

Fine needle cytology features of an atypical presentation of infectious mononucleosis

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Abstract

Infectious mononucleosis (IM) is a very common disease, and although in most instances, the patient develops an asymptomatic infection, other patients progress into an array of signs and symptoms that tend to be characteristic of the pathological process, guiding the clinician into choosing the right laboratory examinations under the suspicion of this illness. The most common symptoms are pharyngitis, lymphadenopathies and pyrexia, and the probabilities to develop this mononucleosis triad become greater with age. In other instances, IM can be a challenging disease to diagnose, mainly because the patient debuts with unusual symptoms such as nausea, skin eruptions, diarrhea and epigastric discomfort. The aim of the present article is to report the case of a 21-year-old female with a reactivation of IM, developing only multiple, asymptomatic lymph node enlargements in the head and neck region, showing no other sign or symptom.

Keywords: Epstein Barr, head and neck, reactivation, smear

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INTRODUCTION

Infectious mononucleosis (IM), sometimes referred to as the kissing disease, is considered a benign, self-limited lymphoproliferative disorder due to the exposure to Epstein–Barr virus (EBV) or cytomegalovirus,^[1] which usually courses as an asymptomatic infection, especially among children when they first become exposed to the virus. On the other hand, infections on the unexposed adult represent a greater risk for developing a symptomatic disease, and after infection, the patient remains as a reservoir for EBV for life.^[2,3]

Spreading of the virus usually occurs through fomites contaminated with saliva or more frequently through

kissing. In adults, 90% of the population is considered carrier of the virus, having detectible EBV antibodies in serum. When developing a symptomatic course, the most common clinical presentation of IM is characterized by pharyngitis, tonsillitis, lymph node enlargement (typically affecting cervical lymph nodes), fatigue and pyrexia.^[2,4,5] Other complications related to the infection include splenomegaly and hepatomegaly, and in some instances, soft palate petechiae may be an intraoral finding.^[6] These signs and symptoms can lead the practitioner to a diagnosis of IM, and proper serological tests to confirm are needed.^[7]

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Sometimes, IM may present itself as a rather difficult entity to diagnose due to unusual clinical presentations. Taga *et al.* reported 17 atypical cases of IM, showing none or only one of the classic signs or symptoms, and even so, some of the chief complaints were otitis media, gastroenteritis, fatigue or cough; therefore, the attending physicians failed to suspect of IM.^[4] Nishikawa described a case of a 34-year-old man with IM, whose main symptoms were fever, fatigue and loss of appetite, symptoms that are nonspecific and thus making the initial diagnosis of IM difficult.^[8] Herein, we report a case of IM with an atypical presentation on a young female patient.

CASE REPORT

A 21-year-old caucasian female was referred to our service with a left preauricular nodular mass at the temporomandibular joint level. According to the patient, it was persistent in growth and had been developing for a period of 2 weeks and a half. At physical examination, the clinical presentation of the lesion was of a round, asymptomatic, well-defined, firm and movable mass [Figure 1] with 2 cm in diameter. During palpation, two other lymph node enlargements were discovered, one in the submandibular region and the other on the mid cervical portion of the sternocleidomastoid muscle, both on the left side. The skin overlying these nodules was of normal appearance. The patient also referred having sporadic tearing out of her left eye. Intraoral examination revealed diffuse petechiae on the soft palate. No other signs or symptoms were recorded. At this point, IM, toxoplasmosis and a lymphoma were considered within the possible diagnosis.

A computed tomography scan was requested, revealing lymph node enlargements of the left preauricular and submandibular areas [Figure 2], along with multiple small enlargements of the posterior cervical lymph nodes. A cytology examination by fine needle aspiration (FNA) was performed, resulting in sheets of normal lymphoid cells, including lymphoblasts, small lymphocytes and centroblasts [Figure 3].

The blood tests were normal, and HIV test came in negative. Antibodies for toxoplasmosis were also tested, but the results were not conclusive. Immunoglobulin (Ig) G and IgM antibodies for EBV both turned in positive [Table 1]. The patient confirmed having had IM 12 months before.

A treatment consisting of ketoprofen was given to the patient, and by the 6th week, the lymph node enlargements



Figure 1: Preauricular lymph node enlargement

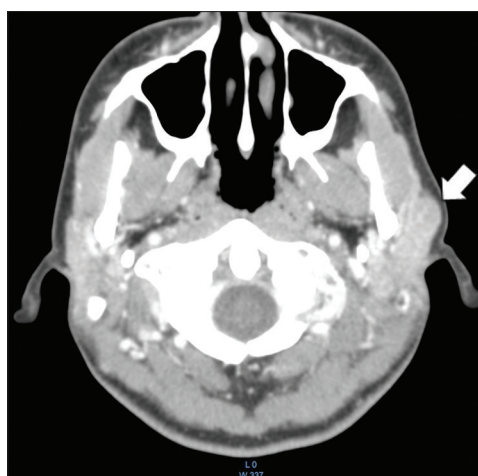


Figure 2: Axial computed tomography section showing an isodense nodular encapsulated enlargement (arrow) in the preauricular region

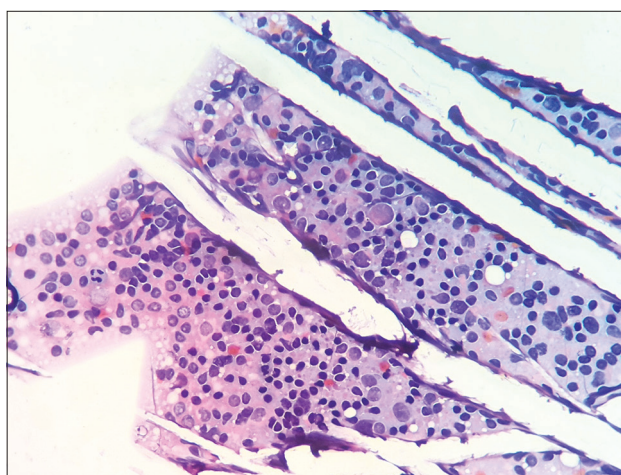


Figure 3: Fine needle aspiration smear demonstrating sheets of lymphoblasts surrounded by small lymphocytes (Giemsa stain, $\times 100$)

begun to reduce in size, and finally to a clinical normal state. No further treatment was indicated. With the resolution of these nodular enlargements, the cytological results and the

patient being positive for EBV IgM antibodies, a definitive diagnosis of a reactivation of IM was made.

DISCUSSION

IM is caused by EBV on 84%–95% of the cases,^[1,3] and it is characterized by pyrexia, pharyngitis, lymphadenopathies and the observation of atypical lymphocytes in blood smears.^[2,4,5] Usually asymptomatic in children, IM symptoms become more prevalent with age, and in developed countries, teenagers and college students are at a greater risk of infection because this virus is transmitted through saliva, hence the name “kissing disease.” In younger patients and children, fomites contaminated with saliva carrying the virus are the main vector of transmission.^[5,6] Blood transfusions and bone marrow transplants have been occasionally implicated in the transmission of EBV.^[9,10]

Once the virus enters the oropharynx, it infects and replicates on epithelial and acinar cells. Later, B-cells become the main target, mainly because EBV shows a tropism for the CD21 coreceptor on the B-cell surface; the production of virions capable of infecting more cells continues, and consequently, the spreading of the virus via blood stream is accomplished.^[3] Lymphoid organs are compromised by the infection, and clinically the patient may develop cervical lymphadenopathies and splenomegaly.^[1] T-cytotoxic cells are the main suppressors against the infection; therefore, if the immunity of the patient is compromised, the virus can proliferate in an uncontrolled manner, causing other types of more serious pathologies such as Burkitt’s and Hodgkin’s lymphoma.^[11,12] The virus can infect the patient for life by establishing latency in memory B-cells, evading the immune system.^[3]

When a patient develops the classic signs and symptoms discussed above, the practitioner is usually able to gather these findings and lead a plausible diagnosis toward IM; at this point, serological tests can be requested to confirm this suspicion.^[7,13] However, cases of patients with IM coursing with an atypical clinical presentation may make the diagnosis process difficult, and this could result in lymph node excision. Further histopathological studies of the biopsy showing an immunoblastic proliferation could accelerate an erroneous diagnosis of a malignant lymphoma.^[14,15] Immunohistochemical analysis has proven to be a resourceful tool to confirm or reject a monoclonal cell proliferation.^[14] Atypical manifestations of IM are detailed in Table 2.

Usually, FNA cytology (FNAC) is not necessary to diagnose IM; however, in atypical cases, it could be used

Table 1: Hepatic function tests and Epstein-Barr virus (EBV) enzyme immunoassay

Measured parameter	Patient's results	Normal values
Total Bilirubin	0.3 mg/dL	0.2-1.3
Direct Bilirubin	0.1 mg/dL	0-0.3
Indirect Bilirubin	0.2 mg/dL	
Total Alkalinity	39.0 U/L	38-126
GOT Transaminase	21 U/L	14-36
GPT Transaminase	27 U/L	9-52
G. Glutamyl Transferase	18 U/L	12-43
C Reactive Protein	0.9 mg/L	0-10
EBV IgM	>50 U	Positive >11.0
EBV IgG	14.8 U	Positive >11.0

Table 2: Atypical symptoms in IM patients reported by other authors (2,5,3,10,11,12,13,14,15)

Author	Signs and Symptoms
Martin, M (1977)	Bone marrow granulomas, fever, malaise, headache and weight loss
McKendrick (1979)	Patient 1: Fever, sweating, dry cough. Patient 2: Fatigue, fever
Freedman, B. (1980)	Painful gingivitis, low fever, atypical lymphocytes (blood smear)
Kato, H. <i>et al</i> (1993)	Exanthema, sore throat, bilateral cervical lymph node enlargement
Kojima M. <i>et al</i> (2002)	Non-tender cervical and inguinal lymph node enlargement, lymph node infarction, low fever
Fujiwara, M. <i>et al</i> (2009)	Gastroenteritis, fever, diarrhea, nausea
Fusilli, G. (2010)	Leucopenia, pharyngitis, fever
Nishikawa, J. <i>et al</i> (2011)	Non-tender lymph node enlargements, mild hepatosplenomegaly, fever and fatigue.
Taga, K. <i>et al</i> (2016)	Patient 1: Fever Patient 2: Cough Patient 3: Fever, cough Patient 4: Fever, cough Patient 5: Fever, diarrhea Patient 6: Low fever Patient 7: Skin eruption Patient 8: Cough Patient 9: Fatigue, headache Patient 10: Epigastric discomfort Patient 11: Malaise, pharyngitis, abdominal pain Patient 12: Fever, cough, vomiting, diarrhea Patient 13: Fever Patient 14: Fever, cough, skin eruption Patient 15: Cough, pharyngitis Patient 16: Lymphadenopathy, cough, rhinorrhea Patient 17: Fever

to rule out the suspicion of lymphoma, in association with blood tests. Stanley *et al.* showed in FNAC that the array of cells that can be observed through this method ranges from lymphohistiocytic aggregates, loose granulomatous formations of epithelioid histiocytes with abundant pale staining cytoplasm, a spectrum of immunoblast maturation toward mature plasma cells to the observance of sheets composed of centroblasts and plasma cells.^[16] In our case, the FNAC was needed to rule out lymphoma, mainly because the clinical and imaging results were not conclusive. The cytological characteristics we observed are similar to those described by other authors,^[16] as the

presence of lymphoblasts and immunoblasts surrounded by lymphocytes of smaller size along with a mixed inflammatory infiltrate including neutrophils, suggesting an acute reactive process.

Lymph node enlargements with absent signs of infection such as tenderness and pain, redness, a local raise of temperature and general malaise and pyrexia could represent a diagnostic challenge. In this case, the only measurable sign was that of the lymph node enlargements, and this could have easily directed our diagnosis toward a neoplasm of lymphoid nature. The blood test results came in normal, except for the enzyme immunoassay for EBV IgG and IgM antibodies, proving an atypical EBV reactivation on the patient. Treatment of IM is merely supportive consisting of symptom relief with nonsteroid anti-inflammatory drugs and liquid intake.^[8]

According to the clinical, imaging and cytological features and the positive results of the enzyme immunoassay for EBV IgG and IgM antibodies, the current case was diagnosed as an IM reactivation due to EBV. In conclusion, atypical manifestations of IM are rare and difficult to diagnose, being necessary to discard the differential diagnosis with complementary examinations before carrying on to the definitive diagnosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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