Aseptic meningitis and hydrocephalus secondary to neurosarcoidosis

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SUMMARY
A 53-year-old woman presented to hospital with gait instability, urinary incontinence and confusion. She had a 4-month history of headache, blurred vision, personality change and memory problems. Magnetic Resonance Imaging of the brain after contrast application showed tectal plate and occipital enhancement, as well as a known hydrocephalus. Cerebrospinal fluid showed aseptic meningitis with no evidence of clonal expansion. After further imaging that showed generalised lymphadenopathy and subsequent tissue biopsy that showed granulomatous lymphadenitis, she was diagnosed with neurosarcoidosis. She was treated with steroids which resulted in immediate cognitive and motor improvements as well as resolution of her urinary incontinence. We discuss the features of this case that pointed towards neoplastic, infective and other autoimmune aetiologies. We describe how they were excluded and provide the rationale for our treatment. This case demonstrates an important sequela sarcoidosis, and we conclude by recommending a multidisciplinary approach towards its diagnosis and management.

BACKGROUND
Sarcoidosis is a multisystemic granulomatous disorder. Its annual incidence in the United Kingdom is between 9.7 and 14.5 per 100 000.1 2 Diagnosis of this condition requires the exclusion of other granulomatous disorders such as lymphoproliferative disorders, infections, drug reactions and other autoimmune conditions. Neurological involvement (neurosarcoidosis) occurs in approximately 5%–26% of cases3 4 and may result in peripheral or central nervous system (CNS) manifestations.

CASE PRESENTATION
In September 2020, a 53-year-old Caucasian woman was admitted to hospital with gait instability, urinary incontinence and confusion. She had a history of hypertension for which she was taking antihypertensives and a maternal history of breast cancer which was diagnosed in the seventh decade. Her symptoms started in the preceding May with a sudden headache and associated blurred vision, which was treated as a migraine. However, over the next 3 months, her headache persisted. During this time, she also developed memory problems. A Magnetic Resonance Imaging (MRI) scan of the brain in August revealed dilated ventricles consistent with hydrocephalus (figure 1). When she was admitted to hospital, on examination, she had mild gait instability and her blood pressure was 220/142 mm Hg. Her routine blood tests were normal aside from a mild lymphopaenia which was present from the onset of her symptoms in May. Serum Angiotensin Converting Enzyme (ACE) was non-elevated at <12 units/L (normal range (NR): 20–70). Her Addenbrooke’s Cognitive Examination–Revised (ACE-R) score was 45/100. Her cerebrospinal fluid (CSF) showed an elevated white cell count of 60 cells/µL (NR: 0–5), an elevated protein of 1.04 g/L (normal range: 0.15–0.45) and a low glucose of 1.6 mmol/L (NR: 2.2–4.0). Subsequent CSF flow cytometry confirmed lymphocytosis with T-cell predominance with no phenotypic evidence of an atypical lymphoid infiltrate. Whole-body imaging showed widespread lymphadenopathy (figures 2 and 3). Imaging of the brain showed enhancement in the occipital lobe and tectal plate (figure 4). A subsequent core biopsy of the right inguinal lymph node showed granulomatous lymphadenitis (figure 5). She underwent extensive testing for infective pathogens and an autoimmune screen, both of which were negative.

DIFFERENTIAL DIAGNOSES
Her differential diagnoses are discussed in table 1. The successful exclusion of the aforementioned diagnoses, along with the findings of her lymph node biopsy and focal areas of cerebral enhancement,
allowed us to arrive at the diagnosis of neurosarcoidosis. The lack of a confirmatory test in diagnosing sarcoidosis means that it remains a diagnosis of exclusion. It is notoriously difficult to ensure that tuberculosis has been excluded, with lymphoma being the other major diagnosis to rule out. The advent of CSF flow cytometry has been very helpful in the latter. Excluding lymphoma was particularly important here as there is a two-way statistical association between an individual and a first-degree relative for breast cancer and non-Hodgkin’s lymphoma. The Neurosarcoidosis Consortium Consensus Group published diagnostic criteria in 2018 for possible, probable, and definite neurosarcoidosis. As per those criteria, the index case qualifies for a diagnosis of probable neurosarcoidosis. To establish a diagnosis of definite neurosarcoaidosis, a CNS biopsy would have been required. However, this is an invasive procedure that carries risk. As we had rigorously excluded other diagnoses, we felt confident that the diagnosis we had established was accurate.

**TREATMENT**

The patient was treated with 3 days of 1 mg methylprednisolone intravenously, followed by 60 mg of daily oral prednisolone. After 5 days of steroid treatment, her ACE-R score increased to 75/100. Her mobility also improved such that it was possible...
to discharge her home. At the time of discharge, the patient’s cognitive problems had significantly improved although she continued to experience mild gait instability. She was discharged on prednisolone 60 mg daily, and this was reduced to 40 mg daily over the next 4 weeks. Four weeks after discharge, she was also started on azathioprine 25 mg daily with a plan to increase to 150 mg daily.

In the context of sarcoid-related hydrocephalus, we could not find any published data as to whether medical or surgical management or a combination of the two, would be the most appropriate treatment. In her case, the rapid response to steroids meant there was no indication for acute neurosurgical intervention. Moreover, active inflammation can also block ventriculo-peritoneal (VP) shunts, meaning that the decision to offer early neurosurgical intervention should be taken carefully. Nonetheless, on discharge, this patient was placed under the care of a specialist multidisciplinary team that did include a neurosurgical opinion. The plan was to consider neurosurgical intervention if medical management failed to control her hydrocephalus-related symptoms. Although hydrocephalus is reported to be present in only 6% of cases of neurosarcoidosis, it is becoming increasingly recognised as a feature of this condition. From our literature review, we found 21 cases of hydrocephalus identified as a presenting feature of neurosarcoidosis. Of these 21 patients, 17 underwent both medical and surgical management for their hydrocephalus, 2 underwent surgery alone

### Table 1 Evaluation and exclusion of differential diagnoses

| Differential diagnosis                  | Features in favour                                                                 | How diagnosis was excluded                                                                 |
|----------------------------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| Lymphoma                               | ► CSF findings of lymphocytosis with raised protein<br► Widespread lymphadenopathy on CT of the chest, abdomen and pelvis<br► Peripheral lymphopenia since the onset of symptoms ranging between 0.5×109/L and 1.0×109/L (NR: 1.4–4.8×109/L)<br► Maternal history of breast cancer | ► Absence of atypical cells on CSF flow cytometry<br► No evidence of lymphoma on tissue biopsy |
| Chronic pathogenic infections           | ► Subacute history with neurological symptoms<br► Lymph node biopsy showing granulomatous lymphadenitis<br► CSF showing raised lymphocytes, low glucose and raised protein suggestive of tuberculosis or fungal infection | ► Negative CSF, serum, urine and sputum analysis for pathogens, including acid-fast bacillus stains, prolonged culture and mycobacterium tuberculosis<br► PCR on CSF<br► Negative staining for microorganisms on lymph node biopsy |
| Carcinomatous meningitis                | ► Subacute history with neurological symptoms and aseptic meningitis | ► Absence of malignancy identified on CT of the chest, abdomen and pelvis/MRI of the brain and spine<br► No malignant cells in CSF |
| Autoimmune vasculitis                  | ► Lymph node biopsy showing granulomatous lymphadenitis | ► Negative auto-antibody screen |
| Phaeochromocytoma                       | ► Headache and visual disturbances<br► Labile blood pressures ranging between 191/114 mm Hg and 220/142 mm Hg | ► Normal 24-hour urinary metanephrines<br► Absence of adrenal mass on CT of the chest, abdomen and pelvis |

CSF, cerebrospinal fluid; NR, normal range.

### Table 2 Summary of treatment of published cases of neurosarcoidosis with hydrocephalus (adapted from Saban et al$^{12}$)

| Author                        | Treatment                                                                 | Outcome                      |
|-------------------------------|---------------------------------------------------------------------------|------------------------------|
| Pandey et al$^{(2021, index case)}$ | Corticosteroids + azathioprine with provisional plan for surgical intervention | Partial recovery             |
| Saban et al$^{(2020)}$        | Corticosteroids + methotrexate, followed by VP shunt months later         | Partial recovery             |
| McKeever et al$^{(2019)}$     | Case 1: Corticosteroids + azathioprine<brCase 2: Initial endoscopic third ventriculostomy followed by multiple neurosurgical procedures 7–10 years later, including a VP shunt insertion, two shunt revisions and endoscopic fenestration of the third and fourth ventricles | Case 1: Complete recovery<brCase 2: Partial recovery after the initial procedure but significant neurological disabilities after 10 years |
| Sugiyama et al$^{(2016)}$     | Corticosteroids + VP shunt                                               | Partial recovery             |
| Chandra et al$^{(2015)}$      | Corticosteroids + VP shunt                                               | Death                        |
| Hitti et al$^{(2015)}$        | Corticosteroids + VP shunt + mycophenolate mofetil                        | Unknown                      |
| Matsuda et al$^{(2015)}$      | Corticosteroids + ventriculostomy followed by VP shunt                    | Complete recovery            |
| Sano et al$^{(2015)}$         | Corticosteroids + VP shunt + methotrexate + infliximab                    | Partial recovery             |
| Yoshitomi et al$^{(2015)}$    | Corticosteroids + endoscopic fenestration foramens of Magendie, followed by VP shunt | Complete recovery            |
| Tabuchi et al$^{(2013)}$      | Corticosteroids + VP shunt                                               | Partial recovery             |
| Zoja et al$^{(2012)}$         | Not applicable as diagnosis established at autopsy                        | Death                        |
| Kim et al$^{(2012)}$          | Corticosteroids + VP shunt                                               | Complete recovery            |
| van Ruijven et al$^{(2011)}$  | VP shunt + corticosteroids                                               | Partial recovery             |
| Berhouma et al$^{(2009)}$     | Corticosteroids + right temporal tip lobectomy                            | Complete recovery            |
| Brouwer et al$^{(2009)}$      | Ventriculoscopy-assisted fenestration of lateral ventricle cyst           | Complete recovery            |
| Westhout et al$^{(2008)}$     | Corticosteroids + VP shunt                                               | Complete recovery            |
| Benzagmout et al$^{(2007)}$   | Corticosteroids + external ventricular drain                              | Partial recovery             |
| Muayyil et al$^{(2006)}$      | Corticosteroids + VP shunt                                               | Partial recovery             |
| Muniesa et al$^{(2006)}$      | Corticosteroids + VP shunt                                               | Complete recovery            |
| Onoda et al$^{(2004)}$        | Corticosteroids + VP shunt                                               | Death from nosocomial pneumonia |
| Chiang et al$^{(2002)}$       | Corticosteroids + VP shunt                                               | Unknown                      |

VP, ventriculo-peritoneal.
and 1 underwent medical management alone. The remaining patient died suddenly and did not receive any treatment as her hydrocephalus was established at autopsy. These results are summarised in table 2 along with the index case. Despite the lack of data on the management of sarcoid-related hydrocephalus, most authors employed the use of medical management prior to surgical management, as in this case. One author even suggested that earlier use of steroids may have precluded the need for surgical placement of a VP shunt altogether.\(^8\)

In general, the management of sarcoidosis can vary depending on the organ system involved. For example, the British Thoracic Society recommends that patients with pulmonary sarcoidosis can be managed without treatment if they remain asymptomatic due to high rates of spontaneous remission.\(^9\) However, neurosarcoidosis rarely undergoes spontaneous remission and remains a severe illness, often requiring long-term treatment. A stepwise approach to management includes using steroids as initial management. The next step up includes methotrexate, mycophenolate mofetil, leflunomide and azathioprine, before finally escalating to biological agents such as infliximab, adalimumab and rituximab.\(^10\)

**OUTCOME AND FOLLOW-UP**

The patient was reviewed 7 weeks after being discharged. At this time, her ACE-R score was 76/100. Her sequential ACE-R assessments with breakdown of scores are shown in table 3.

**DISCUSSION**

It is important to reiterate that establishing a diagnosis of neurosarcoidosis can be challenging and time-consuming. We identified one case where a diagnosis of neurosarcoidosis was established over 10 years after the identification of hydrocephalus. Unfortunately, that patient developed progressive disabilities that did not respond to initial therapy. The authors concluded that establishing a swifter diagnosis could have prevented irreversible neuronal damage, thus highlighting the importance of a timely diagnosis.\(^11\) Histologically, sarcoidosis is characterised by the presence of non-caseating granulomas. A number of immune cell types are found in these granulomas, including macrophages, epithelioid cells and multinucleated giant cells, as well as lymphocytes that are the predominant cell type in the central part of a sarcoid granuloma.\(^12\) Accumulation of activated T cells to the sites of inflammation causes a peripheral lymphopenia which is seen in the majority of patients with sarcoidosis including this case.\(^13\) The epithelioid cells secrete ACE, and this enzyme is widely used as a biomarker in the work-up for sarcoidosis. However, its use is limited, as quoted sensitivity and specificity for elevated ACE in diagnosing sarcoidosis are 41.4% and 89.9%, respectively.\(^16\) Another series of 128 patients with neurosarcoidosis found that CSF protein was raised in 76% of samples, as in this case, with a median CSF protein level of 0.8 g/L, though it may be significantly elevated.\(^17\)

Finally, some of the more common manifestations of neurosarcoidosis include cranial neuropathy, peripheral neuropathy, mononeuropathy, myopathy, psychiatric disorders and cerebellar ataxia.\(^4\) The pathophysiological mechanisms leading to these manifestations are not fully understood, although upregulation of inflammatory cytokines such as tissue necrosis factor α, oxidative damage and alterations in neurotransmitter metabolism are thought to contribute to cognitive deficits.\(^18\)\(^19\) Inflammation of the arachnoid villi may lead to reduced CSF absorption, causing a communicating hydrocephalus and its associated clinical features.\(^20\)\(^21\) The patient’s elevated blood pressure (ranging between 191/114 mm Hg and 220/142 mm Hg) was felt to be due to her poor compliance with antihypertensives secondary...
Learning points

- This case demonstrates an important sequela of sarcoidosis.
- The lack of a confirmatory test and the multisystemic nature of sarcoidosis can make its diagnosis very challenging.
- There is a lack of evidence as to whether medical or surgical management or a combination of the two, would be the most appropriate treatment in sarcoïd-related hydrocephalus.
- Prompt diagnosis may result in more favourable outcomes, and a multidisciplinary approach towards diagnosis and management is recommended.

To her cognitive impairment. Hypertension can also occur in sarcoidosis secondary to autonomic dysfunction caused by a small fibre neuropathy or due to renal dysfunction caused by interstitial granulomatous nephritis or other glomerular pathologies. There was no evidence of renal involvement in this patient at the time this report was written.

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