CASE REPORT

Potential benefit of paracetamol administration in adult-onset Still's disease

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KEY WORDS

adult-onset Still`s disease, diagnostic criteria, paracetamol, treatment

ABSTRACT

Still's disease is a rare, systemic inflammatory disease of unknown etiology, characterized by daily high fever, transient rash, arthritis, and organ involvement including lymphadenopathy, hepatosplenomegaly, pleuritis or pericarditis. The diagnosis of the disease is based on clinical signs and symptoms, and requires exclusion of infectious, neoplastic, and other autoimmune diseases. Treatment options include non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, sometimes in combination with immunosuppressive agents. We report the case of a 21-year-old man with a recent diagnosis of Still's disease. The fever, resistant to NSAIDs, resolved after treatment with paracetamol and the patient's general condition also improved. The present case has been the first to demonstrate that paracetamol may be an effective agent in adult-onset Still's disease.

INTRODUCTION Still's disease usually occurs before the age of 16; however, sometimes it may occur in adults manifesting as systemic idiopathic arthritis. Clinical presentation is not characteristic and the diagnosis can be made only if sepsis, viral infection (especially mononucleosis, glandular fever), neoplasms (particularly lymphomas), and systemic connective tissue diseases are excluded. Due to diverse clinical manifestations the diagnosis may be difficult and requires time as well as collaboration between specialists. The Yamaguchi criteria[1] can facilitate the differential diagnosis. Five or more criteria should be met, of which at least three are major to diagnose adult-onset Still's disease (AOSD). The major criteria include fever ≥39°C lasting more than 7 days, arthritis or arthralgia for at least 2 weeks, typical salmon pink rash on the trunk and proximal portions of the extremities, leukocytosis >10,000/mm^3) with 80% of polymorphonuclear cells. Sore throat, lymph node enlargement, increased activity of hepatic transaminases or lactate dehydrogenase, and negative anti-nuclear antibodies and rheumatoid factor are designated as the minor criteria.

The treatment of both acute and chronic phases of AOSD is symptomatic since the etiology of this disease is still unknown. Because fever and pain are the hallmark symptoms, non-steroidal anti-inflammatory drugs (NSAIDs) and, if there is no improvement, corticosteroids, immunosuppressive or biological medications are used.[2] The disease can be self-limiting, occurring as a single episode with dominant systemic symptoms (20%) or it can have recurrent relapses, intermitted by complete remissions (50%). In 25% of cases AOSD transforms into chronic inflammatory disease in which major joints are affected.[3] We present the case of a young man who was admitted to hospital because of fever of unknown origin, with concomitant hepatosplenomegaly, lymphadenopathy, anemia, and transiently increased liver transaminase levels. Paracetamol has been successfully used as symptomatic treatment, initially intravenously in a water-soluble form of propacetamol, then as an oral preparation.

CASE REPORT A previously healthy 21-year-old male presented with a 3-week history of upper airway infection associated with spiking fever reaching 40°C, myalgia and arthralgia. He was previously treated at the Department of Infectious Diseases as mononucleosis was suspected. Physical examination revealed tonsils covered with white membrane as well as splenomegaly. Moreover, transient wrist and ankle swelling, together

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with an evanescent salmon-colored, non-itching speckled rash on the trunk and upper limbs were observed. Fever, generalized pain and progressive fatigue did not subside, although several antibiotics were given in succession in combination with classic NSAIDs (ibuprofen, diclofenac, metamizol). Following exclusion of mononucleosis (no atypical lymphocytes in peripheral blood smear and a negative immunoglobulin M test performed twice), cytomegalovirus and human immunodeficiency virus infections as well as bacterial and fungal sepsis, the patient was transferred to our department with a suspicion of a neoplasm. Splenomegaly and multiple enlarged painless peripheral lymph nodes were detected on physical examination performed on admission. A body temperature was 38.5°C in the morning and increased to 40°C at night. Hematologic examination revealed normocytic anemia (hemoglobin level 11.6 g/dl; hematocrit 34.3%; erythrocytes 4.0 T/L [4,000,000/mm^3]; leukocytes 10.3 G/L [10,300/mm^3] with 82% of neutrophils; C-reactive protein 44 mg/l [normal range, <5 mg/l] lactate dehydrogenase 955 U/l [normal range, 120–230 U/l]; alanine transaminase 493 U/l; asparagine transaminase 333 U/l; γ-glutamyl transferase 710 U/l; iron 56 μg/dl [normal range, 70–180 μg/dl]). Coagulation tests, urinalysis, hormone and neoplastic markers, and other biochemical tests were within the normal limits. Imaging investigations (ultrasonography and computed tomography scan) showed splenomegaly (16 × 7 cm), a slightly enlarged liver, and evidence of left pleural and pericardial effusion. Upper endoscopy did not reveal signs of either active or past bleeding or macroscopic lesions. Moreover, the wrist X-ray was inconclusive. In the following days, occult fecal blood testing yielded a positive result (nadir of hemoglobin 9.8 g/dl with hematocrit 29.7% on the 11th day of hospitalization) with thrombocytosis (510,000/mm^3) and continuously decreasing transaminase activity in the presence of a persistent night-time fever up to 40°C. Oral ciprofloxacin and locally administered nystatin were used with no improvement. In a differential diagnosis of anemia intravascular hemolysis was excluded as its cause (negative direct and indirect Coombs as well as cryoglobulin tests); ferritin and transferrin levels were measured (17,294 ng/ml, normal range: up to 275; 176.0 mg/dl, respectively). The tests for autoimmune diseases (including rheumatoid arthritis) were negative. A hematologist excluded hematological diseases. The blood, urine, swab culture, and immunological tests (for mononucleosis, toxoplasmosis, brucelosis, listeriosis, leptospirosis, borreliosis, chlamydiosis, HIV and HSV infections, hepatitis A and B) were repeated and the results were negative. Because of iron metabolism imbalance, the liver biopsy specimen was stained for iron with positive (2+) results, mainly in stromal cells. However, a low level of iron and normal transferrin saturation allowed to exclude primary and secondary hemochromatosis. Such high ferritin combined with increased liver transaminases, fever, lymphadenopathy, and splenomegaly could be explained by Still's disease. The diagnosis was based on our own clinical observations and a history of the acute phase reaction observed during previous hospital stays. Characteristic rash and joint edema were observed only at the Department of Infectious Diseases. The entire clinical presentation fulfilled 3 out of the 4 major and minor Yamaguchi criteria for Still's disease.

Symptomatic treatment with classic NSAIDs (metamizol, ketoprofen) did not bring desirable effects. We initiated regular paracetamol administration, initially intravenously (1.0 g twice a day for 4 days) then orally (0.5 g four times a day for 6 weeks, and subsequently in a lower dose up to 3 months). The fever subsided gradually and the patient's condition improved significantly. Ferritin concentration correlated with the severity of patient's condition; it was normal and the patient was free of signs and symptoms of the disease at 5 months. During a 2-year follow-up the patient was in remission free of joint manifestations.

DISCUSSION Although Still described the disease more than 25 years ago, its etiology still remains unknown. It might be a response to an unidentified infectious factor observed in a genetically predisposed patient, because its course resembles a self-limiting viral infection. An extremely elevated ferritin level (the highest ever observed in our department) allowed us to suspect Still's disease. The marker was particularly important for the diagnosis, considering that arthralgia was mild and the characteristic, fading rash was observed only in the initial phase of the disease and prior to admission. According to the available data, hyperferritinemia is observed in 70% of patients with Still's disease, and high ferritin concentrations (>3,000 ng/ml) correlate with the severity of the disease.[4] The follow-up of our patient proves that such associations do exist. During the acute phase the ferritin level was 17,294 ng/ml. It decreased to 14,089 ng/ml on the 10th day of treatment, and to 3,037 ng/ml at discharge. After 5 months it returned to normal and there were no symptoms of the disease. High levels of ferritin and severe condition on admission proved that the patient was in the acute phase of the disease, even though no cutaneous lesions and only mild articular manifestations were observed. However, the diagnostic usefulness of ferritin testing is restricted by the fact that, as one of the acute phase proteins, its levels increase also during other diseases. Such high ferritin levels have been observed in macrophage activation syndrome, severe liver injury, neoplastic diseases (leukemia, lymphomas), hemochromatosis, and after massive blood transfusions.[4] However, we excluded these disorders.

Pharmacotherapy in mild cases of Still's disease is mainly symptomatic with NSAIDs.[2] Currently, paracetamol is not classified as a classic NSAID because it only displays analgesic and antipyretic

activities due to its central effect on cyclooxygenase III. However, it could be an alternative for patients allergic to NSAIDs, and for those who do not tolerate or do not respond to such treatment. The treatment of choice in severe cases are corticosteroids.[2,3] However, we decided against their use for a number of reasons. A differential diagnosis was not fully established. We observed progressive anemia of unknown origin, slight pleural and pericardial effusions, and no marked joint complaints. Classic NSAIDs proved to be ineffective in the patient. We applied paracetamol because of the fever refractory to medications and external cooling. This not only reduced temperature but also improved the patient's condition.

Certainly, the observation of a single patient may not be enough to exclude a potential self-limiting disease, but a particularly beneficial effect of paracetamol, first administered intravenously for 4 days and then orally, speaks for such interpretation, especially that other therapeutic approaches were ineffective. To our knowledge, this is the first case in which paracetamol has proved effective in a monotherapy of Still's disease. In a 24-month follow-up we did not observe a relapse of articular manifestations, and therefore the patient did not require corticosteroids or other immunosuppressants, which are usually recommended in severe cases.[2]

The EULAR's (European League Against Rheumatism) guidelines recommend paracetamol as the first line therapy for pain and fever relief but its anti-inflammatory effect is rated rather low compared to classic NSAIDs, otherwise known for their side effects. Also paracetamol is not free from adverse effects, the most severe of which is liver damage with jaundice and coagulopathy. They typically occur when daily doses are higher than recommended, although therapeutic doses have also been reported to cause liver failure. Despite the possibility of adverse effects, paracetamol administration is not directly counterindicated in patients with increased aminotransferases. Such cases, however, should be treated with due caution.[5] Liver tests performed on admission in our patient were abnormal but they showed a tendency to improve in the course of hospital treatment. Paracetamol did not increase transaminase levels, on the contrary, by reducing the symptoms it normalized them.

Although the follow-up was relatively short and symptoms may still recur, we argue that a 3-month treatment with paracetamol resulted in symptom relief and remission. It is difficult to explain the mechanism of this effect. It might be a result of its inhibitory activity on central cyclooxygenase III[6] or inflammatory cytokines, such as interleukin 1β or tumor necrosis factor-α, whose particularly high levels have been observed in patients with Still's disease[2]. However, literature provides conflicting data.[7,8] The effect might also be caused by the use of paracetamol derivates which show better solubility, e.g., propacetamol[9], or as suggested by a few reports, by adding supplementary substituents to paracetamol (e.g., its derivatives which are NO donors) which enhances the inhibitory effect on cytokine secretion.[8,10]

In conclusion, the present case illustrates the challenge posed by the diagnosis of Still's disease. At the same time, it demonstrates that monotherapy with paracetamol can be a sufficient approach during the first or single disease when there are only minor articular complaints, and there are doubts as to the use of corticosteroids.

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OPIS PRZYPADKU

Możliwość zastosowania paracetamolu w chorobie Stilla u dorosłych

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SŁOWA KLUCZOWE

choroba Stilla pojawiająca się w wieku dorosłym, kryteria diagnostyczne, leczenie, paracetamol

STRESZCZENIE

Choroba Stilla jest rzadką układową chorobą zapalną o nieznanej etiologii, charakteryzującą się codzienną wysoką gorączką, przemijającą wysypką, zapaleniem stawów i zmianami narządowymi: powiększeniem węzłów chłonnych, śledziony, wątroby oraz zapaleniem opłucnej i osierdzia. Rozpoznanie choroby jest kliniczne i stawia się je po wykluczeniu chorób zakaźnych, nowotworów oraz innych chorób układowych tkanki łącznej. W leczeniu stosuje się niesteroidowe leki przeciwzapalne, glikokortykosteroidy, w wybranych przypadkach łączone z lekami immunosupresyjnymi. W poniższej pracy opisujemy przypadek 21-letniego mężczyzny ze świeżym rozpoznaniem choroby Stilla. Występująca u pacjenta wysoka gorączka była oporna na klasyczne niesteroidowe leki przeciwzapalne, dopiero włączenie paracetamolu spowodowało ustąpienie gorączki, jak również znaczną poprawę stanu ogólnego. Opisywany przez nas przypadek jest pierwszym, w którym wykazano korzystne działanie paracetamolu u pacjenta z chorobą Stilla u dorosłych.

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