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Case report

A young man with transitory hemiparesis and lung infiltrates

A 26-year-old male patient was referred to the University Hospital due to headache and several transitory episodes of hemiparesis, facial paresis and diplopias. He had experienced a tick bite and traffic accident without injury 1 month earlier. His medical history included asthma and taking an inhaled corticosteroid plus long-acting β-agonist on a daily basis.

At admission the patient had meningismus, mild left hemiparesis and facioparesis, while other examinations were normal.

Routine laboratory tests showed mildly increased serum calcium 2.54 mmol·L^{-1}, blood eosinophilia (1.1×10^{9} cells per L) and elevated angiotensin-converting enzyme (ACE) 60 U·L^{-1}. ECG and arterial blood gas analysis were normal, but chest radiography showed an infiltrate in the left lung (figure 1a). Thoracic high-resolution computed tomography (HRCT) scan revealed patchy ground-glass opacities with peribronchovascular distribution, dense micronodular interstitial pattern (red arrow) and thickened interlobular septa (white arrow) (figure 1b).

Head CT scan, cerebrospinal fluid analysis and electromyoneurography were unremarkable. Magnetic resonance imaging (MRI) of the brain showed a slightly thickened dura (figure 2), CT and magnetic resonance angiography showed no signs of vascular lesions.

Task 1
What is your differential diagnosis?

a) Neuroborreliosis
b) Traumatic spine injury
c) Eosinophilic granulomatosis with polyangiitis (EGPA)
d) Multiple sclerosis
e) Neurosarcoidosis
f) All of above
g) None of above

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Additional laboratory tests were performed: *B. burgdorferi* serology, which was negative, antinuclear (ANA) and antineutrophil cytoplasmic (ANCA) antibodies were also negative.

Bronchoscopy was performed because of the incidental finding on chest radiography and lung CT which showed normal airways with pale bronchial mucosa and highlighted small submucosal blood vessels. Bronchoalveolar lavage (BAL) was obtained from lingula (cellular composition: alveolar macrophages 92%, lymphocytes 3%, neutrophil granulocytes 2% and eosinophil granulocytes 3%). Transbronchial lung biopsy samples were obtained from the anterior segment of the left lower lobe (figure 3a–c).

Cite as: Ljilja A, Radović N, Tekavec-Trkanjec J. A young man with transitory hemiparesis and lung infiltrates. *Breathe* 2021; 17: 210069.

@ERSpublications
In patients with neurological symptoms when other neurological causes are excluded, a differential diagnosis of neurosarcoidosis should be considered taking into account the clinical picture, radiological and laboratory findings. https://bit.ly/3oMSBap

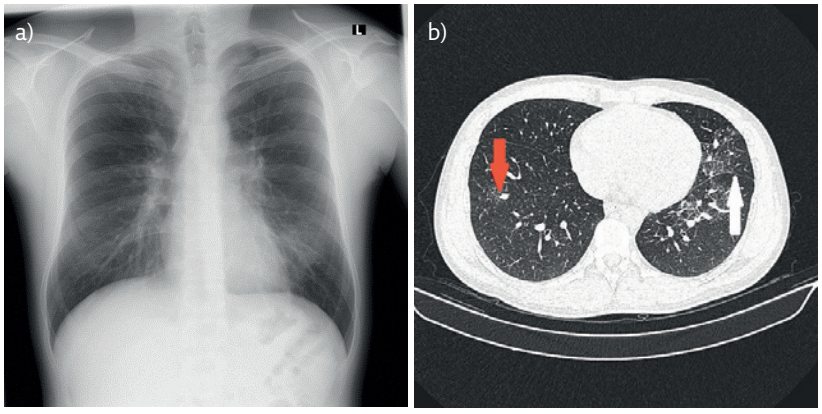

Figure 1 *a) Chest radiograph showing infiltrate in the left lung. b) HRCT of the thorax, red arrow pointing to the micronodular pattern and white arrow pointing to septal thickening.*

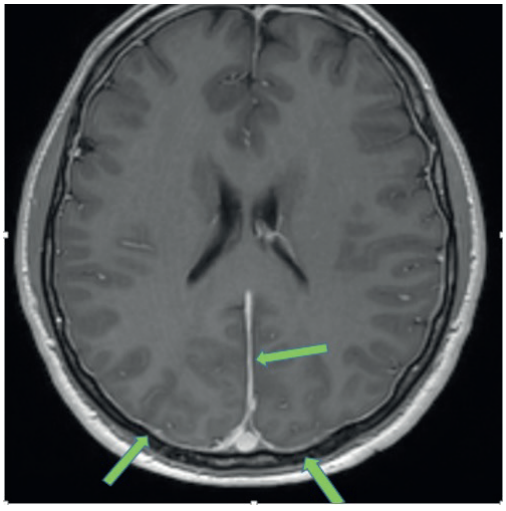

Figure 2 *Thickening and imbibition of dura on brain MRI.*

Task 2
What is the most likely diagnosis based on the transbronchial lung biopsy findings (figure 3)?

a) Tuberculosis
b) Sarcoidosis
c) EGPA
d) Multiple sclerosis
e) Other

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Calcium in daily urine (dU) was mildly elevated (9.16 mmol·dU^{-1}), unfortunately vitamin D and parathyroid hormone (PTH) levels were not obtained during diagnostic evaluation. The patient was referred to the multidisciplinary team for interstitial lung diseases. The multidisciplinary team concluded that the morphology of granulomas and clinical presentation was most suggestive of sarcoidosis, hence the neurological symptoms and MRI findings could be consistent with neurosaroidosis.

Task 3
What would be your first choice of treatment for this patient?

a) "Watch and wait"
b) Prednisone
c) Methotrexate
d) Infliximab

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Knowing that vasculitis of small blood pulmonary vessels could cause pulmonary hypertension, we performed echocardiography which was normal. The patient did not have any cardiac symptoms such as arrhythmias, impaired cardiac function or disproportionate breathlessness. Neurological evaluation (magnetic resonance with angiography, spinal tap) did not confirm vascular changes, but further evaluation would be considered if the patient did not improve on the corticosteroid therapy given.

The patient was admitted to the pulmonary outpatient hospital 1 month later for evaluation, without any respiratory symptoms. Chest radiography showed partial regression of the left lung infiltrate. Spirometry showed mild airflow obstruction (forced expiratory volume in 1 s (FEV_1) 80%, FEV_1/forced vital capacity 0.63) and mildly reduced lung diffusing capacity (77%). He complained only of headache and finger paraesthesia. Prednisone dose was gradually reduced over 1 year to a dose of 10 mg prednisone.

After induction of corticosteroids the patient did not have any further neurological deficits on regular follow-up to a period of 1 year. Hypercalcaemia and hypercalciuria also regressed with corticosteroid therapy.

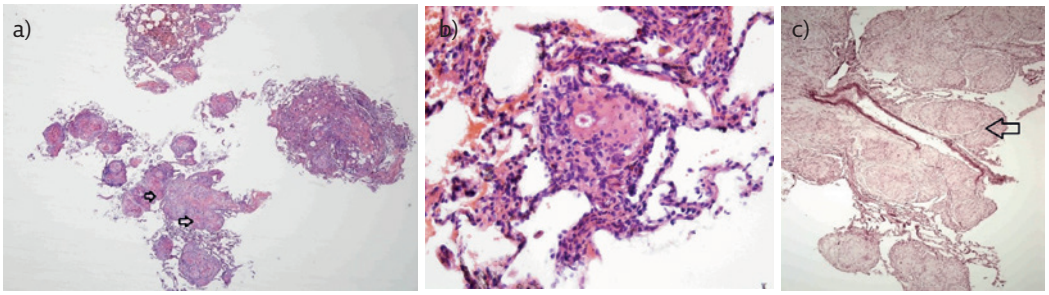

Figure 3 *a–c) Transbronchial lung biopsy samples.*

The diagnosis of neurosarcoidosis in this case was clinical and was supported by the response to therapeutic challenge with corticosteroids. In some cases, such as this one, only extensive diagnostic procedures and close follow-up can make the right diagnosis possible.

Discussion

Sarcoidosis is a systemic granulomatous disease of unknown aetiology [2]. The incidence is estimated to be between 10 and 20 per 100000 population [3]. The respiratory system is the most commonly affected, but it can affect almost every organ system. Mortality rate is 1–5%, most commonly due to pulmonary, cardiac or neurological disease [2].

The diagnosis of sarcoidosis relies on the presence of noncaseating well-defined granuloma on histopathological examination, compatible clinical presentation, and exclusion of other granulomatous diseases [4].

BAL fluid analysis can be an aid in the differential diagnosis with a grouping of features commonly seen in sarcoidosis: increased cellularity with predominantly lymphocytic alveolitis and elevated CD4/CD8 ratio. However, sometimes it depends on clinical presentation, activity and chronicity at the time the BAL is performed as well as the smoking status [5]. The patient had BAL lymphocytes in normal range, probably because he was smoker. At the time of the bronchoscopic procedure the patient did not receive any immunosupressive or other "ex juvantibus" treatment.

Neurosarcoidosis was initially not considered as a differential diagnosis in the emergency department setting, but with extensive diagnostic evaluation multiple features of an often complex disease have been linked together.

Exclusion of multiple sclerosis and other neuroinflammatory diseases was a diagnostic challenge. The patient did not have the typical clinical picture for multiple sclerosis and there were no characteristic lesions on brain and spinal cord MRI [6]. IgG oligoclonal bands were not present in the spinal fluid. There were no typical signs of other neuroinflammatory diseases (such as acute disseminated encephalomyelitis, acute optic neuritis, transverse myelitis *etc.*) on neuroradiological examination. Ultimately, the clinical picture with laboratory and radiological examination pointed to the neurosarcoidosis diagnosis.

Vitamin D and PTH levels unfortunately were not sought in this patient, but they should be routinely tested in patients with hypercalcaemia and hypercalciuria as well as information on vitamin D and calcium intake. Hypercalcaemia and hypercalciuria are often present in sarcoidosis, but could also be caused by primary hyperparathyroidism. In this patient hypercalcaemia and hypercalciuria also regressed with corticosteroid therapy which supports our diagnosis.

EGPA was also one of the differential diagnoses because of asthma, eosinophilia, lung infiltrates and neurological symptoms. However, eosinophils were not present in high percentage in the BAL fluid, neither in lung biopsy specimens which would support that diagnosis. Immunological laboratory tests suggesting autoimmune disease (ANA, ANCA) were negative. The patient had findings of granulomatous vasculitis on lung biopsy, which is seen in many diseases, from primary systemic vasculitides to inflammatory, autoimmune or lymphoproliferative diseases and also in systemic granulomatous diseases with vasculitis. Vasculitis in sarcoidosis may affect vessels of any size. Treatment is mostly empiric and usually includes the use of glucocorticoids [7].

Diagnosis of neurosarcoidosis is often made by exclusion of other neurological diseases [8], after histopathological confirmation of pulmonary sarcoidosis and with supportive laboratory markers. Overall frequency of central nervous system involvement in sarcoidosis is about 5–10% [9]. Symptoms of neurosarcoidosis may include headache, ataxia, seizures, cognitive disturbances, aphasia, tremor, sensory disturbances, *etc.* [3]. Every part of central and peripheral nervous system can be affected, and long-term therapy is often necessary.

According to the literature, the mean age of neurosarcoidosis presentation is around 43 years and the most commonly reported symptom of neurosarcoidosis was cranial neuropathy, with the facial and optic nerve often affected. MRI of the brain showed abnormalities in 70% of patients and is a gold standard for diagnosis [9]. Common changes on MRI are white matter lesions, meningeal enhancement, *etc.* Electroencephalography is usually normal unless patients are having seizures [10].

Glucocorticoids are accepted as the first-line treatment: usually prednisone at a dose of 0.5–1.0 $mg \cdot kg^{-1}$, which is gradually tapered according to the degree of symptoms [11]. In cases of glucocorticoid resistance other therapy is given, such as methotrexate, azathioprine, mycophenolate mofetil, tumour necrosis factor-α antagonists, *etc.* [12], but there is a need for prospective randomised treatment trials.

Answers

Answer 1

f. All of the above listed diagnoses could potentially be the cause of the neurological symptoms in this patient. He suffered a tick bite which could have potentially infected him with *Borrelia burgdorferi*. Lyme disease can present with face palsy, meningitis, visual disturbances, *etc*. He also

suffered a traffic accident which could cause traumatic spine injury. The patient had a history of asthma, blood eosinophilia, pulmonary infiltrates of unknown cause and new onset neurological symptoms, which all could be symptoms of EGPA. A diagnosis of neurosarcoidosis could explain his neural symptoms, pulmonary infiltrates and elevated ACE.

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Answer 2

b. Histopathological examination of transbronchial lung biopsy samples revealed well-defined noncaseating epithelioid granulomas (figure 3a) with asteroid bodies (figure 3b) and noncaseating granulomas of the vascular wall, granulomatous vasculitis (figure 3c), which are indicative of sarcoidosis.

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Answer 3

b. Prednisone was initiated at a dose of 1 $mg \cdot kg^{-1}$ with tapering.

For patients with clinically significant neurosarcoidosis, initial treatment with glucocorticoids is recommended.

For patients that have already been treated with glucocorticoids but have continued disease, methotrexate is suggested as a second-line agent (conditional recommendation, very low quality of evidence). For the group of patients that have been treated with both glucocorticoids and a second-line agent but have continued disease, the addition of infliximab is recommended [1].

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Conflict of interest

A. Ljilja has nothing to disclose. N. Radović has nothing to disclose. J. Tekavec-Trkanjec reports payment or honoraria for lectures from Roche and Boehringer Ingelheim; and participation on a Data Safety Monitoring Board or Advisory Board for Boehringer Ingelheim, outside the submitted work.

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