Granulomatous inflammation (GI) in the lung can be associated with infection (mycobacterial) or immunological conditions (granulomatosis with angiitis), or it may be idiopathic (sarcoidosis) [1]. The pathological features (presence of necrosis, cohesiveness and coalescence of granulomas, fibrosis and type of inflammatory infiltrate), microbiological data (fungal and mycobacterial cultures) and radiological characteristics of the granuloma are essential measures to determine the primary diagnosis of granulomatous disease of the lungs [1].

Primary involvement of the lung parenchyma in systemic lupus erythematosus (SLE) is quite rare [2], and a new pulmonary infiltrate is more frequently the result of common and opportunistic infections. Granulomatous disease in the lungs of patients with SLE is very rare. While a literature search identified only a single case report of a patient with acute lupus pneumonitis who presented with a miliary pattern on chest and lung histopathology of bronchocentric granulomatosis [3], the development of sarcoidosis among patients with SLE has been reported.

We report here two patients with SLE on treatment with low dose steroids who presented with pulmonary findings proven in transbronchial biopsies to be non-necrotizing epithelioid GI.

**Patient Descriptions**

**Patient 1**
A 23 year old single woman, born in Israel, presented with irritating dry cough of 4 months duration. The cough did not disturb her at night, but for 6 weeks before her assessment she began to suffer from night-time sweating. The chest X-ray was normal but high resolution chest computed tomography (CT) showed a fine bilateral micronodular pattern [Figure 1A].

Five years earlier, at age 17, she had been diagnosed with SLE based on skin rash, arthritis, peritonitis, positive antinuclear antibodies (ANA), positive anti-DNA, and high titer of anticardiolipin antibodies. She was started on prednisone, aspirin and hydroxy-chloroquine. One year later she presented with nephritis,
and renal biopsy revealed diffuse proliferative glomerulonephritis. She was treated with intravenous cyclophosphamide every other week, enalapril and high dose of prednisone. After 3 months on this therapeutic regimen the cyclophosphamide was replaced by azathioprine and prednisone was gradually reduced to 5 mg/day. For 30 months she continued this regimen with normalization of the renal function until her present complaints.

She worked as a bank teller and was not subject to any environmental exposures; however, she smoked 6–10 cigarettes a day.

The physical examination did not reveal skin rash, lymphadenopathy or clubbing. The lung, heart and abdomen examination was normal. Laboratory tests showed a hemoglobin level of 12.2 g/dL. The white blood cell count (WBC) was 5100/ml with 79% neutrophils. Platelet count was 375,000/ml. Serum electrolytes, kidney and liver functions tests were normal. Globulin level was 3.3 g/dl. Pulmonary function tests revealed a moderate restrictive ventilatory defect with a reduction in monoxide diffusion capacity (DLco). Forced vital capacity (FVC) was 2.23 L (61%), slow vital capacity (SVC) 2.19 L (61%), total lung capacity (TLC) 2.65 L (68%), monoxide diffusion capacity (DLco) 46%, percentage predicted for gender, age and height.

A bronchoscopy was performed, revealing normal airways without secretions. Bronchoalveolar lavage (BAL) showed 320 cells/ml; 12% were neutrophils, 10% lymphocytes, and 78% macrophages. The transbronchial biopsy showed non-necrotizing granulomatous inflammation with giant multinucleated cells [Figure 1B]. There was no evidence of Mycobacterium, fungi or Pneumocystis jiroveci in the special stains or in the cultures.

Within a few weeks of increasing the dose of systemic steroids to 30 mg/day the cough and night-time sweating resolved, as did the restrictive ventilator defect, and DLco increased to 69%. Eighteen months later a repeat high resolution chest CT showed no evidence of the radiological findings. At her last assessment at the clinic her clinical condition is stable.

**PATIENT 2**

A 65 year old man with SLE presented with fever, cough, and weight loss of 4 kg over 2 months. He was born in South America and immigrated to Israel in 1980. He is retired but previously worked in a factory without chemical exposures. He is a non-smoker.

The chest X-ray showed a right middle lobe infiltrate. He was treated with antibiotics. Six weeks later he was examined in the pulmonary clinic at which time the cough had resolved. He denied fever, fatigue and excessive sweating, and felt well, but the chest X-ray showed that the infiltrate had not resolved.

At the age of 46 he had been diagnosed with SLE based on acute lupus rash, arthritis, positive ANA, positive anti-DNA, low complement levels and leukopenia. His kidney functions were normal. He was treated with systemic steroids. At age 52 he presented with renal failure (creatinine 2.2 mg/dl). A kidney biopsy was not performed. An increase in the systemic steroid dosage resulted in normalization of his kidney function and he continued on 5 mg/day prednisone until his referral.

The physical examination showed temperature of 36.6°C, breath rate 14/minute, blood pressure 150/80 mmHg and regular pulse of 66/min. The skin examination demonstrated vitiligo. There were no palpable lymph nodes. Examination of the lungs, heart and abdomen was normal. Laboratory tests demonstrated hemoglobin 15.3 g/dl, WBC count 6930 cells/ml with 81.3% neutrophils, and platelet count 192,000 cells/ml. He had normal electrolytes, kidney and liver functions. The globulin level was 3.3 g/dl. Pulmonary function tests were normal with a slightly reduced DLco, 65%.

The chest CT scan showed an infiltrate with air bronchogram in the right middle lobe and a slight bilateral reticular nodular pattern without lymphadenopathy. This did not resolve after 3 months of follow-up. Bronchoscopy with transbronchial biopsy showed multiple non-necrotizing granulomata with many multinucleated giant cells. The culture for Mycobacterium was sterile. He attends our follow-up clinic and is not on any additional treatment apart from his maintenance regimen of prednisone 5 mg/day. He is clinically stable and his chest CT has not changed.

**COMMENT**

We present two patients with SLE who subsequently developed a pulmonary granulomatous inflammation (GI) while treated with low dose systemic steroids; the first patient also received azathioprine.

The pathogenesis of GI in both cases is unknown. Pulmonary infections contribute significantly to the morbidity and mortality of patients with SLE [2]. In a large European study, 11.7% of patients with SLE developed major lower respiratory tract infection during a mean follow-up of 10 years. Mycobacterial and fungal infections were excluded in our cases. The histopathological report and cultures from the BAL did not identify microbial agents.

Non-infectious causes of pulmonary GI include, among others, hypersensitivity pneumonitis, vasculitis, berylliosis and, most frequently, sarcoidosis [1]. In both our patients the pathologist noted the presence of well-formed GI consistent with sarcoidosis [Figure 1B]. The occurrence of sarcoidosis in patients with SLE has been reported from two centers [4]. In the first study sarcoidosis was diagnosed in 1 of 144 SLE patients (0.7%), and in the second study in 3 of 300 SLE patients (1%). This prevalence is higher than that of sarcoidosis in the general population, which in Israel has been reported to be 0.8/100,000 and in Europe and the United States 7–50/100,000 [5]. Of 34 Israeli patients with sarcoidosis, 10 had a positive antinuclear antibody and 2 had positive antibodies to double-stranded dsDNA, but none of these patients had clinical evidence of SLE, nor did they develop it over time [5]. In the European report, of 1000 SLE patients none was reported to suffer concomitant sarcoidosis.

During the period 1979–2007, 19 patients (mean age 46 years, range 20–82)
were reported with a concomitant diagnosis of SLE and sarcoidosis; only one was male. Ten patients were initially diagnosed with SLE and subsequently with sarcoidosis, 5 patients were diagnosed with both conditions simultaneously, while 4 were first diagnosed with sarcoidosis and subsequently developed SLE. The development of the second condition was reported to be associated with a reduction in the dosage of systemic steroids in 9 of 14 patients. This was not the case in our two patients.

In addition to the presence of pulmonary GI and excluding other etiologies, the diagnosis of sarcoidosis requires the demonstration that more than one organ is involved, which we did not identify in our two patients. Both of them had normal liver function, calcium levels, normal globulin and no hematological disturbance. The lack of other organ involvement in both cases could be explained by the chronic treatment with low dose systemic steroids.

The radiological findings in sarcoidosis may exhibit considerable diversity, the more characteristic findings being symmetric hilar and mediastinal lymphadenopathy; this was not present in our two patients. Among the reported patients with pulmonary GI associated with SLE, five had bilateral hilar adenopathy and two had mediastinal lymphadenopathy.

Acute lupus pneumonitis and acute alveolar hemorrhage are recognized but rare complications of SLE [2]. A recent case report suggested a new and separate entity of SLE-associated acute granulomatous pneumonitis [3]. The chest CT scan of their patient showed very similar findings to that of our first patient [Figure 1A]. Similarly, the patient did not have extrapulmonary involvement and the pathological report was not characteristic of the well-defined granuloma associated with sarcoidosis [3].

It remains debatable whether to consider the occurrence of GI in SLE as two separate clinical entities, an overlap syndrome, or an unrecognized feature of SLE. Based on the clinical course of our patients and the data of the reported cases, GI in SLE responds well to systemic steroids and is associated with a benign course.

In conclusion, we present two patients with SLE, who while on treatment with low dose systemic steroid presented with systemic complaints and radiological and pathological findings of GI. Although the histopathological features of the GI were consistent with sarcoidosis, our patients did not have classic features of sarcoidosis characterized by multisystem involvement. The combination of pulmonary GI with SLE should perhaps be considered yet another overlap syndrome, which appears to occur in up to 1% of SLE patients.

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References

Capsule
Efficacy and long-term safety of a dengue vaccine in regions of endemic disease
A candidate tetravalent dengue vaccine is being assessed in three clinical trials involving more than 35,000 children between the ages of 2 and 16 years in Asian Pacific and Latin American countries. Hadinegoro et al. report the results of long-term follow-up interim analyses and integrated efficacy analyses. The authors are assessing the incidence of hospitalization for virologically confirmed dengue as a surrogate safety endpoint during follow-up in years 3–6 of two phase 3 trials, CYD14 and CYD15, and a phase 2b trial, CYD23/57. They estimated vaccine efficacy using pooled data from the first 25 months of CYD14 and CYD15. Follow-up data were available for 10,165 of 10,275 participants (99%) in CYD14 and 19,898 of 20,869 participants (95%) in CYD15. Data were available for 3203 of the 4002 participants (80%) in the CYD23 trial included in CYD57. During year 3 in the CYD14, CYD15, and CYD57 trials combined, hospitalization for virologically confirmed dengue occurred in 65 of 22,177 participants in the vaccine group and 39 of 11,089 participants in the control group. Pooled relative risks of hospitalization for dengue were 0.84 among all participants, 1.58 among those < 9 years old, and 0.50 among those ≥ 9 years. During year 3, hospitalization for severe dengue, as defined by the independent data monitoring committee criteria, occurred in 18 of 22,177 participants in the vaccine group and 6 of 11,089 participants in the control group. Pooled rates of efficacy for symptomatic dengue during the first 25 months were 60.3% for all participants, 65.6% for those ≥ 9 years, and 44.6% for those < 9 years old. Although the unexplained higher incidence of hospitalization for dengue in year 3 among children < 9 years of age needs to be carefully monitored during long-term follow-up, the risk among children 2–16 years old was lower in the vaccine group than in the control group.

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