

Adult Onset Still's Disease in Tropical Area: Illustration of Diagnostic and Therapeutic Difficulties from 3 Senegalese Observations

Nafy Ndiaye, Ngoné Diaba Diack, Michel Assane Ndour, Biram Codou Fall, Ghislain De Chacus, Daouda Thioub, Ameth Dieng, Yakham Mohamed Leye, Abdoulaye Leye*

Internal Medicine Department, Teaching Hospital of Pikine, Dakar, Senegal

Email: *ablayeye@hotmail.com

How to cite this paper: Ndiaye, N., Diack, N.D., Ndour, M.A., Fall, B.C., De Chacus, G., Thioub, D., Dieng, A., Leye, Y.M. and Leye, A. (2017) Adult Onset Still's Disease in Tropical Area: Illustration of Diagnostic and Therapeutic Difficulties from 3 Senegalese Observations. *Open Journal of Internal Medicine*, 7, 135-143.

<https://doi.org/10.4236/ojim.2017.74014>

Received: October 2, 2017

Accepted: November 13, 2017

Published: November 16, 2017

Copyright © 2017 by authors and Scientific Research Publishing Inc.

This work is licensed under the Creative

Commons Attribution International

License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

Abstract

Introduction: The Adult Onset Still's Disease (ASD) is a systemic auto-inflammatory affection of unknown cause seldom described in sub-Saharan Africa. We report 3 observations of ASD illustrating the diagnostic and therapeutic difficulties of this affection in our areas. **Observation 1:** Our first patient is a 56 years old schoolteacher presenting an ASD in its chronic articular form. She had been followed for an inflammatory arthralgia for 10 years and of the pharyngeal pains without exact diagnosis. She presented ASD's criteria of Yamaguchi and of Fautrel. The prednisone was begun at the dose of 0.8 mg/kg/day with fast appearance of a progressive muscular weakness. Use of methotrexate at a rate of 15 mg per week, associated with low dose of prednisone was effective in long-term without any flare of the disease so far. **Observation 2:** Our second patient is a 30 years old dressmaker presenting an ASD in its complicated systemic form of lymphohistiocytic activation syndrome. She validated the criteria of Yamaguchi and Fautrel for ASD. She also presented resistance to corticosteroid therapy. The evolution was marked by a hospital-acquired septicemia and a multi-organ failure leading to death. The diagnosis was retrospectively confirmed after that, with the low level of the glycosylated ferritin serum value. **Observation 3:** The third patient is a 22 years old Guinean student who presented prolonged fever and inflammatory polyarthralgia without articular deformation. He had been misdiagnosed for ASD with diagnostic wandering of several months. He was treated successfully with prednisone after set up of ASD diagnosis according common criteria. Corticosteroid therapy was stopped after 8 months without any relapse noted so far. **Conclusion:** Caring for ASD is difficult in our context mainly because of high cost of several explorations needed to set up its exact diagnosis while making differential one. Evolution under corticosteroid therapy is usually favorable but diagnostic delay may lead

to severe complications and death.

Keywords

Still's Disease, Diagnosis, Treatment, Tropical Area

1. Introduction

The Adult Onset Still's Disease (ASD) is an auto-inflammatory systemic affection of unknown cause [1]. Its diagnosis is often tiresome because no sign is pathognomonic. Also it constitutes a diagnosis of exclusion. This diagnosis is made more difficult in tropical context where the presence of fever makes confusion with the endemic infectious causes. Also, the access to the key complementary examinations allowing the diagnosis of ASD is not always easy. It is what explains certainly the low number of cases of ASD brought back in sub-Saharan Africa [2] [3].

Caring for this affection is not facilitated because of lack of codified treatment. Moreover, most therapeutic having been the proof of their effectiveness in this pathology is either heavy of consequences in particular infectious concerns or no available in our areas.

We proposed to illustrate the diagnostic and therapeutic problems of ASD in our context through the study of 3 observations put together in an internal medicine department of Dakar.

2. Observations

2.1. Observation 1

A 56 years old woman, schoolteacher, was addressed to our internal medicine department for febrile cervical adenopathies and arthralgias. As antecedents, she had asymmetrical peripheral inflammatory arthralgias of the large articulations (elbow, shoulder and especially knee) for 10 years evolving by push. Also she had been followed for 6 months for a trailing angina resistant to antibiotics having led to a tonsillectomy.

She presented 1 month before her admission a flu syndrome with cephalgias, intense asthenia, fever with night prevalence with shivers and sweats. A quasi-generalized pruriginous skin eruption accompanied these feverish episodes. It also described a persistence of a pharyngeal pain with painful swallow and recrudescence of the arthralgias. This symptomatology justified several consultations without improvement. At her admission, the temperature was up to 40.9°C and a heart rate of 118 pulse/min. The physical examination found cervical inflammatory adenopathies, mobile and not fistulized. She presented also erythematous and maculopapular skin lesions located on face, neck, back (**Figure 1**) and the inner face of the thighs. There were neither articular tumefactions nor deformations.



Figure 1. Erythematous and maculopapular skin lesions of the back.

The complementary examinations found hyperleucocytosis (total white cell count was 12.6×10^9 g/L) with 90% neutrophilia, anaemia (hemoglobin was 11.1 g/L) hypochromic mean corpuscular volume at 67 fl (normal range 80 - 100 fl), a biological inflammatory syndrome, a moderate hepatic cytolysis and cholestasis. She presented a very high level of serum ferritin up to 20.948 mg/L (100 fold the normal range) with a low level of glycosylated fraction of ferritin at 16%. All biological examination looking for infectious disease background remain negative: blood culture, cytobacteriologic examination of urines, test for malaria, search for mycobacterias on the phlegm, markers of viral hepatitis B and C, anti-VIH antibodies. Radiographies of the painful articulations were normal as well the thoraco-abdominal tomodesitometry. The research of rheumatoid factor, anti-nuclear and anti CCP antibodies was also negative. All in all, our patient presented six criteria out of eight for the Yamaguchi's criteria [4] as well for those of Fautrel [5], thus making us retain the diagnosis of ASD.

She has been treated with 0.8 mg/kg/day of prednisone. This treatment had allowed the fast disappearance of cutaneous lesions, arthralgias and progressive normalization of the biological anomalies. However, it was noted the appearance of muscular weakness of the 4 members quickly progressive having required a degression of the corticosteroid therapy. The patient complained a reappearance of the arthralgias then. In front of this situation we introduced methotrexate with the weekly dose of 20 mg associated with folic acid and continuation of the progressive decrease of corticoids up to the daily dose of 2.5 mg of prednisone. This biotherapy allowed the stable and complete disappearance of the whole of symptomatology and the normalization of the serum level of ferritin. All the treatment has been completely stopped 9 months later without any relapse so far.

2.2. Observation 2

A 30 years old woman without particular pathological antecedents was referred to our department for exploration of an unexplained prolonged fever. She had been hospitalized for 6 weeks in a hospital for a symptomatology which had evolved

for 2 months. It was made of a permanent fever without shiver or sweat; but associated with a hepatomegaly and arthritis of the knee, ankle and of the wrist. This evolved in a context of deterioration of the general state. Several examinations with infectious aiming (thick drop, haemocultures, cyto-bacteriologic examination of urines) were carried out without any positive result. She had received before treatment against malaria and several protocols of antibiotic therapy without improvement of the symptomatology.

At admission in our department, the examination found febrile jaundice with fever at 39.5°C associated with sensitive regular hepatomegaly. There was a diffuse cutaneous xerosis, an acquired ichthyosis on the lower extremities (**Figure 2**) and pruritic cupboard on the back.

The joints of the wrist and the knees were tumefied, inflammatory with presence of an articular outpouring whose puncture brought back a viscous yellow liquid rich with no altered neutrophile polynuclear. The peripheral ganglionic areas were free and spleen was not palpable.

The biological examinations revealed an aregenerative pancytopenia, an inflammatory syndrome with high level of CRP at 192 mg/l (reference < 6 mg/l), a cytotoxicity and a hepatic cholestasis. The serum ferritin level was very high up with 80-fold the normal range (20.168 µg/L). The search for autoantibodies (antinuclear, anti-CCP2) was negative. The rate of alpha foeto-protein was normal. At the same time, viral serologies for the HIV, B and C hepatitis and the search for tuberculosis by PCR remain negative. The examination after medullar ponction revealed an inflammatory aspect of bone marrow. The tomodensitometry found a magma of compressive adenopathies on the level of the cœlio-mesenteric and latero-aortic chains with inflammatory shape. The diagnosis of ASD probably associated with a syndrome of lymphohistiocytic activation was then strongly suspected.

She was put under bolus of methylprednisolone during 3 days followed by a relay with prednisone at a rate of a 1 mg/kg/day. She had also received iterative transfusions of concentrated platelet and packed red blood cell besides the additive treatment of the corticosteroid therapy. The evolution was marked after one short period of apyrexia, by febrile peaks reaching 41°C, associated with a cardiovascular



Figure 2. Diffuse cutaneous xerosis and acquired ichthyosis of the legs.

collapse. Strong corticosteroid amounts were then maintained besides the symptomatic treatment. Methotrexate or immunosuppressant agents could not have been used because of hematologic instability and lack of result of different test performed to check for infectious disease. Moreover, hemocultures carried out during the second week of hospitalization had isolated *Providencia stuartii* in nosocomial context. An antibiotherapy adapted to the antibiogramme was then quickly performed besides the corticosteroid therapy. In spite of this treatment, the patient presented one week after a persistence of the hectic fever (**Figure 3**), generalized tonic-clonic convulsions, a right pleurisy (**Figure 4**) rich with non altered neutrophiles polynuclear.

No other germ was identified in hemoculture, neither in urines nor in pleural and lumbar liquids. She died 6 days later in a context of multi visceral failure. The results of the dosage of glycosylated fraction of ferritin came back to us later showing low level at 18%. It thus validated the ASD's criteria of Yamaguchi and Fautrel [4] [5] with a score of 5/8 for each classification.

2.3. Observation 3

This observation is about a young Guinean student, 22 years old. He had presented for 3 months an inflammatory bilateral localised to the shoulder, wrist, ankle and hip. Those symptoms evolved in a context of intermittent fever with shivers. This fever persisted in spite of a prior presumptive antimalarial treatment, antibiotics and paracetamol prescribed in his country before reaching our department in Dakar. It was associated with a progressive deterioration of his general state.

At the admission, he presented fever at 39°C and tachycardia at 108 pulse/min. The physical examination was normal apart from an exacerbate pain while mobilizing the painful articulations. The complementary exploration highlighted an acceleration of VS at 58 mm, a rate of CRP 15.5 mg/L (N < 6), and also discreet thrombocytosis and lymphopenia. The rate of white globules was normal. The serum protide electrophoresis showed a hypo albuminemia at 26.3 g/L (N = 30 - 40)

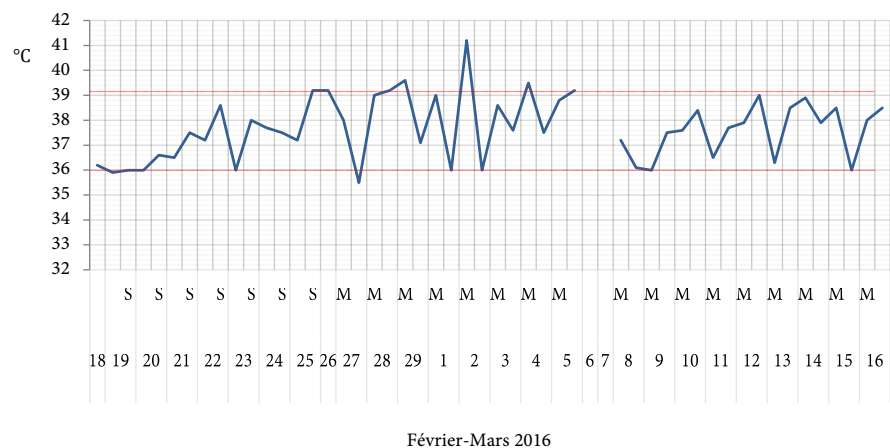


Figure 3. Hectic fever curve during hospitalization.

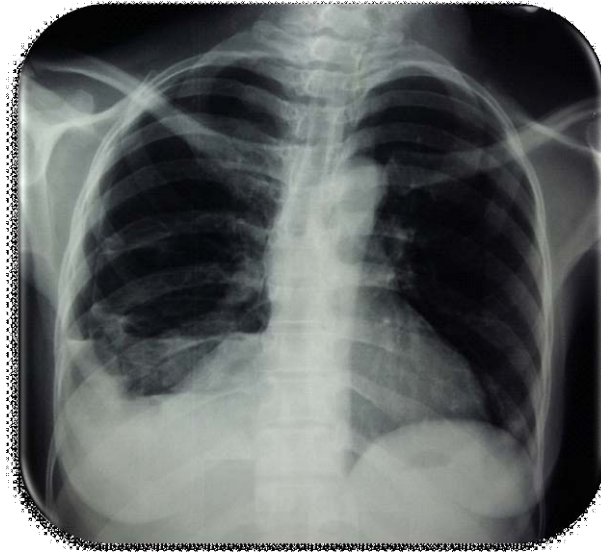


Figure 4. Right basal pleurisy.

and an increase diffuses γ -globulines. There was a hepatic cytolysis with 4 fold increase of ASAT/ASAT. We noticed a hyperferritinemia up to 4 fold (1120 $\mu\text{g/L}$) and the glycosylated fraction of ferritin was low at 42%, but under corticosteroid therapy and delayed blood sampling because of lack of financial resources. The repeated hemocultures were negative. Abdominal and cardiac ultrasound examinations were normal. The later research of the rheumatoid factor and common auto-antibodies was negative.

The diagnosis of ASD was retained early for this patient and 0.85 mg/kg/day of prednisone was begun. It had allowed a rapid and stable apyrexia, a progressive improvement of arthralgias and general state as well a normalization of the biological disturbances. The initial amount of prednisone was gradually decreased until an amount of maintenance of 5 mg/day reached in the 4th month of treatment. The evolution had not ceased improving and the general state had been restored. He stopped the treatment 8 months after the hospitalization without relapse so far.

3. Discussion

ASD is a polygenic systemic disease of unknown cause [6]. In sub-Saharan Africa, works on ASD are summarized with some reports of case [2] [3]. In the majority of these African observations, it is noted a clear prevalence of female as found in our study. However, in the literature the sex-ratio currently tends to balance and the female prevalence seem to interest the chronic articular forms [1].

Indeed, there exist two phenotypes distinct of ASD. A systemic form with noisy polymorphic symptomatology exposing to the severe complications in particular the lymphocytic activation, and a chronic articular form of indolent evolution associated with the presence of arthritis being able to be destroying [1]. Our study is representative of these two clinical forms. The second patient presented the systemic

form while the two others had a chronic articular form.

The diagnosis of ASD is based on a cluster of arguments. On the clinical level, the articular attack primarily related to the knees, ankles and wrists was noted among all our patients. The cutaneous lesions found for 2 patients among 3 were variable. Generally, it is described in ASD a macular skin eruption evanescent localized on the trunk and the root of the members [1] [6].

Our 2nd patient presented however atypical cutaneous manifestations in the form of acquired ichthyosis and pruritic cupboard. Pruritic papules and/or plaques are recently reported in cases of ASD [7]. Most patients in this study had persistent and severe ASD, with a considerable frequency of clinical complications and reactive hemophagocytic syndrome as found in our 2nd observation [7].

In the same way, the neurological attack in the forms of generalized convulsive crises found at the 2nd observation is seldom described during ASD [8].

The most typical hematologic abnormality during ASD is hyperleucocytosis with polynuclear neutrophile [1]. At the opposite, leucopenia being integrated within the framework to a pancytopenia was found in the second case thus making us think of an association with a lymphocytic activation syndrome. Indeed, the presence of cytopenia or the absence of hyperleucocytosis is elements of orientation towards a lymphocytic activation syndrome during ASD [9] [10]. The medullar ponction did not allow to find hemophagocytosis, however in our case. In a series of 52 patients with ASD, 8 presented a reactive hemophagocytic syndrome [11].

Moreover, all our three patients presented a hyperferritinemia higher than 1000 µg/L with reduction of the glycosylated fraction of ferritin. The fall of the glycosylated fraction of ferritin below 20% is a major diagnostic marker of MSA with a specificity of 93% [12]. Glycosylated fraction of ferritin was available in our context but not affordable for our patients with a delay of 4 to 8 weeks before obtaining the results.

In addition, it was noted in all our observations a diagnostic wandering. Our patients attended several medical structures before the diagnosis. They also received various anti-infectious non-successful treatments. This situation is source of important diagnostic delay noticed in most cases reported in sub-Saharan Africa [2] [3] but also in the whole world [13]. This delay is explained partly by the difficulty of differential diagnosis in front of suspected ASD which remain a diagnosis of elimination. Specifically, infectious pathologies must initially be excluded especially in tropical zone making the diagnosis more difficult.

The therapeutic strategy in ASD is still empirical. The first line corticosteroid therapy was efficient for two patients. The acute cortisonic myopathy as side-effects of the corticosteroid therapy are frequently reported and the early addition of cortisonic savings treatment can prevent it [1]. In this case, the introduction of methotrexate allows cortisonic savings with control of articular symptomatology. This molecule is recognized as being the first relay with empirical corticosteroid treatment in this aim [14]. It should be noted that in this systemic form, the blocking of the way of the interleukine-1 by using anakinra is effective, in the case

of cortico-dependence [15]. These therapies are not accessible in our context.

4. Conclusion

ASD is a rare pathology but whose prevalence is probably under estimated in sub-Saharan Africa. Its nonspecific clinical presentation, lack of pathognomonic diagnostic biomarker, and the obligatory exclusion of systemic infectious pathologies before retaining the diagnosis explain the diagnostic difficulties of this pathology in particular in our tropical context. The treatment is not therefore easy with the side-effects of the corticosteroid therapy, optionally associated with methotrexate, but also the inaccessibility of the biotherapies in our areas.

References

- [1] Gerfaud-Valentine, M., Sap, P., Hot, A., Broussolle, C. and Jamilloux, Y. (2015) Data Brought up to Date on Physiopathology, Phenotypes and Treatments of the Disease of Still of the Adult. *Revue de Médecine Interne*, **36**, 319-327.
- [2] Diallo, S., Pouye, A., Ndongo, S., Fall, S. and Diop, T. (2008) Disease of Still of the Adult: Study of 10 Senegalese Observations. *Revue Du Rhumatisme*, **75**, 1105.
- [3] Akintayo, R. and Adelowo, O. (2015) Adult-Onset Still's Disease in a Nigerian Woman. *BMJ Case Reports*. <https://doi.org/10.1136/bcr-2015-210789>
- [4] Yamaguchi, M., Ohta, A., Tsunematsu, T., *et al.* (1992) Preliminary Criteria for Classification of Adult Still's Disease. *The Journal of Rheumatology*, **19**, 424-430.
- [5] Fautrel, B., Zing, E., Golmard, J., *et al.* (2002) Proposal for a New Set of Classification Criteria for Adult-Onset Still Disease. *Medicine (Baltimore)*, **81**, 194-200. <https://doi.org/10.1097/00005792-200205000-00003>
- [6] Efthimiou, P., Paik, P.K. and Bielory, L. (2006) Diagnosis and Management of Adult Onset Still's Disease. *Annals of the Rheumatic Diseases*, **65**, 564-572. <https://doi.org/10.1136/ard.2005.042143>
- [7] Narvaez Garcia, F.J., Pascual, M., Lopez de Recalde, M., *et al.* (2017) Adult Onset Still's Disease with Atypical Cutaneous Manifestations. *Medicine (Baltimore)*, **96**, e6318. <https://doi.org/10.1097/MD.0000000000006318>
- [8] Gallou, T., Gendrot, A., Clement, C., *et al.* (2009) Disease of Still of the Adult and Neurological Attack. *Revue de Médecine Interne*, **30**, S465.
- [9] Michota, J.M., Tamper, M., Galicier, L., *et al.* (2013) The Syndrome of Lymphohistiocytic Activation of the Adult. *Revue de Médecine Interne*, **34**, 85-93.
- [10] Rist, S., Manceron, V., Bartolucci, P., *et al.* (2005) Disease of Still and Leucopenia: In Connection with Two Observations. *Revue de Médecine Interne*, **26**, 670-672. <https://doi.org/10.1016/j.revmed.2005.04.031>
- [11] Hot, A., Toh, M.L., Coppéré, B., *et al.* (2010) Reactive Hemophagocytic Syndrome in Adult-Onset Still Disease: Clinical Features and Long-Term Outcome: A Case-Control Study of 8 Patients. *Medicine (Baltimore)*, **89**, 37-46. <https://doi.org/10.1097/MD.0b013e3181caf100>
- [12] Fautrel, B., Moël, G., Saint-Marcoux, B., *et al.* (2001) Diagnosis Been Worth Of ferritin and Glycosylated Ferritin in Adult Onset Still's Disease. *The Journal of Rheumatology*, **28**, 322-329.
- [13] Park, S. and Pham, C. (2017) Delay in the Diagnosis of Adult-Onset Still's Disease. *Cureus*, **9**, 1321.

- [14] Fautrel, B., Borget, C., Rozenberg, S., *et al.* (1999) Corticosteroid Sparing Effect of Low Amount Methotrexate Treatment in Adult Still's Disease. *The Journal of Rheumatology*, **26**, 373-378.
- [15] Moulis, G., Sailler, L., Astudillo, L., Pugnet, G. and Arlet, P. (2010) May Anakinra Be Used Earlier in Adult Onset Still Disease? *Clinical Rheumatology*, **29**, 1199-1200. <https://doi.org/10.1007/s10067-010-1459-6>