A case of systemic lupus erythematosus with multiple nodules in the bilateral lungs and vertebrae

Abstract

We encountered a case of a middle-aged woman with systemic lupus erythematosus. As the patient had progressive peripheral neuropathy including foot drop, we intended to treat her with intensive immunosuppressive therapy as soon as possible. Pretreatment assessment, however, revealed multiple nodular lesions in the lungs and bones, suggesting disseminated tumor metastasis or miliary tuberculosis. To our surprise, gallium and bone scintigraphy as well as cytodiagnosis revealed no sign of malignancy or infection, leading us to suspect the presence of another multisystem disorder. The presence of subependymal nodules and a periungual fibroma strongly suggested tuberous sclerosis (TS). A genetic test revealed a mutation in the TSC1 gene and confirmed the diagnosis. Thus, the multiple nodular lesions were most likely a hyperplasia due to TS. Although the odds of a comorbidity of more than one multisystem disorder are considered to be quite low, it should be kept in mind that when such a situation does exist, the comorbidity may make the presenting symptoms extremely diverse.

Keywords: Systemic lupus erythematosus, tuberous sclerosis, multiple pulmonary nodules

Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease that affects multiple organ systems. Intensive immunosuppressive therapy, usually with high doses of glucocorticoids that are used with or without other immunosuppressive agents, is required when there is involvement of major organs such as the kidneys and nervous system. However, immunosuppressive therapy may negatively impact a patient’s condition when he or she has an underlying infection. In addition, extra caution must be taken in the case of coexistence of malignancies as an increased risk of malignancies has been reported in SLE patients (1). Here we report a female SLE patient with multiple nodular lesions in the lungs and bones, which first made us suspect a malignancy or infection. It turned out to be because of a rare multisystem disease, tuberous sclerosis (TS).

Case Presentation

A 50-year-old woman recently diagnosed with SLE was admitted to Saitama Medical University Hospital for further evaluation and treatment. Her initial symptom was malar rash. She then developed myalgia and edema in the lower extremities and visited a local clinic. She had lymphopenia and also had positive test results for antinuclear and anti-double-stranded DNA antibodies. When she was admitted she also had foot drop, which was considered to be the result of mononeuritis multiplex, and this condition was still progressively worsening.

Unexpectedly, a computed tomography (CT) scan performed to screen interstitial pneumonia revealed multiple masses in the lungs as well as in the vertebrae, suggesting the presence of a metastatic tumor (Figure 1a, b). An abdominal CT scan with contrast material was performed to search for the primary lesion. Thickening of the uterine wall was detected (data not shown), and a gynecologist was consulted. However, a cytological examination did not identify any malignancy. The biopsy of an enlarged left inguinal lymph node (3 cm in diameter) also did not uncover any evidence of malignancy. Moreover, no hot lesions were detected on gallium and bone scintigraphy. Sputum cytology was found to be class III (Papanicolaou classification). No acid-fast bacillus was detected in the sputum, and Quantiferon-TB Gold was negative.

As metastatic neoplasms had been rendered unlikely, we next considered diseases with systemic benign tumors. We suspected TS because of the presence of subependymal nodules (Figure 2a, b) and a periungual fibroma (Koenen's tumor), even though she did not have any of the classic disease triad of learning disability, seizures, and facial angiofibroma. Genetic testing was performed, and a mutation in the TSC1 gene was detected (c.2503-2A>G, Figure 3a, b) (2). She was treated with high doses of prednisone and with three courses of monthly intravenous cyclophosphamide. She is now undergoing follow-up treatment in the outpatient clinic of this hospital.
The presence of multiple lesions in multiple aspects that were not explained by SLE was one of the important findings that cast doubt on the presence of infection or tumors. Moreover, the finding of subependymal nodules that were incidentally detected by a neck CT scan, which was performed to check for goiter. Similar lesions were also observed by a head CT scan performed later.

To the best of our knowledge, this is the second report of a comorbidity of SLE and TS. Singh et al. (6) reported a case of a TS patient with seizures and facial angioedema complicated with fulminant SLE. They suggested a link between the two disorders in that dysregulation of the mammalian target of rapamycin pathway, which is caused by mutations in either the TSC1 or TSC2 gene, is also implicated in the pathogenesis of SLE (7). The patient subsequently died because of worsening diffuse alveolar hemorrhage despite aggressive treatment (6). In contrast, our patient hardly noticed any symptoms of TS. It is highly likely that she would never have discovered she had TS if she had not developed SLE. In addition, most of her lupus symptoms were promptly ameliorated by glucocorticoids and cyclophosphamide. We obtained a careful familial history again and learned that her mother also had similar nail deformities (i.e., Koenen’s tumors). The patient’s mother lived into her nineties without any major health problems, such as collagen vascular diseases. Taken together, the relationship between TS and SLE appears to be coincidental in our case.

Because the genetic defects of TS (TSC1 and TSC2) have been elucidated, milder cases are more commonly diagnosed, and it has become obvious that TS is a disease that occurs much more frequently than previously thought. If the multiple masses observed had been malignant, this would have greatly impacted our therapeutic strategy. Thus, it is important to accurately diagnose the comorbidity of such systemic diseases, even if one of them is so mild that it does not exhibit any severe symptoms.

**Figure 1. a, b.** Multiple masses detected by a chest CT scan. Axial section (a) showed bilateral lung nodules with a random distribution pattern (arrows) and multi-planar reconstruction coronal section image (b) revealed multiple sclerotic round bone lesions (arrowheads) in the vertebral bodies.

**Figure 2. a, b.** Subependymal nodules. Calcified nodules in the lateral ventricles (a) were incidentally detected by a neck CT scan, which was performed to check for goiter. Similar lesions (b) were also observed by a head CT scan performed later.

**Figure 3. a, b.** Direct sequencing of the TSC1 gene. Nucleotide sequence data of the TSC1 gene derived from the patient (a) and a healthy control (b). A heterozygous conversion of a single nucleotide A to G in intron 19 was identified (c.2503-2A>G: a splice-acceptor variant).

At first, this case was indicative of “Hickam’s dictum,” which states that patients can have a number of diseases at one time. Nevertheless, its counterargument in favor of parsimony, “Occam’s razor,” also turned out to be relevant here because most of the symptoms unexplained by SLE were due to a single other disease (i.e., TS) (3). The lesions in the lungs were likely to be multifocal micronodular pneumocyte hyperplasia. It is different from lymphangioleiomyomatosis, which is a well-known complication of TS (4). As for the bone abnormalities, sclerotic bone lesions have been reported to coexist in patients with TS (5). No biopsy was performed for these lesions, but there was no increase in size or number that was observed upon re-examination with a CT scan performed 6 months after the first scan.

**Discussions**

Although SLE is a systemic disease that can present with diverse symptoms, this case had multiple aspects that were not explained by SLE alone. The presence of multiple lesions in the lungs and bones (Figure 1a, b) first made us suspect miliary tuberculosis or disseminated metastasis of a malignant tumor and hesitant to treat the patient with high doses of glucocorticoids and cyclophosphamide. On the other hand, the progression of mononeuritis multiplex was apparent, and the delay in treatment was highly likely to cause permanent damage. The absence of increased intake on both gallium and bone scintigraphy was one of the important findings that cast doubt on the presence of infection or tumors. Moreover, the finding of subependymal nodules that were incidentally detected by a neck CT scan (Figure 2a), which was performed to examine non-functional goiter, strongly indicated TS. It was difficult to detect these pathognomonic lesions by magnetic resonance imaging, which in this case was performed to screen for central nervous system lupus.

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References