ISSN 1669-9106 MEDICINA (Buenos Aires) 2024: 84: 764-768

Case report

NEUROSARCOIDOSIS AS A RAPIDLY PROGRESSIVE DEMENTIA ASSOCIATED WITH NORMAL PRESSURE HYDROCEPHALUS

FERNANDO JABIF[1], MÁXIMO ROUSSEAU-PORTALIS[1], CLAUDIA BURBANO[2], DIEGO ANDRESIK[3], BERNARDO MARTÍNEZ[1]

[1]Medicina Interna, [2]Departmento de Neurología, [3]Unidad de Investigación de Sarcoidosis, Medicina Interna, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

Postal address: Máximo Rousseau-Portalis, Hospital Italiano de Buenos Aires, Tte. Gral. Juan D. Perón 4190, 1199 Buenos Aires, Argentina
E-mail: maximo.rousseau@hospitalitaliano.org.ar
Received: 29-XI-2023
Accepted: 27-III-2024

Abstract

Neurosarcoidosis (NS) is a rare subtype of sarcoidosis with a poor prognosis and diverse clinical presentations that often poses a diagnostic and therapeutic challenge.

We describe the case of a 53-year-old male with an initial diagnosis of lingual sarcoidosis, who subsequently developed ataxia and rapidly progressive cognitive impairment. A lumbar puncture revealed hypoglycorrhachia, hyperproteinorrachia, lymphocytic pleocytosis, and elevated IL-6 levels (600 pg/ml). Cerebrospinal fluid flow cytometry showed an elevated CD4 lymphocyte concentration and a CD4+/CD8+ ratio of 3.91, indicative of NS. Brain MRI showed hyperintense periventricular and subcortical lesions on FLAIR/T2 resembling progressive multifocal leukoencephalopathy (PML), although negative PCR for JC virus ruled out the differential diagnosis. Following a favorable evolutionary course with corticosteroid pulses, the patient relapsed with normotensive hydrocephalus, treated with immunosuppressants and ventriculoperitoneal shunting with a good response to date.

This case underscores the importance of maintaining a high index of suspicion for NS in individuals with sarcoidosis and neurologic symptoms. In these cases, cerebrospinal fluid biomarkers such as IL-6 and CD4+/CD8+ ratio are essential to guide the diagnosis. Furthermore, it highlights that hydrocephalus is a rare complication and requires a multidisciplinary approach, including medical and neurosurgical treatment.

Key words: neurosarcoidosis, progressive multifocal leukoencephalopathy, normal pressure hydrocephalus

Resumen

Neurosarcoidosis como demencia rápidamente progresiva asociada a hidrocefalia normotensiva

La neurosarcoidosis es un subtipo raro de sarcoidosis con mal pronóstico y diversas presentaciones clínicas que a menudo plantea un reto diagnóstico y terapéutico.

Describimos el caso de un varón de 53 años con diagnóstico inicial de sarcoidosis lingual, que posteriormente desarrolló ataxia y deterioro cognitivo de rápida evolución. Una punción lumbar reveló hipoglucorraquia, hiperproteinorraquia, pleocitosis linfocítica y niveles elevados de IL-6 (600 pg/ml). La citometría de flujo del líquido cefalorraquídeo mostró una concentración elevada de linfocitos CD4 y un cociente CD4+/CD8+ de 3.91, indicativo de neurosarcoidosis. La RM cerebral evidenció lesiones hiperintensas periventriculares y subcorticales en FLAIR/T2 que se asemejaban a una leucoencefalopatía multifocal progresiva (LMP), aunque la PCR negativa para el virus JC descartó el diagnóstico diferencial. Tras

un curso evolutivo favorable con pulsos de corticoides, el paciente recayó con hidrocefalia normotensiva, tratada con inmunosupresores y derivación ventriculoperitoneal con buena respuesta hasta la fecha.

Este caso subraya la importancia de mantener un alto índice de sospecha de neurosarcoidosis en individuos con sarcoidosis y síntomas neurológicos. En estos casos, los biomarcadores del líquido cefalorraquídeo tales como la IL-6 y el cociente CD4+/CD8+ son esenciales para orientar el diagnóstico. Además, destaca que la hidrocefalia es una complicación poco frecuente y requiere un abordaje multidisciplinario, que incluya tratamiento médico y neuroquirúrgico.

Palabras clave: neurosarcoidosis, progressive multifocal leukoencephalopathy, normal pressure hydrocephalus

Sarcoidosis is an idiopathic multi-system disease characterized by non-necrotizing granulomas. Although it can affect any organ, the lungs are the most frequently involved site[1]. The average age of onset ranges from 40-55 years, with a younger peak age at diagnosis for men compared to women[2]. Certain factors, such as age over 40 years at presentation and central nervous system involvement, are linked with a poorer prognosis [3].

Neurosarcoidosis (NS) was historically reported to occur in 5%-10% of all patients with sarcoidosis, although this number might be influenced by sampling bias from cohorts focusing on pulmonary sarcoidosis[3,4]. Neurologic manifestations are the presenting syndrome in 50%-70% of patients with NS[5]; conversely, approximately 75% of patients with systemic sarcoidosis who develop NS will do so within 2 years of sarcoidosis diagnosis[6]. The most commonly reported feature of NS is cranial neuropathy (50%-70%). Other common features are meningeal involvement (leptomeningitis), parenchymal disease, peripheral neuropathy, as well as mood symptoms such as depression and cognitive impairment or dementia[7].

In this case report, we present a patient who initially had suspected tongue involvement due to sarcoidosis and presented with ataxia and rapidly progressive cognitive impairment years later.

Clinical case

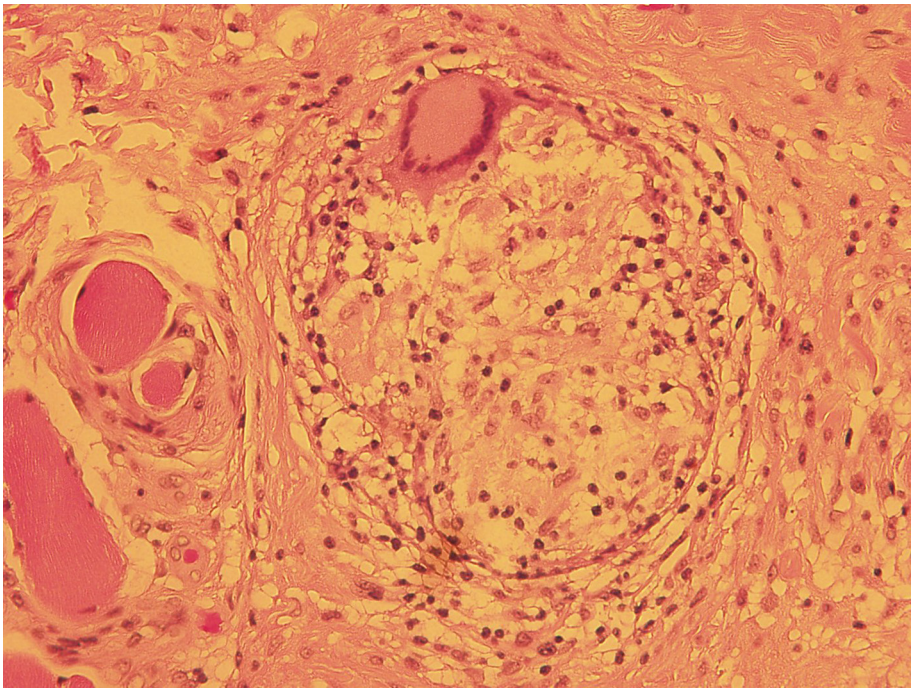
A 53-year-old male was referred to an emergency room with a 1-year history of progressive gait disturbances and cognitive impairment. These symptoms had worsened over the past two weeks. His past medical history was significant for hypertension and diabetes. Furthermore, the patient had undergone a hemiglossectomy two years earlier, during which a histopathological assessment unveiled the presence of an inflammatory granulomatous process characterized by epithelioid histiocytes, multinucleated giant cells, and surrounding peripheral lymphocytes (Fig. 1). Notably, there was an absence of any atypical cellular features. Following thorough evaluations to exclude fungal and mycobacterial infections, a provisional diagnosis of sarcoidosis was considered. However, no treatment was provided due to the absence of proof of involvement of other organs.

Upon examination, he was disoriented in time and space, with marked gait imbalance and a positive Romberg sign. He had no fever, and meningeal signs were absent. An initial Montreal Cognitive Assessment (MOCA) test yielded a score of 7 out of 30. Laboratory analysis showed a white blood cell count of 11538/mm3 (normal range 5000-10 000) with 70% of neutrophils. Total serum proteins were slightly elevated at 7.93 g/dl (normal range 6.3-7.8), total calcium of 11 mg/dl (normal range 8-10.5), and C-reactive protein was 2.5 mg/l (reference range 95th percentile minor than 7).

Following a normal brain computer tomography (CT) scan, a lumbar puncture was performed and was remarkable for hypoglycorrhachia of 10 mg/dl (normal range 40-70) with serum glucose of 87 mg/dl, hyperproteinorrachia of 154 g/dl (normal range 15-40) and lymphocytic pleocytosis with 110 white cells (normal range 0-5) and 76% of lymphocytes. Cerebrospinal fluid (CSF) cultures were negative for bacteria, fungi and Koch's bacillus. CSF VDRL was negative, and interleukin-6 (IL-6) was 600 pg/ml.

Subsequent CSF flow cytometry analysis demonstrated a total lymphoid population comprising 97% of the cell population, with 89% of these cells identified as T lymphocytes. Within the T lymphocyte subset, 77% were CD3+ CD4+ cells, while 19% were CD3+ CD8+ cells. The CD4+/CD8+ ratio was calculated as 3.91. Oligoclonal bands were detected in the CSF, though no evidence of monoclonality or cytometric aberrations was observed. Serology for HIV, hepatitis, Chagas disease, and toxoplasmosis were negative.

Figure 1 | Toung biopsy showing a non-necrotizing granuloma characterized by epithelioid histiocytes, multinucleated giant cells, and surrounding peripheral lymphocytes at x40 augmentation.



A brain MRI with gadolinium was performed, which showed an increased hyperintense signal on fluid-attenuated inversion recovery images (FLAIR)/T2 sequence, and hypointensity in T1 at the bilateral periventricular and subcortical levels (Fig. 2). These findings were compatible with progressive multifocal leukoencephalopathy (PML). However, the polymerase chain reaction (PCR) test for JC virus in CSF was negative. A PET-scan CT demonstrated left axillary nodes with increased fixation and another ipsilateral supraclavicular millimeter node with a non-specific inflammatory appearance.

Given the rapid disease progression, it was decided to start treatment with five 500-mg pulses of methylprednisolone in agreement with rheumatology and neurology. The treatment was well-tolerated, and the patient exhibited significant symptom improvement within a few days. Subsequently, the patient was discharged on an oral steroid regimen.

A follow-up MOCA test was performed 2 weeks after discharge, yielding a score of 24 out of 30.

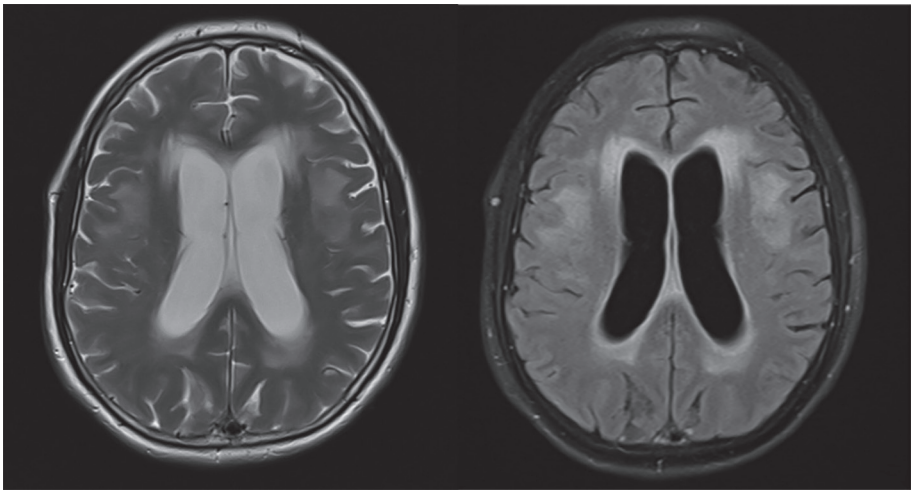
After a span of 8 months following discharge, the patient encountered a recurrence of gait disturbances. During this period, he remained under corticosteroids and azathioprine treatment regimen. A subsequent brain scan-CT revealed a marked progression of ventricular enlargement, compared with previous MRI and a fresh lumbar puncture revealed a normal opening pressure and reduced inflammatory markers. Consequently, a diagnosis of normal pressure hydrocephalus was established.

The patient's treatment plan was revised to address this condition, incorporating cyclophosphamide alongside a renewed course of methylprednisolone pulses. Despite these interventions, a follow-up CT scan showed no discernible improvement in the ventriculomegaly. So, the decision to proceed with ventriculoperitoneal shunting was made. This surgical procedure yielded a noteworthy enhancement in the patient's gait, contributing to his overall improvement.

This study adheres to ethical principles outlined in the Declaration of Helsinki and Good Clinical Practice guidelines. The involvement of human subjects was conducted in accordance with the ethical standards of the Ethics Committee of the Italian Hospital of Buenos Aires

The patient willingly and voluntarily provided his informed consent before participating in study. Copies of the signed informed consent forms are securely stored and are available for review by the upon request. Confidentiality and privacy of the participant were strictly maintained throughout the research process.

Figure 2 | MRI showing bilateral asymmetric leukoencephalopathy predominantly on FLAIR/T2 sequences without post-contrast pathological enhancement and mild ventricular enlargement.



Discussion

We present a case of a patient with probable NS diagnosis (according to the diagnosis criteria of the 2018 Neurosarcoidosis Consortium Consensus[8], with ataxia and cognitive impairment, and a history of a hemiglossectomy with histopathological examination consistent with sarcoidosis.

Oral involvement, including tongue manifestations, is considered a rare complication of sarcoidosis, and its prevalence is unknown. Nevertheless, a multicenter retrospective study of 12 cases of oral sarcoidosis by the French Sarcoidosis Group found that tongue involvement was the most frequently affected site and often marked the initial manifestation of sarcoidosis[9].

As mentioned above, NS often develops within two years after systemic sarcoidosis diagnosis, which is consistent with our case.

Although uncommon, NS is a possible diagnosis in patients with rapidly progressive dementia (RPD), and its frequency is estimated at about 1.5% of non-prion RPD[10].

Many patients with NS have abnormal CSF examinations, but no test is specific for NS. The main utility of CSF samples is to confirm intrathecal inflammation and exclude other disorders, such as infections or neoplasms. Frequent but non-specific findings include hyperproteinorrachia, hypoglycorrhachia, lymphocyte pleocytosis, and CSF-unique oligoclonal bands, all of which were present in our patient. Recent research has indicated that interleukin-6 (IL-6) levels and the CD4+/CD8+ ratio can serve as valuable biomarkers for NS. A retrospective study evaluating CSF biomarkers in patients with NS found that IL-6 levels were higher in sarcoidosis patients when compared with other CNS disorders like multiple sclerosis (MS). Moreover, they found that the CD4+/CD8+ ratio was higher in sarcoidosis patients than in MS patients and in patients with other inflammatory disorders. Furthermore, IL-6 levels were higher among patients with active NS when compared with those with no active NS, and IL-6 levels above 50 pg/ml were associated with a higher risk of relapse or progression-free survival. Our patient had 600 pg/ml IL-6 and a 3.91 CD4+/CD8 ratio, which supports the NS diagnosis[11,12].

Regarding imaging, leptomeningeal and dural gadolinium enhancement, intraparenchymal lesions and pituitary gland and hypothalamic involvement are the most common features[4]. Multiple intraparenchymal lesions are seen more frequently than solitary mass-like lesions and present as T2/FLAIR hyperintense periventricular lesions in some cases that should prompt the exclusion of demyelinating diseases[13].

Progressive multifocal leukoencephalopathy (PML), a rare demyelinating disease caused by the JC virus, has been associated with sarcoidosis and is often triggered by immunosuppression[12]. In our case, periventricular and subcortical lesions

were compatible with PML, which may be present in patients with sarcoidosis even in the absence of immunosuppressants[14]; however, negative PCR for JC virus excluded the differential diagnosis.

Hydrocephalus is a relatively uncommon occurrence in neurosarcoidosis, observed in roughly one-tenth of affected individuals. Notably, a retrospective cohort study conducted by ten Dam et al. underscores that merely 9% of patients with NS and hydrocephalus present with non-obstructive hydrocephalus[15]. In cases where hydrocephalus arises, a comprehensive approach encompassing both immunosuppressive therapy and neurosurgical intervention emerges as the preferred management strategy. This dual-pronged approach is imperative, given the potential fatality associated with this rare complication of neurosarcoidosis.

We present a case involving a patient with a prior history of sarcoidosis affecting the tongue, who subsequently developed neurological symptoms. The CSF parameters strongly indicated a probable diagnosis of NS. Notably, the patient's radiological presentation deviates from the typical pattern and eventually progresses to the development of communicating hydrocephalus, necessitating a dual therapeutic approach for effective symptom alleviation.

This case underscores the importance of clinical practitioners maintaining a high index of suspicion for NS in individuals with existing sarcoidosis and white matter lesions resembling PML and the need for a multidisciplinary approach, given the complexity of this pathology.

Acknowledgements: The authors would like to thank the internal medicine service and its chief, Dr. Javier Pollan, for their support in the preparation of this publication.

Conflict of interest: None to declare

References

1. Grunewald J, Grutters JC, Arkema EV, Saketkoo LA, Moller DR, Müller-Quernheim J. Sarcoidosis. *Nat Rev Dis Primer* 2019; 5: 1–22.
2. Arkema EV, Grunewald J, Kullberg S, Eklund A, Askling J. Sarcoidosis incidence and prevalence: a nationwide register-based assessment in Sweden. *Eur Respir J* 2016; 48: 1690–9.
3. Nunes H, Bouvry D, Soler P, Valeyre D. Sarcoidosis. *Orphanet J Rare Dis* 2007; 2: 46.
4. Bradshaw MJ, Pawate S, Koth LL, Cho TA, Gelfand JM. Neurosarcoidosis: pathophysiology, diagnosis, and treatment. *Neurol - Neuroimmunol Neuroinflammation* 2021; 8: e1084.
5. Fritz D, van de Beek D, Brouwer MC. Clinical features, treatment and outcome in neurosarcoidosis: systematic review and meta-analysis. *BMC Neurol* 2016; 16: 220.
6. Krumholz A, Stern BJ. Chapter 21 - Neurologic manifestations of sarcoidosis. In: Biller J, Ferro JM, editors. Handbook of Clinical Neurology. Elsevier; 2014. pp 305–33. (Neurologic Aspects of Systemic Disease Part I; vol. 119). In: https://www.sciencedirect.com/science/article/pii/B9780702040863000217; accessed October 2023.
7. Quertermous BP, Kavuri S, Walsh DW. An old disease with a new twist: CNS and thyroid sarcoidosis presenting as subacute dementia. *Clin Case Rep* 2021; 9: e04829.
8. Stern BJ, Royal W III, Gelfand JM, et al. Definition and Consensus Diagnostic Criteria for Neurosarcoidosis: From the Neurosarcoidosis Consortium Consensus Group. *JAMA Neurol* 2018; 75: 1546-53.
9. Bouaziz A, Le Scanff J, Chapelon-Abric C, et al. Oral involvement in sarcoidosis: report of 12 cases. *QJM Int J Med* 2012; 105: 755-67.
10. Fortes GCC, Oliveira MCB, Lopes LCG, et al. Rapidly progressive dementia due to neurosarcoidosis. *Dement Neuropsychol* 2013; 7: 428-34.
11. Chazal T, Costopoulos M, Maillart E, et al. The cerebrospinal fluid CD4/CD8 ratio and interleukin-6 and -10 levels in neurosarcoidosis: a multicenter, pragmatic, comparative study. *Eur J Neurol* 2019; 26: 1274-80.
12. Davis MJ, Khan A, Royal WI. Progressive multifocal leukoencephalopathy as the first manifestation of occult sarcoidosis: case report and review of the literature. *Neurologist* 2013; 19: 26-9.
13. Nowak DA, Widenka DC. Neurosarcoidosis: a review of its intracranial manifestation. *J Neurol* 2001; 248: 363-72.
14. McEntire CRS, Fletcher A, Toledano M, et al. Characteristics of progressive multifocal leukoencephalopathy associated with sarcoidosis without therapeutic immune suppression. *JAMA Neurol* 2023; 80: 624-33.
15. ten Dam L, van de Beek D, Brouwer MC. Clinical characteristics and outcome of hydrocephalus in neurosarcoidosis: a retrospective cohort study and review of the literature. *J Neurol* 2022; 269: 2727-33.