Tuberculosis Lymphadenitis in Association With Celiac Disease Mimicking Kikuchi-Fujimoto Disease

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Introduction: Kikuchi-Fujimoto disease (KFD) is an uncommon idiopathic self-limited cause of lymphadenitis that most commonly presents with cervical lymphadenopathy with or without systemic signs and symptoms, which is also called histiocytic necrotizing lymphadenitis (1-6). Although infection and autoimmune etiology have been suggested, the cause of KFD is unknown. Several features that support a role for an infectious cause include the generally self-limited courses and association with symptoms similar to upper respiratory tract infection. Many viral infections have been proposed including cytomegalovirus, varicella zoster virus, human herpes virus, Epstein-Barr virus, parainfluenza virus, parvovirus B19, paramyxovirus, Yersinia enterocolitica, and Toxoplasma gondii. In a Korean study on 147 patients presenting at an outpatient clinic, KFD (34.7%) and tuberculous (TB) adenitis (22.4%) were the most common causes of cervical adenitis (7-14).

Case Presentation: We presented a case of TB lymphadenitis in association with celiac disease that mimicked KFD in a young child.

Conclusions: Celiac disease, also known as gluten-sensitive enteropathy and nontropical sprue, is an autoimmune disease with chronic inflammation of small intestine, which is associated with increased risk of TB infection. TB lymphadenitis can mimic KFD. Therefore, in each case of unusual lymphadenitis, TB should be considered and if it is associated with failure to thrive, celiac disease should be suspected.

Keywords: Kikuchi Disease; Celiac Disease; Tuberculous Lymphadenitis; Necrotizing Lymphangitis; Young Child

1. Introduction

Kikuchi-Fujimoto disease (KFD), which was first diagnosed in Japan, has been reported throughout the world and in all races, with most cases reported from East Asia fewer cases from Europe and North America. KFD is generally benign with self-limited course that typically affects young adults (mean age, 20-30 years). Females are affected more than males with a ratio of 3:1; moreover, disease in females occurs in a wide range of ages (2-75 years). KFD can be clinically and histologically mistaken with lymphoma or systemic lupus erythematosus. Several authors have reported an association between KFD and SLE. We report a case of TB lymphadenitis in association with celiac disease that mimicked KFD (15).

2. Case Presentation

The patient was a 16-year-old girl that was well up to six months ago. Then she presented with fever, weakness, malaise, anorexia, epigastric abdominal pain, nausea, and generalized variable-sized lymphadenopathy. In addition, she complained of headache, bone pain, diarrhea and 10 kg weight loss over six months. Her mother was a case of pulmonary tuberculosis (TB) and had received full course of anti-TB drugs two years ago. She had close contact with her mother. She was referred to our center for further evaluation.

2.1. Physical Examination

At the first visit, she was febrile with a temperature of 37.9°C, pulse rate of 120 beat/min, and blood pressure of 95/60 mm Hg. General appearance was cachectic and ill but nontoxic. Conjunctiva and nails were pale. She had multiple variable-sized lymph nodes in the cervical, submandibular, supraclavicular, axillary, and inguinal regions that some of them were tender with maximum size 19 × 26 mm. Abdomen was soft without organomegaly, but had vague tenderness without guarding or localized tenderness. Results of the central nervous system evaluation were insignificant.

She had microcytic hypochromic anemia, white blood cells of 4.3 × 10⁹/L (polymorphonuclear cells, 70%; and lymphocytes, 29%), hemoglobin of 9.4 gr/dL, mean corpuscular volume (MCV) of 65.3, mean corpuscular he-
moglobin (MCH) of 19 pg/cell, mean corpuscular hemo
globin concentration (MCHC) of 291 g/L, red blood cells
of $4.9 \times 10^{12}$/L, platelet $545 \times 10^{9}$/L, elevated erythrocyte
sedimentation rate (90 mm/h), and C-reactive protein
of 30 nmol/L. Other laboratory findings for serum asp-
partate aminotransferase, alanine aminotransferase, alkalic
phosphatase, uric acid, lactate dehydrogenase, blood
urea nitrogen, calcium, and creatinine were in-
significant. In next step, excisional lymph node biopsy
was done from two site of cervical and supraclavicular
regions that revealed necrotizing granulomatous lymph-
adenitis suggestive for KFD. Thereafter, to rule out cause
of lymphadenitis, acid fast staining was done on lymph
node for detecting Mycobacterium specious, which yield-
ed positive result. In addition, PCR on lymph nodes was
positive for Mycobacterium tuberculosis. Results of viro-
logy studies for cytomegalovirus, human herpes viruses
6 and 8, Epstein-Barr virus, herpes simplex virus, and hu-
man immunodeficiency virus were negative. In addition,
results of nitroblue tetrazolium (NBT), serum immuno-
globulin electrophoresis, flow cytometry, dsDNA, lupus
erythematosus cell (LE cell), C3, and C4 were in normal
limits. Findings of the imaging study includes chest X-
ray were normal. No active infiltration was seen in lungs
fields; however, high-resolution computed tomography
showed multiple asymmetrical lymph nodes. The PPD
test yielded positive results with 20 mm indurations.

Other imaging includes ultrasonography of abdomen and
computed tomography findings were normal. Due to
raised anti-tTG-IgA to 73, EmA-IgA to 80 and posi-
tive HLA-DQ2, upper esophagogastroduodenoscopy with
biopsy was done that revealed severe erythema in lower
third of esophagus, mucosal erythema of gastric body,
and erythematous mucosa of duodenum with atro-
phic villi. Biopsy confirms celiac disease as Marsh clas-
sification IIIc. Bone marrow aspiration revealed only
increase in megakaryocyte. No malignant cell was seen.
The patient was placed on gluten-free diet and standard
anti-TB drugs (isoniazid, rifampin, ethambutol, and pyra-
nizidine) for six month and other supplementations in-
cluding vitamin B6, calcium, vitamin D, and ferrous sul-
fate. During 18-months follow-up, she had good response
to medication with corrected hemoglobin, increased
apetite and weight, and resolved lymph nodes. The results
of the latest PPD test was negative and anti-tTG Ab and
EmA-Ab were in normal ranges.

3. Discussion

Celiac disease, also known as gluten-sensitive enteropa-
thy and nontropical sprue, is an autoimmune disease
with chronic inflammation of small intestine because of
specific immunologic response to gluten proteins in
wheat, barley, and rye, which leads to villous atrophy. Ce-
liac disease is common in the white population with prev-
ance of approximately 0.5% to 1% (16, 17). Clinical presen-
tation of celiac disease may be asymptomatic (silent) or
has wide spectrum (classic form) including chronic diar-
rhea, abdominal distension, abdominal pain, anorexia,
iron deficiency anemia, constipation, symptoms of intest-
inal malabsorption such as malnutrition and failure to
thrive (18-21). Celiac disease is associated with a number
of complications including malignant lymphoma and autoimmunity disorders.

TB affects a large proportion of the world population
and is more common in individuals with malnutrition.
Mycobacterium tuberculosis infects about one-third of
the world’s population, although active TB is less common
(6). TB can affect any part of the body but most often
involves the lungs, where it causes tissue destruction.
Several researches have suggested a positive association
between celiac disease and TB.

In the large cohort study by Ludwigsson et al. (18) celiac
disease was associated with an increased risk of TB in-
fected (hazard ratio [HR], 3.74; 95% CI, 2.14-6.53; and P =
0.001). Similar risk estimates were seen when the popu-
lation was stratified for sex and age at celiac disease di-
agnosis. Patients with celiac disease had also more prob-
ability of making the diagnosis of TB in departments of
pulmonary medicine, infectious diseases, pediatrics,
or thoracic medicine (HR, 4.76; 95% CI 2.23-10.16; and P
= 0.001). The odds ratio for celiac disease in individuals
with prior TB was 2.50 (95% CI, 1.75-3.55; P = 0.001) (22).
In this study, celiac disease was associated with three-
to-four-fold increase in the risk of developing TB; the mal-
nutrition associated with celiac disease, particularly vita-
min D deficiency, might perform an important role in the
increased risk of TB. Individuals with celiac disease were
at increased risk of TB (HR, 2.0; 95% CI, 1.3-3.0); during fol-
low-up, 31 individuals with celiac disease and 74 reference
individuals had a diagnosis of TB (23). Peters et al. found a
six-fold increase in the risk of death from TB in individu-
als with celiac disease (24).

In another study, several cases of TB lymphadenitis pre-
sented similar to KFD (25, 26). This case demonstrates the
coeexistence of mycobacterial lymphadenitis and histio-
cytic necrotizing lymphadenitis in the patient with celiac
disease. However, it is unclear whether this represents a
coincidental event or whether the infection agent caus-
ing unusual immune response leads to histiocytic nec-
rotizing lymphadenitis. Therefore, additional evidence
is necessary to link these two entities to define their re-
lationship. In an unusual presentation of KFD, infection
with TB and celiac disease should be considered.

Authors’ Contributions

Dr. Naghi Dara: study design, literature search, drafting,
and review of the manuscript. Dr. Abdullah Karimi. Study
design, supervision, and review of manuscript. Dr. Ali
Amanati, Dr. Farid Imanzadeh, Dr. Ali Akbar Sayyari, and
Dr. Peyman Eshghi were teamwork in concept.