VIA MEDICA

CASE REPORT

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Multifocal ischaemic brain stroke as a clinical manifestation of the Trousseau syndrome in a patient with lung adenocarcinoma

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ABSTRACT

Lung adenocarcinoma is the most common of all the histological lung cancer types, while Trousseau syndrome is the second leading cause of death — apart from the cancer itself — among affected people in this group. Based on the presented case and literature review, the authors discuss the current guidelines related to the diagnosis, as well as primary and secondary prevention of ischaemic stroke, and the treatment of acute stroke in cancer patients.

Keywords: ischaemic stroke, adenocarcinoma, thrombosis, neoplasm metastasis, anticoagulants, heparin, low-molecular-weight

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Introduction

The Trousseau syndrome (TS) is a state of increased blood coagulation in cancer illness. It has a sudden onset, often shortly after the neoplasm or its metastasis is diagnosed [1]. Patients with mucin-secreting tumours (e.g. ovary cancer, stomach cancer, glioma, lung or pancreatic adenocarcinoma are particularly affected [2].

It was first described in 1865 by Armand Trousseau, who died of stomach cancer with concomitant hypercoagulopathy, in line with the symptoms he had noticed himself in his patients. In 1977, G.H. Sack identified the mechanism of strokes linked with mucin-positive tumours. Currently, the syndrome is defined by many terms related to thrombotic events before cancer diagnosis or during oncological illness, and the multiplicity of definitions is a result of the multiple mechanisms that trigger overcoagulation.

This paper aims to highlight the importance of an in-depth diagnostic process in the differentiation of potential reasons for neurological dysfunction; to underline the necessity of a holistic and individualized patient approach during therapy; and to present a rare case of multifocal stroke that occurred shortly after cancer diagnosis.

Case description

Due to exacerbating vision problems, a 68-year-old male patient had been transferred from the Centre of Oncology to the Neurology Department of the Antoni Jurasz Clinical Hospital no. 1 in Bydgoszcz. The patient had adenocarcinoma in his right lung (T2 N3 M0 IIIB according to the 8th edition of TNM) and had been treated for one month using chemotherapy (one cycle; cisplatin + pemetrexed). Moreover, he confirmed the patient history gathered previously in other facilities: arterial hypertension, hypercholesterolemia and hyperuricemia, as well as abdominal pain.

The neurological exam confirmed cortical visual impairment in both eyes, hemiparesis on the left side and pyramidal signs on the right side. His cognitive abilities were ranked as “moderate” (MMSE-21).

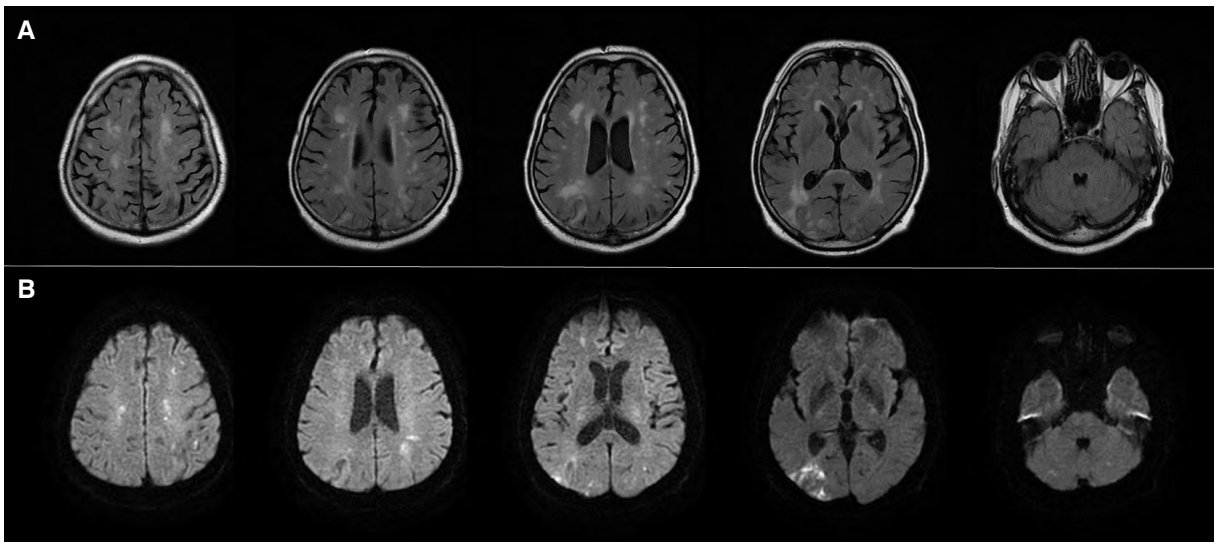

Figure 1. (A — FLAIR; B — DWI). Numerous diffuse hyperintensive lesions and striae, some with restricted diffusion (recent ischaemia). The largest area of restriction is clearly visible in the right occipital area. Many lesions and bands of enhancement are visible along cortical gyri; several similar enhancement bands are visible in both hemispheres of the cerebellum

Deviations: elevated d-dimer (19458 ng/mL), troponin (55.33 ng/L) and fibrinogen (581 mg/dL). The above parameters were controlled within a few days. Elevated CRP on admission (86.16 mg/L), without clinical signs of infection and elevated white blood cell count probably caused by the cancer illness. During hospitalization, there was an additional increase of lab results related to inflammation, associated with the inflammatory response on the left forearm (after the IV catheter). Empirical antibiotic therapy was administered with a positive clinical result.

Head CT performed at another facility described recent ischaemic lesions in the right occipital area with partial reperfusion. Additionally, a small patch of ischaemia was observed in the left occipital lobe. Initially, in order to prevent further ischaemic events, the patient received ASA and atorvastatin.

MRI (Fig 1.) confirmed the observed changes and allowed us to recognize that only some ischaemic lesions were recent. The ventricular system was slightly enlarged. Moreover, the MRI revealed lesions that were identified as possible cancer metastases to the L1 vertebral body.

ECG showed a left-axis deviation. ECHO test and Holter ECG were normal.

Due to the patient complaining of pain, abdominal and pelvic CT was ordered, which revealed swollen lymph nodes in the retroperitoneal space, the mesentery and the hepatic hilum. The image suggested meta lesions in the liver, a left kidney infarction (disturbed perfusion including the capsule), as well as characteristics typical of the median arcuate ligament syndrome in the diaphragm. Moreover, a hypocontrast region visible in the central part of the right femoral artery (6 mm) suggested the presence of a blood clot, and hypocontrast regions in the arteries VIII and IX in the left lung lobes revealed signs of pulmonary embolism. Therefore, the ASA treatment was replaced with low molecular weight heparin in the recommended doses (*Clexane* 80 mg/0.8 mL (100 mg/mL); 0.8 mL 2/day).

Ultrasonography of the carotid arteries revealed numerous, but haemodynamically insignificant, atherosclerotic plaques. Due to the above-mentioned abnormal coagulation protein levels and the preoccupying CT results, the diagnostic process was extended by ordering ultrasonography of the lower extremities. The exam revealed thrombosis in the left popliteal vein.

After stabilizing the patient, a subtle remission of neurological symptoms was observed. The man, in good general condition, was discharged from the hospital and referred to an oncological clinic in order to continue his treatment.

Discussion

Lung adenocarcinoma is the most common of all the histological lung cancer types and corresponds to about 40% of lung cancers [3] while TS is the second most frequent cause of death — apart from the cancer itself — in this group of cancer patients [4]. This shows the necessity to continue research on the

pathophysiological basis of this disorder, in order to develop more efficient prevention methods to avoid its dangerous manifestations and to improve patients' quality of life.

TS has a diversified pathogenesis. The mechanism leading to its development that is most frequently mentioned in literature is the induction of excessive secretion of mucins — the glycoproteins produced by the epithelium. Mucins enter into interaction with the P and L selectins, aggregating platelets into white clots, and also — with the help of sialic acid radicals — they activate factor X directly. Another mechanism is the increased secretion of the tissue factor that participates in the cysteine proteinase and exogenous coagulation pathway, activating factor X. The tissue factor also increases in case of tumour hypoxia, together with the plasminogen activator inhibitor-1, by inducing the MET oncogene expression.

States of increased coagulability can lead to potentially life-threatening complications like deep vein thrombosis or pulmonary embolism, in the venous system, and promote clot formation, in arterial vessels, which can lead to strokes and infractions. However, doctors also must remain sensitive to less obvious manifestations of mentioned disorders such as cerebral venous thrombosis, which is rare, commonly associated more often with young women using oral contraception rather than oncological patients and occurs with a prevalence of 0.3% in patients with malignancy [5].

Carcinoma entails a hypercoagulative state — Trousseau syndrome, but clinicians should be aware of a multitude of causes of cancer-related strokes. Studies describe procoagulant factors like major vessel compression by cancer tumours, especially arteries of the head and neck, intratumoral bleeding characteristic for intracranial tumours and metastases or dural vessel rupture due to dural metastasis [6]. There are known cases of cancer-mediated non-bacterial thrombotic endocarditis, in which the sterile left heart's valvular vegetations embolize distal vessels and cause stroke [7].

Furthermore, it has to be considered that hypercoagulability can be the result of adverse events accompanying anti-cancer treatment. There are several described reports of pembrolizumab (a humanised monoclonal antibody that is used to improve prognosis in non-small cell lung cancers by blocking PD-1 protein — a molecule produced by neoplastic cells to inhibit T-lymphocytes and diminish their response [8]) causing immune-related adverse events increasing the risk of thrombosis, such as antiphospholipid syndrome [9]. There are also studies which proved a significantly higher risk of venous thromboembolism while using cisplatin [10] and isolated descriptions of pemetrexed leading to thrombotic complications in the form of thrombocytopenic thrombotic purpura [11]. Another form of treatment — radiotherapy, can cause vasculopathy during cancers of the head and neck treatment by accelerating inflammation and atherosclerosis throughout NF-κB factor induction [12]. Radiation ionises water molecules and produces free radicals, which disrupt redox regulation inhibiting the NF-κB factor and allowing it to involve expression of cytokines and chemokines. Oncological surgery is fraught with risk of perioperative stroke [13]. Also, some aspects of a patient's hospitalization, namely motionless or infections accompanying long periods of cancer treatment determine a hypercoagulability state [14]. As seen in the examples above finding the source of hypercoagulability requires a complex analysis of potential risk factors and in many cases, discontinuing or replacing a harmful drug is crucial for further treatment.

Regardless of the procoagulation mechanism, tumour-related stroke has characteristic clinical features and a reproducible radiological appearance. There is a specific radiological sign, not pathognomonic but strongly connected to malignancy called a Three-Territory Sign (TTS) observed in MRI-DWI. To recognize the symptom there are needed lesions involving three arterial territories [15], which are: the left and right anterior circulation areas and posterior circulation area. TTS was recognised in the study patient (Fig. 1B). The Presence of TTS jointly with elevated D-dimers in the blood (up to 550 ng/mL) [6] allows us to make certain diagnoses about the close relationship between stroke and cancer.

Besides, patients with an acute ischaemic stroke, mainly with undetermined stroke aetiology, and CRP greater than 20 mg/L or fibrinogen greater than 600 mg/dL should be examined for occult malignancy. Laboratory markers drawing attention to cancer-associated ischaemic stroke characterized by hyperlipidaemia, increased levels of D-dimer, CRP, fibrinogen and low levels of haemoglobin and albumin.

Other clinical factors suggesting TS in ischaemic stroke are age over 65 years, weight loss, smoking history, subfebrile condition/fever, blood in the sputum or lack of typical acute ischaemic stroke risk factors, for example, diabetes and hypercholesterolemia. Also, ischaemic stroke characteristics such as higher initial NIHSS score, acute multiple cerebral infarctions and occurrence of venous thromboembolism or pulmonary embolism are specific for active cancer. When it comes to TOAST classification, cryptogenic stroke and large artery atherosclerosis subtypes may raise suspicions of a cancerous process.

Certain clinical situations suggest the presence of cancer, such as multiple haemorrhagic foci, especially those surrounded by finger-like swelling, or the location of the haemorrhagic focus unusual for hypertension. Also, sinus thrombosis, higher age, smoking, oestrogen use, heredity, sun exposure, male sex and absence of headache should be suspected TS which is necessary for further therapy.

Stroke patients younger than 75 years are good candidates for cancer screening if they have got D-dimer equal to 3 mg/L or greater, Hb equal to 12.0 g/dL or less and a positive smoking history — one point assigned for each factor. The probability of active cancer was 13% and 53% consecutively for 2 and 3-scored patients when assuming cancer prevalence is calculated to be 5% [16].

Further, a retrospective study, estimated the risk of active cancer consisted of increased serum levels of D-dimer, fibrinogen and the lack of hyperlipidaemia history. One point is given for no history of hyperlipidaemia, another one for a D-dimer level greater than 2.00 μg/mL and the last one for fibrinogen greater than 4.00 g/L. In patients with ischaemic stroke and the clinical total score equal to 3 the probability of active cancer was 59%, but 27% with a total score equal to 2. Moreover, that system was significantly superior to the previous one [17].

Another 4-item-score used the levels of (a) white blood cells greater than 9,600/μL, (b) platelets count greater than 400,000/μL, and (c) d-dimers equal and greater than 3 mg/L, which were independently associated with cancer diagnosis within 1 year after stroke. Also, the occurrence of (d) "ischaemic lesions in equal and greater than 2 vascular territories not attributed to cardioembolic stroke" was associated with the risk of cancer diagnosis after stroke in univariable but not in multivariable analysis. To estimate the risk give 1 or 0 points for each one from (a) to (d). The score sum over and equal to 2 was associated with a sensitivity of 43% and specificity of 92% for diagnosis of cancer within 1 year after stroke [18].

Despite the relatively high frequency of TS, as of now, there are not many uniform treatment protocols; and due to the scarcity of research in this area, there is still a lack of consensus as to whether an anticoagulant or antiplatelet therapy should be administered in specific cases [19].

The routine medication to prevent recurrent ischaemic events is the antiplatelet treatment with the use of ASA on its own (SAPT) or ASA together with another antiplatelet drug (DAPT). In spite of the potential benefits that can be obtained thanks to the DAPT treatment, the guidelines of the American Heart Association/American Stroke Association recommend it only for short-term therapies in selected cases. The recommendations are based on studies that suggested that long-term DAPT use correlated with a higher risk of haemorrhages while having the same efficiency as SAPT [20].

The treatment of thrombotic complications such as pulmonary thrombosis or deep vein thrombosis is, of course, based on a wide spectrum of anticoagulants. Until today, physicians rarely make use of Unfractionated Heparin [4], which refers to a mixture of sulphated polyanionic polysaccharides with acidic pH. It works by attaching to the molecules of antithrombin III, thrombin and the active factor X, leading to the deactivation of the latter two. It also binds with L and P selectins, blocking them against binding with other molecules. It is a useful mechanism for anticoagulant treatment in mucin-positive cancer patients because it makes it impossible for mucins to attach to blood platelets and prevents their aggregation into white clots. Moreover, it leads to the release of a higher amount of the tissue factor pathway inhibitor (TFPI), which significantly reduces the prothrombotic effects of the tumour.

Nonetheless, as of today, low-molecular-weight heparin (LMWH) remains the first-line drug and the highest-class recommendation, the golden standard in the treatment of vein thrombosis, independently of its aetiology [21]. Unlike its predecessor, it only inhibits the activity of factor X, but it does not release the tissue factor inhibitor, while its polymer molecules are too short to be able to block the L and P selectins. As a result, its activity is much easier to predict (there is no need to control the therapy with regular APTT monitoring) and safer due to a lesser risk of heparin-induced thrombocytopenia (HIT). Research shows that low-molecular-weight heparin, within the first three months of therapy, significantly reduces mortality, without a noticeable increase of bleeding risk [22]. It can be used both in initial therapy, as well as in long-term treatment, in which case its efficiency is higher than warfarin. The use of fondaparinux is limited, among others due to the lack of specific antidote and its long half-life. That is why it is applicable almost exclusively in initial anticoagulation to prevent the recurrence of venous thromboembolism [23].

In times of the CARAVAGGIO trial, the use of new oral anticoagulants (DOAC) has gained popularity, and they can also be used for TS prevention. They do not require INR monitoring, which is the case, among others, with vitamin K antagonists. Additionally, rivaroxaban and apixaban, at reduced doses, can be used in people with severe chronic renal failure, contrary to low-molecular-weight heparin [24]. Rivaroxaban, according to the randomized SELECT-D trial, in a half-a-year perspective,

is a more efficient drug than dalteparin (4% of thrombosis relapse vs. 11%), but it causes bleeding more often (6% vs. 4%), especially in patients with oesophageal or stomach cancer [25]. The statistics are similar in the case of edoxaban, where bleeding occurs more often (6.9% vs. 4%), but the recurrence of thrombosis is less frequent (3.6% vs. 6.7%) [26]. Research is underway to compare the activity of apixaban and dalteparin [27]. As to dabigatran, there is not enough information comparing its efficacy to heparin. The results of the CANVAS trial show that DOACs are non-inferior to LMWH for preventing recurrent VTE in adults with cancer [28] over a 6-month follow-up. Although the CANVAS trial cannot prove the superiority of DOAC due to its limitations.

Considering that TS combines both a higher risk of stroke recurrence, as well as a higher risk of thrombosis, the choice of adequate pharmacotherapy is very difficult. In the case described herein, the detection of VTE (both DVT and PE) was the decisive factor for initiating treatment with LMWH. However, it must be borne in mind that TS patients, due to long-term oncological therapy, can develop thrombosis after they have been admitted to the hospital. Therefore, these patients need to be treated with extreme caution.

It also must be considered that, despite everything, heparin does increase the risk of the stroke becoming haemorrhagic again. What is more, cancers that cause TS are often metastatic, so there is a hypothetical possibility of metastatic brain tumours becoming haemorrhagic [29].

However, there are more and more analyses indicating that this direction of development is promising, because the risk of intracranial bleeding in this kind of patient grows only slightly, while the risk of new thrombotic events is significantly reduced [30]. Nonetheless, we still lack conclusive, globally universal criteria for cancer-related coagulopathies. For this reason, it is necessary to continue research in this field.

Conclusions

Doctors should be particularly vigilant towards oncological patients and their anticoagulant protection and explain carefully to patients the principles of anticoagulant prophylaxis and the possible consequences of neglecting it. As far as specific guidelines for the treatment of TS are concerned, it can be expected that in the coming years, DOACs will officially gain an equivalent rank to LMWH, and the decision-making process to implement therapy may be shortened.

Article information

Ethics statement: *The patient's data were fully anonymised and presented in a manner that prevents the patient from being recognized. The authors of the following article also obtained consent from the Bioethics Committee for publication. The number of consent is KB 70/2024.*
Author contributions: *Each author of the following article has made a substantial effort to design the study, write the manuscript, review the literature, and analyse the patient's medical records. Particularly, the abstract was written by Andrzej Kędracki, the introduction by Andrzej Felski, the case presentation by Andrzej Kędracki, the discussion and conclusions by Andrzej Felski, Andrzej Kędracki, Pola Altmajer. All authors took part in the literature review. All authors also read and accepted the final version of the article. Due to the fact, that all authors were students, the following study was patronised by PhD Beata Kukulska-Pawluczuk from Neurological Clinic in Antoni Jurasz University Hospital No. 1 in Bydgoszcz.*
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