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CASE REPORT

Hairy Cell Leukaemia in Oman

Four cases

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ابْيِضاضُ دَّم الخلايا الشعرية في سلطنة عمان
أربع حالات

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الملخص: ابْيِضاضُ دَّم الخلايا الشعرية هو اضطراب تَّكاثُريُ لِّمْفِيّ نَسيلِيّ نادر ومزمن غالبا ما يصيب الذكور في أواسط العمر. قِلَّةُ الكُرَيَّاتِ الشَّامِلَة في الدم وتَضَخُّمُ الطِّحال الجسيم من أكثر العلامات السريرية انتشارا. يتم التشخيص بواسطة اكتشاف الخلايا الليمفاوية ذو سايتوبلازم غزير ينتشر على شكل أطراف شعرية في لُطاخَة الدم المحيطي ونقي العظم. ومن هنا أخذت اسمها. رُشَافَة نقي العظم تؤدي في الغالب إلى بزل جاف. خَزْعَةٌ المِنْقَب لها صفات خاصة تشبه مظهر قُرْصُ العَسَل (المُخَرَبَة). وعد الكريات الانسيابي يكون نمطيا CD103, CD25, FMC7, CD11c وسِّلْسِلَةُ غاما أو كابًّا الخفيفة ايجابية مع واصمات الخلايا الليمفاوية الكلاسيكية CD19, CD20, CD79a . مُضاهِئات البورين المتبوع بالعامِلُ المُنَبِّهُ للمُسْتَعْمَرات المحببة لعلاج قِلَّةُ العَدِلات الناتج عن الحمى هو العلاج الأمثل في الوقت الحالي. أمكن تسجيل عشر سنوات خالية من المرض بواسطة ذلك العلاج. الاستعمال التجريبي لمضاد CD20 و CD22أظهر أيضا نتائج واعدة لعلاج هذا المرض. ندرج هنا أربع حالات من المرض المذكور شخصت خلال سنتين في المستشفى السلطاني بمسقط في سلطنة عمان.

مفتاح الكلمات: ابْيِضاضُ دَّم الخلايا الشعرية . اضطراب التكاثر اللمفي . تقرير حالات. سلطنة عمان.

ABSTRACT Hairy cell leukaemia (HCL) is a rare, clonal, chronic lymphoproliferative disorder commonly seen in males in the middle years of life. Pancytopaenia with moderate to massive splenomegaly is the most common clinical presentation. Diagnosis is made on detecting the lymphocytes with abundant cytoplasm which spread into hair-like processes on peripheral blood and bone marrow smears, thus giving the name, "hairy cell leukaemia". The bone marrow aspirate is frequently a dry tap. The trephine biopsy has the characteristic features of a honey comb appearance and flow cytometry is typically CD103, CD25, FMC7, CD11c, gamma or kappa light chain positive with the classic B lymphocyte markers CD19, CD20, CD79a. Purine analogues followed by granulocyte-colony stimulating factor (G-CSF) to manage the febrile neutropenia is currently the treatment of choice. A 10 year disease free survival is recorded with these management strategies. Experimental use of anti CD20 and CD22 has also shown promising results in the treatment of this disease. We report four cases of HCL diagnosed in a span of two years at the Royal Hospital, Muscat, Oman.

Key words:: Hairy cell leukaemia; Lymphoproliferative disorder; Case report; Oman.

Hairy cell leukaemia (HCL) is a rare chronic B lymphoproliferative disorder representing 2% of all leukaemias.[1] The name HCL was coined in 1964 by Shrek and Donnelly.[2] It was first identified as a clinical entity in 1958 and was known as leukaemic reticuloendotheliosis.[2] At present the hairy cell has not been identified to have a known normal counterpart in lymphocyte ontogeny. We describe four cases of hairy cell leukaemia, the first to be reported from the Sultanate of Oman.

CASE 1

An Omani male, 61 years of age, presented with recurrent anaemia to another hospital in Muscat. He was transfusion dependent and admitted to the Royal Hospital with fever and pancytopaenia and found to have a splenomegaly of 8cm and hepatomegaly of 6cm. His complete blood count (CBC) showed: Hb% - 3.2G/dL,

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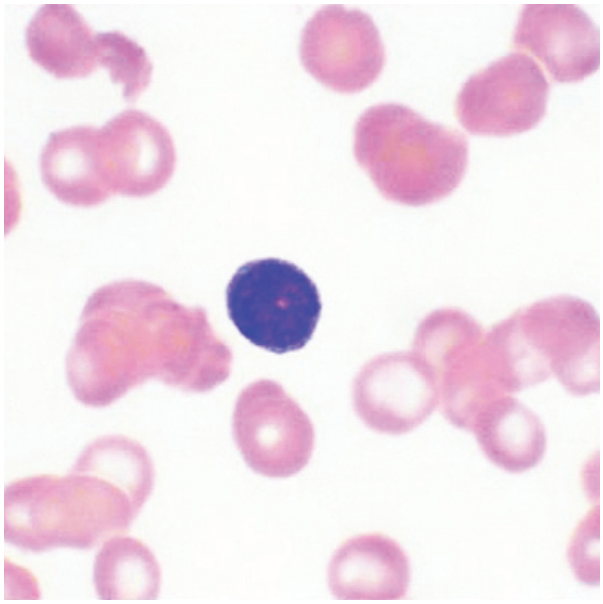

Figure 1: ***Normal lymphocyte in peripheral blood (Magnification x 400)***

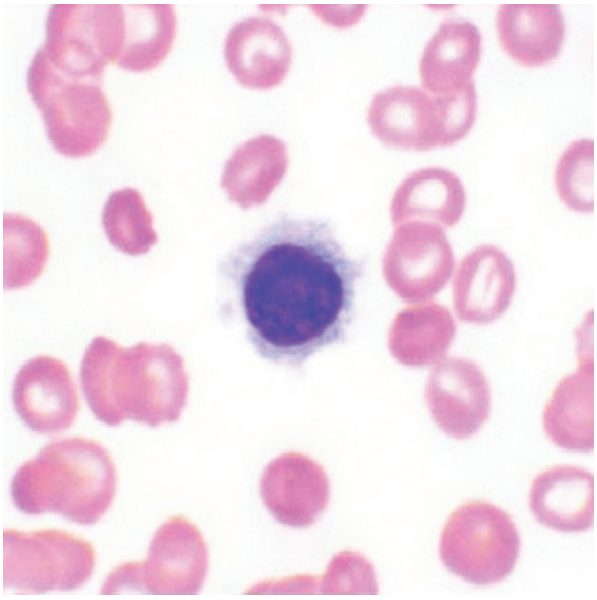

Figure 2: ***Hairy cell from peripheral blood from patient 1 (Magnification x 4000)***

white blood cells (WBC) - 0.8 x 10^9/L, absolute neutrophil count (ANC) 0.3 x 10^9/L, platelets - 48 x 10^9/L. Renal and liver function tests were normal other than for a low serum albumin. The blood picture confirmed the presence of pancytopaenia with no blast cells or dysplastic changes. He was resuscitated with blood transfusion and intravenous antibiotics. Nursed in isolation, the bone marrow aspirate was performed once his condition stabilised.

The bone marrow aspirate and trephine biopsy showed hairy cells. The cytochemistry was positive with tartrate resistent acid phosphatase (TRAP).

The immunohistochemistry on the trephine biopsy showed the lymphocytes were positive for CD20, CD79a and DBA 44.

Flow cytometry (FCM) on the bone marrow aspirate was positive for CD19, CD20, CD22, CD25, CD103, CD11c, FMC7 and kappa light chain and negative for CD3, CD5, CD7, CD10, CD23, CD38.

The diagnosis of hairy cell leukaemia was established, but the patient refused intravenous chemotherapy and received three mega units of interferon alpha subcutaneously thrice a week for six months. He achieved a complete haematological response and his CBC remained stable six months after cessation of therapy.

CASE 2

An Omani male, aged 62 years, was referred from another hospital for pancytopaenia, diagnosed with myelodysplasia (MDS) and treated with blood transfusions, erythropoietin and granulyte-colony stimulating factor (G-CSF) without significant response. He was admitted to the Royal Hospital with fever, malena, haematemesis and had cervical lymphadenopathy, bilateral basal crepitations with a splenomegaly of 6cm and a hepatomegaly of 4cm. His CBC revealed a severe pancytopaenia with: Hb% - 3.4 g/dL, WBC – 3.1 x 10^9/L, ANC -0.4 x 10^9/L, platelets 5.0 x 10^9/L. His blood picture and the bone marrow aspirate showed hairy cells positive for TRAP. The immunohistochemistry was positive on the trephine for CD20, CD79a and DBA44 confirming the diagnosis of hairy cell leukaemia. The flow cytometry (FCM) results on the bone marrow aspirate was positive for CD19, CD20, CD22, CD25, CD11c, FMC7 and kappa light chain.

He was admitted to the Intensive Care Unit with acute renal failure and septic shock and the blood culture showed a heavy growth of yeast. He succumbed to septicaemia and died a few weeks after admission despite intensive supportive care, broad spectrum antibiotics and antifungal therapy.

CASE 3

An Omani male, aged 47 years, a known diabetic on oral hypoglycaemics, was referred from a peripheral hospital for investigation of pancytopaenia, hepat-

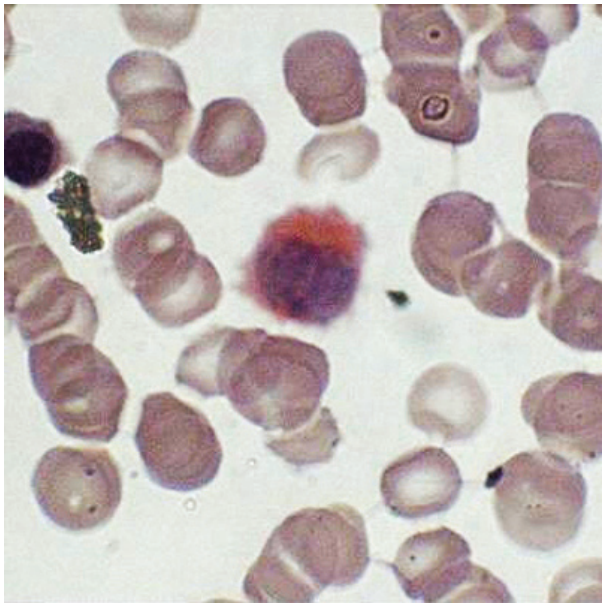

Figure 3: ***Tartrate resistent acid phosphatase reaction of hairy cell (Patient 2) (Magnification x 400)***

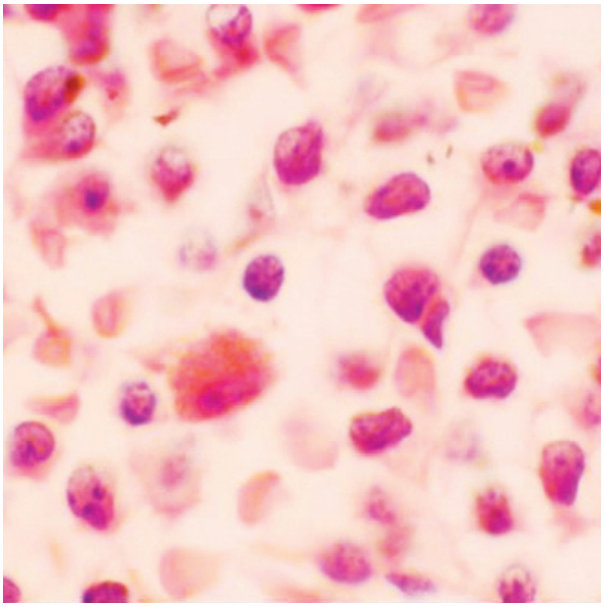

Figure 4: ***Trephine biopsy of patient 3 - 'fried egg' appearance with retraction of cytoplasm around the nucleus (Magnification x 400)***

osplenomegaly and fever. He had diarrhoea positive for salmonella which was treated before he arrived at the Royal Hospital. He recounted a two month history of backache and fever. He had hepatosplenomegaly with no lymphadenopathy. A computed tomography (CT) scan showed no evidence of mediastinal lymphadenopathy. His CBC revealed an Hb% - 8.9 g/dL, WBC – 2.6 x10^9/L, ANC 0.4x10^9/L, platelets – 94.0 x 10^9/L. The blood picture, bone marrow aspirate and the trephine biopsy showed hairy cells. The TRAP was unsatisfactory. The marrow aspirate was inadequate for FCM. The trephine biopsy was positive for CD79a, CD20 and DBA44.

He was treated with cladribine 0.14 mg/kg infusion over two hours for five days. He had two episodes of febrile neutropenia which were treated successfully with intravenous antibiotics. Six months later, his blood count improved to Hb 10.2 G/dL, WBC 3.1x10^9/L, ANC 1.9 x10^9/L and platelets – 141.0 x 10^9/L.

CASE 4

An Iraqi woman, aged 36 years, was referred for pancytopaenia detected on a routine CBC following a lower segment caesarian section. A CT scan showed a para-aortic lymphadenopathy in her chest and moderate hepatosplenomegaly. Her haematological parameters confirm the presence of bilineage cytopenia: Hb% -12.0 G/dL, WBC - 1.7 x10 ^{9}/L with ANC 0.2x10^9/L, platelets – 102.0x 10 ^{9}/L. The bone marrow aspirate and trephine biopsy showed hairy cells. The trephine biopsy was positive for CD20, CD79a and DBA44.

The FCM on the bone marrow aspirate was positive for CD19, CD20, CD22, CD25, CD103, FMC7 and kappa light chain.

She was treated with intravenous cladribine 0.1mg/kg continuous infusion for seven days. She continues to be followed up in the region where she lives and her CBC is normal.

DISCUSSION

Middle aged people are more affected by HCL, with a male-female ratio of 5:1.[1] Three of our patients were male and one was a female. The characteristic presentation is with pancytopaenia in more than 50% of patients, [3] moderate to massive splenomegaly in 85%, with or without hepatomegaly in 40% and bone marrow infiltration. Opportunistic infections are common. Rare presentations include vasculitis,[4] splenic rupture,[5] bony involvement,[6] neuropathy,[7] and autoimmune haemolytic anaemia.[8] Guillian-Barré syndrome has been reported in association with HCL or following cladribine treatment.[9, 10]

The peripheral blood shows the lymphocytes with shaggy hair like cytoplasmic projections in 90% of patients.[3] Although it leads to a distinct morphological diagnosis, sometimes a severe pancytopaenia, a dry bone marrow aspirate due to reticulin fibrosis could deprive us of this diagnostic information because of

the paucity of cells. Then the diagnosis is often based on the trephine biopsy which shows a patchy, diffuse infiltrate of the hairy cells, described as having a fried egg or honey comb appearance.[3] This occurs because the lymphocyte nuclei are spaced far apart due to the retraction of the cytoplasmic processes. The characteristic infiltrate of the spleen is in the red pulp and this is the only small B cell non Hodgkin's lymphoma which infiltrates the red pulp of the spleen.[3] If the bone marrow is not infiltrated, the splenic pathology can be used to diagnose the condition.

Infiltration of the kidneys, colon, adrenal glands, myocardium, meninges, pancreas and connective tissue have been reported.[3]

Cytochemistry and immunohistochemistry play an important role in the diagnosis of HCL. Cytochemistry on the hairy lymphocytes in blood or bone marrow aspirate with acid phosphatase is resistant to tartrate (TRAP). This is also done as immunohistochemistry on the trephine biopsy. There are no specific chromosomal abnormalities or molecular genetic alterations that are diagnostic of this disease.[1] Thus, morphology, cytochemistry and immunohistochemistry on the trephine biopsy/flow cytometry are useful tools in diagnosis of this uncommon lymphoma in its leukaemic phase. The hairy cells strongly express CD 103, CD25, FMC7, CD11c, and the B cell markers CD20, CD 79a and monoclonal kappa or lambda light chains.[1]

Supportive care with packed red cells and platelets were the mainstay of replacement therapy for the cytopaenias in our patients.

The current treatment of HCL is with the purine analogues, 2 chlorodeoxyadenosine (2CdA/cladribine) and pentostatin. Treatment is indicated for patients with significant cytopaenia, syptomatic splenomegaly, recurrent serious infections and constitutional symptoms. Cladribine is used as a single infusion or a course of subcutaneous injections.[11] The two widely used infusion regimens are either 0.1 mg/kg continuous intravenous infusion over 24 hours for seven days or 0.14 mg /kg intravenous infusion over two hours for five days, with no statistically significant difference in the rate of response or complications between the two regimens.[12, 13] A high incidence of febrile neutropaenia is recorded with this treatment.[14-17] G–CSF is used to overcome this side effect. It is rare that more than one course of treatment is required. In a recently published randomised study in 132 patients with untreated HCL, one group of patients were treated with the standard regimen of cladribine 0.14mg/kg daily for 5 days, while the other group was treated with a weekly dose of cladribine for six weeks. Both regimens where found to be equally effective; the weekly regimen was not, in fact, safer nor did it reduce toxicity or the risk of infections.[18] Treatment is discontinued once complete remission (CR) or partial remission (PR) is achieved with normalisation of peripheral blood counts.[19] Cladribine could induce a durable and long lasting remission in the majority of patients with only a single cycle of therapy and the relapsed patients could be treated successfully with a repeated cycle of cladribine.[20-22] There is a good correlation between minimal residual disease as demonstrated by DBA44 immunostaining and risk of relapse.[22]

Single IV pentostatin is administered intermittently for a longer treatment duration, but may result in a lower incidence of febrile neutropenia. [23, 24] It is usually administered in cycles of 4 mg/m2 twice weekly, repeated every 8 weeks [25] for three cycles. It was found to be highly effective in treating HCL with prolonged remission duration and without an increase in subsequent risk of malignancy.[25, 26]

Most patients remain disease free for ten years following treatment with purine analogues. CR is achieved in 80- 85% of patients. No patient has been followed up long enough to assess cure.[27, 28] The role of consolidation and maintenance therapy in preventing relapse or progression of the disease has not been evaluated. Interferon alfa is also used for those patients with intercurrent infections and severe cytopenias.[29] CR is seen in 20-30% of patients.[30] For patients with severe thrombocytopaenia and massive spleens, splenectomy is considered.[31] Monoclonal antibodies against CD20 (rituximab) and CD22 have now shown activity against HCL.[30] These antibodies seem to achieve good responses in the group relapsing on cladribine; however, its main role maybe useful in combination with purine analogues.[30]

CONCLUSION

HCL manifests in the middle years of life, with a male predominance, characterised by pancytopaenia caused by moderate to massive splenomegaly. It is an easy diagnosis to make on the morphology of well made blood and bone marrow smears. Although there are no specific markers for HCL, cytochemistry and flow cytometry readily confirm the diagnosis. This is the first report of HCL in Oman. The diagnosis and

management was based on current guidelines. The outcome of clinical remission was achieved in 3 patients and one patient succumbed to an opportunistic infection.

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