Sarcoidosis in Post–9/11 Military Veterans

Jourdan Brandon, MD; Ford Lannan, MD; Misha Rosenbach, MD

PRACTICE **POINTS**

- Cutaneous sarcoidosis is the most common extrapulmonary manifestation of the disease.
- Cutaneous sarcoidosis can precede systemic manifestations of the disease and should prompt further workup.
- Sarcoidosis is a presumptive diagnosis under the PACT Act and may be a service-connected condition. Veterans with presumptive exposures should be referred to the US Department of Veterans Affairs.

Historically, US servicemembers have faced unique environmental hazards that may increase their risk for developing sarcoidosis. Cutaneous sarcoidosis is the most common extrapulmonary manifestation of sarcoidosis and can precede systemic manifestations of the disease. In this article, we review the literature to examine the risk factors and incidence of sarcoidosis in post–9/11 veterans as well as provide recommendations for workup and management. Importantly, we also highlight that sarcoidosis is a presumptive diagnosis under the recently enacted Promise to Address Comprehensive Toxics (PACT) Act and may be service connected. Veterans with sarcoidosis should be referred to the US Department of Veterans Affairs.

Cutis. 2023;112:127-130, E1.

Sarcoidosis is a chronic inflammatory disease characterized by noncaseating granulomas that can affect many organ systems, most commonly the lungs and skin, with cutaneous involvement in 25% to 30% of patients in the United States.[1] The etiology of sarcoidosis largely is unknown and likely is multifactorial; however, specific environmental, infectious, and pharmaceutical triggers may contribute to its pathogenesis. Sarcoidosis secondary to occupational exposures in US Military veterans historically has been discussed and investigated. Still, it was not considered a service-connected disability until the passing of the Promise to Address Comprehensive Toxics (PACT) Act[2] in 2022. In this article, we review the risk factors and incidence of sarcoidosis in post–9/11 veterans as well as provide recommendations for managing presumptive service-connected sarcoidosis covered under the recently enacted PACT Act.

The PACT Act and Post–9/11 Military Veterans

Veterans of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) have a history of occupational exposures to open-air burn pits, gun smoke, and recurrent high-intensity sandstorms that may cause chronic disease.[3] Burn pits, which were used to dispose of solid waste on forward operating bases, released antigenic particulate matter that was detectable on air sampling.[4,5] Increased respiratory disease rates in veterans that were deployed post–9/11 are well documented, but a causal relationship has not been established.[6] Although burn pits cannot be directly associated with any disease at this time,[5] veterans with assumed exposures can now receive a Veterans Affairs (VA) Disability Rating for presumptive conditions under the PACT Act.[2] The major points of this legislation include expanding and extending eligibility for veterans with toxic exposures, providing access to toxic exposure screening for all veterans receiving VA health care, and increasing research related to toxic exposures in US servicemembers. The PACT Act expands health care benefits, making it easier for veterans exposed post–9/11

Drs. Brandon and Lannan are from the Department of Dermatology, Walter Reed National Military Medical Center, Bethesda, Maryland.
Dr. Rosenbach is from the Department of Dermatology, University of Pennsylvania, Philadelphia.
The authors report no conflict of interest.
The identification of specific products or scientific instrumentation is considered an integral part of the scientific endeavor and does not constitute endorsement or implied endorsement on the part of the author, Department of Defense, or any component agency. The views expressed in this article are those of the authors and do not necessarily reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense, or the US Government.
The eTable is available in the Appendix online at www.mdedge.com/dermatology.
Correspondence: Ford Lannan, MD, Department of Dermatology, Bldg 19, 4494 Palmer Rd N, Bethesda, MD 20814 (ford.m.lannan.mil@health.mil).
doi:10.12788/cutis.0852

to receive coverage for 24 new presumptive diagnoses.[2] Of these diagnoses, several are relevant to the practicing dermatologist. Patients with metastasis of primary cancers to the skin as well as melanoma or sarcoidosis may be eligible for coverage depending on the location and time of service. The Table lists service locations where the VA has determined servicemembers may have been exposed to burn pits or other toxins. Servicemembers with a presumptive diagnosis who served in these locations may be eligible for care under the PACT Act. Sarcoidosis is of particular concern due to its increased incidence and prevalence in military veterans compared to civilian populations. An analysis of more than 13 million veterans who received health care benefits through the Veterans Health Administration in 2019 found an annual incidence of sarcoidosis of 52 cases per 100,000 person-years and an annual prevalence of 141 cases per 100,000 individuals.[7] In contrast, the United States has a reported annual incidence of sarcoidosis of 4.9 cases per 100,000 person-years and an annual prevalence of 60 cases per 100,000 individuals.[8] Although the increased rates of sarcoidosis in veterans have been noted for decades, only recently have investigations provided insights into the etiology of sarcoidosis in this population.

Presumptive Exposure Locations Eligible for Care Under the PACT Act[a]

On or after August 2, 1990	On or after September 11, 2001[b]
Bahrain	Afghanistan
Iraq	Djibouti
Kuwait	Egypt
Oman	Jordan
Qatar	Lebanon
Saudi Arabia	Syria
Somalia	Uzbekistan
United Arab Emirates	Yemen

[a]Including the airspace above the location.

[b]In addition to the prior locations.

Data from the US Department of Veterans Affairs.[2]

Sarcoidosis and Environmental Factors

Sarcoidosis is a multisystem granulomatous inflammatory disease that can present in any organ system[9]; however, it most commonly affects the lungs, skin, and eyes—all of which are subjected to direct contact with environmental toxins. The cause of sarcoidosis is unknown, but environmental exposures are theorized to play a role.[9,10] It has been hypothesized that exposure to various immunologically active triggers may invoke the granulomatous inflammatory response that characterizes the disease.[11] The World Trade Center disaster on 9/11 has provided insight into the potential environmental component of sarcoidosis. Firefighters who spent extensive amounts of time at the World Trade Center site experienced intense exposure to inorganic particulate matter; it was later found that there was a marked increase in the incidence of sarcoidosis or sarcoidosislike granulomatous pulmonary disease in exposed firefighters. It has been speculated that the elevated exposure to potentially antigenic particulates may have induced granulomatous inflammation, resulting in the manifestation of the disease.[12] Other known occupational exposures associated with an increased risk for sarcoidosis or sarcoidosislike illness include mold, silicates, metal dust, and microbial contaminants.[11] Servicemembers commonly are exposed to several of these aerosolized toxins, which theoretically could increase their risk for developing sarcoidosis.

Sarcoidosis in the Military

Servicemembers historically have faced unique environmental hazards that may increase their risk for developing sarcoidosis. Studies of naval veterans have shown relationships between occupational location and increased rates of sarcoidosis. Sailors assigned to aircraft carriers with nonskid coatings containing particulate matter such as aluminum, titanium, and silicates had a higher prevalence of sarcoidosis than those stationed on "clean" ships.[13,14] Although no one trigger was identified, the increased rates of sarcoidosis in populations with extensive exposure to toxins raise concern for the possibility of occupationally induced sarcoidosis in post–9/11 veterans.

Environmental exposures during OIF and OEF may be associated with sarcoidosis. A retrospective review of lung biopsy data collected from Department of Defense military treatment facilities was conducted to identify associations between lung disease and deployment to the Middle East.[15] The study included 391 military patients divided into deployed and nondeployed groups undergoing lung biopsies for various reasons from 2005 to 2012. An analysis of the reported lung histology showed an increased frequency of nonnecrotizing granulomas in those with a history of deployment to the Middle East compared to those who had never been deployed. Development of disease was not associated with confounding factors such as age, ethnicity, sex, or tobacco use, raising suspicion about similar shared toxic exposures among deployed servicemembers.[15] A 2020 study of sarcoidosis in active-duty military personnel reported that the incidence of observed cases was 2-times those seen in civilian Department of Defense employees from 2005 to 2010; however, data collected in this study did not indicate an increased risk for developing sarcoidosis based on deployment to the Middle East. Still, the higher prevalence of sarcoidosis in active-duty military personnel suggests similar shared exposures in this group.[16]

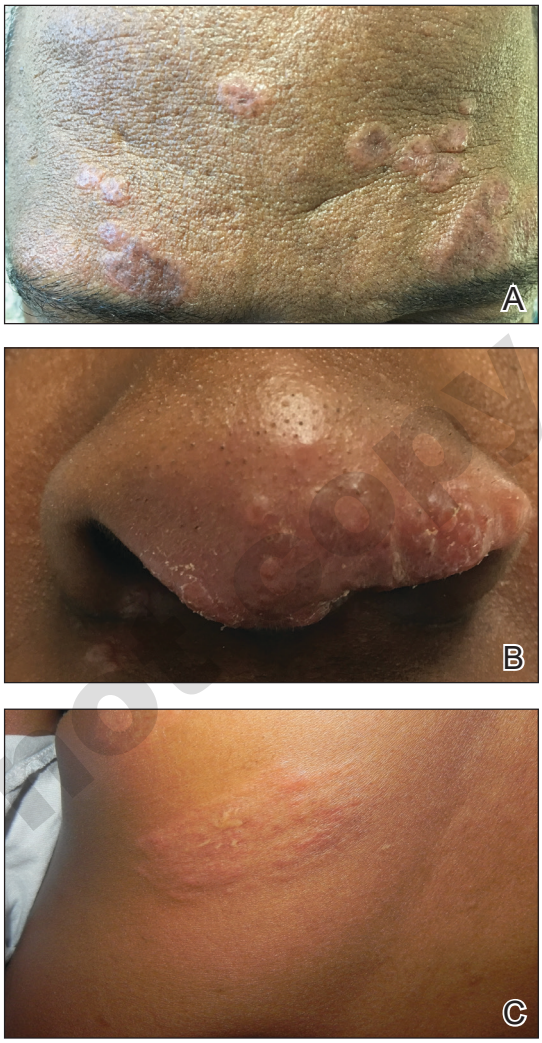
Identification of exposures that may potentially trigger sarcoidosis is difficult due to many confounding variables; however, the Airborne Hazards and Open Burn Pit Registry questionnaire has been used to extrapolate prospective hazards of concern. Results from the questionnaire identified that only veterans exposed to convoy activity had a statistically significant (odds ratio, 1.16; 95% CI, 1.00-1.35; P=.046) increased risk for developing sarcoidosis.[17] Interestingly, enlisted personnel had a higher rate of sarcoidosis than officers, comprising upwards of 78% of cases in the Military Health System from 2004 to 2013.[9] This finding requires further study, but increased exposure to toxins due to occupational specialty may be the cause.

Veterans with sarcoidosis may have a unique pathophysiology, which may point to occupational exposure. Studies show that affected veterans have unique plasma metabolites and metal ions compared to civilians, with lower anti-inflammatory amino acid concentrations and downregulated GABA synthesis. The environmental exposures in OIF and OEF may have primed deployed servicemembers to develop a distinct subtype of sarcoidosis.[3] Overall, there is a dearth of literature on post–9/11 veterans with sarcoidosis; therefore, further investigation is necessary to determine the actual risk for developing the disease following exposures related to military service.

Clinical Presentation and Diagnosis

Cutaneous sarcoidosis protean morphology is considered an imitator of many other skin diseases. The most common sarcoidosis-specific skin lesions include papules and papulonodules (Figure, A), lupus pernio (Figure, B), plaques (Figure, C), and subcutaneous nodules. Lesions typically present on the face, neck, trunk, and extremities and are associated with a favorable prognosis. Lupus pernio presents as centrofacial, bluish-red or violaceous nodules and can be disfiguring (Figure, B). Subcutaneous nodules occur in the subcutaneous tissue or deep dermis with minimal surface changes. Sarcoidal lesions also can occur at sites of scar tissue or trauma, within tattoos, and around foreign bodies. Other uncommon sarcoidosis-specific skin lesions include ichthyosiform, hypopigmented, atrophic, ulcerative and mucosal lesions; erythroderma; alopecia; and nail sarcoidosis.[18]

When cutaneous sarcoidosis is suspected, the skin serves as an easily accessible organ for biopsy to confirm the diagnosis.[1] Sarcoidosis-specific skin lesions are histologically characterized as sarcoidal granulomas with a classic noncaseating naked appearance comprised of epithelioid histocytes with giant cells amidst a mild lymphocytic inflammatory infiltrate. Nonspecific sarcoidosis skin lesions do not contain characteristic noncaseating granulomas. Erythema nodosum is the most common nonspecific lesion and is associated with a favorable prognosis. Other nonspecific sarcoidosis skin findings include calcinosis cutis, clubbing, and vasculitis.[18]



A, Erythematous to violaceous, flat papules and small plaques with some scaling across the forehead in a patient with sarcoidosis. B, Scattered scaly papules and subcutaneous plaques damaging the nasal alar cartilage in a patient with lupus pernio. C, Two flesh-colored to faintly erythematous plaques on the mid back—one with a biopsy-site scar within the lesion—in a patient with plaque sarcoidosis.

Workup

Due to the systemic nature of sarcoidosis, dermatologists should initiate a comprehensive workup upon diagnosis of cutaneous sarcoidosis, which should include the following: a complete in-depth history, including occupational/environmental exposures; a complete review of systems; a military history, including time of service and location of deployments; physical examination; pulmonary function test; high-resolution chest computed tomography[19]; pulmonology referral for additional pulmonary function tests, including diffusion capacity for carbon monoxide and 6-minute walk test; ophthalmology referral for full ophthalmologic examination; initial cardiac screening with electrocardiogram; and a review of symptoms including assessment of heart palpitations. Any abnormalities should prompt cardiology referral

for evaluation of cardiac involvement with a workup that may include transthoracic echocardiogram, Holter monitor, cardiac magnetic resonance imaging with gadolinium contrast, or cardiac positron emission tomography/computed tomography; a complete blood cell count; comprehensive metabolic panel; urinalysis, with a 24-hour urine calcium if there is a history of a kidney stone; tuberculin skin test or IFN-γ release assay to rule out tuberculosis on a case-by-case basis; thyroid testing; and 25-hydroxy vitamin D and 1,25-dihydroxy vitamin D screening.[1]

Treatment

Cutaneous sarcoidosis is treated with topical or intralesional anti-inflammatory medications, immunomodulators, systemic immunosuppressants, and biologic agents. Management of cutaneous sarcoidosis should be done in an escalating approach guided by treatment response, location on the body, and patient preference. Response to therapy can take upwards of 3 months, and appropriate patient counseling is necessary to manage expectations.[20] Most cutaneous sarcoidosis treatments are not approved by the US Food and Drug Administration for this purpose, and off-label use is based on available evidence and expert consensus (eTable).

An important consideration for treating sarcoidosis in active-duty servicemembers is the use of immunosuppressants or biologics requiring refrigeration or continuous monitoring. According to Department of Defense retention standards, an active-duty servicemember may be disqualified from future service if their condition persists despite appropriate treatment and impairs their ability to perform required military duties. A medical evaluation board typically is initiated on any servicemember who starts a medication while on active duty that requires frequent monitoring by a medical provider, including immunomodulating and immunosuppressant medications.[21]

Final Thoughts

Military servicemembers put themselves at risk for acute bodily harm during deployment and also expose themselves to occupational hazards that may result in chronic health conditions. The VA's coverage of new presumptive diagnoses means that veterans will receive extended care for conditions presumptively acquired during military service, including sarcoidosis. Although there are no conclusive data on whether exposure while on deployment overseas causes sarcoidosis, environmental exposures should be considered a potential cause. Patients with confirmed cutaneous sarcoidosis should undergo a complete workup for systemic sarcoidosis and be asked about their history of military service to evaluate for coverage under the PACT Act.

REFERENCES

1. Wanat KA, Rosenbach M. Cutaneous sarcoidosis. *Clin Chest Med*. 2015;36:685-702. doi:10.1016/j.ccm.2015.08.010
2. US Department of Veterans Affairs. The Pact Act and your VA benefits. Updated August 15, 2023. Accessed August 18, 2023. https://www.va.gov/resources/the-pact-act-and-your-va-benefits/
3. Banoei MM, Iupe I, Bazaz RD, et al. Metabolomic and metallomic profile differences between veterans and civilians with pulmonary sarcoidosis. *Sci Rep*. 2019;9:19584. doi:10.1038/s41598-019-56174-8
4. Bith-Melander P, Ratliff J, Poisson C, et al. Slow burns: a qualitative study of burn pit and toxic exposures among military veterans serving in Afghanistan, Iraq and throughout the Middle East. *Ann Psychiatry Clin Neurosci*. 2021;4:1042.
5. Military burn pits and cancer risk. American Cancer Society website. Revised August 25, 2022. Accessed August 18, 2023. https://www.cancer.org/healthy/cancer-causes/chemicals/burn-pits.html
6. McLean J, Anderson D, Capra G, et al. The potential effects of burn pit exposure on the respiratory tract: a systematic review. *Mil Med*. 2021;186:672-681. doi: 10.1093/milmed/usab070
7. Seedahmed MI, Baugh AD, Albirair MT, et al. Epidemiology of sarcoidosis in U.S. veterans from 2003 to 2019 [published online February 1, 2023]. *Ann Am Thorac Soc*. 2023. doi:10.1513/AnnalsATS.202206-515OC
8. Arkema EV, Cozier YC. Sarcoidosis epidemiology: recent estimates of incidence, prevalence and risk factors. *Curr Opin Pulm Med*. 2020;26:527-534. doi:10.1097/MCP.0000000000000715
9. Parrish SC, Lin TK, Sicignano NM, et al. Sarcoidosis in the United States Military Health System. *Sarcoidosis Vasc Diffuse Lung Dis*. 2018;35:261-267. doi:10.36141/svdld.v35i3.6949
10. Jain R, Yadav D, Puranik N, et al. Sarcoidosis: causes, diagnosis, clinical features, and treatments. *J Clin Med*. 2020;9:1081. doi:10.3390/jcm9041081
11. Newman KL, Newman LS. Occupational causes of sarcoidosis. *Curr Opin Allergy Clin Immunol*. 2012;12:145-150. doi:10.1097/ACI.0b013e3283515173
12. Izbicki G, Chavko R, Banauch GI, et al. World Trade Center "sarcoid-like" granulomatous pulmonary disease in New York City Fire Department rescue workers. *Chest*. 2007;131:1414-1423. doi:10.1378/chest.06-2114
13. Jajosky P. Sarcoidosis diagnoses among U.S. military personnel: trends and ship assignment associations. *Am J Prev Med*. 1998;14:176-183. doi:10.1016/s0749-3797(97)00063-9
14. Gorham ED, Garland CF, Garland FC, et al. Trends and occupational associations in incidence of hospitalized pulmonary sarcoidosis and other lung diseases in Navy personnel: a 27-year historical prospective study, 1975-2001. *Chest*. 2004;126:1431-1438. doi:10.1378/chest.126.5.1431
15. Madar CS, Lewin-Smith MR, Franks TJ, et al. Histological diagnoses of military personnel undergoing lung biopsy after deployment to southwest Asia. *Lung*. 2017;195:507-515. doi:10.1007/s00408-017-0009-2
16. Forbes DA, Anderson JT, Hamilton JA, et al. Relationship to deployment on sarcoidosis staging and severity in military personnel. *Mil Med*. 2020;185:E804-E810. doi:10.1093/milmed/usz407
17. Jani N, Christie IC, Wu TD, et al. Factors associated with a diagnosis of sarcoidosis among US veterans of Iraq and Afghanistan. *Sci Rep*. 2022;12:22045. doi:10.1038/s41598-022-24853-8
18. Sève P, Pacheco Y, Durupt F, et al. Sarcoidosis: a clinical overview from symptoms to diagnosis. *Cells*. 2021;10:766. doi:10.3390/cells10040766
19. Motamedi M, Ferrara G, Yacyshyn E, et al. Skin disorders and interstitial lung disease: part I—screening, diagnosis, and therapeutic principles. *J Am Acad Dermatol*. 2023;88:751-764. doi:10.1016/j.jaad.2022.10.001
20. Wu JH, Imadojemu S, Caplan AS. The evolving landscape of cutaneous sarcoidosis: pathogenic insight, clinical challenges, and new frontiers in therapy. *Am J Clin Dermatol*. 2022;23:499-514. doi:10.1007/s40257-022-00693-0
21. US Department of Defense. *DoD Instruction 6130.03, Volume 2. Medical Standards for Military Service: Retention*. Published September 4, 2020. Accessed August 18, 2023. https://www.med.navy.mil/Portals/62/Documents/NMFSC/NMOTC/NAMI/ARWG/Miscellaneous/613003v2p_MEDICAL_STANDARDS_RETENTION.PDF?ver=7gMDUq1G1dOupje6wf_-DQ%3D%3D

APPENDIX

eTABLE. Treatment Options for Cutaneous Sarcoidosis[1,20]

Type of Treatment	Modality	Comment
Topical	High-potency topical steroids (eg, clobetasol, halobetasol, betamethasone), tacrolimus, retinoids (eg, tretinoin, tazarotene)	Can be used for limited cutaneous involvement or in conjunction with systemic therapy
Intralesional	Triamcinolone (5–40 mg/mL)	Can be used independently or in conjunction with topical treatments
Physical	Photodynamic therapy, phototherapy, laser therapy, surgical excision	Exercise caution, as cutaneous sarcoidosis may flare or reoccur in manipulated areas
Immunomodulatory	Antimalarials (eg, hydroxychloroquine, chloroquine), tetracycline antibiotics (eg, minocycline, doxycycline[a]), phosphodiesterase type 4 inhibitors (eg, pentoxifylline)	Can be used when topical therapy fails or in patients who present with extensive disease; if monotherapy with these agents fails, a stepwise combination therapy can be considered
Immunosuppressants	Prednisone, methotrexate, mycophenolate mofetil,[b] azathioprine[b]	Can be used in moderate to severe disease
TNF inhibitors	Adalimumab, infliximab	Reserved for severe treatment-resistant disease; although the therapeutic action of anti-TNF is well documented, it is essential to be aware of its potential to cause paradoxical sarcoidosislike lesions
Emerging therapies	JAK inhibitors; IL-6, IL-12, IL-17, IL-23 inhibitors; rituximab; phosphodiesterase inhibitors; combination antimycobacterial agents	Research on efficacy is ongoing

Abbreviations: JAK, Janus kinase; TNF, tumor necrosis factor.

[a]Due to side effects of hyperpigmentation and autoimmunity associated with minocycline, doxycycline may be a more favorable choice.

[b]Limited data for use; can be considered when other therapies are not an option.