Chapter 19

FOLLOW-UP MEDICAL CARE OF SERVICE MEMBERS AND VETERANS: CASE REPORTS—USUAL AND UNUSUAL

MICHAEL R. LEWIN-SMITH, MB*; RUSSELL A. HARLEY, MD†; JEFFREY R. GALVIN, MD‡; AND TERI J. FRANKS, MD†

*Senior Environmental Pathologist, The Joint Pathology Center, Joint Task Force National Capital Region Medical, 606 Stephen Sitter Avenue, Silver Spring, Maryland 20910-1290

†Senior Pulmonary and Mediastinal Pathologist, The Joint Pathology Center, Joint Task Force National Capital Region Medical, 606 Stephen Sitter Avenue, Silver Spring, Maryland 20910-1290

‡Professor, Departments of Diagnostic Radiology, Thoracic Imaging, and Internal Medicine, Pulmonary/Critical Care Medicine, University of Maryland School of Medicine, 685 West Baltimore Street, Baltimore, Maryland 21201

INTRODUCTION

Two case reports are presented from the perspective of pulmonary and environmental pathologists who have reviewed many pulmonary pathology specimens from US service members deployed to Iraq and Afghanistan. Pulmonary pathology specimens from these service members were sent for expert second opinion review to the former Armed Forces Institute of Pathology (AFIP) and to the current Joint Pathology Center (JPC), Departments of Pulmonary and Mediastinal Pathology. The two cases selected are examples of nonneoplastic pulmonary histopathology that illustrate a breadth of diagnoses seen in biopsies from US military personnel previously deployed to the Iraq theater.

CASE 1

In 2009, a 29-year-old male—active duty, enlisted, US Air Force military service member—presented with fever, chills, productive cough, night sweats, anorexia, myalgia, and general malaise. He gave a history of having cleaned out an unoccupied dusty apartment 1 week prior to the onset of symptoms. The patient's social history included tobacco use, smoking one-quarter to one-half pack of cigarettes per day for a total of 2¼ to 4½ pack-years, but stopping with the onset of his current illness. He reported mild alcohol use, but denied high-risk behavior or the use of illicit substances. His occupational history included working in the communications field repairing computers and electrical systems. He reported having worked in buildings under construction and in disrepair in Iraq. His deployment history included deployments to Iraq in 2004 and to Kuwait in 2007.

His past medical history included sickle cell trait and minor traumas, but nothing else of note. He had no known allergies to medications. The patient was treated with antibiotics, but was seen in the emergency room 1 week after initial presentation, with no improvement in his symptoms. A chest radiograph was obtained in which multiple pulmonary nodules were seen. The patient had a normal chest radiograph in 2007. Computed tomography (CT) of the thorax was performed, which revealed numerous blood vessel-associated consolidative nodules involving all five lung lobes. The majority of the nodules measured between 1.5 and 2.5 cm. Multiple air bronchograms were also noted (Figure 19-1). The radiological impression from this study was of multifocal consolidative nodules, and the differential diagnosis proffered included infection, lymphoma, organizing pneumonia, and sarcoidosis.

He was admitted to the hospital and underwent a bronchoscopy in which his airways were noted to have a "cobblestone" appearance suggestive of a sarcoid or a fungal infection. Cultures were taken, and no growth was reported. An endobronchial biopsy was also performed that showed acute and chronic inflammation, but no granulomas were seen. Bronchoalveolar lavage (BAL) revealed a lymphocytosis, and both the bronchoalveolar lavage and sputum were negative for acid-fast bacilli by examination of smears and polymerase chain reaction. A fine-needle aspiration cytology specimen was obtained from lymph nodes that were reported as showing a reactive process. No granulomas or malignancy were seen. The patient was treated with antibiotics and voriconazole,

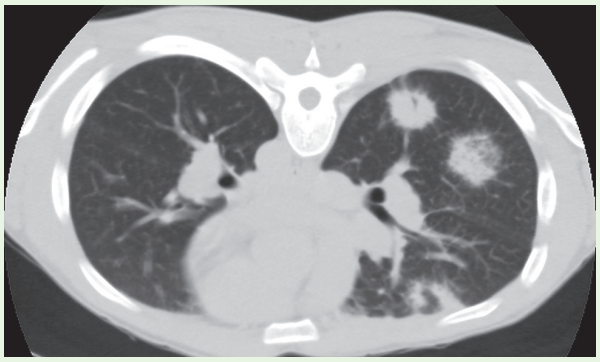

Figure 19-1. Case 1. Axial chest computed tomography scan acquired in the prone position demonstrates multiple pulmonary nodules.

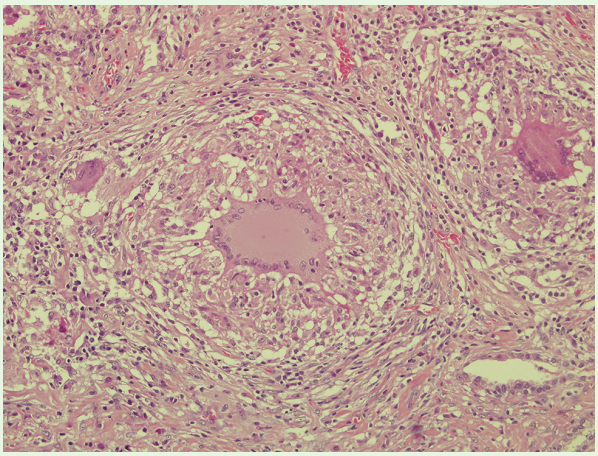

Figure 19-2. Case 1. Lung wedge biopsy showing nonnecrotizing granulomas. (Hematoxylin & eosin stain; original magnification 20×.)

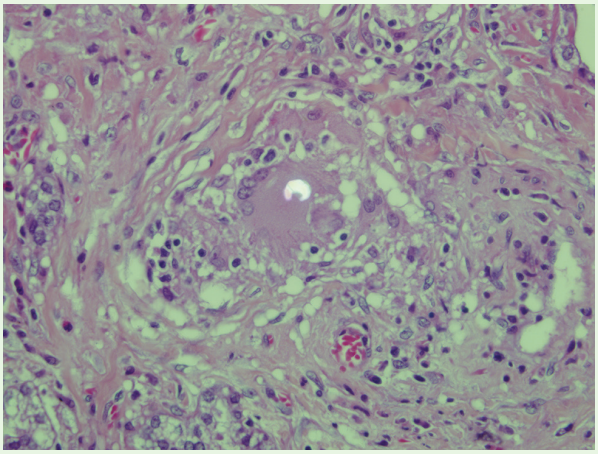

Figure 19-3. Case 1. Lung-wedge biopsy showing a multinucleated giant cell containing a birefringent cup-shaped particle of calcium oxalate. (Hematoxylin & eosin, photographed under polarized light; original magnification 40×.)

but failed to improve. He continued to have anorexia, malaise, night sweats, nosebleeds, and back pain. A CT-guided lung biopsy was performed, but was reported as nondiagnostic. A video-assisted thoracoscopic surgery (VATS) biopsy was obtained from the lung after marking with methylene blue. Additional *negative* or normal study results reported at this time included

- serological tests for histoplasma and *Coccidioides* antibodies,
- immunoglobulin E,
- quantitative immunoglobulins,
- myeloperoxidase antibody,
- proteinase antibody,
- human immunodeficiency virus, and
- *Legionella* urine antigen.

Positive laboratory findings included

- antinuclear antibody titer of 1:160 with a speckled pattern,
- double-stranded deoxyribonucleic acid antibody of 30 IU/mL (normal: 0–24 IU/mL),
- C-reactive protein of 10 mg/dL,
- erythrocyte sedimentation rate of 66 mm/h, and
- complement factor 4 of 40 mg/dL (high normal).

A rheumatology consult was arranged to rule out an autoimmune process.

After the VATS biopsy and the results of fungal stains, which were negative, the patient was treated with high-dose intravenous steroids followed by oral prednisone. His clinical status showed significant improvement. Clinically

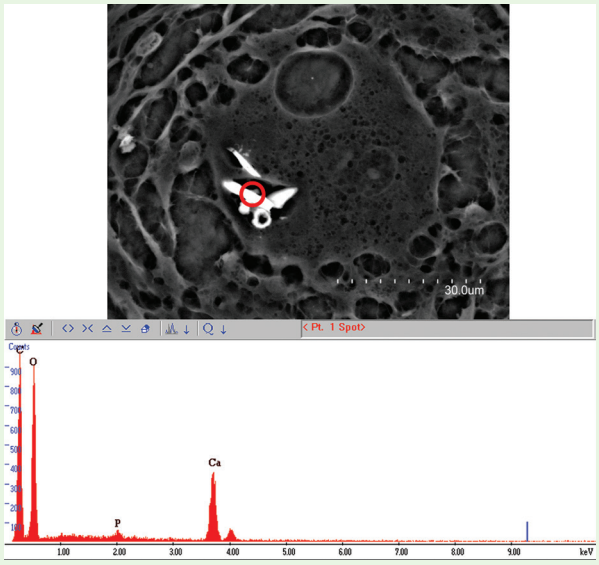

Figure 19-4. Case 1. Scanning electron microscopic image of a multinucleated giant cell containing calcium oxalate crystals and energy dispersive X-ray analysis (*red circle*), demonstrating the presence of carbon (C), oxygen (O), calcium (Ca), and a small phosphorus (P) peak.

and radiologically, the patient's illness was considered to be consistent with sarcoidosis, but particulate matter noted in the VATS biopsy material was not considered to be

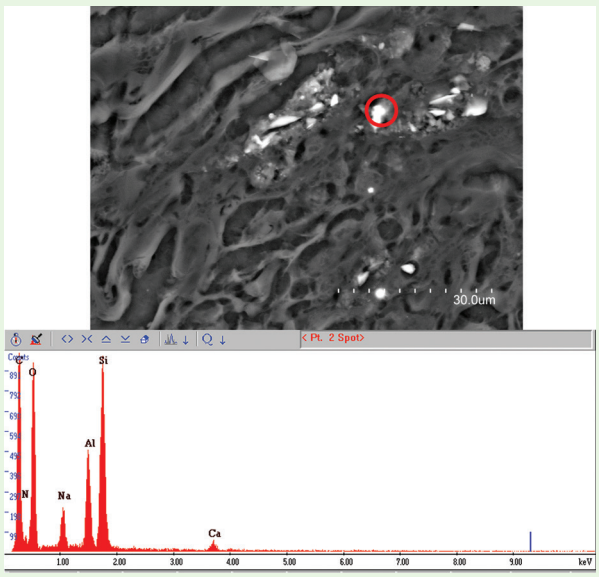

Figure 19-5. Case 1. Scanning electron microscopic image of a small birefringent particle consistent with a silicate and energy dispersive X-ray analysis (*red circle*), demonstrating the presence of carbon (C), nitrogen (N), oxygen (O), sodium (Na), aluminum (Al), silicon (Si), and calcium (Ca).

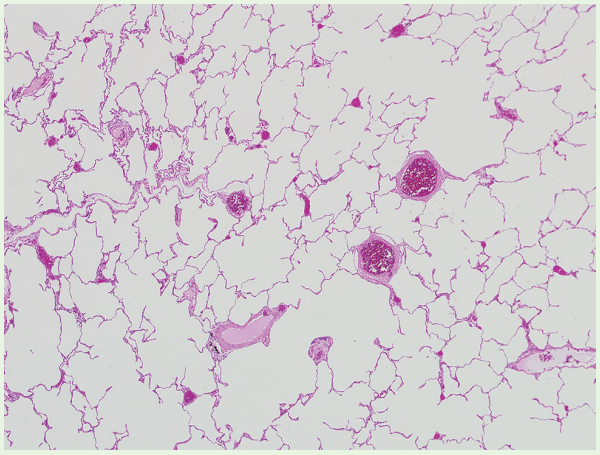

Figure 19-6. Case 2. Lung wedge biopsy showing an area of emphysematous change. (Hematoxylin & eosin; original magnification 2×.)

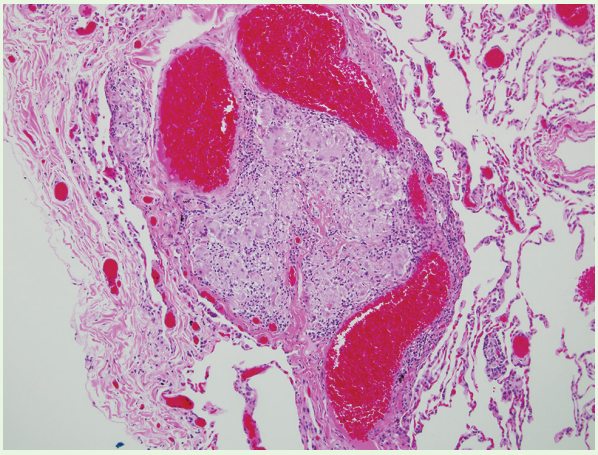

Figure 19-7. Case 2. Lung-wedge biopsy showing poorly formed granulomas adjacent to blood vessels. (Hematoxylin & eosin; original magnification 10×.)

classically consistent with sarcoidosis. Consideration was given to performing a lymphocyte proliferation assay, but the patient's history was not thought to be consistent with significant beryllium exposure. The contributing pathologist's diagnosis of the two wedge biopsies obtained from the VATS procedure was of noncaseating granulomatous inflammation with polarizable foreign material detected within granulomas and within giant cells. Special stains for fungi and mycobacteria were negative.

The pathology specimen was sent in consultation with the AFIP to rule out pneumoconiosis because of the birefringent material seen, with beryllium, aluminum, or talc being considered. The AFIP diagnosis rendered was nonnecrotizing and rare necrotizing granulomas. Birefringent material located in giant cells was characterized as calcium oxalate by scanning electron microscopy with energy dispersive X-ray analysis (SEM-EDXA) and infrared spectroscopy. This material was considered to be endogenous in origin (not a "foreign body"). Smaller rod-shaped birefringent particles containing silicon, oxygen, magnesium, and aluminum consistent with silicates were also detected. Rare particles consistent with silica and possibly talc (a magnesium silicate) were also identified (Figures 19-2 to 19-5). Inductively coupled plasma mass spectroscopy was

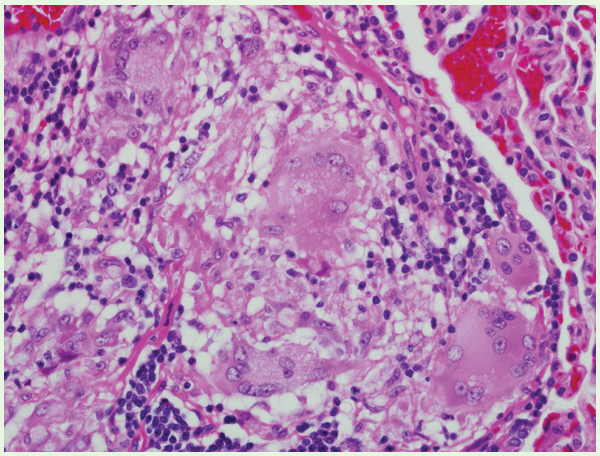

Figure 19-8. Case 2. Lung-wedge biopsy higher magnification from Figure 19-7 showing a poorly formed granuloma with an endogenous asteroid body in a multinucleated giant cell. No "foreign bodies" are seen. (Hematoxylin & eosin; original magnification 40×.)

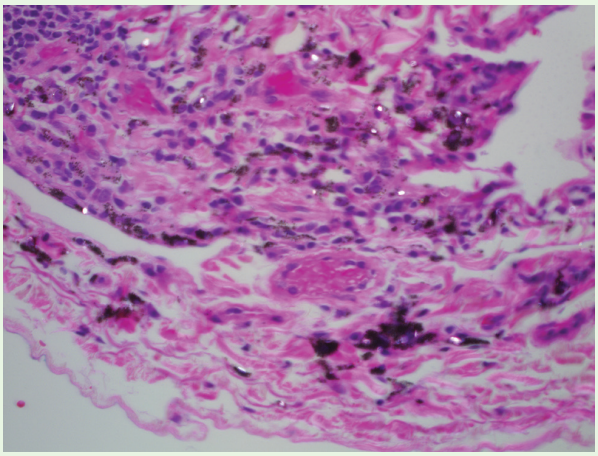

Figure 19-9. Case 2. Lung wedge biopsy showing a subpleural pigment deposit containing black carbon and birefringent silicate particles. (Hematoxylin & eosin, photographed under partially polarized light; original magnification 40×.)

also performed on the formalin-fixed lung tissue, but no abnormalities were detected. A possible small increase in nickel was reported.

Limited follow-up information was available, but the patient responded to steroid treatment with tapering doses of prednisone. The rheumatology consult included noting that the patient had a family history of lupus, but he was felt to have sarcoidosis responding to treatment with tapering steroids. The immunology studies were reviewed and thought to be nonspecific abnormal findings.

CASE 2

In 2011, a 42-year-old male—active duty, enlisted US Army service member—presented with pulmonary follow-up after being noted as hypoxemic on air evacuation from the Iraqi theater for musculoskeletal injuries. The patient's social history included tobacco use and smoking 1 to 1½ packs of cigarettes per day for a total of 25-pack years. He reported rarely consuming alcohol. The patient's occupational history included working as a combat medic, and his deployment history included deployments to Iraq in 2004, 2005, and 2007, and deployments to Kuwait and Iraq in 2009 to 2010.

Low oxygen saturation was confirmed on polysomnography as mild (88%–92% range), and after titrated continuous positive airway pressure lying flat from nocturnal oximetry. Spirometry revealed mild obstruction. Other normal or negative studies included a methacholine challenge, diffusing capacity of the lung for carbon monoxide, high-resolution CT scan, and shunt study. The patient's medications included chronic opioid use for musculoskeletal injuries. His past medical history included posttraumatic stress disorder, psoriasis, and obstructive sleep apnea. His body mass index was 30.

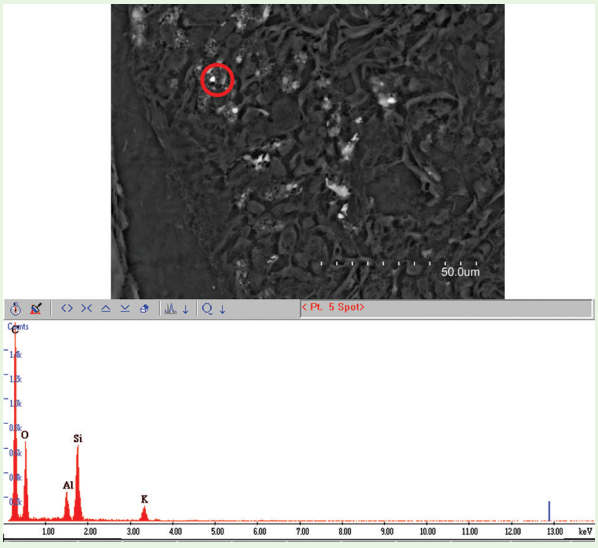

Figure 19-10. Case 2. Scanning electron microscopic image of a particle-rich area of lung, and energy dispersive X-ray analysis data showing the presence of carbon (C), oxygen (O), aluminum (Al), silicon (Si), and potassium (K) at the point indicated by the *red circle*.

Deployment-related exposures to benzene and beryllium were included in his record.

The patient underwent a VATS lung biopsy to rule out interstitial lung disease, with the sole abnormality being low arterial oxygen tension (to the low 70 mm Hg) on multiple arterial blood gases.

The contributing pathologist's diagnosis was nonnecrotizing granulomatous inflammation and emphysematous changes. The case was sent in consultation with the JPC and the contributor favoring a diagnosis of sarcoidosis. The JPC diagnosis was microgranulomatous pneumonitis. The JPC pathologist noted that the granulomas were not as well-formed as usual for sarcoidosis. He favored hypersensitivity pneumonitis, but the granulomas were located in lymphatics adjacent to small vessels, and there was minimal lymphocytic infiltration. No constrictive bronchiolitis and no nonspecific interstitial pneumonia were seen (Figures 19-6 to 19-8).

Scanning electron microscopy with energy dispersive X-ray analysis was performed on the biopsy, and particle counting was performed on particle-rich and particle-poor fields. In the richest deposit, 103 particles were counted (in a 1.5K magnification field). Twenty-seven particles had an area of <0.25 μm^2. All but five particles contained silicon. Of these, three particles contained titanium and oxygen. Most (>90%) were aluminum silicates (Figures 19-9 to 19-12). Rare silica particles (with higher silicon content) were identified. In a particle-poor area, all of the particles had an area of >0.39 μm^2. Few contained silicon. Most contained oxygen, iron, aluminum, and some titanium.

Follow-up information was available for this patient. His blood beryllium level was normal, and his lymphocyte stimulation test was negative. The patient's pulmonary function testing stabilized with an improved PaO_2 of 88 mm Hg. He reported no exposure history to suggest a potential etiology for hypersensitivity pneumonitis. In particular, he reported no contact with birds or other animals (except a cat), no hot tub use, and so forth. The patient still experienced dyspnea with exertion that "he felt was slightly worse," but he had none at rest. The patient had obstructive sleep apnea and continued to use continuous positive airway pressure unchanged. He was noted as having mild polycythemia persisting after reported smoking cessation and resolving hypoxia. Etiology was uncertain, and a hematology oncology consultation was performed that favored a respiratory hypoxic etiology.

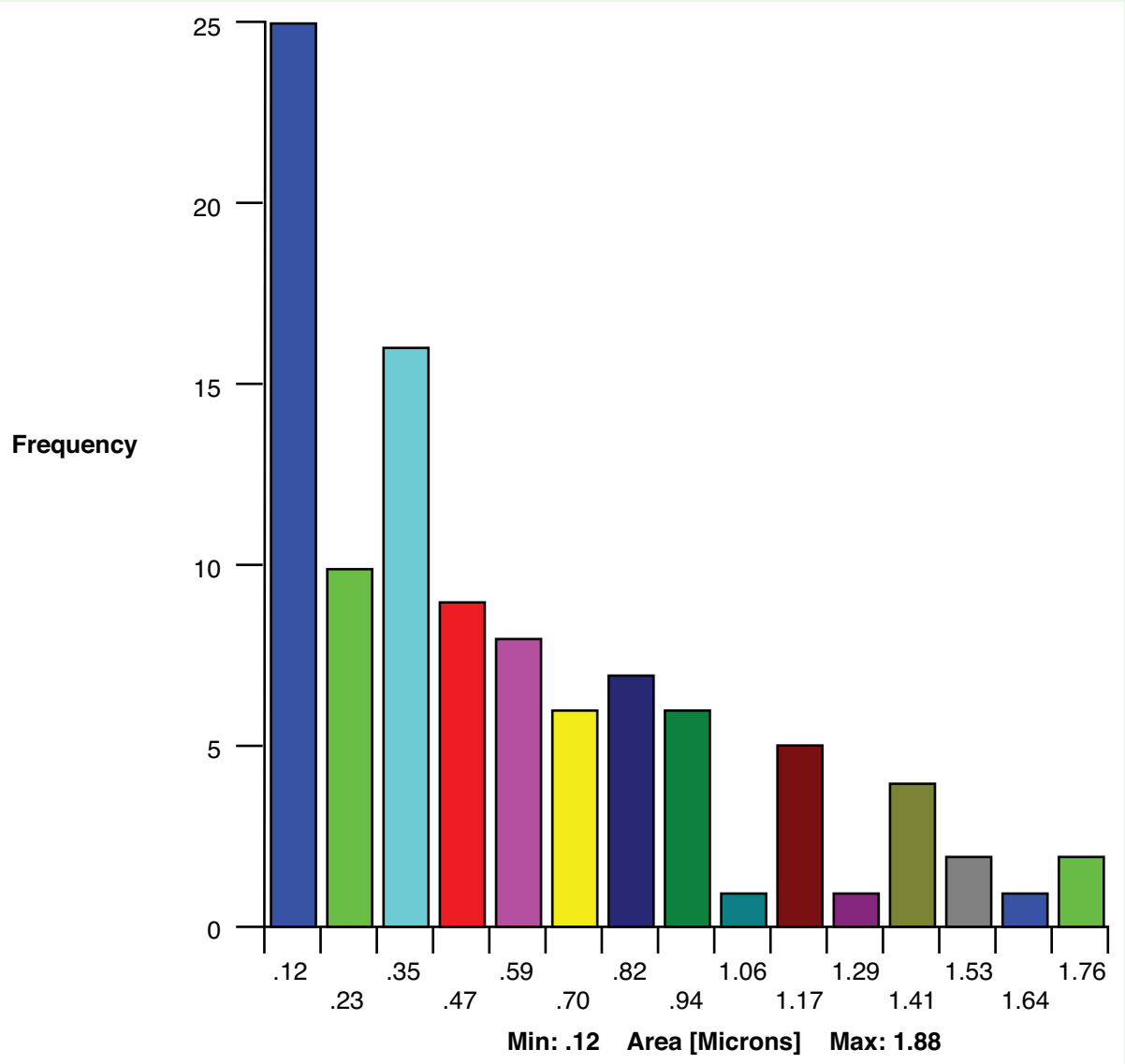

Figure 19-11. Case 2. Particle size (area) distribution histogram for a particle-rich area of the lung biopsy.
Max: maximum; Min: minimum

SUMMARY

Since the start of the wars in Iraq and Afghanistan, several hundred cases have been reviewed by the Departments of Pulmonary and Mediastinal Pathology, Environmental Pathology, and Radiologic Pathology at the AFIP and the JPC, from US military personnel previously deployed to Iraq and Afghanistan. There is a breadth of histopathological diagnoses in this population. Two of these cases with nonneoplastic histopathology have been described in this chapter. The working/clinical diagnosis for case 1 was sarcoidosis. In case 2—involving a patient with a more complicated clinical picture—hypersensitivity pneumonitis was considered, but was not supported by the available clinical information. Because a certain number of respiratory illnesses occur in any population, their presence in previously deployed military personnel is not of itself an unexpected finding. What is difficult to determine is what proportion of lung injury in the previously deployed military population can be specifically attributed to exposures encountered during deployment.

The human lung has a limited repertoire of responses to inhaled materials, which are categorized by histopathologists into various patterns based on light microscopy. Although there are a few notable exceptions, broadly speaking these categories are not pathognomonic for exposure to a single specific environmental agent. Indeed, there are also examples

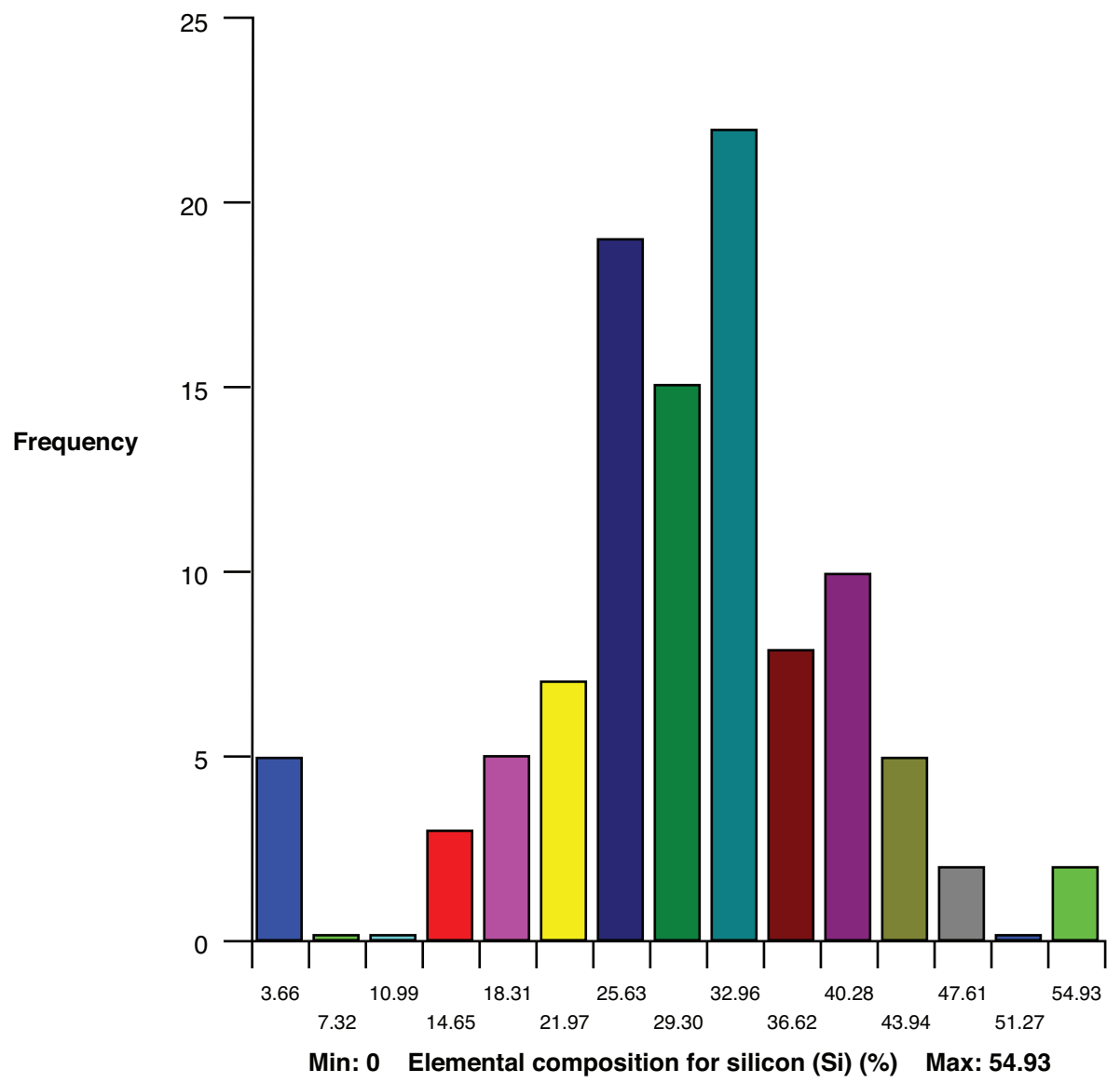

Figure 19-12. Case 2. Histogram of the same particles as seen in Figure 19-11 sorted by silicon content. A small number of particles containing the most silicon may represent silica.
Max: maximum; Min: minimum

of single environmental agents giving rise to more than one histopathological pattern. The histopathological assessment is often only part of reaching a specific diagnosis, coupled with clinical, laboratory, and radiological findings. In this assessment, factors such as occupational history, cigarette smoking, and body mass index are known to have a significant impact in many cases and should not be ignored. In each case, a link to a specific etiology is sought. Although the question of etiology is straightforward, a confident determination of etiology is frequently elusive.

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THERE ARE NO REFERENCES IN THIS CHAPTER