

## **Case study**

### **AA amyloidosis secondary to Horton's disease complicated by pulmonary fibrosis. A Very Challenging Diagnosis and therapy.**

#### **Abstract**

AA amyloidosis is a classic and serious complication of many chronic inflammatory processes, whether of infectious, autoimmune, or neoplastic origin. It is frequently complicated by kidney damage, often in the form of a nephrotic syndrome. Giant cell arteritis is a common inflammatory arteritis in the elderly; however, it rarely causes AA amyloidosis. We report a rare case of Horton disease causing AA amyloidosis in an elderly patient with history of myopericarditis and repeated episodes of congestion heart failure. Patient was treated initially with dual therapy based on corticoids and anti TNF therapy (Tocilizumab) associated with heart failure therapy recommended by the European society of cardiology (ESC 2022). The initial outcome was favorable but later complicated by the involvement of the lungs, pulmonary fibrosis, responsible for repeated episodes of pleural effusion non controlled in spite of high dose of loop diuretics and repeated pleural puncture. Patient died shortly after her second hospitalization due to respiratory insufficiency.

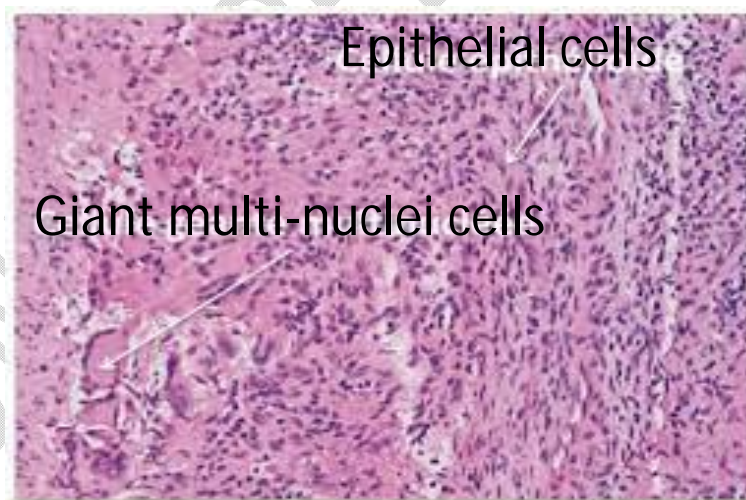
**Keywords:** Horton disease, AA amyloidosis, pulmonary fibrosis, Cardiac MRI, corticosteroids and Tocilizumab.

#### **Introduction**

Horton's disease is an inflammatory gigante-cellular arteritis, selectively affecting the large arteries, and in particular the branches of the external carotid artery. Arterial involvement can affect other trunks and be expressed by variable symptomatology depending on the territories concerned [1]. AA amyloidosis is a classic and serious complication of many chronic inflammatory processes, whether of infectious, autoimmune, or neoplastic origin. It is frequently complicated by kidney damage, often in the form of a nephrotic syndrome. Giant cell arteritis is a common inflammatory arteritis in the elderly; however, it rarely causes AA amyloidosis [2, 19]. We report a rare case of gigante-cellular inflammatory arteritis causing AA amyloidosis in a 73-year-old elderly subject complicated by the onset of pulmonary fibrosis whose therapeutic management was very challenging.

#### **Case Report**

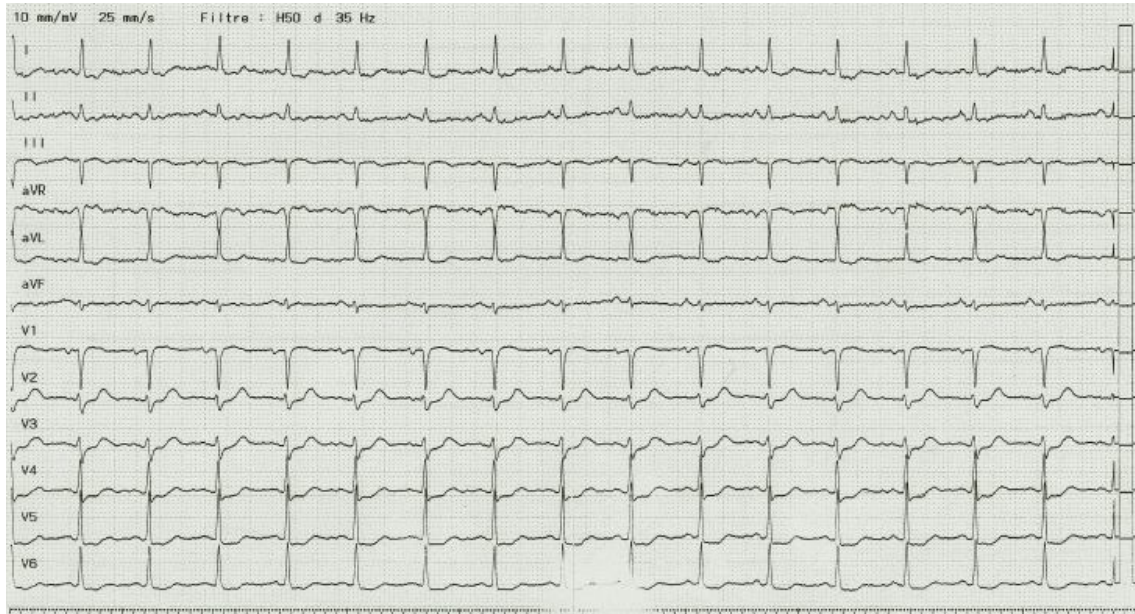
73-year-old elderly patient was brought by non-medical rescuers to the emergency department for worsening dyspnea that had been evolving for 2 weeks without sudden chest pain. Noted that the patient had two repeated episodes of congested heart failure with preserved ejection fraction requiring hospitalization, the first of which, myopericarditis (involved in the median and basal segments of the heart walls associated with pericardial effusion) was confirmed by cardiac MRI which was treated by medical therapy including beta-blockers (bisoprolol), converting enzyme inhibitor (Ramipril) and furosemide with good clinical outcome. Five months later the patient was re-hospitalized for suspected Horton's disease in front of clinical symptoms of clustered headaches radiating to the jaw (jaw claudication) and dizziness without loss of vision orodynophagia, not relieved by usual analgesia associated with congested heart failure whose decompensating factor was an acute bacterial pneumopathy. A biopsy of the temporal artery revealed inflammatory arteritis with giant cells (Figure 1) for which the patient was put on corticosteroid therapy alone with a marked improvement and in view of the difficulty in reducing the dose of corticosteroids; a combination therapy, immunotherapy (anti-TNF therapy) with Tocilizumab (ROACTEMRA) associated with corticosteroid therapy was initiated in the patient with regression of symptoms allowing the diagnosis of Hortons disease to be retained.



**Figure 1:** Histology findings after biopsy of the right temporal artery: transverse cut section: showing giants multi-nuclei cells.

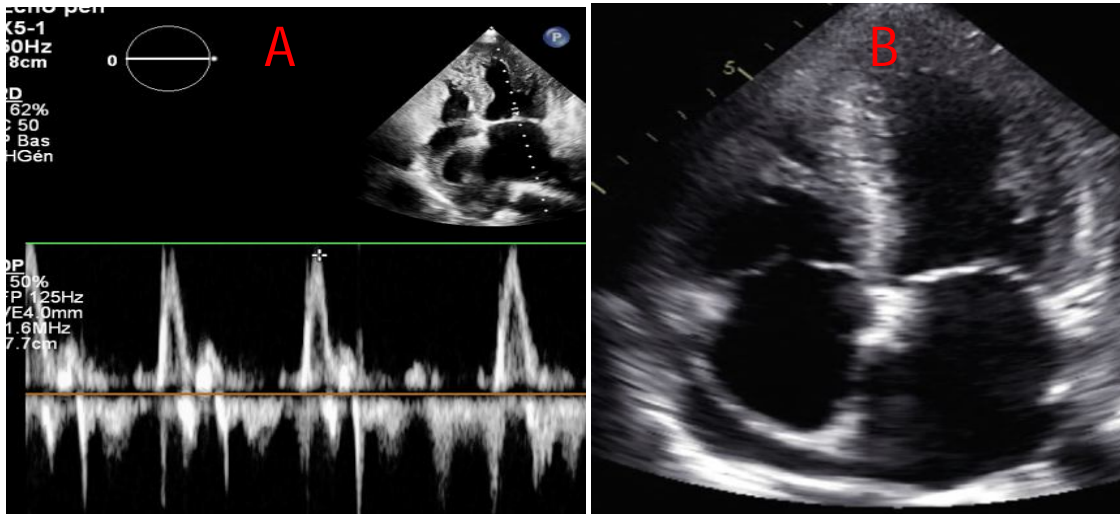
This time, the patient was hospitalized for an attack of predominantly left-sided heart failure with NYHA stage III dyspnea, 85% desaturation on room air without signs of peripheral hypoperfusion. Cardiorespiratory examination

found bilateral crackles symmetry at mid-pulmonary fields, left basal predominantly fluid effusion syndrome, slight tachycardia at 110 beats per minutes (bpm) with a decline in general condition. Electrocardiogram performed objectified a regular sinus rhythm at 100 bpm with biphasic T waves in the lower lateral peripheral leads in changed compared to his old electrocardiogram (Figure 2).

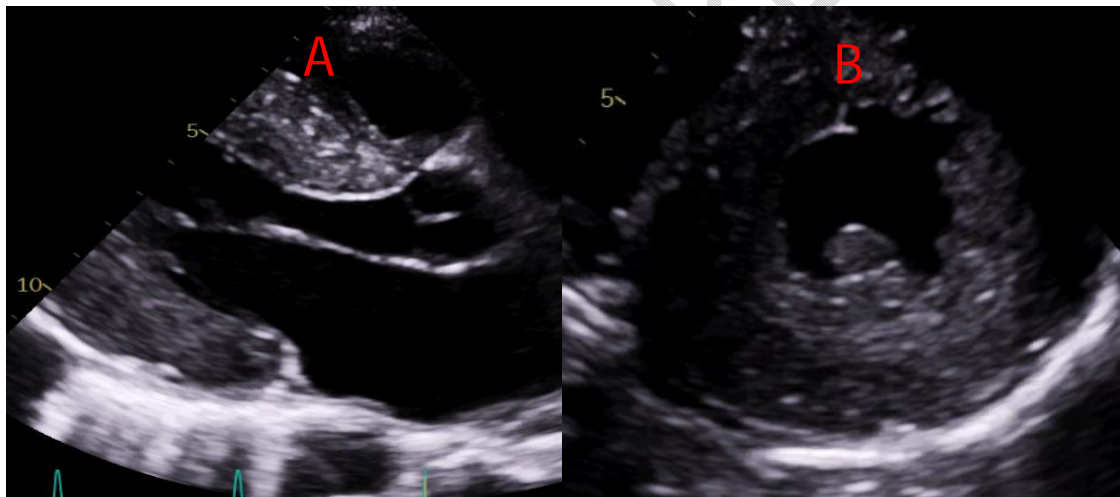


**Figure 2:** Electrocardiogram: Sinus tachycardia at 110 bpm with biphasic T waves in lower lateral peripheral leads.

The result of the transthoracic echocardiography was surprising with an aspect of a strong hypertrophy heart disease probably amyloid in front of a significant myocardial hypertrophy with a predominance location on the septum measuring 15mm wide with systolic dysfunction of the left ventricle, hypertrophy of the interauricular septum measuring 11mm wide, moderate thickness of the heart valves; mitral and tricuspid valve, restrictive mitral flow with moderate mitral insufficiency, minimal pericardial effusion on lateral wall of the right atrium (Figure 3 and 4) irrelevant to the echocardiography findings during his first hospitalization.



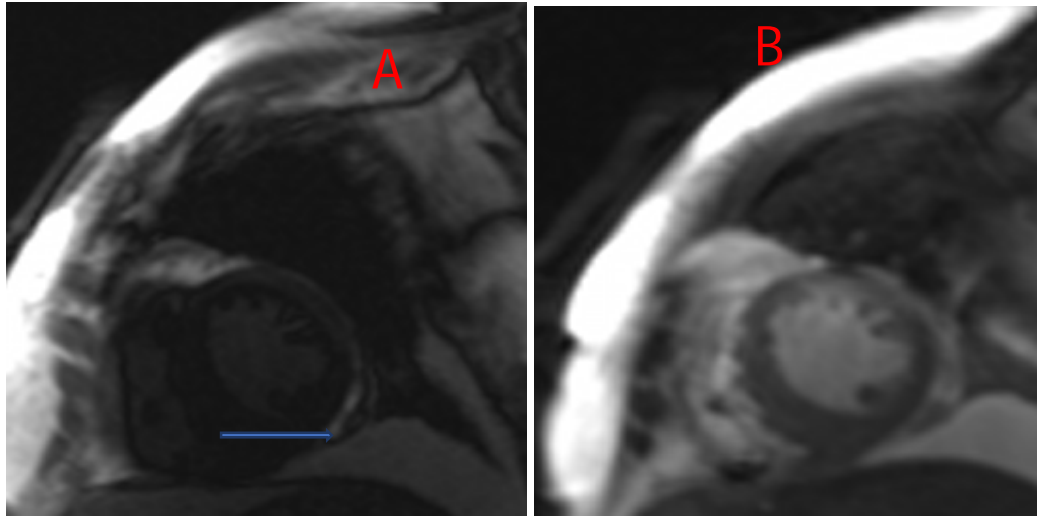
**Figure 3 :** Trans thoracic echocardiography (TTE): A – Continuous wave Doppler at the junction of the mitral valve showing a restrictive mitral flow. B-4 chambers apical view showing minimal pericardial effusion of the lateral wall of the right atrium.



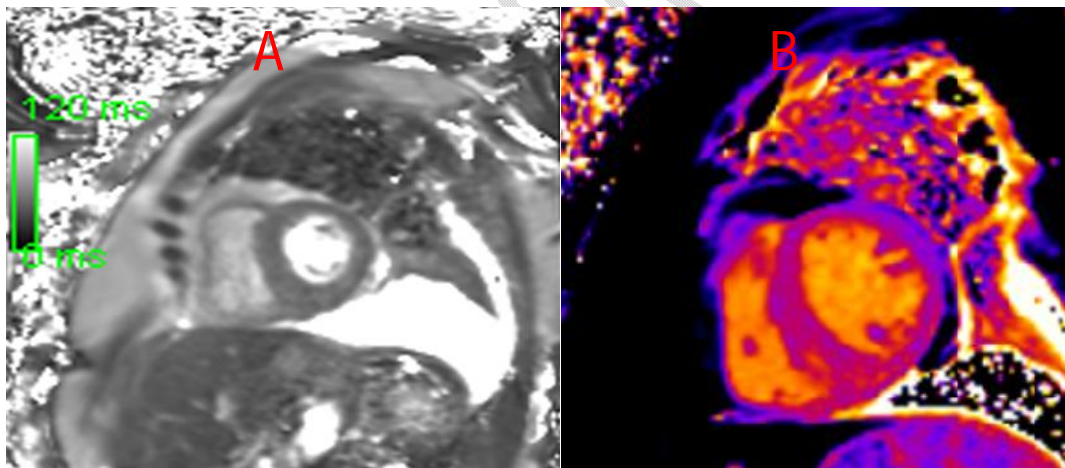
**Figure 4:** TTE: A- Parasternal long axis view showing hypertrophy of the left ventricular with a septum measuring 15mm. B-Short axis view showing a global hypertrophy of the left ventricle.

The initial NT pro BNP levels were high at 22,000 ng/l with a negative C-reactive protein level and moderate renal failure with creatinine at 110umol/l, eGFR (estimated glomeruli function) 45ml/min, negative urine analysis. Patient put on furosemide (Lasilix 125mg/24hr) in IVS with oxygen therapy under 4 liters of oxygen goggles. The diagnostic and etiological confirmation of cardiac amyloidosis was completed by electrophoresis of serum proteins by venous samples which objectified a drop in immunoglobins. Bone scintigraphy was not

in favor of transthyretin amyloidosis with a semi-quantitative visual score of zero. Cardiac MRI confirms the diagnosis of cardiac amyloidosis, showing late diffuse epicardial enhancement and onset of myocardial fibrosis (Figure 5 and 6).



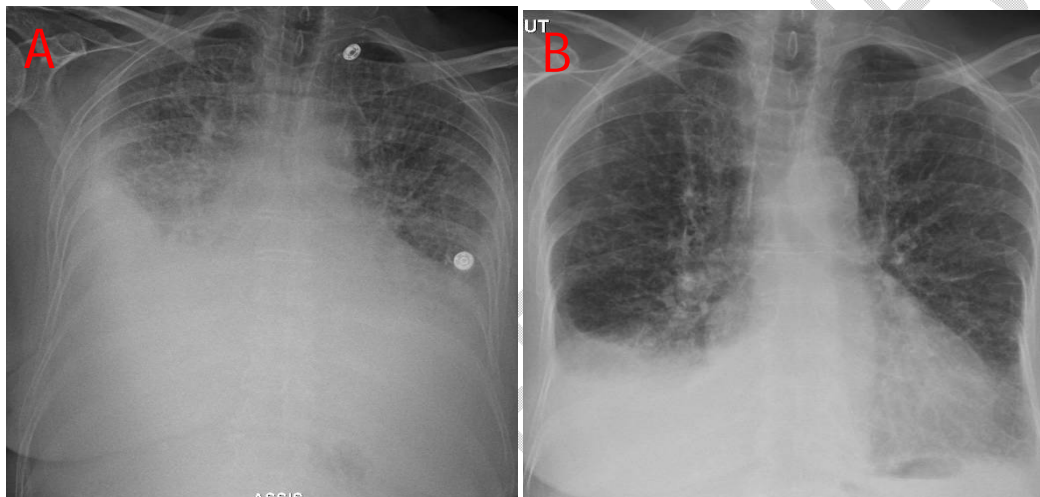
**Figure 5:** Cardiac MRI: A- T2 hypersignal showing late diffuse epicardial enhancement and onset of myocardial fibrosis (blue arrow). B- Hypertrophy of the left ventricle



**Figure 6:** Cardiac MRI: A- T2 mapping: showing hypertrophy of the left ventricle and fibrose diffuse epicardial. B- T1 mapping showing hypertrophy of the left ventricle more important at the septum with diminution gadolinium due to fibrose development en favor of amyloidosis.

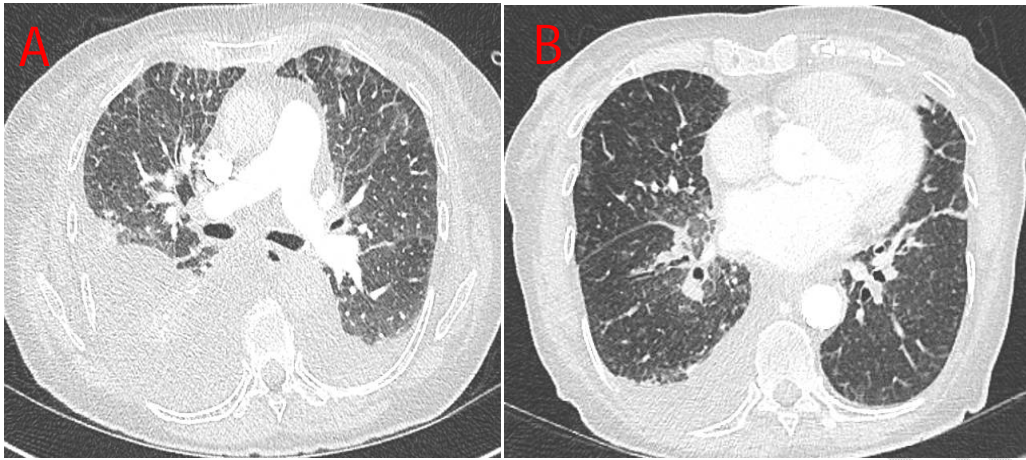
Up to this point, AA amyloidosis secondary to his autoimmune vasculitis (Horton's disease) was suspected. The treatment was reinforced by injectable corticosteroid therapy, Methylprednisolone (sulomedrol) 60mg IV for 10 days before dose regression, maintaining its dual therapy as background treatment

for Horton's disease. At the initiation of the recess treatment, the patient was orthopnea with significant respiratory discomfort. A chest x-ray performed on the patient showed a bilateral pleural effusion of great abundance on the left, (Figure 7A) punctured with removal of 750ml of clear liquid without post puncture complication probably of hemodynamic origin for which loop diuretics were increased to 500mg/24hr in electric syringe. A second pleural puncture on the right side with the removal of 650cc of clear liquid was carried out in front of the non-improvement of the respiratory difficulty. A favorable evolution was observed in the patient with regression of the NT pro BNP levels to 14000 ng/l versus 22000 ng/l initially and regression of the pleural effusion on control chest X-ray (Figure 7B).



**Figure 7:** chest X-ray: A- showing bilateral pleural effusion more important on the left lung associated with interstitial syndrome. B-Regression of pleural effusion after puncture with removal of 750ml on the left pleural space and 650ml on the right pleural space respectively.

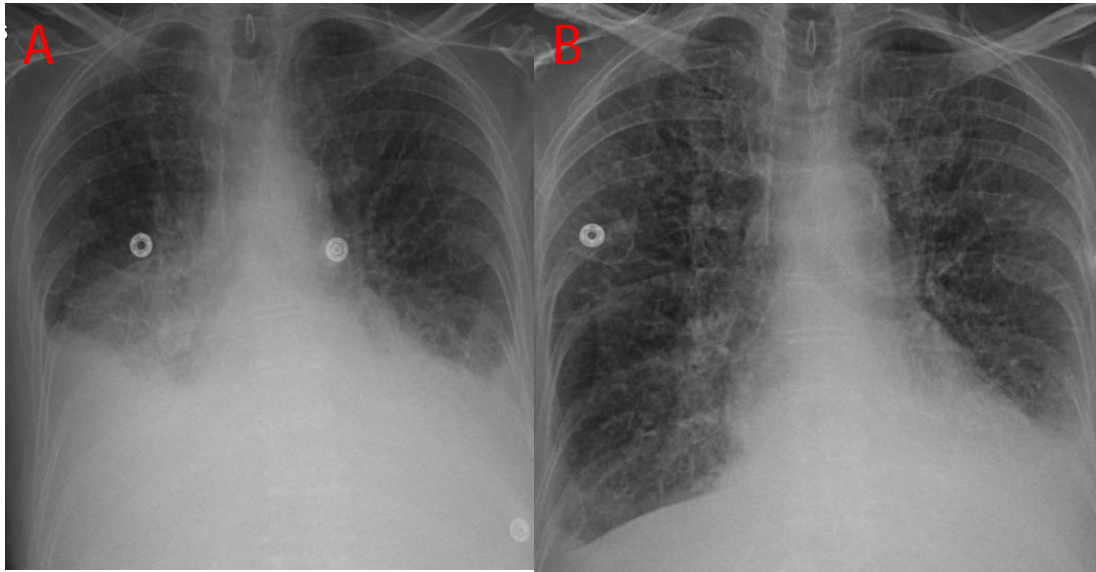
A chest CT angiography was performed to look for secondary pulmonary involvement which showed resorption of the posterior pleural effusion with persistence of a left postero-basal effusion blade estimated at 34 mm (versus 47 mm), stability of the mediastinal adenomegaly, diffuse and bilateral reticulation with images of thickening of the inter intra lobular septa at the level of the upper lobes with peri-bronchial right hilar thickening, thickening of the interlobular septa in the bilateral antero-basal and next to left S8 (related to an early fibrosis) compared to the pulmonary CT angiography performed 2 months previously (Figures 8).



**Figure 8:** computed tomography chest scan (CT scan): A- Before pleural puncture, showing abundant bilateral pleural effusion and alveolo-interstitial syndrome with thickening interlobular septa (lung fibrosis) and adenomegaly. B- After pleural puncture, showing regressed pleural effusion and stabilized mediastinal adenomegaly.

Faced with this marked clinico-biological improvement, a biopsy of the accessory salivary glands performed and research of "Bence Jones" proteins by urinary protein electrophoresis was negative which finally affirmed our diagnosis of AA amyloidosis. The etiological treatment of AA amyloidosis, which is Horton's disease was maintained, by bolus corticosteroid therapy associated with basic treatment of Tocilizumab, one injection per week plus prednisolone 5mg per day. The evolution was spectacular with complete weaning of the patient from oxygen with a good hemodynamic state. A close consultation every 2 weeks for the first 2 months then spaced was programmed for better control of his disease and optimization of treatment of heart failure. One of the challenges that we faced in the patient was the difficulty of lowering the dose of furosemide due pulmonary involvement of the disease. The haptoglobin assay was negative before discharge, which was our reference marker for inflammation.

2 months after discharge, the patient re-consulted for progressively worsening dyspnea, the chest X-ray of which showed a very abundant pleural effusion on the right with withdrawal of 1400cc of serous fluid by pleural puncture (Figure 9).



**Figure 9:** chest X-ray: A- showing recurrent moderate to abundant pleural effusion of the right lung. B- showing regressed pleural effusion post pleural puncture with persistent interstitial syndrome.

The patient was put on loop diuretics (furosemide 500mg/24hr IV by electrical syringe). A clear and initial improvement observed, the control chest X-ray showed fibrotic infiltrates of the bronchi and septa. Patient died 48 hours later due to respiratory insufficiency complicated by congestive heart failure due to rapid residual of pleural effusion.

### **Discussion**

AA amyloidosis (AAAm) is a rare disease, the incidence of which is estimated at approximately 1 to 2 cases per million inhabitants per year, according to certain European studies [3]. It is a pathology that can occur during various chronic inflammatory processes, of which inflammatory rheumatism, chronic infections, autoinflammatory diseases, and Crohn's disease are the most frequent causes [4]. During these diseases, the continual secretion of pro-inflammatory cytokines (in particular:  $\text{TNF}\alpha$ , IL-1, IL-6, etc.) is at the origin of a stimulation of the synthesis, mainly hepatic, of serum amyloid A (SAA), one of the proteins involved in the inflammatory response. Amyloid protein form deposits adopting a  $\beta$ -folded, congophilic structure, which are associated, as in any form of amyloidosis, with the P component and the matrix glycosaminoglycans. These amyloid deposits can occur in many organs (kidneys, liver, spleen, digestive tract, heart, adrenals, etc.), within which the parenchymes will then be disorganized, thus leading to a functional deficit [5].

AA amyloidosis is a serious complication associated with various inflammatory disorders [6]. Vasculitis, an autoimmune chronic inflammatory disease, is characterized by elevated levels of acute phase proteins, including SAA and CRP, similar to other inflammatory disorders [7,18]. We described an elderly patient with Horton disease with repeated episodes of congestive heart failure secondary AA amyloidosis almost simultaneously with temporal arteritis. In the present case, persistent vascular inflammations caused by Horton disease for five months was regarded as the primary inflammatory focus for AA amyloidosis. After intensive workup, cardiac MRI affirmed amyloidosis with the exclusion of another types of amyloidosis with the lack of possibility to do myocardial biopsy due to patient's condition. We concluded that the repeated episodes of congestive heart failure and the presence of Horton disease was caused by cardiac AA amyloidosis secondary to temporal arteritis (Horton disease). The most frequent clinical manifestations of AA amyloidosis are renal dysfunction and proteinuria [8]. However, AA amyloidosis induced by Horton disease is a rare entity and only few cases are reported [1,6]. Thus, it is important the carry out exhaustive cardiac and extra cardiac screening for AA amyloid deposits [9]. In our case patient had a moderate renal failure due to cardio-renal syndrome type 1 frequent in heart failure patient with systolic dysfunction under loop diuretics.

The severity and durations of the primary inflammatory diseases may contribute to the development of AA amyloidosis [10]. In the present case, patient was stabilized on her symptoms of Horton disease with combined therapy of corticosteroid and Tocilizumab (TCZ) but not on the inflammatory level of the disease. Thus, controlling certain inflammatory markers such as haptoglobin was crucial compared to CRP which can be falsely negative during TCZ treatment [11]. The durations between clinical manifestations of AA amyloidosis and the underlying inflammatory diseases can vary [12]. Studies investigating AA amyloidosis in RA patients reported that the period of latency between the onset of rheumatoid arteritis and AA amyloidosis are 17–26 years [13]. Our case of AA amyloidosis which was almost simultaneously complicated with the new onset on temporal arteritis; Horton disease (approximately five months).

Positive histology is required for the diagnosis of amyloidosis, but a negative result does not exclude the presence of amyloidosis. In general, histology is a very poor method to establish the extent or distribution of amyloid, as deposits can be patchy [9]. In our case cardiac MRI affirmed the diagnosis as myocardial biopsy was not carried out due to patient condition.

Organ involvement and staging of AA amyloidosis should be established to design the treatment plan. For cardiac function, evaluation should include an echocardiogram with an assessment of strain, NT-proBNP, troponins, ECG, Holter ECG, and cardiac MRI should be solicited and for kidney function, evaluation 24-hour urinary protein and eGFR are needed. Liver function tests and imaging (ultrasound (US), MRI, or CT scan) can help with hepatic function assessment [14]. In our case, pulmonary fibrosis started developing in spite of re-enforced treatment of Horton disease aggravating respiratory function due to repeated pleural effusion non-controlled by high-dose loop diuretics.

The mainstay of temporal arteritis (Horton disease) treatment is glucocorticoid therapy [14]. However, the Giant-Cell Arteritis Actemra (GiACTA) trial showed that tocilizumab (TCZ) greatly increased the rate of sustained remission of giant cell arteritis [15]. The ability of tocilizumab to improve AA amyloidosis complicated with RA has already been reported in a case-control study [16] as well as in Horton disease [1]. In our case, clinical symptom like dyspnea was persistent due to lung involvement whereas Horton disease was controlled. Thus, explaining the pejorative prognosis in our patient raising the question; if Horton disease was lately diagnosed due to masked symptoms of congestive heart failure initially with conserved systolic function or other causes as her medical history noted a myocarditis of which its etiology was not elucidated. It has been reported that Horton disease could be responsible for CD4<sup>+</sup>-rich lymphocyte alveolitis [20] causing dyspnea and pleural effusion. In our case both mechanisms; pulmonary infiltration by AA amyloidosis and Horton disease could be responsible for patient respiratory symptoms. It's known that congestive heart failure accounts for the death of about 40% of patients that have primary systemic amyloidosis [17]. Further studies in the near future should be conducted to evaluate the efficacy of TCZ in AA secondary to Horton disease and the interest of other therapeutic classes; anti-IL 1 therapy, anti-T-cell therapy in stabilizing amyloid deposit.

### **Conclusion**

In conclusion, we described a temporal arteritis patient with refractory congestive heart failure due to high probability of AA amyloidosis. The present case suggests that refractory congestive heart failure and Horton disease was a consequence of AA amyloidosis. Although the underlying mechanisms for the rapid occurrence of this rare association between Horton disease and amyloidosis remain unclear. AA amyloidosis remains a life-threatening disease,

with an unmet need for prevention and effective treatment, thus, treatment of amyloidosis involves a multidisciplinary approach. Depending on the disease severity and the organs affected a clinical hematologist, cardiologist, nephrologist, pathologist, or other subspecialty specialists can be involved.

### **ETHICAL APPROVAL**

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

### **CONSENT**

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

### **Reference**

1. W. Ammouri , H. Tassine, A. Maghraoui, H. Khibri, M. Maamar, Z. Tazi Mezalek, H. Harmouche, M. Adnaoui. Amylose AA compliquant une maladie d'Horton traitée avec succès par du tocilizumab. Revmed.2019 ; 10 : 150
2. J.-P. Hamelin, G. Cardon , M. Reberolle , F. Moulonguet , Y. Neugebauer , G. Raybaud , V. Gnemmi , E. Hachulla. Giant cell aortitis complicated by AA amyloidosis diagnosed with imaging techniques: Report of a case. Revmed.2016; 03: 009
3. B. Bienvenu et al. "Groupe d'étude français des artérites des gros vaisseaux (GEFA)", under the aegis of the "Filière des maladies auto-immunes et auto-inflammatoires rares (FAI(2)R)". Management of giant cell arteritis: recommendations of the French Study Group for Large Vessel Vasculitis (GEFA). Rev Med Interne:2016.
4. C. Agard et al. Abdominal aortic involvement in active giant cell (temporal) arteritis: a study of 20 patients by Doppler ultrasonography and computed tomographic angiography. Presse Med:2009.
5. A. Mekinian et al. Usefulness of imaging in large vessel vasculitis. Rev Med Interne: 2016.
6. Shuhei Yoshida, Haruki Matsumoto, Jumpei Temmoku, Norshalena Shakespear, Yuichiro Kiko, Kentaro Kikuchi, Yuya Sumichika, Kenji Saito, Yuya Fujita, Naoki Matsuoka, Tomoyuki Asano, Shuzo Sato, Eiji Suzuki, Hiroshi Watanabe, Hiromasa Ohira<sup>3</sup> and Kiyoshi Migita. Case report: Rapid development of amyloid A amyloidosis in temporal arteritis with SAA1.3 allele; An unusual case of intestinal amyloidosis secondary to temporal arteritis. Front Immunol. 2023; 21:1144397.

7. Gillmore JD, Lovat LB, Persey MR, Pepys MB, Hawkins PN. Amyloid load and clinical outcome in AA amyloidosis in relation to circulating concentration of serum amyloid a protein. *Lancet*. 2001; 358 :24–9.
8. Lachmann HJ, Goodman HJ, Gilbertson JA, Gallimore JR, Sabin CA, Gillmore JD, et al. Natural history and outcome in systemic AA amyloidosis. *N Engl J Med*. 2007 ; 356 :2361–71.
9. Riccardo Papa, Helen J. Lachmann. Secondary, AA, Amyloidosis. *Rheum Dis Clin N Am*. 2018; 04 :006.
10. Baba S, Masago SA, Takahashi T, Kasama T, Sugimura H, Tsugane S, et al. A novel allelic variant of serum amyloid a, SAA1 gamma: Genomic evidence, evolution, frequency, and implication as a risk factor for reactive systemic AA-amyloidosis. *Hum Mol Genet*. 1995 ; 4 :1083–7.
11. H. S. Lyons, V. Quick, A. J. Sinclair, S. Nagaraju, S. P. Mollan. A new era for giant cell arteritis. *Eye* (2020) 34:1013–1026.
12. Lachmann HJ, Goodman HJ, Gilbertson JA, Gallimore JR, Sabin CA, Gillmore JD, et al. Natural history and outcome in systemic AA amyloidosis. *N Engl J Med*.2007 ;356 :2361–71.
13. Pamuk ON, Donmez S, Pamuk GE, Puyan FO, Keystone EC. Turkish Experience in rheumatoid arthritis patients with clinical apparent amyloid deposition. *Amyloid*. 2013; 20:245–50.
14. Proven A, Gabriel SE, Orces C, O'Fallon WM, Hunder GG. Glucocorticoid therapy in giant cell arteritis: Duration and adverse outcomes. *Arthritis Rheum*. 2003; 49:703–8.
15. Stone JH, Tuckwell K, Dimonaco S, Klearman M, Aringer M, Blockmans D, et al. Trial of tocilizumab in giant-cell arteritis. *N Engl J Med*. 2017 ; 377:317–28.
16. Okuda Y, Ohnishi M, Matoba K, Jouyama K, Yamada A, Sawada N, et al. Comparison of the clinical utility of tocilizumab and anti-TNF therapy in AA amyloidosis complicating rheumatic diseases. *Mod Rheumatol*. 2014; 24:137–43.
17. Desai HV, Aronow WS, Peterson SJ, Frishman WH. Cardiac amyloidosis: approaches to diagnosis and management. *Cardiol Rev*. 2010;18:1-11.
18. M. Delplanque, J. Pouchot , S. Ducharme-Bénard , B.J Fautrel , A. Benyamine , L. Daniel , T. Gendre , G. Grateau , S. Georgin-Lavialle. AA amyloidosis secondary to adult-onset Still's disease: About 19 cases. *Semarthrit*.2019; 50; 156-165.
19. Giant cell arteritis "causing" AA-amyloidosis with rapid renal failure. Strasser F, Hailemariam S, Weinreich T, Speich R, Salomon F. *Schweiz Med Wochenschr*. 2000 ;130:1606-9.

20.Madiha Mahfoudhi, Habiba Mamlouk, Sami Turki, Adel Kheder. Maladie de Horton révélée par une dyspnée. Pamj.2015 ; 20 :465.

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