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Multiple Ischemic Strokes Associated with Pulmonary Embolism Revealing Occult Pulmonary Adenocarcinoma: About Two (2) Cases and Review of the Literature

Camara Mamady, Diallo Mohamed Tafsir, Toure Laila*, Sacko Aboubacar Sidiki, Camara Baky Dominique Batoumbla, Camara Idrissa Aissatou, Camara Alpha, Konate Ibrahima Sory, Toure Fatoumata, Toure Mohamed Lamine, Barry Souleymane Djigué, Cisse Fodé Abass

Neurology Department, Ignace Deen National Hospital, Conakry University Hospital, Conakry, Guinea
Email: *lailatoure49@gmail.com

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Abstract

A rare clinical phenomenon has been reported. Patients with pulmonary adenocarcinoma consulted the neurology department due to multiple initial symptoms of cerebral ischaemia. Examination of each patient revealed pulmonary embolism, the underlying cause being a malignant lung tumour. Multiple ischaemic strokes (IS) associated with pulmonary embolism (PE) rarely indicate pulmonary adenocarcinoma. The concomitant presence of IS, PE and pulmonary adenocarcinoma increases the risk of complications and mortality. We report two (2) cases of diagnostic cascades marked by the discovery of multiple ischaemic strokes, followed by pulmonary embolisms and finally lung adenocarcinoma. Our patients, aged 58 and 55, were both smokers. Initially, the patients presented with focal neurological deficits symptomatic of multiple ischaemic strokes. The aetiological assessment revealed a state of hypercoagulability, which led to the discovery of pulmonary embolisms and lung adenocarcinoma. In terms of treatment, all of our patients received antiplatelet therapy and low molecular weight heparin. The outcome was marked by recurrent ischaemic strokes followed by the death of the patients from general complications.

Keywords

Multiple Stroke, Pulmonary Embolism, Adenocarcinoma

1. Introduction

Ischemic stroke (IS) may be the initial manifestation of cancer (Navi et al., 2007). The risk of acute cerebral ischaemia is potentially increased during cancer; approximately 5% - 10% of cryptogenic IS are secondary to active cancer, with an increased risk of recurrence and three times higher mortality (Sener & Keser, 2022; Meschia et al., 2014).

The risk of stroke is higher in lung cancer than in other types of cancer (Navi et al., 2017). Lung cancer accounts for approximately 30% of primary tumours associated with stroke (Cestari et al., 2004).

The presence of multiple cerebral ischaemias and certain biological markers, such as D-dimers, troponin and C-reactive protein (CRP), could point to a tumour aetiology of an ICH (Meschia et al., 2014; Ohara et al., 2020; Bravo Anguiano et al., 2023).

The incidence of pulmonary and venous thromboembolic complications ranges from 4% to 20% in cancer patients; these complications are associated with a poor prognosis (Suzuki et al., 2020). Thromboembolic complications most often occur at an advanced stage of cancer, during the first few months after diagnosis of lung cancer and after the start of chemotherapy (Maia et al., 2019).

Acute reperfusion by intravenous thrombolysis and mechanical thrombectomy appears to be safe in the presence of cancer and may be considered in eligible patients; however, severe haemorrhagic complications remain possible (Geraldes et al., 2017).

We report a rare clinical picture of multiple cerebral ischaemias associated with pulmonary embolism revealing adenocarcinoma.

2. Observations

Observation 1:

58-year-old male patient, civil engineer, smoker with 25 pack-years, no significant medical history. Admitted for headaches, right hemiparesis with ataxia, and sudden onset of homonymous lateral hemianopsia. NIHSS score on admission was 5, vital signs were normal. Brain MRI (**Figure 1**) revealed left and right vertebrobasilar and left superficial sylvian ischaemia. Left parietal haemorrhagic remodelling. Electrocardiogram, cardiac ultrasound and supra-aortic trunk (SAT) ultrasound were normal. The blood test results showed the following abnormalities: D-dimers > 25,000 ng/ml; troponin 2011 ng/ml, total cholesterol 2.40 g/l, LDL 1.95 g/l, triglycerides 1.53 g/l. Given this state of hypercoagulability, we performed a thoracoabdominal pelvic (TAP) scan, which revealed bilateral segmental pulmonary embolism with multiple mediastinal-hilar adenomegaly associated with a right posterobasal lobar mass. After consulting with the pulmonology department, the patient underwent a PET scan (**Figure 2**), which revealed pathological hyperfixation of the right hilar lymph nodes extending to the mediastinum, associated with a hypermetabolic tissue lesion in the right posterobasal lung. Pathological analysis following echoendoscopic biopsy of the pulmonary mass con-

cluded that it was a pulmonary adenocarcinoma. Doppler ultrasound of the lower limbs showed deep vein thrombosis of the left posterior tibial vein. On day 3 of hospitalisation, three days after these neurological events, low molecular weight heparin (LMWH) was administered at a dose of 6000 IU every 12 hours, combined with clopidogrel 75 mg per day, which had been started on day 1 of this neurological event, and atorvastatin 40 mg per day.

Twenty-four hours after the PET scan corresponding to day 21 of his first vascular event, he presented with mutism, right hemiplegia and drowsiness with an NIHSS score of 21. A brain MRI (**Figure 3**) revealed acute ischaemia of the right superficial sylvian artery. LMWH was reduced to a dose of 4000 IU due to the risk of haemorrhage associated with the new lesion. During his rehospitalisation, the patient developed aspiration pneumonia, and sputum cytology revealed Streptococcus pneumoniae. Administration of amoxicillin and clavulanic acid 1200 mg/8 hours and oxygen therapy with a therapeutic target of SpO2 > 94%. Ten (10) days later, he died from respiratory distress.

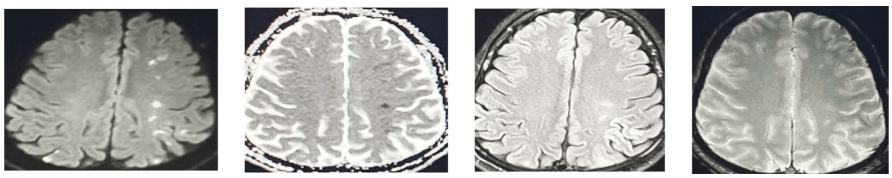

Figure 1. Acute sylvian and bilateral posterior cerebral artery ischaemia.

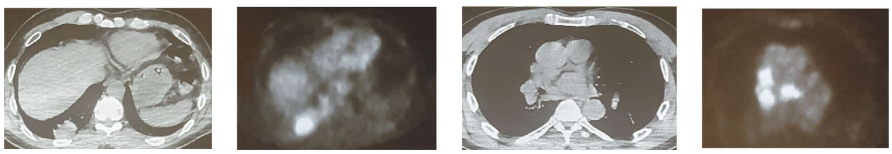

Figure 2. Hypermetabolism of a right posterobasal mass and mediastinal and right hilar lymph nodes.

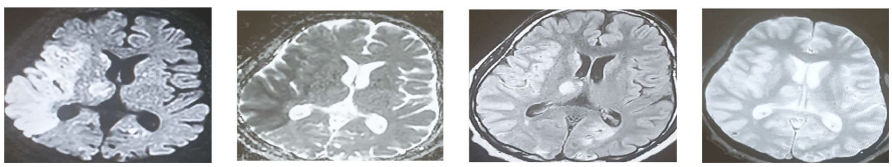

Figure 3. Acute ischaemia of the right superficial sylvian artery.

Observation 2:

55-year-old male civil servant, smoker of 30 packs per year and alcoholic consuming seven (7) glasses of wine per day. Admitted three (3) days after the sudden onset of language evocation disorder, left brachiofacial plegia and vertigo, NIHSS 6. Pulmonary auscultation revealed crackles in both lung bases.

Brain MRI (**Figure 4**) revealed subacute cerebral ischaemia in both hemispheres and the cerebellum. A chest CT angiogram showed a left lower lobe embolism and multiple mediastinal-hilar lymphadenopathy associated with two

well-defined nodules measuring 21 × 16 mm in the left lower lobe. Cardiac and TSA Doppler ultrasounds and electrocardiogram were normal. Blood test results were as follows: CRP 80 mg/l, D-dimers > 25,000 ng/ml, troponins 629 ng/l. From day 1, 100 mg of aspirin and 4000 IU of LMWH were administered for two (2) days, then 14000 IU of LMWH per day from day 3, which was suspended 24 hours before being resumed on day 5. Following consultation with the pulmonology department, a PET scan (Figure 5) was performed, which revealed an intensely hypermetabolic nodule in the left lower lobe, associated with ipsilateral hilar adenomegaly and extensive mediastinal adenomegaly in the right and left subclavian regions. LMWH was also discontinued twenty-four (24) hours before bronchoscopy with endobronchial aspiration. The pathological analysis concluded that the patient had lung adenocarcinoma. Six (6) hours after bronchoscopy, five (5) days after his first vascular event, the patient was found to have dysphagia, dysphonia and central facial diplegia. Cerebral MRI (Figure 6) revealed a slight increase in subacute right superficial sylvian ischaemia and the onset of left pre-Rolandic ischaemia. A nasogastric tube was inserted and HBPM 12,000 IU was administered on day 5 after his first event.

In terms of progression, the pseudobulbar syndrome was complicated by inhalation pneumonia, and amoxicillin-clavulanic acid 1200 mg/8 hours was administered. After an interdisciplinary consultation between a neurologist and a pulmonologist, no antitumour treatment was indicated given the patient's altered general condition, but rather palliative treatment. The patient died ten (10) days later from multiple organ failure.

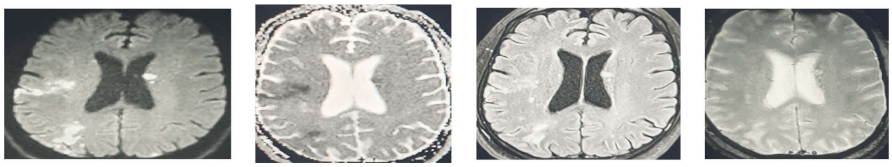

Figure 4. Subacute bilateral cerebral ischaemia.

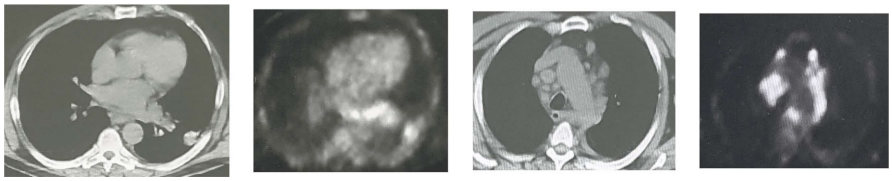

Figure 5. Intensely hypermetabolic nodule in the left lower lobe, ipsilateral hilar adenomegaly, right and left mediastinal adenomegaly.

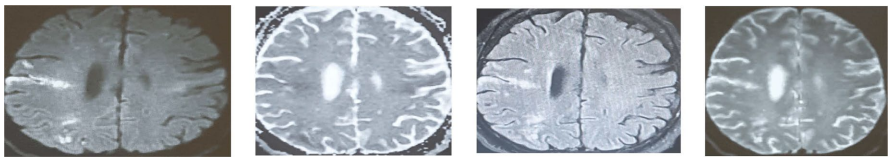

Figure 6. Increase in right superficial sylvian subacute ischaemia, and appearance of left pre-Rolandic ischaemia.

3. Discussion

Ischemic stroke as the first manifestation of cancer is extremely rare (Chi et al., 2020). Tumour embolisms, although rare, may be an underestimated source of cryptogenic stroke in cancer patients (Baker et al., 2024).

Arterial thromboembolism is a less common complication of cancer than venous thromboembolism. However, the risk of arterial thromboembolism is particularly high in patients with lung or kidney cancer (Brenner et al., 2018; Grilz et al., 2018). Approximately 6% of patients with cryptogenic ischaemic stroke are diagnosed with cancer within one year of the event (Leentjens et al., 2023). The median time between ischaemic stroke and cancer diagnosis is variable and can be up to 14 months (Selvik et al., 2015).

There are many reasons for the increased short-term risk of thromboembolic complications during cancer. Cancer and cardiovascular disease share several risk factors, including age, smoking and obesity. In addition, cancer can induce a state of hypercoagulability. Finally, invasive procedures and thrombocytopenia, which are common in cancer patients, sometimes require the interruption of preventive antithrombotic treatments (Dardiotis et al., 2019; Gomes & Khorana, 2014).

Certain anticancer treatments, such as sunitinib and sorafenib, are associated with a significant increase in the risk of arterial thromboembolic events (Choueiri et al., 2010). Thromboembolic complications should be diagnosed early in patients with high-risk lung adenocarcinoma, as they are a marker of poor prognosis (Jin et al., 2022). In lung cancer, the occurrence of thromboembolic complications is associated with longer hospital stays, higher mortality, increased treatment costs and greater disability upon discharge (Steuer et al., 2015). Some data in the literature report up to a fourfold increase in mortality risk in lung cancer patients with thromboembolic complications (Grilz et al., 2018).

Several indicators of occult tumours during ischaemic stroke have been described in the literature. A significantly elevated D-dimer level is the most common tumour marker found in stroke patients and is a factor associated with poor prognosis (Kim et al., 2012; Nezu et al., 2018). Elevated D-dimer levels associated with multiple ischaemic infarcts may be a good indicator of occult cancer in patients with cryptogenic stroke and warrants further investigation (Gon et al., 2017; Guo et al., 2020). However, the optimal threshold for the reliability of D-dimers in identifying cancer remains to be determined (Mai et al., 2015; Wang et al., 2018).

According to Kassubek et al. (2017), the combination of significantly elevated C-reactive protein, relative granulocytosis and elevated serum lactate dehydrogenase has a sensitivity of 75% and a specificity of 95% for predicting a tumour aetiology in patients with ischaemic stroke. Similarly, Selvik et al. (2018) showed that a clinical score incorporating elevated D-dimers ≥ 3 mg/L, haemoglobin ≤ 12.0 g/dL and current or previous smoking could predict the presence of active cancer in patients with ischaemic stroke.

Elevated high-sensitivity troponin T (hsTnT) levels in patients with ischaemic

stroke are associated with poor prognosis and may extend beyond myocardial damage related to neurological stress. Our data suggest that, in the oncological context, this elevation reflects a state of systemic hypercoagulability characterised by diffuse arterial microthrombosis. The high prevalence of cancers, including occult cancers, in patients with elevated hsTnT, associated with the presence of NETosis markers and myocardial and cerebral microthrombosis, supports the hypothesis of a common thrombo-inflammatory mechanism linking stroke, myocardial damage and cancer (Thålin et al., 2016).

To date, there is no validated diagnostic score that can reliably identify cancer during an ischaemic stroke. C-reactive protein (CRP) appears to be an independent factor in mortality after an ischaemic stroke, with prognostic performance comparable to that of the NIHSS score (Ghabaee et al., 2014). A fibrinogen level above 600 mg/dL could also be a relevant indicator of occult cancer in patients who have suffered an ischaemic stroke (Cocho et al., 2015).

Intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA) in acute cerebral ischaemia associated with malignant tumours is feasible, and the presence of active cancer should not be considered an absolute contraindication (Graber et al., 2012). The rates of recanalisation and complications associated with intravenous thrombolysis, with or without associated malignant tumours, are comparable (Xie et al., 2024).

Treatment with mechanical thrombectomy also appears to be beneficial in patients with ischaemic stroke and concomitant malignant tumours, both in the short and long term (Włodarczyk et al., 2024). In addition to acute recanalisation, long-term anticoagulation is frequently initiated as part of secondary prevention of cancer-associated ischaemic stroke.

Patients received treatment combining an anticoagulant and a platelet antiaggregant. The clinical justification for this dual therapy is based on the high thrombotic risk associated with cancer-induced hypercoagulability, combined with the prevention of cerebral arterial recurrence, although this strategy must be evaluated on a case-by-case basis due to the risk of haemorrhage.

Low molecular weight heparins (LMWHs) are generally preferred to vitamin K antagonists (VKAs) in cancer patients (Lee et al., 2003). Direct oral anticoagulants may be an alternative, but remain contraindicated in certain gastrointestinal malignancies. Although LMWHs are considered the standard treatment for cancer-associated thromboembolic complications, their use is not systematically recommended. In the absence of a clear indication for anticoagulation, the net benefit of anticoagulation compared to aspirin has not been clearly demonstrated (Aloizou et al., 2023; Lyman et al., 2013).

4. Conclusion

This case study is based on limited data, but it highlights that the combination of an ischaemic stroke and pulmonary embolism is an exceptional way of revealing lung adenocarcinoma. The simultaneous occurrence of these two events, recog-

nised as independent factors for poor prognosis, is associated with a significant increase in the risk of mortality.

Our observations highlight the value of certain biological markers, particularly elevated D-dimer and troponin levels, as indicators of a tumour aetiology in patients with ischaemic stroke, especially when multiple ischaemic lesions are present.

Although the management of cancer-associated ischaemic stroke is not yet clearly codified, anticoagulation remains a major therapeutic pillar in the prevention of thromboembolic recurrence, with a privileged place for low molecular weight heparins. Nevertheless, despite these strategies, the prognosis remains poor, highlighting the need to develop more targeted diagnostic and therapeutic approaches in this high-risk population.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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