

# Pneumonitis in Adult Onset Still's Disease: Uncommon or Under Diagnosed?

## Pneumonite na Doença de Still do Adulto: Rara ou Subdiagnosticada?



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### ABSTRACT

The adult onset Still's Disease is an uncommon entity characterized by multiple clinical manifestations. Pneumonitis, less often considered, deserves particular emphasis given the need for differential diagnosis and because it can progress to severe respiratory failure. With the aim to highlight the pulmonary parenchyma involvement in patients with adult onset Still's Disease, we present a case report which progresses with pneumonitis.

**Keywords:** Lung Diseases/etiology; Pneumonia/etiology; Still's Disease, Adult-Onset/complications

### RESUMO

A doença de Still do adulto é uma entidade pouco comum que se caracteriza por manifestações clínicas muito variadas. A pneumonite, menos frequente, merece particular destaque dado a necessidade do seu diagnóstico diferencial e pela possível progressão para insuficiência respiratória grave. Com o objetivo de destacar a relevância do envolvimento do parênquima pulmonar na doença de Still do adulto, descrevemos um caso clínico que cursou com pneumonite.

**Palavras-chave:** Doença de Still de Início Tardio/complicações; Doenças do Pulmão/etiologia; Pneumonia/etiologia

### INTRODUCTION

Adult onset Still's disease (AOSD), described by Bywaters in 1971, is an uncommon systemic inflammatory disease characterized by multiple clinical manifestations, with fever, evanescent rash and arthritis as the more frequent ones.<sup>1</sup> Regarding laboratory tests, stands out leukocytosis with neutrophilia, increased erythrocyte sedimentation rate and serum ferritin levels.<sup>2</sup> The prevalence of lung involvement varies according to the sample and the structure of the published studies, and pleuritis is the most common manifestation.<sup>3,4</sup> Although less often considered, pneumonitis deserves particular emphasis given the need for differential diagnosis and because it can progress to severe respiratory failure.<sup>3</sup>

In order to highlight the importance of pulmonary parenchyma involvement in AOSD, we describe a case report that progresses with pneumonitis.

### CASE REPORT

A 35-year-old black woman, Jehovah's witness, with previous diagnosis of unspecified hemoglobinopathy, presented with odynophagia, fever and evanescent mildly pruritic maculopapular skin rash in the upper and lower limbs, which disappeared during afebrile periods. One month after the beginning of the symptoms, she was treated with amoxicillin plus clavulanic acid. Due to maintenance of the symptoms, later associated with mild productive cough, with mucoid sputum, and myalgia she was admitted to the emergency room. Physical examination documented fever (38.3°C), tachycardia (108 bpm), hyperemic pharyngeal mucosa, mildly pruritic maculopapular skin

rash and Koebner phenomenon detected in the trunk and extremities. Chest auscultation did not reveal any abnormal respiratory sounds. Regarding laboratory tests: hemoglobin (Hb) - 10.4 g/dL; mean corpuscular volume - 68.9 fL; mean corpuscular hemoglobin - 21.8 pg; leucocyte count 25510/ $\mu$ L with 88.2% neutrophil; aspartate aminotransferase - 58 U/L; lactate dehydrogenase - 869 U/L and C-reactive-protein(CRP) - 25.3 mg/dL. Chest radiography did not display any alterations. She was then admitted to the Hematology Department with the diagnosis of hemolytic crisis, which was not confirmed. Since infectious etiology was hypothesized, she started empirical antibiotic therapy. During hospitalization, and despite antibiotic escalation (ceftriaxone, meropenem), the patient maintained recurrent fever, even though no infectious agent was isolated. Furthermore, she presented polyarthritis, abdominal pain, generalized lymphadenopathy and decreased bibasal respiratory sounds but no adventitious breath sounds at chest auscultation. She maintained mild productive cough, with mucoid sputum. Chest radiograph was repeated revealing diffuse patchy infiltrates and small bilateral pleural effusion (Fig. 1). Abdominal ultrasound showed hepatosplenomegaly and a small amount of free peritoneal fluid. Computerized tomography (CT) scan documented densification with a mosaic pattern in the lung parenchyma, predominantly in the upper lobes, and moderate bilateral pleural effusion, conditioning passive atelectasis of the lower lobes (Fig.s 2A, 2B). It also showed generalized lymphadenopathy and hepatosplenomegaly. Bronchoscopy was performed, and the microbiological tests

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Figure 1 - Chest radiography - diffuse patchy infiltrates and small bilateral pleural effusion

of bronchial secretions and bronchoalveolar lavage were negative. Histopathological study revealed lung tissue with inflammation, pneumocytes hyperplasia and fibrosis (Fig. 3). Still stands out the negativity for other microbiological (blood and urine culture), serological tests, immunological tests, and tuberculin sensitivity test. Ferritin value was 2861.7 ng/mL, the sickling test was positive, and the hemoglobin electrophoresis showed 33.1% hemoglobin S and 1.2% hemoglobin F.

AOSD diagnosis was admitted, and the patient began therapeutics with prednisone (60 mg/day). Given the Hb value of 6.6 g/dL and the refusal of the patient to perform erythrocyte concentrate transfusion, she was treated with darbepoetin and folic acid. At the fourth day of steroid therapy the patient was afebrile and progressive regression of the remaining disease manifestations was documented. Laboratory evolution was also favorable (Table 1). Chest CT scan, performed two weeks later, displayed complete resolution of parenchymal and pleural abnormalities. After 28 days of hospitalization she was discharged for the outpatient clinic, remaining asymptomatic.

## DISCUSSION

In the absence pathognomonic symptoms, signs or laboratory findings in AOSD, the diagnosis is based on clinical and laboratorial findings, and exclusion of other diseases. Our patient met the Yamaguchi major criteria (fever, arthralgia, typical rash, leukocytosis), four minor criteria (sore throat, lymphadenopathy and/or splenomegaly, liver dysfunction, and negative immunologic study) and rheumatic, infectious and neoplastic diseases were excluded or were very unlikely.<sup>5</sup>

The pulmonary manifestations in AOSD patients include pleurisy, acute or chronic pneumonitis and functional anomalies.<sup>3</sup> However, pulmonary complications that threaten the patient's life, such as the syndrome of acute

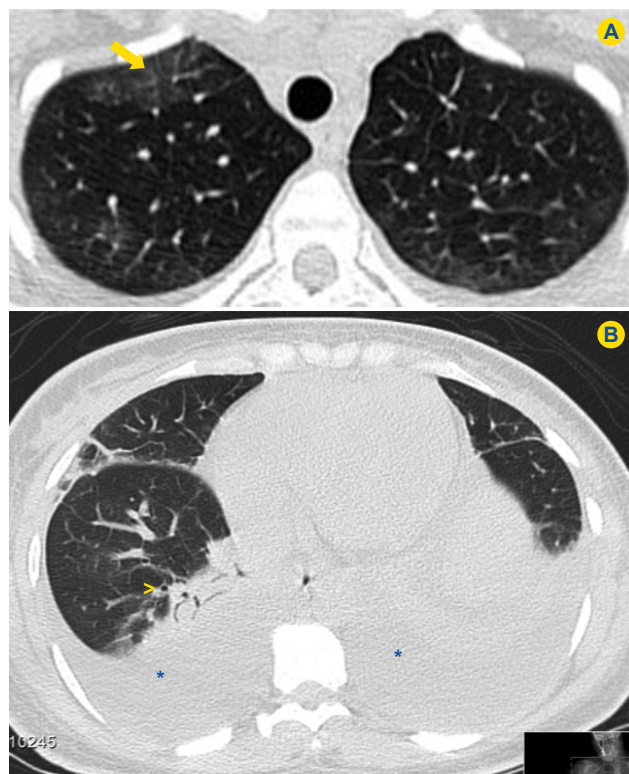


Figure 2 - Chest CT: densification with a mosaic pattern (arrow) in the lung parenchyma, predominantly in the upper lobes (A), and moderate bilateral pleural effusion (asterisk), conditioning passive atelectasis of the lower lobes (arrow head) (B)

adult respiratory distress and diffuse alveolar hemorrhage, are rare.<sup>4,6,7</sup> When present, the most frequent respiratory symptoms are cough, pleuritic chest pain and mild dyspnea. Pleuritis is the most common pulmonary manifestation, and can be present in up to 53% of patients.<sup>6</sup> Regarding pneumonitis, and according to the main studies (Table 2), it affects from 1.9% up to 27% of patients.<sup>3,6-13</sup> This variability may reflect the sample size, the follow-up duration and the distinct demographic characteristics. Described in 27% of the reported cases by Pouchot et al, pulmonary infiltrates are transient, usually associated to pleural effusion, and are frequently located in the lower or upper lobes, as observed in our patient.<sup>6</sup> A longer period of follow-up, with an average of 72 months, can explain a higher frequency of pulmonary involvement in this Canadian study.<sup>6</sup> Furthermore, pneumonitis can be the initial form of this

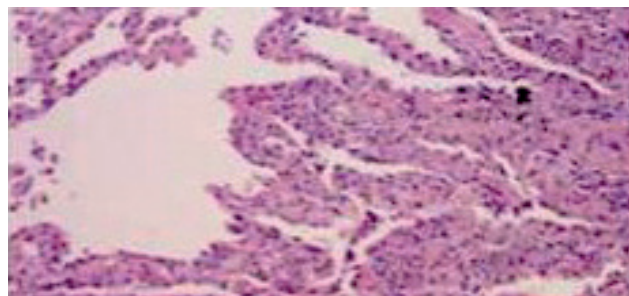


Figure 3 - Lung biopsy- lung tissue with inflammation, pneumocytes hyperplasia and fibrosis

Table 1 - Analytical parameters evolution

|                    | 18 / 2  | 21 / 2 | 2 / 3    | 13 / 3    | 26 / 3  | 23 / 5  |
|--------------------|---------|--------|----------|-----------|---------|---------|
| Hb (g/dL)          | 10.4    | 9.2    | 8.1      | 6.6       | 9.6     | 12.4    |
| Leukocytes (cel/L) | 25 510  | 22 240 | 16 760   | 7800      | 12 520  | 7930    |
| Neutrophils (%)    | 88.2    | 92.2   | 83.5     | 78.3      | 70.7    | 67.4    |
| ESR (mm/h)         |         |        |          | 105       | 104     | 12      |
| Ferritin (ng/mL)   |         | 2861.7 | 57 480.3 | 35 318.4  | 9371.6  | 557.1   |
| Creatinine (mg/dL) |         | 0.52   | 0.31     | 0.4       | 0.47    | 0.6     |
| AST/ALT (U/L)      | 63 / 59 |        | / 100    | 130 / 117 | 41 / 36 | 17 / 29 |
| LDH (U/L)          | 869     | 1328   | 1407     | 1701      | 830     |         |
| CRP (mg/dL)        | 25.3    | 31.3   | 30,7     | 18        | 3.89    | < 0.04  |

Hb: haemoglobin; ESR: erythrocyte sedimentation rate; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; CRP: C-reactive protein

Table 2 - Pulmonary involvement in AOSD series

| Study                        | n  | Pleuritis (n/%) | Pneumonitis (n / %) | Source; Notes   |
|------------------------------|----|-----------------|---------------------|---|
| Reginato, 1987 <sup>8</sup>  | 23 | 5% / 21.7%      | 2% / 8.7%           | USA   |
| Ohta, 1990 <sup>9</sup>      | 90 | 11% / 12.2%     | 5% / 5.6%           | Japan   |
| Pouchot, 1991 <sup>6</sup>   | 62 | 33% / 53%       | 17% / 27%           | Canada; 1 case of interstitial pneumonitis progressed to ARDS |
| Zeng, 2009 <sup>4</sup>      | 61 | 11% / 18%       | 7% / 11.5%          | China; pleurisy and pneumonia associated with worse prognosis |
| Cagatay, 2009 <sup>10</sup>  | 84 | 8% / 9.5%       | 3% / 3.6%           | Turkey  |
| Riera, 2011 <sup>11</sup>    | 41 | 6% / 14.6%      | 2% / 4.9%           | Spain   |
| Chen, 2012 <sup>12</sup>     | 61 | 7% / 11.5%      | 3% / 4.9%           | China   |
| Baxevanos, 2012 <sup>7</sup> | 22 | -               | 1% / 4,5%           | Greece; 1 case of fatal ARDS                                  |
| Kim, 2012 <sup>13</sup>      | 54 | 11% / 20.4%     | 1% / 1.9%           | Korea   |

n: number of patients; ARDS: acute respiratory distress syndrome; USA: United States of America

disease, associated to fever, leukocytosis with neutrophilia and elevated acute phase proteins, leading to consider the diagnosis of pneumonia.<sup>14</sup>

Actually, pulmonary involvement may be more frequent than currently thought. Indeed, a clinical case described by Zhao and colleagues, where no signs or symptoms of lung involvement were documented, revealed a slight lung inflammatory infiltrate at the time of autopsy, suggesting that transient inflammatory infiltrates in the lung parenchyma may occur asymptotically and may not be detected in the chest radiograph.<sup>15</sup> Histopathological findings, previously described in the literature, like nonspecific interstitial fibrosis, acute alveolitis with thickening of the alveolar walls, hyperplasia of type II pneumocytes, hyaline membrane formation, and lymphocytic infiltrate, include those found in our patient. Angiitis has not been described.<sup>3,15</sup>

Generally, pulmonary involvement has a favorable clinical evolution, but studies on prognosis of these patients are limited.<sup>3</sup> A retrospective review suggested that interstitial pneumonia and pleurisy, as well as high levels of ferritin and persistent fever after three days of treatment with prednisone 1 mg/kg/day were factors of less favorable prognostic.<sup>4</sup> In this case report there was a complete resolution of the lung involvement after initiation of corticosteroid therapy at the dose of 1 mg/kg/day of prednisolone, in accordance with current clinical practice.

The clinical report described highlights AOSD pulmonary involvement in the form of pneumonitis, which may be more frequent than we currently expect given its, probably often, silent course. Furthermore, although usually associated to a favorable clinical progression, pneumonitis has been reported as a negative prognostic factor, requiring appropriate diagnosis, with exclusion of potentially fatal pulmonary events, and therapeutics.

#### PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association.

#### DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

#### CONFLICTS OF INTEREST

All authors report no conflict of interest.

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## Family Phenotypic Heterogeneity Caused by Mitochondrial DNA Mutation A3243G

## Heterogeneidade Fenotípica de uma Família Causada pela Mutação no ADN Mitocondrial A3243G



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## ABSTRACT

Maternally inherited diabetes and deafness is a rare form of diabetes caused by a mitochondrial DNA mutation. The index case is a 55-year-old woman who was admitted with hypertrophic cardiomyopathy. She had a history of diabetes mellitus and hearing loss. The patient's mother, two brothers and two sisters also had a history of diabetes and hearing loss. This pattern suggests a maternally inherited disorder. All siblings carried the A3243G mitochondrial DNA mutation. The identification of people with monogenic forms of diabetes mellitus is a diagnostic challenge. This condition should be considered whenever there is a history of diabetes associated with hearing loss and a relevant family history. Cardiopathy is also known to be an important feature of mitochondrial disease. In order to identify this aetiology, family screening, genetic counselling and screening of associated comorbidities are encouraged.

**Keywords:** Child; Deafness/genetics; Diabetes Mellitus/genetics; DNA, Mitochondrial/genetics; Mutation

## RESUMO

A síndrome diabetes e surdez de transmissão materna é uma forma rara de diabetes que resulta da mutação A3243G do ADN mitocondrial. Expõe-se o caso de uma doente do sexo feminino, 55 anos de idade, admitida por cardiomiopatia hipertrófica. A doente possui antecedentes de diabetes mellitus e surdez. Da história familiar, destaca-se a mãe e os seus dois irmãos e duas irmãs, que apresentam diabetes e surdez. Este padrão sugere uma doença de herança materna. Todos são portadores da mutação A3243G do ADN mitocondrial. A identificação de pessoas com formas monogénicas de diabetes mellitus é um desafio diagnóstico. Deve ser considerado sempre que há história de diabetes associada a surdez e história familiar de diabetes. A cardiomiopatia hipertrófica é uma característica importante da patologia mitocondrial. Nestes doentes deve ser considerada a avaliação da família, aconselhamento genético e triagem de comorbilidades associadas.

**Palavras-chave:** Criança; Diabetes Mellitus/genética; DNA Mitocondrial/genética; Mutação; Surdez/genética

## INTRODUCTION

Diabetes mellitus (DM) and its clinical features may arise as a result of genetic disorders.<sup>1</sup> Mitochondrial diabetes encompasses a group of pathologies that are caused by a dysfunction of the mitochondrial respiratory chain.<sup>2</sup>

Maternally inherited diabetes and deafness (MIDD) is a rare form of DM. The most common mutation in MIDD results from the presence of an A instead of a G in the

position 3243 (A3243G) of the mitochondrial DNA (mtDNA) that encodes the gene for tRNA. Other mitochondrial DNA point mutations have been associated with MIDD, but are extremely rare.<sup>2</sup>

The condition is maternally inherited as mitochondrial DNA is practically only derived from oocytes.<sup>3</sup> Some pathophysiological mechanisms that may lead to

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