Case 14

An 18-year-old medical student who complained of bone pain following alcohol ingestion and a swelling on the right side of her neck

Sylvia Le Roy, an 18-year-old medical student, presented to the haematology clinic with a 4-week history of fatigue and general malaise. She had been to her family doctor on two occasions during this period for a sore throat for which she received antibiotics. Sylvia had noticed a swelling on the right side of her neck about 3 weeks ago.

What could be causing these symptoms?
Recurrent sore throat in a young person with fever and swelling in the neck suggests a viral infection. However, the degree of fatigue and malaise should make you suspicious of a more serious underlying disease such as a lymphoma.

What is your differential diagnosis?
Infectious mononucleosis, cytomegalovirus (CMV) infection, HIV primary infection, hepatitis A or B, rubella, adenovirus, toxoplasma infection, β-haemolytic streptococcal infection, a malignant lymphoma.

What should be done next?
A full history should be taken with emphasis on weight loss, anorexia, fever or night sweats, known as B symptoms. Any change in size of the swelling, pain or tenderness should be enquired about.

Sylvia admitted to a weight loss of 4 kg and night sweats on six occasions during the last month. The swelling had increased in size, but was never painful and was not tender to touch. She had an unproductive cough for 4 days. She had mild asthma for which she took bronchodilators with good effect. Sylvia noticed bone pain on a few occasions after consuming alcohol. There was no other history apart from the usual childhood illnesses.

What is the significance of the night sweats, weight loss and bone pain induced by alcohol?
They are highly suggestive of non-Hodgkin's lymphoma or Hodgkin's disease. Although fever, sore throat and malaise can be found in a viral infection such as infectious mononucleosis, bone pain induced by alcohol, although rare, is a finding that appears to be specific to patients with Hodgkin's lymphoma.

What should be done next?
A full physical examination.

On examination, Sylvia was pale and appeared unwell. She had a mass in the right supraclavicular area (which measured 2 × 2 cm, was non-tender and fixed). There were no other enlarged lymph nodes and her liver and spleen were not enlarged. Sylvia had a temperature of 38°C.

What do the physical findings suggest?
Swellings in the supraclavicular area (usually lymph nodes) are almost invariably pathological. The pallor suggests anaemia and the fixed non-tender mass suggests a malignancy.

What type of anaemia would be most common in a girl of this age?
Iron deficiency anaemia would be the most common. The anaemia of chronic disease is a possibility especially in view of the likelihood of an underlying lymphoid malignancy.

What questions should be asked if iron deficiency is suspected?
A full dietary history, details of menstrual blood loss and any other evidence of bleeding.

A low iron intake is common in adolescence and can contribute to iron deficiency. Bleeding, particularly
menorrhagia, is also a common cause of iron deficiency in this age group.

**What is the significance of the fever?**

A viral infection or an upper respiratory tract bacterial infection could cause a fever (she has a history of asthma and complained of an unproductive cough); however, fever can be a manifestation of lymphoproliferative diseases (B symptoms).

**What investigations should be carried out?**

A full blood count (Table 42), a blood film, biochemical screen (Table 43), erythrocyte sedimentation rate (ESR), viral screen, a chest radiograph and analysis of the sputum for evidence of infection.

The ESR was 60 mm/hour (normal female 0–15 mm/hour). The blood film showed an increased number of platelets, but no other abnormalities.

**What blood film abnormalities would you expect to see in infectious mononucleosis?**

The presence of atypical mononuclear cells (Fig. 95). The serology would be positive with immunoglobulin M (IgM) antibodies to the virus capsid antigen (VCA). This is an IgM antibody which appears during the acute infection and persists for a number of months. Epstein–Barr nuclear antigen (EBNA) develops after the acute illness and persists for life.

**What could be the cause of the high platelet count?**

An increased platelet count is commonly found in response to acute haemorrhage. It can also be found in malignancies and may be a manifestation of myeloproliferative diseases, e.g. chronic myeloid leukaemia (Case 10), polycythaemia rubra vera (Case 16) or iron deficiency (Case 1).

**What is the significance of the elevated ESR?**

The elevation is a non-specific finding in infections or malignancies.

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**Table 42** Results of the full blood count.

<table>
<thead>
<tr>
<th></th>
<th>Patient’s results</th>
<th>Normal values (female)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>8.3 g/dL</td>
<td>11.5–16.4 g/dL</td>
</tr>
<tr>
<td>MCV</td>
<td>69 fL</td>
<td>83–99 fL (μm$^3$)</td>
</tr>
<tr>
<td>WBC</td>
<td>8.1 × 10$^9$/L</td>
<td>4–11 × 10$^9$/L (10$^3$/μL)</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>5.4 × 10$^9$/L</td>
<td>2–7.5 × 10$^9$/L (10$^3$/μL)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>2.7 × 10$^9$/L</td>
<td>1.5–3.5 × 10$^9$/L (10$^3$/μL)</td>
</tr>
<tr>
<td>Platelets</td>
<td>746 × 10$^9$/L</td>
<td>140–450 × 10$^9$/L (10$^3$/μL)</td>
</tr>
<tr>
<td>Reticulocytes</td>
<td>85 × 10$^9$/L</td>
<td>50–100 × 10$^9$/L (0.5–15%)</td>
</tr>
</tbody>
</table>

Hb, haemoglobin; MCV, mean corpuscular volume; WBC, white blood cell count.

**Table 43** Biochemical screen.

<table>
<thead>
<tr>
<th></th>
<th>Patient’s results</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td>5 μmol/L</td>
<td>0–17 μmol/L (0.3–1.1 mg/dL)</td>
</tr>
<tr>
<td>Alkaline</td>
<td>376 IU/L</td>
<td>40–120 IU/L</td>
</tr>
<tr>
<td>phosphatase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GGT</td>
<td>100 IU/L</td>
<td>5–40 IU/L</td>
</tr>
<tr>
<td>LDH</td>
<td>240 IU/L</td>
<td>230–450 IU/L</td>
</tr>
<tr>
<td>Ferritin</td>
<td>150 μg/L</td>
<td>20–300 μg/L (20–300 ng/mL)</td>
</tr>
</tbody>
</table>

GGT, gamma glutamyl transferase; LDH, lactic dehydrogenase.

**Figure 95** Atypical mononuclear cells in the blood of a patient with infectious mononucleosis.
The ESR measures the rate of sedimentation of red cells in a tube. Red cells are normally kept apart by van der Waal’s forces. In patients with infection or malignancies, high levels of immunoglobulin (antibodies) or fibrinogen (a plasma coagulation protein) can inhibit these forces, allowing the red cells to stick together.

**What test would you carry out to elucidate the mechanism of the raised ESR?**

Serum protein electrophoresis and a coagulation screen.

The serum protein electrophoresis shows a polyclonal gammopathy. This indicates a normal response to infection, but can be a non-specific finding in malignancy. The coagulation screen revealed a fibrinogen of 12 g/L (normal 1.5–4.0 g/L), which explains the raised ESR. The synthesis of fibrinogen may be increased in malignancies. The viral screen including EBV serology was negative excluding a diagnosis of infectious mononucleosis. The chest radiograph (Fig. 96) showed enlargement of the right paratracheal nodes.

**Now what is your differential diagnosis?**

Sylvia is anaemic with a low MCV suggesting iron deficiency or the anaemia of chronic disease. The serum ferritin of 150 μg/L excludes iron deficiency. The high platelet count could be associated with a malignancy as there is no clinical evidence of acute haemorrhage. Sylvia’s liver blood tests are abnormal suggesting a viral infection or malignancy. The chest radiograph confirms enlarged lymph nodes in the neck and upper mediastinum. These results together with her symptoms suggest a malignant lymphoproliferative disease including Hodgkin’s lymphoma, non-Hodgkin’s lymphoma or acute lymphoblastic leukaemia. Sarcoidosis could also present with hilar lymphadenopathy.

**KEY POINT**

Fever, night sweats and weight loss are known as B symptoms and are commonly found in Hodgkin’s lymphoma, non-Hodgkin’s lymphoma and chronic lymphocytic leukaemia.

**How should this patient be managed?**

Sylvia should be referred immediately to hospital for further investigation.

**What further investigations should be carried out in the hospital?**

A bone marrow aspirate and biopsy (Fig. 97) and a computed tomography (CT) scan of thorax and abdomen.

The bone marrow aspirate and biopsy showed increased iron stores in keeping with the diagnosis anaemia of chronic disease. The CT of thorax and abdomen showed adenopathy in the anterior mediastinum (Fig. 98).

**Figure 96** Chest radiograph showing paratracheal lymphadenopathy (N).

**Figure 97** Bone marrow with Reed–Sternberg cells (RS) (i.e. Hodgkin’s lymphoma).
Can you now construct an algorithm for a young patient with fever, night sweats and lymphadenopathy?

Yes.

**Figure 98** Computed tomography (CT) of thorax showing lymphadenopathy in the superior mediastinum (L).

**Figure 99** Lymph node biopsy shows Reed-Sternberg (RS) cells and collagen bands: nodular sclerosing Hodgkin’s lymphoma.

**KEY POINT**

Bone marrow involvement in Hodgkin’s lymphoma (Fig. 97) is extremely uncommon and occurs in less than 5% of patients. Marrow involvement significantly worsens the prognosis. Marrow involvement is extremely common in non-Hodgkin’s lymphoma and does not have the same prognostic significance as in Hodgkin’s disease.

**KEY POINT**

Hodgkin’s lymphoma is most frequently seen in adolescents and young adults, but there is a second peak after the age of 50 years.

**How do the investigations influence the management?**

The extent of the disease will influence the type of management.

**What are the principles of management of Hodgkin’s lymphoma?**

Hodgkin’s lymphoma has been one of the earliest malignancies to be cured by combination chemotherapy. However, extensive nodal disease may also require radiotherapy.

**KEY POINT**

The long-term cure rate for Hodgkin’s lymphoma is now so good that the emphasis is being placed on limiting the toxicity of therapy.

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The anaemia of chronic disease is characterized by a low MCV, but normal ferritin and bone marrow iron stores. It is commonly seen in association with malignancy or chronic infectious diseases such as tuberculosis. Hepsidin synthesis is increased in the anaemia of chronic disease and inhibits the escape of iron from macrophages thereby limiting its availability to form haem.

**What should be done next?**

A lymph node biopsy.

A lymph node excision biopsy reveals nodular sclerosing Hodgkin’s disease (Fig. 99).

Hodgkin’s lymphoma is a malignancy most commonly of B-cell origin. It is manifested by enlarged lymph nodes, hepatosplenomegaly and B symptoms. The classic cell associated with Hodgkin’s lymphoma is the Reed-Sternberg cell. There is evidence of EBV infection in many patients with Hodgkin’s lymphoma, but a direct causative role has not been demonstrated.
Night sweats, fever, anaemia and supraclavicular lymphadenopathy in a young patient with a raised ESR

Viral infection (infectious mononucleosis) or lymphoproliferative disease

Atypical mononuclear cells on blood film. Positive EBV serology

Infectious mononucleosis

Raised platelet count in the absence of other abnormalities in the blood film

Assessment of extent of lymphadenopathy by CT scanning

Lymph node biopsy

Hodgkin’s lymphoma

CASE REVIEW

A young girl presents to the doctor with a history of fatigue, malaise, weight loss and a sore throat. The most common diagnosis would be a fairly innocuous viral infection. Many patients with malignant lymphomas, Hodgkin’s lymphoma or acute leukaemia are initially diagnosed incorrectly because these diseases are rare compared with common viral infections, such as infectious mononucleosis, adenovirus infections or even streptococcal throat infection.

What makes you suspicious is the persistence of symptoms and signs, and the marked degree of malaise, fatigue and weight loss. The presence of lymphadenopathy in the neck of a young person is always difficult as it may be associated with localized infection; in this case it is described in the supraclavicular area which is always pathological. The size of the node, the site and the fact that it is not painful and fixed suggest something more serious. The presence of anaemia would be unusual in a girl of this age unless it was totally unconnected, such as an iron deficiency resulting from menorrhagia. Anemia should make you suspicious of a systemic disorder in association with the symptoms and signs of sore throat, malaise, weight loss and lymphadenopathy.

Outcome. Sylvia was treated with combination chemotherapy to which she had a complete response. She returned to her medical studies 6 months from the time of her diagnosis. Sylvia is currently a senior house officer in a large teaching hospital and remains in complete remission from her disease.
**KEY POINTS**

- The presence of B symptoms together with persistent signs, symptoms, lymphadenopathy and weight loss alerts one to the suspicion of a malignant lymphoma
- In this age group, Hodgkin’s lymphoma must be suspected although non-Hodgkin’s lymphoma and acute lymphocytic leukaemia can also occur
- The relationship between EBV infection and Hodgkin’s lymphoma is difficult to unravel. Epidemiology suggests that 50% of young adults (late teenagers and those in their early twenties) will develop infection with EBV. Symptoms and signs of infection will only appear in half of these and the reason for this is unknown
- The association of infectious mononucleosis and Hodgkin’s lymphoma is strongest in young adults, but virus found in tumour cells is least frequently detected in tumours in this population
- It is still not clear whether primary infection with EBV in the form of infectious mononucleosis is a risk factor for EBV-positive Hodgkin’s lymphoma
- It is possible that vaccination against EBV may modulate the course of infection and may reduce the risk of Hodgkin’s lymphoma. This remains unproven
- Patients who fail to respond to chemotherapy or who relapse quickly after treatment may be cured with high-dose therapy and autologous stem cell transplantation

**Further reading**


Horning SJ. Risk, cure and complications in advanced Hodgkin lymphoma. *asheducationbook.hematologylibrary.org/cgi/content/full/2007/1/197*