Rheumatoid Arthritis in Thalassemia Intermedia: Coincidence or Association?

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Beta-thalassemia is an inherited hemoglobin disorder resulting in chronic hemolytic anemia. Depending on the clinical severity, two forms are distinguished – thalassemia major and thalassemia intermedia. When compared to thalassemia major, the intermediate type has a later clinical onset and a milder anemia, no need for transfusions in most cases, and a longer life expectancy.

Thalassemic patients often present with arthritis of the knee and hip and less often of other joints, and several immunologic abnormalities have also been described, including an increased prevalence of autoantibodies. Although various factors have been implicated as responsible for these laboratory findings and clinical manifestations, a pathophysiologic correlation between these phenomena and the presence of a frank connective tissue disease has not yet been established. We describe a patient with thalassemia intermedia, rheumatoid arthritis and a concurrent decrease in hemoglobin level, and discuss the possible correlation.

Patient Description

A 43 year old thalassemic woman was admitted to our hospital for further investigation of continuing symmetric arthralgias and arthritis and concomitant fall of hematocrit level of the last few months. She had been diagnosed with thalassemia intermedia at age 3 months. Molecular analysis showed that the beta-thalassemia genotype was IVS I:6(T→C)/IVS I:110(G→A). At the age of 3 years she started receiving transfusions (hemoglobin 5.5 g/dl) regularly every 2 weeks. Chelation therapy (30 mg/kg 5 days a week) was started at age 6 years. At the age of 11 she underwent a splenectomy, and due to maintenance of a steady hemoglobin level of 7.5–10 g/dl with a median of 8.4 g/dl, regular transfusions were stopped. She was transfused only occasionally to maintain hemoglobin above 7 g/dl. Chelation was implemented when ferritin exceeded 800 ng/ml and was stopped at 300 ng/ml. Ferritin ranged between 1,890 and 350 ng/ml (mean life time value 580 ng/ml). Being osteoporotic, the patient had been taking oral compounds of vitamin D and calcium for the previous 10 years.

She reported that for the previous 18 months she had arthralgia of the hands and knees and morning stiffness in both hands lasting more than 1 hour after rising. On clinical examination, arthritis of the metacarpophalangeal and proximal interphalangeal joints in both hands and inflammation of the wrists and knees had been noted. The diagnosis of rheumatoid arthritis was established based on the laboratory tests (Hb 9.5 g/dl, erythrocyte sedimentation rate 140 mm/hour, rheumatoid factor 17,000 IU/ml, antinuclear antibodies 1:160). Non-steroidal anti-inflammatory therapy was initiated, but after a slight clinical improvement the patient discontinued treatment and follow-up and she gradually relapsed.

On admission to our hospital, the patient acknowledged a weight loss of 3 kg during the preceding 2 months; she was pale and tachycardic (heart rate 90/minutes, blood pressure 110/80 mmHg) and had a low grade fever (37.5°C). A systolic ejection type murmur (2/6) was auscultated. Clinical signs of arthritis, swelling and tenderness of the hips, elbows, shoulders and metacarpophalangeal joints were present, characterized by symmetric joint pain aggravated by movement, along with ulnar deviation of the digits. Palpable nodules in the right elbow and the left sole were also observed. A leg ulcer, present for many years with intervals of remission, was found at the right inner malleolus. Her family history was negative for rheumatic diseases.

A complete blood count revealed hemoglobin 6.6 g/dl, white blood cell count 9,200/µl (neutrophils 55%, lymphocytes 35%, erythroblasts 20%, platelets 758,000/µl). Blood smear demonstrated hypochromic red blood cells, anisocytosis, basophilic stippling and thin macrocytosis, as well as target cells, acanthocytes and Howell-Jolly bodies. ESR was 64 mm/hr and serum ferritin 337 ng/ml. Serologic and immu-

ESR = erythrocyte sedimentation rate

nologic tests showed serum RF 25,600 IU/ml, antinuclear antibody 1:320, C3 186 mg/dl (normal 75–140 mg/dl) and hyperglobulinemia [total immunoglobulin 3.42 g/dl (normal 0.6–1.3), IgG 2,020 mg/dl (normal 690–1,400), IgA 508 mg/dl (normal 70–370), IgM 893 mg/dl (normal 40–240)] without monoclonic fraction, according to the immunoelectrophoresis. Anti-extractable nuclear antigens, cytoplasmic and perinuclear anti-neutrophiil cytoplasmic antibodies, and anti-DNA antibodies were negative. A 24 hour urine collection was negative for proteinuria or monoclonal protein. Direct Coombs' test was negative. She was negative for anti-hepatitis C virus and HBsAg. Chest X-ray revealed cardiomegaly. Erosions, clear deformities or other radiographic findings specific for rheumatoid arthritis of the affected joints were not detected. X-ray also showed diffuse severe osteoporosis, which was attributed to her thalassemic syndrome. We concluded that the patient had a relapse of rheumatoid arthritis, and treatment with NSAIDs as well as a transfusion program was initiated. Glucocorticoids and/or immunosuppressive medication was not chosen as first-line treatment due to the thalassemia-related severe osteoporosis, the ineffective erythropoiesis and the previous satisfactory response to NSAIDs.

Comment

To the best of our knowledge this is the first report of a patient with homozygous thalassemia intermedia presenting with RA according to the criteria of the American College of Rheumatology. The likelihood of another disorder, such as IgM monoclonal gammopathy, that could also explain the high level of RF and the joint involvement was excluded by specific laboratory tests. The persistent leg ulcer was considered to be related to the persistent hypoxemia due to low hemoglobin levels, the persistence of HbF as well as to the elastic tissue abnormalities, commonly seen in thalassemia [1], than to a RA concomitant vasculitis.

Until now, arthritis encountered in patients with thalassemia has been attributed either to iron deposition on the synovial tissues or to the iron chelators (e.g., deferiprone), which may induce a self-limited recurrent arthritis due to the synovial damage incurred by the production of free radicals during iron interchange [2]. Laboratory investigation of thalassemia patients – with or without arthritis – reveals a variety of alterations in cellular immunity: defective innate effector functions of the phagocytes, T cell reduction, thymus atrophy, inhibition of the differentiation of lymphocytes, and changes in CD8+/CD4+ lymphocyte ratio [3]. Immunoglobulins and circulating immune complexes are increased, while C4 complement fractions are reduced. Significantly elevated levels of several autoantibodies (antinuclear antibodies, anticardiolipin and other antiphospholipid antibodies, RF, anti-histone antibodies, islet cell antibodies, cryoglobulins – hepatitis C virus related or not) have been observed and are considered to behave more as natural autoantibodies than as pathogenic ones. Different causative factors, including the frequent blood transfusions, the iron overload and the use of iron chelators are believed to be responsible for these alterations in thalassemia, generating a persistent immunologic stimulation and presenting an immunoregulatory effect on B and T lymphocytes, immunoglobulin and complement production [4]. The coexistence of viruses, like hepatitis C, is also correlated with such autoantibodies and cryoglobulins in affected thalassemic patients. In this particular patient, significant hypergammaglobulinemia, hypercomplementemia, and increased RF and antinuclear antibody titers were observed, along with the clinical manifestations of overt RA.

In RA patients a wide spectrum of immunologic changes is present, quite similar to those reported in thalassemia, and these changes are believed to be triggered by infectious agents or other stimuli. If the presence of thalassemia and RA is not coincidental, a generative linkage may exist, in terms of an altered immunologic response caused by thalassemia itself.

An increased prevalence of thalassemia trait in patients with RA recently reported by other investigators provides another insight to the possible relation between thalassemia and RA [5]. Since carriers of the thalassemia trait do not require transfusions, we have an indication that in thalassemic patients, transfusions and iron overloading of the tissues are not the sole factors responsible for the observed immunologic abnormalities, which could be related to the thalassemia gene itself. Individuals with the thalassemia trait and RA have aberrations in T lymphocyte function, not found in individuals lacking the thalassemia gene. On clinical grounds, the onset, course, type and severity of joint involvement and clinical features of the two groups do not differ significantly, but in beta-thalassemia carriers, there is a notable reduction in the number of systemic complications usually seen in RA, especially of the rheumatoid nodules, along with a more severe degree of osteoporosis and a lower ESR value. These results allow the speculation that the so-called arthritis of the beta-thalassemia trait is probably not a distinct clinical entity as previously thought, and may be regarded as a mild form of seronegative RA. Similarly, an association between the thalassemia gene in its homozygous form and the presence of RA in these patients may exist, while an uncommon and rather atypical clinical course can be expressed.

In this context, this patient experienced a form of RA, modified probably by the presence of thalassemia intermedia, which may account for the clinical and immunologic alterations, such as the highly increased RF and the absence of particular radiologic findings. It should be noted that the factors usually considered as causing the arthritis and the immunologic status of thalassemic patients, e.g., the frequent transfusions and the iron overload status, did not apply in this case because of the intermediate, thus milder, form of the disease.

In conclusion, thalassemia intermedia

RF = rheumatoid factor
IgG = immunoglobulin G
NSAIDs = non-steroidal anti-inflammatory drugs
RA = rheumatoid arthritis

is rare and RA is not very common either. Their coexistence in this case may be a matter of pure chance, but taking into consideration the points mentioned above we may have a working hypothesis about a possible relation between beta-thalassemia and rheumatoid arthritis. The increased prevalence of RA in a population with the thalassemia trait augments this possibility for the homozygotic state. The presence of arthritis in such patients, attributed previously to iron overload or iron chelators, should raise the suspicion of a limited or milder form of RA and should be investigated further. Ongoing research will reveal whether the genes of beta-thalassemia are in any other way related to changes in the immune system of these patients. As the mean life expectancy of thalassemic patients has increased, the natural history of this disease is constantly changing and physicians should be alert to new complications. Thus, the overall clinical significance of immunologic abnormalities in thalassemia patients and its relation to their morbidity remains to be seen.

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