

Wissler–Fanconi syndrome and related diagnoses: a case report

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Introduction: Wissler–Fanconi syndrome is a rare rheumatic syndrome that was first described during the 1940s in Europe. Since then, many papers have been written that cover all aspects of this syndrome, most of which are in French and German language, with only a very few in English (none of them recent). We report here a case that fulfils the criteria for Wissler–Fanconi syndrome. Under the more general descriptive umbrella of Wissler–Fanconi syndrome, our patient also fulfils the Modified Jones criteria, and the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for rheumatoid arthritis, and was interpreted by other internists and another rheumatologist as fulfilling the Yamaguchi criteria for adult onset Still’s disease.

Case presentation: A middle-aged female presented to the emergency department with shortness of breath and chest pain associated with fever, polyarthritis, and had a chronic polymorphic rash on the back and lower extremities. Blood analysis showed highly elevated inflammatory markers and rheumatoid factor. After ruling out other possible differential diagnoses and reviewing the medical literature, the patient was diagnosed with Wissler–Fanconi syndrome. A combination of nonsteroidal anti-inflammatory drugs and steroids achieved complete remission.

Conclusion: This case report highlights the important differential diagnosis that may be included under the nomenclature of Wissler–Fanconi syndrome (subsepsis hyperergica). Features of Wissler–Fanconi syndrome can be found in a differential diagnosis that includes true sepsis, acute rheumatic fever, rheumatoid arthritis, and adult onset Still’s disease.

Keywords: Wissler–Fanconi syndrome, adult Still’s disease, subsepsis hyperergica, subsepsis allergica

Introduction

Wissler–Fanconi syndrome, also known as subsepsis hyperergica, is a rare rheumatic syndrome that was first described by Wissler in 1944 and Fanconi in 1946. It has a similar presentation to sepsis and is characterized by four typical symptoms: polymorphous exanthemas, recurrent high fever, leukocytosis, and arthralgia.^{1,2} This syndrome is sometimes considered closely related to Still’s disease. Both Still’s disease and Wissler–Fanconi syndrome onset may occur in adulthood. The clinical picture includes acute, often migratory, polyarthritis, polymorphic exanthema, and a major inflammatory syndrome with fever (often intermittent) and high polymorphonuclear leukocyte counts. The grounds for this double designation are not clearly stated in the medical literature: are they two separate entities, or not? Some authors plainly stand for a unitary opinion.³ We report a case that fulfils criteria for Wissler–Fanconi syndrome. Under the more general descriptive umbrella of Wissler–Fanconi syndrome, our patient also fulfils the Modified Jones criteria for acute rheumatic fever, and the 2010 ACR/

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EULAR classification criteria for rheumatoid arthritis. Yamaguchi criteria require five or more criteria to diagnose adult onset Still's disease. Two or more criteria must be major, which are: fever $>39^{\circ}\text{C}$ lasting ≥ 1 week, arthralgia or arthritis lasting ≥ 2 weeks, typical rash, and leukocytosis $>10,000/\text{mm}^3$ with $>80\%$ polymorphonuclear cells. Minor criteria are sore throat, recent development of significant lymphadenopathy, hepatomegaly or splenomegaly, abnormal liver function tests, and negative tests for antinuclear antibody and rheumatoid factor (immunoglobulin M).^{4,5} Historically, in children with fever and polyarthritis, the differentiation between Still's disease and rheumatic fever was of particular diagnostic importance because of the requirement for prophylactic antibiotic drugs in cases of acute rheumatic fever. Early stage of Wissler–Fanconi could easily be confused as septicemia as they both share same presentation, which was one of the reasons why it was known as subsepsis hyperergica in Europe. This syndrome was considered by some authors as a premature stage of adult Still's disease, whereas other authors considered it a separate entity, and this remains open to debate.²

Case presentation

A 42-year-old Caucasian female came to the hospital with complaints of shortness of breath and nonradiating retrosternal chest pain that persisted for 1 week, associated with 2 days of high spiking fever. The patient had migratory polyarthritis and polymorphic maculopapular rash on the back and lower extremities for 4 months. She had been treated briefly with glucocorticosteroids and pain medication, with minimal response. The patient has no known drug allergies, a negative past medical history, and no history of heavy alcohol use, herbal treatments, insect bites, or animal contact.

Physical examination revealed a high fever (38.6°C), pulse rate (106/min), respiration rate (38/min), and blood pressure (117/52 mm Hg). There were no signs of jaundice, lymphadenopathy, or goiter. Auscultation of the lungs revealed decreased chest expansion, but no rales. Auscultation of the heart was normal. Muscle tenderness was detected in the arms and legs. Skin exam showed a purplish polymorphic eruption over the lower legs bilaterally, including the feet. Similar lesions that did not blanch under pressure and were nonpruritic were noted on lower back and upper thigh.

Computed tomography scan of the chest ruled out pulmonary embolism and revealed a pericardial effusion. Echocardiography confirmed moderate effusion and was negative for endocarditis. Blood sample analysis revealed high levels of

CRP (42.9 mg/dL, normal: 0–0.3), erythrocyte sedimentation rate (113 mm/h normal: 2–20), white blood cell count (21,000 cells per μL , $>95\%$ neutrophils and 28 bands), hemoglobin (9.3 g/dL, normal: 10.1–14.5 g/dL), and platelet count ($212 \times 10^9 \text{ L}^{-1}$, normal: $180\text{--}427 \times 10^9 \text{ L}^{-1}$). Urinalysis showed hematuria with white blood cells and bacteria. Urine and multiple blood cultures were negative. Ferritin was significantly high at 29,349 ng/mL (normal: 10–291 ng/mL). Renal function and liver enzymes were both within normal limits.

Serology tests were positive for rheumatoid factor 146 IU (normal: 0–19 IU) and cyclic citrullinated peptide antibody 20 (normal: 0–19 IU). The patient also had a total complement of $>10,000$, with normal C3 and C4 levels. Antistreptolysin O was elevated, 179 IU/mL (normal: 0–120 IU/mL). Tests were negative for antinuclear antibodies, anti-DNA antibodies, antineutrophil cytoplasmic antibodies, and anti-Jo-1 antibodies. There was no marker of recent infection, including hepatitis B antigen, hepatitis C virus, human immunodeficiency virus antibodies, histoplasma antigen, Epstein–Barr virus.

On admission, the patient was thought to be septic, with the source of infection either the urinary tract or endocarditis. Bacterial endocarditis was ruled out after echocardiogram and blood cultures. The patient was started empirically on antibiotics for presumed sepsis and disseminated intravascular coagulation. A few days later, the patient's symptoms persisted. An infectious disease consultant did not think that the patient had an active infection. The patient's rash was thought to be due to an autoimmune process. Leukocytosis and polymorphic exanthemous rash persisted. A dermatologist biopsied the rash. According to a dermatopathologist, the findings were consistent with urticarial vasculitis. A quotidian fever persisted for 3 days and then resolved when naproxen therapy was started. The patient's arthralgias also responded well to naproxen. Shortness of breath and chest pain resulting from pericarditis resolved after the pericardial effusion was drained and the patient was started on dapsone.

A combination of naproxen, dapsone, and prednisolone therapy resulted in significant improvement of the patient's arthralgias and rash. The inflammatory markers decreased gradually. On day 18 of hospitalization, the patient was discharged home after resolution of her acute symptoms and improvement of her rash and joint pain. Discharge diagnoses included rheumatoid arthritis and rheumatic fever. Adult onset Still's disease was considered in the differential diagnosis, but was considered less likely as the patient failed to fulfil the Yamaguchi criteria (the patient's documented fever was present for less than a week, the rash was not typical

for adult onset Still's disease, there was no sore throat, and rheumatoid factor was positive).

Soon after discharge from our facility, the patient was admitted to another hospital where she was diagnosed as having adult onset Still's disease based on a different interpretation of her rash. She is currently doing well on adalimumab, methotrexate, and prednisone for rheumatoid arthritis and secondary prophylaxis with monthly benzathine penicillin for rheumatic fever with carditis, after taking into consideration that she developed pericarditis that can be defined as a form of carditis (pericarditis is a form of carditis). The University of Oklahoma College of Medicine ethics committee does not require ethical approval for case reports. Written informed patient consent was obtained.

Discussion

Here we describe a recently encountered patient who fulfills criteria for Wissler-Fanconi syndrome. We see the Wissler-Fanconi syndrome as a more general diagnosis under whose umbrella may be found the important differential diagnoses of acute rheumatic fever, rheumatoid arthritis and adult onset Still's disease. This case report demonstrates the difficulty in differentiating among acute rheumatic fever, rheumatoid arthritis, and adult onset Still's disease.

Before diagnosing Wissler-Fanconi syndrome, other conditions to exclude are sepsis/infection, neoplastic diseases (eg, lymphoma), and other autoimmune diseases (eg, Schnitzler-like and dermatomyositis). In our patient, the diagnosis of Wissler-Fanconi syndrome was made after ruling out infection, neoplastic disease and other autoimmune diseases. Extensive examination and evaluation included skin biopsy, blood tests and computed tomography scan. Our patient fulfilled criteria for rheumatoid arthritis and acute rheumatic fever. We did not find the patient to fulfil the Yamaguchi criteria for adult onset Still's disease because documented fever was present for less than a week, rash was not typical, there was no sore throat, and rheumatoid factor was positive.

However, adult onset Still's disease was diagnosed by others because of different interpretation of the Yamaguchi criteria.

Historically, Wissler first described the syndrome in 1944. Subsequent case reports focused on main characteristics of high, intermittent fever; irregular, recurrent exanthemata of different types; neutrophilic leukocytosis; increased sedimentation rate; and negative cultures,^{1,2} all of which were satisfied in our patient. In a study by Bywaters⁶ in 1971 discussing the differential diagnosis of adult onset Still's disease, he listed Wissler–Fanconi syndrome on top of the list, as he believed Wissler–Fanconi syndrome is another description of Still's disease.

Conclusion

This case report highlights an important differential diagnosis that may be included under the umbrella of Wissler–Fanconi syndrome (subsepsis hyperergica). Features of Wissler–Fanconi syndrome can be found in a differential diagnosis that includes true sepsis, acute rheumatic fever, and adult Still's disease. Suspicion of Wissler–Fanconi syndrome should lead to a thorough evaluation to rule out infection, including sepsis, acute rheumatic fever, and adult onset of Still's disease.

Disclosure

The authors report no conflicts of interest in this work.

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