Clinical Problem-Solving

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Pleuritic Chest Pain; Where Should We Search for?

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Abstract

Pleuritic pain is not an unusual problem in children. Other concomitant symptoms should be considered for diagnostic approach in a child with pleuritic chest pain. In this report we discuss chest pain in a 6-year-old child with regard to other signs and symptoms. Finally, we found a rare life-threatening complication of juvenile systemic lupus erythematosus (JSLE) in our patient.

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Introduction

Pleuritic pain is not an unusual problem in children. Other concomitant symptoms should be considered for diagnostic approach in a child with pleuritic chest pain. In this report we discuss chest pain in a 6-year-old child with regard to other signs and symptoms.

Case presentation

This six-year old boy was presented to the emergency department of Children's Medical Center, Tehran, with dyspnea and pleuritic chest pain. The symptoms had begun two months ago and gradually aggravated for the past two weeks. The patient awoke by chest pain at night. He preferred to remain in up-right position.

Pleuritic chest pain has a broad differential diagnosis. Pain is exaggerated by deep breathing, coughing, and straining. Some of the differential diagnoses of chest pain in the pediatric patient are pneumonia, pleurisy, pneumothorax, pericarditis, endocarditis, costochondritis (tietze syndrome), herpes zoster (cutaneous), angina (familial hypercholesterolemia, anomalous coronary artery), epidemic pleurodynia, trauma and rib fracture, lesions of the dorsal root ganglia, tumors of the spinal cord, and gallbladder disease. Gastro-intestinal diseases like peptic ulcer, esophagitis (gastroesophageal reflux, infectious, pill), cholecystitis, perihepatitis (Fitz-Hugh-Curtis syndrome), esophageal foreign body and spasm are less common causes of chest pain in children.

The chronicity of the symptom indicates that a systemic chronic problem could be the main cause.

Cardiac diseases like pericarditis, endocarditis, mitral valve prolapse, and arrhythmias are among the "must not miss" diagnoses and should be ruled

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out. However chest pain is not a usual presentation of cardiac diseases in childhood.

He had short stature and a cachectic appearance. Heart beat was 110/min, respiratory rate 38/min, blood pressure 110/70, temperature 39°C, body weight 15 kg and height 107 cm.

Both weight and height were under the 3rd percentile. The low growth indicators suggesed a chronic disease involved.

The medical history was notable for 25 days of hospitalization at 4 years of age, because of a history of 3 months fever and bad appetite. He had received antibiotics during hospitalization and one month after discharge. The medical files were not available, but his mother had been told that her son was treated for typhoid.

Six months after getting discharged from the hospital, the patient again developed fever and general asthenia, and his mother noted that since then he continuously felt weak, had low growth rate, and developed fever occasionally. One year ago the patient contracted pneumonia and was hospitalized for treatment. He also had an intermittent fever which according to his mother lasts for a few years. As his mother told, he has not received vaccination since four years of age.

The main reason of his past hospitalization is not known. However, we had to check for typhoid, but it should be considered that another underlying chronic febrile disease involvement was probable. He developed dyspnea, which progressed gradually. Now in physical examination we searched for signs and symptoms of a chronic disease and specific organ involvement.

At admission, the patient was in apparent respiratory distress, which worsened on supine position and he preferred to remain in semi-sitting position. Chest x-ray and ECG were normal.

Conjunctivae were pale, and auscultation of heart and lung was normal. On abdominal examination, a generalized tenderness interfered with the examination process. Right wrist and heap joints were tender. He had no symptoms of clubbing, edema or cyanosis.

The mother reported of a generalized bone pain, weight loss, nocturnal sweating and fever during the last three months. His father also had a three years history of night-fever and cough without any medical evaluation.

The symptoms of pale conjunctivae, weight loss, night sweating and fever, indicate the chronic pattern of the illness. Iran is an endemic area for tuberculosis, so it also had to be considered, especially with the positive suspicious family history. Because of bone pain, malignancies should be among the list of differential diagnoses. Cardiopulmonary causes had to be ruled out, because of pleuritic chest pain and orthopnea.

Echocardiography performed soon after his admission, revealed mild pericardial effusion.

The pericardial effusion could justify the chest pain and the respiratory symptoms. Infectious, rheumatologic and maybe malignant causes of serositis are among the possible diagnoses, which could be the reason for other signs and symptoms of the patient.

The first blood-work tests showed the following results (normal values in parentheses):

Complete blood count: WBC 8130/µl (Neutr 59%, Lymph 34%, Mono 6%, Eosin 0%), RBC 3.600,000/µl, Hb 8.1 g/dl, MCV 75.7 fl, MCH 22.5 pg, Plt 377000 /µl,

ESR 125 mm/h.

Blood glucose 102 mg/dl, Creatinine 0.6 mg/dl (0.3-0.7), Blood urea nitrogen 10 mg/dl (5-20), C-reactive protein 24 mg/l (<6). A bactech blood culture was negative for bacterial growth.

The most important findings were the very high level of ESR, and low hemoglobin level. Again we searched for infectious, rheumatologic and malignant causes. However, malignancies were less probable as the ill condition of the patient started four years ago and malignancies would have caused much more problems during this period of time.

Because of fever and elevated ESR, the patient was admitted to the Infectious Disease Ward. The following tests were completed and respective results obtained.

Negative PPD test, bone marrow aspiration with normal cellularity and negative for Ziehl-Neelson staining, and negative culture results for typhoid. Radionucleotide scan showed some hyperactivity in the right hip and ankle. Wright, Coombs Wright,

and Widal tests, as well as blood and urine cultures were also negative.

These results indicate a low probability of infectious and malignant diseases, so rheumatologic diseases had to be taken into account and evaluated.

More laboratory tests were performed with suspicion to malignancies, rheumatologic, autoimmunity and immunodeficiency. Anti nucleotide antibody (ANA) was positive [16 (neg <0.8, pos >1.2)]. The complete blood count series obtained for seven days showed no significant changes. Amylase, lipase, uric acid, cholesterol, triglycerides, calcium, phosphorous, liver function tests, lactate dehydrogenase, total protein and albumin were normal.

Positive ANA, justified more tests and examinations for rheumatologic diseases to be done. The presence of serositic arthritis and a positive ANA made the rheumatologic diseases, especially SLE to be the first in the list of the differential diagnosis. Systemic-onset juvenile rheumatoid arthritis could also be a possible cause.

Some more tests, especially anti-dsDNA, and RF were needed. Antinuclear Antibodies (ANAs) can be positive in systemic lupus erythematosus, drug-induced lupus, juvenile arthritis, juvenile dermatomyositis, vasculitis syndromes, sclera-derma, infectious mononucleosis, chronic active hepatitis and hyperextensibility.

The latest CBC: WBC 3180 (Neut 58%, Lymph 36%, Mono 14.6%, Eos 0, Baso 0.3%), RBC 3.18, Hb 7 g/dl, MCV 69.2, MCH 21.6, Platelets 293000. Results of the new tests are as follow:
AntiCCP 1.7µ/ml (within normal range, neg <6.25), C3 132 mg/ml (88-155), C4 57 mg/dl (12-32), Anti-dsDNA 585 IU/ml (neg <100, pos >100), RF ++++, ASO 100 Todd units (up to 200 Todd units).

On the criteria for lupus, diagnosis of SLE was made (Table 1) and treatment with prednisolone tablets (2mg/kg/day) and hydroxy-chloroquine (5mg/kg/day) initiated. A few days later, the patient's condition improved gradually and the fever subsided.

Table 1: Criteria for Systemic Lupus Erythematosus

Criterion	Definition	Our patient
Malar rash	Fixed erythema, flat or raised on the malar areas sparing the nasolabial folds	
Discoid rash	Erythematous raised patches in the company of adherent keratotic scaling and follicular plugging	
Photosensitivity	Rash as a result of unusual reaction to sunlight	
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician	
Arthritis	Non-erosive arthritis in two or more peripheral joints, (tenderness, swelling, or effusion)	+
Serositis	Pleuritis: history of pleuritic pain or rub proved by a physician , pleural effusion	+
Renal disorder	Pericarditis: (ECG, rub, pericardial effusion) Persistent proteinuria >0.5 g/day or >3 plus (+ + +) Cellular casts: (red blood cell, hemoglobin, granular, tubular, or mixed)	
Neurologic disorder	Seizures: in the absence of drugs that can be the cause or metabolic impairments (e.g., uremia, ketoacidosis, electrolyte imbalance) Psychosis: in the absence of drugs that can be the cause or metabolic impairments (e.g., uremia, ketoacidosis, electrolyte imbalance)	
Hematologic disorder	Hemolytic anemia, with reticulocytosis, or Leukopenia: <4,000/mm^3 (two or more occasions) or Lymphopenia: <1,500/mm^3 (two or more occasions) or Thrombocytopenia: <100,000/mm^3	
Immunologic disorder	Anti-DNA antibody abnormal titer or Anti-Smith: Antibody to Smith nuclear antigen or Positive Antiphospholipid antibodies	+
Antinuclear antibody	An abnormal titer in the absence of drugs recognized to be associated with "drug-induced lupus syndrome"	+

The diagnosis of lupus is established by combination of clinical and laboratory manifestations. The company of 4 (serositis, arthritis, abnormal titer of anti-DNA antibody, antinuclear antibody) of 11 criteria serially or simultaneously strongly suggests the diagnosis. Patients who are suspect to have lupus, but show fewer than 4 criteria should receive proper medical treatment. A positive ANA test is not necessary for diagnosis; absence of ANA in lupus is very rare. Hypocomplementemia is not diagnostic, and very low levels or absence of total hemolytic complement suggests the likelihood of complement component insufficiency. The treatment for SLE should be started.

Having different pictures, lupus must be among the differential diagnoses of many problems, from fevers of unknown origin to arthralgias, anemia, and nephritis. The differential diagnosis depends on the presenting manifestation and affected organ and includes systemic-onset juvenile rheumatoid arthritis, acute poststreptococcal glomerulo-nephritis, acute rheumatic fever, infective endocarditis, leukemia, immune thrombocytopenic purpura, and idiopathic hemolytic anemia. Sometimes the early presentation is atypical such as parotitis, abdominal pain, transverse myelitis, ordizziness. Lupus should also be considered in patients with multiorgan involvement, especially in the presence of hematologic or urinalysis problems.

Clinical manifestations of SLE include constitutional symptoms (fatigue, prolonged fever, anorexia, lymphadenopathy, weight loss), musculoskeletal (arthralgias, arthritis) cardiovas-cular, pulmonary (pulmonary hemorrhage, pleuritic pain), skin, renal, hematologic, neurologic (seizures, psychosis, stroke, cerebral venous thrombosis, pseudotumor cerebri, aseptic meningitis, chorea, global cognitive deficits, mood disorders, transverse myelitis, and peripheral neuritis (mononeuritis multiplex).

On the sixth day of treatment our patient's condition suddenly deteriorated. He was found in apparent respiratory distress, high fever, dyspnea and having an enlarged liver span.

He was then transferred to PICU, and cotrimoxazole, ceftazidim, and stress dose of hydrocortisone was initiated.

CBC showed decrease in WBC, Hgb and Platelets. The trend of CBC tests in PICU is seen in Table 2. Other blood work test results in PICU were as follow:

Ferritin 8654 ng/ml (7-140), Fibrinogen 1300 mg/dl (172-539), Cholesterol 199 mg/dl (120-200), Triglycerides 398 mg/dl (60-165), Adenosine deaminase 18 u/l (0-15), Calcium 8 mg/dl, Na 127 meq/l (135-145), AST 57 u/l (up to 40), ALT 24 u/l (up to 40), C-reactive protein 48 mg/dl (neg <6), ESR 148 mm/h, reticulocytes 0.8%, C3 89 mg/dl (88-155), C4 56 mg/dl (12-32), CH50 0 u (70-150), IgG 1256 mg/dl (633-1280), Lactate dehydrogenase 705 IU/L (120-300).

Other tests such as creatine phosphokinase, serum IgA and IgM, BUN, creatinine, blood glucose and serum potassium were in normal range.

After respiratory distress as the first presenting manifestation, we evaluated our patient for pulmonary and cardio-vascular involvement, which may occur in the course of SLE. He developed fever again while receiving immunosuppressive medications and empirical antibiotics for opportunistic infections started.

The acute deterioration of the patient's condition during treatment of SLE, is suggestive of macrophage activation syndrome (MAS). The diagnosis is supported by acute leucopenia, high liver function tests, hepatomegaly, and high ferritin level. This diagnosis was suggested by clinical presentation and confirmed by bone marrow biopsy. In the most cases of MAS, bone marrow demonstrates hemophagocytosis. Urgent treatment

Table 2: Trend of CBC tests in the patient in PICU

	The 1st day	The 3rd day	The 5th day	The 7th day	The 8th day
Whit Blood Cell	480	280	130	520	960
Neutrophils	12.5%	3.6%	-	67%	68.3%
Lymphocytes	72.9%	85.7%	-	26.9%	27.2%
Hemoglobin	5.9mg/dl	8.9	7.8	6.6	9.9
Platelet	293000	211000	122000	121000	73000

with intravenous pulse of methyl-prednisolone, cyclosporine, and sometimes, etanercept, are generally effective. Administration of IVIG, is useful in infections and MAS syndrome and was highly recommended in our immunodefficient patient. Performing a CXR, echocardiography, and bone marrow aspiration would help doctors in deciding appropriately. Having MAS in mind, which is an occasionally fatal condition, may save the patient. MAS may not have its typical manifestation at the beginning, but if it progresses, it would be more difficult to manage.

Intravenous immunoglobulin IVIG 2mg/kg was administered. A chest x-ray showed the possibility of atypical bronchopneumonia and patchy bilateral paracardiac opacities. The size of the heart was at the upper normal limit.

Echocardiography revealed no pericardial effusions, no vegetation, no Limbman-Sacks lesion, good systolic and diastolic function, and an ejection fraction of 50%.

Cardiac enzyme test results: CK-MB-Mass 1.14 ng/ml (0-4.94), CPK 43 u/l (24-229), Troponin T 0.011 ng/ml (<0.05 neg), Troponin I 0.147 ng/ml (<0.16 neg), NT-PRO BNP 5287 pg/ml (0-100).

A new bone marrow aspiration showed: Hypo-cellular marrow without any specific diagnosis.

As no significant improvement was observed, a three-day pulse-therapy with methylprednisolone (30mg/kg/day) was prescribed and cyclosporine A added to the regimen. Because of severe neutropenia, Granulocyte Colony Stimulating Factor (GCSF) was initiated on the fifth day of admission to ICU. Packed cells were also transfused several times.

The level of serum B-type natriuretic peptide (BNP), raised in response to abnormal ventricular wall tension, heart failure, systolic dysfunction, volume overload and cardiomyopathy. Measurement of BNP (elevated in heart disease), can help distinguish cardiac from pulmonary causes of pulmonary edema. A BNP >500pg/mL suggests heart problems, <100pg/mL suggests lung disease. The level of ESR, creatine phosphokinase, lactate dehydrogenase, and BNP may be elevated in acute or chronic myocarditis[1].

We expect that treatment with immunosuppressives along with antibiotics and supportive care, may cause the presenting critical condition to subside and also improve heart condition involved in the process of background disease.

Receiving medication for opportunistic infections, MAS and supportive care, the patient's respiratory distress and general condition improved gradually and he was transferred to Rheumatology Ward and after 2 weeks he was discharged with an appropriate regimen for SLE.

In long time follow up the disease went into reemission and treatment was reduced gradually. A flare up of the disease after 1.5 years forced to increase the drugs which could be decreased again after remission. After 3 years follow up, the disease is in remission and he is on low dose prednisolone (5 mg/daily) and hydroxychlroquine (100 mg/daily).

Commentary

The patient initially came to the emergency room with mild respiratory distress, pleuritic chest pain and other signs and symptoms that indicate a chronic disease. The initial evaluation revealed diminished growth pattern, bone pain, night sweating and fever, pleuritic dyspnea, high ESR and serositis, which have a long list of differential diagnosis (cardiopulmonary, infectious, rheumato-logic and malignancies), but the chronic pattern of the illness made the malignancies less probable. The infectious causes were ruled out by laboratory tests, and soon after, the rheumatologic causes were taken into consideration.

MAS is a potentially fatal complication of childhood systemic inflammatory diseases [2,3]. It can be one of the causes of secondary hemophagocytic lymphohistiocytosis (HLH) [3,6]. High ferritin level is one of the diagnostic criteria for HLH [12]. This syndrome is characterized by excessive activation of T lymphocytes and macrophages and massive production of cytokines[4]. The clinical presentation of MAS includes persistent high fever, pancytopenia, hepatosplenomegaly, hepatic dysfunction, ence-phalopathy and coagulation abnormalities[2,5]. MAS can occur as a complication of rheumatic diseases or triggered by an infection or by a

change in treatment regimen [2,7,8]. There are few case reports, that describe MAS as the first manifestation of rheumatic and also Kawasaki disease [9]. Abnormal immune system reaction and regulation that leads to the lack of control of an exaggerated immune response is one of the mechanisms suggested for MAS [9].

The diagnostic criteria for MAS that complicates systemic juvenile idiopathic arthritis (s-JIA), include decreased platelet count, elevated aspartate aminotransferase, decreased white blood cells, hypofibrinogenemia, central nervous system impairment, hemorrhages, hepatomegaly and histologic evidence of macrophage hemophagocytosis in bone marrow aspirates [1].

MAS is seen most commonly in s-JIA[10]. It is also diagnosed in systemic lupus erythematous [11,13]. In our patient, MAS happened during the treatment of SLE, and it should always be kept in mind, if the condition of a rheumatologic patient deteriorates acutely without any obvious reason rapid initiation of the treatment is very important and critical.

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