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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Adult-onset Still's disease and Muckle–Wells syndrome – two sides of the same coin?

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SUMMARY

Introduction Adult-onset Still's disease (AOSD), a systemic inflammatory disorder, often represents a heterogeneous entity and diagnosis requires the exclusion of mimicking disorders, including autoinflammatory diseases. We present a patient who meets the diagnostic criteria for AOSD and Muckle–Wells syndrome (MWS).

Case outline A 35-year-old male presented with lymphadenopathy and a chronic nonspecific rash, fever spikes, widespread arthralgia, and joint effusions. Laboratory results showed increased inflammation, leukocytosis, neutrophilia, thrombocytosis, and elevated liver enzymes, accompanied by negative immunoserological tests. Patient was diagnosed with AOSD and prednisone (15 mg/d), methotrexate (10 mg/w) and chloroquine (250 mg/d) are introduced in therapy. Due to refractory course, patient was introduced with anti IL-6 biological agent tocilizumab in 2014 (8 mg/kg monthly). However, after three doses, the drug is stopped due to disease exacerbation. In 2015, there was suspicion that there was another underlying disease from the autoinflammatory spectrum, but DNA analysis of the most common mutations in the NLRP3 gene was negative. In 2017, an ear, nose, and throat specialist confirmed bilateral sensorineural hearing loss, and in 2019, amyloidosis was confirmed after biopsy of the duodenum. Patient fulfilled a new-proposed diagnostic criteria for MWS and confirmation of mutation in *NLRP3* gene is not obligatory according to Eurofever registry.

Conclusion The symptoms of AOSD and MWS partly overlap, as well as their diagnostic criteria. In chronic refractory cases of AOSD, evaluation of diagnosis should be performed and autoinflammatory syndromes must be kept in mind.

Keywords: adult-onset Still's disease; Muckle–Wells syndrome; autoinflammatory diseases

INTRODUCTION

Adult-onset Still's disease (AOSD), a rare systemic inflammatory disorder, is often considered a part of the spectrum of the better-known systemic-onset juvenile idiopathic arthritis, with later age onset. The diagnosis is primarily clinical and necessitates the exclusion of a wide range of mimicking disorders. AOSD is a heterogeneous entity, usually presenting with high fever, arthralgia, typical salmon-pink skin rash, lymphadenopathy, and hepatosplenomegaly accompanied by systemic manifestations and hyperferritinemia. Clinical presentation is exceedingly variable and the disease has no clinical, biochemical, or radiological biomarker. The diagnosis is based on clinical and empirical evidence, with patients meeting inclusion and exclusion criteria and having negative immunoserological results [1, 2].

Autoinflammatory diseases are increasingly recognized and are in the differential diagnosis of many disease states [3]. Cryopyrin-associated periodic fever syndrome (CAPS) is a group of monogenetic diseases consisting of familial cold autoinflammatory syndrome and presenting with urticaria triggered by cold, Muckle–Wells syndrome (MWS) with fever, hearing loss, rash and joint pain, and neonatal onset multisystem inflammatory disease, a severe neonatal disease. This CAPS entity represents a third most common autoinflammatory disease, besides familial Mediterranean fever and tumor necrosis factor receptor-associated periodic syndrome [4]. CAPS is associated with mutations in the *NLRP3* gene (Nod-like receptor Family Pyrin Domain Containing 3) which encodes for protein cryopyrin. Cryopyrin associates with the apoptosis-associated speck like protein and pro-caspase 1 to form the *NLRP3* inflammasome, which is important for activation of pro–interleukin 1β (IL-1β) to mature IL-1β [5]. Consequently, CAPS can be treated with anti-IL-1β therapy [6]. Some patients with more diffuse inflammatory symptoms together with *NLRP3* mutations have been classified as "atypical" CAPS.

According to recently published papers, AOSD and CAPS (especially MWS) share a few similarities in pathogenesis. That explains a similar epidemiology, clinical presentations of both conditions which is difficult to differentiate and good response to anti IL-1 treatment [6, 7]. We describe a patient with inflammatory

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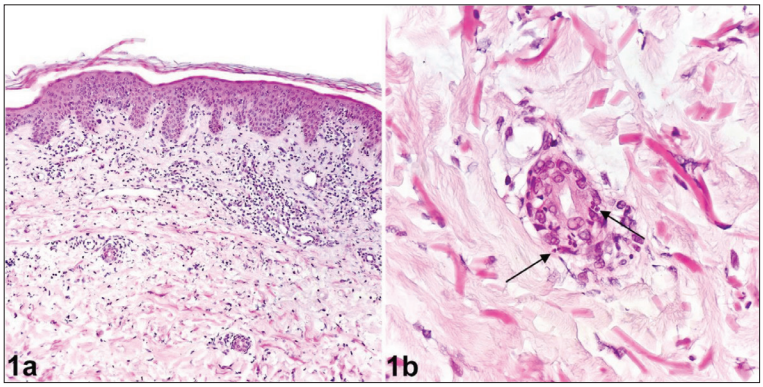

Figure 1. Mixed inflammatory infiltrate composed of neutrophils, eosinophils, and lymphocytes is present in the papillary and reticular dermis (1a); at high magnification, the presence of neutrophils within the sweat gland ducts (epitheliotropism) can be observed (arrow) (1b)

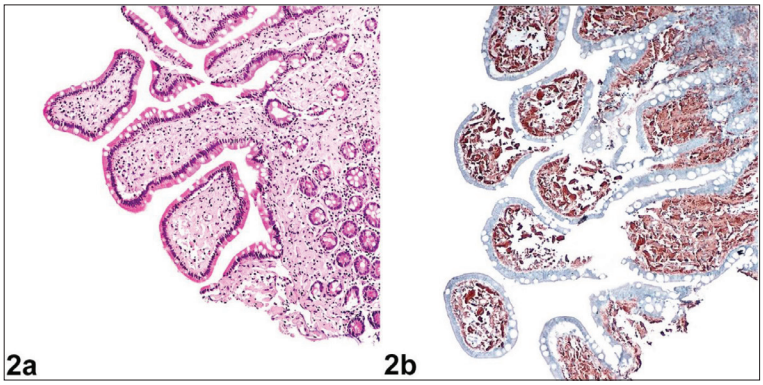

Figure 2. Eosinophilic deposits of amyloid are observed in the lamina propria of the duodenum (2a); immunohistochemical staining for amyloid A shows positivity (2b)

symptoms fulfilling a few proposed sets of diagnostic/classification criteria of AOSD but also fulfilling a new proposed diagnostic criterion of MWS.

CASE REPORT

In late 1999, a 35-year-old man presented with chronic nonspecific maculopapular exanthema of the trunk, upper, and lower limbs, accompanied by axillar and inguinal lymphadenopathy. In 2000, the patient was admitted to the Clinic of Allergology and Immunology of the Clinical Centre of Serbia. Laboratory results showed increased markers of inflammation [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)], leukocytosis, thrombocytosis and elevated hepatic enzymes [aspartate transferase (AST), alanine transferase (ALT), gamma-glutamyl transferase]. After exclusion of hematological malignancies (lymph node and bone marrow biopsy was performed on two occasions) and infections (virus serologies, hemocultures, stool, and urine cultures were negative) patient was diagnosed with idiopathic chronic urticaria and reactive lymphadenopathy. In 2003, the patient was hospitalized twice during a short period: first at the Clinic of Dermatovenereology and then at the Institute of Rheumatology due to lymphadenopathy and chronic non pruritic urticaria resistant to treatment. Urticarial rash was associated with fever spikes (< 38°C), widespread arthralgia and left knee effusion. Analysis of the left knee aspirate showed nonspecific inflammatory synovial fluid. Laboratory results showed increased inflammation (ESR 48 mm/h, CRP 80 mg/l), leukocytosis (19.1 × 10^9/L), neutrophilia (12.5 × 10^9/L), thrombocytosis (654 × 10^9/L), anemia of chronic disease and elevated enzymes, slight above upper reference limit (AST, ALT, lactate dehydrogenase), with negative immuno-serological tests: rheumatoid factor, anti-citrullinated protein antibodies, anti-double stranded DNA antibody, anti-Smith antibody, anti-SSA/Ro autoantibodies, anti-SSB/La autoantibodies, antineutrophil cytoplasmic antibodies, and cryoglobulins. Ultrasound of the abdomen revealed slight hepatosplenomegaly, while conventional radiography of the knees, hands, and feet excluded chronic erosive arthritis. A specialist of infectious diseases and a hematologist were again consulted for exclusion of these diseases (most common tumor markers were negative). According to patient history, clinical findings and course of the disease, imaging techniques results and laboratory findings patient is diagnosed with AOSD; diagnosis is based on presence of lymphadenopathy, slight hepatosplenomegaly, leukocytosis, neutrophilia and thrombocytosis, elevated hepatic enzymes, non-erosive polyarthritis, fever, and atypical urticarial rash. The patient met the proposed diagnostic and classification criteria for AOSD, as outlined by Cush et al. [8], Fautrel et al. [9], and Calabro, primarily using the Yamaguchi criteria. Prednisone (15 mg/d), methotrexate (10 mg/w) and chloroquine (250 mg/d) are introduced in the therapy. From 2003 to 2011 the patient was hospitalized at the Institute of Rheumatology several times due to persistent low-grade fever, articular and skin symptomatology, which were resistant to treatment (instead of chloroquine leflunomide was introduced, dosage of prednisone and methotrexate was increased with wide symptomatic therapy). According to literature, the first line treatment for chronic refractory (dominantly articular) of AOSD is IL-6 inhibitors and tocilizumab is proposed for further therapy [10]. Biological agent was introduced to therapy in 2014 (8 mg/kg monthly) and after three doses of tocilizumab, the drug was stopped due to disease exacerbation. Laboratory findings indicated intense increase in inflammatory markers, with marked leukocytosis, neutrophilia and thrombocytosis. Due to the exacerbation of the skin changes, skin biopsy was performed, and results showed urticaria with the mixed lymphocyte/neutrophil infiltration (Figure 1A and 1B).

At that time, the patient reported a bilateral hearing impairment which was a new symptom in clinical course of the disease, accompanied by persistent slight proteinuria (< 300 mg). All immune-serological tests for vasculitis and other systemic rheumatological conditions were negative

again. In 2015, for the first time, there was suspicion about another underlying disease, and blood sample for DNA analysis is sent to a foreign laboratory for testing for the most common mutations in *NLRP3* gene, but the tests was negative. In 2016, the patient was prescribed with anti-gout agent colchicine 0.6 mg daily with dosage increase up to 1.8 g daily in 2018, with poor medication compliance. Regarding the clinical course of the disease, in 2017 an ear, nose, and throat specialist confirmed bilateral sensorineural hearing loss after severe hearing impairment. Serum amyloid A (SAA) was highly increased in the sera of the patient in April 2019 (968 mg/L, cut off 6.4), biopsy of abdominal fat pad was inconclusive due to severe weight loss, but amyloidosis is definitely confirmed after biopsy of duodenum in 2019 due to persistent gastrointestinal bleeding (Figure 2A and 2B).

These three manifestations – urticaria, hearing loss, and amyloidosis – were first described as *UDA syndrome* in 1962 by Muckle and Wells [11]. In July 2019, due to the chronic course of the disease and no response to previous therapy, there was a request from a rheumatologist to the Republic Expert Committee for Rare Diseases for anti IL-1 drug treatment (anakinra or canakinumab). However, this request was not approved, so patient continued to take 10 mg of prednisone daily and 15 mg of methotrexate, and this was the very last data from patient's medical record.

All procedures were carried out in compliance with the institutional and/or national research committees' ethical standards, as well as the 1964 Helsinki Declaration and its revisions or similar ethical standards. The patient provided written permission to publish all shown material.

DISCUSSION

The patient fulfilled a newly proposed diagnostic criteria for MWS and confirmation of mutation in *NLRP3* gene is not obligatory according to Eurofever registry [12, 13]. To the best of our knowledge, and after extensive literature search, only two papers are published about association of AOSD and MWS in the past ten years [14, 15], but the diagnosis was still uncleared in our patient only. However, authors of recently published papers report new mutation in *NLRP3* gene, thus, directing all of us to look for new mutations and variants [16, 17]. Both MWS and AOSD are characterized by urticaria which exhibit specific histological characteristics that distinguish them from urticaria not associated with systemic diseases. Specifically, urticaria seen in MWS and AOSD is characterized by the presence of epitheliotropism (neutrophils within epithelial structures of the epidermis or eccrine sweat glands) [18]. The presence of epitheliotropism in skin biopsies of patients with urticaria should raise suspicion and warrant further investigations for underlying autoinflammatory conditions.

Both, MWS and AOSD, can present with secondary amyloid A (AA) amyloidosis as a complication [19]. It is characterized by the extracellular deposition of fibrils composed of fragments of the SAA protein; a major acute-phase reactant protein primarily produced by hepatocytes. AA can be detected through histochemical staining with Congo red or immunohistochemical staining for AA (Figure 2A and 2B).

The symptoms of AOSD and CAPS, especially MWS, overlap, as well as diagnostic criteria, so different sets of criteria may be challenging. Our patient fulfilled the Yamaguchi (and other proposed) criteria, responded partially to higher doses of steroids and conventional synthetic disease-modifying antirheumatic drugs, with lymphadenopathy, hepatosplenomegaly and elevated liver enzymes supporting AOSD as primary diagnosis. Bilateral sensorineural hearing loss is suggestive for phenotypic CAPS/MWS. Other characteristics such as arthralgia/arthritis, leukocytosis, thrombocytosis, neutrophilia and anemia can be seen in both conditions. Regarding the nonspecific urticarial rash as well as confirmed amyloidosis, they also can be seen in both conditions.

Unfortunately, the patient died at home, in late 2019; an autopsy was not performed, so a possible cause of death could be macrophage activation syndrome [20], the most severe complication, gastrointestinal bleeding, or a cardiovascular event.

The treatment of choice for both conditions, refractory AOSD and MWS, is IL-1 inhibition (anakinra or canakinumab), with canakinumab showing long-term efficacy and safety [21]. In September 2022, the first anti IL-1 drug (canakinumab) was registered in Serbia for pediatric monogenic autoinflammatory diseases as well as refractory AOSD. In chronic refractory cases of AOSD, evaluation of diagnosis should be performed, and autoinflammatory syndromes must be kept in mind in differential diagnosis because both diseases are highly heterogeneous and share wide similarities.

Conflict of interest: None declared.

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Стилова болест одраслих и Макл–Велсов синдром – две стране исте медаље?

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САЖЕТАК

Увод Стилова болест одраслих је системско запаљенско обољење код којег постављање дијагнозе захтева претходно искључивање сличних обољења као што су аутозапаљенске болести. Приказаћемо болесника са системском запаљенском болешћу који истовремено испуњава дијагностичке критеријуме за Стилову болест одраслих и Макл–Велсов синдром.

Приказ болесника Код 35-годишњег мушкарца се манифестовала лимфаденопатија са хроничним неспецифичним кожним променама, скоковима повишене телесне температуре, боловима и отоцима зглобова. У лабораторијским анализама су виђени повишени маркери запаљења, леукоцитоза, неутрофилија, тромбоцитоза и повишени јетрени ензими, док су сви имуносеролошки тестови били негативни. Постављена је дијагноза Стилове болести одраслих и у терапију су укључени пронисон® (15 *mg/d*), метотрексат (10 *mg/n*) и хлороквин (250 *mg/d*). Због рефракторног тока болести, 2014. године је укључен биолошки анти *IL*-6 лек тоцилизумаб (8 *mg/kg* месечно), али је лек обустављен после три дозе због погоршања болести. Током 2015. године постављена је сумња на друго обољење из спектра аутозапаљенских болести, али је ДНК анализа најчешћих мутација у гену *NLRP3* била негативна. Специјалиста ОРЛ је 2017. године потврдио дијагнозу обостраног сензоринеуралног оштећења слуха, а 2019. године је потврђена и дијагноза амилоидозе на основу биопсије дуоденума. На основу нових симптома, болесник је испунио новопредложене дијагностичке критеријуме за Макл–Велсов синдром и потврда мутације у *NLRP3* гену није била неопходна за дијагнозу.

Закључак Симптоми Стилове болести одраслих и Макл–Велсовог синдрома делимично се преклапају, као и њихови дијагностички критеријуми. Потребна је реевалуација дијагнозе Стилове болести код свих болесника са рефракторним током болести, са освртом на аутозапаљенске болести.

Кључне речи: Стилова болест одраслих; синдром Макл–Велс; аутозапаљенске болести