

Management of mantle cell leukemia with cardiac involvement leading to cardiogenic shock

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Abstract Mantle cell lymphoma is an aggressive subtype of B cell non-Hodgkin lymphoma. It can progress to leukemic phase but frank leukemic picture at initial presentation is not common. Leukemic phase indicates advance stage of the disease and generally associated with extensive extra-nodal involvement. Pericardial invasion has been reported, however we could not find a report of myocardial infiltration by this disease since the appraisal of the term “mantle cell lymphoma” in 1992. Here we report a case of cardiac involvement by mantle cell leukemia leading to cardiogenic shock which complicates the treatment decisions.

Keywords mantle cell lymphoma; bendamustine; cardiogenic shock

Introduction

International Lymphoma Study Group (ILSG) in 1992 classified mantle cell lymphoma as a distinct subtype of B cell non-Hodgkin lymphoma [1]. Previously several terms including centrocytic lymphoma, lymphocytic lymphoma of intermediate differentiation, mantle-zone lymphoma, and intermediate lymphocytic lymphoma were used in the literature to describe this entity [1,2]. The name derived from the distribution of tumor cells, making a cuff around the germinal centers in its early stage resembling the mantle zone of secondary lymphoid follicles [2,3]. It comprises 3%–10% of all non-Hodgkin lymphomas [4,5]. Clinical course of the disease is very heterogeneous, but generally it is regarded as an aggressive lymphoma [4,6]. Histologically two subtypes have been described. Classical subtype is characterized by monotonous proliferation of small to medium-sized mature looking lymphocyte whereas blastic variant is composed of medium to large cells with round or irregular nuclei with finely dispersed chromatin [3]. Immuno-phenotypically malignant lymphocytes express CD5, Bcl-2, cyclin D1 and pan-B cell markers with absence of CD10, Bcl-6 and CD23. Characteristically, malignant lymphocytes possess a distinct

chromosomal translocation t(11;14)(q13;q32). This juxtaposes the proto-oncogene *CCND1* at 11q13 to the immunoglobulin heavy chain complex (IGH) at chromosome 14q32 causing overexpression of cyclin D1 that deregulate cell cycle at G₁/S phase transition [7].

Patients typically present with generalized lymphadenopathy with or without B symptoms. Extra-nodal involvement is frequent. Common extranodal sites include bone marrow, peripheral blood, Waldeyer's ring, gastrointestinal tract, reticulo-endothelial system and central nervous system. Involvement of orbits, salivary glands, breast, pleura, skin, liver and kidney has been reported [8,9]. However, diffuse myocardial infiltration is extremely rare. Absolute lymphocytosis $\geq 4 \times 10^9/L$ or presence of any lymphocyte with characteristic immuno-phenotype in peripheral blood is regarded as leukemic phase of the disease [2,8]. This indicates advance stage of the disease with higher incidence of extra-nodal involvement [10].

Here we describe a case of mantle cell lymphoma that progressed to leukemic phase and presented with cardiogenic shock.

Case summary

A 53-year-old previously healthy Caucasian female underwent a work-up for constitutional symptoms and generalized

lymphadenopathy six months ago. Only remarkable laboratory findings at that time were mild anemia (11.2 mg/dl) and leucopenia ($3.4 \times 10^9/L$). Computed tomographic (CT) scan confirmed axillary, retroperitoneal, pelvic and inguinal lymphadenopathy with moderate splenomegaly. Excisional biopsy of the right inguinal lymph node revealed preserved nodal architecture with kappa restricted monoclonal B cell population positive for CD5, CD19, CD20 and cyclin D1. These malignant B lymphocytes were negative for CD10, CD23 and Bcl-6. This immunophenotype was consistent with the diagnosis of mantle cell lymphoma. Bone marrow was positive for malignant B lymphocytes which comprised 25% of the marrow cellularity on the biopsy specimen. The mantle cell lymphoma international prognostic index (MIPI) score was 5.2 (low risk, WBC $3.4 \times 10^9/L$, LDH 222 U/L, ECOG-1, Ki67 = 35%). She was offered standard treatment options but she declined and pursued alternative medicine and holistic measures.

She was brought to our emergency department (ED) for worsening shortness of breath and upper abdominal pain. Her condition rapidly deteriorated in the ED and she became unresponsive with pulseless ventricular tachycardia. After 20 min of cardiopulmonary resuscitation she regained spontaneous circulation. Electrocardiogram at that time showed changes consistent with antero-lateral myocardial ischemia. She underwent emergent cardiac catheterization which revealed normal coronary arteries. However, ventriculogram revealed diffuse hypokinesis with a left ventricular ejection fraction of 20%. Right ventricular endomyocardial biopsy was performed. She required CentriMag Extra-Corporeal Membrane Oxygenation (ECMO) pump, Intra-aortic Balloon Pump (IABP), and inotropic support for hemodynamic stabilization. She also required bilateral chest tubes to drain pleural effusions. She was kept on amiodarone infusion but she continued to have recurrent episodes of non-sustained ventricular tachycardia. Therefore CT scans of the chest, abdomen and pelvis were postponed. Her blood work at admission displayed leukocytosis (WBC $20.3 \times 10^9/L$) with lymphocyte predominance (67%). These lymphocytes on peripheral blood smear were small to medium in size with cleaved nuclei containing coarse chromatin (Fig. 1A). Flowcytometric analysis of peripheral blood confirmed that these lymphocytes were monoclonal and expressed markers of mantle cell lymphoma. Result of the endo-myocardial biopsy also revealed infiltration by sheets of atypical lymphocytes into the myocardium causing disintegration of muscle fibers. Immuno-phenotypic markers on these lymphocytes were identical with that of peripheral blood (Fig. 1B–1F). These malignant lymphocytes were negative for TP53 deletion. In the next few days her leukocyte count progressively increased, highest on day 5 ($133.4 \times 10^9/L$) with lymphocyte predominance (86%) despite the fact that she was receiving high dose steroids. On day 6, she was started on rituximab 375 mg/m² weekly for 4 weeks. With the 1st dose of rituximab she also received vincristine 1.4 mg/m².

To our surprise her leukocyte count dropped from $133 \times 10^9/L$ to $9 \times 10^9/L$ within 24 h of administration of immunotherapy. She did develop mild degree of tumor lysis syndrome which was managed appropriately. In the next few days she was weaned down of the steroids. CentriMag ECMO was successfully removed when echocardiogram on day 10 showed improvement in left ventricular ejection fraction. On day 12, IABP was also removed but she continued to require inotropic support. CT scans of the chest, abdomen and pelvis performed during the second week of her hospitalization failed to reveal any significant lymphadenopathy. Subsequently, she improved remarkably and inotropic support was stopped on day 21. Repeat echocardiogram after one dose of vincristine and four weekly doses of rituximab showed left ventricular ejection fraction of 30%. Implantable Cardioverted Defibrillator was inserted for secondary prevention before the discharge from the hospital.

At this point she underwent a bone marrow biopsy and PET (positron emission tomography) /CT scan. Both studies were negative for any residual disease. She was documented to have achieved complete remission after four doses of rituximab and one dose of vincristine. She has now completed three cycles of rituximab and bendamustine given every 4 weeks. She will start maintenance therapy with rituximab every two months.

Discussion

Extra-nodal disease either primary or secondary is commonly seen in patients with mantle cell lymphoma [8,9,11]. A population based study of more than 4000 patients demonstrated that 20% of new cases have primary extra-nodal disease. Gastrointestinal (GI) tract, oropharynx, reticulo-endothelial system and orbital adnexa comprise 80% of the primary sites in such cases [12]. Overall, bone marrow (50%–82%) and peripheral blood (30%) are the most common involved extra lymphatic sites, followed by gastrointestinal tract, spleen, liver, head and neck and body cavity linings. Rarely skin, breast and central nervous system (CNS) can be involved [3,6,8,9,11,13]. CNS disease is more commonly associated with blastic variant of mantle cell lymphoma [14,15].

Despite frequent occurrence of extra-nodal disease, cardiac involvement is extremely rare. So far no explicit case series or reports have described this issue since the recognition of mantle cell lymphoma as a distinct subtype of a B cell non-Hodgkin lymphoma. Recently, Ambinder *et al.* analyzed SEER data from 18 registries that include 4477 patients with mantle cell lymphoma [12]. They categorized patients based on primary site of the lymphoma. The study grouped thymus, mediastinum and heart in a single anatomic category. Out of 4477 patients with mantle cell lymphoma only 4 patients fell into this category as the primary site of their lymphoma. It is unknown if any of these patients actually had myocardial

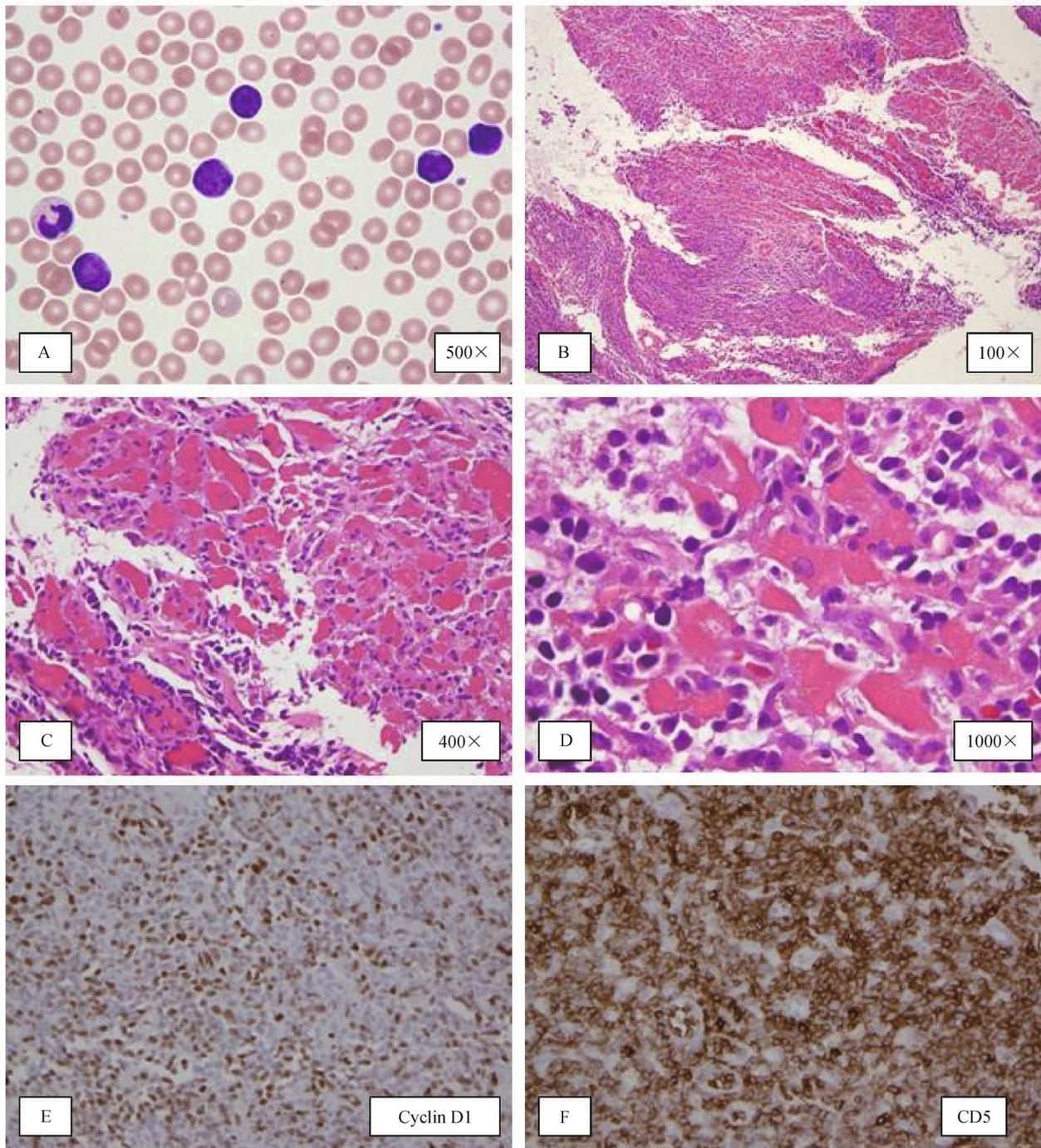


Fig. 1 Mantle cell lymphoma involving myocardium. (A) Peripheral blood smear showing several medium-sized lymphocytes with cleaved nuclei. (B–D) H & E stained myocardial tissue shown at different magnifications to demonstrate disintegrated cardiac muscle fibers with sheets of mononuclear infiltrate. (E–F) Cyclin D1 and CD5 immunohistochemical staining of endomyocardial biopsy tissue depicting positivity of cyclin D1 and CD5 by mononuclear cells infiltrating the myocardium.

infiltration as the retrospective analysis did not specify this. In contrast to myocardial involvement, pericardial disease has been reported [8,9]. It is unclear about the mechanism of the myocardial involvement in this case. Whether the lymphoma cells in this case expressed cardiotropic factors remains

unknown.

Other important aspects of this case include the disease course and the challenges involved in its management. At the time of initial diagnosis this patient had low risk, stage IV mantle cell lymphoma with MIPI score of 5 which progressed

to frank leukemia with myocardial invasion in a few months. This kind of disease course is not unusual and attests to the fact that it is an unpredictably aggressive disease even without *p53* mutation. For that reason, most newly diagnosed patients start receiving treatment early on, however some experts do think that a select group of patients can be offered wait and watch strategy [16,17].

In the case described above, control of the primary disease was required on an urgent basis. Without treatment it was unlikely that cardiac function could recover especially when exponential increase in circulating lymphocytes was observed despite the treatment with high dose steroids. However, prerequisite of therapeutic anticoagulation with multiple mechanical invasive devices and extracorporeal circulation precluded the option for more myelosuppressive cytotoxic therapy. Another concern is of unknown pharmacokinetic properties of any chemotherapeutic option in such a situation. Therefore rituximab and vincristine were given at the beginning. Her response to this regimen was dramatic with complete remission after four doses of rituximab and one dose of vincristine.

Efficacy of rituximab as a single agent, though a perfect choice in our patient, is not very impressive in patients with mantle cell lymphoma when compared to other indolent lymphomas. Reported overall response rate ranges between 20%–40% with complete response rate of only 2%–6% [6,18,19]. In addition, these responses are not durable. However, rituximab when given in combination with chemotherapy significantly increases response rate, disease control rate and over all survival, which was demonstrated in a meta-analysis of 260 patients with mantle cell lymphoma [20]. Among the various immuno-chemotherapy regimens, anthracycline containing combinations of immuno-chemotherapies like R-CHOP or R-HyperCVAD/HD-MTX-Ara-C produces the best responses in the front line setting [21–24]. Patients eligible for high dose chemotherapy then undergo autologous stem cell transplant to consolidate the initial response [25]. However, these regimens could not be considered as an option in our case given their cardiotoxicities and myelosuppressive nature since this patient required ECMO and IABP with continuous anticoagulation. A combination of bendamustine with rituximab has recently been shown to have significant activity in MCL [26]. It was better tolerated and perhaps more effective than R-CHOP in patients with indolent and mantle cell lymphomas. However, data regarding its long-term sequelae and impact on quality of stem cell collection are currently not available [27].

In conclusion, mantle cell lymphoma remains an unpredictably aggressive disease despite the availability of various prognostic scales and can involve several organs especially in leukemic phase. Bendamustine-rituximab is an attractive treatment option, particularly for patients who cannot tolerate anthracycline containing regimens. Novel agents for lymphoid malignancies may also offer alternatives to this specific population of patients [28–34].

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Compliance with ethics guideline

Muhammad Furqan, Yamei Chen, Akintunde Akinleye, Judy Sarungbam, Alan Gass, Karen Seiter, and Delong Liu declare that they have no conflict of interest. Informed consent from the patient was obtained for this report.

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