Case Reports in Dermatology

Case Rep Dermatol 2023;15:40–44
DOI: 10.1159/000529159
Received: April 25, 2022
Accepted: January 4, 2023
Published online: February 15, 2023



**Single Case**

# Cutaneous Manifestations of Sarcoidosis Seen in a Patient with a History of Tuberous Sclerosis

Seth Bernacki[a] Paarth Dodia[a] Mikél Elizabeth Muse[b] Luke Maxfield[c]

[a]Campbell University College of Osteopathic Medicine Transitional Year Resident, Clinton, NC, USA; [b]Campbell University College of Osteopathic Medicine Dermatology Resident, Clinton, NC, USA; [c]Deparment of Mohs surgery, Campbell University College of Osteopathic Medicine, Clinton, NC, USA

**Keywords**
Autoimmune diseases · Tuberous sclerosis · Sarcoidosis

**Abstract**
This case report details a patient with a history of tuberous sclerosis presenting with new-onset cutaneous lesions that turn out to be sarcoidosis. There may be a shared dysfunction of mTOR present in sarcoidosis and tuberous sclerosis. As a dermatologist, it is worth understanding the cutaneous manifestations of both diseases and maintaining a wide differential when new lesions arise in a patient with a history of either disorder.



## Introduction

Tuberous sclerosis complex (TSC) is a multisystem genetic condition of highly variable clinical features that is commonly associated with various neurologic, ophthalmologic, cardiac, pulmonary, and cutaneous abnormalities. The first and most common sign is hypopigmented macules seen in over 90% of patients with TSC [1], followed by facial angiofibromas, then shagreen patches, and periungual fibromas. Central nervous system tumors are also seen often in patients with TSC and are most commonly glial-neuronal and retinal hamartomas as well as subependymal giant cell tumors. As a result, another one of the common findings in TSC is seizures at a young age. There is a rare association with sarcoidosis, a chronic granulomatous disease involving the lungs and also commonly the skin. Although

Correspondence to:
Paarth Dodia, paarthdodia@gmail.com

the pathophysiology is poorly understood, the mechanisms of each disease have been explored.

TSC results from mutations in either TSC1 or TSC2. TSC1 is a tumor suppressor gene that encodes hamartin, while TSC2 is responsible for encoding tuberin. Both products are involved in regulating cell proliferation and differentiation by creating a complex that activates GTPase. This GTPase inactivates RHEB in order to inhibit the mammalian target of rapamycin (mTOR) pathway. The mTOR pathway is responsible for protein and lipid biosynthesis and growth factor-related cell cycle progression. The mutations in either TSC1 or TSC2 can lead to hyperactivation and dysregulation of the mTOR pathway causing varying abnormalities in the cell cycle.

On the other hand, while sarcoidosis has been linked to various HLA and immune-related genes, no single predominant gene has been identified yet [2]. The current hypothesis is that these genes place the patient at a genetic susceptibility to increased macrophage activation via T cells (which use HLA to facilitate this interaction), causing excessive granuloma formation through mTORC1 pathways [3]. How adaptive and innate immune factors maintain these granulomas to cause the manifestations seen in sarcoidosis is beyond the scope of this presentation, but it should be noted that the pathophysiology is regarded as an "unresolved immunological paradox" that is largely not well understood [4].

## Case Presentation

A 38-year-old female presented to the clinic with the complaint of multiple nontender "bumps" that were present over her upper and lower extremities, as well as her scalp. These "bumps" had been progressing in size for over a year. Upon physical exam, the patient had multiple compressible and nontender subcutaneous nodules distributed throughout her scalp and extremities. Past medical history was notable for tuberous sclerosis that required the patient to have a brain tumor removed at age 18, seizures, and asthma. She denied any recent illness, fever, weight loss, or other constitutional symptoms. The patient was not on any home medications.

Two 6-mm punch biopsies were obtained from the right superior frontal scalp and right proximal ulnar dorsal forearm. The biopsies were sent for hematoxylin and eosin staining and review by dermatopathology. The results of the biopsies showed a histopathological diagnosis of the biopsy was consistent with sarcoidosis (Fig. 1, 2a, b). The biopsy ruled out possible vasculitides and lacked any cholesterol clefting or refractive material.

The patient's workup included a complete blood count (CBC), complete metabolic panel (CMP), and serum angiotensin-converting enzyme (ACE) due to the biopsy result suggesting sarcoidosis. The CBC and CMP were mostly normal; minor fluctuations were noted, for example, white blood cells at 4.02 K/μL with the lower limit of 4.00 K/μL. The patient's calcium levels were just within normal limits at 10.1 mg/dL, with an upper limit of 10.4 mg/dL. However, the patient's serum ACE level was elevated at 151 U/L, with an upper limit of 67 U/L. This was consistent with diagnosis of sarcoidosis. Chest x-rays and a CT scan of her chest ruled out any pulmonary involvement.

The patient in our case did not receive any intervention for her subcutaneous nodules. She was counseled by the dermatology team on possible management of the lesions, including high-potency topical steroids, intra-lesional steroids, methotrexate, and anti-malarials. She proceeded with conservative management. Referrals were made to nephrology and urology due to declining renal function. The patient was also referred for an eye exam due to potential ocular manifestations, such as anterior uveitis [5]. The patient has since been contacted for follow-up. Her subcutaneous nodules resolved without intervention after several months. She

Case Rep Dermatol 2023;15:40–44
DOI: 10.1159/000529159




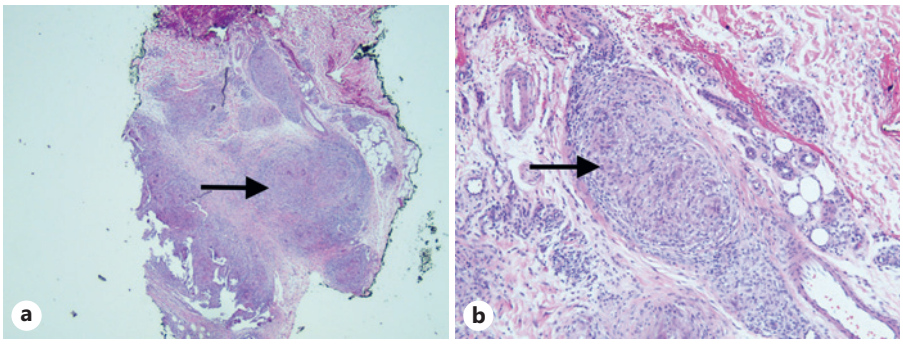


**Fig. 1. a** Punch biopsy of forearm at 2.5 times magnification. Arrows indicate granulomas. **b** Punch biopsy of forearm at 10 times magnification. Arrows indicate granulomas.

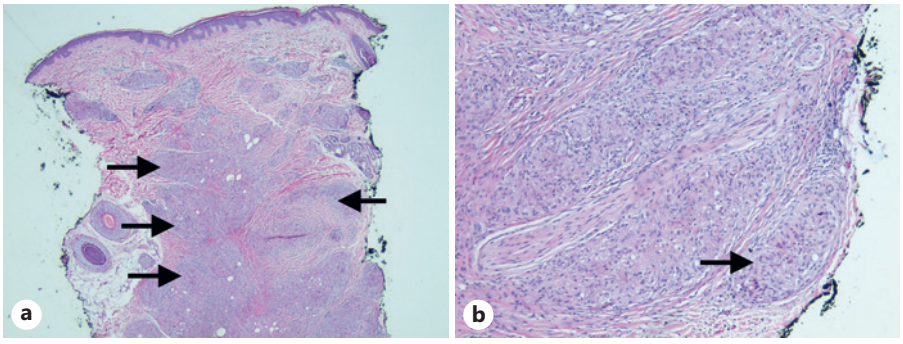


**Fig. 2. a** Punch biopsy of scalp at 2.5 times magnification. Arrows indicate granulomas. **b** Punch biopsy of scalp at 10 times magnification. Arrows indicate granulomas.

has had regular chest x-rays and eye exams that showed no involvement of either organ system. Her kidney function has stabilized.

## Discussion

This case describes an interesting finding of sarcoidosis in a female patient with a history of TSC. Both diseases are relatively rare with the presence of TSC estimated at roughly 17 in 100,000 [1] and sarcoidosis being estimated at roughly 11 in 100,000 in whites in the USA [2]. The co-incidence of multiple rare diseases in any single patient should prompt the thought of related pathways and pathophysiology. The mTOR signaling pathway may be that shared piece between both conditions seen in our patient.

An article written by Zhang et al. [3] has seemed to find a potential tie between the TSC and sarcoidosis: lymphangioleiomyomatosis (LAM). LAM is a disease that primarily affects women, causing "cystic lung destruction, lymphatic infiltration, and renal angiomyolipomas, resulting from proliferation of smooth muscle-like LAM cells." LAM can arise sporadically, but there is also an association of the condition with alterations in TSC genes. The authors found evidence of loss of heterozygosity in TSC2 among LAM cells in the blood of sarcoidosis patients. While none of the patients from the study were noted to have TSC and sarcoidosis concomitantly, both diseases share a disruption in normal mTOR signaling. Clinical trials of mTOR inhibitors in the management of TSC patients has proved their usefulness. Sirolimus and everolimus have been shown to be safe and efficacious in managing TSC disease

manifestations [6]. There have been case reports that show mTOR inhibitors may serve a role in some cases of recalcitrant sarcoidosis [7].

Another study by Linke et al. [4] has found that activation of Mtorc1 via deletion of the gene encoding TSC2 induced hypertrophy and proliferation of macrophages, resulting in excessive granuloma formation in vivo. One could speculate that a condition like TSC where TSC2 abnormalities are seen could also play a role in these granulomatous diseases, like sarcoidosis.

While there is no strong evidence at this time to support a connection between sarcoidosis and tuberous sclerosis, the aforementioned studies hint that there may be a shared dysfunction of mTOR present in both diseases. Both diseases have remarkably variable findings; as dermatologists, it is important to maintain a wide differential when new cutaneous lesions arise in a patient with a history of either disorder. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material at www.karger.com/doi/10.1159/000529159.

## Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines.

## Conflict of Interest Statement

The authors have no conflict of interest to declare.

## Funding Sources

This article has no funding source.

## Author Contributions

Seth Bernacki and Paarth Dodia wrote the original draft of the document. Mikel Muse and Luke Maxfield made substantial contributions to guiding the overall direction and design of the manuscript and assisted with reviewing and editing. They also aided in literature review.

## Data Availability Statement

All data related to this case report are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

## References

1 Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. Lancet. 2008;372(9639):657–68.
2 Llanos O, Hamzeh N. Sarcoidosis. Med Clin North Am. 2019;103(3):527–34.

3 Zhang L, Pacheco-Rodriguez G, Steagall WK, Kato J, Haughey M, Fontana JR, et al. Tuberous sclerosis complex 2 loss of heterozygosity in patients with lung disease and cancer. Am J Respir Crit Care Med. 2015;191(3):352–5.
4 Linke M, Pham HTT, Katholnig K, Schnöller T, Miller A, Demel F, et al. Chronic signaling via the metabolic checkpoint kinase mTORC1 induces macrophage granuloma formation and marks sarcoidosis progression. Nat Immunol. 2017;18(3):293–302.
5 Polverino F, Balestro E, Spagnolo P. Clinical presentations, pathogenesis, and therapy of sarcoidosis: state of the art. J Clin Med. 2020;9(8):2363.
6 MacKeigan JP, Krueger DA. Differentiating the mTOR inhibitors everolimus and sirolimus in the treatment of tuberous sclerosis complex. Neuro Oncol. 2015;17(12):1550–9.
7 Kelleher KJ, Russell J, Killeen OG, Leahy TR. Treatment-recalcitrant laryngeal sarcoidosis responsive to sirolimus. BMJ Case Rep. 2020;13(8):e235372.