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Original Communication

Pitfalls in the diagnosis and care of patients with suspected neurosarcoidosis: A retrospective analysis

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ABSTRACT

Neurosarcoidosis is a rare disease. Diagnosis and treatment can be very challenging since clinical examination, laboratory and imaging findings are often non-specific. Neural tissue biopsy is frequently not feasible because of the location of suspicious lesions, and biopsy results can be misleading. We screened the local database at our University Hospital, offering an outpatient unit for patients with neurosarcoidosis, for patients with major obstacles and turnarounds during diagnostic work-up or treatment for suspected neurosarcoidosis. We identified 4 patients with a challenging work-up and unexpected final diagnosis. The first patient showed an intramedullary lesion suspicious for a malignant brain tumor. Diagnostic reevaluation showed mediastinal lymphadenopathy with non-caseating granulomas. Another patient turned out to have cerebral tuberculosis after two misleading biopsies and was being treated for neurosarcoidosis for almost one year. The third patient with only minor imaging findings showed severe problems with hydrocephalus after lumbar puncture despite having a ventriculoperitoneal shunt. The last patient turned out to have an intracranial germinoma after three biopsies and more than 6 months of treatment for suspected neurosarcoidosis. Neurosarcoidosis is known to mimic several neurological diseases and even with histopathology diagnosis can be challenging. The final diagnoses that were made in our patients had dramatic impact on treatment. Therefore, diagnosis and treatment should be preferentially done at tertiary hospitals in a wide interdisciplinary setting. In particular, the necessity of obtaining multiple biopsies in order to establish a reliable diagnosis emerges from the experience with the case series presented here.

KEYWORDS: neurosarcoidosis, histopathology, biopsy, ventriculoperitoneal shunt, germinoma, differential diagnosis, tuberculosis, brain tumor, hydrocephalus.

INTRODUCTION

In 5-13% of cases sarcoidosis affects the nervous system [1-3]. Neurosarcoidosis can affect the nervous system in different ways and thereby can mimic several neurologic diseases [4, 5]. Therefore, diagnosis of neurosarcoidosis can be challenging. Biopsy of inflamed tissue is the gold standard for diagnosis but is often not warranted due to the usually critical location of the lesions [6, 7]. Moreover, imaging findings vary heavily and laboratory markers like angiotensin converting enzyme (ACE) or the soluble interleukin 2 receptor lack sensitivity and specificity

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[4, 8-10]. In most cases subclinical systemic involvement can help to reach the diagnosis. Especially, mediastinal lymphadenopathy is often more easy to reach with a biopsy. Sarcoidosis may affect every organ but patients with neurosarcoidosis usually present with neurologic symptoms before systemic sarcoidosis is diagnosed.

Neurosarcoidosis is a very rare disease. Therefore, larger patient cohorts or randomized clinical trials are lacking and single case reports or case series have particular relevance for clinical practice. We screened the local database at our University Hospital, offering an outpatient unit for patients with neurosarcoidosis, for cases with major obstacles and turnarounds during diagnostic work-up or treatment.

PATIENTS AND METHODS

Study design

At the Center of Neurology and Neurosurgery (University Hospital Frankfurt, Germany) we are offering an outpatient unit for neurosarcoidosis. We screened our database for patients with major obstacles and turnarounds during diagnostic work-up or treatment. Patient characteristics and the course of the disease were recorded, based on our medical records. Chest x-rays, magnetic resonance imaging (MRI) and computed tomography (CT) scans were retrospectively evaluated during diagnostic work-up and follow-up.

RESULTS

We identified 4 patients with suspected neurosarcoidosis with a challenging work-up and unexpected final diagnosis.

Patient 1

The 42-year old female was admitted to our center after a 4-week period of sensory deficits in both arms and neck pain. On the day of admission she additionally recognized sensory deficits in her legs. Initial MRI scans of the spine showed an extensive lesion on post contrast T1 and T2 sequences (Figure 1 A). Chest x-ray was normal (Figure 1 B). Cerebrospinal fluid (CSF) analysis showed lymphocytic pleocytosis (40/µl) but negative polymerase chain reaction (PCR) results for viral or bacterial pathogens. Screening for vasculitis, rheumatoid diseases and ACE (serum) was negative. As visual-evoked potentials showed a pathologic delay from the left eye, a longitudinal extensive transverse myelitis was suspected, despite aquaporin-4 antibodies suggestive for neuromyelitis optica (NMO) were negative. Therefore, intravenous methylprednisolone (1000 mg) was administered for 5 days. This led to a relief in her pain and her sensory deficits improved as well. Within a few days after this initial improvement she deteriorated again with mild spastic paraparesis and urinary incontinence. Then, 12 cycles of plasmapheresis together with

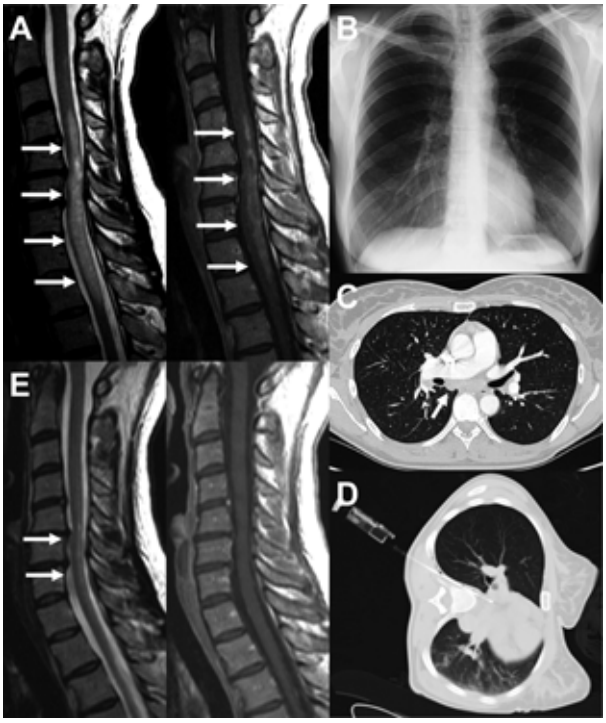

Figure 1. Female patient with initially suspected longitudinal extensive transverse myelitis (LETM) that turned out to be neurosarcoidosis.

Initial MRI (A) showed an extensive signal alteration on T2 sequences (left, arrows) with marked contrast enhancement on T1 (right, arrows). Initial diagnostic work-up showed a normal chest x-ray (B). At reevaluation after futile short-term steroid treatment a CT scan (C) was performed which showed mediastinal lymphadenopathy (arrow). A CT-guided biopsy was done (D) and histopathology showed non-caseating granulomas. After long-term oral steroid treatment the lesion resolved (E).

another intravenous steroid pulse was administered. Again she showed a marked clinical improvement and was transferred to rehabilitation. Nonetheless, MRI follow-up showed an increase in the lesion volume. Therefore, the possibility of a neoplastic process was discussed. Due to the localization, a biopsy was associated with an increased risk for perioperative morbidity. Therefore, diagnostic reevaluation was done 6 months after initial symptom onset. A CT scan of the lungs showed mediastinal lymphadenopathy (Figure 1 C), and a bronchoalveolar lavage including an ultrasound-guided biopsy of a lymphnode was done. CD4/CD8 ratio increased to 3.75 but histopathology was normal. Therefore, a CT-guided biopsy was done (Figure 1 D). Now histopathology showed an epithelioid granuloma suggestive for sarcoidosis. The patient was put on continuous oral steroids and the intramedullary lesion almost completely regressed within 6 months (Figure 1 E) with only mild residual symptoms.

Patient 2

This 35-year old male patient was referred to our department of neurosurgery by a smaller hospital because of a first epileptic seizure and a suspected brain tumor on MRI scans. Initial diagnostic work-up including screening for tuberculosis was reported to be without pathological findings. Initial MRI scans showed a contrast enhancing lesion in the left frontal lobe (Figure 2 A). Additional MRI including perfusion and spectroscopy did not corroborate the diagnosis of a brain tumor. CSF analysis showed normal values. Therefore, a vascular pathology (i.e. hemorrhage) was discussed and a MRI follow-up including MR angiography was recommended. As the lesion slightly increased a vascular pathology was regarded unlikely and an inflammatory process was suspected. A CT scan of the lungs showed mediastinal lymphadenopathy (Figure 2 B), and a bronchoalveolar lavage including an ultrasound-guided biopsy of a lymphnode was done. CD4/CD8 ratio was normal and histopathology showed an epithelioid granuloma suggestive for sarcoidosis without acid-fast bacilli, necrosis or signs of neoplastic tissue. Culture of *mycobacterium tuberculosis* from bronchoalveolar lavage was negative. At this time-point we started continuous oral steroid treatment for suspected neurosarcoidosis. Lymphadenopathy resolved quickly, but during further MRI follow-up (Figure 2 C) the brain lesion showed an increase despite steroid treatment. Due to this increase a stereotactic biopsy was performed. Histopathology showed a granulomatous, necrotizing process with focal mineralization. Acid-fast bacilli or signs of neoplastic tissue were not found. A PCR for *mycobacterium tuberculosis* DNA on the biopsy tissue was negative but an interferon-gamma release assay (QuantiFERON-TB Gold Plus) now was positive. Therefore, the suspected diagnosis of sarcoidosis was rejected and a tuberculostatic therapy was started. Further MRI follow-up revealed that the lesions regressed within 2 months of therapy (Figure 2 C, last panel).

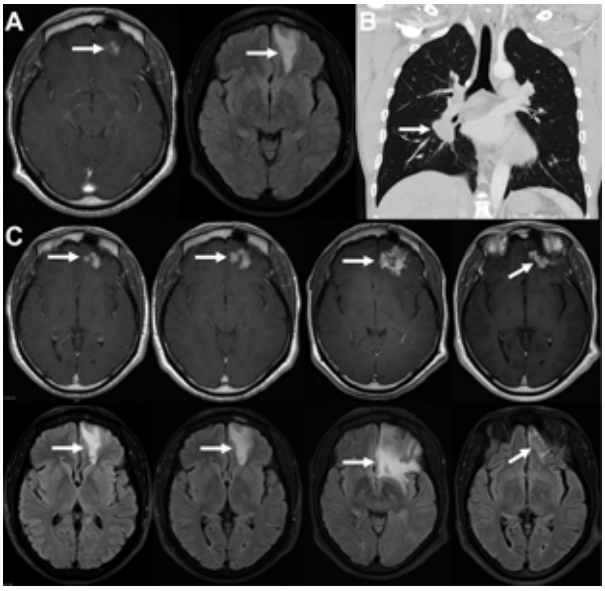

Figure 2. A Patient with contrast-enhanced lesion in the left frontal lobe that turned out to be cerebral tuberculosis.

Initial MRI (A) showed a small lesion with contrast enhancement on T1 (left, arrow) with marked signal alteration on fluid-attenuated inversion recovery (FLAIR) sequences (right, arrow). The CT scan (B) revealed marked mediastinal lymphadenopathy (arrow) and histology revealed non-caseating granulomas. During steroid treatment (C, first three panels from the left) the lesion increased on T1 (upper panel, arrows) and on FLAIR (lower panel, arrows). After reevaluation and initiation of tuberculostatic therapy the lesion markedly regressed (C, last panel from the right, arrows).

Patient 3

The initial diagnostic work-up and treatment in this 29-year old woman was done at a smaller hospital. Her first symptom was headache without any other neurological symptoms. Initial MRI showed several nodular contrast-enhancing lesions in the third and fourth ventricle (Figure 3 A, arrows). These were minor lesions hardly detectable on the MRI scans but resulted in impaired CSF flow and enlarged lateral ventricles. Despite the hydrocephalus a lumbar puncture was done and CSF analysis showed leukocytosis (345/µl, mostly monocytes) without any other abnormalities or acid-fast bacilli. Interferon-gamma release assay (QuantiFERON-TB Gold Plus) was negative but ACE and interleukin-2-receptor were also within normal range. CT scan of the lungs showed mild mediastinal lymphadenopathy and a bronchoalveolar lavage showed a CD4/CD8 cell ratio of 7.2. Nonetheless, central nervous system (CNS) tuberculosis was suspected and tuberculostatic therapy was started. Short-term follow-up MRI did not show any relevant improvement. Two months later she presented at our emergency department with dramatically increasing headache. Due to massive enlargement of the lateral ventricles she immediately received a ventricularperitoneal shunt (Figure 3 B, before and after shunt implantation). Further, diagnostic reevaluation still revealed mediastinal lymphadenopathy and an ultrasound-guided endobronchial biopsy was done. Histopathology showed epithelioid granuloma suggestive of sarcoidosis. Tuberculostatic therapy was stopped and steroid treatment was started. The clinical symptoms and the MRI scans improved. Three months later when the steroid dose was reduced to 20 mg daily, she showed up in our outpatient unit. Her clinical symptoms had slightly improved but the MRI scan showed an increase in the nodular contrast-enhancing lesions. Methylprednisolone was increased to 50 mg and an immunosuppressive therapy with azathioprine (50 mg daily) was started. During the following weeks she showed massively elevated transaminases and was admitted to hospital again. Transaminases normalized after cessation of azathioprine. Cerebral MRI now showed absent contrast enhancement and normal lateral

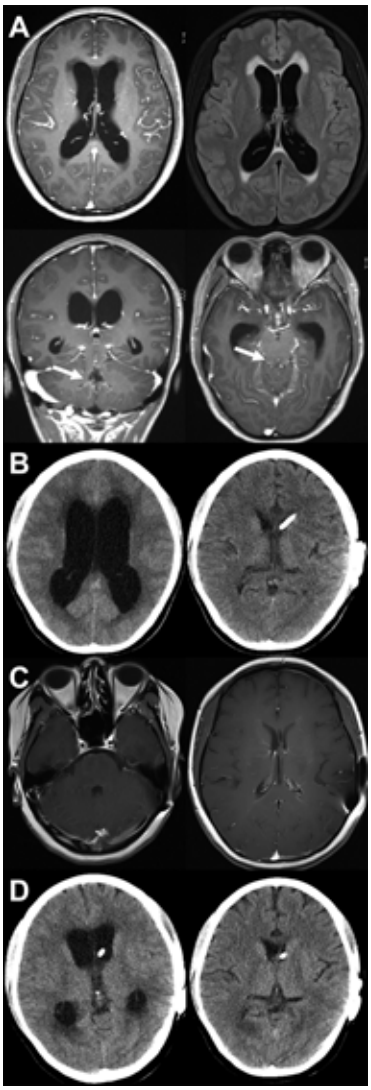

Figure 3. A Patient with minor contrast enhancement in the third and fourth ventricle and repetitive hydrocephalus.

Initial MRI showed small nodular contrast-enhancing lesions in the third and fourth ventricle resulting in hydrocephalus (A, arrows). A CT scan two months later, requested because of increasing headache, showed further enlargement of lateral ventricles (B, left). After shunt implantation the follow-up CT scan showed normal ventricles (B, right). After combined immunosuppressive treatment with steroids and azathioprine contrast enhancement fully resolved (C). Because of a blurred vision a lumbar puncture was done three days after this MRI (C). Within a few hours the patient deteriorated and a CT scan showed hydrocephalus (D, left). After 20 ml CSF has been withdrawn from the reservoir of the shunt system the patient rapidly improved (D, right).

ventricles (Figure 3 C). Due to mild reduction in vision on both eyes, a lumbar puncture was done three days after the MRI. CSF analysis mainly showed lympho-monocytic leukocytosis (52/µl). Within several hours after this lumbar puncture the patient deteriorated with signs of increased intracranial pressure and the CT scan now showed a hydrocephalus with enlarged lateral ventricles and enlarged third ventricle (Figure 3 D). Further diagnostics did not show an obvious malfunction of the shunt system. After 20 ml CSF were withdrawn from the reservoir of the shunt system the patient rapidly improved. Interestingly, the disturbed vision also improved, suggesting that she already suffered from increased CSF pressure before developing the hydrocephalus. Nonetheless, this sequence suggests that there must have been some kind of valve mechanism between the third and the fourth ventricle and a malfunction of the shunt system. Now she was put on infliximab and weekly methotrexate while prednisolone was reduced slowly. As she progressed again when prednisolone was reduced to 7.5 mg, methotrexate was changed to mycophenolate mofetil. Until today, two years after initial symptoms, MRI scans did not show abnormalities and she is still on infliximab, mycophenolate and 7.5 mg prednisolone.

Patient 4

This 22-year old male was referred to our institution from a smaller hospital. He reported of nausea and vertigo in combination with a weight loss. Gastroscopy and colposcopy were normal. After discharge from hospital a cerebral MRI scan was done (Figure 4 A). This showed mainly periventricular contrast enhancement at the lateral ventricles, the third and the fourth ventricles. Further, contrast enhancement was seen in the area of the pituitary gland and the lateral ventricles were enlarged (Figure 4 A). Now a lumbar puncture was done and due to the elevated CSF protein and the contrast enhancement seen in the MRI scans, bacterial meningoencephalitis was assumed and the patient was treated with ceftriaxone and ampicillin. As CSF, clinical condition and MRI did not improve he was transferred to our institution. As enlargement of the lateral ventricles increased he needed a ventriculoperitoneal shunt.

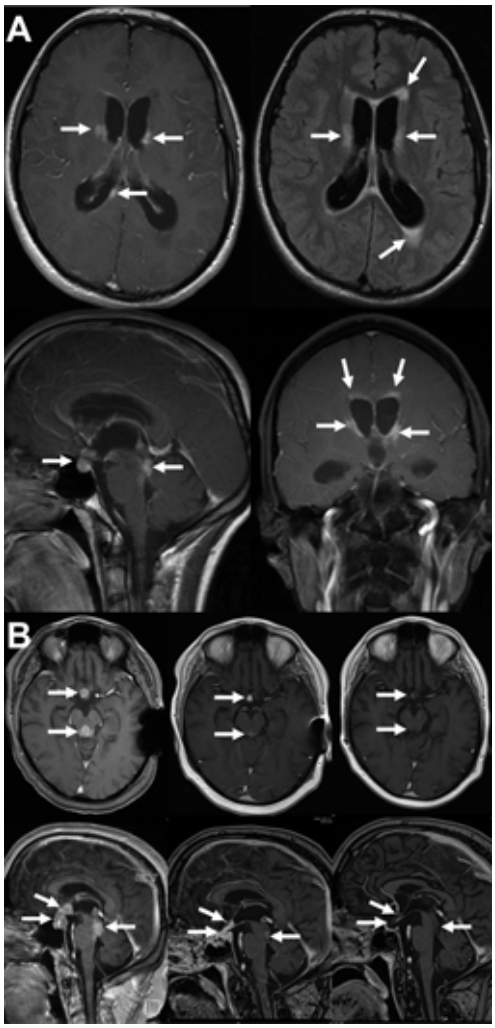

Figure 4. A Patient with multifocal contrast enhancement that turned out to be a bifocal germinoma.

Initial MRI (A) showed multifocal and diffuse contrast enhancement (arrows) with a focus on the periventricular area (upper left and lower right), the pituitary gland (lower left) and the pineal region (lower left). FLAIR sequences were rather moderately affected (upper left, arrows). The further MRI follow-up is shown in B. The first panel shows an increase in the lesions in the pituitary gland and the pineal region (arrows) while the periventricular enhancement completely resolved during steroid treatment. After a third biopsy showed an intracranial germinoma, chemotherapy was initiated and the tumor responded (B, second and third panel, arrows).

During this intervention a stereotactic biopsy of a periventricular lesion was performed. Histopathology showed marked lymphocytic

inflammation around blood vessels suggestive of encephalitis. All analyses for tuberculosis were negative and a diagnostic work-up for neurosarcoidosis was done. Except for a slightly elevated interleukin-2-receptor (663 U/ml) results were normal. Nonetheless, neurosarcoidosis was suspected and an intravenous steroid therapy was initiated. This resulted in a marked clinical improvement and contrast enhancement partly resolved. During dose reduction to 15 mg prednisolone a clinical deterioration developed and MRI worsened. Despite escalation of prednisolone and additional treatment with methotrexate the contrast enhancement progressed around the pituitary gland and the pineal region and another biopsy from the pituitary gland was performed (Figure 4 B, first panel). Now we suspected an intracranial, bifocal germinoma despite the fact that alpha-fetoprotein (AFP) and beta human chorionic gonadotropin (ß-hCG) were normal. Histopathology did not give a clear result, especially no signs of inflammation or neoplastic cells. Therefore, another biopsy was performed. Now histopathology showed the morphology of an intracranial germinoma. Chemotherapy consisting of carboplatin, etoposide and ifosfamid (SIOP CNS GCT II study) was started and the contrast-enhancing lesions responded completely within 2 months (Figure 4 B, second and third panel).

DISCUSSION

Our case series illustrates some of the frequent challenges when neurosarcoidosis is on the list of differential diagnoses. Neurosarcoidosis could cause nearly every neurological symptom, but due to its low incidence detailed experienced with this disease is often lacking. Differential diagnoses include infectious diseases (tuberculosis, mycosis, toxoplasmosis, etc.), tumors (leptomeningeal metastases, meningioma, glioma, lymphopma, etc.) and other neurological diseases (Multiple sclerosis, acute demyelinating encephalomyelitis). Less important are other granulomatous diseases (Wegener´s granulomatosis, Churg Strauss syndrome, lymphomatoid granulomatosis), vasculopathies (vasculitis, Behcet´s disease), amyloidosis and lymphocytic adenohypophysitis. Therefore, diagnostic work-up for suspected neurosarcoidosis is challenging. Diagnosing neurosarcoidosis requires a compatible radiological and clinical picture as well as a histology of noncaseating granulomas [4]. Other relevant differential diagnoses have to be excluded.

In our first patient a longitudinal extensive transverse myelitis was initially suspected and the patient was treated with intravenous methylprednisolone and later with plasmapheresis. As both did not result in a sustained clinical improvement and MRI scans worsened, a tumor was suspected and a possibility of radiotherapy was discussed. Reevaluation now revealed pulmonary involvement and histopathology suggested sarcoidosis. Continuous treatment with steroids resulted in a marked and sustained regression of symptoms and MRI lesions. This case points at two important issues. First, it illustrates that systemic diagnostic work-up is useful in these cases and second, steroid treatment of neurosarcoidosis should be done on a continuous and oral basis [4]. In critical patients an intravenous steroid pulse may precede oral treatment [4]. Regarding systemic diagnostics this case speaks in favor of performing CT scans of the lung. Further, bronchoalveolar lavage should be done including flow cytometric analyses of lymphocytes and biopsy if mediastinal/hilar lymphadenopathy is accessible.

Our second patient showed the classical history of a brain tumor patient presenting with an epileptic seizure but no neurological deficits. Screening for tuberculosis was reported to be negative and the referring hospital suspected a primary brain tumor. As MR perfusion and spectroscopy did not corroborate this diagnosis we decided to do MRI follow-up. As the lesion increased in size and a tumor was regarded unlikely we started systemic diagnostic work-up for suspected neurosarcoidosis. Histology of mediastinal lymphadenopathy was suggestive of sarcoidosis and steroid treatment was initiated. As the brain mass increased during steroid treatment a stereotactic biopsy was performed. Again histopathology was suggestive of sarcoidosis while tuberculosis could not be fully excluded because of necrosis. Analyses for tuberculosis on biopsy specimen were negative including PCR. Interestingly, it has been shown that necrosis is not sufficient to discriminate between sarcoidosis

and tuberculsosis [11, 12]. With this uncertainty we repeated an interferon-gamma release assay that now was positive. With this result we decided against escalation of immunosuppressive treatment and initiated tuberculostatic treatment which resulted in a prompt and marked reduction in the lesion. This illustrates how difficult it can be to distinguish between neurosarcoidosis and tuberculosis. This is of particular importance as immunosuppressive treatment for sarcoidosis could have adverse and even life-threatening effects on patients with tuberculosis.

The diagnostic work-up on the third patient was not a major challenge but points to the critical complication of hydrocephalus due to neurosarcoidosis in or around the third and fourth ventricles [13]. As hydrocephalus might occur suddenly this could rapidly lead to a life-threatening situation. In our patient the manifestation in third and fourth ventricles even resulted in a rare complication after lumbar puncture during treatment. Shortly after lumbar puncture she developed acute hydrocephalus despite already having a shunt, and MRI did not show relevant contrast enhancement. In this specific case we assume a valve mechanism between the third and the fourth ventricle and some kind of malfunction of the shunt system. Therefore, decision on lumbar puncture in such patients should always be made cautiously and usually not without a recently performed brain MRI.

In the fourth patient it needed three biopsies to clarify the diagnosis. Initial histopathology showed marked lymphocytic inflammation and soluble interleukin-2 receptor was slightly elevated. As follow-up MRI showed a mixed response during steroid treatment a second and third biopsy were done. Now a germinoma could be diagnosed. This illustrates that germinomas may show a lymphoplasmacellular reaction that could obscure neoplastic elements, can resemble sarcoidosis or tuberculosis and hamper correct diagnosis [14, 15]. Germinoma is often associated with granulomatous inflammation [16-18]. This might lead to pitfalls in the assessment of e.g. pineal or pituitary gland lesions. The diagnosis of granulomatous inflammation in these particular areas should remind one of the differential diagnosis of germinoma; thus further clinical examination or laboratory investigation should be performed. Further, this patient also suffered from acute hydrocephalus and needed immediate surgical intervention. In our patients with probable neurosarcoidosis ACE and soluble interleukin-2 receptor were negative, while in this case of intracranial germinoma soluble interleukin-2 receptor was at least slightly elevated. This exemplifies that these biomarkers might be helpful but are usually not reliable.

CONCLUSION

Neurosarcoidosis is a rare disease and the list of differential diagnoses is usually long. Therefore, diagnostic work-up is often challenging. Our retrospective series corroborates that patients with suspected neurosarcoidosis should usually be referred to a tertiary hospital to ensure an interdisciplinary and experienced work-up. Probable diagnoses should always be critically scrutinized as different diseases need contrary treatment approaches. In particular, the necessity of obtaining multiple biopsies in order to establish a reliable diagnosis emerges from the experience with the case series presented here.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

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