Granulocyte macrophage colony-stimulating factor-specific autoantibodies and cerebral nocardia with pulmonary alveolar proteinosis

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We report here the history of a 40-year-old man with a primary cerebral abscess caused by *Nocardia abscessus* that led to the discovery of autoimmune pulmonary alveolar lipoproteinosis (anti-GM-CSF autoantibodies). Anti-GM-CSF autoantibodies promote immunodeficiency and should be monitored to prevent opportunistic and disseminated infections and to diagnose asymptomatic pulmonary alveolar lipoproteinosis.

In April 2018, a 40-year-old man, who was an active smoker (10 pack-years), consulted the hospital for subacute left brachiofacial deficit and headaches. He had no medical history. He previously worked as an order picker and reported a former professional exposure to dust. On admission, he presented with moderate left facial paralysis and left brachial deficit (4/5). Pulmonary auscultation was normal. A voluminous right parietal lesion compatible with a cerebral abscess was identified on cerebral imaging and quickly drained by neurosurgeons (Figure 1). The patient underwent a full body Computed Tomodensitometry (CT) scan, that did not show any secondary infectious focus but did identify an unexpected diffuse interstitial lung disease with “crazy paving” aspect (Figure 1). Further pulmonary examinations showed a restrictive ventilatory disorder with a decrease in vital capacity and 60% decrease in total pulmonary capacity, associated with a severe alteration of alveolocapillary diffusion (DLCO at 31%).

Per operative samples of surgical drainage showed partially necrotic polymuclear neutrophils in histopathology, with negative direct examination. Cultures returned positive after 72 hours for *Nocardia spp*. The MALDI-TOF technique was used to identify *Nocardia abscessus*. Molecular biology performed on abscess samples to eliminate other pathogens such as aspergillus, mycobacteria, candidas, cryptococcus, histoplasma and cysticercus was negative. Bronchoalveolar lavage (BAL) fluid was opalescent, microbiological culture and molecular biology searching for pneumocystis, aspergillus, mycobacteria, *Streptococcus*
pneumoniae, mycoplasma, Bordetella pertussis, as well as for cytomegalovirus, herpes simplex virus, enterovirus, rhinovirus, respiratory syncytial virus, metapneumovirus and influenza virus were negative as well. Histopathologic BAL analysis revealed extracellular periodic acid-Schiff staining (PAS)-positive material evocative of pulmonary alveolar lipoproteinosis. Less than 1% of lymphocytes were detected in the BAL fluid, with mainly T cells and an inverse CD4/CD8 ratio. Phenotypic and functional analyses of circulating lymphocytes did not reveal any obvious immunodeficiency: CD4+ T, CD8+ T, B and NK cell counts were normal, as were mitogen-induced T cell proliferation and Th1/Th2/Th17 cytokine production. Similarly, B cell function indicated by immunoglobulin production evaluation was normal. Anti-granulocyte-macrophage colony-stimulating factor (GM-CSF) autoantibodies, evaluated by the functional method of TF1 cell line proliferation inhibition were highly positive in the serum (titer of 155), confirming the neutralizing power of antibodies and therefore the autoimmune origin of PAP.

The patient was treated with a combination of meropenem administered intravenously for 6 weeks and high dose of trimethoprim-sulfamethoxazole relayed per os (800/160 mg three times a day) from the 7th day; treatment was continued for one year and then replaced with a secondary prophylactic regimen with sulfamethoxazole-trimethoprim at 800/160 mg once a day (ongoing treatment). The patient clinically improved, with total neurological recuperation and total regression of the cerebral abscess on cerebral CT scan control imaging performed in October 2019. Primary pulmonary alveolar proteinosis was initially treated with dose escalation of recombinant GM-CSF (Sargramostim/LEUKINE) subcutaneous injection, at 500 µg per day. Despite excellent hematopoietic tolerance, recombinant GMCSF was not effective enough, as the patient presented three respiratory distress syndromes during the year, requiring hospitalization in intensive care units and whole lung lavages. Inefficient
LEUKINE treatment was interrupted and second-line Rituximab was initiated with good tolerance and clinical stabilization.

Here, we report the first case of *N. abscessus* cerebral infection with anti-GM-CSF autoantibodies and documented PAP (tables 1 & 2). In the literature, 3 cases of nocardial infection with anti-GM-CSF antibodies and documented PAP have been reported: 36 cases of PAP associated with nocardial infection without specifying the presence of anti-GM-CSF autoantibodies and 4 cases of nocardial infection with anti-GM-CSF autoantibodies without PAP were found (tables 1 & 2). These observations highlight the promotive role of anti-GM-CSF autoantibodies in the occurrence of these two diseases, nocardial infection and PAP.

PAP is mostly autoimmune (90% of cases), and in such cases, it is characterized by high level of anti-GM-CSF autoantibodies, whereas hereditary PAP results in mutations in genes encoding the GM-CSF receptor 7,9.

Secondary infection is the most common and threatening complication of PAP, occurring in 5-13% of cases and accounting for 10-20% of deaths 7. Patients with PAP are known to be more susceptible to bacterial, mycobacterial and fungal infections such as nocardiosis, mycobacteriosis, aspergillosis and cryptococcosis 7. The association between PAP and opportunistic infection has been reported since the first description of the disease in 1958 by Rosen et al., with 2 cases of cryptococcosis and 2 cases of nocardiosis among the 27 patients described 14. More recently, a review of opportunistic infections occurring in 75 patients with PAP found 43% positivity for *Nocardia spp.* infection, followed by mycobacterial and fungal infections representing 37% and 20% of the patients, respectively (table 1)11. Disseminated or meningeal cryptococcal infections have led investigations to identify the presence of anti-GM-CSF autoantibodies in patients without a history of PAP (Table 2)13. Similarly, by screening the serum of 7 patients presenting with central nervous system or disseminated nocardiosis, Rosen et al. detected anti-GM-CSF autoantibodies in 5
of the 7 samples. None of the patients had PAP initially, and 2 developed PAP during follow-up (table 2)\(^8\).

We decided to treat the patient with prolonged trimethoprim-sulfamethoxazole as a secondary prophylaxis because we considered the patient immunocompromised. In addition, whereas whole-lung lavage is still the gold standard for autoimmune PAP, subcutaneous and inhaled GM-CSF supplementations were reported to be beneficial \(^7\). In prospective studies, daily injection of GM-CSF was effective in 43\% to 75\% of patients at one year and 12 weeks, respectively. Additionally, inhaled GM-CSF presents several advantages: reduced cost, reduced side effects and 66\% efficiency at 3 years. Two clinical trials evaluating the effect of inhaled GM-CSF on PAP patients are ongoing: IMPALA and PAGE \(^7\). More recently, rituximab has been proposed as a therapeutic option for the treatment of autoimmune PAP with controversial results. Some series of patients treated with rituximab showed PaO\(_2\), pulmonary function test and chest CT scan lesion amelioration, whereas retrospective reports on 13 PAP patients did not support rituximab as a second-line therapy \(^7,17\). Plasmapheresis has not shown promising results, and few cases of lung transplantation to treat severe PAP have been reported \(^7\).

GM-CSF, a cytokine produced by T cells, B cells, macrophages, endothelial cells and fibroblasts, is involved in proinflammatory functions such as the differentiation, adhesion, chemotaxis, and activation of inflammatory and immune cells such as monocytes, macrophages, neutrophils, microglia and dendritic cells \(^2\). GM-CSF is also a hematopoietic growth factor that activates the proliferation of myeloid cells from bone marrow progenitors \(^2,20\). While overproduction of GM-CSF is associated with rheumatoid arthritis, multiple sclerosis, juvenile myelomonocytic leukemia and chronic myelomonocytic leukemia, GM-CSF deficiency induces a lack of maturation of alveolar macrophages and accumulation of surfactant in the alveolar space, leading to PAP \(^7\). Anti-GM-CSF antibodies neutralize and
clear GM-CSF in cases of PAP, which could induce an immune deficiency favoring opportunistic diseases \(^{10}\). Indeed, GM-CSF deficiency causes impaired antigen presentation, and reductions in dendritic cell numbers in nonlymphoid tissues, as well as in phagocytosis and bactericidal activities of neutrophils, promoting immunodeficiency \(^{10}\). Thus, the role of GM-CSF is not limited to the lungs and seems to be decisive in the host’s defense against pathogens, especially against opportunistic infections such as nocardia. On the basis of our experience and the research developed here, we therefore propose to test all patients with cerebral or disseminated nocardiosis for immunodeficiency with at least serum protein electrophoresis, immunophenotyping of circulating lymphocytes, presence and neutralizing activity of anti GM-CSF antibodies and chest CT scan to diagnose asymptomatic pulmonary alveolar lipoproteinosis.

In conclusion, the presence of anti-GM-CSF autoantibodies should be considered an underdiagnosed immunodeficiency. Systematic screening of these autoantibodies in patients with nocardial, fungal or mycobacterial infection will allow us to characterize this immunodeficiency and prevent the outbreak of disseminated infectious and pulmonary diseases.
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Patient Consent Statement:

The patient’s written consent was obtained.

The design of the work has been approved by local ethical committees under the number of registration : 2016-024
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**Figure 1.** Cerebral and thoracic imaging of a 40-year-old man with cerebral nocardiosis and pulmonary alveolar proteinosis. **A-C.** Magnetic resonance imaging showing a voluminous cerebral parietal abscess. **D-E.** Thoracic CT scan showing diffuse and bilateral interstitial syndrome with thickening of the interlobular septa and a “crazy paving” aspect, which is classically found in pulmonary alveolar lipoproteinosis.
Table 1. Nocardiosis (cerebral and/or disseminated) associated with with Pulmonar Alveolar Proteinosis with or whithout anti GM-CSF autoantibodies

| Number of patients / date/country | Age/sex | Infectious focus | Species | Anti GMCSF antibodies | Treatment | Evolution | Ref |
|---------------------------------|---------|------------------|---------|-----------------------|-----------|-----------|-----|
| 32 patients 1950 – 2010 Worldwide | 65% male 35% female Mean age 35 | 75% pulmonar (n=24) 19% (n=6) cerebral 6% other (n=2) | N. asteroides 19 (59%) N. brasiliensis 1 (3%) N. farcinica 1 (3%) Nocardia spp. 11 (34%) | Not performed | Unspecified antibiotherapy (n=20) Surgery (n=6) | 41% died | 11 |
| 1 patient 2010 Japan | 37/male | Pulmonar | NA | Presence | NA | NA | 21 |
| 2 patients 1990 – 2010 China | NA | NA | NA | NA | NA | NA | 6 |
| 1 patient 2014 Spain | 50/male | Pulmonar | N. farcinica | Not performed | Amikacin 6weeks and TMP-SMX 6 months | Full recovery | 5 |
| 1 patient 2015 Iran | 42/male | Cerebral abscesses | N. asteroides | Not performed | TMP-SMX, meropenem and amikacin 2months, relayed TMP-SMX | No improvement | 16 |
| 1 patient 2017 Spain | 49/male | Cerebral abscess | N. farcinica | Not performed | 12 months of AMC and minocycline | Full recovery | 3 |
| Patient | Year | Gender | Location | Manifestation | Pathogen | Treatment | Outcomes | Notes |
|---------|------|--------|----------|---------------|----------|-----------|----------|-------|
| 1 patient 2002-2016 Brazil | NA | NA | Not performed | Adapted antibiotherapy (not specified) | Full recovery | 1 |
| 1 patient 2020 US | 62/male | Pulmonar | N. brasiliensis | Presence | Amikacin 6 weeks and TMP-SMX 6 months | Full recovery | 4 |
| 1 patient 2018 France | 40/male | Cerebral abscess | N. abscessus | Presence | Meropenem 6 weeks and TMP-SMX 12 months | Full recovery | Our case |

Abbreviations: AMC, amoxicillin/clavulanate; AmphoB, amphotericin B; CNS, central nervous system; FLC, fluconazole; GM-CSF, granulocyte macrophage colony-stimulating factor; IgG, immunoglobulin G; LP, lumbar puncture; MXF, moxifloxacin; NA, not available; PAP, pulmonary alveolar proteinosis; TMP-SMX, trimethoprim-sulfamethoxazole; 5-FC, 5-flucytosine.
Table 2. Reported cases of opportunistic infections associated with anti GMCSF autoantibodies without Pulmonary Alveolar Proteinosis

| Infectious agent | Age/sex | Infection focus | Species | Anti GMCSF antibodies | Presence of PAP | Treatment                        | Outcome               | Ref  |
|------------------|---------|-----------------|---------|------------------------|-----------------|----------------------------------|-----------------------|-----|
| Nocardiosis      | 1       | 44/male cerebral | *N. paucivorans* | Presence              | Scanographic infiltrates but normal respiratory function tests, PAP diagnosis not retained | Amikacin and TMP-SMX 8weeks, TMP-SMX and linezolide 8 weeks, then TMP-SMX alone | Full recovery         | 13  |
|                  | 2       | 73/male cutaneous, pulmonary and subsequent cerebral nocardiosis -pulmonary aspergillosis | *Nocardia spp A. fumigatus* | Presence              | No evidence of PAP | Imipenem amikacin voriconazole, then TMP-SMX, AMC, voriconazole per os + subcutaneous GMCSF | Neurologic relapse    |     |
|                  | 3       | 61/male cerebral nocardiosis | *N. farcinica* | Presence              | No evidence of PAP | Imipenem amikacin IV 8weeks and TMP-SMX and moxifloxacin | Neurologic relapse    |     |
|   | Age | Sex | Diagnosis                          | Pathogen   | Presence | Treatment                                      | Outcome            |
|---|-----|-----|------------------------------------|-------------|----------|------------------------------------------------|--------------------|
| 4 | 50  | male| cerebral nocardiosis N. paucivorans| Presence    | No evidence of PAP | 12 months of TMP-SMX, imipenem, and moxifloxacin | Full recovery      |
| 5 | 52  | female | cerebral and pulmonary nocardiosis and disseminated cryptococcosis N. asteroides | Presence | No evidence of PAP | NA | NA |

**Cryptococcus**

|   | Age | Sex | Diagnosis                          | Pathogen   | Presence | Treatment                                      | Outcome            |
|---|-----|-----|------------------------------------|-------------|----------|------------------------------------------------|--------------------|
| 1 | 49  | female | meningitidis C. gattii | Presence | NA | NA | NA |
| 2 | NA  | female | meningitidis C. gattii | Presence | NA | NA | NA |
| 3 | NA  | female | meningitidis C. gattii | Presence | NA | NA | NA |
| 4 | NA  | male | meningitidis C. gattii | Presence | NA | NA | NA |
| 5 | NA  | female | meningitidis C. gattii | Presence | NA | NA | NA |
| 6 | NA  | female | meningitidis C. gattii | Presence | NA | NA | NA |
| 7 | NA  | male | meningitidis C. gattii | Presence | NA | NA | NA |
| 8 | 20  | female | meningitidis C. neoformans | Presence | Develop PAP a year later | AmphoB + 5-FC, relayed by FLC | Full recovery |
|   | Age/sex | Diagnosis | Pathogen | Presence | Therapies | Course |
|---|---------|-----------|----------|----------|-----------|--------|
| 9 | 31/female | Meningitis | *C. gattii* | Presence | NA | AmphoB + 5FC, relayed by FLC + 5FC | Full recovery |
| 10 | 48/male | Cryptococcal meningitis | *C. neoformans* | Presence | NA | AmphoB, relayed by FLC | Antifungal therapy | Full recovery |
| 11 | 47/male | Meningitis | *C. neoformans* | Presence | Develop asymptomatic PAP 4 years later | AmphoB + FLC, relayed by FLC | Full recovery |
| 12 | 26/male | Meningitis | *C. gattii* | Presence | NA | AmphoB + 5FC | Full recovery |
| 13 | 34/male | Meningitis | *C. gattii* | Presence | NA | AmphoB + 5FC + therapeutic LP | Sequelae |
| 14 | 32/male | Meningitis | *C. gattii* | Presence | NA | AmphoB + 5FC + therapeutic LP | Sequelae |
| 15 | 48/male | Pulmonary cryptococcoma, and subsequent cerebral cryptococcosis | *C. gattii* | Presence | Scanographic infiltrates but normal respiratory function tests, PAP diagnosis not retained | AmphoB + 5-FC, relayed by FLC | Full recovery |
|   | Patient No. | Age | Gender | Location of Infection | A. | Presence | NA | Therapy for Infection | Outcome |
|---|-------------|-----|--------|-----------------------|----|----------|----|-----------------------|---------|
| 16 | 43/male     | 43  | Male   | Solitary cerebral abscess | C. gattii | Presence | NA | Surgically treated, amphoB + 5-FC, relayed by several triazoles | Full recovery |
| 17 | 37/male     | 37  | Male   | Disseminated | NA | Presence | No evidence of PAP | AmphoB + 5FC + therapeutic LP | Death |
| 18 | 40/male     | 40  | Male   | Disseminated | NA | Presence | No evidence of PAP | AmphoB + 5-FC, relayed by FLC | Severe sequelae |
| 19 | 59/female   | 59  | Female | Ocular | NA | Presence | No evidence of PAP | Intraoculaire amphoB relayed by voriconazole | Full recovery |
| 20 | 37/male     | 37  | Male   | meningitidis | NA | Presence | No evidence of PAP | AmphoB + 5-FC 2 weeks, relayed by FLC | Full recovery |

Abbreviations: AMC, amoxicillin/clavulanate; AmphoB: amphotericin B; CNS, central nervous system; FLC: fluconazole; GM-CSF, granulocyte macrophage colony-stimulating factor; IgG, immunoglobulin G; LP: lumbar puncture; MXF, moxifloxacin; NA: not available; PAP, pulmonary alveolar proteinosis; TMP-SMX, trimethoprim-sulfamethoxazole; 5-FC: 5-flucytosine.
