Severe anemia of unknown origin. Don't forget renal tuberculosis

Anemia severă de origine necunoscută. Nu uitați tuberculoza renală

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Abstract

Tuberculosis is a specific multi-systemic infection that can lead manifestation in any organ system. We report a case with severe long- standing anemia with no tuberculosis exposure and no suggestive symptoms for this disease. The only diagnostic characteristic element was a recurrent urinary tract infection despite repeatedly antimicrobial therapy. As the incidence of tuberculosis is still high worldwilde, when we investigate anemia we should consider tuberculosis because because TB - associated anemia is usually resolved with anti-TB treatment.

Keywords: microcytic anemia, renal tuberculosis, urinary tract infection

Rezumat

Tuberculoza este o infecție specifică multisistemică cu manifestări în majoritatea organelor. În lucrarea de față prezentăm un caz de anemie severă cu istoric îndelungat, fără expunere şi fără simptomatologie sugestivă pentru tuberculoză. Singurul element caracteristic util pentru diagnostic a fost o infecție urinară recurentă în ciuda unui tratament antimicrobian correct condus. Având în vedere faptul că tuberculoza are încă o frecvență mare în populație şi că anemia asociată acesteia necesită administrare de tuberculostatice, lucrarea atrage atenția asupra necesității de a lua în considerare etiologia specifică în protocolul de investigare al unei anemii cu istoric îndelungat.

Cuvinte cheie: *anemie microcitară, tuberculoză renală, infecția tractului urinar*

Introduction

According to the World Health Organization, approximately one third of the world population is infected with tubercle bacilli, with 9.27 million incident cases in 2007. Even if the incidence is lower than in other regions, in Europe 445 000 people become sick with tuberculosis (TB) every year and 8 people die of TB every hour (1).

Extrapulmonary sites of infection commonly include lymph nodes, pleura, and osteoarticular areas, although any organ can be in-

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volved. The genitourinary system is frequently involved by the disease, especially in patients with HIV, diabetes mellitus, urinary tract abnormalities, etc.

The clinical manifestations are often nonspecific and insidious, and diagnosis may be delayed for years.

A variety of hematological manifestations can be expected in TB due to its chronic inflammatory nature: chronic disease anemia, leucopenia with lymphopenia, leukocytosis, monocytosis, thrombocytopenia or pancytopenia, are frequently described (2-6).

Case report

A 74 year woman with an 18 month history of anemia presented to the Nephrology department with lower urinary tract symptoms, dyspnea, weakness, fatigue on minimum efforts, arthralgias and flank pain.

Her medical history was positive for hypertension and diabetes mellitus. She was hypertensive from the age of 60. Diabetes mellitus had been diagnosed at the age of 72.

One year before this presentation she was investigated in the primary care setting by barium meal and barium enema for a microcytic anemia. Because none of these examinations showed any pathological finding, solely iron treatment was indicated.

She reported having been hospitalized in a cardiology department 7 months prior the admission in our department for the same symptoms, where she was investigated for anemia (hemoglobin 7.6 g/dl, hematocrit 21.5%) by using upper digestive endoscopy. Because all other laboratory investigations were normal (leukocytes, platelets, serum proteins, serum creatinine, urea nitrogen, alkaline phosphatase, bilirubin etc.) no other investigation for anemia was performed. The drug history obtained was suggestive for administration of 3 units of erythrocyte concentrate. She was discharged with a hemoglobin value of 9.4g/dl, hematocrit 30.5%.

On this occasion, urinalysis showed leucocyturia (500/µl) and urine culture was suggestive for significant bacteriuria with Escherichia coli; in this setting the patient was treated with antimicrobials for 7 days.

On presentation to our clinic, she had been receiving metformin 500 mg bid, glimepiride 1 mg od, furosemide 40 mg od, lisinopril 20 mg od, amlodipine 5 mg od, valsartan 80 mg od, rosuvastatin 10 mg od, aspirin 75 mg od, with intermittent administration of oral iron therapy.

The family history was noncontributory. She had no known allergies and no history of smoking or alcohol consumption. She had a good social status, good life conditions, she had had two normal pregnancies, her weight was 92 kg, and her height was 157 cm. No other chronic diseases except diabetes, hypertension and anemia were known. She reported no history of tuberculosis or contact with this disease.

Her diet was appropriate for a diabetes patient, with low salt ingestion because of hypertension. She was not a vegetarian and did not have any sign and symptom of malabsorption and malnutrition.

She denied fever, nocturnal sweating, cough, jaundice and nausea. No weight loss was reported.

Physical examination revealed pallor, midsystolic ejection murmur, heard best over the "aortic area" with radiation into the right neck, peripheral edema, a blood pressure of 150/80 mm Hg, pulse 90/min, 18 respirations/min and a body temperature of 36.8 Celsius degrees, taken orally. There was no submandibular, cervical, supraclavicular, axillary or inguinal lymphadenopathy. The remainder of the examinations was normal.

The initial complete blood count revealed a WBC of 5.42 x 10^9/l, RBC of 3.28 x 10^{12}/l, hemoglobin 5.1 g/dL, hematocrit 19.2%, MCV 62 fl, MCH 17.5 pg, MCHC 28.4 g/dl, platelet count 288 x 10^9/l. Reticulocytes were 23‰. Erythrocyte sedimentation rate was 68 mm/h. Serum ferritin was 70 ng/Ml and serum iron was 3.5umol/l. Direct bilirubin was 0.15 mg/dl, total bilirubin 0.38

mg/dl, total serum proteins 7.4 g/dl, with 49.6% albumins, 3.3% alpha 1 globulins, 11.3% alpha-2 globulins, 9.5% beta globulins and 21.8% gamma globulins. IgG was 2000 mg/dl, IgA 350 mg/dl, IgM 325 mg/dl. Blood glucose was 129 mg/dl. Blood urea, serum creatinine, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase level, alkaline phosphatase, electrolytes, prothrombin time (PT), activated-partial thromboplastin time (aPTT) were normal.

Blood smear revealed anisocytosis with a predominance of hypocromic microcytes and 23‰ reticulocytes. No patognomonic changes were observed for leukocytes (70% neutrophils, 2% eosinophils, 4% monocytes, 24% lymphocytes) and platelets.

The patient was referred to a hematologist but did not give her consent for bone marrow biopsy.

Gynecology consult revealed a cystocele with stress urinary incontinence, without evidences of genital tract bleeding.

Urinalysis showed the presence of leukocytes (500/µl) and a positive nitrite test with urine culture indicating *Escherichia coli* surpassing 100000 CFU/ml. No significant proteinuria and glycosuria were found in the 24 hour urine specimen. Abdominal ultrasonography showed no splenomegaly, with no evidence of chronic liver or kidney damage.

The stool specimen was negative for occult blood. However, because of the very low value of hemoglobin, we decided to repeat upper and lower gastric tract endoscopy. These showed no evidences of mucosal abnormalities that could explain the anemia.

Plain radiography of the skull and pelvis showed no lytic lesions and diffuse osteoporosis. Plain radiography of lumbar column was positive for anterior syndesmophytes at T12-L1, L1-L2 and L2-L3, osteophytes at L4, dextroconvex scoliosis, diffuse osteoporosis. A radiograph of the chest showed pachypleuritis in the right lung, diffuse bilateral fibrosis, and enlargement of the right side of the mediastinum. Computer tomography revealed no pleural effusion, a single focal alveolar consolidation lesion of about 13 mm in the right lung, next to the heart, with no mediastinal lymph nodes. No lesions were found in the liver, pancreas, kidneys and spleen.

We decided to further extend the investigation with tests for tuberculosis, keeping in mind the recurrent E coli urinary tract infection, the aspect of lungs on radiography and the lower urinary tract symptoms.

The acid-fast staining of early morning first voided two urine specimens was positive. The culture was also positive for M. tuberculosis. Moreover, three acid-fast bacillus sputum smears were positive, so the patient was referred to a TB expert. The growth of the microorganisms was also confirmed on Löwenstein–Jensen media.

The patient received anti-TB drugs (rifampicin 600 mg, isoniazid 450 mg, ethambutol 2000 mg and pyrazinamide 2000 mg orally) daily for two months. This regimen was followed by a 3 days a week treatment with rifampicin 600 mg and isoniazid 600 mg orally for four months.

She also received 3 units of erythrocyte concentrate with a hemoglobin increment to 7.9 g/dl (hematocrit 26.7%).

In the follow-up period, four months after the TB treatment initiation, the patient had no dyspnea, she was capable to perform average efforts, her quality of life was very much improved, and her laboratory parameters were: hemoglobin 13.7 g/dl, hematocrit 43.7%, MCH 27.1 pg, MCHC 31.4 g/dl, MCV 86.5 fl.

Discussion

We report the case of a patient with long standing severe anemia, who frequently accessed medical services for this condition, with a history of repeated blood transfusions.

Although our patient did not have a history of close contact with an individual with active tuberculosis and did not have signs or

symptoms suggestive for TB, our final diagnosis was urinary and pulmonary tuberculosis with secondary anemia.

When evaluating anemia in an older adult we must remember the fact that this category of patients can have multiple causes for their anemia.

Faced with microcytic anemia, the three main diagnostic possibilities include iron deficiency anemia, thalassemia, and anemia of chronic disorders. A fourth possibility, sideroblastic anemia, is a very rare condition, and therefore was not considered in the initial diagnosis (7).

Although serum ferritin was normal, suggesting chronic disease rather than iron deficiency, in the absence of the bone marrow biopsy, the final differential diagnosis between iron deficiency and anemia of chronic disorder was impossible (8).

During the investigation, we took into account the fact that our patient received iron therapy without an increase of hemoglobin or reticulocytes, so we concluded that iron deficiency was not the cause (or not the single cause) of anemia.

Anemia of chronic disease is the most prevalent form of anemia after iron deficiency in the general population, the underlying causes being multiple: acute and chronic infections, neoplasia, autoimmune diseases, rejection of solid organ transplantation, chronic renal disease, etc (9-11).

Our patient had no signs and symptoms for malignancy, she had no evident chronic renal disease, but a chronic infection would have been possible.

The diagnosis of extrapulmonary TB depends on the physician considering the possibility of TB in patients at risk and submitting material for mycobacterial culture and pathological examination.

Possible mechanisms for the development of anemia in mycobacterial infection include nutritional deficiency, marrow suppression, and shortened duration of RBC survival (hemolysis) (6;12;13).

Anemia of inflammation as well as of iron deficiency has been implicated. It is well known that patients with TB have anemia with low serum iron; this condition seems to be mainly the result of chronic disease, more than of Fe deficiency. Moreover, because some authors demonstrated that Fe is needed for both host defense and survival of the pathogen, Fe supplementation must not routinely prescribed (14).

Genitourinary TB is commonly a late manifestation of an earlier symptomatic or asymptomatic pulmonary TB infection. Genitourinary TB accounts between 2 to 20% of the infections outside of the lungs with a more destructive behavior in developing countries. Tuberculosis of the urinary tract is easily overlooked (15).

Extrapulmonary tuberculosis is the result of dissemination of tubercle bacilli from an initial focus in the lungs soon after primary infection. The kidney is usually the first infected organ of the urinary tract and other parts are then infected by direct extension. Disease development depends on interaction between the pathogen and the host immune system (16;17).

Some studies showed that in the last years the rate of extrapulmonary disease manifestation is increasing especially among female patients (18).

There may be concomitant but not invariable pulmonary TB.

Diagnosis of genito-urinary TB is difficult, especially in a case with lack of clinical signs and symptoms.(19) The patient's complaints can include flank pain, back pain, fever, urgency, hematuria, weight loss, night sweating (20).

A number of patients present with lower urinary symptoms with positive urine culture and no response to antibacterials; sterile pyuria is frequent (21).

The gold standard for diagnosis of the disease is detection of the etiologic agent, Mycobacterium tuberculosis, by using Ziehl-Neelsen staining and culture (20;22;23).

Our patient had lower urinary tract symptoms and recurrent bacteriuria with Escherichia coli, and she was treated with antimicrobials for lower urinary tract infection. The response to antibacterials was low, but because of a concomitant

genital condition (cystocele), this did not raise any other suspicion (for example urinary tuberculosis).

Only after the chest radiography was performed and showed diffuse fibrosis and pachypleuritis, we started to think about a condition who could explain all signs, keeping in mind also the anemia.

In tuberculosis the recovery from anemia occurs only with recovery from the primary disease (24;25).

This was also true in our patient who was treated with iron and who received repeated transfusions in about 2 years of disease evolution. None of the measures taken has led to treat anemia as did the TB therapy.

Disappearance of hematological abnormalities with antituberculous therapy was a proof that TB was the underlying cause of this condition.

This patient is of interest for a number of reasons. First because long standing severe symptomatic anemia quickly reversible after blood transfusion makes one think of a bleeding mechanism rather than a chronic disease. Second, because our patient had no tuberculosis exposure, had no other risk factor for the disease except the age and a well controlled diabetes mellitus. Third, because the recurrent urinary tract infection despite the antimicrobial therapy was the single detail and aid used for the diagnosis of urinary tuberculosis.

Conclusion

Tuberculosis should be listed among the etiologies of infection-associated anemia even in the case of lack of signs and symptoms or exposure to the disease. Physicians should start rapid antituberculosis therapy without hesitation in the appropriate clinical setting.

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