The Egyptian Journal of Internal Medicine

CASE REPORT Open Access

Neuro-sarcoidosis with isolated optic neuropathy: unmasking the chameleon

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Abstract

Isolated optic nerve involvement is rare in sarcoidosis. We report three cases describing atypical clinical and radiological features of isolated optic nerve involvement in sarcoidosis to expand the spectrum of neuro-ophthalmic sarcoidosis. Bilateral optic neuritis, sudden vision loss, primary optic atrophy, long segment optic neuritis, and isolated intraorbital sarcoidosis are described as atypical features of optic nerve involvement in this case series.

Keywords Optic atrophy, Optic neuritis, Sarcoidosis

Background

Sarcoidosis is a multisystem granulomatous disease with frequent affection of the lung, lymph nodes, skin, and eyes. In the eye, sarcoid can affect many structures including the eyelid, conjunctiva, anterior chamber, retina, and optic nerve. While uveal tract abnormalities are the most common ocular findings, optic nerve involvement has been reported in only 1–5% of patients with sarcoidosis [1]. Diagnosis of ocular sarcoidosis is challenging without the classical features of granulomatous uveitis as outlined by the Revised International Workshop on Ocular Sarcoidosis (IWOS) criteria. The Sarcoidosis Diagnostic Score is pivotal in making an accurate diagnosis of sarcoidosis [2]. This case series describes three cases of unusual clinical and radiological features of optic nerve involvement in sarcoidosis without any other ophthalmic features aiming to expand the spectrum of neuro-ophthalmic sarcoidosis.

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Case 1

A 34-year-old lady presented with sudden, bilateral painful diminution of vision for one month. On examination, left grade 1 lower motor neuron facial weakness with bilateral visual acuity, 6/60, was found. The ophthalmological examination revealed edema of the right optic nerve without any other abnormality, excluding any infectious, malignant, toxic, or nutritional causes. Magnetic Resonance Imaging (MRI) brain and orbit showed non-enhancing hyperintensity in intraorbital and intracanalicular segments of left optic nerve with no other abnormalities in brain and spinal cord (Fig. 1A). Complete blood counts, liver function test, renal function test, serum, and urinary calcium were normal. Erythrocyte sedimentation rate (ESR) was 40 mm in the first hour. CRP (C-reactive protein), anti-nuclear antibodies (ANA) and rheumatoid factor (RF), anti-serum neuromyelitis optica (NMO), and myelin oligodendrocyte glial protein (MOG) antibodies were negative, and serum angiotensin converting enzyme (ACE) level was normal. Chest and abdomen computed tomography (CT) showed para-esophageal, bilateral upper paratracheal, subcarinal, and bilateral hilar lymphadenopathy with hepatosplenomegaly (Fig. 2A). Cerebrospinal fluid (CSF) studies were normal with negative oligoclonal bands. The patient was treated with a high dose of intravenous methylprednisolone (1000 mg/day) for 5 days, followed by oral steroids and azathioprine. She reported a dry non exertional dry

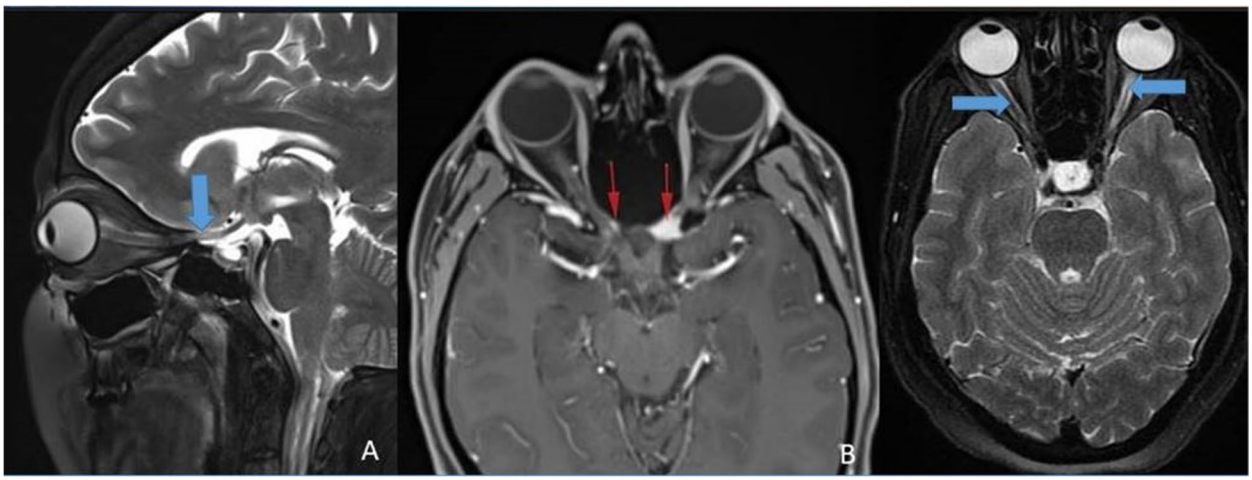

Fig. 1 **A** Sagittal T2 fat saturated image showing hyperintensity in intraorbital and intracanalicular segments of left optic nerve. **B** Post-contrast T1-weighted axial image showing meningeal thickening and contrast enhancement in left optic canal and mild enhancement in right optic canal. **C** Axial T2-weighted image showing bilateral optic atrophy

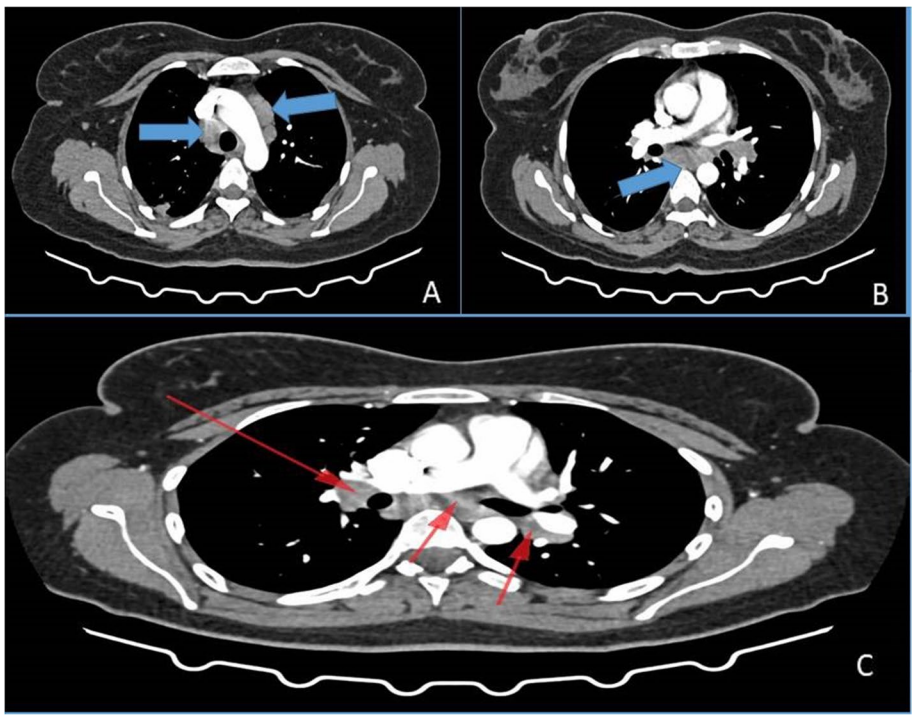

Fig. 2 **A** contrast CT scan axial image showing enlarged lymph nodes in paratracheal and prevascular region. **B** contrast CT scan axial image showing subcarinal and hilar lymphadenopathy. **C** contrast CT scan axial image showing hilar lymphadenopathy

cough for three years. Echocardiography (ECHO) was normal. In order to confirm the diagnosis, a bronchoscopy with bronchial mucosa biopsy, bronchoalveolar lavage (BAL), and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS TBNA) of the subcarinal lymph nodes were performed. Histopathological examination revealed fragments of the bronchial mucosa with non-necrotizing granulomas. Cultures of the bronchial fluid were negative for bacterial, fungal, and mycobacterial pathogens. The sarcoidosis diagnostic score was five, involving lung (highly probable), eye (highly probable), neurological (highly probable), liver and spleen (at least probable), and biopsy positive for the lung. A diagnosis of sarcoidosis with optic neuritis was

established. At follow-up of 2 months, she showed clinical resolution with normal fundi and regression of mediastinal lymphadenopathy.

Case 2

A 26-year-old girl presented with occasional holocranial headaches since two years with left-sided painless diminution of vision for five days. On examination, left eye visual acuity was 6/36 with left optic disc edema. No other abnormalities were found in a detailed ocular examination, excluding any infectious, malignant, toxic or nutritional causes. MRI showed post contrast T1 weighted axial image showing meningeal thickening and contrast enhancement in left optic canal and mild enhancement in right optic canal with no other abnormalities in brain and spinal cord (Fig. 1B). Complete blood counts, liver function test, renal function test, serum, and urinary calcium were normal. Erythrocyte sedimentation rate (ESR) was 55 mm in the first hour. CRP (C-reactive protein), antinuclear antibodies (ANA) and rheumatoid factor (RF), and serum NMO-MOG antibodies were negative and serum ACE was normal. CT chest showed bilateral upper paratracheal and bilateral hilar lymphadenopathy with hepatosplenomegaly (Fig. 2B). CSF studies were normal with negative oligoclonal bands. The patient was treated with a high-dose of intravenous methylprednisolone (1000 mg/day) for 5 days, followed by oral steroids and mycophenolate mofetil. Echocardiography (ECHO) was normal. Histopathological examination from the paratracheal lymph node showed non-necrotizing granulomas. The sarcoidosis diagnostic score was five, involving lung (highly probable), eye (highly probable), neurological (highly probable), liver and spleen (at least probable), and biopsy positive for the lung. At follow-up of 3 months, clinical resolution and regression of the hilar lymph nodes were observed.

Case 3

A 29-year-old man presented with left eye diminution of vision for one month. He has past history of left lower motor neuron type facial weakness two years ago, which spontaneously resolved. He also complained of right subacute vision impairment (untreated) since one year. On examination, right eye visual acuity 6/36 and left eye visual acuity 6/60 with fundi showing right eye optic atrophy and left eye mild disc pallor. MRI demonstrated bilateral optic atrophy with no other abnormalities in brain and spinal cord (Fig. 1C). Complete blood counts, liver function test, renal function test, serum, and urinary calcium were normal. Erythrocyte sedimentation rate (ESR) was 40 mm in the first hour. CRP (C-reactive protein), anti-nuclear antibodies (ANA), and rheumatoid factor (RF) were negative. Serum ACE level was 86 (lab cutoff: 60 IU/L). Serum anti-NMO and MOG antibodies were negative. Chest CT showed para-esophageal, bilateral upper paratracheal, subcarinal, and bilateral hilar lymphadenopathy (Fig. 2A). CSF studies were normal with negative oligoclonal bands. The patient was treated with a high dose of intravenous methylprednisolone (1000 mg/day) for 5 days, followed by oral steroids. A diagnosis of sarcoidosis with optic neuritis was established. The sarcoidosis diagnostic score was five, involving the lung (highly probable), eye (highly probable), neurological (highly probable), liver, and spleen (at least probable). His left eye visual acuity had improved at 6 months with radiological regression of pulmonary lymphadenopathy.The visual acuity in the right eye showed little improvement.

Discussion

We describe three cases of optic neuropathy as presenting isolated manifestations of sarcoidosis with unique features: (i) bilateral optic neuritis presenting as sudden vision loss and primary optic atrophy as presenting features of neurosarcoidosis (NS) without any anterior chamber involvement, (ii) long segment optic neuritis (involvement of intracanalicular and intraorbital segments) and optic atrophy as radiological manifestations of neuro-opthalmic sarcoidosis (NoS), (iii) isolated intraorbital sarcoidosis without any other neuraxis involvement, and (iv) thoracic computed tomography as an ancillary non-invasive investigation to diagnose sarcoidosis with normal angiotensin converting enzyme (ACE) levels. The diagnosis requires both demonstration of multi-organ involvement consequent to sarcoidosis along with central nervous system (CNS) involvement and exclusion of reasonable alternative causes. Serving this purpose, the sarcoidosis diagnostic score is an excellent score for the diagnosis with a reliable cutoff of six [2]. Presence of mediastinal lymphadenopathy, absence of other brain and spinal cord abnormalities, negative results for NMO, MOG, oligoclonal bands, and granulomatous inflammation as demonstrated in the second case excluded primary CNS demyelinating syndromes as the cause of optic neuritis.

Cranial neuropathy is the most common neurological manifestation of sarcoidosis, seen in up to 70% of patients with NS. Involvement of the anterior visual pathway, pupils, and extraocular muscle function denotes neuro-ophthalmic sarcoidosis (NOS). Following facial nerve, optic nerve is the second most common nerve to be involved. The protean features range from optic neuritis (papillitis/neuroretinitis/retrobulbar neuritis), optic atrophy, optic nerve granuloma to papilledema [3]. Fundoscopically, optic disc pallor is the most common sign

(55%), followed by optic disc edema (29%), periphlebitis, and optic disc granulomas [3].

The only large prospective observational study on 52 patients of optic neuropathy with systemic sarcoidosis identified two clinical subtypes: a subacute optic neuropathy with radiological resemblance to optic neuritis and steroid responsiveness and a gradual progressive optic neuropathy secondary to dural-based mass lesions involving the optic nerve, poorly responsive to immunotherapy. Bilateral optic neuritis was rare, associated pain infrequent, severe visual loss at onset common, concurrent intraocular inflammation mild, and spontaneous improvement being the rule. Involvement of the optic chiasm and perineuritis (enhancement and thickening of optic nerve sheath) were characteristic features [4]. Our cases had some differing observations of bilateral synchronous severe visual loss (Patient 1), ocular pain present in all three cases, and irreversibility with delayed immunotherapy (Patient 3). Inflammation of the intraorbital optic nerve is less frequent than intraocular or chiasmal involvement, while intraorbital involvement heralds widespread NS affecting the hypothalamus or central nervous system [5]. Similar to three cases reported earlier [5], our patients (Patients 1 and 2) demonstrated intraorbital nerve infiltration without any other concurrent CNS involvement.

A unique feature which deserves mention is primary optic atrophy in NOS. In Patient 3, past history of facial nerve palsy, visual loss responding to steroids, elevated ACE, and CT chest findings of sarcoidosis hint towards a possible NS, although biopsy proven diagnosis could not be obtained. Furthermore, optic atrophy was the radiological finding in this case, without any high signal or enhancement involving the optic nerves. This case adds to the repertoire of reversible causes of optic atrophy. However, the earlier affected eye with optic atrophy could not be salvaged, necessitating early identification and management, emphasizing the decreased response to treatment with time, unlike multiple sclerosis associated optic neuritis which often resolves with or without treatment [5].

Multiple mechanisms underlying involvement of optic nerve include primarily through compression, infiltration by an adjacent mass, nerve inflammation, disc granulomas, and optic perineuritis and secondarily through ischemic complications of retinal and choroidal inflammation [6].

The lack of typical clinical and laboratory features except elevated ACE in one case compounded the clinical scenario. Presence of past or concurrent facial nerve palsy was a useful clinical pointer. Spontaneously remitting facial nerve palsy is the most common cranial neuropathy described in NS [6, 7]. While optic nerve sarcoidosis is known to have refractory disease and relapse on corticosteroid dose reduction, we demonstrate good response to steroids with successful addition of steroid sparing agent without relapses at one year of follow-up.

More than 80% of patients with NS have associated systemic sarcoidosis (mainly in the lungs and lymph nodes) [7]. The American Thoracic Society (ATS) postulates three main criteria for diagnosis of sarcoidosis: A suitable clinical manifestation demonstrated non-necrotizing granulomatous inflammation on histopathology and exclusion of alternative causes [8]. All but one patient in this series had biopsy proven sarcoidosis. Inaccessibility and non-feasibility plague a histopathological examination. Patients with a high clinical suspicion for sarcoidosis without clinical evidence of multi-organ involvement, chest CT, or functional molecular imaging can localize metabolically active lymph nodes, providing an alternative biopsy site if lymphadenopathy is found.

Treatment guidelines propose using glucocorticoids for NS, with high-dose intravenous steroids therapy in vision loss and additional second-line medications: Methotrexate, azathioprine (AZA), and mycophenolate mofetil (MMF) used concurrently with glucocorticoids for initial treatment [9]. Tumor necrosis factor (TNF)-alpha inhibitors—infliximab and adalimumab—are recommended when NS relapses on steroids. The Delphi Consensus recommends early or simultaneous use of steroid-sparing non-biologic immunosuppressive therapy, in patients with severe or multi-organ disease [10]. Optic neuritis, being severe NS, warrants aggressive second-line immunosuppressive therapy in case of poor response to first-line agents.

Abbreviations

ACE	Angiotensin converting enzyme
ANA	Anti-nuclear antibody
CSF	Cerebrospinal fluid
CT	Computed tomography
DTR	Deep tendon reflexes
ECHO	Echocardiography
ENA	Extractable nuclear antigen
F	Female
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
LMN	Lower motor neuron
M	Male
MOG	Myelin oligodendrocyte glycoprotein
MRI	Magnetic resonance imaging
NMO	Neuromyelitis optica
OCB	Oligoclonal bands
PET	Positron emission tomography
RAPD	Relative afferent pupillary defect
VDRL	Venereal disease research laboratory

Acknowledgements
Nil.

Authors' contributions
SJ and SKP contributed equally in conceptualization, data collection, writing the first draft, and review of manuscript. MT provided the figures and reviewed the manuscript.

Funding
Nil.

Availability of data and materials
Available with the authors.

Declarations

Ethics approval and consent to participate
Informed consent has been obtained from the patients.

Consent for publication
Informed written consent has been obtained from the patients.

Competing interests
Nil.

Received: 4 March 2024 Accepted: 18 May 2024
Published online: 27 May 2024

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