Case Report

A Rare Occurrence of Hairy Cell Leukemia in the Thai Population: A Case Report

Ekapun Karoopongse MD*,
Archrob Khuhapinant PhD, MD*, Chirayu U Auewarakul MD, PhD*

**Division of Hematology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*

Hairy cell leukemia (HCL) has been mainly reported from the Western countries. Herein we describe a case of HCL diagnosed in a Thai patient. A 36-year-old man presented with abdominal discomfort, frequent gum bleeding and significant weight loss for 2 months. Physical examination revealed moderate anemia, petechial hemorrhage on the extremities and an enlarged spleen down to the umbilicus. No hepatomegaly or lymphadenopathy was detected. Complete blood counts revealed a hemoglobin (Hb) of 6.6 g/dL, a white blood cell (WBC) count of 1.6x10^9/L (neutrophil 16%, lymphocyte 71%, monocyte 11%, atypical lymphocyte 1%), and a platelet (PLT) count of 17x10^9/L. Abnormal large mononuclear cells with villous projections were seen in the blood smear. Although bone marrow (BM) aspiration resulted in a dry tap, abnormal lymphocytes with villous projections could again be identified in the touch preparation. Flow cytometric analysis showed a distinct population above the normal lymphocyte region on CD45/SSC gates with a strong expression of CD19, CD20, CD22, CD25, CD11c, and kappa. CD5, CD23, CD10, CD4, and CD8 were all negative. BM biopsy was consistent with HCL. The patient was treated with splenectomy followed by 8 cycles of fludarabine and cyclophosphamide chemotherapy. At 21 months after diagnosis, the patient was doing well with a Hb of 16.9 g/dl, a WBC count of 6.8x10^9/L, neutrophil 49.9%, lymphocyte 39.6%, monocyte 8.6%, and a PLT count of 329x10^9/L). No abnormal lymphoid cells were detected in the blood smear. This present report represents the first Thai HCL case that was immunophenotypically confirmed by flow cytometry and successfully treated at Siriraj Hospital.

Keywords: *Hairy cell leukemia, lymphoid neoplasms, flow cytometry, splenectomy, fludarabine*

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Hairy cell leukemia (HCL) is an uncommon type of mature B-cell lymphoid neoplasm characterized by splenomegaly and pancytopenia[1,2]. The diagnostic hallmark of HCL is the detection of abnormal lymphoid cells with circumferential hair-like cytoplasmic projections in the blood, marrow, spleen, and/or liver, and unique exhibition of mature B-cell antigens and monoclonal surface immunoglobulin[3-5]. Typically, patients are middle-aged to elderly men who present with a palpable spleen, usually a least 5 cm below the left costal margin as well as symptoms related to anemia, neutropenia, and thrombocytopenia, although some patients may be asymptomatic and some may have elevated white blood cell (WBC) counts[1,6]. HCL occurs more frequently in Caucasians, particularly in Ashkenazi Jews, with rare occurrence in persons of Asian and African descents. The incidence of this disease in the United States and the United Kingdom appear to be similar, with approximately 600-800 newly diagnosed cases a year[6-8]. In Asian countries, HCL cases were rarely reported[8-13]. Herein a clinical description of a classical case of HCL in a Thai man is presented, which epitomizes the first successfully treated HCL ever reported from Thailand.

Correspondence to: Auewarakul C, Division of Hematology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkoknoi, Bangkok 10700, Thailand. Phone: 0-2419-4418, Fax: 0-2411-2012. Email: sicaw@mahidol.ac.th

Case Report

A 36-year-old Thai man presented with a his-

tory of abdominal discomfort for 4 months. The patient had been in good health until four months earlier when he started to feel that his abdomen was gradually enlarged. A firm mass in the left upper abdomen was noted. He felt generally tired and had a 15-kilogram weight loss without spiking fevers. He subsequently developed petechial hemorrhage all over his arms and legs associated with frequent episodes of bleeding per gum which prompted him to seek medical advice. The patient denied tobacco and alcohol abuse and was not using any medications. Physical examination revealed a moderately pale man without jaundice and fever. Scattered petechial hemorrhage was found on both of his arms and lower legs. The respiratory, cardiovascular and nervous system was within normal limits. Abdominal examination revealed a firmly enlarged spleen extending down to the level of his umbilicus. Liver was not palpable and no sign of chronic liver disease nor ascites was present. All superficial lymph nodes were not palpable. The basic laboratory investigations were performed as shown in Table 1. The patient had pancytopenia with hemoglobin (Hb) of 7.5 g/dL, a white blood cell (WBC) count of 2.4 x 109/L, absolute neutrophil count (ANC) of 0.48 x 10^9/L and a platelet (PLT) count of 28 x 10^9/L. Peripheral blood smear showed normochromic normocytic red blood cells with decreased platelets. Abnormal small to medium-sized mononuclear cells with circumferential cytoplasmic projections were found as shown in Fig. 1. Radiologic investigation was also performed which demonstrated marked splenomegaly with the dimension of 23 cm, mild hepatomegaly, and celiac node enlargement.

As the provisional diagnosis was HCL, bone marrow (BM) aspiration and biopsy were subsequently performed. BM aspiration resulted in a dry tap but numerous mononuclear cells with hairy projections were again identified in the touch preparation. BM biopsy revealed moderate to marked hypercellularity with diffuse infilttration by widely-spaced lymphoid cells with abundant cytoplasm and prominent cell borders, producing a "fried-egg" appearance (Fig. 2). These cells were intensely marked with CD20 (as shown in Fig. 3A), focally marked with CD79a, and not marked with CD3 (Fig. 3B).

The BM biopsy staining for CD5, CD10, CD23, CD 34, CD68, cyclin D1, TdT, myeloperoxidase, kappa and lambda light chain was all negative. Flow cytometric analysis of peripheral blood revealed a distinct population of cells above the lymphocytic region in the CD45/SSC gates with expression of CD19, CD20, CD22, CD25, CD11c, and FMC7, as shown in Fig. 4. CD5, CD23, CD10, CD4, and CD8 were negative. The pathological and immunophenotypic results were thus consistent with HCL.

Due to symptomatic pancytopenia and splenomegaly, it was decided to perform splenectomy to relieve the symptoms. The patient received pneumoccal and hemophilus influenza vaccines and blood transfusion with 2 units of packed red blood cells and 12 units of platelet concentrates in preparation for surgery. The spleen was removed with no immediate complications. The gross review of the spleen showed a large spleen measuring 35 x 24 x 9 cm and weighing 4,000 gm. Histopathology study showed extensive involvement by small lymphoid cells with monocytoid features and presence of few microscopic blood lakes consistent with HCL. The follow-up CBCs after surgery are shown in Table 1. The patient was subsequently treated with oral chemotherapy regimen consisting of fludarabine (F) 25 mg/m^2 and cyclophosphamide (C) 150 mg/m^2 for 4 days every 4 week. Co-trimoxazole was also prescribed in order to prevent infection during chemotherapy. The patient did well and completed 8 cycles of FC regimen without complications. CBC at 21 months after the initial diagnosis was normal. No abnormal cells were detected in the blood smear or by flow cytometry. Abdominal imaging study revealed a normal-sized liver with no intraabdominal or intrapelvic lymph nodes.

Discussion

Fifty years have passed since the original report of HCL by Bouroncle et al in 1958[14]. In the recent 2008 report by the US National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program, there were 2,856 cases of HCL diagnosed during 1978-2004 with the age-specific incidence rates (IR) of 0.32 per 100,000 person-years[6]. IRs were about 4-fold greater among men than women and more than 3-fold higher for whites than blacks. A bimodal age distribution was revealed in this large study with a dominant early-onset and late-onset modes near ages 45 and 80 years, respectively, in females. Among males, the peak frequency was near age 55 years with a less prominent late-onset mode. The majority of patients presented with pancytopenia (50-70%) and splenomegaly (80%)[1]. Other features include monocytopenia and myelofibrosis[3].

In Asian countries, there are a limited number of reports on HCL. The largest study came from Japan but the Japanese HCL cases appeared to have a different feature from the classical HCL reported from the West. In a series of 40 cases reported by Machii T et al,

only 9 cases were classical HCL, 2 cases were HCL-prolymphocytic variant and the remainder was the so-called "HCL-Japanese variant" as they frequently presented with a high WBC count and had a distinct CD25-negative hairy morphology[15]. In a small Taiwanese series of 5 cases with the age range of 27 to 77, all 5 patients had splenomegaly, 3 of them had pancytopenia and 2 of them had leukocytosis[11]. In another Chinese series from Hongkong, 18 cases were reported with the incidence of HCL of 0.035 per 100,000 population per year which was much lower than the US SEER's data[12]. The clinical features such as male dominance and clinical presentations, however, were similar to the Western reports. In an India series from New Delhi, 15 cases of HCL, aged 32-57 years (median 47 years) were reported[13]. The clinical presentations included splenomegaly, hepatomegaly and fatigue. The commonest laboratory features were monocytopenia, neutropenia, anemia, and pancytopenia. The patients in India were relatively young, similar to our case, as contrast to the older ages of HCL cases in the Western countries.

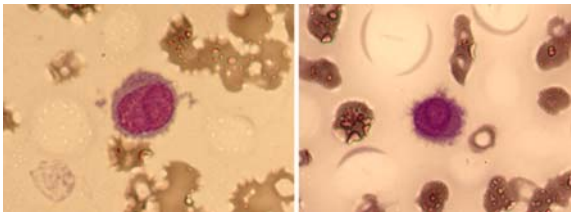

Fig. 1 Representative blood smears reveal two abnormal mononuclear cells with oval nuclei and numerous circumferential "hairy" cytoplasmic projections.

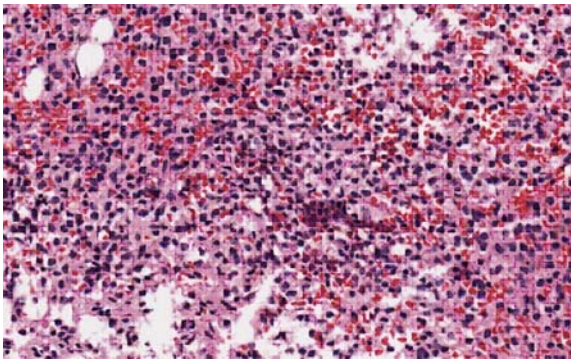

Fig. 2 Bone marrow biopsy demonstrates diffuse infiltration by widely-spaced lymphoid cells with abundant cytoplasm and prominent cell borders, producing a "fried-egg" appearance.

Although the disease is rare and it is difficult to establish the series, there has been much progress in the treatment which has led to the improvement in the natural history of the disease. With the introduction of new drugs such as purine nucleoside analogues (PNA) in the 1980s-1990s, the overall survivals of HCL

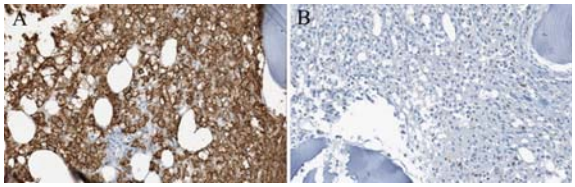

Fig. 3 Bone marrow biopsy demonstrates CD20-positive hairy B-cells (A) that do not express CD3 T-cell marker (B).

Table 1. Complete blood counts (CBCs) at the initial presentation and after treatment with splenectomy and chemotherapy

	At initial presentation	At 1 month after splenectomy	After 2nd cycle of FC regimen	After 8th cycle of FC regimen	At 21 months after diagnosis
Hb (g/dL)	7.5	9.9	14.3	17.1	16.9
Hct (%)	23.7	33.9	43.2	48.1	48.1
RBC count	2.53	3.55	4.94	5.33	5.41
MCV (fL)	93.6	92	87	90	89
WBC count ($x10^9$/L)	2.40	6.0	2.2	4.4	6.8
Neutrophil (%)	20	36.9	58.6	59.9	49.9
Lymphocyte (%)	70	29	35.9	19.0	39.6
Monocyte (%)	-	25.3	2.3	18.5	8.6
Eosinophil (%)	1	8.5	2.7	2.1	1.6
Basophil (%)	-	0.5	0.5	0.5	0.3
Atypical lymphocyte (%)	9	-	-	-	-
PLT count ($x10^9$/L)	28	348	296	274	329

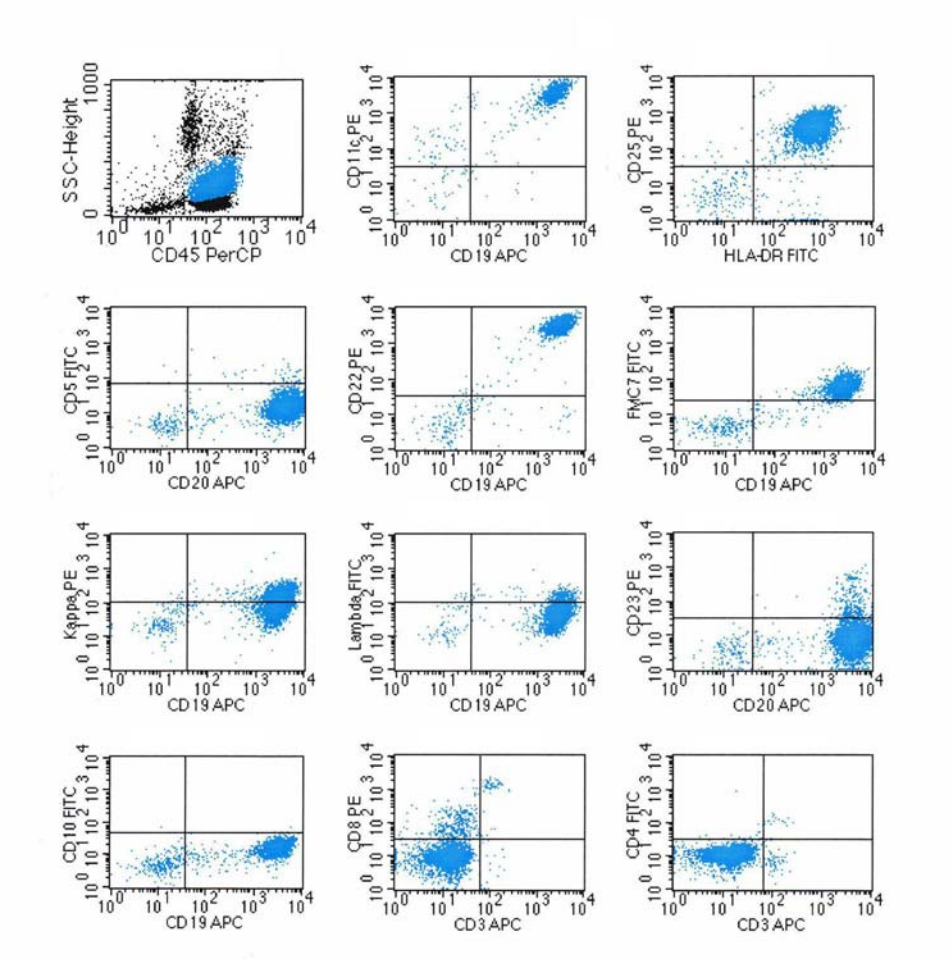

Fig. 4 Flow cytometric dot plots show the existence of an abnormal population of cells with expression of CD19, CD20, CD22, CD25, CD11c and FMC7.

patients are now over 10-15 years[16,17]. As HCL is a disease with an indolent course, some patients may not need to be treated at the initial diagnosis if they do not have significant symptoms. Therapy is indicated only when the patient has significant anemia (Hb < 11g/dL), neutropenia (ANC < 1 x 10^9/L), thrombocytopenia (PLT< 100 x 10^9/L), symptomatic organomegaly, bulky adenopathy, or infections and constitutional symptoms such as fever, night sweats, or fatigue. Prior to the treatment era with PNA, which is now the standard treatment, splenectomy, chlorambucil and interferon treatment were able to induce some good responses[18-20]. Splenectomy was able to rapidly relieve symptoms and 40-60% of patients had an improvement in their blood counts. However, splenectomy is not a curative treatment as a median duration of response was only 5-20 months. Interferon treatment could induce a partial remission in the majority of cases but only 10% of patients achieved complete remission. After the 1990s, PNA has been used in place of interferon treatment as PNA has been shown to induce more partial and complete remissions than interferon.

Two PNA drugs frequently used in HCL treatment are 2-deoxycoformycin (2-DCF, pentostatin)[15] and 2 chlorodeoxyadenosine (2-CdA, cladribine)[16]. Flinn et al reported an overall survival rate of 90% at 5 years and 81% at 10 years with pentostatin treatment[21]. As for cladribine treatment, patients achieved 98-100% overall response (76-91% CR and 7-24% PR) with the relapse-free survival of 80% and overall survival of 95% after five year follow-up[22-24]. Long-term follow-up of 233 patients treated initially with pentostatin or cladribine treatment showed no differences in responses between the two drugs with a complete response rate of 80% and a median relapse-free survival of 16 years[24]. Patients who were still in complete remission at 5 years had only a 25% risk of relapse by 15 years[24]. Therefore, both PNA drugs are now considered the standard

first line therapy for HCL. In patients who have recurrent disease, an option is rituximab which is a monoclonal antibody against CD20, a B-cell marker, that can be used alone or in combination with either PNA, or even after stem cell transplantation to induce remission[24-26]. In our case, we decided to perform splenectomy because the patients had symptomatic cytopenias and splenomegaly with constitutional symptoms and we did not have either of the preferred PNA drug available in Thailand. We pursued an alternative PNA drug, *i.e.* fludarabine which is typically used in patients with chronic lymphocytic leukemia (CLL), and had a successful outcome in this case without any complications. More data is needed to confirm the curative effect of fludarabine in HCL.

Conclusion

The present case represents the first immunophenotypically confirmed clinical description of HCL from Siriraj Hospital. Malignant hairy cells were detectable in the blood smear as well as in the BM biopsy. The patient was treated with splenectomy followed by fludarabine-based regimen with good success. HCL should always be considered in the differential diagnosis of patients who present with marked splenomegaly and pancytopenia. A unique hairy cell should be looked for and further investigated in order to avoid missing the diagnosis of this rare disease. Fludarabine may be an alternative choice of treatment in the countries where penstostatin and cladribine are not available.

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รายงานผู้ป่วยไทย 1 ราย ที่เป็นโรคมะเร็งเม็ดเลือดขาวชนิดเซลล์มีขน (Hairy cell leukemia)

เอกพันธ์ ครุพงศ์, อาจรบ คูหาภินันทน์, จิรายุ เอื้อวรากุล

มะเร็งเม็ดเลือดขาวชนิดเซลล์มีขน (Hairy cell leukemia) เป็นโรคที่มีการรายงานจากประเทศตะวันตกเป็นส่วนใหญ่ รายงานครั้งนี้นำเสนอผู้ป่วยชายไทยอายุ 36 ปีที่มาด้วยอาการไม่สบายท้อง มีเลือดออกตามไรฟันและน้ำหนักลดลงในระยะเวลา 2 เดือนก่อนมาโรงพยาบาล การตรวจร่างกายพบภาวะโลหิตจางปานกลาง มีจุดเลือดออกที่แขนและขาทั้งสองข้าง ม้ามโตขยายลงไปถึงระดับสะดือ ตับไม่โต และต่อมน้ำเหลืองคลำไม่ได้ การตรวจความสมบูรณ์ของเม็ดเลือด ได้ผลดังนี้ ฮีโมโกลบิน 6.6 กรัมต่อเดซิลิตร ระดับเม็ดเลือดขาว $1.6x10^9$ เซลล์ต่อลิตร เป็นนิวโตรฟิลร้อยละ 16 ลิมโฟซัยท์ร้อยละ 71 โมโนซัยท์ร้อยละ 11 และลิมโฟซัยท์ที่ผิดปกติร้อยละ 1 และเกร็ดเลือด $17x10^9$ เซลล์ต่อลิตร การตรวจสเมียร์เลือดพบเซลล์ขนาดใหญ่ที่มีนิวเคลียสเดี่ยว และมีการยื่นของซัยโตพลาสซึมออกมารอบๆ คล้ายผม แม้ว่าการเจาะไขกระดูกจะไม่สามารถเอาไขกระดูกออกมาได้ แต่สามารถตรวจพบเซลล์ดังกล่าวได้เช่นกันจากการทำ touch preparation การวิเคราะห์เซลล์ด้วยเทคนิคโฟลซัยโตเมทรีพบกลุ่มเซลล์ลิมฟอยด์เพิ่มผิดปกติโดยมีการแสดงออกของ CD19, CD20, CD22, CD25, CD11c และ kappa แต่ไม่พบการแสดงออกของ CD5, CD23, CD10, CD4 และ CD8 การตรวจชิ้นเนื้อไขกระดูกยืนยันว่าเป็น Hairy cell leukemia ผู้ป่วยได้รับการรักษาด้วยการตัดม้าม ตามด้วยเคมีบำบัดสูตร fludarabine และ cyclophosphamide จำนวน 8 รอบ การติดตามผู้ป่วย ณ เวลา 21 เดือนหลังการวินิจฉัย พบว่าผู้ป่วยสบายดี โดยมีค่าฮีโมโกลบิน 16.9 กรัมต่อเดซิลิตร ระดับเม็ดเลือดขาว 6.8×10^9 เซลล์ต่อลิตร เป็นนิวโตรฟิลร้อยละ 49.9 ลิมโฟซัยท์ร้อยละ 39.6 โมโนซัยท์ร้อยละ 8.6 และเกร็ดเลือด 329×10^9 เซลล์ต่อลิตร และไม่มีเซลล์ผิดปกติในสเมียร์เลือด รายงานนี้นับเป็นรายงานแรกของผู้ป่วยไทยที่เป็น Hairy cell leukemia ที่ได้รับการตรวจยืนยันระดับแอนติเจนด้วยเทคนิคโฟลซัยโตเมทรี ณ โรงพยาบาลศิริราช และถือว่าการรักษาประสบความสำเร็จอย่างดี