QUESTION 10

A 25-year-old man presents with recent onset of lethargy, fever, bruising and abdominal pain. On examination, he is clinically anaemic and is noted to have scattered bruises, bilateral pleural effusions, an abdominal mass and cervical and axillary lymphadenopathy.

Full blood examination shows:

- Haemoglobin: 76 g/L [128-175]
- Mean corpuscular volume (MCV): 100 fL [80-97]
- White cell count: 3.2 x 10^9/L [3.9-12.7]
  - Neutrophils: 1.6 x 10^9/L [1.9-8.0]
  - Lymphocytes: 1.1 x 10^9/L [0.9-3.3]
  - Monocytes: 0.2 x 10^9/L [0.3-1.1]
  - Eosinophils: 0.2 x 10^9/L [0.0-0.5]
  - Basophils: 0.1 x 10^9/L [0-0.1]
- Platelet count: 32 x 10^9/L [150-396]

More than 90% of the nucleated cells in the bone marrow aspirate have the appearance shown below (examples indicated by arrows).

Coagulation parameters are normal.

The most likely marrow karyotypic abnormality is:

A. monosomy 7.
B. t (9;22).
C. 5q minus.
D. t (8;14).
E. t (15;17).

Presentation:
- Pancytopenia (anaemia, neutropenia, thrombocytopenia)
- Bruising
- Pleural effusions
- Abdominal masses
- Cervical and axillary lymphadenopathy

This bone marrow shows cells with vacuoles where the arrow is pointing. These cells in the bone marrow and peripheral blood are typical in Burkitts lymphoma.
Burkitt's lymphoma | t(8:14) | vacuoles

Burkitt's lymphoma
- Aggressive NH lymphoma
- B-cell lymphoma

Burkitt's lymphoma tumor cells are monomorphic, medium-sized cells with round nuclei, multiple nucleoli, and basophilic cytoplasm
- Cytologically, Burkitt's lymphoma (BL) cells resemble the small non-cleaved cells within normal germinal centers of the secondary lymphoid follicle.
- These cells differ from lymphoblastic lymphoma cells in two respects; they have intermediate sized non-convoluted nuclei with coarse chromatin, and the cells have more abundant cytoplasm.
- Cytoplasmic lipid vacuoles are usually evident on imprints or smears.

Defining features of Burkitt's lymphoma —
- c-myc deregulation, as a consequence of which the tumor cells remain constantly in cycle. It is this phenomenon that results in both its morphologic homogeneity and its clinical behavior.
- Unfortunately, detection of c-myc translocation is not practical in all clinical specimens for technical reasons.
- In addition, some DLBCLs have t(8;14) and c-myc deregulation, and it is not clear if all such cases should be treated like BL.
- The best practical surrogate for c-myc deregulation is thought to be the proliferation fraction: in a tumor with c-myc deregulation, 100 percent of viable cells should be in cycle, and should express Ki-67.
- Thus, the WHO committees concluded the following:
  - Diagnosis of BLL should only be made in a tumor with morphologic features intermediate between BL and DLBCL, in which the Ki-67 fraction of viable cells is at least 99 percent. This tumor will be considered a subtype of BL in the WHO classification.
  - Cases with morphologic features of DLBCL with a high proliferation fraction [or t(8;14)], and cases that are morphologically borderline between BL and DLBCL with a lower proliferation fraction, should be classified as DLBCL.

Gene expression profiling may be helpful in enhancing current pathologic methods for distinguishing DLBCL from BL, as well as establishing prognosis, and, ultimately, appropriate treatment

Translocations involving the c-myc oncogene — In 90 percent of the cases studied, BL involves a translocation between the long arm of chromosome 8, the site of the c-myc oncogene (8q24), and one of three locations:
- The Ig heavy chain region on chromosome 14: t(8;14)
- The kappa light chain locus on chromosome 2: t(2;8)
- The lambda light chain locus on chromosome 22: t(8;22).

CLINICAL FEATURES — Three distinct clinical forms of Burkitt's lymphoma can be recognized: endemic, sporadic, and immunodeficiency-associated. Although they are histologically identical and have similar clinical behavior, there are differences in epidemiology, clinical presentation, and genetic features between the three forms:
- The endemic (African) form presents as a jaw or facial bone tumor that spreads to extranodal sites including mesentery, ovary, testis, kidney, breast, and especially to the bone marrow and meninges.
- The nonendemic or American form has an abdominal presentation, most often with massive disease and ascites, involving distal ileum, stomach, cecum and/or mesentery, kidney, testis, ovary, breast, bone marrow, or central nervous system.
- Immunodeficiency-related cases more often involve lymph nodes; both these and sporadic cases may present as acute leukemia.

Myelodysplasia, acute myeloid leukaemia | monosomy 7 |
Aplastic anemia versus hypocellular MDS — Although most patients with MDS have normal or increased bone marrow cellularity, 8 to 28 percent have bone marrow cellularity of less than 25 percent and/or cellularity which is lower than expected based upon the patient's age. The distinction between aplastic anemia and hypocellular MDS is important because the clinical course and management of these two entities may differ.

Presence of a clonal chromosomal abnormality (eg, 5q-, monosomy 7) confirms the diagnosis of MDS. Expression of the tumor necrosis factor (TNF) receptor on bone marrow stem cells by flow cytometry may discriminate AA from MDS. Patients with AA have a markedly greater TNF receptor expression than those with MDS. Patients with hypocellular MDS may have a better prognosis than those with normal/hypercellular marrows.

**Chronic myeloid leukaemia | Philadelphia chromosome t(9; 22) |**

Chronic myelogenous leukemia (CML, also known as chronic myelocytic or chronic myeloid leukemia) is classified as one of the myeloproliferative disorders, along with polycythemia vera (PV), essential thrombocythemia (ET), and agnogenic myeloid metaplasia (AMM).

Philadelphia chromosome t(9; 22) — present in 90% CML

**Myelodysplasia | 5q minus | monolobula megakaryocytes**

PRIMARY MYELODYSPLASTIC SYNDROMES — Clonal chromosomal abnormalities can be detected in bone marrow cells in 40 to 70 percent of patients with primary MDS. This fraction is somewhat lower than the 70 to 95 percent detected in patients with AML de novo.

There are two features that distinguish the cytogenetic changes in primary MDS from those in AML de novo:

- Although +8 (trisomy 8), -5/del(5q) [11-14], -7/del(7q) [15], and del(20q) are common in both disorders, the specific structural rearrangements (balanced translocations) that are closely associated with distinct subsets of AML de novo are almost never seen in MDS. Deletions of chromosomes 5 and 7 are particularly characteristic of therapy-related MDS induced by alkylating agents and/or radiation therapy. How these deletions might promote myeloid leukemogenesis is described elsewhere.

- With occasional exceptions (such as the 5q- syndrome), chromosomal abnormalities in MDS have not correlated with specific clinical or morphological subsets using the FAB or WHO criteria (show table 2).

Cytogenetics as a predictor of prognosis — The ability of cytogenetic analysis to predict the outcome of any individual patient with MDS is made difficult because many patients die from persistent and profound pancytopenia, regardless of whether or not transformation to acute leukemia occurs. Despite this limitation, there are data demonstrating the prognostic significance of particular cytogenetic abnormalities for predicting survival as well as progression to AML, which occurs in 22 to 35 percent of patients overall.

- Patients with a normal karyotype have a low likelihood of progression to AML.
- Among patients with an abnormal karyotype, the outcome is
  - more favorable for those with del(5q) or del(20q) as single defects
  - intermediate with most other single abnormalities, and
  - poor with complex karyotypes (most also have abnormalities of chromosome 5 or 7, or both)
- The outcome is also poor in patients with a single defect involving chromosome 7, particularly band 7q32

**Acute promyelocitic leukaemia | t(15;17) | auer rods**
Peripheral smear from a patient with acute myeloid leukemia. There are two myeloblasts, which are large cells with high nuclear-to-cytoplasmic ratio and nucleoli. Each myeloblast has a pink/red rod-like structure (Auer rod) in the cytoplasm (arrows)

Auer rods within leukemic blasts are rare but their presence serves to identify the FAB category of RAEB-T. However, with the WHO recommendation that the blast count for the diagnosis of acute myeloid leukemia (AML) should be dropped from 30 to 20 percent, it was the consensus that the RAEB-T category within MDS should be dropped. Thus, the presence of Auer rods in a patient with a prior diagnosis of MDS should lead to the suspicion that the patient has already transformed into AML.

15;17 translocation in APL — Acute promyelocytic leukemia (AML-M3) is typically characterized by a structural rearrangement involving the long arms of chromosomes 15 and 17; the rearrangement is defined as t(15;17)(q22;q11-12). This rearrangement is highly specific for acute promyelocytic leukemia (APL) and has not been found in patients with any other type of leukemia or with a solid tumor.

APL is a unique clinicopathological entity characterized by infiltration of the bone marrow by promyelocytes in association with clinical or laboratory evidence of disseminated intravascular coagulation, which may worsen during the initial cytolytic response to chemotherapy. A characteristic folded, reniform (kidney-shaped), or bilobed nucleus is invariably found in some of the promyelocytes; coarse azurophilic granules and multiple Auer rods are also common. The microgranular variant of APL differs from the more frequent hypergranular type in that the cytoplasmic granules in the leukemia cells are smaller and sometimes beneath the limit of resolution of the light microscope.

The leukemic cells in patients with APL and the t(15;17) are exquisitely sensitive to the differentiating effect of ATRA. The optimal use of ATRA therapy has not yet been determined, but it has become a mandatory component of treatment. The PML/RAR-alpha gene can now be routinely identified within 24 hours by PCR methods, allowing confirmation of the diagnosis of APL and appropriate remission induction therapy (ATRA and anthracycline). Having achieved a remission, many patients remain disease-free after intensive consolidation chemotherapy using an anthracycline (daunorubicin or idarubicin). Cases of APL that lack the t(15;17) do not respond to ATRA; the PLZF/RAR-alpha fusion protein that is produced in the t(11;17) rearrangement in rare cases shows reduced sensitivity to retinoic acid that cannot be overcome by pharmacologic doses of ATRA alone.