

# Carpal tunnel syndrome associated with sarcoidosis in identical twin patients

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## Abstract

Sarcoidosis is a multisystemic disease that may lead to neurologic complications in 10% of the patients. Carpal tunnel syndrome is very rare in sarcoidosis. We present two identical twin sarcoidosis patients with carpal tunnel syndrome. A number of factors may cause carpal tunnel syndrome like wrist anatomy, occupation, diabetes, rheumatoid arthritis, pregnancy and renal failure. Although the above factors do not directly cause carpal tunnel syndrome, they may increase your chances of developing or aggravate median nerve damage as it is in sarcoidosis. Sarcoidosis relevant neuropathy and granulomas may be the primary mechanism of sarcoidosis associated carpal tunnel syndrome.

Although rare, carpal tunnel syndrome may be a feature of sarcoidosis that may lead to irreversible damage in cases of delayed diagnosis. The presence of this syndrome in identical twin patients may shed light into the pathogenesis and the genetic transmission of sarcoidosis with the associated carpal tunnel syndrome.

## Introduction

Neurologic involvement occurs in approximately 5 to 10% of sarcoidosis patients [1-4]. Neurosarcoidosis is a consideration with previously known sarcoidosis patients and approximately half of the patients of these subjects present with diagnostic diffi-

culties while one third may have more than one neurologic manifestation. Any portion of the peripheral nervous system may be involved in sarcoidosis. Sarcoidosis associated carpal tunnel syndrome is very rare and has been reported mostly as case reports [5-8]. HLA genes are highly polymorphic with many different alleles that may pose a significant risk in certain diseases, primarily sarcoidosis. HLA-DRB1 alleles have been associated with the sarcoidosis course, severity and organ involvement [9].

We introduce this case report to remark the significance of carpal tunnel syndrome in sarcoidosis patients. Patients with neurosarcoidosis may present with different or inconsistent manifestations affiliated to the part of the neurologic axis involved that may cause a diagnostic predicament in clinical practice. The presence of this syndrome in identical twins with the same HLA allele polymorphism may enlighten the genetic mechanism of sarcoidosis and the associated carpal tunnel syndrome.

## Case #1

A 43-year-old female was admitted for dry cough, fatigue, paresthesia involving the first three digits of both hands with pain and tingling at the wrist. The patient was a non-smoker. She had a history of sarcoidosis and ulcerative colitis. Family history revealed sarcoidosis in her twin sister and hypertension in both parents. The patient did not have a stressful manual job that may have led to her wrist pain and tingling. Sarcoidosis had been identified by the histopathologic examination of the endobronchial and cutaneous biopsy six years before. Physical examination was normal except for positive Tinnel's and Phalen's tests. ECG showed a sinus rhythm of 80/min. Blood tests results were: WBC,  $4.9 \times 10^3/\text{mm}^3$ ; RBC,  $4.7 \times 10^6/\text{mm}^3$ ; Hgb, 12.5 g/dL; Htc, 35.5%; PLT,  $207 \times 10^3/\text{mm}^3$ ; Neut, 52.2%; Lymp, 33.7%; Eos, 2.9%; Baso, 0.75%; glucose, 93 mg; creatinine, 0.79 mg/dL; total protein, 8.6 g/dL; Alb, 4.6 g/dL; AST, 30 IU/L; ALT, 32 IU/L; LDH, 471 IU/L; GGT, 19 IU/L; ALP, 188 IU/L; CK, 129 IU/L; Ca, 9.6 mg; and CRP, 0.06 mg/dL. Urine analysis was within normal limits. Serum ACE was 86.4 U/L. Chest x-ray and thorax CT revealed normal lung parenchyma and mediastinum (Figure 1). Pulmonary function tests, DLCO/VA and arterial blood gases were normal. BAL CD<sub>4</sub>/CD<sub>8</sub> ratio was 2.4 and bronchoscopy revealed normal findings. HLA-DRB1\*07 allele was positive. MR of the hand showed bowing of flexor retinaculum, segmental swelling of the median nerve and edema and loss of fat within the carpal tunnel (Figure 2). Nerve conduction studies revealed bilateral sensory and motor electrophysiological changes compatible with the carpal tunnel syndrome. Median nerve motor latency was 4.76 ms and sensory latency was 4.48 ms that indicated carpal tunnel syndrome. Treatment with methylprednisolone 32 mg/day

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with a wrist splint was not successful and the patient underwent surgical operation.

## Case #2

A 43-year-old female presented with dry cough, tingling and numbness in the first and second digits of both hands. The patient was a non-smoker. She had a history of sarcoidosis, osteomyelitis in the fifth metatarsal bone of the left foot and nasal septum deviation. Sarcoidosis had been identified by the histopathologic examination of the eye excisional and cutaneous biopsy eight years ago.



Figure 1. Case #1. Normal chest x-ray.

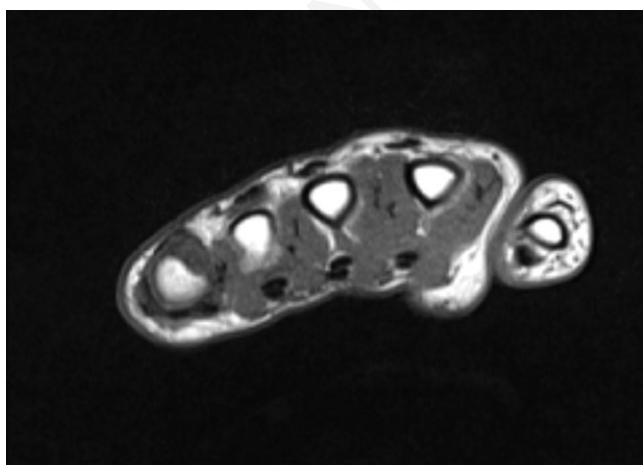


Figure 2. Case #1. MRI of the hand showed bowing of flexor retinaculum, segmental swelling of the median nerve, edema and loss of fat within the carpal tunnel.

Family history revealed sarcoidosis, ulcerative colitis in her twin sister and hypertension in both parents. The patient did not have a stressful manual job that may have caused tingling and numbness in her first and second digits of the hand. Physical examination was normal while Tinnel's and Phalen's tests were positive. ECG showed sinus rhythm of 78/min. Blood tests results were: WBC,  $8.7 \times 10^3/\text{mm}^3$ ; RBC,  $4.6 \times 10^6/\text{mm}^3$ ; Hgb, 14 g/dL; Htc, 42.9%; PLT,  $207 \times 10^3/\text{mm}^3$ ; Neut, 67%; Lym, 38.9%; Eos, 0.6%; Baso, 0.3%; glucose, 81 mg; creatinine, 0.67 mg/dL; total protein, 8 g/dL; albumine, 4.7 g/dL; AST, 19 IU/L; ALT, 17.6 IU/L; LDH, 228 IU/L; ALP, 45 IU/L; GGT, 24 IU/L; ALP, 45 IU/L; CK, 118 IU/L; Ca, 9.6 mg and CRP, 0.4 mg/dL; serum ACE was 80.2 U/L. Urine analysis was normal; chest x-ray (Figure 3) was normal; thorax CT (Figure 4) showed bilateral nodules less than 4 mm. Pulmonary function tests, DLCO/VA and arterial blood gases revealed normal results according to age. BAL CD4/CD8 ratio was 2.8 and bronchoscopy was normal. Laryngoscopic examination identified bilateral vocal cord nodules. The patient was HLA-DRB1\*07 allele positive. MR of the hand showed enlargement due to diffuse swelling of the median nerve at the level of the pisiform and edema within the carpal tunnel (Figure 5). Nerve conduction studies revealed bilateral moderate sensory and mild motor defects associated with carpal tunnel syndrome. Median nerve motor latency was 4.70 ms and sensory latency was 4.40 ms that were compatible with carpal tunnel syndrome. Final diagnosis was carpal tunnel syndrome associated with sarcoidosis. A wrist splint was prescribed and the patient was commenced on 32 mg methylprednisolone daily. Wrist surgery was carried out as the conservative medical treatment did not resolve the symptoms.

## Discussion

Sarcoidosis is multisystemic granulomatous disease of



Figure 3. Case #2. Normal chest x-ray.

unknown cause that may give rise to neurologic disorders in 5% to 10% of the patients [2,10-12] while the actual prevalence may be much higher than the clinically estimated as subclinical neurologic involvement has been detected in up to 27% of sarcoidosis patients postmortem. As any part of the central or peripheral nervous system may be affected, neurosarcoidosis presents with a broad range of manifestations and protean clinical findings that may cause a diagnostic dilemma for the clinician [13,14]. We present two identical twin sisters with carpal tunnel syndrome relevant to sarcoidosis carrying the same HLADRB1 polymorphism that may enlighten the pathogenetic mechanisms related to this morbidity and the hereditary basis of sarcoidosis.

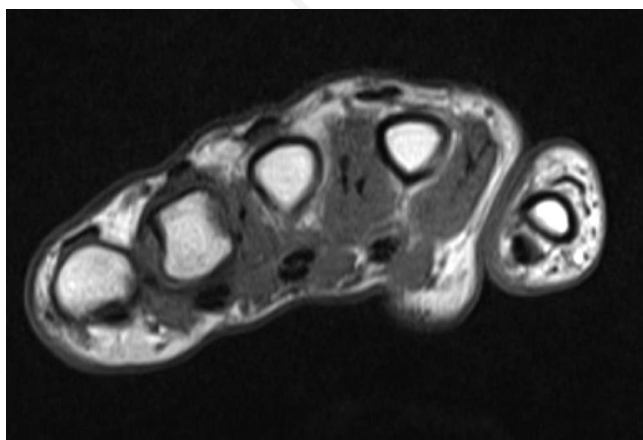
The mechanism of neurologic involvement in sarcoidosis is currently unknown. In the peripheral nervous system, neurosar-

coidosis commonly presents as neuropathy. Granulomatous inflammation, demyelination, panangitis, vasculitic neuropathy, compression by granulomas and edema under the perineural tissue are the suggested inductive mechanisms for sarcoidosis neuropathy [2,4,14]. Personal history of both patients did not reveal a disorder or a stressful manual job that may have led to carpal tunnel syndrome. Consequently, the presence of sarcoidosis and the same HLA allele polymorphism in both patients confirmed the final diagnosis of carpal tunnel syndrome due to sarcoidosis. Carpal tunnel syndrome relevant to sarcoidosis is a rare occurrence and the pathogenesis is unknown. As clinical manifestations of neuropathy are similar and almost alike with the carpal tunnel syndrome, the diagnosis may cause a diagnostic impasse for the clinician thereby leading to a detrimental outcome for the patient. The presence of HLA-DRB1\*07 allele positivity, sarcoidosis and carpal tunnel syndrome in both patients may justify the role of hereditary disposition for sarcoidosis [9] and the associated carpal tunnel syndrome. Positive HLA-DRB1\*07 allele indicates that the genetic trend may play a dominant role in the development of this syndrome in sarcoidosis patients as well as sarcoidosis itself and the persistent disease as it is the case in both of our patients.

It is reported that most of the patients with sarcoidosis associated carpal tunnel syndrome are asymptomatic or clinically silent while only 21.4% are symptomatic [6,15]. Therefore, the diagnosis requires a high degree of suspicion. The diagnostic pathway necessitates the use of nerve conduction studies for the identification of carpal tunnel syndrome in sarcoidosis. More frequent extrapulmonary organ involvement may also be a feature of this syndrome in these patients. Our patients had lung, skin, eye sarcoidosis with neurologic involvement. Another crucial aspect was the presence of HLA-DRB1\*07 positivity in both of the patients. Existence of HLA-DRB1\*07 positivity may be regarded as a significant diagnostic hallmark and the genetic basis for the transmission of this syndrome in sarcoidosis. Polymorphism of HLA-DRB1 alleles play a crucial role in sarcoidosis. Presence of such a polymorphism may also influence the prognostic outcome including the extent of extrapulmonary organ involvement and may be the hallmark for the existence of carpal tunnel syndrome in our patients.



**Figure 4.** Case #2. Chest CT revealed nodules less than 4 mm in both lungs.



**Figure 5.** Case #2. MRI of the hand revealing enlargement due to diffuse swelling of the median nerve at the level of the pisiform and edema within the carpal tunnel.

## Conclusions

Carpal tunnel syndrome is a rare manifestation of sarcoidosis. The clinically silent profile of this syndrome causes a diagnostic impasse while the delayed identification of carpal tunnel syndrome may lead to a deleterious outcome for the patients. Determination may be difficult as peripheral neuropathy of sarcoidosis presents with almost the same clinical scenario as the carpal tunnel syndrome. The presence of HLA-DRB1\*07 positivity on the other hand may be a useful marker both for diagnosis and the illumination of the hereditary mechanism for this syndrome. HLA-DRB1 allele polymorphism may be the fundamental hallmark of the genetic basis in sarcoidosis patients and the associated carpal tunnel syndrome.

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