Two paraneoplastic autoimmune syndromes: limbic encephalitis and palmar fasciitis in a patient with small cell lung cancer

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Abstract

Small cell lung cancer (SCLC) is characterized by a relatively high rate of autoimmune phenomena. Paraneoplastic limbic encephalitis (PLE) is an autoimmune syndrome in which a non-neural tumor containing an antigen normally present in the nervous system precipitates an antibody attack on neural tissues. Patients with PLE usually present with rapidly progressive short-term memory deficits, confusion or even dementia. Palmar fasciitis and polyarthritis syndrome (PFPAS) is another autoimmune syndrome characterized by rheumatologic manifestations, especially involving the palms of the hands. We report a case of a 59-year old woman who presented with worsening neurological symptoms of two-week duration, and later coma. The combined clinical, serological, and imaging studies suggested a diagnosis of PLE. A chest computed tomographic scan showed a 1.2 cm-diameter mass in the upper lobe of the left lung that was surgically removed and showed SCLC. Following surgery, neurological symptoms rapidly improved, allowing the patient to receive adjuvant chemotherapy. While in remission for both SCLC and PLE, the patient developed pain, soft-tissue swelling, and stiffness in both palms, suggesting the diagnosis of PFPAS. Five months following the diagnosis of palmar fasciitis, SCLC relapsed with mediastinal and cervical lymphadenopathy. This case report underlines the continuous interaction of SCLC with the immune system, expressed by coexistence of two rare paraneoplastic diseases, PLE, and PFPAS, in a patient with SCLC. While symptoms related to PLE preceded the initial diagnosis of SCLC, other symptoms related to PFPAS preceded relapse.

Introduction

Neoplastic diseases may initially be manifested by a wide range of autoimmune syndromes. Patients with small cell lung cancer (SCLC) commonly suffer from symptoms related to paraneoplastic autoimmune disorders, including paraneoplastic limbic encephalitis (PLE). PLE is usually marked by rapidly progressive short-term memory deficits, confusion or even coma. The diagnosis of PLE in many cases remains difficult, and the presenting symptoms may be different from those considered typical of the disorder.[1] Antibodies against onconeural antigens (ONAs) may be detected in about 60% of all PLE cases. Tumors most commonly associated with PLE are small cell lung cancer (SCLC), testicular and breast cancers, and malignant thymoma.[2]

Palmar fasciitis and polyarthritis syndrome (PFPAS) is a rare paraneoplastic rheumatic syndrome most commonly described with gynecologic malignancies.[3] Only one case report has described PFPAS in association with SCLC.[4] Patients present with pain and diffuse synovitis of the hands (usually at the MCP and PIP joints), and symmetric polyarthritis with rapid progression of palmar fasciitis with flexion contractures of the hands.[5] We report a case of SCLC in a 59-year old woman manifested by symptoms related to two rare autoimmune syndromes, PLE and PFPAS, This case report emphasizes the importance of the interaction of the immune system with the tumor in cases of SCLC.

Case Report

A 59-year-old female patient was admitted to the department of neurology in a tertiary hospital for apathy, memory disturbances, and progressive drowsiness of two-week duration in March 2013. The patient was a heavy smoker and suffered from chronic obstructive lung disease with rare attacks of exacerbation. Her medical history was marked by gastric banding for morbid obesity nine years before her admission, and severe low back pain with degenerative spinal changes. The patient had no history of alcohol or drug abuse. On admission, the temperature was 37.10°C, the blood pressure was 125/65, the pulse rate was 50/min, and the respiration rate was 16/min. On physical examination, the patient was not dyspneic. The chest and abdomen were normal. The neurological examination revealed disorientation, normal motor function, bilateral increased tendon reflexes and Babinsky's sign on the left. Cerebellar signs, autonomic dysfunction and sensory deficits were absent. The Glasgow coma scale was 15. Laboratory studies showed hemoglobin of 15.5 g/dL, white blood cell (WBC) 11.2×10^9/L, platelet 246×10^9/L, blood glucose 119 mg/dL, and normal blood oxygen saturation. Her liver and kidney function studies were normal. Electrocardiogram, chest radiograph, and brain computed tomography (CT)-scan were unremarkable. A lumber puncture showed normal opening pressure (140 mm H_2O), and the cerebrospinal fluid (CSF) displayed mild pleocytosis, (30/µL, predominantly lymphocytes), and normal protein (40 mg/dL) and glucose (65 mg/dL) levels. During the initial days of hospitalization, her neurological status rapidly deteriorated and she became comatose. Empiric treatment with thiamine, diazepam, phenytoin for presumed diagnosis of seizures of limbic origin, and acyclovir for suspected diagnosis of viral encephalitis was initiated, but there was no clinical improvement. Magnetic resonance imaging (MRI) of the brain showed high signal intensity in both medial temporal lobes on fluid-attenuated inversion recovery image, and restriction of the limbic lobes on diffusion-weighted echo-planar image (Figure 1A). These findings suggested a diagnosis of limbic encephalitis (LE). Electroencephalogram (EEG) showed general slow waves suggestive of cerebral dysfunction, without eleptiform discharges. Polymerase chain reaction (PCR) tests for the human immunodeficiency, West-Nile, varicella-herpes zoster, and herpes-simplex viruses were all negative. The CSF Tau protein concentration was 582 pg/mL (N<870 pg/mL). Serologic tests for the antigens Hu, Ma, CV2, amphiphysin, Yo, and Ri were all negative. Following the

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diagnosis of LE, all empiric treatments were stopped, and immunotherapy consisting of pulse-therapy with methylprednisolone (1000 mg/day, for three consecutive days) combined with plasmapheresis was started, resulting in a higher level of alertness. A chest CT-scan showed a 1.2 cm in diameter mass in the upper lobe of the left lung, with no mediastinal lymphadenopathy (Figure 1B). Surgical resection of the tumor showed SCLC that was limited to the chest. Following surgery, cognitive functions rapidly improved, allowing the patient to receive chemotherapy consisting of carboplatin and etoposide. Four months after completing chemotherapy, the patient developed symmetric pain, and swelling of both palms and fingers (Figure 2), with no other joints involved. X-rays of both hands showed no bony erosions, and serology for the antigens: nuclear, double-strand DNA, myeloperoxidase, and proteinase-3, as well as rheumatoid factor were negative. PFPAS was treated with systemic steroids with some relief. Six months later exacerbation of PFPAS was observed, not accompanied by new neurological symptoms. Chest CT scan showed mediastinal lymphadenopathy and FDG-PET scan showed increased uptake in mediastinal lymph nodes consistent with relapse of SCLC.

Discussion

Our patient presented with progressive depression and behavioral changes developing over two weeks. The diagnosis LE was based on clinical grounds and was supported by MRI findings despite negative serology for ONAs. Although a number of patients with LE have been reported in the literature, its diagnosis remains challenging.[1,2,6] Patients commonly present with cognitive dysfunction, including memory loss and confusion (92%); seizures that are either psychomotor or focal (58%); and psychiatric symptoms (50%).[2,7] Neurological symptoms typically develop over days or weeks (82%), slower development of symptoms over months occurs less frequently. Usually, patients are not known to have cancer and no specific symptoms are related to any type of malignancy. Symptoms of involvement of areas of the nervous system distant from the limbic system (particularly the brainstem and the cerebellum) are frequent in patients with LE, and isolated LE is found in only a minority of patients.[8]

The differential diagnosis of cases suspected of LE is extensive and includes herpes simplex virus encephalitis, progressive multifocal leucoencephalopathy, Wernicke-Korsakoff syndrome, Hashimoto's encephalopathy, psychiatric disorder, central nervous system vasculitis, acute demyelinating encephalomyelitis as well as brain tumors. Early diagnosis of LE is of paramount importance, as each of the other diagnoses requires a different therapeutic strategy. The CSF in patients with LE usually shows lymphocytic pleocytosis, increased protein concentration, and oligoclonal bands, but is not specific to LE.[8] EEG may show focal or generalized slow wave abnormalities or eliptiform discharges in the temporal lobes, and T2-weighted or FLAIR MRI usually shows hyperintense signal of the medial temporal lobes.[7] Fluorodeoxy glucose-positron emission tomography (FDG-PET) may detect hypermetabolism in the medial temporal lobes, even when MRI is normal.[9] Our patient was diagnosed with LE despite a negative serology for six ONAs, based

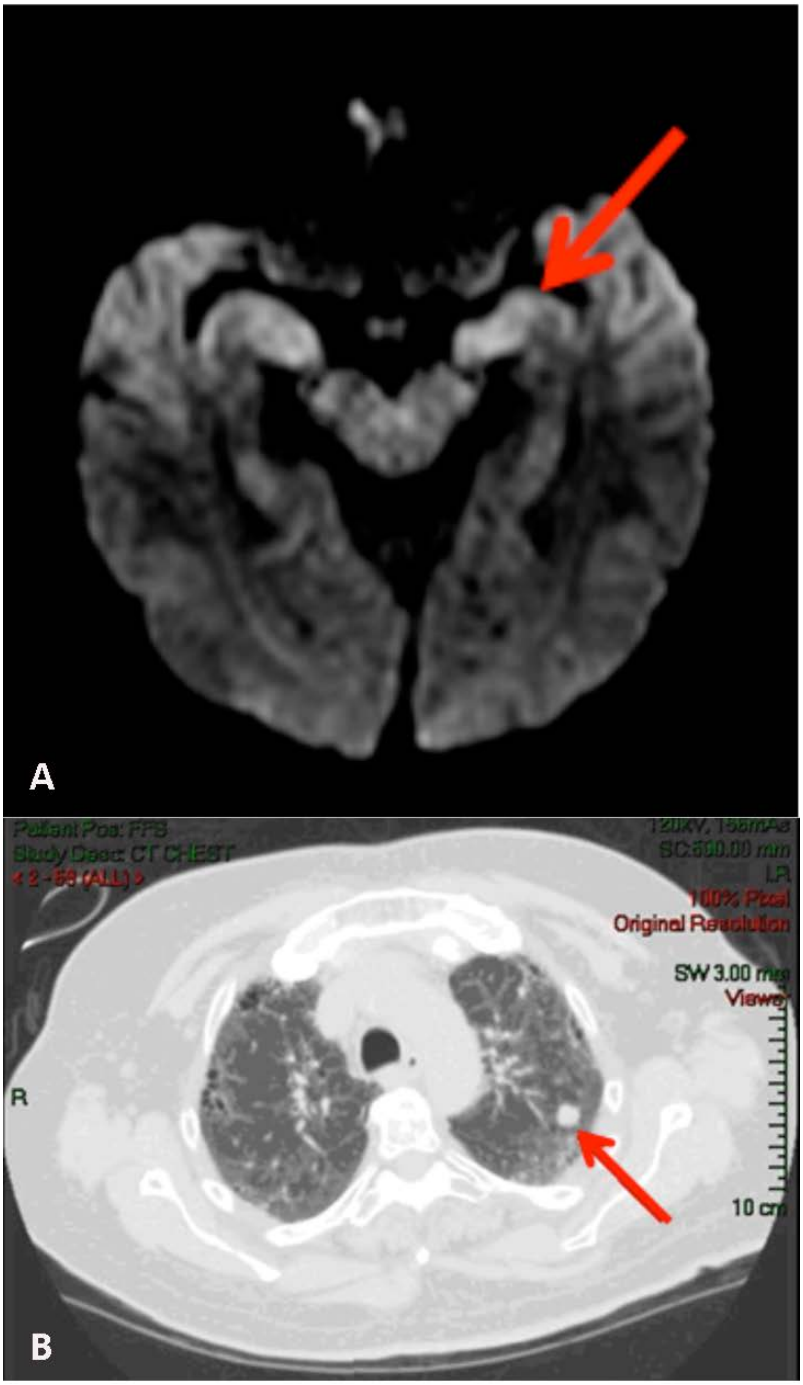

Figure 1. A) Magnetic resonance imaging of the brain. Diffusion-weighted echo-planar image (5400/103/1; b-value of 1000 s/mm^2) shows the restriction of the limbic lobe (arrow). B) Chest computed tomography-scan showing 1.2 cm-diameter mass in the upper lobe parenchyma of the left lung (arrow).

on clinical presentation, and elimination of other possible diagnoses. The diagnosis of a paraneoplastic etiology for LE was later supported with the finding of SCLC.

The pathophysiology of PLE is believed to be autoimmune-related, triggered by autoantibodies against ONAs which are common to both the cancer and the nervous system. Autoantibodies may be detected either in the sera or CSF, although the absence of autoantibodies does not exclude the diagnosis of PLE.[2] The autoantibody type may give some guidance as to the location of the tumor. The two most common autoantibodies associated with the diagnosis of PLE are the anti-Hu (also called the antineural antibody type 1, ANNA-1), and anti-Ma2 (also called anti-Ta) antibodies.[10,11] PLE in SCLC patients is most frequently associated with the anti-Hu antibody, while testicular and breast cancer, and thymoma are most commonly associated with the anti-Ma2, anti-amphiphysin, and anti-CRMP5 antibodies, respectively.[2,10,12] Neuronal antibodies against cell surface antigens such as voltage-gated potassium channel (VGKC) and N-methyl-D-aspartate (NMDA) receptor also may be detected in a number of patients with LE, but are not necessarily associated with cancer.[11] Although PLE may occasionally be associated with other tumors, SCLC is by far the most frequent underlying tumor. Unlike most other paraneoplastic syndromes of the central nervous system, which do not improve with treatment, PLE responds favorably to therapy. Most patients with PLE associated with SCLC who respond to immunosuppressive therapy, show a high titer of anti-Hu antibodies. In a study of Hu antibodies in patients with SCLC, treatment of the associated tumor was more effective in bringing about neurological improvement compared with the use of immunosuppressive therapies, prompting the authors to suggest that early treatment of SCLC offers the best chances for improvement, particularly in anti-Hu seronegative patients.[13] As most patients with PLE associated with SCLC are diagnosed in limited stage, prompt detection and treatment of SCLC may improve not only the neurological deficits, but also improve the prognosis in regard to SCLC.[14,15] Although SCLC patients who develop paraneoplastic syndromes may have a better prognosis compared to other patients with SCLC but without neurological deficit it has not been clarified whether such an improvement is related to a lead-time bias in detecting SCLC, or whether immune response against cancer favorably influences the prognosis.[16,17]

Despite an initial poor performance status, our patient underwent lung surgery, followed by chemotherapy with improvement of neurological symptoms. Later exacerbation of PFPAS preceded relapse of SCLC in the form of mediastinal lymphadenopathy. The diagnosis of PFPAS in our patient was based on clinical grounds only, as no other arthritic symptoms were noted and no positive serology was detected. In paraneoplastic PFPAS, rheumatologic symptoms can precede initial detection of the underlying malignancy, but more often occur prior to recurrence or progression as was probably the case in our patient.[5] Laboratory tests, such as acute-phase reactants and the presence of antibodies are generally unremarkable in PFPAS. Antinuclear antibodies and rarely rheumatoid factor are the most common antibodies detected in PFPAS cases. However, these antibodies are not specific, and are often present at low titers.[18] PFPAS was the second autoimmune syndrome developing in our patient. Only one report previously described PFPAS in association with SCLC.[6] The underlying mechanism for paraneoplastic PFPAS is currently unknown. Autoimmune mechanisms produced by the tumor are probably responsible for the development of PFPAS, because complement and immunoglobulin deposits have been found in some of the fascial tissues,[3] although there has been no direct or consistent link with any particular autoantibodies. It is unlikely that autoantibodies to the same antigen are responsible for the development of both PLE and PFPAS, since the diseases developed asynchronously. The putative pathogenesis of autoimmune diseases is either mediation by cytotoxic CD8+ T cells, or by antibodies mounted against surface membrane antigens. It has been suggested that aberrant expression of peptides by tumor cells mediates autoimmunity in tumors like SCLC, while dysregulation of the immune system mediates autoimmunity in cases of thymoma.[19,20] The systems (and probably also antigens) involved in PLE and FSPAS are different: CNS in cases of PLE, and connective tissues in cases of FSPAS. Antibodies commonly elevated in PLE and in FSPAS, were all negative in our patient, suggesting that the pathogenesis for both diseases involved cytotoxic CD8+ T cells. PLE was the first manifestation of SCLC in our patient, while PFPAS only (but not PLE) preceded relapsed SCLC, implying the possibility that a new clone of SCLC which emerged after the patient received first-line chemotherapy, was responsible for the development of PFPAS.

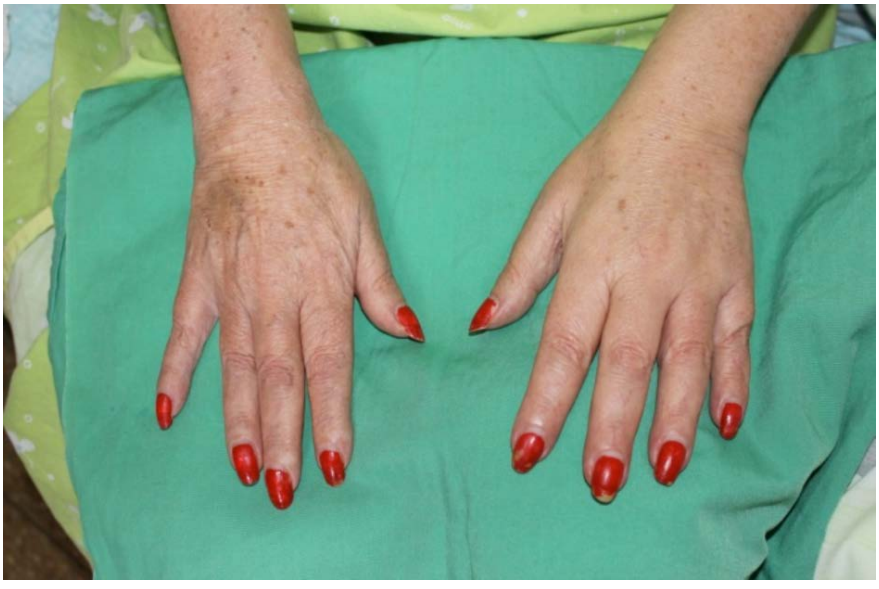

Figure 2. Photograph of both palms in a patient with small cell lung cancer showing swelling, most prominent in the left hand.

Conclusions

In summary, we describe a case of two autoimmune diseases, PLE and PFPAS, each involving an immune reaction to a different organ system, in a patient with SCLC. To the best of our knowledge, such an association has not been described before in patients with SCLC.

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