FELTY SYNDROME ASSOCIATED WITH BILIARY CIRRHOSIS - A CASE REPORT

Rodica Mihaescu¹², Elena Sirbu¹³, Daniela Dragomir⁴

INTRODUCTION

Felty syndrome was first described by Dr. Augustus Felty, in 1924. This syndrome is an atypical form of progressive chronic arthritis characterized by the obligatory association of rheumatoid arthritis (RA) with splenomegaly, thrombocytopenia and neutropenia. This disease has a low incidence, affecting less than 1% of patients with rheumatoid arthritis. Felty syndrome is more common in females with an approximate female-to-male ratio of 3:1.¹

The cause of this syndrome is unknown but it is sure that it pertains to the autoimmune diseases which arise from an overactive immune response of the body against substances and tissues normally present in the body.² Studies in medical literature showed that this syndrome often induces extra-articular manifestations, where the major and most severe manifestation involves the liver. Several cases have been described presenting lesions of the hepatic parenchyma, nodular regenerative hyperplasia, liver portal fibrosis, and even cirrhosis.³

CASE REPORT

The patient S.Z. (32 years) presented in 2005 with moderate jaundice and nocturnal cutaneous pruritus, for which she went to her family physician, who

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suggested performing some gastroenterological tests. The clinical examination revealed mucous and skin jaundice, pruritus, moderate hepatomegaly without splenomegaly; while the laboratory demonstrated an important cholestasis syndrome without obstructive pathology. The biological investigations are presented as a comparison to normal values in Table 1.

The hepatic biopsy confirmed the primitive biliary cirrhosis diagnosis (stage II), with destructive lesions and ductal proliferation, which led to a 50% loss of interlobular bile ducts, hepatic fibrosis coupled with piece-meal necrosis and perportal cholestasis. The patient started treatment with ursodeoxycholic acid (UDCA), hepatotrophic pro-drugs along with an appropriate diet that significantly improved the symptomatology.

### Table 1. Laboratory Data on Admission in 2005

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Chemistry</th>
<th>Serological test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data on admission</td>
<td>Normal values</td>
<td>Data on admission</td>
</tr>
<tr>
<td>RBC 3.69 mil</td>
<td>3.8-5.8 mil</td>
<td>Total protein 80.3g/l</td>
</tr>
<tr>
<td>Hb 11.1 g/100ml</td>
<td>12-16g/100ml</td>
<td>Albumin 42.0g/l</td>
</tr>
<tr>
<td>Ht 33.3 %</td>
<td>37-47 %</td>
<td>Alpha 1 globulins 6.1 g/l</td>
</tr>
<tr>
<td>MCV 90.24fl</td>
<td>82-92 fl</td>
<td>Alpha 2 globulins 12.9 g/l</td>
</tr>
<tr>
<td>MCH 30.2 pg</td>
<td>27-31 pg</td>
<td>Beta-globulins 12.0 g/l</td>
</tr>
<tr>
<td>MCHC 33.4 g/dl</td>
<td>32-36 g/dl</td>
<td>Gamma-globulins 27.0 g/l</td>
</tr>
<tr>
<td>Platelets 182 x103/mm3</td>
<td>150-450 x103/mm3</td>
<td>Total bilirubin 0.30mg%</td>
</tr>
<tr>
<td>WBC 4070/mm3</td>
<td>4000-8000/mm3</td>
<td>Direct bilirubin 1.76mg%</td>
</tr>
<tr>
<td>Granulocytes 57.49%</td>
<td>45-70%</td>
<td>AST 99UI/l</td>
</tr>
<tr>
<td>Eosinophils 6.17%</td>
<td>1-3%</td>
<td>ALT 104 UI/l</td>
</tr>
<tr>
<td>Monocytes 10.61%</td>
<td>3-7%</td>
<td>ALP 1072UI/l</td>
</tr>
<tr>
<td>Basophils 2.33%</td>
<td>0-1%</td>
<td>GGTP 582UI/l</td>
</tr>
<tr>
<td>ESR 53mm/h</td>
<td>2-10mm/h</td>
<td>Cholesterol 263mg/dl</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cholinesterase 7440 UI/l</td>
</tr>
</tbody>
</table>

ESR = erythrocyte sedimentation rate, MCV = mean cell volume, MCH = mean cell hemoglobin, MCHC = mean cell hemoglobin concentration, WBC = white blood cell count, AST = aspartate aminotransferase, ALT = alanine aminotransferase, ALP = alkaline phosphatase, GGTP = gamma glutamyl transpeptidase, AMA = antimonychondrial antibodies, RF = rheumatoid factor, ANA = antinuclear antibodies

### Table 2. Laboratory Data in 2007

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Chemistry</th>
<th>Serological test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data on admission</td>
<td>Normal range</td>
<td>Data on admission</td>
</tr>
<tr>
<td>RBC 4.06x105/μl</td>
<td>3.8-5.8 mil</td>
<td>Total protein 72.9g/l</td>
</tr>
<tr>
<td>Hb 11.2 g/100ml</td>
<td>12-16g/100ml</td>
<td>Albumin 44.3g/l</td>
</tr>
<tr>
<td>Ht 34.9 %</td>
<td>37-47 %</td>
<td>Alpha 1 globulins 8.0%</td>
</tr>
<tr>
<td>MCV 83.9fl</td>
<td>82-92 fl</td>
<td>Alpha 2 globulins 12 %</td>
</tr>
<tr>
<td>MCH 27.1 pg</td>
<td>27-31 pg</td>
<td>Beta globulins 9.7 %</td>
</tr>
<tr>
<td>MCHC 33.1 g/dl</td>
<td>32-36 g/dl</td>
<td>Gamma globulins 26 %</td>
</tr>
<tr>
<td>Platelets 78.4 x103</td>
<td>150-450 mii</td>
<td>Total bilirubin 0.83 mg%</td>
</tr>
<tr>
<td>WBC 3400/mm3</td>
<td>4000-8000/mm3</td>
<td>Direct bilirubin 0.43mg%</td>
</tr>
<tr>
<td>Granulocytes 58.53%</td>
<td>45-70%</td>
<td>AST 23UI/l</td>
</tr>
<tr>
<td>Lymphocytes 30.59%</td>
<td>1-3%</td>
<td>ALT 27UI/l</td>
</tr>
<tr>
<td>Eosinophils 1.35 %</td>
<td>3-7%</td>
<td>ALP 179UI/l</td>
</tr>
<tr>
<td>Monocytes 7.82%</td>
<td>0-1%</td>
<td>GGTP 96UI/l</td>
</tr>
<tr>
<td>Basophils 1.74%</td>
<td>2-10mm/h</td>
<td>Cholesterol 254 mg%</td>
</tr>
<tr>
<td>ESR 45mm/h</td>
<td></td>
<td>Serum iron 54μg%</td>
</tr>
</tbody>
</table>

ESR = erythrocyte sedimentation rate, MCV = mean cell volume, MCH = mean cell hemoglobin, MCHC = mean cell hemoglobin concentration, WBC = white blood cell count, AST = aspartate aminotransferase, ALT = alanine aminotransferase, ALP = alkaline phosphatase, GGTP = gamma glutamyl transpeptidase, AMA = antimonychondrial antibodies, RF = rheumatoid factor, ANA = antinuclear antibodies
In 2007, two years after the primitive biliary cirrhosis diagnosis the patient experienced bilateral side pain and tumefaction of her hands joints (radio-carpal, metacarpophalangeal, proximal and distal interphalangeal), elbows, ankles and foot joints (metatarsophalangeal, proximal and distal interphalangeal of the third finger). In time, symptomatology became more severe leading to the patient's admission to the Balneophysiotherapy Clinic. At the physical examination the patient was in good health condition, she was overweight and non-feverish, presenting slightly pale teguments and periorbital xanthelasma without adenopathy. The examination of the locomotory system revealed a dextroconvex scoliosis, along with a sensitive to touch medial and lateral condyles of the bilateral elbow joint, associated with pain at the metacarpophalangeal and at the bilateral proximal interphalangeal joints, bilateral sensitive to touch humeral spots, tumefaction proximal to the left radio-carpal joint, as well as a “swan neck” deformity of the third finger of the left hand. The physical exam also found crepitus associated with bilateral mobilization of the knees, as well as pain associated with sensitive to touch bilateral metatarsophalangeal and interphalangeal foot joints. The Gaenslen's maneuver was positive, the finger-ground test was insignificant, and Schober's flexibility test indicated 10/14 cm. Laboratory data at this time are presented in Table 2.

The patient was given a specific treatment of corticotherapy (Prednisone 1.5 mg/day), and later on Methotrexate (7.5 mg/week). On the following clinical reexaminations despite a good health condition, pancytopenia was detected without a clinical painful joint symptomatology. Because the pancytopenia was still present in the body a hematological test was run in order to exclude a hemopathy.

At this time, the patient presented in a good health condition, normal colored teguments, while the examination of the digestive system revealed an increased liver size (4 cm below the edge of the costal margin) and a 3rd degree splenomegaly (half a way between the edge of the costal margin and the navel).

Biological samples detected a hypochromic anemia, leucopenia accompanied by neutropenia, thrombocytopenia, an increased level of alkaline phosphatase and gamma-glutamyl transferase (GGTP). We also noted a high titer of the rheumatoid factor (RF), antinuclear antibodies (ANA), C citrullinated anti-peptides (anti-CCPs) and antimitochondrial antibodies (AMA). (Table 3)

The ultrasound examination showed a hypechoico hepatomegaly and an enlarged spleen (that appeared more than 20 cm, larger than the screen), the splenic vein of 11 mm with no ascitis liquid, and the portal vein of 12 mm, and uninhabited hypechoico gall bladder. No hepatic viral markers were detected; the gastroscopy test did not confirm the presence of esophageal varices, while the radiological examination of the hands and feet showed marginal erosions and osteoporosis.

The results of the investigations pointed to a clear-cut diagnosis: seropositive rheumatoid arthritis stage II. Due to the fact that the patient was suffering from associated conditions of rheumatoid arthritis

### Table 3. Laboratory Data in 2008

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Chemistry</th>
<th>Serological test</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC 4.380x10^12/μl</td>
<td>Total protein 74.6g/l</td>
<td>CRP 1mg/l</td>
</tr>
<tr>
<td>Hb 11.5 g/100ml</td>
<td>Albumin 49.3g/l</td>
<td>RF 193UI/ml</td>
</tr>
<tr>
<td>Ht 35.8 % (37-47)</td>
<td>Alpha 1 globulins 8.0 %</td>
<td>ANA (+)</td>
</tr>
<tr>
<td>MCV 81.8fL</td>
<td>Alpha 2 globulins 10 %</td>
<td>AMA (+)</td>
</tr>
<tr>
<td>MCH 26.3 pg</td>
<td>Beta globulins 7.7 %</td>
<td>ACCP 20.2 U/ml</td>
</tr>
<tr>
<td>MCHC 32.1 g/dL</td>
<td>Gama globulins 25 %</td>
<td></td>
</tr>
<tr>
<td>Platelets 74.700/mm3</td>
<td>Total bilirubin 1.18 mg%</td>
<td></td>
</tr>
<tr>
<td>WBC 3300/mm3</td>
<td>Direct bilirubin 0.78mg%</td>
<td></td>
</tr>
<tr>
<td>Granulocytes 32.53%</td>
<td>AST 25U/l</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes 49.17%</td>
<td>ALT 36U/l</td>
<td></td>
</tr>
<tr>
<td>Eosinophils 6 %</td>
<td>ALP 207U/l</td>
<td></td>
</tr>
<tr>
<td>Monocytes 10.3%</td>
<td>GGT 81U/l</td>
<td></td>
</tr>
<tr>
<td>Basophils 3%</td>
<td>Cholesterol 254 mg%</td>
<td></td>
</tr>
<tr>
<td>ESR 45mm/h</td>
<td>Serum iron 28 μl/100ml</td>
<td></td>
</tr>
</tbody>
</table>

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and splenomegaly, thrombocytopenia and leucopenia, we considered that a more suitable diagnosis was Felty syndrome. The diagnosis of primitive biliary cirrhosis stage II was supported by the specific laboratory changes.

The patient received a treatment consisting of the following: anti-inflammatory drugs, analgesic drugs if needed, ursodeoxycholic 4x250mg/day, immunosuppressant 50 mg/day, gastric antacids and protectors, hepatotrophic prodrugs, iron pills. The patient was also recommended to periodically undergo hematological and gastroenterological follow-up and return in 3 months for a reevaluation.

**DISCUSSIONS**

The subject studied on this case presented an association of two autoimmune conditions, primitive biliary cirrhosis and Felty syndrome.

Felty syndrome is a form of progressive chronic rheumatoid arthritis that can be usually encountered in diseases that progress in a long period of time. The syndrome is characterized by the obligatory association of rheumatoid arthritis with splenomegaly, thrombocytopenia and neutropenia. Low blood count was considered the consequence of either hypersplenism or autoimmune phenomena.

Studies in specialized literature show that this syndrome is associated to autoimmune hepatic manifestations. In several cases, lesions of hepatic parenchyma, nodular regenerative hyperplasia, portal fibrosis and even cirrhosis have described. Moreover, patients affected by this disease have a high risk of portal hypertension and this is the reason they must be carefully supervised in order to early detect esophageal varices.

The indicators of inflammation, the quantum of inflamed joints and the presence of specific factors of the disease such as the auto-antibodies, the rheumatoid factor, and the anti cyclic citrullinated peptide antibodies were considered to be predictors of negative prognosis.

The anti-cyclic citrullinated peptide antibodies (ACCPs) were associated with the persistence of the disease and the presence of lesions. As in the case of rheumatoid factor (RF), the respective antibodies can be present for many years before the clinical beginning of the disease; but it is important to notice that unlike RF, the anti-cyclic citrullinated peptide antibodies present a great degree of specificity. Our patient presented (starting from 2007) high titer of RF and a high level of ACCP that indicated the progress of the disease.

The etiology of primitive biliary cirrhosis is unknown, but several observations have shown that an altered immune response may be involved. It is of great importance that in more than 90% of patients with primitive biliary cirrhosis circulating IgG-type anti-mitochondrial antibodies (AMA) can be detected, as these are rarely encountered in other types of hepatic diseases.

Even from the beginning our patient presented a high titer of AMA and of serum alkaline phosphatase (ALP) associated with increased levels of aminotransferases (AST and ALT). The positive determination of the AMA offers important diagnostic proof, but there can be false negative results; that is why a hepatic biopsy was performed in order to confirm the diagnosis.

Although the specific treatment ameliorated the symptoms, it had a limited effect on the progress of the illness. Biologically, the cholestasis syndrome was persistent while the bilirubin values dropped to normal. It is possible that during the progress of primitive biliary cirrhosis the formation of some typical signs of rheumatoid arthritis may occur due to the fact that both illnesses are on the list of immune diseases.

The characteristic of this case represents the development of rheumatoid arthritis symptoms, both clinically and biologically, in a rather short period of time (two years of progression) after it had been detected. The most difficult fact to explain is the advancement of splenomegaly in the same time with rheumatoid arthritis, with no symptoms of portal hypertension. The onset and the persistence of pancytopenia due to a splenomegaly and most of all the onset of neutropenia raised the suspicion of concomitant Felty syndrome and the association of these two diseases, despite the fact that the medical literature quotes the appearance of this syndrome several years after the onset of rheumatoid arthritis.

Numerous studies have shown that the tumor necrosis factor-alpha (TNFα - a proinflammatory cytokine) plays a significant part in the pathogenesis of the disease, and its blockage leads to an amelioration of the illness.

The availability of TNF-α antagonists (be it monoclonal anti-TNFα antibodies/receptors as a result of fusion) led to reference studies that proved the efficiency of these agents in patients where anti-rheumatic medication, including Methotrexate, had no effect on.

Thus, we can say that, in order to obtain a significant improvement in delaying the progression of the disease, the patient should benefit from a new therapeutic approach. In order to achieve this, we
suggest starting a treatment based on monoclonal antibodies either as a monotherapy, or together with Methotrexate considering the progress of biliary cirrhosis.

CONCLUSIONS

The association of Felty syndrome with biliary cirrhosis is an extremely rare situation encountered in medical practice and the early tracking down and treatment of such diseases may considerably improve prognosis. We cannot draw any important conclusions taking into account the short time of simultaneous progress of these two illnesses. Only the periodical observation of the patient along with an adequate treatment may confirm in time the credibility of the diagnosis.

REFERENCES