A Case of Fever of Unknown Origin: Co-existence of Kikuchi-Fujimoto Disease and Acute Disseminated Encephalomyelitis (ADEM)

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Abstract

It is believed that viral infections and the hyperimmune reaction due to these infections are involved in the etiology of Kikuchi-Fujimoto Disease (KFD), a rare cause of fever of unknown origin. Axillary lymphadenopathy and neurologic involvement are rare in KFD. We present a patient diagnosed with KFD histopathologically during an investigation of the origin of fever and axillary lymphadenopathy. Subsequently, incidental sinus aspergilloma was diagnosed radiologically in the patient and acute disseminated encephalitis developed during follow-up. This report aims to draw attention to the co-existence of KFD and Acute Disseminated Encephalomyelitis, two diseases of which the origins are not clear.

Key words: fever of unknown origin (FUO), Kikuchi-Fujimoto disease, histiocytic necrotizing lymphadenitis, acute disseminated encephalomyelitis (ADEM)

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Introduction

It is believed that viral infections and the hyperimmune reaction that occurs due to these infections are involved in the etiology of Kikuchi-Fujimoto Disease (KFD), which is a rare cause of fever of unknown origin (FUO). It is reported that neurological manifestations including aseptic meningitis, cerebellar ataxia, mononeuritis multiplex, hemiparesis and brachial neuritis may be detected during the course of the disease (1). However, to date, acute disseminated encephalomyelitis (ADEM) following KFD has not been reported. ADEM is classified under demyelinating diseases of the central nervous system with a monophasic course and its diagnosis can only be made after all of the other possible diseases are ruled out. Although the etiology of both ADEM and KFD still remains obscure, it is believed that previous infections may play a role in their pathogenesis. The present patient was diagnosed with KFD histopathologically during the investigation aimed at discovering the origin of her fever and lymphadenopathy. Subsequently, she was diagnosed with incidental sinus aspergilloma radiologically and developed ADEM during her follow-up. The present report aims to draw attention to the co-existence of two diseases of unknown origin, KFD and ADEM, which probably share the same etiology.

Case Report

A 36-year-old woman applied to our clinic with complaints including fever (39.5°C), lack of appetite, vomiting and diarrhea, which had been present for about one month. She stated that all of these complaints had appeared 10 days after the formation of a painful swelling under her axillary region. During the 40 days that she had spent without receiving hospital treatment, the patient had used amoxicillin, clavulanic acid, levofloxacin and third generation cephalosporins on an irregular basis. She had no history of close

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contact with pets; she did not travel often and similar complaints were not present in her social circle. According to the patient’s physical examination, her general health status was good; body temperature, pulse, and blood pressure were 39°C, 84/min and 100/60 mmHg, respectively. She was alert, oriented and co-operative. On the right side of the axillary region, markedly mobile, painless lymphadenopathies (LAPs), of which the largest was 3×2 cm in size, were present. Cardiac examination revealed a 2/6 systolic murmur. Organomegaly and LAPs in the inguinal region were not palpated. Examination of the respiratory and neurologic systems revealed normal findings.

Laboratory examinations revealed the following findings (Table 1). No positive results that could explain high body temperature were found during the serological tests for Epstein Barr virus (EBV), cytomegalovirus (CMV), hepatitis A, B, and C, Toxoplasma, Brucella, and Salmonella spp. Blood cultures were incubated for 6 to 8 weeks and Brucella spp did not grow in them. Vegetation was not detected by transthoracic echocardiogram; her body temperature could not be lowered by routine anti-inflammatory drugs and intravenous paracetamol. Rheumatologic markers (ferritin, anti-nuclear antibody, anti-neutrophil cytoplasmic antibody, anti-cyclic citrullinated peptide antibodies, extractable nuclear antigen antibody panel, anti-double stranded DNA, rheumatoid factor) were negative.

On the 7th day of hospitalization, an excision biopsy of axillary lymph node was performed. Microscopic examination revealed effacement of nodal architecture by patchy necrosis. The necrotic areas included nuclear dust and cellular debris, but not polymorphonuclear neutrophilic leucocyte. These necrotic areas were surrounded by histiocytes which express myeloperoxidase (MPO) and CD68 (Fig. 1A, 1B). Residual germinal centers and activated lymphocytes were also found in the paracortical areas. Lymphoid cells showed mainly T-cell phenotype. Only a low number of CD20 posi-

### Table 1. The Laboratory Findings of the Patient

<table>
<thead>
<tr>
<th>Laboratory findings</th>
<th>In admission</th>
<th>At the discharge</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte count</td>
<td>3400</td>
<td>7400</td>
<td>4000 - 10300/mm³</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>10.5</td>
<td>10.0</td>
<td>12 -16 gr/dL</td>
</tr>
<tr>
<td>Platelet</td>
<td>203 000</td>
<td>156 000</td>
<td>156 000 - 373 000/µL</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>144</td>
<td>21</td>
<td>0.1 - 8.2 mg/L</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>55</td>
<td>11</td>
<td>0 - 20 mm/hr</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>84</td>
<td>35</td>
<td>5 - 34 U/L</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>52</td>
<td>54</td>
<td>0 - 55 U/L</td>
</tr>
<tr>
<td>Lactic dehydrogenase</td>
<td>185</td>
<td>215</td>
<td>125 - 243 U/L</td>
</tr>
<tr>
<td>Creatinin</td>
<td>0.79</td>
<td>0.65</td>
<td>0.6 - 1.1 mg/dL</td>
</tr>
<tr>
<td>Albumin</td>
<td>2.7</td>
<td>4.3</td>
<td>3.5 - 5 g /dL</td>
</tr>
</tbody>
</table>

Cerebrospinal fluid:
- Glucose: 49, <40 mg/dL
- Protein: 61, 15 - 45 mg/dL
- Cell count: 40 neutrophilic, 1 - 10 cells / mm³
- IgG: 366, 6.3 - 33.5 mg/L
- Albumin: 718, 100 - 300 mg / L
- IgG index: 0.66, 0.3 - 0.7

Figure 1. A: Karryorrhetic debris, histiocytes, and lymphoid cells are seen in the necrotic areas. ×400, Hematoxylin and Eosin staining. B: Numerous MPO positive histiocytes are revealed in the necrotic area. ×400, MPO
was above the upper limit and pleocytosis was observed.

band was not detected in the CSF sample. CSF protein level
erase chain reaction (PCR) tests were negative. Oligoclonal
by ophthalmic fundus examination, brain magnetic reso-
alyzed internal iliac chains, of which the largest was 1.5 cm in
diameter. Thus, one of the lymph nodes located in the right
axillary region was removed and sent to pathology for
revealed splenomegaly; lymph nodes were predominantly lo-
tive B-cells were found.

Thorax and abdomen computerized tomography (CT) scan
revealed splenomegaly; lymph nodes were predominantly lo-
cated on the right side of the bilateral axillary region, in ad-
tion to lymph nodes in the paracaval, paraaortic and bilat-
eral internal iliac chains, of which the largest was 1.5 cm in
diameter. Thus, one of the lymph nodes located in the right
axillary region was removed and sent to pathology for
analysis. Since subtle vasculitic alterations were determined
by ophthalmic fundus examination, brain magnetic reso-
nance imaging (MRI) was scheduled. Before MRI could be
performed, the patient had a generalized tonic clonic seizure
on the 13th day of hospitalization. After the seizure, the pa-
tient was no longer oriented and cooperative. Urinary incon-
tinence developed and the patient’s agitation could not be
controlled by sedative drugs. CT was urgently performed.
Since CT exam revealed subtle hypodensity in the temporal
region, acyclovir treatment was started because it was not
possible to rule out encephalitis. After the patient’s status
was stabilized, MRI was performed under sedation and it re-
vealed aspergilloma in the sphenoid sinus and transverse
FLAIR-weighted image showed areas of high signal in the
medial temporal lobes and pons. These lesions, of which the
diffusion was not consistent with lymphoma, suggested the
presence of limbic encephalitis, encephalitis of viral origin,
central nervous system tuberculosis and ADEM (Fig. 2).

Lumbar puncture was performed. The CSF sample was
submitted for bacteriologic, mycologic and mycobacteri-
ologic examination and evaluated with serological and
pathological tests (Table 1). Growth was not observed in the
non-specific or mycotic cultures of the CSF sample. Ziehl-
Nielseen staining and culture were negative. Additionally,
the Herpes simplex virus (HSV), Varicella zoster virus
(VZV), Enterovirus, Adenovirus and M. tuberculosis polyn-
erase chain reaction (PCR) tests were negative. Oligoclonal
band was not detected in the CSF sample. CSF protein level
was above the upper limit and pleocytosis was observed.

At the end of the second week of hospitalization, the fre-
quency and duration of the patient’s apnea episodes in-
creased and her general status worsened during these epi-
isodes. Since ADEM was highly suspected, prednisolone

treatment (1 g/day iv) and follow-up in the intensive care
unit were started. Following 24 hours of steroid treatment,
the patient demonstrated a significant clinical response, her
level of awareness improved and her body temperature re-
turned to normal. Acyclovir treatment was prolonged to 10
days and pulse steroid treatment was continued for 10 days.
Neurological status dramatically improved from the third
day of steroid treatment. After the stabilization of the pa-
tient’s general status, an endoscopic sinus intervention was
performed due to the incidental sphenoidal sinus aspergil-
loma and a 2-week long antifungal treatment was started.
Aspergillus fumigatus grew from the culture of the sample
taken during the endoscopy. The steroid treatment was
gradually tapered and terminated after 3 months. Axillary
lymphadenopathies and splenomegaly disappeared during
the follow-up. MRI investigation of the brain revealed that
the previous abnormalities were no longer present. When
this finding combined with significant response to steroid
treatment diagnosis of clinical status was confirmed as
ADEM. Treatment has been discontinued and the patient has
been followed up for a year; no complications have been
observed to date.

Discussion

Kikuchi-Fujimoto Disease, which was first described in
Japan in 1972 and is mostly seen in the Far East, has begun
to be reported in the other parts of the world recently (1-3).
Although the etiology of the disease remains unknown, in-
fected or autoimmune pathogenesis is held responsible.
The factors which likely result in the infection include EBV,
CMV, Human herpes virus-6, VZV, Human immunodefi-
ciency virus, rubella, measles, coronavirus, Coxsackie virus,
hepatitis A and B, Yersinia enterocolitica, toxoplasma, influ-
enza viruses, streptococci, leptospira and chlamydia. It has
also been reported that the disease may occur after rabies,
diphtheria-tetanus, poliomyelitis, hepatitis B and influenza
vaccines are injected (4). The disease may initially be mis-
taken for various benign and malignant diseases, such as tu-
berculosis, lymphoma, systemic lupus erythematosus (SLE)
and FUO. In the studies on FUO patients conducted in Tur-
key, KFD has not been mentioned as a cause of fever (5,6).
According to the English language literature, KFD is a rare
cause of fever of unknown origin (7) and cervical LAP is
seen in 70-98% of KFD cases while the rate of axillary
LAP is lower (8). The co-existence of axillary lymphadenopa-
thy and KFD is the least common clinical picture of
KFD, which is usually mistaken for lymphoma. Thus, KFD
should be included in the differential diagnosis in patients
with axillary LAPS. The definitive diagnosis can be based
on histopathological examination. In the present case, the
histopathological features were characterized by presence of
necrosis with histiocytes and cellular debris. We considered
a necrotizing type of Kikuchi-Fujimoto disease. Three different histological subtypes of this disease have been defined: proliferative, necrotizing and xanthomatosum (9, 10).

Neurological involvement is also rarely reported in studies investigating patients diagnosed with KFD (11). In their study evaluating 244 KFD patients, Kucukardali et al reported the rate of neurologic involvement findings including aseptic meningitis, mononeuritis multiplex, hemiparesis, brachial neuritis and photophobia as 5% (1). Since the present patient was diagnosed with KFD histopathologically but generalized tonic clonic seizure occurred during the continuing examinations aimed at determining the etiology of the disease, the differential diagnosis had to be reconsidered. Because viral encephalitis could not be ruled out, antiviral treatment was started. However, the treatment of the patient was changed due to the fact that central nervous system involvement could not be explained by encephalitis or KFD and the lesions detected by MRI were consistent with ADEM. In general, MRI findings include multifocal areas of high signal intensity in the supratentorial white matter, brain stem and cerebellum. The deep gray matter is frequently involved as well. After the initiation of corticosteroid therapy, follow-up imaging demonstrates decrease in size and number of the lesions (12). According to the consensus definition for ADEM reported by Sonneville et al, the present patient’s status fulfilled all of the diagnostic criteria of ADEM with acute clinical attack of inflammatory disease of CNS, affected multifocal areas of CNS, polysymptomatic presentation including encephalopathy, and clear improvement on clinical and neuroradiological measures (4). It was advantageous that corticosteroid treatment was used for the treatment of both KFD and ADEM. The incidental aspergilloma that was detected by radiological imaging during the high-dose corticosteroid therapy, which was required for the treatment of ADEM, could not be overlooked. Antifungal treatment was started along with the corticosteroid therapy. Due to the lack of knowledge related to the co-existence of these two diseases and the consequent impairment of immune response, antifungal therapy was used in addition to endoscopic sinus intervention. No bacterial or viral infections were detected during the available tests except HHV-6 of which serological tests could not be performed. It was striking that allergic inflammatory or autoimmune response played a role in the etiology of all three clinical manifestations (aspergilloma, ADEM and KFD) (2, 4, 13, 14). A review of the accessible literature did not show any reports of the co-existence of aspergilloma and KFD or co-existence of aspergilloma and concomitant KFD and ADEM (1, 4, 15). We supposed that, instead of infectious etiology, the clinical picture in this first case of ADEM and KFD co-existence might have resulted from the patient’s autoimmune response or immune reconstitution (IRIS).

As a result, unexpected clinical findings may be encountered during the follow-up of patients with diseases of unknown etiology such as KFD. In such patients, the existence of neurological involvement particularly worsens the clinical status and contributes to mortality. Thus, ADEM, which can reach a mortality rate of 25%, should be considered in the differential diagnosis when central nervous system involvement is detected during the follow-up of a patient with KFD.

References