What can be hidden behind a persistent fever syndrome?

Anca Cardoneanu1,2, Ana Leca1, Alexandra Maria Burlui1,2, Luana Andreea Macovei1,2, Elena Rezus1,2

1Clinical Rehabilitation Hospital, 1st Rheumatology Clinic Iasi, Romania, 2“Grigore T. Popa” University of Medicine and Pharmacy Iasi, Romania

ABSTRACT

Fever is a defence mechanism of the body that occurs in various pathological situations, most often being secondary to an infectious disease. A prolonged febrile syndrome can hide many clinical problems, thus delaying a correct diagnosis and treatment. We present the case of a 52-year-old patient who addressed with a high fever associated with a generalized skin rash, arthralgia, myalgia and fatigue. Initially, the patient was referred to the infectious disease clinic where numerous paraclinical investigations were performed which ultimately ruled out an infectious cause of fever. Prompt response to corticosteroid therapy after performing numerous combinations of antibiotics, led to a possible autoimmune disease, the patient being redirected to the rheumatology clinic. Following the biological, immunological and radiological investigations, the diagnosis of adult Still’s disease was supported and the corresponding immunosuppressive treatment was initiated with good clinical-biological evolution.

Keywords: prolonged fever, skin rash, adult Still’s disease

INTRODUCTION

Fever is one of the main causes of presenting to the doctor, often having an infectious cause. However, in 3% of cases, doctors are faced with a fever of unknown etiology (FUE) which makes diagnosis and treatment difficult [1]. In 1961, Petersdorf and Beeson developed the first definition of FUE as a fever over 38.3 degrees Celsius that lasted more than 3 weeks and for which no diagnosis was made after 1 week of hospitalization [2]. In order to facilitate and urgently diagnose, in 1991 FUE was divided into 4 categories: classic, neutropenic, nosocomial and human immunodeficiency virus (HIV)-associated FUE [3]. A few years later, in 1997, a list of mandatory clinical and paraclinical investigations was developed for these patients, referred to as “minimum diagnostic evaluation” [4].

In adults, the main causes of FUE have been divided into 4 categories: infectious diseases (bacterial, viral, parasitic and fungal diseases), non-infectious inflammatory diseases (adult Still’s disease, vasculitis, sarcoidosis, rheumatoid arthritis, systemic lupus erythematosus), malignancies (solid tumors, leukemia, lymphoma) and miscellaneous [5-7]. The latter category includes many conditions such as Sweet syndrome, hemophagocytic syndrome, inflammatory bowel disease, De Quervain thyroiditis, drug-induced fever and hereditary auto-inflammatory diseases such as Familial Mediterranean fever, cryopyrin-associated periodic syndromes or tumor necrosis factor receptor-associated periodic syndrome [6,7].

Depending on the clinical course of the fever, FUE may be continuous or recurrent [7,8]. Recurrent or episodic form of FUE is the most difficult to diagnose because the intervals between febrile episodes can be very long, ranging from a few weeks to several years [7,9].

This paper describes the case of a patient who presented with a persistent high fever associated with fatigue, arthritis, myalgias and erythematosus rash, symptoms that raised both diagnostic and treatment problems.
The 52-year-old male patient from the rural area, known with a personal history of gastroenterological pathology - perforated gastric ulcer operated in 2003 and chronic venous insufficiency class C3 CEAP was redirected by “Sfanta Parascheva” Infectious Diseases Hospital from Iasi following the detection of a prolonged febrile syndrome of undetermined etiology.

The symptoms began in May 2022, with a itching, generalized erythematous rash, for which he presented at “Sfantul Spiridon” Emergency Clinical Hospital, at the Department of Clinical Immunology and Allergology; a coproparasitological examination was performed which revealed the presence of Blastocystis hominis; the diagnosis of spontaneous acute urticaria was established and treatment with Prednisone, Metronidazole and Levocetrizine was recommended; the evolution was favorable for only a few days.

After about 10 days, in June 2022, the patient presented with high fever of 39 to 40 degrees Celsius, generalized pruritic erythematous rash, headache, arthralgia, myalgia and severe physical asthenia. The patient addressed to Infectious Diseases Hospital where it was found: an altered general condition, fever, generalized erythematous lesion, pharyngeal congestion, subaural tongue, sinus tachycardia of 140/min and bilateral basal crackling rales; biologically, leukocytosis with discrete monocytes and eosinophilia was detected, interpreted at that time in the context of corticosteroid administration; normochromic normocytic anemia, a significant inflammatory syndrome due to the erythrocyte sedimentation rate (ESR=112 mm/h) and C-reactive protein (CRP = 174.44 mg/l); ionogram within normal limits, also a normal liver and kidney function. An abdominal ultrasound was performed which showed hepatosplenomegaly and a chest X-ray within normal limits.

Between 5 and 16.06.2022, empirical antibiotic treatment was initiated with Ampicillin 4 g/day for 3 days, then changed with Ceftriaxone 4 g/day in combination with Doxycycline 200 mg/day (the patient developed a positive intradermal test for Ciprofloxacin) for 9 days, with subsequent rescheduling of Ceftriaxone to Imipenem-Cilastatin 2g/day, therapy under which the patient remains febrile, with inflammatory markers at very high values (CRP=235 mg/L, ESR> 100 mm/h).

In this important inflammatory context and in the situation of a slight heart murmur, the suspicion of infectious endocarditis was raised, the patient being transferred between 16-17.06.2022 to the cardiology clinic for additional investigations; following the cardiological examination and the transesophageal ultrasound, the diagnosis of infectious endocarditis has not been confirmed.
per, middle and lower lobes), centrilobular and paraseptal emphysema lesions, adenopathy in the right hilum due to inflammation and hepatomegaly (Figure 2).

Given the specific clinical manifestations, the results of paraclinical investigations, the exclusion of infections and other autoimmune rheumatic diseases, the diagnosis of Adult Still's Disease was supported. During the hospitalization, the patient was treated with Methylprednisolone 125 mg intravenous therapy, subsequently 32 mg/day orally. He was discharged with an improved, afebrile general condition. At home, it was recommended to initiate immunosuppressive therapy with Methotrexate 15 mg/week subcutaneous and to continue corticosteroid therapy with Methylprednisolone 32 mg/day for 1 month, after which it will return for re-evaluation.

DISCUSSIONS

We presented the case of a 52-year-old man whose onset of the disease was due to a prolonged febrile syndrome that posed diagnostic problems, the patient being investigated in several medical specialties such as allergology, infectious diseases and cardiology. Following detailed and numerous paraclinical investigations, a possible infectious or neoplastic cause of the disease was denied, the patient being redirected to the rheumatology clinic. In the rheumatology department, corroborating clinical data, biological, immunological and radiographic investigations and excluding other systemic autoimmune diseases that may be associated with prolonged fever such as rheumatoid arthritis, collagen diseases or vasculitis, the diagnosis of adult Still's disease was supported and appropriate treatment was initiated with a good and prompt evolution.

Adult Still's disease is a sporadic, non-familial systemic inflammatory condition, with a prevalence of 1 up to 34 cases in 1 million people [10,11]. The disease has an equal frequency in women and men and has a bimodal distribution in terms of age of onset [12]. Thus, it has 2 peaks of incidence between 15-25 and 36-46 years old [12-14]. The onset in older people over 65 years of age has been described in several cases and is associated with a more severe evolution of the disease, with atypical disease manifestations, with more frequent complication development and with a higher mortality [13-20].

Adult Still's disease has 4 main manifestations that were also present in our patient: high fever > 39
Celsius degrees with spikes, evanescent skin rash of salmon-pink color, leukocytosis over 10,000/mm$^3$ with neutrophilia ≥80%, arthritis or arthralgia [21]. These specific signs of the disease are associated with other symptoms quite common such as: myalgia or myositis, pharyngitis, hepatosplenomegaly, lymphadenopathy, serositis. Biologically, patients have an increase in serum ferritin, a decrease in glycosylated ferritin and an intense inflammatory syndrome [22]. Many of these findings were highlighted in the case of the presented patient, which helped us to support the diagnosis.

For the final diagnosis we took into consideration the classification criteria used and validated at international level. The 2 sets of criteria with high specificity and sensitivity are Yamaguchi criteria, the most used in clinical practice published in 1992, and Fautrel criteria [23-25]. Fautrel criteria point ferritin and glycosylated ferritin as biomarkers, but do not include exclusion criteria that refer to the presence of malignancies, infections or other autoimmune diseases, especially polyarteritis nodosa [23,24].

Our patient presented with a systemic form of the disease because he developed skin rash and high fever. Literature data point to the presence of 2 subtypes of Still’s disease. A systemic form that is associated with an increase in IL-18 and IL-1β interleukins and with a more severe course due to the development of severe systemic complications [22,26,27]. The second form, the articular subtype, correlates with elevated levels of IL-6 and joint pain occurs simultaneously with fever. At first, arthritis can be migratory, but becomes stable during the disease course [22,26,27]. The radio-carpal joint is the most frequently affected, but the condition can affect any joint, the long-term evolution being associated with a chronic erosive arthritis [22,28]. Moreover, it appears that there are predictive factors for each subset of the disease. Thus, the joint form is more frequently associated with the female gender and proximal arthritis, while the systemic form has high fever, increased ferritin and CRP levels and thrombocytopenia [27,29,30].

The disease can be complicated by particularly serious clinical manifestations that can become life-threatening: macrophage activation syndrome, disseminated intravascular coagulation, myocarditis and cardiac tamponade or fulminant hepatitis [22]. Fortunately, these complications did not occur in the presented case even if the diagnosis was delayed by about 1 month.

Regarding the management of Still’s disease, the data published so far is quite limited, requiring more large prospective studies. Treatment must take into consideration the form of the disease (systemic or articular type), as well as the activity of the disease (mild, moderate or severe) [31]. In mild forms, it is recommended to use nonsteroidal anti-inflammatory drugs or low doses of corticosteroids. If the disease becomes chronic, immunosuppression is initiated with methotrexate, cyclosporine or azathioprine [31,32]. Low doses of steroids and methotrexate are administered in the articular form, while in refractory cases the use of IL-1, IL-6 or TNFα inhibitors may be considered [31]. In moderate and severe systemic forms, therapy with high doses of steroids must be started; in severe, non-responsive situations, IL-1, IL-6, JAK inhibitors may be administered, as well as investigational drugs such as IL-18 blockers [31].

**CONCLUSION**

Adult Still’s disease remains a condition that is quite difficult to diagnose, being more an exclusion diagnosis. A high, prolonged fever that cannot be linked to an infectious or a tumoral disease should raise the suspicion of a possible autoimmune cause. A multidisciplinary collaboration is necessary for these patients, the aim being to establish a correct diagnosis as soon as possible and to initiate an appropriate treatment.

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**REFERENCES**


