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Adult-onset Still's Disease in a 65-Years-Old Woman Successfully Treated with Oral Deflazacort

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Abstract – *Adult-onset Still's disease (AOSD) is a rare inflammatory condition of unknown etiology characterized by fever, rash, arthritis, and other systemic manifestations. Our clinical report describes a course of a 65-year-old Georgian woman who had a sore throat, spiking fever, a rash affecting the body and the extremities, arthritis, elevated WBCs, CRP and ESR, and hyperferritinaemia. The diagnosis was established based on the Yamaguchi criteria after exclusion of the mimicking disorders. The combined initial therapy with NSAID and Deflasacort 48 mg/d provided symptomatic improvement during the hospitalization period and eliminated all above-mentioned symptoms after discharge.*

Keywords – *Adult-onset Still's Disease (AOSD); Anti-cyclic citrullinated peptide (Anti-CCP); Antinuclear antibody (ANA); Arthritis/arthralgia; C-reactive protein (CRP); Deflazacort; Elevated ESR; Elevated WBCs; Hyperferritinemia; Non-steroidal anti-inflammatory drugs (NSAIDs); Rheumatoid arthritis (RA); Rheumatoid factor (RF); Salmon-colored rush; Spiking fever.*

I. INTRODUCTION

Adult-onset Still's disease (AOSD or Wissler-Fanconi syndrome) is a rare systemic inflammatory disorder with unknown aetiology (genetic factors and infectious triggers have been suggested as important[1-6]). It is characterized by multi-organ involvement, but the most common features are high spiking fever, evanescent rash, and arthritis/arthralgia.6 The eponymous term "Still's disease" comes from Sir George Frederic Still who first described systemic juvenile idiopathic arthritis in 1896.[7]

Subsequently, in 1971 Bywaters described 14 adult patients with features similar to the children with systemic juvenile idiopathic arthritis but did not fulfill the criteria for rheumatoid arthritis (RA).[8] The disease primarily affects young adults between the ages of 16-35 but can also occur in older individuals. An incidence of AOSD is between 1 and 34 people per million.[9]

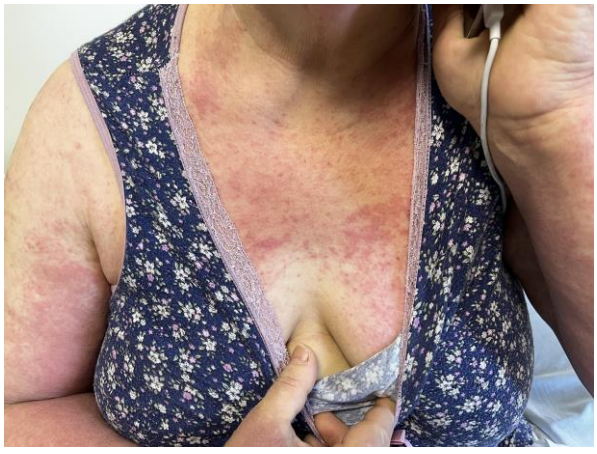
Despite high interpersonal variability of symptoms and severity, the three main patterns of AOSD have been identified: (i) monophasic or monocyclic AOSD with a single episode of symptoms that typically lasts less than a year, (ii) polyphasic or intermittent AOSD with more than one episode of symptoms and remission periods lasting for weeks to years between episodes, and (iii) chronic AOSD with persistent symptoms.[9,10] In the present article we describe the case of intermittent AOSD in a 65-years-old woman successfully treated with oral deflazacort.

II. CASE REPORT

A 65-year-old Georgian non-smoking, non-diabetic, obese woman was admitted to the Department of Internal Medicine of Tbilisi Heart Center (THC, Tbilisi, Georgia) with a history of high-grade fever, polyarthritis, polymyalgia, and skin rash for the last ten days, preceded by a self-limited sore throat. The fever was high grade, with a maximum temperature reaching 39.7°C, and had two spikes, usually in the late afternoon or early evening. A trunk, arms, and legs were affected by a slightly itching maculopapular and salmon-colored rash. The patients had been suffering from severe joint pains involving the hip, knee, shoulder, wrist, metacarpophalangeal, and proximal and distal interphalangeal joints.

Further history revealed that she had two similar episodes with a four-year symptom-free interval for the past six years. During both presentations, the patient was mainly treated with non-steroidal anti-inflammatory drugs (NSAIDs) and antihistamine agents as an idiopathic polyarthritis with an allergic rush.

Examination revealed an obese female with a fever of 39.7°C, cervical lymphadenopathy, and no hepatomegaly or splenomegaly. The patient had acute synovitis of the knee, talocrural, radiocarpal, and metacarpophalangeal joints. The trunk and all extremities were covered with a maculopapular salmon-colored rash (Fig. 1).



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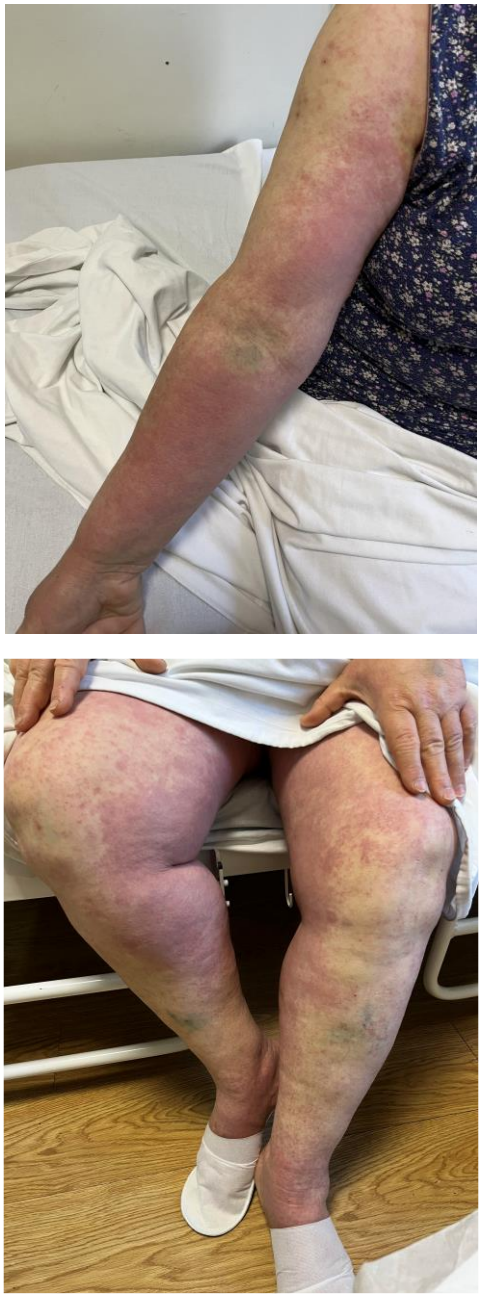

Fig. 1. The salmon-colored maculopapular rush affecting trunk and extremities.

Pulmonary, cardiovascular, neurological, and other examinations were unremarkable. Hematological investigations showed elevated WBCs: 13.9×10^9/L (88.0% neutrophils) vs 17.8×10^9/L (91.0% neutrophils) during previous episode in 2020; hypochromic anemia (RBC: 3.29×10^{12}/L; HGB: 9.18 g/L; HCT: 26.20%; MCV: 79.60 fl). The acute phase reactants were elevated with C-reactive protein (CRP): 159.33 mg/L (273.6 mg/L in the previous episode) and erythrocyte sedimentation rate (ESR): 40 mm/h (65 mm/h in the previous episode). There was a markedly elevated level of serum ferritin: 1500 ug/L (> 2000 ug/L in the previous episode). Anti-cyclic citrullinated peptide (Anti-CCP), antinuclear antibody (ANA), and rheumatoid factor (RF) were all negative. Kidney and liver functions, as well as coagulation tests, were normal. Blood and urine cultures revealed no evidence of bacterial, fungal, or viral infections. All classes of immunoglobulins were within normal limits and paraproteins were not detected in urine. Cryopyrin-associated periodic syndromes (familial cold auto-inflammatory syndrome, CINCA/NOMID, and Muckle-Wells syndrome), hyperimmunoglobulin D syndrome (HIDS), familial Mediterranean fever (FMF), TRAPS, Schnitzler syndrome and mevalonate kinase deficiency were excluded. Computerized tomographic scans of the thorax and abdomen were normal.

Based on history, clinical examination, laboratory investigations, and Yamaguchi criteria diagnose of AOSD were made. The treatment with Ibuprofen 200 mg/d, Deflazacort 48 mg/d (equivalent dose of 40 mg prednisolone), and Pantoprazole 40 mg/d was started. After three days of treatment the patient became afebrile, the rash began to resolve, and the frequency and intensity of arthralgia episodes decreased. She was discharged with a tapering dose of Deflazacort (6 mg weekly) and proton-pump inhibitor (PPI). One month after discharge she is doing well and is completely symptom-free.

III. Discussion

Adult-onset Still's disease (AOSD) described by Eric Bywaters in 1971, is a rare (incidence: 1-34 per million) inflammatory systemic disorder characterized by quotidian fevers, arthritis, and an evanescent rash.[10] It is the adult form of systemic juvenile idiopathic arthritis or juvenile Still's disease, which was named after Sir George Frederic Still, a British physician who first described a form of childhood arthritis associated with fever in the medical literature in 1896.[7,10]

AOSD is an idiopathic disease. The hypothesis of a combination of genetic factors and an abnormal or exaggerated response to infections (numerous viruses and bacterial pathogens including Yersinia enterocolitica and Mycoplasma pneumoniae) or other environmental exposures has been no proof.[1-6,10] The cytokines include interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-18 (IL-18), and tumor necrosis factor-alpha (TNF-alpha) are also believed to play a role in the development of AOSD.[10-14]

The typical clinical presentation of AOSD includes a spiking fever (>39^0C), a skin salmon-colored rash, myalgia, and arthritis (mostly knees, wrists, ankles, and hips). In most cases, fever spikes occur twice a day, usually in the late afternoon or early evening (as in our case). The pruritic or nonpruritic evanescent rash usually but not always develops during a fever episode, mostly affecting the trunk and thighs, but can also affect the extremities and face.[10,15-21] Untreated AOSD can destroy the affected joints due to chronic inflammation. Other symptoms of AOSD include a sore throat, abdominalgia, splenomegaly, hepatomegaly, lymphadenopathy, anorexia, and weight loss.[10,15-21] More rarely, AOSD can cause pericarditis, myocarditis, and/or pleuritis with or without pleural effusion.[10] Another rare and extremely dangerous complication of AOSD might be macrophage activation syndrome (MAS), also called

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secondary hemophagocytic lymphohystiocytosis (HLH), with an overactive and abnormal response of the immune system.[10]

There are three different patterns of AOSD: (i) monophasic AOSD, (ii) polyphasic or intermittent AOSD, and (iii) chronic AOSD. In the first pattern patients have a single episode of symptoms that typically lasts weeks to months. The patients with intermittent AOSD develop more than one episode with symptom-free periods (weeks to years) between episodes. The patients with chronic AOSD have persistent symptoms.[15-20]

Affected individuals usually have elevated WBCs, platelets, and/or anemia. Other common laboratory findings are elevated inflammatory markers (CRP, ESR) and ferritin. Some patients have high blood levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH).

There are no pathognomonic signs, specific tests, or laboratory findings for AOSD, and diagnosis is usually made based on Yamaguchi criteria16 after exclusion of autoimmune disorders (systemic lupus erythematosus [SLE], dermatomyositis, and rheumatoid arthritis [RA]), inflammatory bowel disease (IBD), Sweet syndrome, lymphoma and leukemia, and tuberculosis, mononucleosis, and toxoplasmosis.[10] It is very important to differentiate AOSD from the cryopyrin-associated periodic syndromes (familial cold auto-inflammatory syndrome, CINCA/NOMID, and Muckle-Wells syndrome), hyperimmunoglobulin D syndrome (HIDS), familial Mediterranean fever (FMF), TRAPS, Schnitzler syndrome and mevalonate kinase deficiency.[10]

To fulfill at least five (including 2 major criteria) from the below listed Yamaguchi criteria[16] (Table 1) is confirmatory for AOSD. In our case, the patient met all four major and three of five minor criteria (Table 1).

TABLE 1. Yamaguchi criteria of AOSD

	In our case
Major criteria	
Fever ≥39^{0}C that lasts ≥1 week	+
Arthralgia/arthritis lasting ≥2 weeks	+
Salmon-colored rash during fever	+
Elevated WBCs	+
Minor criteria	
Sore throat	+
Lymphadenopathy	+
Hepatomegaly or splenomegaly	-
Elevated liver enzymes	-
Negative tests for ANA and RF	+

+: fulfilled; -: not fulfilled

Nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, steroids, and/or "steroid-sparing agent" Methotrexate are treatment options for AOSD. Recently cytokine IL-1 blocker Canakinumab (Ilaris) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of Still's disease, including AOSD. Other IL-1 blocker Anakinra, TNF-alpha antagonists Infliximab and Etanercept, IL-6 blocker Tocilizumab (Actemra), intravenous immunoglobulin, cyclosporin A, azathioprine, leflunomide, cyclophosphamide, and thalidomide currently are under investigation.[10]

IV. Conclusion

Adult-onset Still's disease is a systemic disease of unknown etiology and pathogenesis, which should be considered in patients with the following symptoms: spiking fever with rash, arthritis, elevated WBCs, and hyperferritinemia.

AOSD might be difficult to diagnose given its rarity. Making a timely and accurate diagnosis is important for appropriate patient care and insurance of quality of life.

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