EUROPEAN JOURNAL OF INFLAMMATION Vol. 11, no. 1, 237-241 (2013)

LETTER TO THE EDITOR

AN UNUSUAL CASE OF INFECTIOUS MONONUCLEOSIS PRESENTING WITH ADVANCED LYMPHADENOPATHY AND ASCITES

F.S. CHIU[1], C.P. SHIH[1], H.C. CHEN[1], Y.Y. LIN[1], C.Y. KUO[1] and C.H. WANG[1,2,3]

[1]Department of Otolaryngology-Head and Neck Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, Republic of China; [2]Institute of Microbiology and Immunology, National Defense Medical Center, Taipei, Taiwan, ROC; [3]Institute of Undersea and Hyperbaric Medicine, National Defense Medical Center, Taipei, Taiwan, ROC

Received February 28, 2012 – Accepted January 10, 2013

We report a case of infectious mononucleosis initially presented with lymphoma-like features. Examinations revealed abdominal ascites, splenomegaly, elevated lactic dehydrogenase, extensive lymphadenopathy from neck to the mediastinum, and a high ^{18}F-fluoro-2-deoxy-D-glucose uptake pattern on positron emission tomography scan. The impression of lymphoma could not be ruled out based on the clinical manifestations, most importantly the diffuse necrosis with focal monotonous pattern and a high Ki-67 proliferation index found on pathological examination. Our presentation emphasizes the potential challenge in misdiagnosis of advanced infectious mononucleosis. Knowledge of its unusual clinical features is therefore essential to avoid misdirected interventions when it mimics diseases like lymphoma.

Case report

A previously healthy 15-year-old boy was referred to our hospital with a one-week history of progressively enlarging cervical masses. Two weeks before this referral, he had visited the local clinic with the chief complaint of a sore throat and received medication for presumed acute pharyngitis. One week later, the child was brought to visit the local clinic doctor again because palpable masses in the neck had gradually enlarged; he was referred for further investigation.

Upon physical examination, unilateral congestion, tonsil enlargement on the left side, and bilateral multiple mild-tender lymphadenopathies were noted, of which the largest, measuring 2.5 cm in diameter, was located on the left cervical level II. There were no significant abnormal findings in the nasopharynx, hypopharynx, or larynx as assessed by nasopharyngoscopy and laryngoscopy. The patient's vital signs on admission were: temperature 38°C, pulse 112 beats/min, blood pressure 135/70 mm Hg, and respiratory rate 18 breaths/min. Laboratory tests showed evident leukocytosis (white blood cell count 22,500/mm^3), lymphocytosis (neutrophil, 31%; lymphocytes, 60%; and monocytes, 8%), elevated hepatocellular enzyme levels (AST: 194, ALT: 354, LDH: 531), and the presence of 33% atypical lymphocytes. EBV serology tests showed elevated IgG anti-viral capsid antigen (VCA) titers, but negative in IgM detection. Chest X-rays revealed infiltration and prominence of the bilateral hilar regions, which are seldom observed in cases of

Key words: infectious mononucleosis, Epstein-Barr virus, lymphoma, lymphadenopathy, ^{18}F-fluoro-2-deoxy-D-glucose, positron emission tomography, polymerase chain reaction

Mailing address: Chih-Hung Wang, MD, PhD
Department of Otolaryngology Head and Neck Surgery,
Tri-Service General Hospital, National Defense Medical Center
325, Section 2, Cheng-Kung Road,
Neihu District, Taipei 114, Taiwan, ROC
Tel.: +886 2 8792 7192 Fax: +886 2 8792 7193
e-mail: chw@ms3.hinet.net

1721-727X (2013)

DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

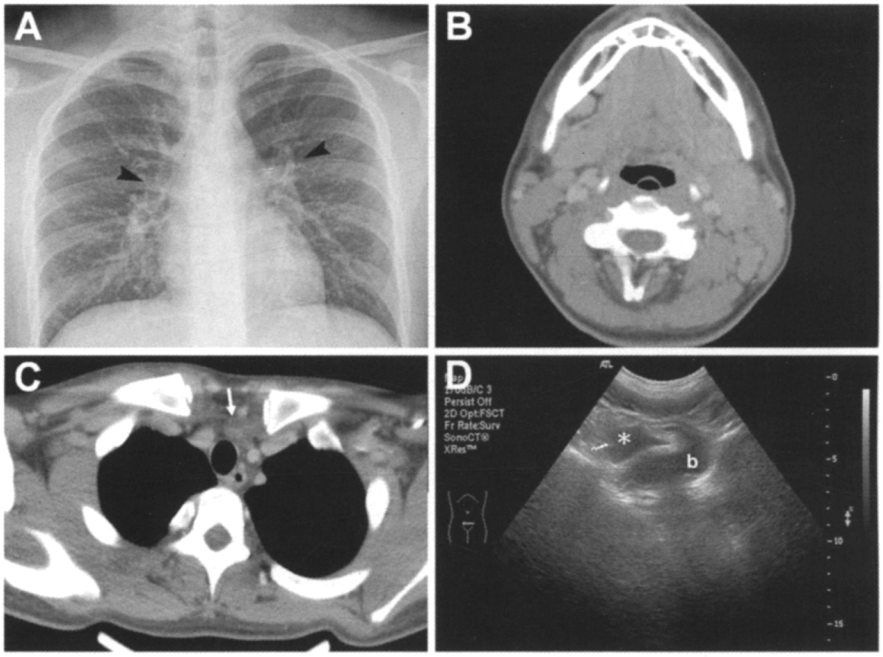

Fig. 1. *Chest x-ray revealed infiltration and moderate prominence of the bilateral hilar regions (arrowheads on **A**). The coronal computed tomography scan revealed multiple enlarged lymph nodes at bilateral neck (**B**) and superior mediastinum (arrow on **C**). Abdominal sonography revealed the existence of ascites (asterisk on D, b = bladder).*

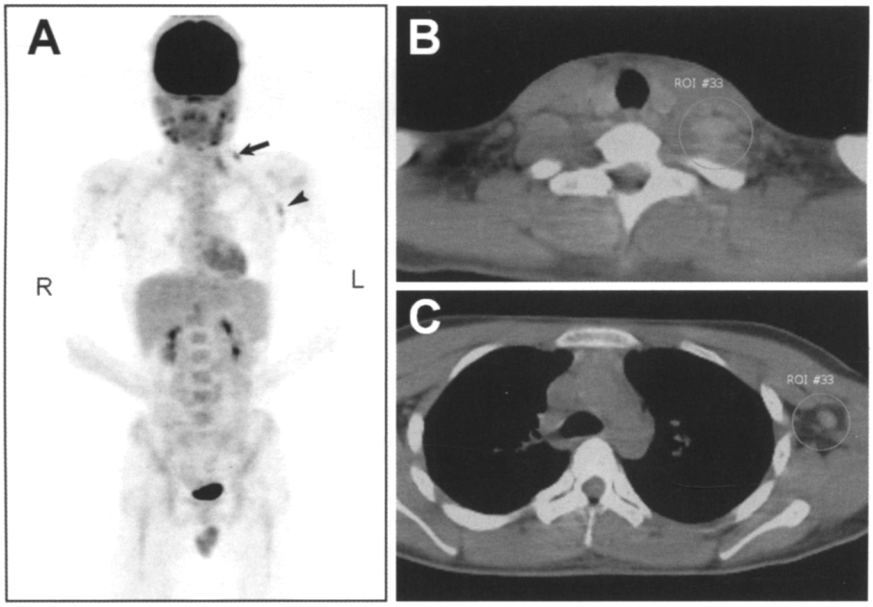

Fig. 2. *Multiple focal areas of increased FDG uptake were seen in the bilateral neck (level II–IV), left supraclavicular (arrow), and axillary (arrowhead) regions in the PET scan (**A**). PET-CT fusion imaging shows high FDG uptake in the left supraclavicular region (circle ROI on **B**, SUV 3.3) and in the left axillary region (circle ROI on **C**, SUV 2.8). ROI: region of interest; SUV: standardized uptake value.*

infectious mononucleosis (Fig. 1A).

Although the patient's clinical triad symptom was strongly suggestive of infectious mononucleosis, certain observations and abnormal data raised the suspicion of lymphoma. Computed tomography (CT) scan of the neck further revealed multiple enlarged nodes at the bilateral neck (Fig. 1B) and superior mediastinum (Fig. 1C). Abdominal sonography revealed the existence of ascites (Fig. 1D) and splenomegaly. Thus, these ambiguous clinical presentations raised the concern of possible lymphoma. Accordingly, the patient was evaluated by whole-body FDG-PET imaging and cervical node biopsy. The PET showed several enlarged lymph nodes with increased FDG uptake over the bilateral neck (level II–IV), bilateral submandibular, the left supraclavicular and axillary regions (Fig. 2), suggesting a possible lymphoma involvement. Excisional biopsy of the neck nodes exhibited extensive necrosis and an increased Ki-67 proliferative index. Although CD3/CD20 staining revealed mixed T-cell and B-cell infiltration, malignant lymphoma could not be ruled out. To confirm the diagnosis, molecular investigation by PCR was introduced to detect whether there was any monoclonal proliferation similar to lymphoma; the negative PCR result did not support this impression thereafter.

By the sixth week of illness, the patient gradually recovered from his sore throat and general fatigue. The enlarged tonsil and cervical lymphadenopathy diminished. The rechecked white blood cell count was normal (6,900/mm^3). The LDH value decreased to 239, with AST to 21 and ALT to 49. The splenomegaly and ascites also subsided. Diagnosis of infectious mononucleosis was therefore preferred. The patient had an uneventful recovery without any sequelae at his 12-month follow-up visit.

DISCUSSION

Infectious mononucleosis, a generally benign and self-limited disease, is markedly associated with primary EBV infection. Since EBV commonly works as the infectious trigger of hemophagocytic lymphohistiocytosis, infectious mononucleosis characteristically presents as a triad of fever, pharyngitis, and lymphadenopathy, although the typical manifestations are uncommon in children (1). In addition to the classic clinical triad, infectious mononucleosis may have other manifestations, including hepatosplenomegaly, rash and hepatic dysfunction, and hematological or neurological problems. Unusual presentations related to infectious mononucleosis such as ascites, pleural effusion, or bilateral hilar lymphadenopathy increase the complexity of differential diagnosis, and clinicians should be careful in confirming the diagnosis.

EBV-related lymphadenopathy may be generalized or localized but rarely involves the mediastinum, as shown in our case. Actually, EBV infection not only manifests in the upper airway, but also affects the lower respiratory tract, and this should be taken into consideration in differential diagnosis of hilar lymphadenopathy (2). Due to the overlapping of clinical presentations of infectious mononucleosis and lymphoma, there are some important dilemmas when it comes to confirming a diagnosis of infectious mononucleosis with unusual and advanced presentation. In the literature review, there have been some case reports about mononucleosis mimicking lymphoma (3), or lymphoma that was initially misdiagnosed as mononucleosis (4). Our case presenting mediastinal lymphadenopathy, ascites, and bilateral hilar infiltration, which is seldom observed in cases of infectious mononucleosis, raised the suspicion of lymphoma. It was found that confirming the diagnosis only by clinical features is an unreliable method, because in our case this would have yielded an incorrect lymphoma diagnosis.

In general, the diagnosis of infectious mononucleosis can be confirmed by the clinical presentation and laboratory findings, e.g., the presence of atypical lymphocytes on a peripheral-blood smear and a positive monospot test, which is a form of the heterophile antibody test and relies on the agglutination of horse red blood cells by IgM antibodies in patients' serum to the EBV viral capsid antigen. The monospot test was not ordered in this case because this diagnostic kit has been suspended since 2008 and has been undergoing investigation by the Department of Health in our country. As a policy alternative in most medical centers in our country, serologic tests that detect the levels of serum IgG and IgM antibody to EBV are being substituted

for monospot. It is believed that monospot can be negative in the incubation period and early stages of the illness, and furthermore, it may show low sensitivity for patients younger than 12 years of age (1). On the other hand, a positive monospot test cannot thoroughly rule out the possibility of malignant lymphoma, because a positive monospot finding could occur in patients with lymphoma (5). An elevated serum IgG level or positive IgM antibody to EBV indicates an acute infection that also helps to confirm the diagnosis of infectious mononucleosis (1). Again, positive serologic findings for EBV, such as IgM or IgG antibody, is not only present in patients with mononucleosis, but also sometimes in lymphoma or nasopharyngeal carcinoma (6). Therefore, physicians often have to face a diagnostic challenge, especially in cases with unusual clinical manifestations.

Positron emission tomography (PET) with ^{18}F-fluoro-2-deoxy-D-glucose (FDG) has been widely applied in the early detection of malignancy or cancer workup by means of increased FDG uptake of tumor cells through measuring the standard uptake value (SUV). Therefore, FDG-PET has become an alternative imaging method to access lymphoma patients, and may be more accurate than computed tomography (CT) or magnetic resonance imaging in assessing residual disease (7). Correlations between EBV DNA levels and PET scan results have been studied by Makitie et al. (8) in patients with EBV-related nasopharyngeal carcinoma. It possesses high sensitivity and is supposed to help differentiate tissue inflammation from malignant disorders. However, patients with infectious mononucleosis may develop severe inflammatory lymphadenopathy; the accumulation of the radiotracer in inflamed or infected tissue may lead to false positive PET results. The limitation and pitfall of using FDG-PET in differentiating infectious mononucleosis from lymphoma is not only shown in our case, but has also been reported in literature (3). On the other hand, indolent lymphoma may present a mild to moderate increase of FDG uptake, which can also confuse the physicians and mislead them to diagnose inflammatory lymphadenopathy. As a result, although PET is sensitive to malignant disorders, it is more preferable for cancer workup than as a diagnostic tool.

Histopathologically, one of the most complicated tasks is the diagnosis of lymphoma, because it is necessary to exclude several reactive lesions, including Kikuchi lymphadenitis, autoimmune lymphoproliferative syndrome, immunoglobulin G4-related sclerosing disease, and infectious mononucleosis (9). Under microscopic examination, our case showed diffuse necrosis with focal monotonous pattern in hematoxylin and eosin (H&E) stain. Although immunohistochemical staining revealed mixed T-cell and B-cell infiltration, co-expression of both T and B cell immunomarkers can be encountered in T cell lymphomas (10). In addition, it is believed that elevated Ki-67 index represents a high growth rate and may indicate an underling malignance, which has been additionally applied in diagnostics and the prognosis of human tumors (11). Therefore, the existence of a high proliferation Ki-67 index associated with the patient's aggressive clinical presentation meant that lymphoma could not be ruled out. The development of polymerase chain reaction (PCR) analysis has allowed the B-cell immunoglobulin and T-cell receptor genes to be investigated in order to assess the clonality and lineage of lymphoid lesions (12). This often helps to elevate the diagnostic accuracy of malignant lymphoma by determining whether lesions are polyclonal, which is more common in reactive lymphoid hyperplasia, or monoclonal, which suggests neoplasm.

In conclusion, infectious mononucleosis may display a variety of unusual presentations to challenge physicians and pathologists alike. Our case report showed that ascites and mediastinal and hilar lymphadenopathy can accompany infectious mononucleosis as some of its clinical manifestations. Great caution should be used when applying the imaging study of FDG-PET as a diagnostic intervention in cases of infectious mononucleosis; otherwise, one might be easily misled to an incorrect impression. Specific EBV serology and monospot tests help to provide important information. A further PCR-based molecular genetic approach will allow the defect of conventional histopathological interpretation to be overcome and improve the diagnosis.

REFERENCES

1. Luzuriaga K, Sullivan JL. Infectious mononucleosis.

N Engl J Med 2010; 362:1993-2000.
2. Friedland JS, Santis G, Smith MJ. Infectious mononucleosis: a cause of bilateral hilar lymphadenopathy. Postgrad Med J 1988; 64:799-800.
3. Lustberg MB, Aras O, Meisenberg BR. FDG PET/CT findings in acute adult mononucleosis mimicking malignant lymphoma. Eur J Haematol 2008; 81:154-6.
4. Xie JL, Zhou XG. Infectious mononucleosis-like lesions, a rare manifestation of angioimmunoblastic T-cell lymphoma. Leuk Lymphoma 2010; 51:944-6.
5. Wolf P, Dorfman R, McClenahan J, Collins F. False-positive infectious mononucleosis spot test in lymphoma. Cancer 1970; 25:626-8.
6. Strauss M. Burkitt's lymphoma, nasopharyngeal carcinoma, infectious mononucleosis and the Epstein-Barr virus. Laryngoscope 1972; 82:2049-58.
7. Kazama T, Faria SC, Varavithya V, Phongkitkarun S, Ito H, Macapinlac HA. FDG PET in the evaluation of treatment for lymphoma: clinical usefulness and pitfalls. Radiographics 2005; 25:191-207.
8. Makitie AA, Reis PP, Irish J, et al. Correlation of Epstein-Barr virus DNA in cell-free plasma, functional imaging and clinical course in locally advanced nasopharyngeal cancer: a pilot study. Head Neck 2004; 26:815-22.
9. Chan JK, Kwong YL. Common misdiagnoses in lymphomas and avoidance strategies. Lancet Oncol 2010; 11:579-88.
10. Mohrmann RL, Arber DA. CD20-Positive peripheral T-cell lymphoma: report of a case after nodular sclerosis Hodgkin's disease and review of the literature. Mod Pathol 2000; 13:1244-52.
11. Scholzen T, Gerdes J. The Ki-67 protein: From the known and the unknown. J Cell Physiol 2000; 182:311-22.
12. Medeiros LJ, Carr J. Overview of the role of molecular methods in the diagnosis of malignant lymphomas. Arch Pathol Lab Med 1999; 123:1189-207.