A Girl Case with Pneumonia and Prolonged Fever

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What is your diagnosis?

Previously healthy 11-year-old female patient who had fever for the last several days especially in the evenings, reaching as high as 39.7ºC, head ache and chest pain was prescribed amoxicilline-clavulanic acid treatment with the diagnosis of sinusitis. Since thrombocytopenia (74,000/mm^3) was found in the complete blood count that was examined as patient's fever did not fall in the follow-up and it continued for a week, the patient was referred to our hospital in order to investigate the causes of fever.

There was no specificity in the personal and family history of the patients.

Patient's body temperature was 38˚C (axillar); respiratory rate 30/min.; pulse 110/min.; blood pressure 90/60 mmHg, body weight 30 kg (10-25th percentile); height 136 cm (3-10th percentile). In the physical examination, fatigue, paleness, hyperemia in oropharynx and tonsils, petechia on the palate, small lymphadenopathies on both submandibular regions, tachycardia and liver midclavicular even 1 cm palpable were detected. Other system examinations revealed no specificity. In the complete blood count, hemoglobin concentration was 11.8 g/dL, white cell count 7100/mm^3, absolute neutrophil count 3000/mm^3, platelet count 111,000/mm^3. Peripheral smear was normal. The following values were found; C-reactive protein (CRP) 5.45 mg/dL, erythrocyte sedimentation rate (ESR) 57 mm/sa, alanine amino transferase 73 U/L (0-40), aspartate amino transferase 99 U/L (0-50), lactate dehydrogenase 492 U/L (240-480). In the urine test, 3 leukocytes and 11 erythrocytes were found in the big magnification site. *Salmonella* and *brucella* agglutination tests were negative. In the chest radiography, due to reticular infiltration, clarithromycin and ceftriaxone treatments were given empirically with the provisional diagnosis of atypical pneumonia.

In the electrocardiogram taken due to the continuing fever, chest pain and with the suspicion of tachycardia-related myocardia, mild low voltage suppression in the D1- AVL and low voltage in the extremity derivations were found. Echocardiography was normal. Upon normal test results of creatinine kinas-MB and troponin I, normal, he patient was thought to have subclinical myocardia. No organomegaly was detected in the abdomen ultrasonography and no lymphadenopathy was found in the pathologic level. In abdominal and pelvic regions, there was maximum 2 cm-thick free fluid. Ebstein-Barr virus (EBV), sitomegalovirus (CMV), parvovirus serologies examined to identify the viral causes of fever were negative. The quantitative immunoglobulin (Ig) values of the patient were within normal ranges for her age. In the control echocardiography taken on the 10th day of her fever, as mitral insufficiency (1-2. degree) and minimal pericardial effusion were monitored, naproxen sodium was added to the

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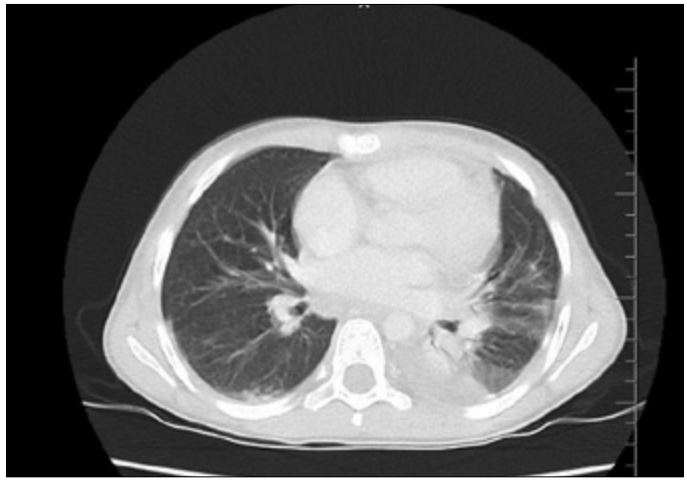
treatment. In the thoracal CT taken because of persisting fever, leukocyte count 6000/mm^3, CRP 1.4 mg/dL, ESR 72 mm/hour, there were consolidate segments and collapse next to the effusion with the accompanying air bronchograms in the inferior lobes of the both lungs especially in the left side (Figure 1, 2). Malignity was not considered. Continuing fever, fatigue and abdominal pain despite the treatment, intraabdominal free fluid and the presence of pleural-pericardial effusion led us to think that the existing symptoms could not only be explained atypical pneumonia. The lipid profile sent for haemophagocytic lymphohistiocytosis was normal, ferritin 367.7 (11-336) ng/mL, fibrinogen 338 mg/dL (200-393). The bone marrow aspiration done on the 16th day of fever, plasma cells increased; malignity was not considered. C3 60.3 mg/dL (83-177), C4 4.98 mg/dL (12-36), antinuclear antibody (ANA) 70 (<1) IU/mL, anti-ds-DNA antibody1129 (0-200) IU/mL, anti-phospholipid IgM-IgG and anti- cardiolipin IgM-IgG resulted negatively. Tuberculin skin test (TST) anergic, direct coombs 2 were positive. No growth was found in the bone marrow and blood cultures. In the 24-hour urine, proteinuria was 720 mg/m^2/day. *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and human immunodeficiency virus (HIV) serologies were negative.



Resim 1. Akciğer tomografisi

Note: Discussion part of this case report on page 95th.

What is your diagnosis? (Continued)

Instructive Case (Continued)

What is your diagnosis of this patient?

Diagnosis: Systemic lupus erythematosus

Our patient was diagnosed with systemic lupus erythematosus based on the diagnosis criteria of *The Systemic Lupus Collaborating Clinics* (SLICC) 2012 on the ninth day of her hospitalization due to the fever, head ache lasting for three days, thrombocytopenia and leukopenia, pleural and pericardial effusion, low level of C3, C4, ANA and anti-ds positivity, hematuria and proteinuria in the 24-hour long urine (1) (Table 1). On the first day of 3-day high dose methylprednisolone treatment (30 mg/kg/day the most 1 gram/day), patient's fever dropped and three days later, leukopenia and thrombocytopenia improved. In the chest radiography five days later, it was found that pleural effusion clearly improved. One week later, in the control ECO, pleural effusion healed completely.

The fever (NBA) identified by Petersdorf and Beeson in 1961 whose classical cause is unknown represents the fever that is over 38,3°C in multiple measurements, lasts for more than three weeks and undiagnosed under one-week-long hospital stay conditions (2). This definition previously underwent some modifications. In accordance with today's conditions, Durack and Street made a new classification in 1991. In addition to the classical definition, nosocomial infections, neutropenia and HIV infection-related NBA was defined. Durack and Street made a suggestion to decrease the period to three days by adding the definitions in nosocomial, neutropenic, and HIV infected patients (3). History of unknown fever, physical examination and pre-laboratory tests and fever lasting more than 8 days are defined as unexplainable cases (4).

Although the causes of unknown fever may vary in relation to age, socioeconomic and social factors, infectious diseases confront us in the first place in the comprehensive series reported in the literature followed by collagen vascular diseases and cancer (5). When the etiology of a total of 1638 NBA pediatric patients in 10 studies in the developed countries were examined, it was found that infections were 51%, collagen vascular disease 9%, cancer 6%, other causes 11% and undiagnosed cases 23% (6). In their study in which they investigated the etiology of 77 unknown pediatric cases in Turkey, Tezer et al. (7) reported that infectious diseases were 50.7%, cancer 14.4%, collagen vascular disease 7.2%, others 27.5% and undiagnosed cases 10.3%. When 19 undiagnosed children were followed up for 3.5 years in a different study, 16 recovered without any diagnosis, two were diagnosed with juvenile idiopathic arthritis and one with recurrent invagination-driven fever (8).

The first stage in identifying the etiology in patient with unknown fever should be to ask for a detailed history. Course of the fever, redness in the eye, recurrent pharyngitis, gastrointestinal complaints, joint and bone pains, contact with sick person, contact with animals and patient's travels should be questioned. Physical examination should be made cautiously and should be repeated; new findings may be acquired in the repeated examination. The findings obtained in the physical examination are important in both making a diagnosis and managing the diagnosis methods. Complete blood count, peripheral smear, urine test and culture, serum electrolytes, kidney and liver tests, TDT, chest radiography, CRP, ESR, blood culture, and HIV serology are present in the basic laboratory examinations of the patients with unknown fever. Based on these examinations and some findings, the investigations are directed; stool as additional tests, bone marrow examination, brucella and salmonella agglutination tests, tularemia tests, EBV, CMV, bartonella serology, ANA and Igs can be tested. In imaging methods, ultrasonography, central nervous system imaging, positron emission scintigraphy examinations can be used (8-11).

Juvenile rheumatoid arthritis, polyarthritis nodosa and systemic lupus erythematosus (SLE) are among the collagen vascular causes of unknown fever. Positivity of ANA supports SLE. Steele RW et al. recommend ANA among the first tests to be made in NBA cases over five years old (10).

Systemic lupus erythematosus; is a chronic collagen tissue disease with an unknown cause, comes together with immunologic disorders, has autoimmune characterized that holds together skin, joint, kidney, lung, neural system, serous membrane or other organs. The incidence of this disease in the United States of America is 1/5000-10,000, female/male ration 8/1. Although it is more prevalent after the age of five, it can emerge at any age. Even though its cause is not exactly known, genetic, hormonal, immunologic and environmental factors are blamed (12). Initial symptoms are variable; it may appear with any organ involvement. The most frequent admission symptoms are fever, weight loss and over all disorders. For its diagnosis, the SLE classification criteria defined by the *American Rheumatology Association (ARA)* in 1982 and reviewed in 1997 was used, but *SLICC* revised the SLE diagnosis criteria of ANA in 2012 to be used in adults and children in an attempt to increase the clinical importance of SLE, meet the strict methodology needs and include the developments in the field of immunology (Table 1) (1). Non-steroid anti-inflammatory drugs, antimalarial drugs, glucocorticoids and immunosuppressives are used in its treatment.

Acute pneumonitis is a rare finding of SLE with the ratio of 10-15%. It is frequently confused with pneumonia. Acute pneumonitis usually appears with high fever, chest pain, coughs, respiratory distress, hypoxia and rarely with hemoptysis. The most frequent auscultation finding is hearing the light rale in the lung basals. It may clinically replicate the bacterial pneumonia. In the chest radiography, displaced patch-like infiltration, common diffuse alveolar consolidation or the infiltration tending to involve the basels may be monitored. Lung damage is prevalent and may clinically replicate acute lung injury syndrome (ARDS) (13, 14). In our case, there were fever, thoracic pain and pleural effusion; however, it is consid-

Table 1. Classification rule

-4 criteria (at least 1 clinical, 1 immunologic criterion)	
or	
-Biopsy-proven Lupus Nephritis + ANA or Anti-ds DNA positivity	
Clinic Criteria	**Immunologic Criteria**
1. Acute skin lupus	1. ANA+
2. Chronic skin lupus	2. Anti-ds DNA+ (2 Times verified)
3. Oral or nasal ulcer	3. Antiphospholipid antibody
4. Alopecia	LAK+
5. Synovitis (swelling or sensitivity)	Pseudo RPR
6. Serositis (pleuritis, pericarditis)	Anticardiolipin+ (medium-high level/IgA, IgG, IgM)
7. Kidney involvement (proteinuria, hematuria)	Anti b2GP-1 (IgA, IgG, IgM)
8. Neurologic involvement	4. Low complement
9. Hemolytic anemia	C3, C4, CH50
10. Leukopenia or lymphopenia	5. Direct Coombs (without hemolytic anemia)
11. Thrombocytopenia	
ANA: antinükleer antikor; LAK: lupus antikoagülanı; RPR: rapid plasma reagin; Ig: immunoglobülin; Anti b2GP-1: anti-beta-2-glycoprotein-1	

ered as pneumonia because of reticular infiltration in the pulmonary rontgenography and bilaterally consolidation and collapse to the next of the effusion at the inferior lobes and accompanying air bronchograms.

Systemic lupus erythematosus has various neuropsychiatric involvements. Headache is a common complaint and may emerge in such conditions as stroke, seizure and chorea. Our patient had a Headache from the beginning of the process and 500 mg/m^2/dose cyclophosphamide treatment was prescribed as the head ache was considered as a symptom of neurologic involvement. Headache ceased after the treatment.

Lupus nephritis has been found in 37% of the patients in the USA (15). The existing proteinuria and haematuria of our patient was evaluated as a renal involvement and phase-2 lupus nephritis was detected in the patalogic examination of the kidney biopsy.

The patient whom fever has fallen and has no headache, cheast pain, weakness was discharged with the steroid, hydroxychloroquine and angiotensin converting enzyme inhibitor therapies. It was seen that the patient did not have any complaints in the policlinic control examination.

Identifying the cause of the etiology of unknown fever requires taking the clues obtained from history, physical examination and basic laboratory examinations into consideration. Especially NBA cases with a multisystem involvement should be investigated in terms of collagen vascular diseases. Early diagnosis and treatment of lupus erythematosus should be borne in mind in order to prevent the likely complications and heal the prognosis.

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