Hairy Cell Leukemia in a Filipino Male during the COVID-19 Pandemic – Report of a Rare Case

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Abstract

Hairy cell leukemia (HCL) is a rare, chronic, mature B-cell lymphoproliferative disorder accounting for 2% of all leukemias. In this paper, we would like to present our experience in the management of HCL in a financially limited setting where other diagnostic tests and chemotherapy are unavailable. The case report aims to emphasize the recognition of the distinctive morphology of hairy cells in the peripheral blood in the consideration of the initial diagnosis.

A 60-year-old Filipino male was incidentally found to have anemia, thrombocytopenia and an absolute neutrophilic count below 1,000 in a pre-operative clearance for elective herniorrhaphy. Blood smear revealed atypical lymphocytes with hair like cytoplasmic projections. CT-scan of the abdomen showed splenomegaly and prominent paraaortic nodes. Flow cytometry of the bone marrow aspirate was consistent with an involvement of a Mature B cell neoplasm markers CD19, CD20, CD22 and surface immunoglobulin lambda and hairy cell leukemia markers CD11c, CD103 and CD25. He responded to six-weekly sessions of Cladribine with remission of the bone marrow and hematologic parameters.

HCL is a rare type of a mature B cell neoplasm characterized by pancytopenia, splenomegaly, bone marrow fibrosis and the presence of atypical lymphoid cells with hairy projections in blood, bone marrow and spleen. Immunophenotyping express CD11c, CD103, CD123, and CD25. BRAF V600E mutation is the disease defining genetic event. Cladribine and Pentostatin are the first line of treatment.

Cases of leukemia can be easily overlooked because of the mild derangement in the complete blood count. A meticulous differential review of the atypical lymphocyte, is the first step in the diagnosis of this rare disease.

Keywords: Hairy cell leukemia, cladribine, Immunophenotyping

Introduction

Hairy cell leukemia remains a mysterious disease despite its characteristic morphologic features. Hence, occurrence of HCL has been documented rarely which occurs in 3/1,000,000 patients.[13] Because of the low proliferation of tumor cells coupled with pancytopenia, the resultant bone marrow aspiration tap is usually dry posing a challenge in the diagnosis of this particular leukemia.[3] The clinical manifestations of HCL can range from non-specific symptoms like weakness and fatigue to pancytopenia. Some patients are asymptomatic and diagnosed only on routine peripheral blood smear by identification of the classic morphology of hairy cells. Diagnosis can be confirmed through flow cytometry.[1]

Case Presentation

A 60-year-old Filipino male, asymptomatic, presented with persistent thrombocytopenia and anemia. History dated back seven months prior to admission when the patient was referred by the Department of Surgery for a hematologic evaluation of an incidental finding of thrombocytopenia and anemia in a routine complete blood count prior to an elective herniorrhaphy. Baseline hemoglobin was 129 g/L, platelet count of 86 x 10^9/L and an absolute neutrophilic count of 787. Surgical procedure was deferred pending hematologic work-up and diagnosis.

Patient was subsequently lost to follow up due to the COVID-19 pandemic. But the persistence of the thrombocytopenia and anemia prompted the patient to seek another hematologic consultation. Review of the blood smear revealed medium to large size mononuclear cells with a round, ovoid and cleaved nucleus with a loose

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to dense chromatin pattern, and an abundant cytoplasm with the characteristic hair like projections (*Figure1*). Patient was then admitted for further diagnostic evaluation.

Past medical history revealed Hypertension Stage II since 2015, maintained on daily Losartan; Dengue Fever in 2017; and Benign Prostatic Hyperplasia Status Post Transurethral Resection of the Prostate in 2018. During that admission, patient had thrombocytopenia of unrecalled level. Personal and social history and review of systems were unremarkable. He had no family history of blood dyscrasia. Pertinent physical findings included splenomegaly and the left inguinal hernia.

Upon admission and laboratory investigation, complete blood count revealed mild anemia (Hgb 127 g/L), thrombocytopenia (Platelet count of 61 x 10^9/L), normal WBC with predominance of lymphocytes (54%) and an absolute neutrophilic count of 938. Bleeding parameters were within normal range. Coombs' test and Hepatitis serology were negative. FBS, BUN, lipid profile, liver function tests, chest x-ray and 12 lead ECG were normal. Creatinine was elevated at 124 umol/L and eGFR was decreased at 54 ml/min. 2-D echocardiogram with Doppler revealed a normal ejection fraction of 68% and mild mitral regurgitation. Triphasic contrast enhanced CT-scan of the abdomen showed splenomegaly with multiple rim-enhancing foci considered to be a metastatic process with prominent paraaortic nodes. Bone marrow with difficult aspiration revealed depression of tri-lineage hematopoiesis and the presence of hairy cells (*Figure 1*).

The immunophenotypic profile by flow cytometry of the bone marrow aspirate was consistent with an involvement of a Mature B cell neoplasm with bright expression of the B cell markers CD19, CD20, CD22 and surface immunoglobulin lambda. It was also most compatible with HCL Leukemia with the expression of the hairy cell markers CD11c, CD103 and CD25. The immunological score was three which was computed by giving one point for each expressed hairy cell marker.

Patient underwent 2-hour six weekly chemotherapy sessions with cladribine 4.5 mg (0.09 mg/kg/day) thru intravenous infusion with renal dose adjustment. The third session was interrupted due to severe neutropenia and pulmonary infection. Remaining sessions were well tolerated. Complete blood count upon follow-up a month after the last dose of chemotherapy was shown to be in hematologic remission. Repeat bone marrow aspirate with flow cytometry was done five months after completion of cladribine which showed a remission marrow.

Discussion

HCL is a rare type of a mature B cell lymphoproliferative neoplasm with lesser reported frequency in the Asian population. Its main characteristics are the cytoplasmic projections of the lymphoid cells.[4]

The clinicopathologic findings of bone marrow

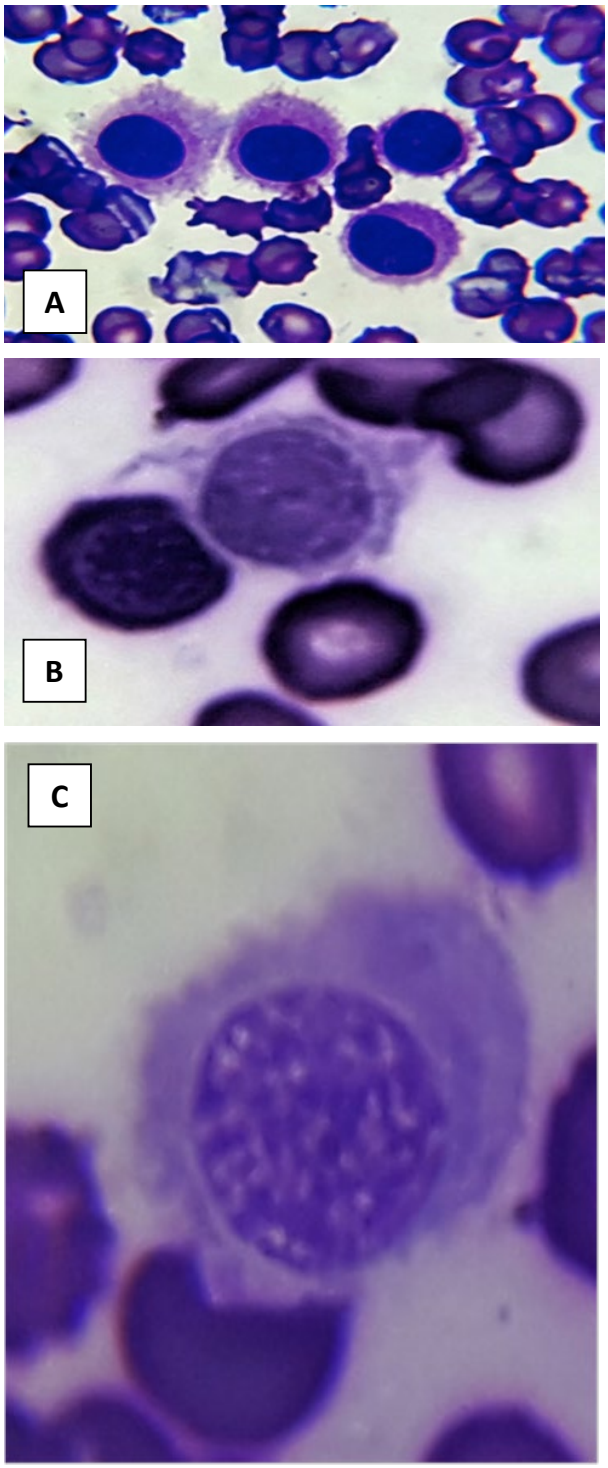

Figure 1. Morphology of hairy cells. A. PBS of patient. Shows atypical lymphocytes with abundant cytoplasm with hair like projections B & C. Bone marrow aspirate of patient showing small to medium-sized lymphocyte exhibiting ovoid to slightly irregular nuclei with dense coarse chromatin with prominent nucleoli and moderate abundant cytoplasm exhibiting short and blunt cytoplasmic projections

infiltration of mononuclear cells with distinct lace like outline of the cell membrane, marrow fibrosis, pancytopenia and splenomegaly were first described by Bertha Bouruncle and colleagues in 1958.[5] The term hairy cell was coined by Schrek in 1966 after describing the undulating ruffles of hair on the cell surface using phase contrast microscopy.[6] In 2008, HCL was recognized as a separate and distinct entity from HCL variant and splenic diffuse red cell pulp lymphoma in the lymphoid classification of neoplasm.[7] In 2011, Tiacci identified the BRAF V600E mutation as the disease defining genetic event in HCL.[8] The hairy morphology was found to be dependent upon this BRAF mutation. The mutation is detectable at diagnosis in more than 97% of HCL patients.[8]

Etiology has not been clearly established. Increasing the risks for HCL include exposure to pesticides, herbicides, petroleum products and ionizing radiation.[4] Though the median age is 63 years old, it can also occur in young individuals. Men are affected more than women. It has a higher incidence in the white than in the Asian population.

The clinical course of HCL is indolent but progressive. As for the other types of hematologic malignancy, generalized body weakness and fatigue are the predominant symptoms. The prevalence of splenomegaly is 96%.[4] Lymphadenopathy when present is usually detected in the abdomen. Pancytopenia occurs in 70 to 90% of patients and in 95% of cases hairy cells can be appreciated in blood films already.[9]

Initial diagnosis requires careful review of the peripheral blood smear. It shows the presence of atypical lymphocytes which are twice as large as the normal lymphocytes with abundant cytoplasm and distinct morphologic features of cytoplasmic projections. In order to confirm the diagnosis of HCL, immunophenotyping by flow cytometry is done to show the immunophenotypic profile of the clonal expansion of mature B cells with bright expression of CD19, CD20, CD22 and surface immunoglobulins and hairy cell markers CD11c, CD103, CD123, CD25.[10]

An immunologic score of hairy cell markers of 3 or 4 is seen in 98% of cases.[11] Bone marrow biopsy will reveal the diffuse, interstitial or focal infiltration of hairy cells. The nuclei are widely separated by a clear halo of cytoplasm creating a fried egg appearance. Reticulin is increased and there is pericellular fibrosis accounting for the difficult bone marrow aspiration. Immunohistochemistry will stain the upregulated proteins such as the Annexin A1, a protein which is both sensitive and specific to HCL and cyclin D1, a cell cycle protein. The hairy projections will be more readily seen with DBA 44 stain. The tartrate resistant acid phosphatase shows a bright red granular cytoplasmic positivity in the leukemic cells. BRAF V600E mutation is detected by a molecular assay or by immunostaining.

Ninety percent of patients requires treatment and a small proportion entails close monitoring until indication for treatment is evident. Criteria for initiation of therapy are the following: hemoglobin < 11 g/dL, platelet count < 100 000/μL, and absolute neutrophil count < 1000/μL. In the absence of the above hematologic parameters, the clinical features for which therapy may be started include symptomatic organomegaly, progressive lymphocytosis or lymphadenopathy, unexplained weight loss of more than 10% within six months and excessive fatigue.[10] Determinants of poor prognosis are the following: splenomegaly, leukocytosis and presence of hairy cells in the blood and elevated beta-2 microglobulin.[1] However, with chemotherapy, prognosis is favorable.

Purine analogs (PNA) like cladribine and pentostatin monotherapy remain to be the first line of treatment for HCL. Although the risk of relapse is an issue, prognosis has been favorable in those treated with PNA and current strategies are capable of reaching prolonged remission. Cladribine and pentostatin are equally effective. Both agents have reported an overall response rate of more than 85% and complete remission rates of 75% with median relapse free survival of up to 15 years and median survival of 27 years.[12] Cladribine tends to be the preferred treatment because of a more convenient infusion schedule. It can be administered thru intravenous or subcutaneous injection for 5-7 days or weekly for 6 weeks.[10]

In our case, the patient presented with thrombocytopenia, mild anemia, an absolute neutrophil count of below 1,000, splenomegaly and abdominal paraaortic lymphadenopathy. Given the rarity of HCL, a careful review of the peripheral smear morphology of hairy cells by a trained and curious eye should drive the clinician to unravel the diagnosis by other diagnostic tools. Although treatment was temporarily interrupted due to infection and severe neutropenia in the early course of chemotherapy, the patient seemed to tolerate and respond to the weekly regimen of cladribine. His platelet count normalized throughout the late course of treatment. In addition, he was also able to undergo surgical repair of hernia without the need for any blood product transfusion. Five months after his last administration of chemotherapy, he achieved bone marrow remission.

Patient Perspective

Immunophenotyping and determination of BRAF V600E mutation are not readily available in all institutions. BRAF V600E mutation was not performed anymore to maximize the funds for the treatment. The price of the said diagnostics, process for transporting the specimen to bigger laboratories, the prohibitive cost and difficult procurement of cladribine which was sourced outside of the Philippines, along with the current struggles in the logistics during COVID-19 pandemic pose a real challenge in the diagnosis and management of this case. But, the team in cooperation with the patient and his family were able to overcome the challenges and institute successful treatment and outcome.

Conclusion

It should be remembered that cases of leukemia can be easily overlooked since they may present only with non-specific symptoms and mild derangement in the complete blood count. In patients presenting with thrombocytopenia and mild anemia, a meticulous examination of the differential picture, particularly the atypical lymphocyte, is the first step in the diagnosis of this kind of rare disease.

Disclosure. The authors have no affiliations with any private or government institutions with financial interest in the subject matter discussed in the manuscript. The authors have secured consent from the patient and relative to publish this case report.

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