Case Report

The spectrum of CNS clinical manifestations in patients with small cell lung carcinoma presented through two case reports

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SUMMARY

Lung cancer is one of the most common neoplasms in the world. In particular, small cell lung carcinoma (SCLC) is one of the most aggressive neoplasms with poor prognosis. Central and peripheral nervous system involvement is very common in this type of cancer due to cerebral metastases, spinal cord compression or even complications from treatment (either chemotherapy or immunotherapy). Paraneoplastic neurological syndromes and hypercoagulability syndrome are two complicated conditions which connect small cell carcinoma and nervous system. In this article, an extensive reference is made to the two latter situations through the description of two incidents: one with subacute cerebellar degeneration and one with hypercoagulable syndrome and multiple ischemic strokes in patients with SCLC.

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INTRODUCTION

Globally, lung cancer is the most common cancer in men and the fifth most common malignancy in women[1]. Small cell lung carcinoma (SCLC) comprises 13% of all lung cancers. Its incidence has fallen during the last few years due to the reduction of smoking rates[2]. It is a very aggressive cancer, with most patients (60-70%) exhibiting a widespread disease, thereby reducing survival rates to 20% and 2% at 7 months and 5 years respectively[3]. The central nervous system is frequently affected in patients with SCLC. Neurological dysfunction can occur due to brain metastases, spinal cord compression, post-treatment complications, nutritional and metabolic causes. Two important but more complex interactions between CNS and lung cancer relate to paraneoplastic neurologic disorders and hypercoaguable states, which will be presented below through two clinical cases.

The term **Paraneoplastic neurological disorders** (PNDs) refers to a

group of syndromes that can affect either the central or the peripheral nervous system and are caused by cancers not located within the aforementioned structures. Their pathophysiology is different from metastases or other cancer complications such as metabolic deficits, infections and coagulopathy. They are associated with various types of tumours, the most common being SCLC. Although they were considered rare syndromes, PNDs are more frequent than previously thought. Our understanding of the underlying pathophysiology has increased through years of observation and now PNDs are considered to have an autoimmune mechanism. This notion is supported by the detection of specific antineuronal antibodies in the CSF and serum of patients with PNDs. Although the classic concept is that these disorders occur exclusively with the co-occurrence of cancer, a few patients with clinical PNDs and specific antineuronal antibodies fail to demonstrate any evidence of tumour presence, despite extensive work-up and follow up imaging. This leads to the reasonable conclusion that PNDs should be considered as autoimmune disorders with a high risk of cancer, rather than a clinical manifestation of the latter.

The interrelationship between a stroke and cancer is complex and not completely understood. The two entities can occur independently in a given patient or cancer may lead to stroke via various mechanisms such as hypercoaguability, non-bacterial thrombotic endocarditis, direct tumor compression of blood vessels and treatment-related effects that can increase the risk of stroke. It is therefore important, especially in cryptogenic strokes, to be aware of this relationship and guide the appropriate workup for occult malignancy under the right clinical circumstances in a stroke patient.

CASE 1

A 66-year old female patient complained of dizziness, somnolence and generalized weakness for 20 days. She was admitted to our clinic for evaluation of her symptoms. She was a smoker and was receiving anti-hypertensive drugs for the last 5 years. No other medical problems or previous hospital stays were mentioned. Her family history was unremarkable. Body temperature and serum glucose were also normal. The first step in the evaluation of this patient was a CT scan which was normal. Meanwhile, she reported that the feeling of dizziness was getting worse. Examination of the CSF via lumbar puncture revealed a mild pleiocytosis (290/mm^3 -90% lymphocytes), mild elevated total protein: 71,7 mg/dl and normal glucose values: 64 mg/dL. The next day the patient reported nausea and began vomiting. Her neurological examination at that point revealed a truncal ataxia, difficulty in gait and nystagmus with a changing fast phase, indicative of a central etiology of her symptoms. MRI of the brain was negative for any structural causes. A second lumbar puncture was conducted but failed to reveal any CSF changes. Serologic examination, CSF PCR, blood- CSF cultures and autoantibodies for autoimmune encephalitis (anti-NMDA, anti-LG1, anti-CASPR2) were negative. Meanwhile the patient became lethargic and laboratory studies showed a moderate hyponatremia. A paraneoplastic disorder was suspected at this stage. Cancer markers (CA 19-9, CEA, CA-125) were negative. CT of the chest revealed a mass located on the upper lobe of the right lung, with enlargement of mesothoracic lymph nodes (Figure 1). Bronchoscopy and lung biopsy that were performed revealed SCLC. Testing of CSF paraneoplastic antibodies (anti-Hu, anti-Yo, anti-Ri, anti CV2-CRMP5, anti-VGCC) was negative. The patient received a 5-day regimen of intravenous Ig (total dose 2g/kg) but failed to show any significant improvement. She was referred to an oncological center for further evaluation and treatment.

CASE 2

A 61-year old male patient suddenly developed weakness and numbness in his right hand along with articulation problems and was admitted for further evaluation. He was a smoker (1 pack/day) and 3 months before he had developed deep venous thrombosis of his right leg, for which he was receiving anticoagulation treatment with rivaroxaban. His brain MRI revealed multiple acute infarcts located in the cerebellum, left occipital and parietal lobe (Figure 2). U/S examination of the carotid and vertebral arteries was normal, as well as his ECG and transthoracic ultrasonography. Rivaroxaban was replaced with low molecular weight heparin (LMWH-tinzaparin 175 mg/kg) and due to his stable medical condition, the patient was discharged and arranged for follow up after 1 month. However, he was admitted in our clinic after 5 days, due to severe dysarthria. Tinzaparin was increased to 200 mg/kg and aspirin 80 mg daily was added to the treatment regimen. The next day the patient complained of dyspnoea and he was evaluated by a pneumonologist. His chest CT revealed a mass located in the right lung and enlarged mesothoracic lymph nodes (Figure 3). Via bronchoscopy the mass turned out to be a SCLC. LMWH was stopped 2 days prior to the procedure and was re-

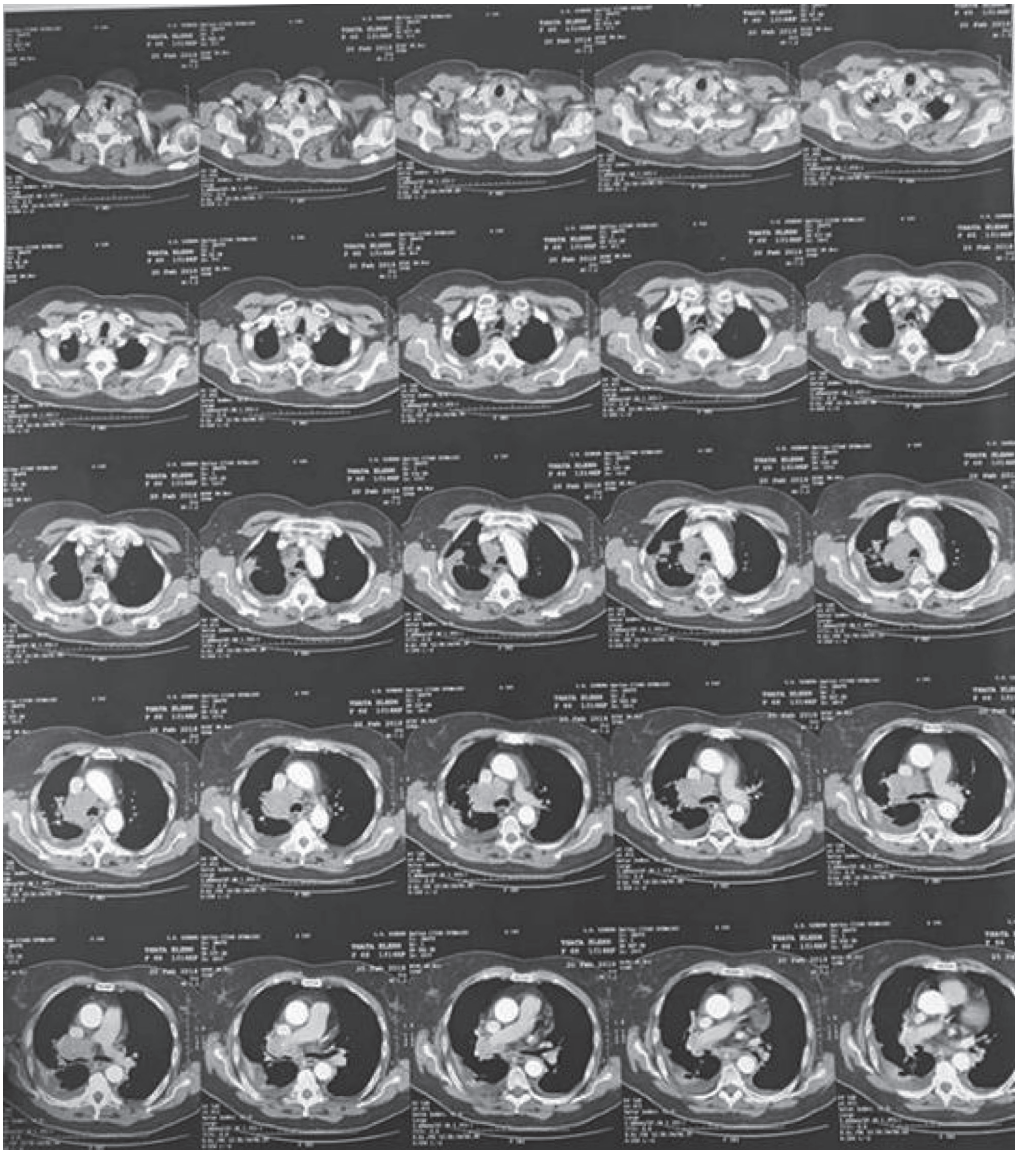

FIGURE 1.

established 5 days later. Meanwhile the patient developed severe chest pain and after cardiological evaluation, he was diagnosed with myocardial infarction. He was admitted to the ICU, where he was stabilized and was later discharged with dual antiplatelet therapy (clopidogrel 75 mg/d plus aspirin 100 mg daily) and cessation of LMWH. The next day he was transferred to the ER with intense abdominal pain, confusion and a reduced level of consciousness. CT of the brain revealed multiple bilateral acute infarcts located bilaterally in the subcortical white matter and CT of the abdomen demonstrated infarcts located on the spleen and both kidneys (Figure 4). Additionally, his ECG revealed acute extensive myocardial infarction and he was immediately transferred to the ICU where he passed away after 12 hours.

DISCUSSION

Paraneoplastic cerebellar degeneration (PCD) constitutes one of the most common PNDs. It is most commonly associated with SCLC, breast and gynaecological cancer, as well as Hodgkin's lymphoma[4,5]. The syndrome develops subacutely over several days or weeks and is often preceded by a viral like illness or nausea-vomiting-dizziness that is often attributed to a peripheral vestibular process[6]. These symptoms are followed by difficulty in gait,

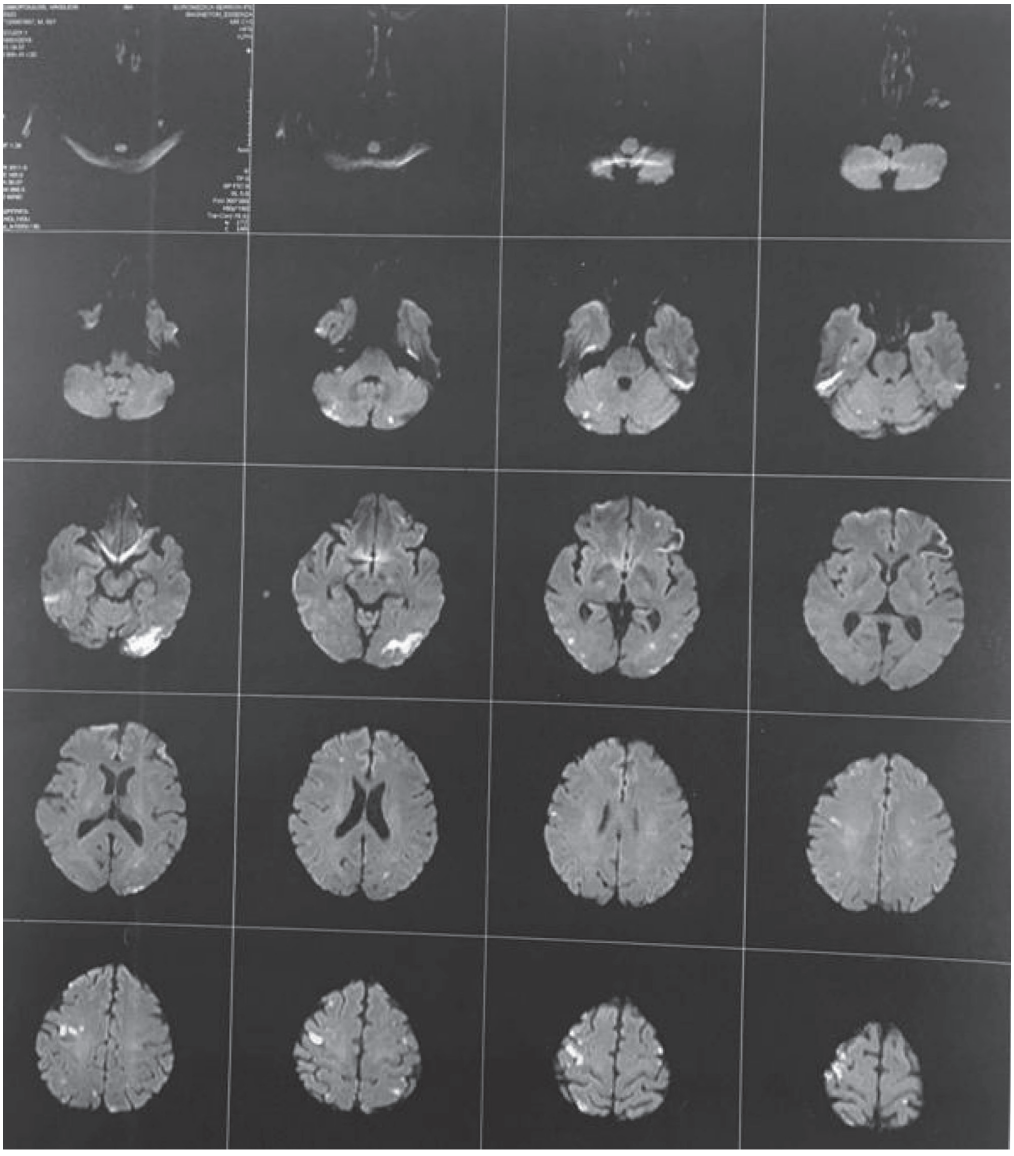

FIGURE 2.

generalized ataxia, diplopia, dysarthria and nystagmus. Some patients may also report blurry vision[7,8].

The initial brain MRI is usually normal, but in later stages of the disease it may exhibit diffuse cerebellar atrophy. Another helpful diagnostic tool in this case is fluorodeoxyglucose-PET which in the early phases of the disease will demonstrate cerebellar hyper- and later on hypometabolism[9]. The pathologic hallmark of PCD is extensive loss of Purkinje cells that can be associated with inflammatory infiltrates located in the cerebellar cortex, deep cerebellar nuclei and inferior olivary nuclei[10]. As with other paraneoplastic syndromes, PCD shares an autoimmune basis for its pathogenesis. An increasing number of immune responses and specific autoantibodies regarding PCD have been recognized. Some of those are specifically associated with cerebellar dysfunction, while others are not specific and mostly represent a tumor-induced immune response. Anti-Yo (associated with breast or gynaecological cancer) and anti-Tr (associated with Hodgkin's lymphoma) are commonly encountered in PCD and are highly specific of this syndrome[11,12].

Patients with SCLC may exhibit various autoantibodies in association with paraneoplastic cerebellar degeneration. 41% of these patients are positive for autoantibodies

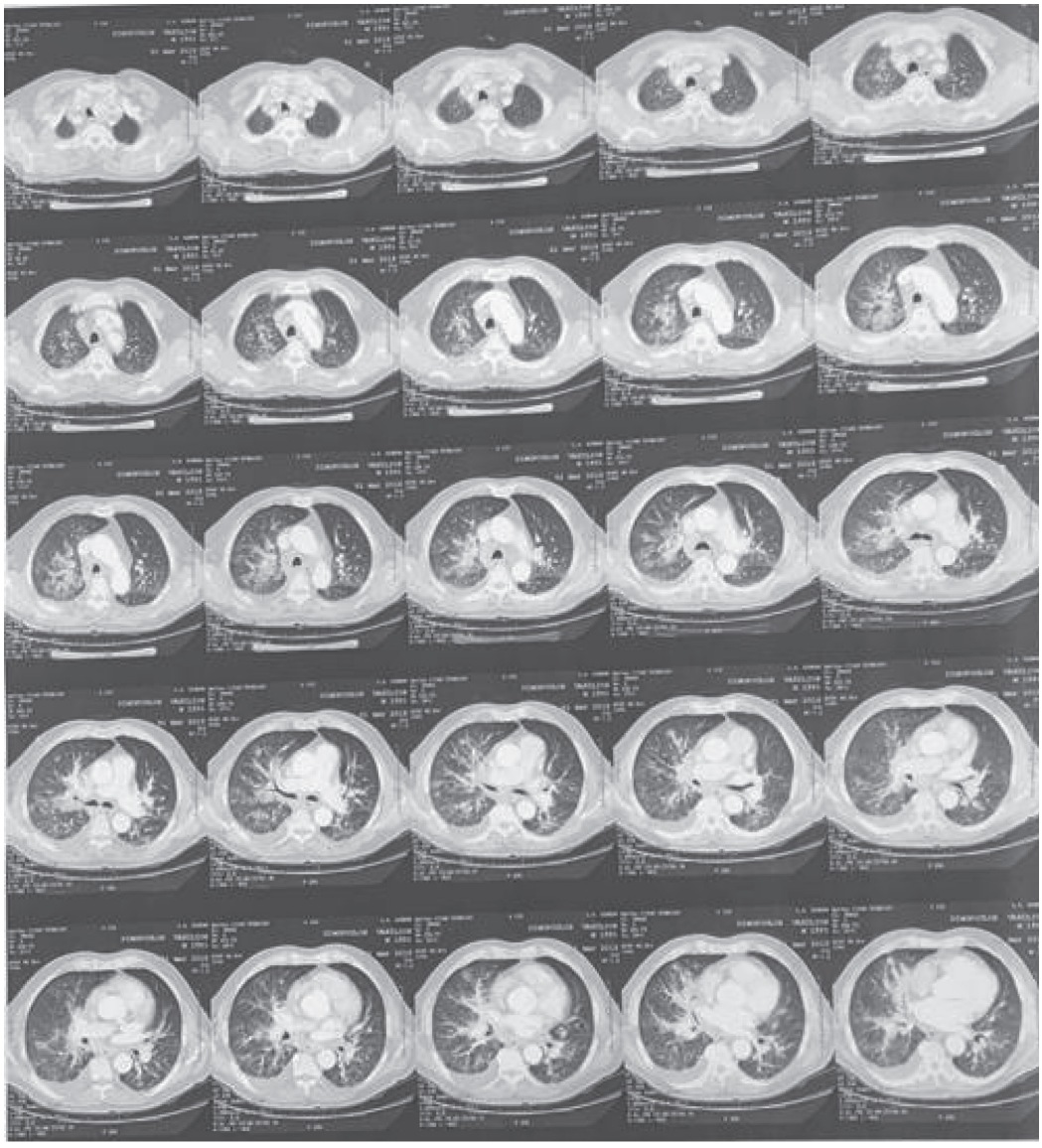

FIGURE 3.

against voltage-gated calcium channels (anti-VGCC). In this setting, Lambert-Eaton myasthenic syndrome may co-exist with PCD. Another 23% of patients exhibit anti-Hu antibodies, while a minority develops autoantibodies against various antigens such as collapsin-response mediator protein 5 (anti- CV2/CRMP5), amphiphysin and Purkinje cell cytoplasmic antigen type 2 (anti-PCA2)[13,14].

There is no standardized treatment for this condition. Case studies have shown some benefit, especially in the early stages of the disease with immunotherapy such as corticosteroids, plasma exchange, intravenous immunoglobulin, cyclophosphamide, and tacrolimus[15]. However, because of early, irreversible neuronal loss most patients with PCD do not improve with any of these treatments. Treatment of the tumour remains the most important step in disease stabilization and halting neurological deterioration.

The most common causes of a stroke in cancer patients are traditional cerebrovascular risk factors such as hypertension, dyslipidemia, diabetes mellitus and smoking[16-18]. However, cryptogenic strokes, meaning that no cause for them was identified despite thorough investigation, appear to be more prevalent in patients with cancer such as SCLC, suggesting an association between the two[16]. In one study, 67% of strokes in cancer patients appear as multiple embolic infarcts in neuroimaging, suggesting

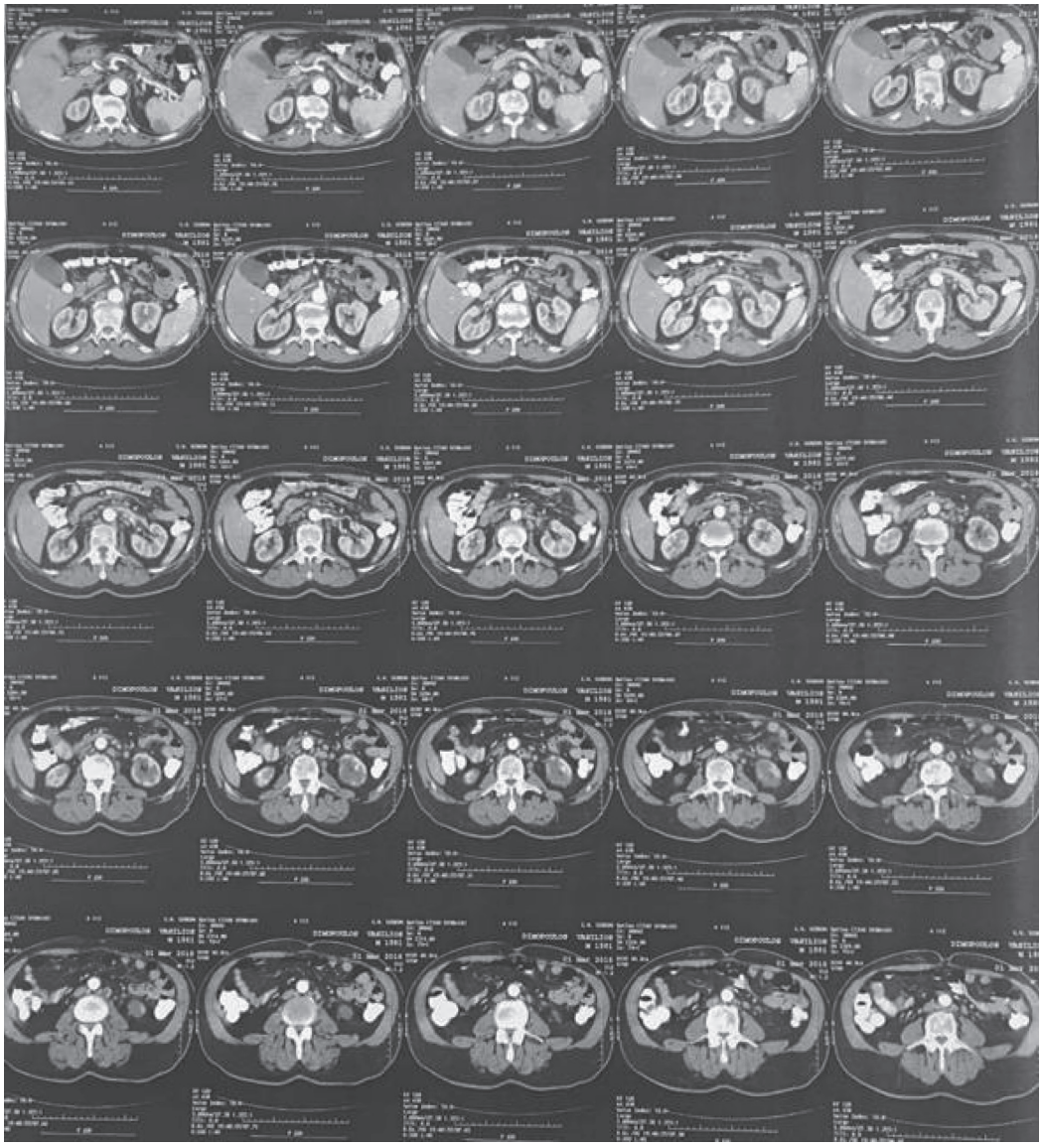

FIGURE 4.

that clot formation and subsequent embolization may be the prevailing mechanism[19]. It is therefore hypothesized that in a subgroup of patients, a stroke may be caused by mechanisms specifically linked to their underlying malignancy. We will present each one of them in the following section.

Hypercoagulability: The most important mechanism that SCLC can lead to a stroke is via abnormal coagulation cascades. Coagulation disorders such as disseminated intravascular coagulation(DIC) are more commonly seen in stroke patients with cancer than those without[17,18]. Furthermore, cancer patients with a cryptogenic stroke were found to have elevated D-dimer levels compared to non-cancer patients[20]. Tumor cells can release pro-coagulant molecules such as tissue factor (TF) and cancer pro-coagulant (CP)[21,22]. TF is a protein that binds to factor VII and potentiates the coagulation cascade, leading to thrombosis. It has been found in high concentrations in symptomatic atherosclerotic plaques, leading to the hypothesis that it plays an important role in plaque de-stabilization and emboli formation[23,24]. CP is a cysteine proteinase that is released by the majority of cancers. It leads to thrombin formation via activation of factor X to Xa[25,26]. Other pro-coagulant cytokines that are secreted by malignant cells are tumor necrosis factor-a (TNF-a), IL-1 and IL-6. These cytokines induce vascular endothelial

cells, monocytes and cancer cells to release TF, thereby potentiating thrombin formation. They also inhibit protein C, a natural brake in the coagulation cascade[25,26]. Finally, platelet aggregation seems to play an important role as well, being the result of multiple mechanisms such as cytokine release and elevated levels of von-Willebrand factor[22].

Venous- to-arterial embolism: Hypercoagulability usually manifests as deep venous thrombosis and pulmonary embolism. However, these venous clots can lead to stroke via venous-arterial shunting, a process that is known as paradoxical emboli. It is hypothesized that this shunting can occur via a patent foramen ovale (PFO). The risk that PFO alone plays in stroke appearance is not well established, however, when combined with an increased rate of pelvic thrombosis it seems to increase stroke risk[27]. It is a fair assumption to assume that increased clot formation can lead to increased paradoxical embolization[28].

Nonbacterial thrombotic endocarditis: Another common mechanism relating to stroke and cancer is nonbacterial thrombotic endocarditis (NBTE), previously known as marantic endocarditis. In NBTE, sterile vegetations develop in the cardiac valves, mainly the aortic and the mitral, and can lead to a stroke through embolization[29]. These vegetations result from abnormal fibrin attachment to previously undamaged valves in areas with high blood flow, thus creating a suitable substrate onto which platelets can adhere. Transesophageal echocardiography (TEE) is thought to be more sensitive than transthoracic echocardiography (TTE) in detecting valvular vegetations, although it is not routinely performed in stroke patients[30]. Up to 50% of patients with NBTE in the context of cancer can present with a stroke, mainly of embolic origin[31]. Diffusion pattern MRI in these patients demonstrates multiple widely distributed small and large vessel infarcts (figure)[32].

Direct Tumor Effects: SCLC can lead to a stroke through direct vessel compression from brain metastases. This compression can result from either direct tumor invasion of the vessel or via vasogenic edema, leading to cerebral ischemia and infraction in the territory distal to the affected vessel[33-35]. It is also worth mentioning that this compression, apart from ischemia, can also lead to a hemorrhagic stroke. This hemorrhagic conversion of brain metastases is exceedingly rare in cases of SCLC and is more commonly associated with melanoma and renal cell carcinoma[36].

Other rare causes of direct cancer effects leading to a stroke include embolism to the brain from metastasis in the heart[37]. Again, this is more commonly associated with melanomas, although in rare cases it can be present in patients with SCLC[38].

Treatment-related stroke: Some chemotherapeutic agents have also been associated with an increased risk of stroke, such as cisplatin, methotrexate and L-aspariginase, however the mechanisms of this adverse action are poorly understood[39,40].

It is extremely important that the clinician be aware of some stroke characteristics that should prompt additional workup for occult malignancy. Cryptogenic strokes, multiple embolic infarcts on neuroimaging (large cortical strokes), absence of traditional risk factors, clinical signs such as clubbing and elevated D-dimer levels are some clues that may indicate the presence of an underlying tumor such as SCLC[41,42]. In these cases, additional diagnostic tests such as TTE (with or without bubble study), coagulation profile and full body FDG-PET may be needed in order to detect an occult cancer and the mechanism responsible for stroke appearance.

These patients present a major therapeutic problem. There are no specific guidelines regarding secondary prevention. The first important step is to address common cerebrovascular risk factors such as hypertension and hyperlipidemia and treat those conditions first. Anticoagulants, mainly LMWH, may be superior to anti-platelet medication in reducing the risk of stroke recurrence in cancer patients, however it should be noted that this group of medications increase the risk of systemic and intracranial bleeding in cancer-stroke patients[43,44]. Depending on the underlying mechanism of a stroke (et NBTE) and patient characteristics (increased bleeding risk) and pending randomized clinical trials, an individualized approach continues to be the mainstay of treatment for those patients.

CONCLUSION

SCLC can present with various neurological complications, the most common being brain metastases. Apart from those, CNS involvement may be associated with metabolic and nutritional deficits as well as treatment-related complications. Two important mechanisms of CNS dysfunction in these patients include paraneoplastic neurologic disorders and cancer-related stroke. The clinician must be aware of these conditions, guide appropriate workup when necessary and immediately begin treatment in order to prevent neurological deterioration and achieve patient stabilization.

ΠΕΡΙΛΗΨΗ

Το φάσμα των κλινικών εκδηλώσεων από το ΚΝΣ σε ασθενείς με μικροκυτταρικό καρκίνο του πνεύμονα, μέσα από την παρουσίαση δύο περιστατικών

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Ο καρκίνος του πνεύμονα είναι μια από τις πιο συχνές νεοπλασίες παγκοσμίως. Ειδικότερα το μικροκυτταρικό καρκίνωμα του πνεύμονα αποτελεί μια από τις πιο επιθετικές νεοπλασίες με κακή πρόγνωση. Η συμμετοχή του κεντρικού και περιφερικού νευρικού συστήματος είναι πολύ συχνή στον συγκεκριμένο τύπου καρκίνου και μπορεί να αφορά εγκεφαλικές μεταστάσεις, συμπίεση του νωτιαίου μυελού ακόμα και επιπλοκές από τη θεραπεία (είτε χημειοθεραπεία είτε ανοσοθεραπεία). Δύο από τις πιο περίπλοκες όμως καταστάσεις που συνδέουν το μικροκυτταρικό καρκίνωμα με το νευρικό σύστημα είναι τα παρανεοπλασματικά νευρολογικά σύνδρομα και το σύνδρομο υπερπηκτικότητας. Στο παρόν άρθρο γίνεται μια εκτενής αναφορά στις δύο τελευταίες καταστάσεις μέσα από την περιγραφή δύο περιστατικών: ένα με υποξεία παρεγκεφαλιδική εκφύλιση και ένα με σύνδρομο υπερπηκτικότητας και πολλαπλά ισχαιμικά εγκεφαλικά επεισόδια σε ασθενείς με μικροκυτταρικό καρκίνο του πνεύμονα.

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Λέξεις - Κλειδιά: *Μικροκυτταρικό καρκίνωμα; παρανεοπλασματικά, σύνδρομο υπερπηκτικότητας, ΑΕΕ*

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