

A Boy With Fever And Sore Throat

Case History:

A 13-year-old boy presented with a 2 weeks history of headache and low grade fever.

He had no significant past medical history, no allergy and he was on no medication.

On examination there were bilateral rubbery, mobile, tender cervical lymph nodes. There were no other palpable lymph nodes elsewhere. The liver was enlarged and the spleen was just palpable. The rest of the examination was normal.

His initial full blood picture, was:

WBC	13.3 × 10 ⁹ /L	Diff: Neutrophils	53%
HAB	12.0 g/dL	Lymphocytes	31%
HCT	37.1 L/L	Monocytes	5%
MCV	80 fL	Eosinophils	11%
PLT	393 × 10 ⁹ /L	ESR: 26 mm/hr	

Question 1: What is the differential diagnosis at this stage?

The patient presented with two weeks' history of low grade fever, bilateral cervical lymphadenopathy and hepatosplenomegaly. The clinical picture suggested a systemic (e.g. a viral infection) rather than a localized disease (e.g. tuberculosis) affecting the reticulo-endothelial system. Liver and spleen can be palpable sometimes in a healthy young child. For older children, however, palpable liver and spleen are abnormal until proven otherwise. Headache is a non-specific symptom, and could be the result of a pathological condition affecting the central nervous system, or it could be reactive to fever or a systemic illness. In this patient, a viral illness particularly infectious mononucleosis as a result of Epstein Barr Virus (EBV) infection should be sought. The classical "kissing disease" or glandular fever in adolescents and youths is a primary EBV infection characterized by fever, rash, generalized

lymphadenopathy and hepatosplenomegaly. The condition is however not commonly seen locally probably because normal subjects often acquire the infection and become seropositive early in life. Other viral infections such as adenovirus, cytomegalovirus (CMV), rubella or hepatitis are possible diagnosis although the clinical course is not typical. Tuberculosis infection should be considered since it is prevalent locally in Hong Kong but hepatosplenomegaly is not a frequent finding. Other bacterial infections e.g. *Staph. aureus*, often lead to localized cervical lymphadenitis. Other unusual infections e.g. toxoplasmosis, malaria, or even parasitic infections are remote possibilities.

Another important group of diseases causing lymphadenopathy and hepatosplenomegaly are neoplastic conditions, e.g. leukemia, lymphoma or solid tumour with distant metastasis. Autoimmune condition such as systemic lupus is a possible differential diagnosis. Reactive hemophagocytic syndrome which is often reactive to a viral or bacterial infection is characterized by pyrexia of unknown origin, lymphadenopathy and hepatosplenomegaly and often runs an aggressive clinical course. Patients with this condition have pancytopenia as a result of excessive hemophagocytosis in the marrow and other body tissues. Kimura's disease which is a rare condition of unknown etiology, is characterized by eosinophilia and eosinophilic infiltration of glandular tissues.

The initial blood count did not reveal cytopenia which is typical of neoplastic condition with marrow involvement. Haemoglobin level of 12 g/dl was within the normal range for the age. ESR was not significantly increased. Mild leucocytosis with eosinophilia (over 1 × 10⁹/L in this patient) was present. The latter is usually defined when eosinophilia count is above 0.6 × 10⁹/L. Nevertheless, eosinophilia is a non-specific finding. It is uncertain whether it is directly related to the primary illness or an incidental finding. There was no marked increase in number of lymphocytes which is typical of infectious mononucleosis syndrome. Platelet count was normal.

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Question 2: What other investigations will you order?

The first thing is to review the blood film. This is simple but very useful to look for increased atypical lymphocytes as in EBV infection or blasts in leukemia. In EBV infection, atypical lymphocytes are activated T cells in response to the infection.

Virus serology in particular for EBV should be tested. This should include IgM and polyvalent IgG against EBV. Monospot test is used for detection of heterophil antibodies against animal tissues. Antibody against Epstein Barr nuclear antigen (EBNA) could be tested and its presence represents previous infection. Serology for adenovirus, CMV, toxoplasmosis and hepatitis should be screened. Mantoux test should be performed to look for evidence of tuberculosis infection. Screen for immune markers and immunoglobulin pattern may be useful.

Various imaging is used to assess the extent of and size of lymphadenopathy. Chest x-ray is used to look for mediastinal mass, hilar lymphadenopathy and also any pulmonary lesion. Ultrasound or CT scan of the abdomen is used to look for abdominal mass, enlarged para-aortic lymph nodes, and splenic involvement.

Question 3: Please make further comments on the case

No significant rise at 4 weeks' interval in antibody titer speaks against recent infection by the corresponding organisms. IgM against EBV was negative and this would not support a recent EBV infection. Other EBV serological tests would be useful. An increase in paired titer of EBV IgG antibodies or positive monospot test will be good evidence of recent infection. The presence of antibody against EBNA, in contrast, is supportive of previous EBV infection.

Marrow was said to be clear. However it did not specify whether it was a marrow aspirate or bone marrow trephine biopsy. Normally both examinations are required to exclude marrow involvement by a tumour since marrow aspirate can sometimes miss patchy

metastatic involvement. CT scan of the thorax and abdomen revealed extensive lymphadenopathy. It also confirmed spleen was involved. However imaging could not tell the nature of lymphadenopathy and could not distinguish lymphomatous involvement from infective cause.

The definitive diagnosis still rests on the histology examination. If lymphoma is suspected, it is essential to proceed with an excisional biopsy of an involved lymph node for proper histology assessment. Needle aspiration is not optimal for the diagnosis of lymphoma but can be a quick test when an infective cause is suspected.

In pediatric practice, lymphoma accounts for about 10% of childhood cancer. Non-Hodgkin's lymphoma (NHL) is much more commonly seen than Hodgkin's disease (HD). The incidence of HD in Hong Kong Chinese is particularly lower than the Caucasian counterparts. If HD does occur, it normally affects older children. The most common NHL subclass in childhood is lymphoblastic lymphoma, Burkitt's lymphoma, and anaplastic Ki-1 lymphoma. Patients with Burkitt's lymphoma typically present with gross abdominal disease. The typical finding of Reed-Sternberg's cells (cells with paired nuclei assuming an owl's eye appearance) is typical of Hodgkin's disease. This patient had at least stage III disease since lymph nodes on both side of the diaphragm were involved. Stage IV disease refers to marrow, pulmonary or liver involvement by lymphoma. The patient is classified to have B symptoms if significant weight loss, fever or excessive sweating is present.

It is worth noting that eosinophilia is an associated feature of Hodgkin's disease. It is also important to know that Hodgkin's disease and tuberculosis infection can co-exist. ■

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