A case of neurosarcoidosis presenting with multiple cranial neuropathies

Moria, Sotaro ; Kurimoto, Takuji ; Ueda, Kaori ; Sakamoto, Mari ; Chihara, Norio ; Satake, Wataru ; Yamada-Nakanishi, Yuko ; Nakamuraa,…

(Citation)
American Journal of Ophthalmology Case Reports,19:100796

(Issue Date)
2020-06-27

(Resource Type)
journal article

(Version)
Version of Record

American Journal of Ophthalmology Case Reports 19 (2020) 100796

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

A case of neurosarcoidosis presenting with multiple cranial neuropathies

Sotaro Mori [a], Takuji Kurimoto [a,*], Kaori Ueda [a], Mari Sakamoto [a], Norio Chihara [b], Wataru Satake [b,c], Yuko Yamada-Nakanishi [a], Makoto Nakamura [a]

[a] Division of Ophthalmology, Department of Surgery, Kobe University Graduate School of Medicine, Kobe, Japan
[b] Division of Neurology, Kobe University Graduate School of Medicine, Kobe, Japan
[c] Department of Neurology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

ARTICLE INFO

Keywords:
Neurosarcoidosis
Oculomotor nerve palsy
Abducens nerve palsy
Computerized tomography
Positron emission tomography
Multiple cranial nerve palsies

ABSTRACT

Purpose: We report a case of neurosarcoidosis that presented simultaneously with oculomotor nerve palsy, contralateral abducens nerve palsy, and paresthesia of both lower limbs.

Observations: A 69-year-old Japanese woman who suffered from repeated diplopia and lower-limb paresthesia was referred to our hospital. Ophthalmic findings included oculomotor nerve and contralateral abducens nerve palsies. No remarkable abnormalities were detected via enhanced brain magnetic resonance imaging (MRI), chest X-ray, and cerebrospinal fluid analysis. Chest computed tomography (CT) was performed to exclude neoplastic lesions; this revealed right hilar lymphadenopathy, and positron emission tomography MRI showed strong 18-F fluorodeoxyglucose uptake in the hilar lymph node. Biopsy of the lymph node showed non-caseating epithelioid granulomatous tissue, leading to a diagnosis of probable neurosarcoidosis. After the initiation of oral prednisolone treatment, the patient experienced complete remission without any recurrence.

Conclusions and importance: When examining a patient presenting with multiple cranial neuropathies of unknown cause, neurosarcoidosis should be considered as a differential diagnosis and chest CT should be performed even when the chest X-ray and angiotensin-converting enzyme appears normal.

1. Introduction

Sarcoidosis is a chronic granulomatous disease that systemically affects multiple organs, including the lungs, heart, nerves, and eyes. Neurosarcoidosis occurs in 5% of patients with sarcoidosis and may impair both the central and the peripheral nervous system.[1,2] A recent meta-analysis of neurosarcoidosis reported that the facial nerve is the nerve most commonly involved, whereas the cranial nerves related to eye movement, including the oculomotor, trochlear, and abducent nerves, are involved in only 2%–7% of cases.[3,4] Here, we report a rare case of neurosarcoidosis that simultaneously presented with oculomotor nerve palsy, contralateral abducens nerve palsy, and paresthesia of both lower limbs.

2. Case report

A 69-year-old woman with a history of hypertension and cholecystectomy abruptly noticed diplopia in upward gaze. Brain magnetic resonance imaging (MRI) at another hospital was reported as normal. One month later, the diplopia spontaneously resolved without treatment. However, 6 months later, she again experienced diplopia together with paresthesia of both lower limbs. Ophthalmic examinations showed simultaneous left abducent and right oculomotor palsies. She was referred to our hospital for treatment.

Our initial examinations showed no decrease in visual acuity or abnormalities of light reflex and pupil size. The patient exhibited moderate blepharoptosis of the right upper lid, limited adduction, elevation, and depression of the right eye, and abduction of the left eye (Fig. 1a and b). Slit-lamp biomicroscopy showed no inflammatory changes in the anterior chambers, and fundus examinations found no vitreous or retinal abnormalities. The laboratory data showed no infectious or collagen disease, and the serum calcium and angiotensin-converting enzyme (ACE) levels were within the normal ranges. There were no abnormal findings on neurological examinations except for the paresthesia of both lower limbs. Repeated gadolinium-enhanced MRI of the brain and spine between cervical and lumbar vertebrae showed no remarkable changes

* Corresponding author. Division of Ophthalmology, Department of Surgery Kobe University Graduate School of Medicine 7-5-2 Kusunoki-cho, Chuo-ku, Kobe, 650-0017, Japan.
E-mail address: kuri1201@med.kobe-u.ac.jp (T. Kurimoto).

https://doi.org/10.1016/j.ajoc.2020.100796
Received 26 February 2020; Received in revised form 17 June 2020; Accepted 17 June 2020
Available online 27 June 2020

in the brainstem, oculomotor and abducens nerves, or spine. Similarly, no abnormalities were seen on the chest X-ray (Fig. 2a) or electrocardiogram. A cerebrospinal fluid analysis showed no tumor cells, no elevation of pressure, no significant infectious changes, and no elevation of angiotensin-converting enzyme levels.

At this point, we suspected multiple cranial neuropathy caused by a paraneoplastic neuropathy. To search for a neoplastic lesion, we investigated tumor markers including CEA, CA19-9, CYFRA, SCC, NSE, and anti-SOX antibody, and acquired thoraco-abdominal computed tomography (CT) and positron emission tomography (PET) MRI scans. The patient was positive for the anti-SOX antibody and the thoraco-abdominal CT revealed right hilar lymphadenopathy, with strong 18-F fluorodeoxyglucose uptake in the lymph node observed on the PET-MRI scan (Fig. 2b and c). On suspicion of paresthesia of limbs caused by paraneoplastic neuropathy, we performed biopsy of the sural nerve. Pathological examinations showed infiltration of CD68-positive cells inside the fascicle of the nerve fiber. In addition, there was perivascular infiltration of CD3-and CD20-positive cells but no non-caseating epithelioid granulomas. These histopathological findings showed nonspecific inflammatory reactions. To date, we have attempted to find a neoplastic lesion with paraneoplastic neuropathy. However, biopsy of the hilar lymph node obtained by thoracoscopy demonstrated non-caseating epithelioid granulomas but without tumor cells, indicating an inflammation response induced by sarcoidosis (Supplementary Figs. 1a and b). Before these evaluations had been completed, the patient's eye movement disturbance and right blepharoptosis spontaneously improved without steroid therapy (Fig. 1c). However, there was a new appearance of left blepharoptosis. The patient was diagnosed with probable neurosarcoidosis according to the diagnostic criteria for this condition.[5] Treatment with oral prednisolone 30 mg daily was initiated, tapering this to 5 mg per 2 weeks. Two months after the initiation of this steroid therapy, the patient's eye movement disturbance and paresthesia of limbs had completely disappeared. The low dose of oral prednisolone, 5 mg a day was maintained, and there had been no recurrence by 20 months after the initiation of the steroid therapy.

3. Discussion

Sarcoidosis is a multisystem granulomatous disorder with unknown etiology. All generations from young to elderly people can possibly be affected with sarcoidosis. Its prevalence is approximately 5–10 per 100,000, which is higher incidence in women and in cold weather regions.[5] In general, the lungs, eye, heart, and skin are affected with major lesions; however, sarcoidosis can also affect various organs such as the digestive system, liver, bone, and joints. The exact pathological mechanisms of sarcoidosis remains unclear; however, the infection that caused propionibacterium acnes is possibly related to the onset.[6] Steroid therapy is established as the first-line treatment, e.g., daily oral medication of 0.5–1.0 mg of prednisolone per kg (body weight) and then gradually tapered according to the degree of symptoms.[5]

Neurosarcoidosis accounts for 5–7% of sarcoidosis[7] and is a relatively rare disease. It could affect various nervous systems, and pathological examination of extraneural or neural samples is absolutely required for its diagnosis.[5] However, many patients were overlooked due to the difficulty of conducting neuronal biopsy. Because of the rarity of neurosarcoidosis, no randomized control studies or large cohort studies have been conducted on its therapies. Thus, treatment strategies for neurosarcoidosis have been based on the discretion of expert opinions derived from evidences on the treatment for pulmonary sarcoidosis and from small retrospective studies.

Multiple cranial neuropathies are associated with numerous etiologies, and in the largest observational study of these, which included 1028 cases of multiple cranial neuropathies, 70% of the cases were caused by tumors, vascular disease, trauma, infections, and Guillain–Barré syndrome. In contrast, autoimmune diseases, including neurosarcoidosis, systemic lupus erythematosus, and chronic demyelinating inflammatory polyneuropathy, accounted for less than 0.01% of the cases.[8] Thus, among all the possible causative diseases, neurosarcoidosis is very rare as a differential diagnosis for multiple cranial neuropathies. Furthermore, a comprehensive assessment should be conducted to patients with multiple cranial neuropathies. The thoracicoabdominal CT and blood test of autoantibodies are critical for the detection of neoplastic lesions such as malignant lymphoma and autoimmune diseases, respectively. Cerebrospinal fluid examination (CSF) is also critical for the assessment of infectious diseases including botulism and syphilis, tumor cells, tuberculosis, and Guillain–Barré syndrome, which shows an albuminocytologic dissociation.

The most common cranial nerve palsy caused by neurosarcoidosis affected the facial nerve.[3,4,9–13] Among them, patients with the triad, facial nerve palsies, parotid gland swelling, and uveitis, were diagnosed as the Heerfordt syndrome. The optic nerve appears to be the second most commonly involved cranial nerve by neurosarcoidosis.[9–11] Neurosarcoidosis very rarely involves other cranial nerves. Rose et al. reported a 32-year-old woman with facial and vestibulocochlear nerve palsies. She was definitely diagnosed with neurosarcoidosis based on pathological findings of the biopsy of supraclavicular lymph node.

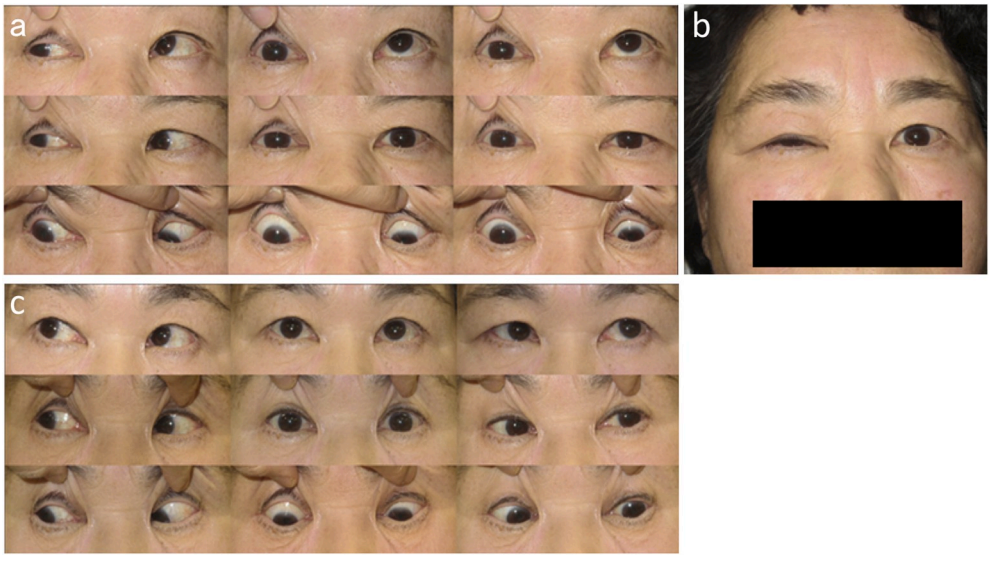

Fig. 1. Photographs of the nine directions of gaze and the patient's face.
(**a** and **b**) At the initial evaluation, the patient exhibited right third nerve palsy with limited adduction, elevation, and depression of the right eye and ptosis, and left sixth nerve palsy with limited abduction. There was no anisocoria. (**c**) During the examination, her oculomotor and abducens nerve palsies improved spontaneously 8 months after initial onset.

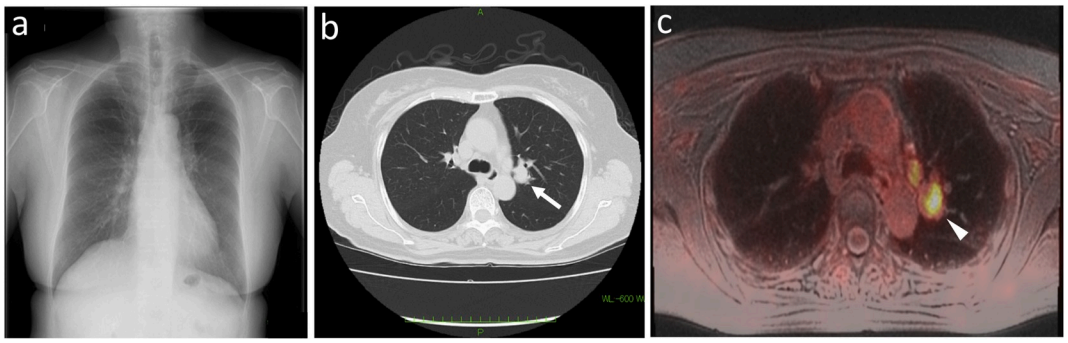

Fig. 2. Chest X-ray, computed tomography (CT), and positron emission tomography magnetic resonance imaging (PET-MRI) images.
(**a**) At the initial examination, the hilar and lung field shadows appeared as normal on the chest X-ray. (**b**) However, CT scan revealed enlargement of the right hilar lymph node (white arrow). (**c**) On PET-MRI, the 18F-fluorodeoxyglucose strongly accumulated in this lymph node (white arrowhead).

Consistent with our case, imaging findings of the chest X-ray and CT were valuable markers for its diagnosis.[11] Miyajlovic et al. documented a 70-year-old woman with multiple cranial neuropathies. This case had an eye movement disturbance associated with oculomotor and trochlear nerve palsies like that in our case.[12] Consequently, elevations of ACE level in the serum and CSF were conclusive findings without undergoing biopsy. Erer-Ozbek et al. presented a 36-year-old woman with oculomotor, facial, glossopharyngeal, and accessory cranial nerve palsies.[13] In this case, a biopsy of hilar lymph nodes revealed a non-caseating granuloma even without increased serum ACE level, which was similar to that in our case. All these cases were treated with prednisolone, which improved their symptoms.[11–13] Different from these cases, the main manifestation of our case was only eye movement disturbance without facial nerve palsies and serum ACE level elevation, which probably made the diagnosis more difficult.

The additional chest CT to exclude neoplastic lesions incidentally detected the hilar lymphadenopathy, which provided evidence of possible neurosarcoidosis as a differential diagnosis. A recent study reported that 34% of 53 patients with ophthalmic sarcoidosis showed abnormalities on chest CT but only one showed any abnormalities on chest X-rays.[14] Furthermore, in a retrospective study of 69 cases of neurosarcoidosis, most had normal pulmonary function evaluated by spirometry but 71% showed abnormal findings on chest CT.[15] Nevertheless, the chest X-ray should be firstly conducted rather than chest CT because of the increment of radiation exposure. However, given the rarity of neurosarcoidosis, the low sensitivity of chest X-ray and the high sensitivity of CT,[16] we should follow the chest CT for further evaluation without delay when X-ray shows negative findings of sarcoidosis. Thus, it is important to perform both chest X-rays and chest CT when examining cases presenting with multiple cranial neuropathies or suspected neurosarcoidosis.

In the present case, the first relapse occurred approximately 6 months after spontaneous remission and then completely disappeared with steroid therapy alone. There was no further recurrence with the patient receiving 5 mg of prednisolone for more than 20 months. However, when the patient becomes resistant to steroid therapy or is compelled to discontinue steroid therapy because of side effects, a second-line treatment should be considered. Immunosuppressants, such as methotrexate, mycophenolate, azathioprine, and leflunomide, or TNF-α inhibitors would be an effective alternative treatment to suppress recurrence and for a safe long-term use.[17–19]

As per the aforementioned previous case reports, multiple cranial nerve palsies involving eye movements is a rare clinical manifestation in the case of neurosarcoidosis, and the present case is extremely rare as it presents with discrete bilateral ocular movement palsies that did not coincide with the innervation. Furthermore, the only critical finding that motivated us to make a diagnosis of neurosarcoidosis was the incidentally discovered right hilar lymphadenopathy on chest CT, which was originally performed to examine tumorous lesions. In consideration of such unique ophthalmic manifestation and difficulty of diagnosis, the present case is considered to be worth as a novel case report of atypical neurosarcoidosis.

In conclusion, when examining a case presenting with multiple cranial neuropathies, neurosarcoidosis should be considered a differential diagnosis. Although multiple cranial nerve palsies is an uncommon presentation of neurosarcoidosis, differential diagnosis should be a critical part of the medical care of neurosarcoidosis. In such cases, chest CT and PET are useful for the detection of pulmonary sarcoidosis and extraneural lesions; these may avoid delays in the diagnosis of neurosarcoidosis.

Patient consent

The patient's legal guardian orally consented to the publication of this case report.

Funding

No funding or grant support.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

CRediT authorship contribution statement

Sotaro Mori: Data curation, Writing - original draft, Resources. **Takuji Kurimoto:** Writing - review & editing, Conceptualization, Software. **Kaori Ueda:** Visualization, Investigation. **Mari Sakamoto:** Visualization, Investigation. **Norio Chihara:** Software, Validation, Resources. **Wataru Satake:** Visualization, Investigation, Resources. **Yuko Yamada-Nakanishi:** Visualization, Investigation. **Makoto Nakamura:** Supervision.

Acknowledgement

We are grateful to Enago (www.enago.jp) for the English language review.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

org/10.1016/j.ajoc.2020.100796.

References

1. Lacomis D. Neurosarcoidosis. *Curr Neuropharmacol*. 2011;9(3):429–436.
2. Tana C, Wegener S, Borys E, et al. Challenges in the diagnosis and treatment of neurosarcoidosis. *Ann Med*. 2015;47(7):576–591.
3. Fritz D, van de Beek D, Brouwer MC. Clinical features, treatment and outcome in neurosarcoidosis: systematic review and meta-analysis. *BMC Neurol*. 2016;16(1):220.
4. Ohno T, Ishihara M, Shibuya E, et al. Sarcoid uveitis in a patient with multiple neurological lesions: a case report and review of the literature. *J Med Case Rep*. 2018;12(1):307.
5. Jain R, Yadav D, Puranik N, et al. Sarcoidosis: causes, diagnosis, clinical features, and treatments. *J Clin Med*. 2020;9(4):1081.
6. Ishige I, Eishi Y, Takemura T, et al. Propionibacterium acnes is the most common bacterium commensal in peripheral lung tissue and mediastinal lymph nodes from subjects without sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 2005;22(1):33–42.
7. Nowak DA, Widenka DC. Neurosarcoidosis: a review of its intracranial manifestation. *J Neurol*. 2001;248(5):363–372.
8. Keane JR. Multiple cranial nerve palsies: analysis of 979 cases. *Arch Neurol*. 2005;62(11):1714–1717.
9. Tana C, Wegener S, Borys E, et al. Challenges in the diagnosis and treatment of neurosarcoidosis. *Ann Med*. 2015;47(7):576–591.
10. Yacoub Hussam A, Al-Qudah Zaid A, Souayah Nizar. Cranial neuropathies in sarcoidosis. *World J Ophthalmol*. 2015;5(1):16–22.
11. Rose Oliver, Ahmad Zahoor, Snow Barry. Multiple cranial nerve palsies as the first presentation of sarcoidosis. *Case Rep Otolaryngol*. 2014:592510.
12. Mijajlovic M, Mirkovic M, Mihailovic-Vucinic V, et al. Neurosarcoidosis: two case reports with multiple cranial nerve involvement and review of the literature. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2014;158:662–667.
13. Erer-Ozbek Sevda, Bora Ibrahim, Yurtogullar Sukran. Acute multiple cranial neuropathy in a patient with neurosarcoidosis. *Neurol Sci*. 2010;31:865–866.
14. Han YS, Rivera-Grana E, Salek S, et al. Distinguishing uveitis secondary to sarcoidosis from idiopathic disease: cardiac Implications. *JAMA Ophthalmol*. 2018;136(2):109–115.
15. Kingah P, Alam M, Chugh K, et al. Role of pulmonary evaluation in diagnosis of neurosarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 2016;33(3):209–215.
16. Stern BJ, Royal 3rd W, Gelfand JM, et al. Definition and consensus diagnostic criteria for neurosarcoidosis: from the neurosarcoidosis consortium consensus group. *JAMA Neurol*. 2018;75(12):1546–1553.
17. Voortman M, Drent M, Baughman RP, et al. Management of neurosarcoidosis: a clinical challenge. *Curr Opin Neurol*. 2019;32(3):475–483.
18. Gelfand JM, Bradshaw MJ, Stern BJ, et al. Infliximab for the treatment of CNS sarcoidosis: a multi-institutional series. *Neurology*. 2017;89(20):2092–2100.
19. Cohen Aubart F, Bouvry D, Galanaud D, et al. Long-term outcomes of refractory neurosarcoidosis treated with infliximab. *J Neurol*. 2017;264(5):891–897.