 million cancer survivors are currently alive in the United States. Increasing survivorship has led to focus on the long-term outcome of malignancies and chemotherapy complications [3]. Lenalidomide which is a less toxic and more potent derivative of its parent drug, thalidomide, has renewed interest in the treatment of plasma cell dyscrasias due to its significant therapeutic activity.

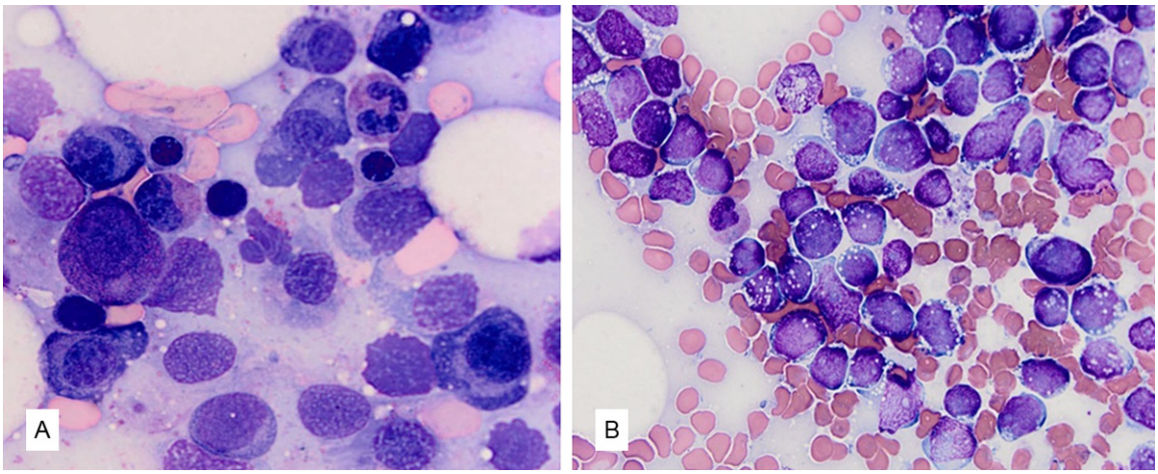

Figure 2. A: Core bone marrow biopsy showing prominence of plasma cells consistent with AL amyloidosis. B: Bone marrow aspirate showing Acute Lymphoblastic Leukemia.

Lenalidomide was examined in multiple phase 2 studies for the treatment of AL amyloidosis in combination with other drugs. These trials demonstrated favorable hematologic and organ response rates, manageable toxicity and no reported cases of second primary malignancy (SPM) [4-9]. Lenalidomide, along with other new targeted agents has dramatically improved the overall median survival of patients with amyloidosis to greater than 3 years [6, 9]. There is a growing concern about an increasing number of cases of SPMs associated with the use of lenalidomide in newly diagnosed and relapsed multiple myeloma [10-12]. Though there are no reported cases of SPM in untreated primary amyloidosis except for the limited number of cases reported of its delayed progression to multiple myeloma, it could be debated that patients with untreated amyloidosis do not survive long enough for other cancers to develop [13]. We describe a patient with AL amylodosis who was treated with lenalidomide and dexamethasone. After 56 months of treatment, she developed B-lymphoblastic leukemia. After thorough review of the literature, we found no reports of B-cell acute lymphoblastic leukemia occurring after a diagnosis of AL amyloidosis.

Before the advent of immunomodulators there have been numerous cases of SPMs in multiple myeloma, MGUS and Waldenström's macroglobulinemia, but were predominantly of non lymphoid origin [13-25]. There are cases reports of B-lymphoblastic leukemia in patients with multiple myeloma who were treated with lenalidomide. However, the increased risk of a SPM with lenalidomide was noted when the drug was used in combination with alkylating agents. The hematologic malignancies found in association with multiple myeloma were predominantly acute myeloid leukemia or myelodysplastic syndromes and a limited number of cases of B cell malignancies including acute lymphoblastic leukemia, Hodgkin and non-Hodgkin lymphoma (NHL) [11, 12, 26].

In a prospective double blind study by McCarthy et al which compared the use of lenalidomide versus placebo for maintenance therapy after autologous hematopoietic stem-cell transplantation in multiple myeloma, 8 cases of SPMs were reported in the lenalidomide group, two of which were NHL and ALL [12]. It is unclear as to whether these 2 patients had received an alkylating agent during the treatment course. The rest of the malignancies were non-lymphoid in origin. A phase 3 placebo-controlled trial for multiple myeloma by M. Attal et al, studied patients under the age of 65 years with non-progressive disease who received consolidation treatment with lenalidomide within six months of autologous stem-cell transplantation [11]. At a median follow-up of 34 months from randomization and 44 months from diagnosis, there were 32 SPMs in 26 patients reported in the lenalidomide group versus 12 SPMs in 11 patients in the placebo group. The incidence of SPMs were 3.1 per 100 patient-years and 1.2 per 100 patient-years for patients

Table 1. Comparison of the incidence of SPMs in lenalidomide (L) maintenance in recent treatment trials

Trial	Follow up months	N	Number of ALL	Total no: of hematologic cancer	Median time to diagnosis of hematologic cancer
(CALGB) 100104 [10]	34	L-231	1	8	28 months (range, 12 to 46)
		P-229	0	1	
IFM 2005-002 study [9]	44	L-306	3	13	-
		P-302	0	5	
MM-015 [26]	30	MPR-R-150	0	7	-
		MPR-152	0	5	
		MP-153	0	1	

Treatment groups: L–lenalidomide, P–Placebo, MPR-R (melphalan, prednisone, and lenalidomide induction followed by maintenance lenalidomide), MPR (melphalan, prednisone, and lenalidomide induction), MP (melphalan and prednisone induction).

receiving lenalidomide and placebo (P=0.002), respectively. There were 13 reported hematologic cancers with lenalidomide and 5 with placebo. There were 3 cases of ALL recorded in the lenalidomide maintenance arm and none in the placebo arm. The MM-015 trial by Palumbo et al showed that the 3 year rate of second malignancies were 7% each in the two lenalidomide treated group versus 3% without lenalidomide. There were a total of 25 cases of SPMs with no reported incidence of ALL in any of the treatment arms [27] (**Table 1**).

In a retrospective pooled analysis of 11 clinical trials of lenalidomide-based therapy of 3846 patients with relapsed/refractory multiple myeloma, the overall incidence rate (IR, events per 100 patient years) of SPMs was 3.62 with a total of 52 invasive SPMs after a median duration of lenalidomide based therapy for 5 months (range, 0.03-58 months). In a separate analysis of pooled data from pivotal phase 3 trials of relapsed or refractory MM involving 704 patients the overall IR of SPMs was 3.98 (95% CI 2.51-6.31) with lenalidomide/dexamethasone and 1.38 (95% CI, 0.44-4.27) with placebo/dexamethasone. In both of these trials there were no reports of second hematologic malignancies [28].

In an earlier issue of this journal, these authors reported on an unusual transformation of 2 cases of MDS 5q- syndrome to acute lymphoblastic leukemia while on lenalidomide for 32 and 72 months respectively [29]. Myelodysplastic syndromes associated with deletion of the long arm of chromosome 5 represent a unique entity with an indolent course that is less likely to transform into acute leukemia. The two patients achieved an initial response with lenalidomide however, later on became refractory to treatment and evolved into B-lymphoblastic leukemia with recurrence of the 5q- along with an additional cytogenetic abnormality of 20q- in both patients. To our knowledge, these are the first two cases reported of MDS evolving into ALL while on lenalidomide.

The present case is unique not only because of lack of reported cases of acute lymphoblastic leukemia after a diagnosis of AL amylodosis, but also there was no leukemogenic potentiation with alkylating agents in our patient as seen in previous cases of multiple myeloma with lenalidomide. This raises questions as to whether the development of ALL in this patient was a consequence of the IMiDs drugs or whether it was a de novo occurrence. Though there are increasing reports of SPM with IMiDs there has been no convincing clinical data to answer these questions. A cytogenetic analysis performed in 21 patients with primary amyloidosis showed that the chromosome damage identified after melphalan therapy was localized to myeloid but not plasma cells [30]. From these data we infer that use of alkylating agents could be associated with the incidence of myeloid neoplasms in the lenalidomide treatment group. In other distinct studies, translocations involving the immunoglobulin heavy-chain locus (IgH 14q32) have been found as the possible early genetic events in patients with primary systemic amyloidosis and multiple myeloma [31-34]. Interestingly similar rearrangements involving the immunoglobulin heavy chain locus (IgH) at chromosome band 14q32 are reported in B-cell precursor acute lymphoblastic leukemia as well [35-43]. To ascertain whether acute lymphoblastic leukemia could be the end result

of such chromosomal translocations during the natural course of light chain (AL) amyloidosis and multiple myeloma, and whether IMiDs potentiates such genetic changes would require longer follow up with meticulous cytogenetic analysis.

Disclosure of conflict of interest

None.

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