Case study

AA amyloidosissecondary 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 congestive heart failure. Patient was treated initially with dual therapy based on corticosteroids and anti TNF therapy (Tocilizumab) associated with heart failure therapy recommended by the European society of cardiology (ESC 2021 guidelines on Heart Failure). 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 punction. Patient died shortly after her second hospitalization due to respiratory insufficiency.

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

Abbreviations

AAAm: AA amyloidosis

IL: Interleukin

MRI: Magnetic Resonance Imaging

NYHA: New York Heart Association

NT pro-NBP: N-Terminal pro B-type Natriuretic Peptide

TNF: Tumor Necrosis Factor

S8: 8^{th} segment of the left lung

Introduction

Horton's disease is an inflammatory giganto-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 elderlysubjects; however, it rarely causes AA amyloidosis [2]. We report a rare case of giganto-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 female 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 congestive 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), angiotensin converting enzyme inhibitor (Ramipril) and furosemide with a 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 or odynophagia, not relieved by usual analgesia associated with congestive heart failure whose decompensating factor was an acute bacterial pneumopathy. A biopsy of the temporal artery was done revealed an 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.

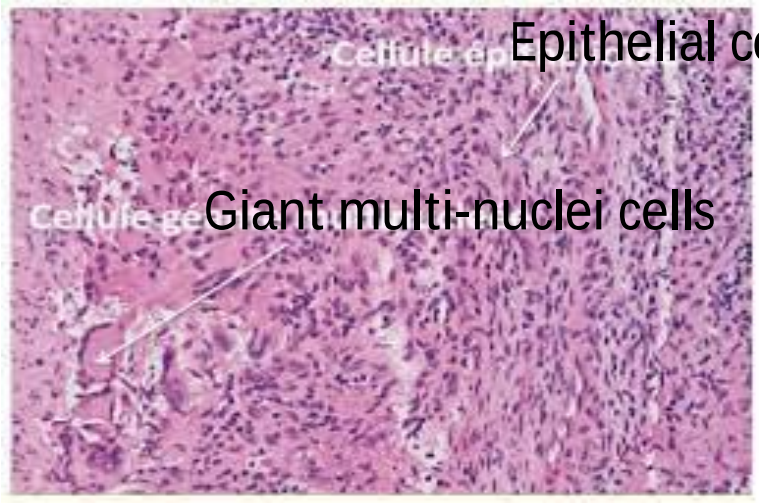

Figure 1: Histology findings after biopsy of the right temporal artery: transverse cut section: showing giants multi-nuclei cells.

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 par 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 lateralperipheralleads in changed compared to herprevious electrocardiogram (Figure 2).

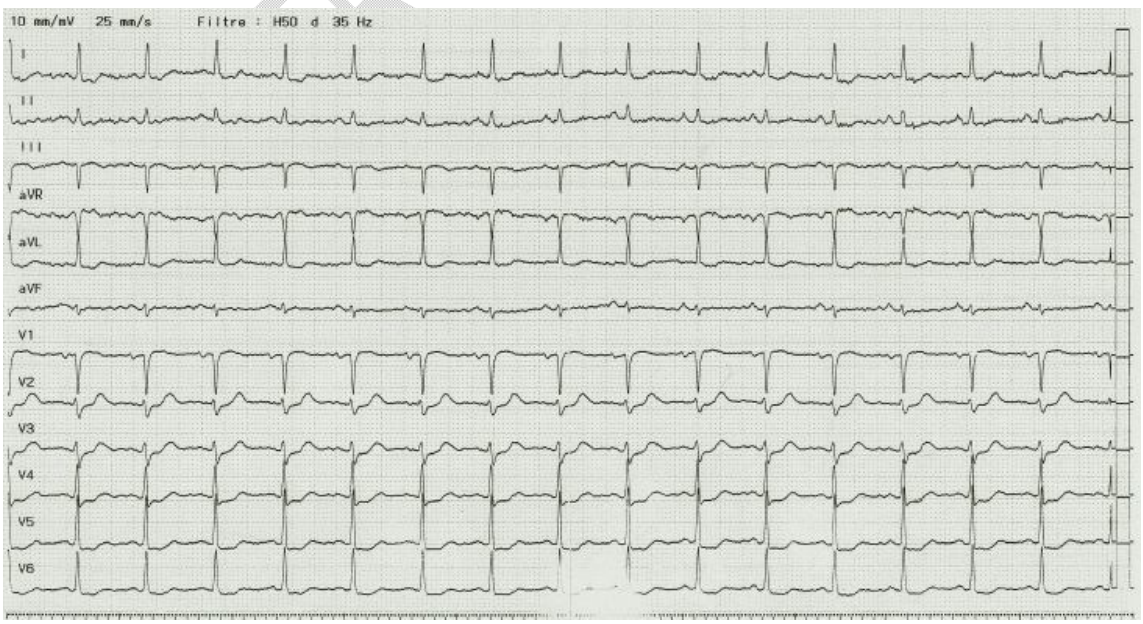

Figure 2: Electrocardiogram: Sinus tachycardia at 110 bpm with biphasic T waves in lower lateral peripheral leads.

The result of the transthoracic echocardiography was surprising with an aspect of a strong hypertrophic heart disease probably amyloid origin in front of a significant myocardial hypertrophy with a predominance location on the inter ventricular septum measuring 15mm wide with systolic dysfunction of the left ventricle. A hypertrophy of the interatrial 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.

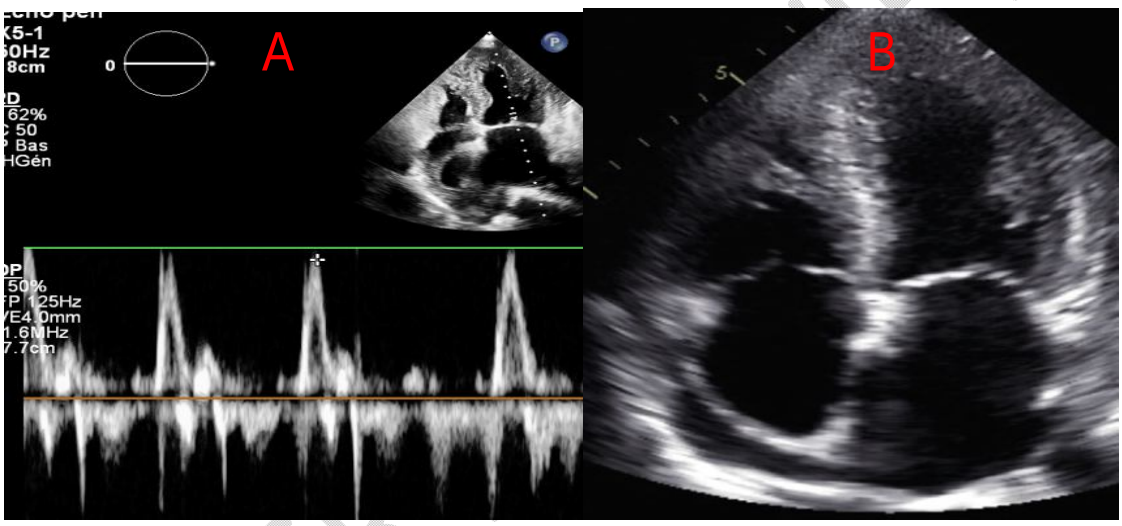

Figure 3 : Trans thoracic echocardiography (TTE): A – Continuous wave Doppler at the jonction of the mitral valve showing a restrictive mitral flow.B-4 chambers apical view showing minimal pericardial effusion of the lateral wall of the right atrium.

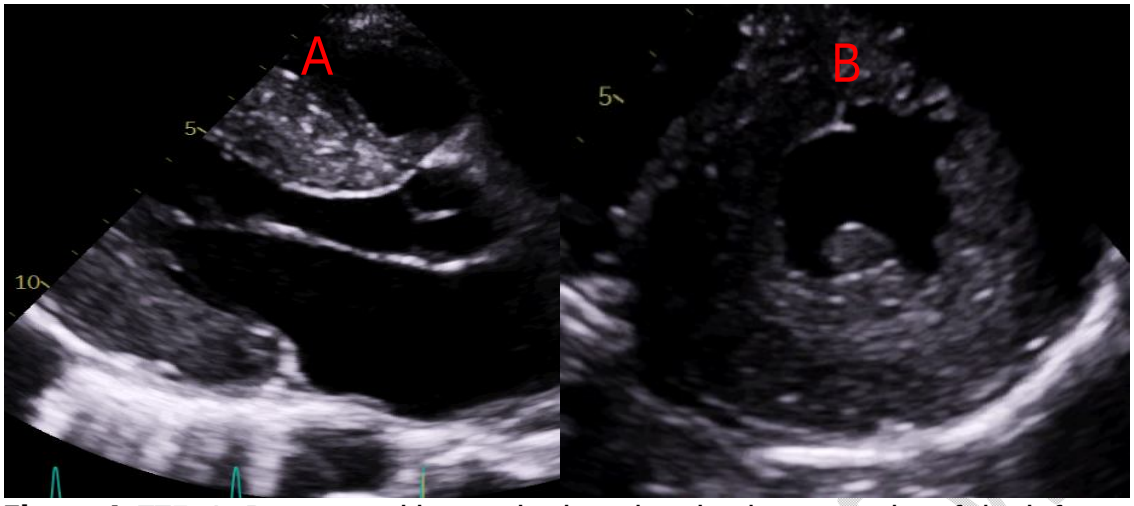

Figure 4: TTE: A- Parasternal long axis view showing hypertrophy of the left ventricular with a septum measuring 15mm. B-Short axis view showing a global hypertrophy of the left ventricle.

The initial NT pro BNP enzyme level washigh 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) of45ml/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).

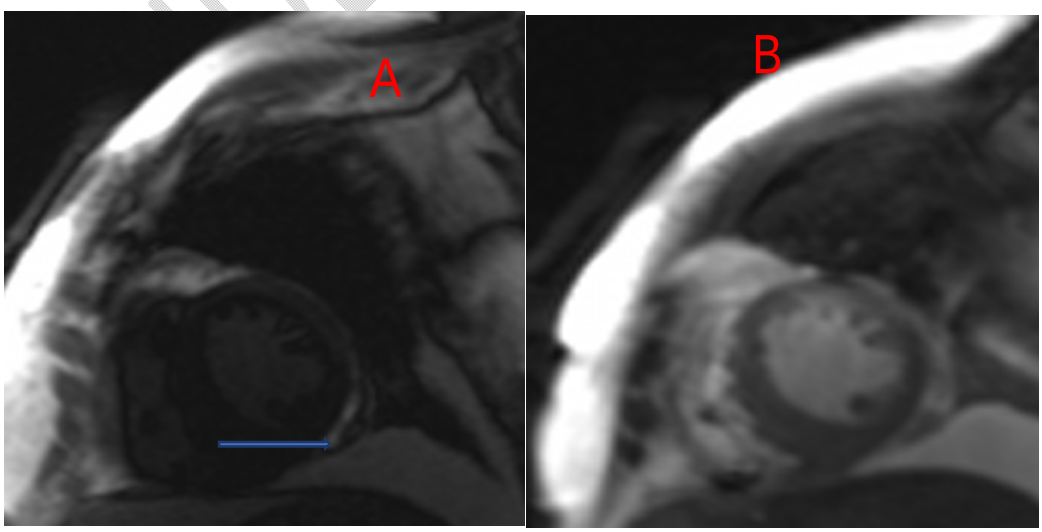

Figure 5: Cardiac MRI: A- T2 hypersignal showing late diffuse epicardial enhancement and onset of myocardial fibrosis (blue arrow).B- Hypertrophy of the left ventricule

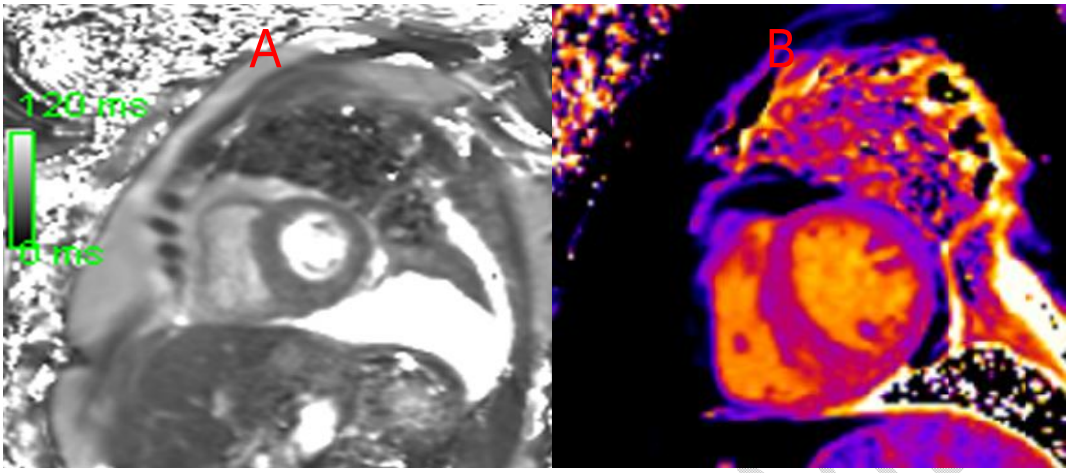

Figure 6: Cardiac MRI: A- T2 mapping: showing hypertrophy of the left ventricule and fibrose diffuse epicardial. B- T1 mapping showing hypertrophy of the left ventricule more important at the septum with diminution godalinium due to fibrose developpment en favor of amyloidosis.

Up to this point, AA amyloidosis secondary to her autoimmune vasculitis (Horton's disease) was suspected. The treatment was reinforced by injectable corticosteroid therapy, Methylprednisolone (sulomedrol) 60mg par dayintravenously for 10 days before dose regression while maintaining her 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-side,(Figure 7A) punctured with removal of 750ml of clear liquid without post puncture complication probably ofhemodynamic 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 650ml of clear liquid was carried out in front of the non-improvement of the respiratory difficulty in the patient.A favorable evolution was observed with regression of the NT pro BNP enzymelevels to 14000 ng/l versus 22000 ng/l initiallyas well as regression of the pleural effusion confirmed on the control chest X-ray (Figure 7B).

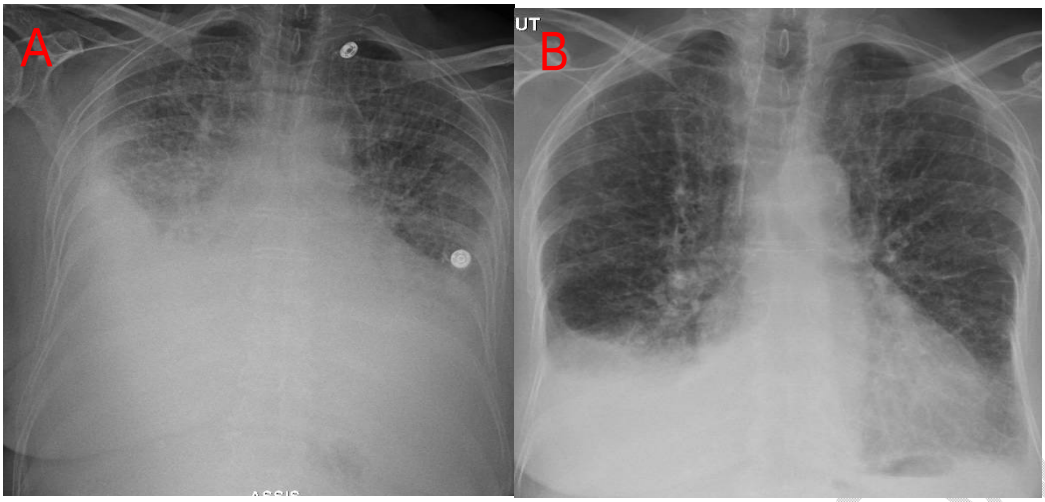

Figure 7: chest X-ray:A- showing bilateral pleural effusion more important on the left lung associated with interstitial syndrome. B-Regression of pleural effusion after punction with removal of 750ml on the left pleural space and 650ml on the right pleural space respectively.

A chest CT angiography was performed to look for secondary pulmonary involvement of AA amyloidosis 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).

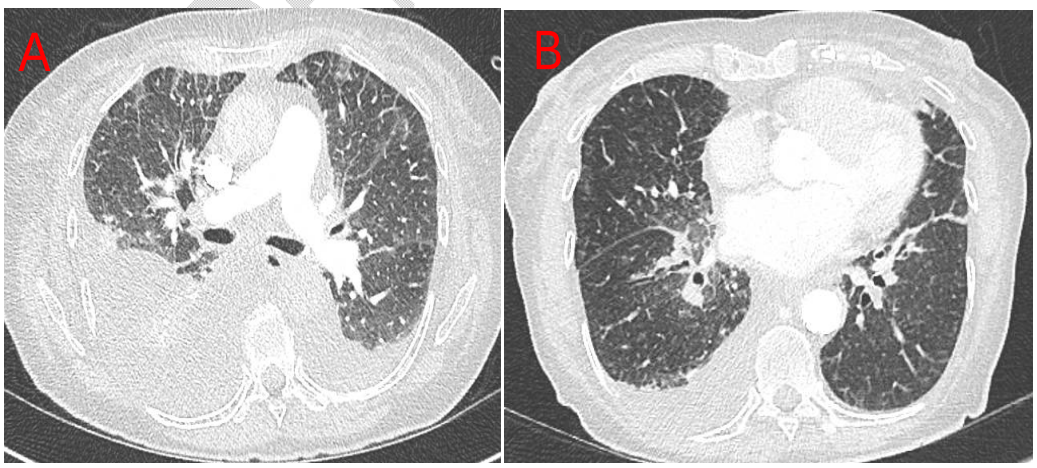

Figure 8: computed tomography chest scan (CT scan): A- Beforepleural punction, showing abundant bilateral pleural effusion and alveolo-interstitial syndrome with thickening interlobular septa (lung fibrosis) and adenomegaly.

B- After pleural punction, showing regressed pleural effusion and stabilized mediastinal adenomegaly.

Faced with this marked clinico-biological improvement, a biopsy of the accessory salivary glands performed and researchof “Bences Jones” proteins by urinary protein electrophoresis was negativewhich finally affirmed our diagnosis of AA amyloidosis. The etiological treatment of AA amyloidosis, which is Horton's disease was maintained, by bolus corticosteroid therapy (60mg per day for 7 days then oral therapy) associated with basic treatment of Tocilizumab(ROACTEMRA 162mg/0,9ml, subcutaneous injection pen), 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 her disease and optimization of treatment of heart failure. One of the challenges that we facedin 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-side with withdrawal of 1400ml of serous fluid by pleural punction (Figure 9).

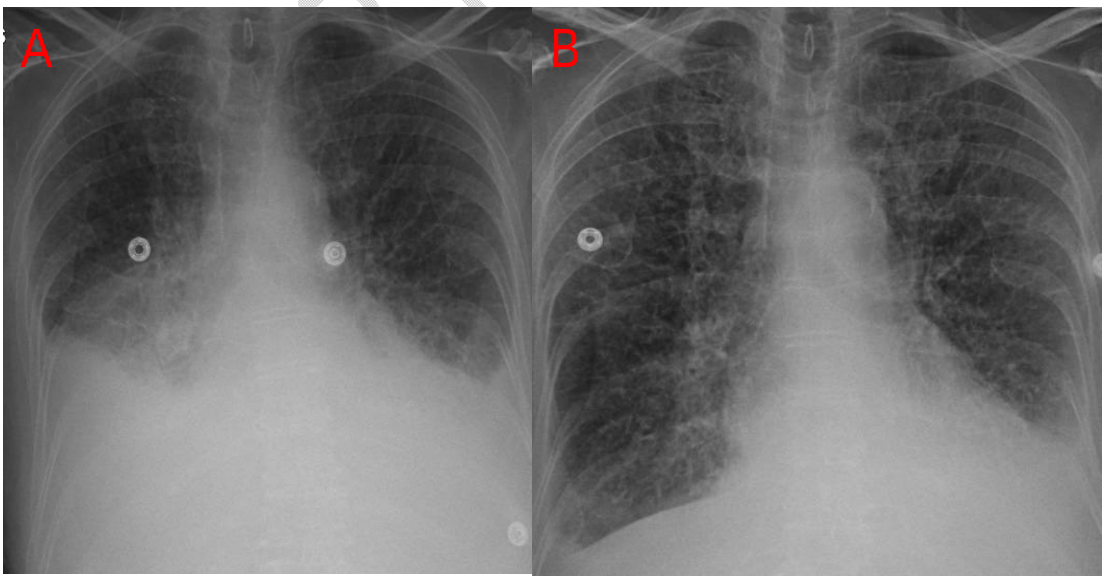

Figure 9: chest X-ray: A- showing recurrent moderate to abundant pleural effusion of the right lung. B- showing regressed pleural effusion post pleural punction with persistent interstitial syndrome.

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 in spite repeated pleural punction.

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: TNFα, 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 β-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 variousinflammatory disorders [6]. Vasculitis, an autoimmune chronicinflammatory disease, is characterized by elevated levels of acutephaseproteins, including SAA and CRP, similar to otherinflammatory 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 thepresent case, persistent vascular inflammations caused by Horton disease for fivemonths was regarded as the primary inflammatory focus for AAamyloidosis.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 mostfrequent clinical manifestations of AA amyloidosis are renaldysfunction 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 reportedthat the period of latency between the onset of rheumatoid arteritis and AAamyloidosis are17–26 years [13]. Our case of AAamyloidosis 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 resultdoes not exclude the presence of amyloidosis. In general, histology is a very poormethod to establish the extent or distribution of amyloid, as deposits can be patchy[9, 19]. 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 kidneyfunction, evaluation24-hour urinary protein and eGFR are needed. Liver function tests andimaging (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 tocilizumabto improve AA amyloidosis complicated with RA has already beenreported in a case-control study [16] as well as in Horton disease [1]. In our case, clinical symptom like dyspnea was persistent due to lungs involvement whereas Horton disease was controlled.Thus, explaining pejorative prognosis in our patient raising the

question; if Horton disease was lately diagnosed due to masked symptoms ofcongestive heart failure initially with conserved systolic function or other causes as her medical history noted a myopericarditis of which its etiology was not elucidated. It has been reported that Horton disease could be responsible to CD4+-rich lymphocyte alveolitis [20] causing dyspnea and pleural effusion. In our case both mechanism;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% ofpatients that have primary systemic amyloidosis[17]. Further studies in the near should be conducted to evaluate the efficacity of TCZ in AAAm 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 probable of AA amyloidosis. The present case suggests that refractory congestive heart failure and Horton disease was a consequence of AAamyloidosis. Although the underlying mechanisms for the rapidoccurrence of this rare association between Horton disease and amyloidosisremain 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).

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