



Sarcoidosis beyond pulmonary involvement: A case series of unusual presentations

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ABSTRACT

Unusual presentations of sarcoidosis pose a diagnostic challenge and warrant attention. **Hematologic associations:** **Case 1** (37-years-old male): Pancytopenia: *myelofibrosis* (leading to sepsis and mortality) following a two-year quiescent course of biopsy-proven-sarcoidosis. **Case 2:** (38-years-old male): Presentation with thrombocytopenia ($5 \times 10^3/\text{cmm}$): *immune thrombocytopenic purpura* (histologically associated with *megakaryocytic emperipolesis*). Biopsied enlarged lymph nodes demonstrated sarcoidosis. Hematologic sarcoid involvement is usually due to granulomatous bone marrow (3.9%) or splenic infiltration (6–30%); however, the presented manifestations are scarcely reported with a potential significance that is yet to be elucidated. **Case 3: Neurologic presentation:** 48-years-old female: presentation with bilateral *sensorineural hearing loss and facial palsy*. Brain magnetic resonance imaging showed *leptomeningeal thickening*. Biopsied enlarged lymph nodes showed sarcoidosis. **Case 4: Neurologic and renal manifestations:** 13-years-old male (family history of sarcoidosis): Presenting with acute headache, investigations showed elevated serum creatinine (2.1 mg/dL) and angiotensin converting enzyme, and computed tomography chest and abdominal findings characteristic of sarcoidosis. Associated *benign increased intracranial and acute tubulointerstitial nephritis (with eosinophils)* were diagnosed upon concordant workup. Of sarcoidosis neurologic affection (5–10%), cranial nerve(s) involvement is among the most common (25–50% of neurosarcoid affection), particularly that of the facial nerve (Case 3). Leptomeningeal enhancement is among the most common neurosarcoid radiologic findings (30–40%). Whereas benign increased intracranial tension (Case 4) is much less reported. Among sarcoidosis renal involvement (35–50%), interstitial nephritis usually presents with granulomatous renal lesions, yet its sole association with sarcoidosis is unusual (Case 4). The portrayed atypical hematologic, neurologic, and renal manifestations further emphasize the masquerading nature of sarcoidosis.

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1. Introduction

Sarcoidosis is a chronic multisystem autoimmune disease that is characterized pathologically by non-caseating granulomas. It could present with a myriad of manifestations ranging from generalized constitutional manifestations of fever, malaise, and weight loss to organ-specific involvement; hence, has been described as a “great imitator” [1]. The importance of addressing the many faces of sarcoidosis rises from the wide variation in its course, implemented treatment, prognosis, and outcome. Herein, we describe four cases of sarcoidosis with unusual hematologic, neurologic, and renal manifestations.

1.1. Hematologic involvement

1.1.1. Case 1

A 37-year-old male patient presented in April 2016 with arthralgia of small joints of the hands and knees, low grade unexplained fever, and unintentional weight loss since November 2015. His past and family history was insignificant. Apart from hepatosplenomegaly, examination was free. Baseline laboratory and serologic investigations are shown in Table 1. Of the radiologic investigations conducted, abdominal

Table 1
Laboratory investigations of presented patients with hematologic involvement.

	Case 1	Case 1	Case 2	Case 2
	At onset	Follow up	At onset	Follow up
<i>Routine laboratory investigations</i>				
ESR	90 mm/hour	130 mm/hour	50 mm/hour	22 mm/hour
CRP	Negative	N/A	Negative	Negative
Hb	12.7 gm/dL	5.8 gm/dL	11.9 gm/dL	13.4 gm/dL
TLC	6×10^3 /cmm	2.8×10^3 /cmm*	7.2×10^3 /cmm	11×10^3 /cmm
PLT	235×10^3 /cmm	64×10^3 /cmm	5×10^3 /cmm	385×10^3 /cmm
ALT	87 U/L	27 U/L	26 U/L	33 U/L
AST	89 U/L	34 U/L	30 U/L	39 U/L
GGT	230 U/L	634 U/L	N/A	N/A
ALP	344 U/L	1442 U/L	N/A	N/A
Total and direct bilirubin	Normal	16.7 & 9.75 mg/dL	Normal	Normal
Serum albumin	3 g/dL	2.5 mg/dL	3.6 gm/dL	4.3 gm/dL
s.Cr	0.8 mg/dL	3.6 mg/dL	0.8 mg/dL	0.6 mg/dL
Urine analysis	Normal	Bilirubin ++	Normal	Normal
SUA	10.3 mg/dL	8.2 mg/dL	4 mg/dL	5 mg/dL
Total calcium	10.3 mg/dL	10.6 mg/dL	8.8 mg/dL	9 mg/dL
ACE enzyme	122 U/L	N/A	N/A	N/A
<i>Virology</i>				
HIV 1 & 2 antigen	Negative	–	Negative	–
Hepatitis markers	Negative	–	Negative	–
CMV IgG & IgM	Negative	–	Negative	–
Tuberculin test	Negative	–	Negative	–
Quantiferon TB Gold	Negative	–	Negative	–
<i>Serology</i>				
ANA	Negative	–	Negative	–
Anti-ds DNA	Negative	–	Negative	–
aPL	Negative	–	Negative	–
Complement 3 and 4	Negative	–	Normal	–
ANCA	Negative	–	Negative	–

Abbreviations: N/A: not available; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; Hb: hemoglobin; PLT: platelet count; ALT: alanine transaminase [Normal (N): 16–63 U/L]; AST: aspartate transaminase (N: 10–50 U/L); GGT: Gamma-glutamyl transferase (N: 71 U/L); ALP: alkaline phosphatase (N:50–136 U/L); s.Cr: serum creatinine; SUA: serum uric acid; ACE: angiotensin converting enzyme (N: 8–53 U/L); HIV: human immunodeficiency virus; CMV Ig: cytomegalovirus immunoglobulin G and M; ANA: antinuclear antibody; *Anti*-ds DNA: anti-double stranded deoxyribonucleic acid; aPL: antiphospholipid antibodies; ANCA: anti-nuclear cytoplasmic antibodies. * TLC: 2.8×10^2 /cmm and neutrophil count: 1×10^2 /cmm.

ultrasound showed a hyperechoic liver mass, splenomegaly, and small rounded lymph nodes and was complemented with a triphasic abdominal computed tomography (CT), which further revealed scattered par-aortic lymph nodes. Chest CT demonstrated bilateral hilar, subcarinal, and retrocarinal lymph node enlargement and increased bronchovascular markings (Fig. 1A and B). Both hepatic lesions and abdominal lymph nodes were biopsied and revealed non-caseating sarcoid granulomas (Fig. 2). Treatment in the form of moderate dose of prednisolone and azathioprine (AZA) (150 mg/day) were initiated in addition to adjunctive therapy, which were adjusted accordingly during follow up with complete clinical and radiographic improvement.

He presented in April 2017 with frequent chest and cutaneous infections and laboratory investigations revealed rapidly progressive pancytopenia with no history of new drug intake, and azathioprine was ceased. Examination at the time revealed no hepatosplenomegaly or lymph node enlargement. Laboratory investigations at the time are shown in Table 1. Bone marrow biopsy revealed evidence of *myelofibrosis* (Fig. 3), with immunohistochemistry showing normal CD34 pattern, occasional scattered CD20 positive cells, marked increase in CD68 positive macrophages, reticulin showing heterogeneous areas of fibrosis grade III, cytokeratin was negative which excluded secondary epithelial tumors, myeloperoxidase was positive with normal distribution, and Ziehl-Neelsen stain was negative. The patient was maintained on low dose prednisolone and received supportive therapy in the form of blood and platelet transfusion, antibiotics in accordance with the clinical situation and site of infection or according to the culture and sensitivities obtained, and filgrastim according to its necessity throughout the course of the disease, however died due to sepsis.

1.1.2. Case 2

A 38-year-old male patient with an unremarkable past or family history, presented in April 2018 with cervical lymphadenopathy and dyspnea on mild exertion. One week later, he developed gross

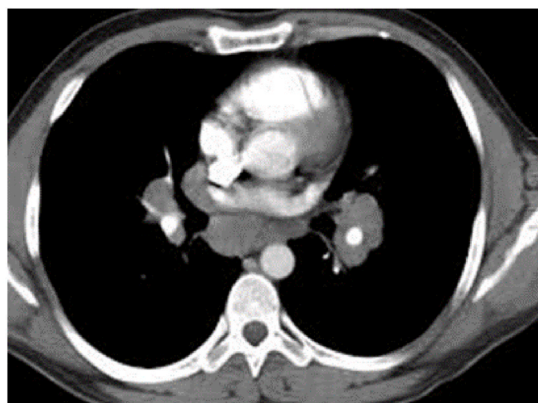


Fig. 1. A and B: Chest computed tomography images showing hilar lymphadenopathy (Case 1).

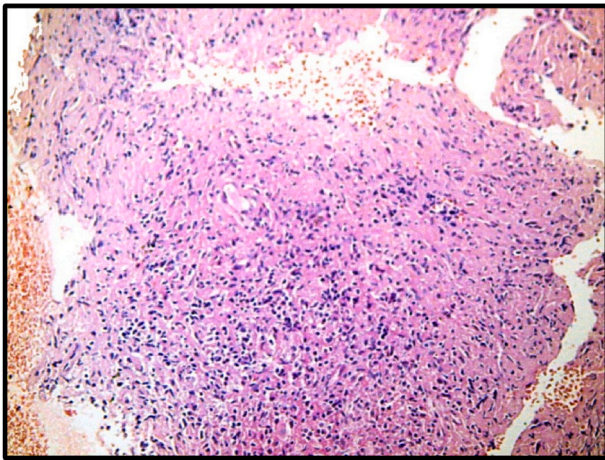


Fig. 2. Liver biopsy showing characteristic granulomatous lesion of sarcoidosis (Case 1).

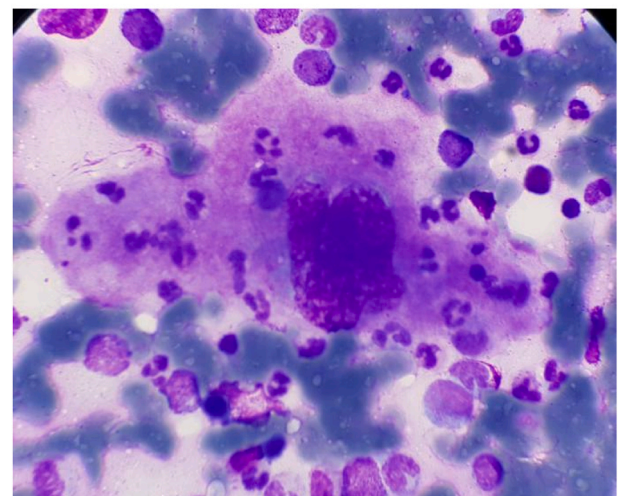
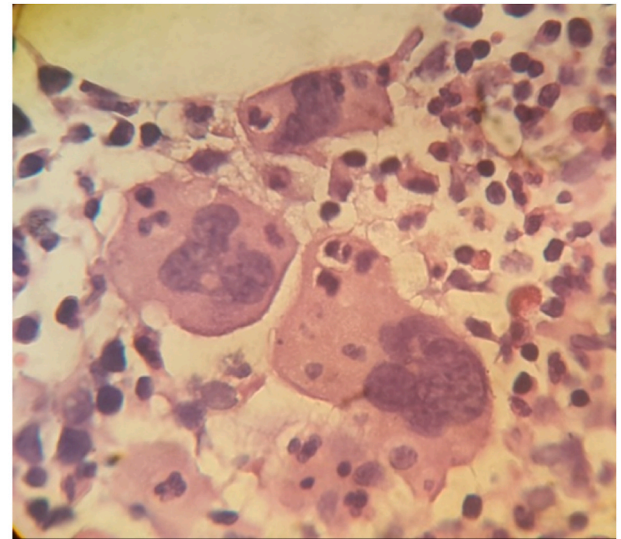


Fig. 4. A. Five megakaryocytes showing emperipolesis and some show nuclear atypia (bone marrow biopsy). B. Extensive emperipolesis in a megakaryocyte (bone marrow aspirate) (Case 2).

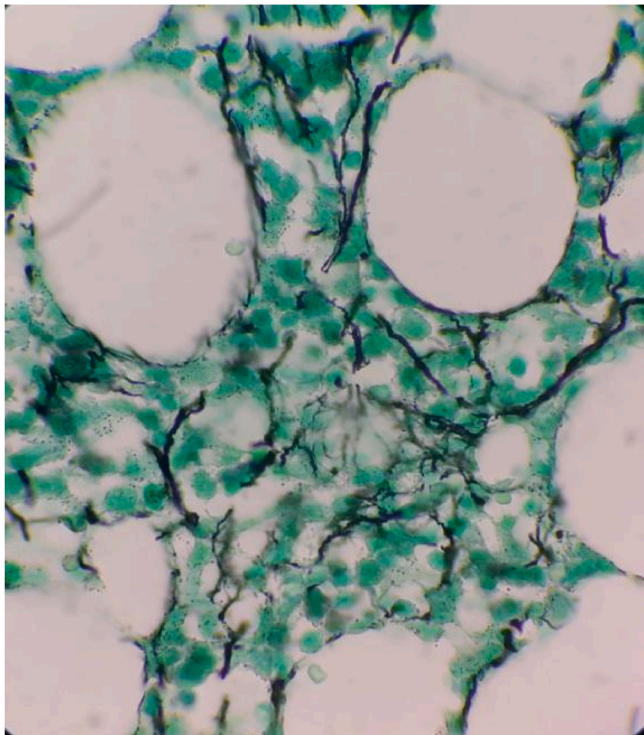


Fig. 3. Reticulin stain showing grade III fibrosis (Case 1).

hematuria, gingival bleeding, and epistaxis. Laboratory investigations showed severe thrombocytopenia ($5 \times 10^3/\text{cmm}$), normocytic normochromic anemia, and the immune profile was negative (Table 1). Chest CT revealed areas of ground-glass opacification and bilateral hilar, aortopulmonary, and paratracheal enlarged lymph nodes, which were biopsied and revealed non-caseating granuloma, upon which a diagnosis of sarcoidosis was established. Bone marrow aspirate and biopsy demonstrated *normal cellular bone marrow with increased megakaryocytes and evidence of emperipolesis* (Fig. 4A and B); hence, was diagnosed with immune thrombocytopenic purpura (ITP) with megakaryocytic emperipolesis associated with sarcoidosis. In addition to adjunctive therapy that included platelet transfusion, methylprednisolone in a dose of 1 g for 3 consecutive days was administered, followed by oral prednisolone in a dose of 1 mg/kg/day, yet with no clinical or laboratory improvement upon which intravenous immunoglobulin G was given in a dose of

2 gm/kg over two days with no improvement; hence, romiplostim once weekly for two consecutive weeks was administered and was followed by sustained normalization of his platelet count (Table 1) over a one-year follow up duration and prednisolone was gradually tapered.

1.2. Neurologic involvement

1.2.1. Case 3

A 48-year-old married female patient with an insignificant obstetric, past, or family history and no special habits of medical importance, presented in May 2017 with sequential bilateral lower motor neuron facial palsy of one-week duration, that was accompanied by partial hearing loss of two-weeks duration. Examination revealed bilateral lower motor neuron facial palsy and bilateral cervical, axillary, and inguinal lymphadenopathy. Baseline laboratory and serologic investigations are shown in Table 2. Among the laboratory investigations conducted angiotensin converting enzyme (ACE) was elevated (Table 2). Audiometry revealed right moderate *sensorineural hearing loss* (SNHL) with good speech discrimination and left mild sensorineural hearing loss with excellent speech discrimination. Chest CT and LN biopsy were characteristic for sarcoidosis. Brain magnetic resonance imaging (MRI) with and without contrast demonstrated leptomeningeal thickening (Fig. 5). Treatment was started in the form of prednisolone 40 mg/day

Table 2
Laboratory investigations of case 3: presenting with neurosarcoidosis.

	At onset	Follow up
<i>Routine laboratory investigations</i>		
ESR	10 mm/hour	15 mm/hour
CRP	Negative	Negative
Hemoglobin	12.9 gm/dL	13 gm/dL
Total leukocytic count	$6.9 \times 10^3/\text{cmm}$	$5.5 \times 10^3/\text{cmm}$
Platelets	$243 \times 10^3/\text{cmm}$	$190 \times 10^3/\text{cmm}$
ALT	22 U/L	24 U/L
AST	23 U/L	27 U/L
GGT	25 U/L	29 U/L
ALP	42 U/L	44 U/L
Total and direct bilirubin	Normal	Normal
Serum albumin	3.8 gm/L	3.9 gm/dL
s.Cr	1.1 mg/dL	0.9 mg/dL
Urine analysis	Normal	Normal
24 hour urinary protein	N/A	N/A
SUA	3.5 mg/dL	4 mg/dL
Total calcium	9.4 mg/dL	9 mg/dL
ACE	106 U/L	N/A
<i>Virology</i>		
HIV 1 & 2 antigen	Negative	–
Hepatitis markers	Negative	–
CMV IgG & IgM	Negative	–
Tuberculin test	Negative	–
Quantiferon TB Gold	Negative	–
<i>Serology</i>		
ANA	Negative	–
Anti-ds DNA	Negative	–
aPL	Negative	–
Complement 3 and 4	Normal	–
Anti-Ro/SSA	N/A	–
Anti-La/SSB	N/A	–
ANCA	Negative	–

Abbreviations: N/A: not available; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; Hb: hemoglobin; TLC: total leukocytic count; PLT: platelets count; ALT: alanine transaminase [Normal (N): 16–63 U/L]; AST: aspartate transaminase (N: 10–50 U/L); GGT: Gamma-glutamyl transferase (N: 71 U/L); ALP: alkaline phosphatase (N:50–136 U/L); sCr: serum creatinine; SUA: serum uric acid; ACE: angiotensin converting enzyme (N: 8–53 U/L); HIV: human immunodeficiency virus; CMV Ig: cytomegalovirus immunoglobulin G and M; ANA: antinuclear antibody; Anti-ds DNA: anti-double strand deoxyribonucleic acid; aPL: antiphospholipid antibodies; ANCA: anti-nuclear cytoplasmic antibody.

which was tapered gradually with concomitant addition of methotrexate in a dose of 20 mg/week, with complete and partial improvement of the facial nerve involvement and hearing defect, respectively, and radiologic regression of the detected hilar lymphadenopathy.

1.3. Neurologic and renal involvement in a juvenile-onset patient

1.3.1. Case 4

A 13-year-old male patient with a rash over the back and extremities, enlarged cervical lymph nodes of two-month duration, and intermittent mild to moderate bursting headache of an acute onset, fronto-temporal, partially relieved by simple analgesics, not interfering with sleep, and was accompanied by blurring of vision, yet was not associated with photophobia, nausea or vomiting, fever, sore throat, malaise or myalgia, or neck stiffness. He was referred to the rheumatology and rehabilitation department of Cairo University owing to a family history of sarcoidosis (second-degree relative). Examination revealed a macular diffuse erythematous rash over the trunk, buttocks, and extremities. There were no signs of meningeal irritation. Ophthalmologic examination revealed grade I papilledema. Laboratory investigations showed elevated serum creatinine (2.1 mg/dL), glucosuria and mild proteinuria, and ACE was elevated (Table 3). Chest CT revealed bilateral ground-glass appearance and prominent mediastinal and hilar lymph nodes, and abdominal CT demonstrated paraaortic lymph nodes. Brain MRI was normal with no meningeal thickening, space occupying lesions, or dilated ventricles

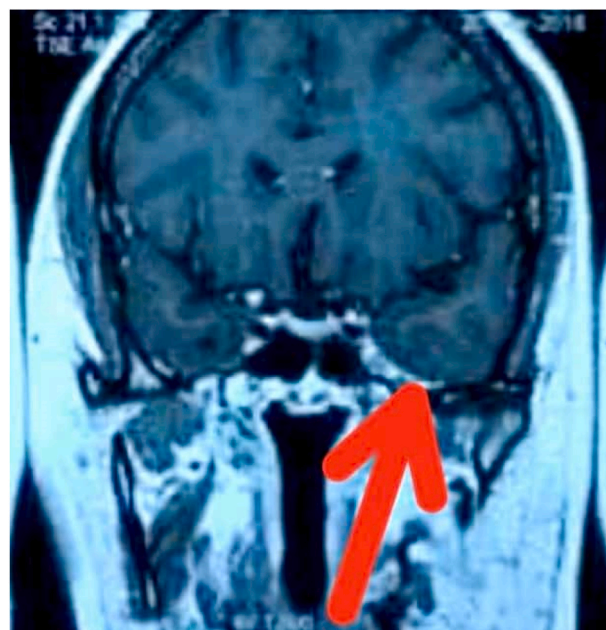


Fig. 5. Brain Magnetic Resonance Imaging showing leptomeningeal enhancement (Case 3).

Table 3
A juvenile-onset patient with neurologic and renal involvement (Case 4).

	At onset	Follow up
ESR	70 mm/hour	13 mm/hour
CRP	Negative	Negative
Hemoglobin	11 gm/dL	13.3 gm/dL
Total leukocytic count	$11 \times 10^3/\text{cmm}$	$8 \times 10^3/\text{cmm}$
Platelets	$220 \times 10^3/\text{cmm}$	$330 \times 10^3/\text{cmm}$
ALT	32 U/L	45 U/L
AST	33 U/L	39 U/L
GGT	44 U/L	50 U/L
ALP	120 U/L	112 U/L
Total and direct bilirubin	Normal	Normal
Serum albumin	4.3 gm/dL	4 gm/dL
s.Cr	2.1 mg/dL	0.4 mg/dL
Urine analysis	Glucose +. Albumin +. No Casts	Normal
24-h urinary protein	0.8 gm/day	0.1 gm/day
SUA	3.3 mg/dL	NA
Total calcium	9 mg/dL	NA
ACE	80.4 U/L	40.1 U/L
<i>Virology</i>		
HIV 1 & 2 antigen	Negative	NA
Hepatitis markers	Negative	NA
CMV IgG & IgM	Negative	NA
Tuberculin test	Negative	NA
Quantiferon TB Gold	Negative	NA
<i>Serology</i>		
ANA	Negative	NA
Anti-ds DNA	Negative	NA
aPL	Negative	NA
Complement 3 and 4	Negative	NA
Anti-Ro/SSA	Negative	NA
Anti-La/SSB	Negative	NA
ANCA	NA	–

Abbreviations: NA: Not available; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; Hb: hemoglobin; TLC: total leukocytic count; PLT: platelets count; ALT: alanine transaminase [Normal (N): 16–63 U/L]; AST: aspartate transaminase (N: 10–50 U/L); GGT: Gamma-glutamyl transferase (N: 71 U/L); ALP: alkaline phosphatase (N:50–136 U/L); sCr: serum creatinine; SUA: serum uric acid; ACE: angiotensin converting enzyme (N: 8–53 U/L); HIV: human immunodeficiency virus; CMV Ig: cytomegalovirus immunoglobulin G and M; ANA: antinuclear antibody; Anti-ds DNA: anti-double strand deoxyribonucleic acid; aPL: antiphospholipid antibodies; ANCA: anti-nuclear cytoplasmic antibodies.

(hydrocephalic changes) (Fig. 6A, B, and C). A renal biopsy was performed and showed *acute tubulointerstitial nephritis with eosinophils*, with no granulomatous lesions, yet the patient's parents refused to conduct a consecutive lumbar puncture. The patient was diagnosed with *sarcoidosis associated with benign increased intracranial tension and renal involvement*. In addition to adjunctive therapy that included acetazolamide, methylprednisolone 500 mg intravenously was administered for three consecutive days followed by prednisolone 30 mg/day, with

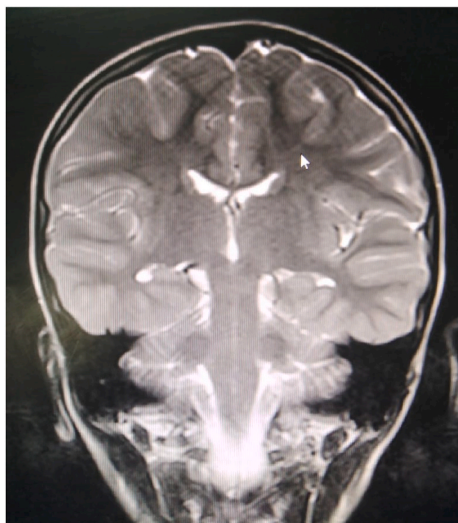
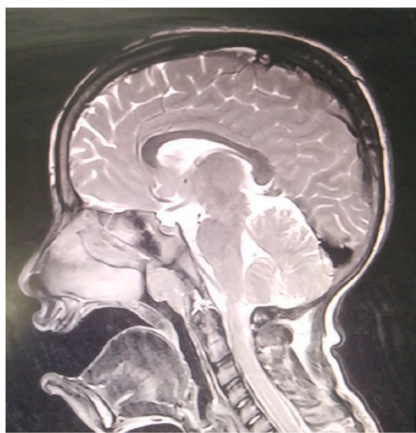


Fig. 6. A, B, and C : Normal brain magnetic resonance imaging (Case 4).

gradual and complete improvement of the headache and normal fundus examination over three months. Serial laboratory investigations showed normalization (Table 3). Prednisolone was tapered gradually to 5 mg/day whilst adding AZA in a dose of 100 mg/day.

2. Discussion

Sarcoidosis is characterized by its heterogeneous presentations that could surpass pulmonary involvement. Moreover, in addition to several renowned extra-pulmonary manifestations, shedding light on unusual presentations is of utmost importance to overcome diagnostic and therapeutic challenges. We present four cases with peculiar extra-pulmonary manifestation.

Our first patient had a peculiar hematologic association in the form of myelofibrosis developing after a two-year quiescent course of biopsy-proven sarcoidosis. Although several hematologic aberrations as malignancies [2] and myelodysplastic syndrome [3] have been associated with sarcoidosis, myelofibrosis is far less common being reported in two previous cases [4,5] to the best of our knowledge. It is note that distinct hematologic sarcoid features are usually due to granulomatous bone marrow infiltration (3.9%) [6], splenic lesions (6–30%) [6,7], and/or hypersplenism (0.6%) [8]; hence, warranting prudent interpretation of concurrent unusual hematologic manifestations.

Our second reported sarcoidosis presented patient had biopsy-proven sarcoidosis that coexisted with ITP which was histologically associated with megakaryocytic emperipolesis. Emperipolesis has been described by Humble et al. [9] as “The active penetration of one cell by another which remains intact”. It could be a physiologic or pathologic phenomenon and is further classified into megakaryocytic or histiocytic emperipolesis [10]. Although to the best of our knowledge emperipolesis has not been reported with sarcoidosis, it has been *histologically* reported in other granulomatous conditions such as Blau's syndrome and Crohn's disease [11], however its impact on the overt clinical characteristics needs further investigation. Interestingly, megakaryocytic emperipolesis has been associated with immune thrombocytopenia (ITP) in a previous case series [12], and in interest in ITP per se, it accounted for 80% of the causes of thrombocytopenia in sarcoidosis [13], yet the diagnostic and prognostic implications of these concurrent findings are yet to be elucidated.

Our third presented case presented with bilateral sequential facial nerve palsy and SNHL, which were investigated owing to generalized lymphadenopathy and revealed CT chest and biopsy findings concordant with sarcoidosis. Interestingly, brain MRI showed leptomeningeal enhancement which has been reported to be among the most prevalent neurosarcoid radiologic features (40%) [14]. The prevalence of neurosarcoidosis varies widely ranging from 5 to 16% of sarcoidosis patients [15]. It could present with a plethora of manifestations, with cranial neuropathies being among the most common affecting 25–50% of patients with neurosarcoidosis, whereby the facial nerve is the most affected [15]. Facial palsy in neurosarcoidosis could be unilateral or bilateral, with bilateral facial palsy occurring either simultaneously or sequentially and could be recurrent [16], yet usually carries a good prognosis [15].

Our fourth case presented had neurologic and renal manifestations in the form of benign increased intracranial tension and acute tubulointerstitial nephritis (with eosinophils), respectively. To the best of our knowledge, benign increased intracranial tension has been scarcely documented as a manifestation of neurosarcoidosis [15]. Contrary to neurosarcoidosis, renal involvement is more common; with a prevalence ranging from 35 to 50% [17]. Interstitial nephritis per se has been associated with granulomatous lesions on biopsy in previous case series [18], unlike our patient with no biopsy findings of granulomas. Nevertheless, interstitial nephritis associated with sarcoidosis in absence of granulomas has been reported previously [17].

It is of interest that our fourth presented patient was of juvenile-onset. The incidence of sarcoidosis among children is estimated to be

much lower than adults and has been reported to usually carry a better prognosis [19]. It is of note that our juvenile-onset patient further had a family history of sarcoidosis. Familial sarcoidosis suggests a genetic implication, with a pooled prevalence of about 10% in a previous study [20].

To conclude, our presented cases had unusual hematologic, neurologic, and renal manifestations that, to the best of our knowledge, were scarcely reported; thus, further highlighting the complexity, heterogeneity, and masquerading nature of sarcoidosis.

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Ethics statement

This work is in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Patients' consent

Consent was obtained from the patients (Cases 2 and 3), relatives (Case 1), and parents (Case 4).

Declaration of competing interest

None.

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