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A rare case of sarcoid myelitis complicating Löfgren's syndrome

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Abstract. Neurosarcoidosis is a rare and serious condition. Rapid diagnosis and treatment are crucial to prevent morbidity and mortality. When neurological symptoms are not present at the time of diagnosis, CNS involvement can be undetected. We present a case of neurosarcoidosis complicating Löfgren's syndrome and discuss the challenges in diagnostics and treatment, that can be encountered.

Key words: Sarcoidosis, Neurosarcoidosis, Infliximab, TNF-alfa-inhibitors

Introduction

Sarcoidosis is an inflammatory, noncaseating, granulomatous disease potentially affecting almost every organ in the body. Manifestation of symptoms varies considerably, and diagnostics of patients presenting with atypical symptoms and without pulmonary involvement may thus be challenging.

Neurosarcoidosis is a rare and serious manifestation, presenting in 5-10% of cases and prompt treatment is often required (1).

The clinical manifestations of neurosarcoidosis are heterogeneous as any part of the nervous system may be affected e.g., the brain, the meninges with cranial nerve affection, the spinal cord, and the peripheral nervous system (2). The most common reported clinical presentation in neurosarcoidosis is cranial neuropathy, most frequently involving the facial and optical nerves. Other frequent presentations are headache, sensory disturbances and, less frequently, motor symptoms (2).

The broad spectrum of symptoms and challenges in diagnostics constitute a risk of underestimation and diagnostic delay leading to increased morbidity and mortality.

Neurosarcoidosis is diagnosed based on clinical symptoms, imaging, cerebrospinal fluid and histopathological findings, and exclusion of differential diagnoses (3,4).

The Neurosarcoidosis Consortium Consensus Group has defined neurosarcoidosis according to the probability of the disease. A diagnosis of probable neurosarcoidosis requires histopathology with noncaseating granulomas outside the nervous system. A definite diagnosis is established with presence of granulomas within the central or peripheral nervous system (5). Often multiple investigations are needed to clarify the extent of the disease and exclude differential diagnoses. Chest radiograms, High Resolution Computed Tomography (HRCT) and [18F]Fluorodeoxyglucose Positron Emission Tomography CT (FDG-PET/CT) can display suitable locations for biopsy. Gadolinium-enhanced magnetic resonance imaging, cerebrospinal fluid analysis and electroneuronography may indicate involvement of the nervous system (3).

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When the diagnosis is established, treatment options are few and evidence of their effect is limited (6). Corticosteroid is first-line treatment; second-line treatment with methotrexate, mycophenolate or azathioprine is often rapidly added. Third-line therapy includes tumour necrosis factor alpha (TNF-alpha) inhibitors, most commonly infliximab (3). Unfortunately, one third of patients with neurosarcoidosis do not respond to the full scale of treatment (2).

We present a case report of the diagnostic pathway and treatment in a patient with neurosarcoidosis with affection of the spinal cord.

Case presentation

A 27-year-old formerly healthy male presented with severe ankle arthralgia causing absence from work. C-reactive protein was elevated to 50 mg/L (normal range < 8 mg/L). The patient was referred to the Department of Rheumatology where ultrasonography of the joints showed only subcutaneous and no intra-articular oedema. Blood tests showed negative rheumatoid factor and cyclic citrullinated peptide and the pain and swelling remitted spontaneously within a few weeks. A chest X-ray showed bilateral hilar adenopathy and a supplementary chest CT confirmed mediastinal lymphadenopathy and showed multiple bilateral parenchymal small nodulus < 4 mm, compatible with pulmonary sarcoidosis.

The patient was referred to the Department of Pulmonology at a regional hospital where supplementary blood tests showed elevated P-Peptidyldipeptidase 79 U/L (normal range 12-60 U/L) and P-Interleukin 2-receptor 1217 kU/L (normal range 158-623 kU/L). Dynamic lung volumes were within the normal range. The clinical history, laboratory test results and imaging were compatible with Löfgren's syndrome, and no biopsy was thus found necessary.

During regular follow-up every four months for two years, the patient remained stable with normal lung function and no treatment was initiated.

Two years after onset of symptoms, the patient consulted his general practitioner with a four-month history of paraesthesia in both arms triggered by neck flexion (Lhermitte's sign). Magnetic Resonance Imaging (MRI) of the brain and spinal cord showed gadolinium enhancement and oedema on T2 FLAIR sequences of the spinal cord. Because of a history with sarcoidosis, neurosarcoidosis was suspected (Figure 1). There was no intracerebral involvement.

Figure 1. Concomitant FDG PET/CT and MRI images obtained at the time of neurological work-up. In the left column, FDG PET/CT demonstrates avid FDG uptake in mediastinal and hilar lymph nodes as well as longitudinal FDG uptake in the spinal cord with maximum SUV values (4.77) exceeding the normal values of the thoracic part of the spinal cord by a factor of 2.5 (black arrow). In the right column, T2 weighted STIR images demonstrates marked hyperintensity of the entire spinal cord from the foramen magnum to the medullary conus with persistent oedema (yellow arrow) in the thoracic part.

Six months after his first contact to his general practitioner the patient was examined at the Department of Neurology, outpatient clinic. His symptoms included fluctuating pain from the neck, between the shoulder blades and the lumbar spine region and hypersensitivity to touch on the abdomen and in the legs.

A clinical neurological examination demonstrated sign of medullary affection with bilateral ankle clonus, hyperreflexia of the patella and achilles tendon reflexes, positive Babinski sign on the right side, non-response on the left, reduced sensibility to pinprick at legs and abdomen with an upper level at Th8. No parasympathetic dysfunction such as urinary retention was present. Due to the leg spasticity, he was hampered by exhaustion in the lower extremities when at work as a truck driver.

Cerebrospinal fluid analysis showed increased white blood cell counts to 123 x 10^6/L (normal range <5 x 10^6/L) and elevated protein levels to 2.48 g/L (normal range 0.15-0.60 g/L). Subsequent analysis was negative for tumour cells, Borrelia Burgdorferi and the 11 most common bacteria and viruses causing meningitis. A FDG-PET/CT scan was performed showing increased activity in enlarged mediastinal and upper abdominal lymph nodes, and in the spinal cord (Figure 1).

A bronchoscopy with endobronchial ultrasound (EBUS) biopsy from the mediastinal lymph nodes and bronchoalveolar lavage (BAL) was performed. Bronchoscopy revealed red oedematous airways with a cobblestone appearance suggestive of endobronchial sarcoidosis. Both mucosal biopsies and EBUS from the mediastinal lymph nodes showed noncaseating granulomas without dysplasia or malignancy. BAL cell differential showed 48% lymphocytes and a high CD4/CD8 ratio of 17.0; BAL cultures were negative. A diagnosis of probable neurosarcoidosis according to the Neurosarcoidosis Consortium Consensus Group diagnostic criteria was made. Immediately after biopsy, treatment was initiated with high dose methylprednisolone 1 g intravenously for three days followed by oral corticosteroids. As soon as histopathology confirmed granulomas, treatment with oral Methotrexate 15 mg once a week was initiated. Initial prednisolone dose following methylprednisolone was 0.5 mg/kg equal to 60 mg. Dose was reduced bi-weekly with 10-12,5 mg until 25 mg. Afterwards dose reduction was adjusted with 5-2,5 mg every four weeks until 10 mg. Subsequently dose was reduced 1,25 mg in relation to out-patient follow up with regards to symptoms. Tapering from 10 mg proceeded over 18 months. At no point the patient needed dose increase because of flair up in symptoms.

Three months after initiation of treatment, spinal cord oedema was reduced on T2 FLAIR MRI. The patient had no progression of symptoms in this time period, but persistent back pain and altered sensibility and spasticity in his lower extremities. After a multidisciplinary team (MDT) conference with participation of doctors from neurology, pulmonology, rheumatology and nuclear medicine, it was decided to initiate TNF-alpha inhibitor treatment to improve disease control. However, after two months, the patient's neurological deficits were unchanged. No other symptom-relieving treatment was initiated.

Discussion

This case demonstrates a rare case and unusual clinical presentation of neurosarcoidosis as well as the challenges in diagnostics and treatment. The patient presented with Löfgren's syndrome, which normally predicts a benign and self-remitting disease course (7). When the patient two years later developed neck and back pain and paraesthesia, the symptoms were not initially linked to sarcoidosis, resulting in the diagnostic delay of neurosarcoidosis of approximately 10 months. The diagnostic delay in the present case is probably also related to the time span between the diagnosis of Löfgren's syndrome and the emergence of a rare type of neurological symptoms not often seen in neurosarcoidosis.

However, it is crucial to keep in mind that neurological symptoms are the initial symptoms in only 50% of patients with neurosarcoidosis, (2). These patients may also lack any pulmonary symptoms, yet they are most likely to have an abnormal chest CT with hilar lymphadenopathy in addition to their neurosarcoidosis (8).

Due to the variety of symptoms, the diagnosis of neurosarcoidosis often requires a specialist multidisciplinary effort. Reduced time to diagnosis and treatment initiation is desirable and probably important to minimise the risk of permanent loss of function. It is crucial to identify the extent of the disease at the time of diagnosis and be aware of additional organ manifestations during follow-up, as these may evolve years after the diagnosis and cause irreversible organ damage. A thorough follow-up programme is

recommended, and patients should be informed of the possible risk of other critical organ involvement and advised to seek medical evaluation rapidly if symptoms develop from e.g., the eyes, the heart and the nervous system.

The gold standard in the diagnosis of interstitial lung disease and cancer (9-10) is MDT conferences, but these are equally valuable in multi-organ sarcoidosis. A MDT set-up for multi-organ and complicated sarcoidosis has been a part of the sarcoidosis programme at our institution for several years, yet this case of neurosarcoidosis complicating Löfgren syndrome is the only case we have encountered.

Standard first-line treatment with glucocorticoid was initiated and rapidly followed by a steroid-sparing agent. The patient experienced some improvement, but in order to achieve better inflammatory control treatment with TNF-alpha inhibitor was initiated. In recent literature considerations regarding advancement of TNF-alpha in treatment of severe neurosarcoidosis has been made and this case supports the relevance of this consideration (11).

Our case emphasises the need for regular and thorough evaluation with high awareness of organ-related symptoms and a low threshold for further diagnostics in patients with sarcoidosis in a MDT set-up.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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