**Case History**

A limited case history was provided with this case with no age or gender given.

A full blood count was performed and the results were:
Hb 10.0/dl, WBC 203.2x10^9/l, PLT 226x10^9/l, RBC 2.93x10^12/l, MCV 108.8fl, 
MCH 34.2 pg, MCHC 31.4 g/dl. The patient also had a positive DCT and 
increased reticulocytes.

**Immunophenotype**

The consensus phenotype obtained from part one of the exercise was:

*Negative Antigens (value less than 30% as defined by BCSH guidelines):*
CD2, surface CD3, CD7, CD10, CD13, CD22, CD79b, FMC-7

*Positive Antigens (value of 30% or greater as defined by BCSH guidelines):*
CD5, CD19, CD20, CD23, CD38, CD45, HLA-DR

**Molecular and Cytogenetics**

No genetic results are available as they were not undertaken in this case.

**Peripheral Blood Morphology**

*Morphology comments from Dr Wendy Erber*

There is a peripheral blood lymphocytosis (Figure 1) of small and small- 
intermediate size. The lymphocytes have mature clumped chromatin and 
basophilic cytoplasm around half to one-third of the nucleus. The larger cells 
have more open chromatin and some have a nucleolus (Figure 2). Smear cells 
are prominent. Neutrophils appear normal. The red cells are normochromic and 
normocytic and the platelet count appears normal.

*Comment: Blood film features of chronic lymphocytic leukaemia.*

Although prolymphocytes are present, there are insufficient to suggest disease 
transformation or progression.
Examples of Digital Images Used

Figure 1: Peripheral Blood x50 magnification (Romanowsky)

Figure 2: Peripheral Blood x100 magnification (Romanowsky)
Exercise Conclusion/Case Discussion

Initial examination of the blood film and the immunophenotype – namely the expression of CD5 and CD19 would immediately suggest chronic lymphocytic leukaemia or possibly Mantle Cell Lymphoma. This is reflected in the conclusions provided by 97.2% of participants with Mantle cell lymphoma suggested by 1.4%. B prolymphocytic leukaemia and B lymphoblastic leukaemia/lymphoma, with t(v;11q23); MLL rearranged were submitted by 0.9% and 0.5% of participants respectively.

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is the most common leukaemia in the western world. It has an incidence rate of 2-6 cases per 100000 persons per year which increases to 12.8 per 100000 at the age of 65. In biopsies, CLL/SLL accounts for between 6-7% of NHL cases\(^1\). It has a male to female ratio of 1.5-2:1. Most patients are asymptomatic with some presenting with Auto Immune Haemolytic Anaemia (AIHA), infections, splenomegaly, hepatomegaly, lymphadenopathy or extra nodal infiltrates.

Morphology of Chronic lymphocytic leukemia/small lymphocytic lymphoma
In both the BM and PB there are small lymphocytes with clumped chromatin and scanty cytoplasm. The proportion of prolymphocytes is usually <2% with increasing numbers seen with more aggressive disease. A >55% proportion of prolymphocytes favours a diagnosis of prolymphocytic leukaemia.

The immunophenotype of CLL/SLL is the expression of CD20, CD22, CD5, CD19, CD79a, CD23, CD43 and CD11c (weak). CD10 is not expressed with FMC 7 and CD79b weakly or not expressed.

The Matutes scoring system for the diagnosis of CLL/SLL is based on the common marker profile of the strong expression of CD5 and CD23, negativity of FMC7, the weak to moderate expression of SmIg and the negative or weak expression of CD79b. A score of 1 is assigned if the antigen expression, whether positive or negative is typical for CLL/SLL. A score of 4 or 5/5 is strongly supportive of a diagnosis of CLL. If the score falls below this the diagnosis is less certain\(^2,3\).

The Matutes score in this case was

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Expression</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD5</td>
<td>(99%)</td>
<td>+1</td>
</tr>
<tr>
<td>CD23</td>
<td>(90%)</td>
<td>+1</td>
</tr>
<tr>
<td>CD79b</td>
<td>(17%)</td>
<td>+1</td>
</tr>
<tr>
<td>FMC 7</td>
<td>(90%)</td>
<td>+1</td>
</tr>
</tbody>
</table>

As can be seen this case has a score of 4 therefore suggesting CLL/SLL.
Although SmIg was not reported, retrospective analysis showed clonality, therefore increasing the score to 5.

Cytogenetic abnormalities
80% of cases have genetic abnormalities detected by FISH. 50% show del 13q14.3, 20% show trisomy 12 and, less commonly, deletions of 11q22-23, 17p13 and 6q21.

As reported in the case history, the patient had a positive DCT and reticulocytosis which is indicative of autoimmune haemolytic anaemia (AIHA). Patients with lymphoproliferative disorders are known to have an increased risk of developing AIHA and this is particularly true of CLL when the disease is advanced.

Mantle Cell lymphoma (MCL) comprises 3-10% of NHL. It occurs in middle aged to older individuals with a marked male predominance of approximately 2:1 or greater. Sites of involvement include lymph nodes, the spleen and bone marrow. There may or may not be peripheral blood involvement. Most patients present with stage 3 or 4 disease which include lymphadenopathy, hepatosplenomegally and bone marrow involvement. At these stages of the disease peripheral blood involvement is common. Some patients have a marked lymphocytosis which mimics prolymphocytic leukaemia.

Morphology of Mantle Cell lymphoma (MCL)
The lymphoma cells are small to medium in size. They are variable in shape and nucleocytoplasmic ratio. Some have a cleft or irregular nuclei. The chromatin condensation is less than in CLL and some cells appear blastic.

The immunophenotype of MCL is positivity for CD5, FMC 7 and CD43 and negativity of CD10. CD23 is weakly or not expressed.

Cytogenetics
t(11;14)(q13;q32) between IGH@ and cyclin D1 gene is present in almost all cases and is considered to be the primary genetic event.

As mentioned above there were no genetic studies carried out in this case so it is not possible to distinguish between the 2 leukaemias. However, the phenotype and morphology favour CLL.

B prolymphocytic leukaemia (B-PLL) is a B cell neoplasm which affects the spleen, bone marrow and peripheral blood. It is a rare disease and accounts for about 1% of lymphocytic leukaemias. The majority of patients are over 60 and there is a similar male to female distribution.
Most patients present with massive splenomegally with absent of minimal lymphadenopathy. There is usually a rapidly rising lymphocyte count commonly >100x10^9/l. Anaemia and thrombocytopenia are also seen.

**Morphology of B prolymphocytic leukaemia (B-PLL)**

There are >55%, usually >90% circulating prolymphocytes. These cells are twice the size of a lymphocyte. They have a round nucleus, moderately condensed chromatin, a predominant central nucleolus and a small amount of faintly basophilic cytoplasm.

The immunophenotype in B-PLL is the expression of CD19, CD20, CD22, CD79a and b and FMC 7. CD5 and CD23 are positive in 20-30% and 10-20% of cases respectively. Zap-70 and CD38 are expressed in 57% and 46% of cases.

**Cytogenetics**
The t(11;14)(q13;q32) translocation is demonstrated in 20% of B-PLL cases and these are now considered to be leukaemic variants of MCL.

**B lymphoblastic leukaemia/lymphoma, with t(v;11q23); MLL rearranged** is the most common leukaemia in infants less than 1 year old. This translocation may occur in utero and the evidence for this is that these leukaemias are frequent in the very young. The translocation has been identified in neonatal blood spots of patients who subsequently develop leukaemia. Patients usually present with a very high white count - >100x10^9/l

There are no unique morphological or cytochemical features to distinguish this from other types of acute lymphocytic leukaemia.

Immunophenotypically, the cells are usually CD19 and CD15 positive, CD10 and CD24 negative.

**EXERCISE CONSENSUS DIAGNOSIS (Classified as Correct)**

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)

**Other Differential Diagnoses (Classified as Minor Errors):**

*Mantle Cell lymphoma (MCL)*

**Other Differential Diagnoses (Classified as Major Errors):**

*B prolymphocytic leukaemia (B-PLL)*

*B lymphoblastic leukaemia/lymphoma, with t(v;11q23); MLL rearranged*
References


