Discussion about diagnostic difficulties in case of a patient with systemic lupus erythematosus and subsequent diagnosis of lung cancer, preceded by occupational exposure to silica dust

Antoni Hrycek, Magdalena Olszanecka-Glinianowicz, Przemysław Życiński
1 Department of Internal Medicine, Autoimmunology and Metabolic, Silesian Medical Academy, Katowice, Poland
2 Chair of Pathophysiology, Silesian Medical Academy, Katowice, Poland

Abstract: An observed case is an example of diagnostic problems in a patient with systemic lupus erythematosus (SLE), who after several years of follow up demonstrated rapid development of lung cancer with liver metastases that had been preceded by years-long exposure to silica dust. The discussion contains an attempt to correlate the observed events.

Keywords: lung cancer, silicosis, systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease with genetic and environmental factors being important factors in its pathogenesis. Factors contributing to development of SLE include exposure to chemical substances (solvents and pesticides) and other substances present in work environment, such as silicon and quartz crystals [1]. Finckh et al. [2] suggest that working in an environment contaminated with silica dust over one year significantly increases the risk of the SLE development. A correlation between autoimmune disorders and occupational exposure to silica dust was also observed by Mulloy [3].

Based on some suggestions, SLE can be one of paraneoplastic syndromes in lung cancer. There are also reports that silicosis can increase the risk of this cancer [4]. Nevertheless, results of other studies fail to confirm this correlation [5].

To our knowledge, there were no articles describing coexistence of silicosis, SLE and small-cell lung cancer. Therefore it seemed interesting to present diagnostic problems observed in a patient with SLE and subsequent rapid development of lung cancer, who had a years-long history of occupational exposure to silica dust.

CASE REPORT

A 62-year-old patient (patient record number 3495/02) was first hospitalized in April 2002 for chest pain, cough with expectoration of purulent sputum and daily temperature elevations to 39°C of two-week duration. These symptoms were associated by potent incapacitating musculoskeletal pains of thoracic spine and large joints of upper and lower extremities with inflammatory reaction. During history taking, the patient reported subfebrile temperatures, general weakness, lack of appetite, body weight loss (10 kg) and sleep disorders lasting about 7 months. Among past diseases, he mentioned myocardial infarction in 2001 and arterial hypertension.

Physical examination revealed the following abnormalities: skin pallor, white coating on the tongue, multiple caries lesions and missing teeth, dullness on percussion and lack of respiratory sounds and vocal fremitus at the left lung basis, heart rate 98/min, louder second tone over the aortic valve and right-sided thoracic scoliosis.

Chest X-ray revealed decreased transparency of the left lower lung field and USG confirmed the presence of fluid in the left pleural cavity. Abdominal USG demonstrated a single concrement in the gallbladder. Doppler ECG revealed thickened and hypokinetic ventricular septum, fine marginal calcifications of mitral valve cusps and 1 grade mitral valve regurgitation.

Multiple abnormalities were observed in laboratory tests (ESR 38/54, CRP concentration 28 mg/l, serum creatinine – 2.17 mg/dl, 24-hour urine protein <1.0, erythrocyturia in repeated assessments of urinary sediment, ALT activity = 70
U/l). Proteinogram demonstrated consistently elevated percentage of α1-globulins, α2-globulins and elevated percentage of γ-globulins up to 28.5% at baseline that decreased during the therapy. IgG concentration shifted in the similar direction (2200 mg/dl at baseline, 664.0 mg/dl after 2 years). Number of erythrocytes ranged from 3.41 to 4.49x10^12/μl, leucocytes from 5.3 to 16.08x10^9/μl, thrombocytes from 137 to 263x10^9/μl, and hemoglobin concentration from 9.9 to 14.4 g/dl over several years of follow up. During this time, abnormal results of immunological tests were obtained: anti-double-stranded (native) DNA (anti-dsDNA) were identified in the initial disease period that were undetectable for further 2 years and reappeared in the third year of follow up. Antinuclear antibodies (ANA) were consistently detected. No anticardiolipin, antimitochondrial, antiparietal cell, antismooth muscle and antiliver-kidney microsomal antibodies were observed. Latex and Waaler-Rose reactions were negative on two occasions. Results of sputum culture for mycobacterium tuberculosis were also negative. Serum C3 complement level was normal.

The clinical picture of the disease and results of ancillary tests (presence of ANA and anti-dsDNA antibodies) lead to diagnosis of SLE and initiation of prednisone therapy at a dose of 50 mg daily. The administered treatment resulted in marked improvement of patient’s general condition (normalization of body temperature, resolution of muscle and joint pains) and normalization of some laboratory parameters – hemoglobin concentration and creatinine concentration. However, steroid diabetes developed after intensive glucocorticosteroid therapy.

However, it should be emphasized that the underlying disease remained in clinical remission for 3 years. Prednisone therapy was continued at a daily dose of 15 mg. The patient was periodically hospitalized for control laboratory tests and evaluation of therapy effectiveness. C-reactive protein concentration evaluated on several occasions ranged from 7.1 to 82 mg/l, but on most occasions remained <10 mg/l. Alanine transferase level diminished, however remained constantly above normal values, similarly to the GGTP serum activity.

During hospitalization in July 2005, physical examination revealed slight peripheral cyanosis, and abdominal USG demonstrated enlarged liver with increased echogenicity, and thickened walls of the gallbladder with the concrement described previously. Both kidneys had irregular borders and blurred structure. In chest X-ray, a weakly saturated and poor window lymph nodes <10 mm in diameter, and packets of enlarged lymph nodes in the right hilus. In addition, a round lesion was described, 41 HU density and 88x41 mm in dimensions, near the posterior chest wall on the right. Abdominal CT revealed liver metastases, with rich vasculature and various diameter, moderately contrast-enhanced in the arterial phase. Serum tissue polypeptide-specific antigen (TPS) concentration was two fold above the upper normal limit.

The consulting oncologist suggested taking material for histological examination with a transthoracic biopsy or bronchofiberoscopy. For further evaluation and management, if possible, the patient was transferred to the Department of Lung Diseases and Tuberculosis of the Silesian Medical University. He had bronchofiberoscopy performed there that demonstrated stenosis of the right superior lobar bronchus with thickened, bright-red mucous membrane. Specimens were taken from this site for histological examination that revealed carcinosma microcellulare (small cell cancer). Bronchial lavage was also taken for cytological examination that demonstrated cancer cells (cellulae carcinomatous).

Due to highly advanced cancer process and patient’s poor general condition, symptomatic treatment was initiated. The patient was discharged from hospital and referred for the outpatient hospice care.

DISCUSSION

As already mentioned, association between silicosis and SLE has been noticed. Studies by Brown et al. [6] carried out in Scandinavia in 1052 Swedish with silicosis, demonstrated SLE in 23.8% of participants. Calvert et al. studied the correlation between exposure to silica dust and development of various diseases [7] and demonstrated that persons exposed to silica dust had higher incidence of silicosis, lung cancer, chronic obstructive lung disease, tuberculosis and rheumatoid arthritis.
On the basis of presence of multiorgan changes (the disease process involved the osteoarticular system, lungs, kidneys), general symptoms (reduced body weight, persistent high body temperature, weakness) and results of immunological tests (presence of anti-dsDNA and ANA antibodies) SLE was diagnosed in this case that met American Rheumatism Association (ARA) criteria, and prednisone therapy was introduced at a daily dose of 50 mg. The SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) score was employed for evaluation of disease process activity. The SLEDAI score was >10 (joint pains, renal injury, pulmonary changes, elevated body temperature, immunological changes, presence of anti-dsDNA and ANA antibodies).

As already mentioned, the disease remained in clinical remission for 3 years.

Improvement was likewise observed in biochemical parameters, γ-globulin and IgG concentration diminished and previously detected anti-dsDNA antibodies were absent. However, blood serum ANA antibodies were consistently detected. In chronic therapy, prednisone at a daily dose of 15 mg was continued.

Because of some clinical features, HRCT description that revealed bilateral subpleural nodules with calcifications and occupational history (years-long work with drilling of mining shafts and tunnels, with exposure to high concentration of silica dust in inhaled air), Caplan’s syndrome was suspected, that is nodular lesions in the lungs, mainly peripheral fields, consisting of collagen, silicon and typical rheumatoid nodules. However, this suspicion was not confirmed in a serological test, where rheumatoid factor was negative on two occasions. At present it seems that anti-cyclic citrullinated peptide antibodies should be determined more frequently. It is worth reminding that for many years ANA antibodies have been detected in miners with pneumoconiosis more frequently (34% of patients) than in healthy population [8]. Association with Caplan’s syndrome was not confirmed in this observation, however it has been recognized that occupational exposure of the observed workers group on silica dust is a causative factor in this phenomenon. In the observed case, clinicians decided to diagnose SLE due to a multiorgan character of the disease and detection of anti-dsDNA antibodies in addition to ANA antibodies; this discovery is an important argument supporting the diagnosis of this disease and titer of these antibodies allows assessment of disease process activity during the treatment.

In December 2005, that is after 3 years of follow up, general condition of the patient deteriorated significantly. Abdominal USG revealed several hepatic foci with irregular echogenicity; on the other hand chest X-ray demonstrated opacity of the middle right lung field, a well saturated round shadow in the right hilus and round shadows in upper fields of both lungs. These observations were consistent with an advanced lung cancer process with liver metastases, as confirmed by chest and abdominal CT and by further diagnostic procedures carried out in the Clinic of Lung Diseases and Tuberculosis.

As mentioned previously, the suggested correlation between silicosis and increased incidence of lung neoplasms has not be unequivocally substantiated [4,5]. There are also no exact data describing the relationship between SLE and pulmonary neoplasms, although some authors suggest that lupus can be a paraneoplastic syndrome accompanying such cancers [9].

During SLE therapy in the described case, elevated ALT and GGTP activity was observed almost constantly; it was considered a sign of liver injury during organ-nonspecific diseases, including SLE.

Moderately increased CRP, despite periodical marked exacerbation of the inflammatory process, is consistent with low concentrations of this acute phase reactant observed in SLE patients, which is in contrast with other autoimmune diseases [10]. Cause of this phenomenon remains unknown.

When assessing consistent presence of ANA in the investigated case one should take into account not only the autoimmune process, but also relatively frequent detection of these antibodies in the elderly (the patient was 62 years old) and above mentioned increased incidence of these antibodies in miners with diagnosed pneumoconiosis. There are also data pointing at presence of ANA in cancer patients; there are suggestions that they may have favorable anticancer effects [11].

Regardless of presence of silicosis in our patient (no direct, autopsy-based examination), this factor had to be considered when establishing the diagnosis of SLE, that is we had to attempt to associate the fact of autoimmune disease development with years-long occupational exposure to silica dust. Subsequent development of small-cell pulmonary carcinoma is an additional problem for this patient treated for several years due to SLE; it has been well documented and refers to the problem of development of cancer diseases in patients with autoimmune diseases [12]. Correlation between autoimmune and cancer diseases is a complex issue. Frequently it is impossible to establish which symptoms and serological abnormalities are primary or secondary. Although it seems that the symptoms observed in our patient can occur in diverse pathological syndromes, considering the temporal pattern of their appearance the simplest explanation is that the autoimmune disease was diagnosed earlier and was followed by development of lung cancer. Despite awareness of nonspecificity of ANA antibodies, they were consistently observed in repeated controls of this parameter. In combination with appearance of anti-dsDNA and the clinical picture it supported the proposed order of pathological processes. Titer of the above mentioned antibodies was not determined, but evaluation of anti-dsDNA antibodies demonstrated fluctuating activity of the autoimmune process reflected by periodical disappearance of these antibodies.

Noteworthy in the reported case is rapid development (about 6 months) of the primary tumor and distant metastases. Therefore it seems that patients with SLE and years-long exposure to silica dust require special clinical monitoring. Variability and diversity of immune system disorders that can occur in such patients suggest the necessity of further detailed experimental and clinical studies aimed at explaining pathogenetic correlations between the described diseases.
REFERENCES