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Pulmonary *Aspergillus fumigatus* and *Cryptococcus neoformans* Co-Infection on an Underlying Sarcoidosis Condition: Report of a Rare Case

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Abstract

Sarcoidosis is a systemic granulomatosis from an unknown etiology, particularly affecting the lungs and the lymphatic system. It is associated with an immune deficiency involving an excessive immune response mediated by TH1 lymphocytes. Its evolution can lead to serious complications such as pulmonary fibrosis, pulmonary hypertension, bronchial stenosis and opportunistic infections. Opportunistic infections rarely occur on an underlying sarcoidosis condition. We report a rare case of pulmonary aspergillary and cryptococcal co-infection, on a patient with sarcoidosis who was finally lost to follow up. It was about a 47 years old female patient, diagnosed in 2015 for mediastino-pulmonary and neurological sarcoidosis. She was in therapeutical rupture after a 3-month period of corticotherapy at a dosage of 20 mg daily. The patient has been lost of sight for 3 years and was seen again on November, 22nd, 2018 at the Internal Medicine/Rheumatology Department of DALAL JAMM Hospital. At his admission she presented: a low grade hemoptysia, a chronic cough, a shortness of breath on exertion CRD Stage 2. At the biological investigation, the CRP was at 71.9 mg/l. Calcium serum levels were at 102.6 mg/l. Sputum culture and AFBS were negative. The screening serology of aspergillary Ig G was positive at 12.4 UA/ml. Thoracic High Resonance CT pointed suggests a Stage 2 Sarcoidosis complicated with aspergillary graft. The bronchoscopy showed out a severe suppurated bronchopathy. Microscopic examination of the BAF found some *Cryptococcus neoformans* settlement. We concluded a diagnosis of pulmonary aspergilloma and crypto-

coccosis co-infection with an underlying condition of Stage 2 Sarcoidosis. We successfully treated our patient with an oral intake of Itraconazole at a dosage of 400 mg daily over a period of 10 days. This is a rare and life-threatening triple association. In our case, the patient was lost to follow up for a long period and this was considered as the first morbidity risk factor.

Keywords

Sarcoidosis, Infection, Cryptococcus, Aspergillus

1. Introduction

Sarcoidosis is a non-autoimmune systemic granulomatosis from an unknown etiology, particularly affecting the lungs and the lymphatic system. It is associated with an immune deficiency involving an excessive immune response mediated by TH1 lymphocytes. Its diagnosis is difficult and features clinical, radiological and histological evidences. Due to a diagnosis delay, its evolution can lead to serious complications such as pulmonary fibrosis, pulmonary hypertension, bronchial stenosis and various opportunistic infections. With a severe prognosis on other immunocompromised conditions, these opportunistic infections that occur on a patient with sarcoidosis, are serious therapeutic emergencies that do not lead to death [1].

We report a rare case of pulmonary aspergillary and cryptococcal co-infection, on a patient with sarcoidosis who was finally lost to follow up.

2. Clinical Case

It was about a 47 years old female patient who was admitted three years ago at Le DANTEC Teaching Hospital (Dakar/Senegal) for: paresthesia of the upper and lower limbs, a chronic dry cough, an unappreciated progressive weight loss.

The clinical examination revealed: a chronic dry cough without neither pulmonary condensation syndrome nor crackling, apolyuro-polydipsic syndrome, a peripheral neurogenic syndrome, a poor general appearance Stage 2 of WHO.

The diagnosis of mediastino-pulmonary and neurological sarcoidosis at radiological stage 2 was made on the basis of evocative clinical presentation, hypercalcemia, the presence of mediastinal adenopathies and multiple symmetric pulmonary nodules located at the upper two-thirds of the parenchyma associated with signs of pneumopathy in process of excavation (HR thoracic CT-Scan), TCD4 alveolar lymphocytosis (BAF), sub-acute to chronic polyradiculoneuropathy (ENMG). Investigations for tuberculosis were negative.

Our patient has been treated with prednisone at a dosage of 20 mg per day for 3 months associated with some adjuvant methods and 10 mg of Anafranil three times daily.

The patient has been lost to follow-up for 3 years before she came back on

November 22nd, 2018 at DALAL JAMM hospital (GUEDIAWAYE/SENEGAL).

At that time, she was seen for a recurrent low grade hemoptysis which has been persisting for a week, a chronic cough (for 3 months) ranged from dry to muco-purulent, a shortness of breath on exertion CRD Stage 2 without a chest pain.

Onphysical examination, we found a superficial polypnea at 20 cpm without respiratory distress and cyanosis; chronic productive cough with bloodstained sputum; infectious syndrome made by prolonged fever without chills and sweats, a poor general appearance Stage 2 of WHO.

At the biological investigation, the CRP was increased at 71.9 mg/l. Leukocytes counts were normal without neutropenia neither lymphopenia. Calcium serum levels were normal at 102.6 mg/l. Sputum culture and AFBS were negative. The Angiotensin Converting Enzyme was not measured out.

Thoracic High Resonance CT pointed out bilateral alveolo-interstitial opacities associated with cavities and spread nodules and micronodules (**Figure 1**, **Figure 2**). CT Scan also showed mediastinal adenopathies and a right-sided aspergillary graft. All these aspects suggest a Stage 2 Sarcoidosis complicated with aspergillary graft.

At the bronchoscopy we noted a severe suppurated bronchopathy aspect, a global infiltration of the upper and middle lobe spurs associated with a decrease of the diameter of the bronchial orifices without obstacle (**Figure 3**).

Microscopic examination of the BAF found *Cryptococcus neoformans* settlement and an absence of aspergillus mycelium fibers.

The research of AFBS and the GenExpert performed on the BAF and BK culture on Lowenstein stain were negative.

The screening serology of aspergillary Ig G was positive at 12.4 UA/ml.

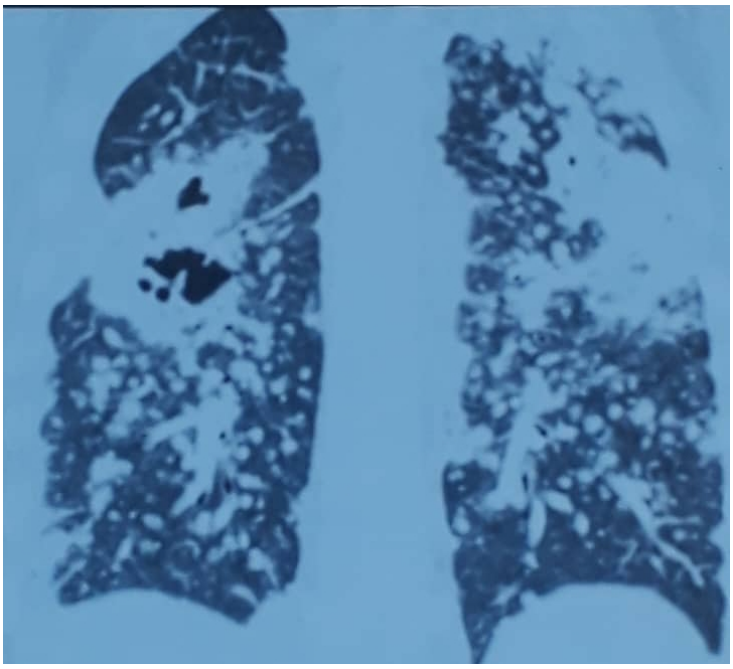

Figure 1. Stage 2 Sarcoidosis complicated with aspergillary graft.

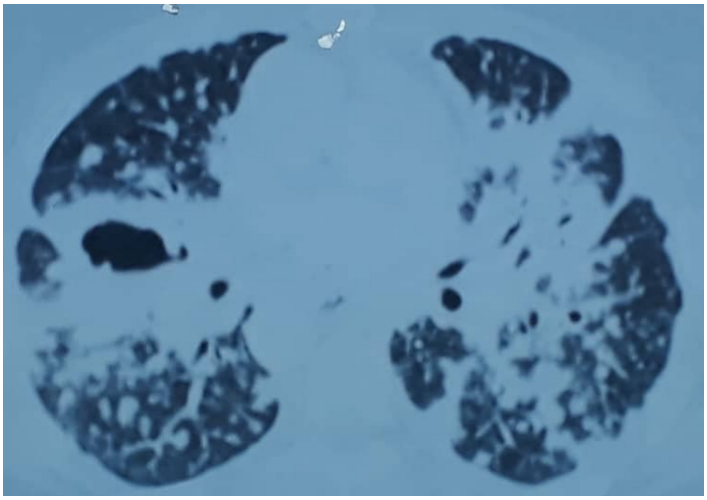

Figure 2. Stage 2 Sarcoidosis complicated with aspergillary graft.

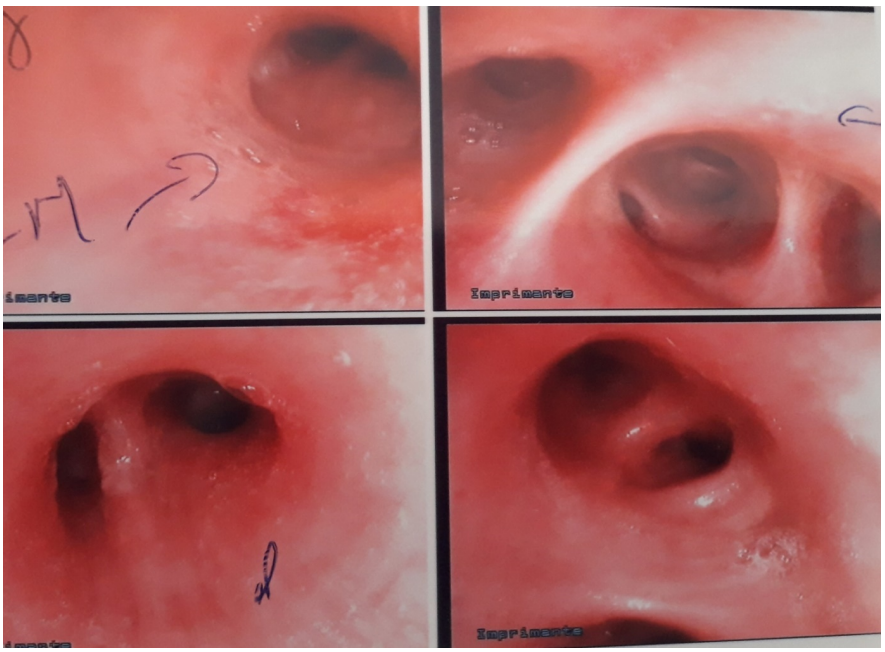

Figure 3. Decrease of the diameter of the bronchial orifices.

We concluded to a diagnosis of pulmonary aspergilloma associated with pulmonary cryptococcosis with underlying condition of Stage 2 Radiograph Sarcoidosis complicated with bronchial stenosis with therapeutic rupture.

Thereby, she was undergoing a daily single-use dosage of 400 mg of Itraconazole during 10 days and a 400 mg/day of fluconazole during 2 months. The time of reintroduction and the dosage of the corticosteroid therapy will be a collective decision at the end of the treatment of these opportunist co-infection.

Under treatment, the evolution was marked by a good clinical improvement marked by the stop of hemoptoic sputum, the disappearance of the cough and the improvement of the general health with the recovery of daily activities. The follow-up of the response to treatment was monthly and based on the clinical

examination and inflammatory assessment. A thoracic CT scans is planned for control after the infectious treatment is completed.

3. Discussion

The diagnosis of sarcoidosis relies on a broad of arguments especially an evocative clinical course, compatible radiological images, the presence of non caseating necrosis epitheloidgiganto-cellular granuloma and the exclusion of others granulomatosis causes. There is no specific biological marker of the disease, leading to a diagnosis delay. In one-third of patients, the disease becomes chronic and active with morbidity outcome. Opportunistic infections rarely occur during sarcoidosis 1% - 10% [2]. This is proven by *Baughman RP* [3] according to some cohort studies. The literature reported only small and isolated series. However sarcoidosis is an inflammatory disease with a paradoxical immune status, a peripheral anergic condition and local inflammatory granuloma formation. It results to a cell-mediated immunedeficiency that can be worsened by the use of corticosteroids and immunosuppressors.

The prevalence of mycosis has increased since many years with the multiplication of patients under immunosuppressive therapy, the increase of patients with organ and bone marrow transplant, the pandemia of HIV infection.

Most common opportunistic infections during sarcoidosis are cryptococcosis, aspergillosis, and mycobacterial infections [4].

Pulmonary aspergilloma is an infection that occurs after a settlement of Aspergillus spores organized into dense mycelial felting from a preformed lung cavity and an impaired immune system. Its incidence in non-neutropenic subjects is increasing.

According to *S. Lachkar* [5], aspergillosis is the most common infectious complication during sarcoidosis. In his studies, *N. Girard* doesn't share the same results [2]. This witness a lack of consent and studies conducted on large cohorts upon opportunistic infections during sarcoidosis. The triggering factors in the occurrence of pulmonary aspergilloma, on an underlying sarcoidosis condition, are the presence of parenchymal fibrocystic lesions, systemic corticosteroid therapy, immunosuppressive treatments and biotherapies, TCD4 lymphopenia, the chronicity of sarcoidosis. However, according to *Baughman RP*, 7 patients recently diagnosed with sarcoidosis and treated with corticosteroids, underwent a fungal infection. This chronological criterion is different from the general propensity but can be attributed to the diagnosis of sarcoidosis [3].

This coexistence is noted in 2% - 12% of cases during sarcoidosis [5]. In the case of our patient, the identified risk factors for aspergillary graft would be an underlying pneumopathy condition in a process of excavation.

Cryptococcosis would be an opportunistic infection usually found during sarcoidosis [6]. Corticosteroid therapy is an irregularly reported immunosuppressive factor [3]. However, even asymptomatic sarcoidosis is a predicting factor of *Cryptococcus neoformans* infection [6]. This could be related to a peri-

pheral immune impairment associated to sarcoidosis. Though, lymphopenia has never been found in our patient. Sarcoidosis itself is the single underlying factor identified, suggesting the existence of immune complex mechanisms that need to be highlighted. Nevertheless, *Boyton RJ* suggests that *Cryptococcosis neoformans* pathogenesis depends on the virulence of the infesting stem [7]. The existence of histological similarities between sarcoidosis and cryptococcosis are some likely pathways for explaining this pathological association. At the end of a cohort study of 585 patients with case-control analysis conducted by *Dureault A and coll*, the probability of developing severe infections during sarcoidosis depended on the male gender, immunosuppressive tritherapy, cyclophosphamide, neurological or cardiac manifestattions during the disease [8].

Clinical and radiological features of cryptococcosis and aspergillosis are non-specific. The medical practitioner should be able to talk about and fear it in case there has been any recent change of clinical and biological presentation with a patient suffering of sarcoidosis. This makes an issue for the differentiel diagnosis with a flare-up of the underlying sarcoidosis condition leading to an intensive corticosteroid therapy that will worsen the infectious condition.

The clinical spectrum of aspergillosis extends from acute invasive aspergillosis of deeply immunocompromised patients to chronic invasive patterns occuring on an underlying broncho-pulmonary condition (simple aspergilloma, complex aspergilloma, semi-invasive aspergilloma, chronic pulmonary aspergillosis).

It's known that the diagnosis of certainty of intracavitary aspergilloma needs invasive techniques. It relies on the positivity of the aspergillary serology and a typical bell image. When aspergilloma is endobronchial, an examination under microscope will provide the diagnosis. An *Aspergillus fumigatus* finding is only valuable in some particular samples: BAF, protected brushing products, protected sputum. HR thoracic CT Scan can show many aspects: pseudo-tumor opacities, rounded-like opacities without crescent gas, air-fluid levels, sequellae. Serology is the key of the diagnosis while the histology provides certainty. In practice, the clinical, biological and scanographic featuring would be enough to retain the diagnosis.

Aspergilloma was conjured up and retained according to: the evocative clinical course, the typical bell aspect on thoracic CT Scan and the positivity of aspergillary serology.

The diagnostic of certainty of pulmonary cryptococcosis will be made by the presence of ring-like yeast, sometimes burgeoning and encapsulated under the microscopic view and culture of the BAF. The diagnosis may be indirect through serology of the circulating capsular antigen with a sensibility and specificity close to 90%. Antibody research is not specific and doesn't contribute to the diagnosis.

Cerebro-meningeal localization is the most common situation on the immunocompromised patient with pulmonary gateway.

We provided the diagnosis of certainty of pulmonary cryptococcosis according to: a suggestive clinical course correlated to the presence of *Cryptococcus neoformans* under microscopic view of the FBA.

There is no high grade recommendation to treat broncho-pulmonary aspergillosis of an immunodepressed patient, non HIV [9]. However the curative attitudes are well codified for the management of fungal infections during systemic diseases [10]. However the preventive treatment has never been assessed in this context.

Hence, it's commonly admitted that the curative treatment of pulmonary aspergilloma is surgical. It will be performed only for symptomatic patients and/or presenting hemoptysia so that to prevent cataclysmic hemoptysia. Surgical indication of pulmonary aspergilloma also depends on its simple and paucisymptomatic radiological aspect with the presence of cavities with fine egdes without adjacent sequellae, the existence of a contact between the aspergillary mass and the pulmonary artery or one of its branches or the rapid growth of the aspergillary mass with the disappearance of the security edge between the latter and the blood vessel [11]. The resections of post therapeutical mycotic sequestrations, that pretend recurrency, constitute surgical indications in case of acute invasive aspergillosis that is lethal in 40% [11]. The general appearance of the patient, his respiratory state at the EFR and the underlying condition of the lung also justify a surgical care [12]. The surgical act will depend on the volume and the location of the lesion. In case of localized aspergilloma, it will consist on a lobectomy or a segmental resection.

There is no proof of an absolute efficiency neither of systemic antifungal treatment nor by endobronchial instillation. However, it's only on small series of unoperable patients where the treatment is documented to be efficient according to *Blandina and coll* with the use of local endobronchic or intracavitary antifungals [13].

Then it would seem for unoperable patients that a systemic medical treatment associated with a local intracavitary antifungal instillation to sterilize the foyer of mycetoma should be provided. American Experts' recommendations suggest the use of oral Itraconazole for the treatment of complex aspergilloma (many cavities with thick wall, poorly circumscribed on the reorganized pulmonary parenchyma: this form is a border of chronic necrotizing aspergillosis); either in peri operative or exclusively on unoperable patients [13]. The rate of therapeutic failure of Itraconazole is less than 40%. The absence of Intravenous form prevents from its use for serious forms. Its absorption is variable and imposes the dosage of serum levels.

Zmeili and coll make easy the management by affirming that oral Itraconazole is the molecule of choice in case of pulmonary aspergilloma due to its efficient tissular penetration [14]. Unlike, according to some authors, amphotericine B would be the core therapy for pulmonary aspergillomas while itraconazole is for patients with neutropenia or in second-line treatment in case of intolerance or inefficiency of amphotericine B and for long-term therapy (persistance of the immunedeficiency) [15].

The first step of the treatment of cryptococcosis is the assessment of the infection's extension.

The first-line treatment of severe pulmonary cryptococcosis or with an increased fungal counts (serum Ag ≥ 1/512) is similar to the one used in case of cerebro-meningeal cryptococcosis with the association of Amphotericin B 0.7 - 1 mg/kg/day (Liposomal Amphotericin B 3 mg/kg/day) + 5 Fluorocystein at the dosage of 100 mg/kg/day 4times during 1 - 3 weeks. Then we use Fluconazole 400 - 800 mg/day during 2 months followed by a dicreased dose at 400 mg/day for a maintenance treatment during 8 weeks. If the Fluconazole is not available, Itraconazole 200 mg × 2 /day (serum dosage) or Voriconazole (serum dosage) are used as alternative medicines. In case there is a resistance against Fluconazole, intraveinous Voriconazole or Amphotericin B can be used. If the pulmonary condition is isolated or slighty severe (after excluding a meningeal involvement), Fluconazole is the first line treatment (400 mg/day) [16].

In our local context, Amphotericin B wasn't available.

Hence, a medical treatment was provided in relation to a low grade hempoptysia, a long-standing aspergillosis and a poor general health and surgical advice was provided.

Thereby, she was undergoing a daily single-use dosage of 400 mg of Itraconazole during 10 days and 400 mg/day offluconazole during 2 months with a good clinical evolution marked by the stop of hemoptoic sputum, the disappearance of the cough and the improvement of the general health with the recovery of daily activities. The time of reintroduction and the dosage of the corticosteroid therapy will be decided by the staff at the end of the treatement of these opportunist co-infections.

Opportunistic infections on immunodepression condition without knowing the type is a serious case, with a poor outcome and require an urgent treatment. However, the evolution of fungal infections during sarcoidosis, under antifungal treatment is favorable [2]. According to *S. Lachkar*, aspergillary graft doesn't represent the first cause of death. The prognosis of these infections seems to be better on this particular condition of sarcoidosis [5].

The evolution would be favorable with antifungal treatment and the decrease of immunosuppressive therapy. The favorable response of the oral treatment of our patient seems to prove it.

4. Conclusion

We reported a rare and life-threatening case of sarcoidosis complicated with cryptococcal and aspergillary opportunistic infections. In our case, the patient has been lost to follow up for a long period. This constitutes the first morbidity risk factor. Even though sarcoidosis can lead to nonspecific pulmonary features, the practitioner should bear in mind the coexistence of opportunistic conditions.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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