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Ex Juvantibus diagnosis of undifferentiated diffuse connective tissue disease

Olga Skosyreva[1], Lola Daminova[2], Makhsud Sabirov[3]
[1-3] Department of therapeutic subjects 2, Tashkent State Dental Institute, St, Makhtumkuli, Tashkent, Uzbekistan

Abstract
The term "undifferentiated connective tissue disease" (UCTD) represents a stage of disease where clinical symptoms and serological abnormalities suggest autoimmune disease, but they are not sufficient to fulfill the diagnostic criteria of any well-established connective tissue disease (CTD). It is diagnosed when there is evidence of an existing autoimmune condition which does not meet the criteria for any specific autoimmune disease. This clinical case is of interest in terms of late diagnosis of undifferentiated diffuse connective tissue disease, that, most likely, was difficult to make due to underestimation of multi-organ manifestations of the disease, including the Sjogren's syndrome which is characteristic for collagenosis, as well as due to refusal of the patient from biopsy. The pulse therapy under the umbrella of the antibiotic have rendered a pronounced positive effect and confirmed the main diagnosis on the basis of the effect of treatment (diagnosis ex juvantibus). Hence, in the presence of signs of multi-organ damage, physicians should keep in mind the possibility of a diffuse connective tissue disease.

Keywords: undifferentiated connective tissue disease, Sjogren's syndrome

Introduction
A 73-year-old man was referred to the 3rd hospital of Tashkent Medical Academy with signs of kidney lesion and the history of treatment at two other medical settings. At first, the diagnosis was pneumonia, later on it was changed to lung TB, and then to fibrosing alveolitis.

Complaints on Admission
Exceptional dyspnea, productive cough, high temperature (38° C) with chill and perspiration, palpitation, dryness in the mouth with no saliva, pain in joints, including the maxillary ones, nausea and vomiting, anorexia, 10 kg weight loss for 3 months, and expressed general asthenia.

History
The man has been ill since for about a year that became apparent by a temperature rise, pains in the chest, cough with mucopurulent sputum, and breathlessness. He was admitted to the hospital with the diagnosis of pneumonia that later was changed to pulmonary tuberculosis. However, the treatment has resulted in no positive effect. The patient was referred to the National Centre for Pulmonology and Phthisiology where the chest CT revealed fibrosing alveolitis. The prescribed therapy included glucocorticosteroids (GCS) in the dose of 8 mg/day, and the patient's condition has improved. However, it was accompanied by an increase in urea and creatinine levels and a decrease in glomerular filtration rate. Due to the signs of renal pathology, the patient was referred to the Nephrology Unit of the 3rd hospital of Tashkent Medical Academy with the preliminary diagnosis of Tubulointerstitial nephritis with impairment of renal functions.

Physical Examination
The general condition of the patient was severe, he was passive. The skin and visible mucous membranes were clean and pale. The submaxillary lymph nodes were pea-sized and sensitive to palpation. No joints had any noticeable changes; they were moderately painful to palpation and moved through their full range of motion. The muscles were painful to palpation, their strength was preserved. The number of respiratory movements was 22/min. The percussion of the lungs in the medioum-lower departments revealed shortened sounds in both sides. The auscultation revealed harsh breath and moist râles. The heart borders were 1.5cm shifted to the left; the heart sounds were moderately muffled, rhythmical, the BP was 90/60 mm.Hg, and his heart rate was 82 beats/min and rhythmical. The abdomen was painless to palpation; the sizes of the liver and spleen were not increased. There was the tendency to constipation. The percussion symptom was positive in both sides. The patient urinated in small portions 5-6 times/day with 800 m/day urine output. The laboratory test results and their dynamics in the course of treatment are given below (Table 1).
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Table 1: Dynamics of laboratory indicators in various terms of treatment

Indicator	Before treatment	day 10	day 24
Blood:			
Hb	87.0	101	109
RBC	3.0	3.1	3.3
Color index	0.8	0.86	0.9

WBC	10	6.3	8.9
Platelets	3.l	3.5	3.55
Stab neutrophils	4%	-	3
Segmented neutrophils	78%	72	74
Eosinophil %	3	4	4
Lymphocytes %	15	16	18
Basophiles %	0	0	0
Monocytes %	4	8	5
ESR mm/h	35	22	18
Blood coagulation time	H-3.4	K – 4.10	H-3,6
ALT U/l	20	23	
Total bilirubin Mmol/l	13.5	10.8	
Conjugated bilirubin Mmol/l	-	-	
Unconjugated bilirubin μmol/l	13.5	10.8	
Glucose Mmol/l Mmol/l	4.0	5.1	
Urea	16.9	13.6	10.3
Creatinine Mmol/l	427.2	214.9	188.3
Total protein g/l	65.0	69.5	68.8
Potassium Mmol/l	4,2	4.0	
Haematocrit	29	32	
Fibrinogen/ antithrombin g/l	6.3	4.1	3.9
Prothrombin ratio/index%	105	90	93
MHO	1,2	1,0	1.1
Urine: Relative density kg/l	1016	1018	1015
Protein	0.33	Traces	Traces
Sugar	-	-	-
Epithelium	6-7	3-4	5-6
WBC	11-13	3-4-5	0-2-3
RBC	Unchanged, 4-6-9	Unchanged, 0-1-3	Unchanged, 0-0-1
Casts			
Hyaline	0-1-1	0-1-1	
Bacteria	(++)	(+)	(+)
Fungi	(+++)	(+)	(+)
WBC/ml	16000	2200	2000
RBC/l	10000	1050	950
Active WBC/ml	-	-	-
Cylinders/ml	8-9	-	-

Instrumental Examination

ECG

Sinus tachycardia, normal rhythm; heart rate 102 beats/min. Electric axis of the heart is sharply deflected to the left. Left His bundle branch block was detected.

Lung CT

Signs of interstitial fibrosis of the lungs, secondary bronchiectasis, pneumosclerosis. Esophagogastroduodenofibros copy: signs of chronic gastritis, reflux-esophagitis, hernia of the esophageal diaphragm hiatus.

Abdominal cavity and kidney ultrasonography

Increased echogenicity of the liver parenchyma, consolidation of the gallbladder walls, signs of chronic bilateral inflammatory process in the kidneys.

The patient refused flatly from biopsies of skin and kidneys.

Dentist Consultation

The diagnosis - the secondary Sjogren's syndrome caused by the basic disease. On the basis of syndromic signs (affection of many organs and systems, confirmed by laboratory tests and instrumental examination, and the past history as well (pneumonia and lung TB exclusion, a GCS positive effect), *the clinical diagnosis* was made, namely: the unspecified system disease of the connecting tissue (ICD X - M 35.9), subacute course, activity III (pneumonitis, polymyositis, carditis, hepatitis, nephritis, renal function disorder, secondary Sjogren's syndrome). *Concomitant diseases*: chronic gastritis, diaphragmatic hernia of the esophageal hiatus, chronic pyelonephritis in the stage of active inflammation. *Complication*: anemia of chronic diseases of grade II.

Given the severity of the patient's condition, the clinical, laboratory and instrumental examination findings demonstrating a high activity of the pathological process, and the absence of contra-indications to GCS application, the pulse - therapy with solu-medrolom was chosen that included: methylprednisolon (1000 mg) + sodium heparin (50,000 U) + 0.9 % physiological solution (200 ml i.v., drip infusion for 3 days), ceftriaxon (1,000 mg) + 0. 25 % novocain (5.0 ml i.v. twice a day after the test) for 7 days; 0.2 % ondansetron (4.0 i.v continuous infusion for 5 days, Infesol (250 ml i.v., drip infusion at days 4 and 9 of treatment, 4.2 % arginin hydrochloride (100.0 i.v., drip infusion; 5 times), enoxaparin sodium (0.6 U S.C. once a day for 5 days), cosmofer (i.v. slow continuous infusion once a day for 7 days, erythropoietin (4000 U S.C. once in 3 days, 3 injections,

Rheosorbilact (200 i.v. drip infusion once a day for 7 days), prednisolon (5mg on day 4 of treatment i.e. after the pulse-therapy with methylprednisolon, 6 tablets a day), omeprasol 40 mg/day twice over). After 10 days of hospital treatment the general condition of the patient has considerably improved: the body temperature normalized, pains in the muscles and joints disappeared; fever, hyperhidrosis, breathlessness, cough, sputum discharge, and dryness in the mouth decreased while salivation increased. Appetite resumed, the patient gained 2.5 kg, and became active. At the 2-week out-patient stage the following therapy was recommended: prednisolon (8 tablets by 5mg), vitamin E (1 capsule by 200 mg twice a day); Calcium D3 (1 tablet once a day); omeprazol (1 capsule by 20 mg twice a day). The check-up was appointed in 14 days.

Examination of the patient 2 weeks later

The general condition is satisfactory, slight general weakness; sometimes coughing with light sputum, 2 kg weight gain. The results of tests are presented in Table.1. Further recommendations for 1 month: prednisolone (8 tab./day), vitamin E (1 caps. by 200 mg twice a day), clopidogrel 75 mg/day. in the evening after meals, calcium D3 (1 tab. twice aday), omeprazole 20 mg/day.

Discussion

This clinical case is of interest in terms of late diagnosis of undifferentiated diffuse connective tissue disease, that, most likely, was difficult to make due to underestimation of multi-organ manifestations of the disease, including the Sjogren's syndrome which is characteristic for collagenosis, as well as due to refusal of the patient from biopsy. The pulse therapy under the umbrella of the antibiotic have rendered a pronounced positive effect and confirmed the main diagnosis on the basis of the effect of treatment (diagnosis ex juvantibus). Hence, in the presence of signs of multi-organ damage, physicians should keep in mind the possibility of a diffuse connective tissue disease. As you know, Sjogren's syndrome occurs at any age, but in women it is almost 10 times more likely (mainly in the postmenopausal period) than in men. In 30% of cases, it is associated with other autoimmune diseases, such as SLE, RA, mixed connective tissue disease, primary biliary cirrhosis, autoimmune thyroiditis, etc. Dry eyes and dry mouth are the most common and easily diagnosed symptoms of this disease. The reason for the development of the disease is unknown today, but it is believed that the autoimmune process can trigger the hepatitis B virus or Epstein-Barre virus. To date, researchers have identified at least 6 genes (6.8.9) associated with Sjögren's syndrome and other autoimmune diseases. Studies have also shown that the nervous and endocrine systems are involved in the onset of the development of the disease. Damage to other organs and systems include general weakness, arthralgia or arthritis, lung damage in the form of interstitial pneumonitis, alveolar pulmonary fibrosis, lymphoid focal infiltration, lymphadenopathy, nephropathy and neuropathy (2,3). Due to the late appearance of some of the more serious symptoms of the disease, the combination of secondary Sjögren's syndrome with other autoimmune diseases, the complexity of this combination prevents the correct setting in the early stages of the disease, as was the case in the present case. In the described case, the patient's categorical refusal from a biopsy, the impossibility of conducting a genetic examination, the underestimation of the Polysyndromy of the clinical manifestations of the disease, which were interpreted as each individual disease (for example, changes in the lungs), adequate therapy was started on time only after the appearance of vivid signs of "dry syndrome". Thus, to determine the causes of the development of autoimmune diseases in combination with Sjogren's syndrome and their relationship with hormonal, infectious, genetic and other factors, further studies are needed that will help early diagnosis and treatment to improve the quality and prolong the life of such patients (9).

Conclusion

1. Polysyndromism of the clinical manifestations of the disease is an important sign of diffuse diseases of the connective tissue.
2. In case of suspicion of a diffuse disease of connective tissue and the absence of contraindications to the appointment of glucocorticosteroids, they are used in doses of at least 0.5 mg / kg / day.
3. With a high degree of process activity, the administration of glucocorticosteroids in the pulse therapy mode is indicated.
4. The modern level of knowledge about autoimmune diseases requires their further in-depth study.

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