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.

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. 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 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. Burn pits, which were used to dispose of solid waste on forward operating bases, released antigenic particulate matter that was detectable on air sampling. Increased respiratory disease rates in veterans that were deployed post–9/11 are well documented, but a causal relationship has not been established. Although burn pits cannot be directly associated with any disease at this time, veterans with assumed exposures can now receive a Veterans Affairs (VA) Disability Rating for presumptive conditions under the PACT Act. The major points of this legislation include expanding and extending eligibility for veterans exposed post–9/11 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 to receive care.

**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 service connected.
- Veterans with presumptive exposures should be referred to the US Department of Veterans Affairs.

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to receive coverage for 24 new presumptive diagnoses. 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. Sarcoïdosis 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 sarcoïdosis of 52 cases per 100,000 person-years and an annual prevalence of 141 cases per 100,000 individuals. In contrast, the United States has a reported annual incidence of sarcoïdosis of 4.9 cases per 100,000 person-years and an annual prevalence of 60 cases per 100,000 individuals. Although the increased rates of sarcoïdosis in veterans have been noted for decades, only recently have investigations provided insights into the etiology of sarcoïdosis in this population.

Sarcoïdosis and Environmental Factors

Sarcoïdosis is a multisystem granulomatous inflammatory disease that can present in any organ system; however, it most commonly affects the lungs, skin, and eyes—all of which are subjected to direct contact with environmental toxins. The cause of sarcoïdosis is unknown, but environmental exposures are theorized to play a role. It has been hypothesized that exposure to various immunologically active triggers may invoke the granulomatous inflammatory response that characterizes the disease. The World Trade Center disaster on 9/11 has provided insight into the potential environmental component of sarcoïdosis. 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 sarcoïdosis or sarcoïdosis-like 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. Other known occupational exposures associated with an increased risk for sarcoïdosis or sarcoïdosis-like illness include mold, silicates, metal dust, and microbial contaminants. Servicemembers commonly are exposed to several of these aerosolized toxins, which theoretically could increase their risk for developing sarcoïdosis.

Sarcoïdosis in the Military

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

Environmental exposures during OIF and OEF may be associated with sarcoïdosis. 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. 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. A 2020 study of sarcoïdosis 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 sarcoïdosis based on deployment to the Middle East. Still, the higher prevalence of sarcoïdosis in active-duty military personnel suggests similar shared exposures in this group.

### Presumptive Exposure Locations Eligible for Care Under the PACT Act

<table>
<thead>
<tr>
<th>On or after August 2, 1990</th>
<th>On or after September 11, 2001</th>
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<tbody>
<tr>
<td>Bahrain</td>
<td>Afghanistan</td>
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<tr>
<td>Iraq</td>
<td>Djibouti</td>
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<tr>
<td>Kuwait</td>
<td>Egypt</td>
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<td>Oman</td>
<td>Jordan</td>
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<td>Qatar</td>
<td>Lebanon</td>
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<td>Saudi Arabia</td>
<td>Syria</td>
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<tr>
<td>Somalia</td>
<td>Uzbekistan</td>
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<tr>
<td>United Arab Emirates</td>
<td>Yemen</td>
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</table>

*Including the airspace above the location. In addition to the prior locations.

Data from the US Department of Veterans Affairs.
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.\(^1\) 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.\(^3\) 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.\(^{18}\)

**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 intral- esional anti-inflammatory medications, immunomodula- tors, 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 immuno- suppressants or biologics requiring refrigeration or continuous monitoring. According to Department of Defense retention standards, an active-duty service- member 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 immunosup- pressant medications.²¹

Final Thoughts
Military servicemembers put themselves at risk for acute bodily harm during deployment and also expose them- selves 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

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## Treatment Options for Cutaneous Sarcoidosis

<table>
<thead>
<tr>
<th>Type of Treatment</th>
<th>Modality</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Topical</td>
<td>High-potency topical steroids (eg, clobetasol, halobetasol, betamethasone), tacrolimus, retinoids (eg, tretinoin, tazarotene)</td>
<td>Can be used for limited cutaneous involvement or in conjunction with systemic therapy</td>
</tr>
<tr>
<td>Intralesional</td>
<td>Triamcinolone (5–40 mg/mL)</td>
<td>Can be used independently or in conjunction with topical treatments</td>
</tr>
<tr>
<td>Physical</td>
<td>Photodynamic therapy, phototherapy, laser therapy, surgical excision</td>
<td>Exercise caution, as cutaneous sarcoidosis may flare or reoccur in manipulated areas</td>
</tr>
<tr>
<td>Immunomodulatory</td>
<td>Antimalarials (eg, hydroxychloroquine, chloroquine), tetracycline antibiotics (eg, minocycline, doxycycline), phosphodiesterase type 4 inhibitors (eg, pentoxifylline)</td>
<td>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</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>Prednisone, methotrexate, mycophenolate mofetil, azathioprine</td>
<td>Can be used in moderate to severe disease</td>
</tr>
<tr>
<td>TNF inhibitors</td>
<td>Adalimumab, infliximab</td>
<td>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 sarcoidosis-like lesions</td>
</tr>
<tr>
<td>Emerging therapies</td>
<td>JAK inhibitors; IL-6, IL-12, IL-17, IL-23 inhibitors; rituximab; phosphodiesterase inhibitors; combination antimycobacterial agents</td>
<td>Research on efficacy is ongoing</td>
</tr>
</tbody>
</table>

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

1Due to side effects of hyperpigmentation and autoimmunity associated with minocycline, doxycycline may be a more favorable choice.

2Limited data for use; can be considered when other therapies are not an option.