

An Unusual Case of Atypical Lymphocytosis

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حالة غير اعتيادية لكثرة اللِّمفاويَّات اللا نمطية

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ملخص: كَثْرَةُ اللِّمفاويَّات اللا النمطية بسبب الالتهابات عادة ما يلاحظ في الالتهابات الفيروسية والجراثومية المزمنة. ندرج هنا حالة ولد عمره أربع سنوات مصاب بالتهاب حاد بالعُقَدِيَّات والتي ظهرت على هيئة التهاب في اللوزتين والتهاب العُقَدِيَّة العنقية في الجهتين. لقد أظهر الفحص المجهرى لشريحة أن نسبة الكريات الليمفاوية اللا نمطية 33%. كان أضداد الجلوبيولين المناعي (M) إيجابيا للفيروس المَصْحَمُ للخَلَايا . وفيروس الهَرِيْسُ البَسِيْط . وفيروسُ إِيْبِسْتاين- بار ومع هذا استجاب المريض بشكل كبير للمضادات الحيوية.

مفتاح الكلمات: الخلايا الليمفاوية اللا نمطية . التهاب العُقَدِيَّات الحاد . الغدة الليمفاوية . تقرير حالة . عمان .

ABSTRACT Atypical lymphocytosis due to infections is classically seen in viral and chronic bacterial infections. A four year old boy with acute streptococcal infection presented at Al-Nahdha Hospital, Muscat, Oman, with follicular tonsillitis and bilateral cervical lymphadenitis. The blood film showed 33% atypical lymphocytes. Serologically, immunoglobulin M (IgM) antibodies were positive for cytomegalovirus, herpes simplex virus, and Epstein Barr virus, but the patient responded dramatically to antibiotics.

Key words: Atypical lymphocytes; Acute streptococcal infection; Lymphnode; Case report; Oman.

Acute bacterial infections usually produce neutrophilic leucocytosis. Chronic bacterial and viral infections typically cause lymphocytosis. However, acute streptococcal infections can lead to atypical lymphocytosis as well as elicit false positive viral antibody results.

CASE REPORT

A 4 year old boy from Barka, Oman, came to the Ear, Nose and Throat (ENT) Department of Al-Nahdha Hospital, Muscat, Oman, on 4 November 2007 complaining of fever and difficulty in swallowing for the last 4 days. On clinical examination, both the tonsils were huge and studded with follicles. There were bilateral cervical lymphnodes, each measuring 7cm x 6cm, tender, soft and hot. The clinical diagnosis entertained was follicular tonsillitis with bilateral cervical lymphadenitis. The patient was immediately admitted to the ENT. A complete blood count (CBC) on admission showed Hb = 11.5 g/dl. The total white blood cell count (WBC) count = $7.6 \times 10^9/L$ and the platelet

count = $237 \times 10^9/L$, which was normal, but the erythrocyte sedimentation rate (ESR) was 15 mm at 1 hour, which was mildly above the normal range of 10 mm at 1 hour. A sample sent for blood culture subsequently revealed no growth. The throat culture grew normal flora, but the swab showed gram positive cocci. The CBC was repeated 3 days later on 7 November and showed Hb = 10 g/dl; total WBC count = $14.7 \times 10^9/L$ and platelet count = $141 \times 10^9/L$. A differential WBC count showed 33% atypical lymphocytes. We advised that a monospot test be done and the clinicians put the patient on a course of intravenous augmentin. The same day (7 November), the monospot test results were negative. We immediately requested an Epstein Barr virus (EBV) immunoglobulin M (IgM) antibody test and a TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex) test. Next day, the CMV (cytomegalo virus) IgM came out positive. We requested a polymerase chain reaction (PCR) test to detect CMV DNA. On 9 November, the herpes simplex IgM test came out positive. On 10th November,

the EBV IgM antibody test also came out positive. Clinically, the patient was afebrile, the lymphnode enlargement on both the sides had vanished, and he had responded very well to antibiotics. He was discharged on the same day. The PCR test result arrived on 12 November and did not detect any CMV DNA in the plasma. But an antistreptolysin O (ASO) titre done on the sample was increased and measured 400 IU. The boy came for a follow up in December 2007. Clinically and haematologically (CBC, differential WBC count and ESR) he was absolutely normal.

DISCUSSION

This 4 year old boy had an acute onset of fever and dysphagia. The dysphagia was due to the severe enlargement of both the tonsils. Contributing to the above was bilateral, tender, soft and hot cervical lymph node swellings. His tonsils were studded with follicles and tender soft and hot. A diagnosis of lymphadenopathy fitted well with an acute bacterial infective pathology. Sensing the severity of the condition, the boy was admitted to the hospital. The throat swab revealed many gram positive cocci, but the throat swab culture grew normal flora and the blood culture did not reveal any growth. This could be explained by the fact that this patient was referred from Barka and was already on oral antibiotic treatment. It is well known that a prior antibiotic treatment can lead to no growth on culture.¹

The CBC repeated 2 days later on the automated haematology analyzers revealed mild anaemia, leucocytosis and mild thrombocytopenia. A blood film was prepared. The most striking feature on this film was the presence of numerous atypical lymphocytes with deep basophilic cytoplasm and large, round to oval to indented to irregular nuclei. No blasts were seen [Figure 1]. A differential count revealed 16% neutrophils, 51% lymphocytes and 33% atypical lymphocytes. A diagnosis of atypical lymphocytosis was made. Viral infections are one of the commonest causes of lymphocytosis and atypical lymphocytosis.² Such a large percentage of atypical lymphocytes made the laboratory entertain the diagnosis of viral infection.

We advised a monospot test to rule out infectious mononucleosis, but the clinicians thought and acted otherwise. They were sure that it was an acute bacterial infection and put the patient on a course of intravenous augmentin.

To our surprise, the subsequent monospot test result came out negative. We immediately requested an

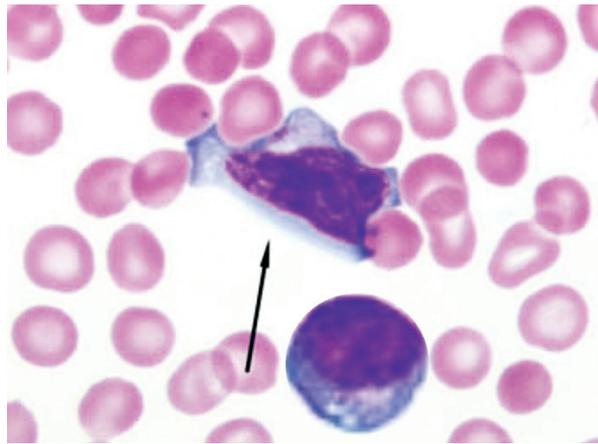


Figure 1: Blood smear showing atypical lymphocytes

EBV antibody test to increase the specificity of the test and also asked for a TORCH test. Unlike the clinicians, we were pursuing the viral etiology. When CMV IgM antibody test came out positive, the laboratory entertained the diagnosis of cervical lymphadenitis due to acute CMV infection and requested a blood PCR test to detect CMV DNA.

The next day, the *herpes simplex* virus IgM antibody test came positive. We were puzzled. A day later when EBV IgM antibody also came positive for this patient, we were confused. A diagnostic dilemma set in. Was the patient suffering from cytomegalovirus infection or a *herpes simplex* virus infection or an EBV infection?

We turned our attention to the patient in the ward. We were amazed to see the patient afebrile, with tonsillar and lymphnode enlargement having disappeared, playing in the toy room and ready for discharge. After 7 days of antibiotic treatment, the sick looking boy was perfectly normal. The experience and expertise of the clinicians had won the case.

The laborious laboratory scientists looked lost. The PCR test result arrived two days after the patient's discharge and did not reveal CMV DNA in the plasma, confirming that the patient did not have CMV infection. Did he have *herpes simplex* or EBV infection? Facilities for doing a PCR test for *herpes simplex* and EBV were not available. Fortunately, one of our scientists had done an ASO titre on this patient and it was increased and measured 400 IU. An ASO titre of >166 Todd units is seen in 80% of children with streptococcal pharyngitis.³

By now, things were getting clearer. We analysed the case comprehensively. Here was a patient who pre-

sented acutely with fever, swollen, follicle studded tonsils and enlarged bilateral tender, soft and hot cervical lymphnodes. The throat swab had showed numerous gram positive cocci. The ASO titre was increased and the patient dramatically and completely responded to antibiotics. Taking into consideration, the presenting symptoms and signs, the laboratory data and clinical response, the diagnosis was crystal clear. The patient suffered from an acute streptococcal infection.

However, two features demanded explanation. One was the high percentage of atypical lymphocytes in an acute bacterial infection and the second was the CMV IgM, *herpes simplex* IgM and EBV IgM, all positive in a patient with acute streptococcal infection. Lymphocytosis often occurs in young children in response to infections which produce a neutrophil reaction in adults.⁴ This explains the lymphocytosis and atypical lymphocytes seen in our case with acute streptococcal infection which typically produces a neutrophilic leucocytosis in adults. However, it is worthwhile noting that according to the literature, lymphocytosis is usually rare during such acute bacterial infections except in pertussis.⁵ The rarity and paucity of literature on this subject prompted the publication of this report. It is well documented in the literature that in response to stress, lymphocytes that are characterised by nuclear and cytoplasmic distortion appear in the blood.⁵ Thus, another explanation for atypical lymphocytosis in this child could be the stress caused by dysphagia. False positive CMV IgM can be due to cross-reactions between infections caused by closely related viruses like the acute EBV infection. The CMV IgM assay shows a lack of specificity in acute EBV infection hence precautions must be taken when CMV IgM results are interpreted.⁶ The above mentioned published fact, plus the absence of CMV DNA in plasma in this patient, proves that the CMV IgM result was false positive. Acute *herpes simplex* virus infections typically produce pharyngitis and stomatitis and very rarely lead to such huge bilateral tonsillar enlargement. Failure of a patient with suspected streptococ-

cal throat infection to improve within 48 hours should evoke suspicion of infectious mononucleosis,⁷ but our patient responded very well to antibiotics thus ruling out a primary infection by EBV.

Thus in this patient with acute upper respiratory and lymphnode inflammation due to streptococci, well known for its immunological warfare, and taking into consideration the entire clinical, pathological and therapeutic scenario, IgM antibodies to CMV, HSV and EBV were false positive.

CONCLUSION

Haematologically, a large number of atypical lymphocytes can be seen in the blood film of a patient with severe, acute upper respiratory streptococcal infection. Immunologically, false positive IgM antibodies to CMV, HSV and EBV can be observed in patients with such severe acute streptococcal infections.

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