Critical Reviews in Oncology / Hematology 157 (2021) 103181

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

European school of Oncology – Review

Ischemic stroke: A paradoxical manifestation of cancer

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ARTICLE INFO

Keywords:
Stroke
Cancer
Prognosis
Risk factors
Mortality
Hypercoagulability (MeSH)

ABSTRACT

Introduction: Approximately 5–10 % of the patients with cryptogenic stroke have an underlying malignancy. Stroke as a complication of cancer increases the morbidity and mortality among cancer patients, leading to increased disability and healthcare costs.
Objective: To provide elements to guide physicians for when to suspect and evaluate for cancer in stroke patients.
Development: We performed a narrative review, portrayed in a question-answer format, to report relevant aspects of cancer stroke patients in the clinical practice and provide a guide based on the state-of-the-art literature. Conventional stroke mechanisms are only found in a fraction of patients with cancer. Although cardiovascular risk factors play an important role in both cancer and stroke pathogenesis, the recognition of more specific cancer-associated risk factors raises clinical suspicion for occult malignancy. We also expose the main type location and histology of tumors that are most commonly associated with stroke as well as potential blood biomarkers and current treatment considerations in the scenario of cancer associated stroke.
Conclusion: Subjects with active cancer are a patient population at increased risk for developing an ischemic stroke. Cryptogenic stroke patients have a higher risk of cancer diagnosis in the following 6–12 months. We recommend a multidisciplinary approach considering the high probability of a hidden malignancy and running a comprehensive evaluation including neurologic imaging, serological biomarkers and tight follow up.

1. Introduction

Stroke is a heterogeneous pathologic process that results in acute neurologic injury. Cancer is one of the many risk factors associated to it. Globally, both stroke and cancer, represent a significant public health burden. In the specific case of Colombia, both are leading causes of death, stroke in the second place and cancer occupying the third place (Stefan et al., 2009; Gobierno de colombia, 2018; Rodríguez-García et al., 2017). Concurrently, the incidence and prevalence of both entities appears to be increased among the aging population. Likewise, among patients with cancer, cerebrovascular disease is the second most common neurological manifestation following metastases (Zhang et al., 2006). Yet, this association is often disregarded in clinical practice. Stroke can occur at any point during malignancy and it can even be the first manifestation of an occult malignancy in up to 3% of patients (Uemura et al., 2010). Furthermore, autopsy findings of cancer patients reveal stroke in 15 % of cases; half of which are asymptomatic (Kim et al., 2010). Given that stroke can be a potential first sign of neoplasia (Uemura et al., 2010), it demands an accurate etiological diagnosis in order to gear therapy accordingly and improve clinical outcomes (Uemura et al., 2010; Kim et al., 2010). Prognosis, disability and health expenses are greater in patients with cancer and stroke compared with subjects without cancer (Dearborn et al., 2014). Therefore, it is important to search for occult malignancy in acute stroke patients (Uemura et al., 2010). The aim of the present review is to describe the clinical characteristics, risk factors, biomarkers and treatment approaches in patients with cryptogenic stroke associated with neoplasia. Additionally, we will provide physicians with some additional clues for

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https://doi.org/10.1016/j.critrevonc.2020.103181
Received 3 December 2019; Received in revised form 1 October 2020; Accepted 11 November 2020
Available online 16 November 2020

suspecting occult malignancy as the potential silent cause of cerebrovascular disease.

2. What are the possible scenarios in which cancer can be associated with ischemic stroke?

Currently, there is no consensus on how to identify cancer risk in acute stroke patients.

In the clinical practice, there are four situations in which cerebral ischemic disease could be associated with neoplasia: i. Subjects with recent cancer diagnosis who present with a stroke of unknown mechanism (cryptogenic stroke with active cancer), ii. A known cancer patient with a typical stroke etiology; iii. A stroke in a patient who had cancer but has now recovered (cryptogenic stroke with inactive cancer) and iv. A patient with an occult malignancy that manifests with a stroke; (cryptogenic stroke with unknown neoplasia) (Kneihsl et al., 2016). The first and second groups have been cataloged as the active cancer group. This represents a common clinical scenario. Usually these patients have been recently diagnosed (within the last 6–12 months) and underwent any type of cancer treatment and may or may not have local or distant recurrences (Kim et al., 2012; Lee et al., 2014). The patients in the inactive cancer group (group three); represent disease survivors. Commonly, their time since diagnosis is above 12 months (Kassubek et al., 2017; Guo et al., 2014). Finally, and probably the most frightening and challenging group corresponds to the cryptogenic stroke patients whose cancer is yet to be uncovered (Selvik et al., 2015). As the case depicted on Fig. 1 In this situation, the clinician's high level of suspicion and expertise drives the subsequent clinical conduct. Therefore, this latter group represents a real challenge, as it is not necessary to screen for cancer in every case of cryptogenic stroke since it isn't cost effective (Selvik et al., 2015). Consequently, it is primordial to limit the scenarios in which cancer should be considered as part of the differential diagnosis in patients with stroke of unknown etiology.

3. What is the relationship between cryptogenic stroke patients and cancer

A stroke of cryptogenic etiology is an ischemic stroke with no identified cause despite an exhaustive investigation (Dearborn et al., 2014; Saver, 2016). The underlying mechanisms are varied and categorized as embolic and non-embolic. Common causes of embolic stroke are cancer, occult paroxysmal atrial fibrillation, among others (Fig. 2) (Fonseca and Ferro, 2015). In the general population, the frequency of cryptogenic stroke is 20–40 % (Fonseca and Ferro, 2015; Bayona-Ortiz et al., 2017). However, an etiology is not found in up to 40–51 % of patients with cancer (Quintas et al., 2018; Gon et al., 2016; Navi et al., 2014). Strikingly, approximately 20 % of patients with stroke of undetermined cause could have an occult malignancy at the time of presentation (Selvik et al., 2018). Simultaneously, stroke has been described as the first manifestation of an unknown neoplasia in up to 3% of patients (Cocho et al., 2015). Therefore, patients who present with a cryptogenic stroke are at increased risk of having an occult malignancy. The pathogenesis of stroke seems to be different in subjects without neoplasia compared with cancer patients, but the evidence is controversial (Cocho et al., 2015; Grisold et al., 2009). Even though classic etiologies of stroke such as large artery disease and cardioembolic source are frequent among

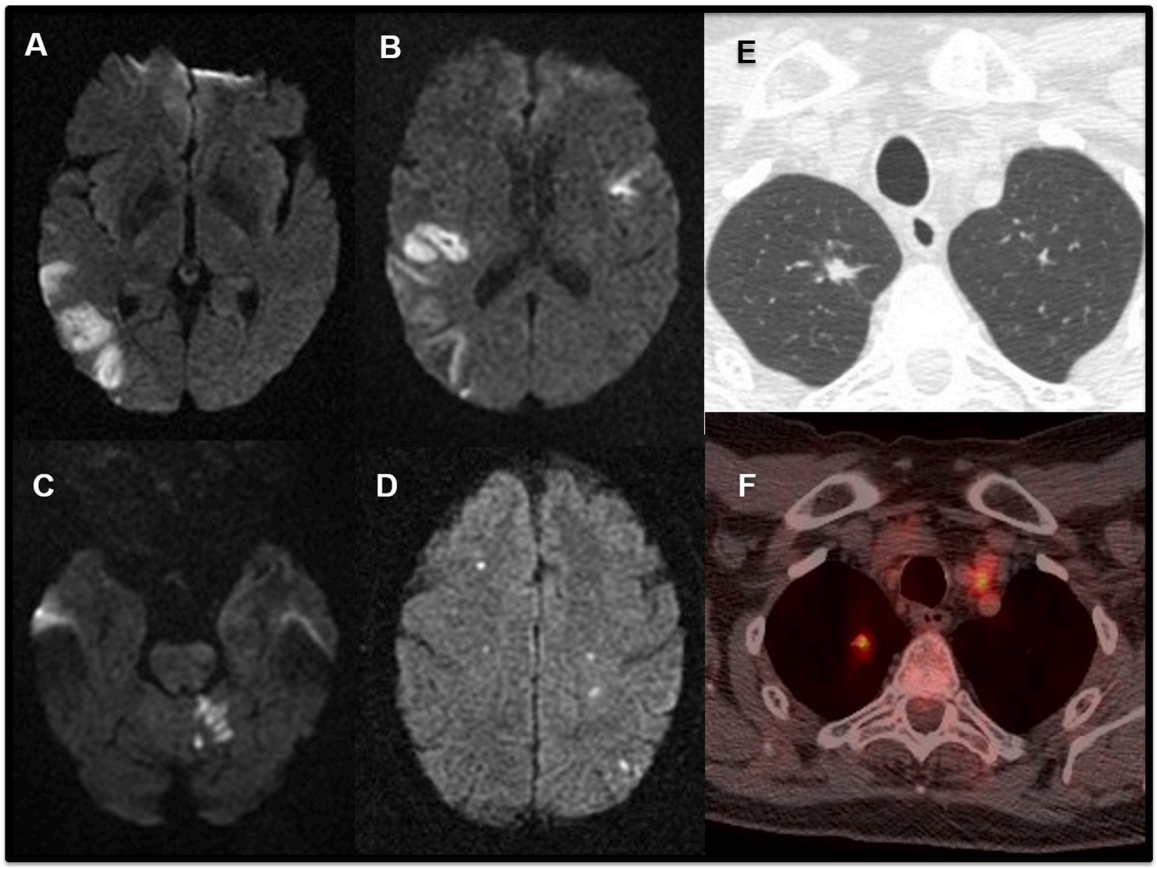

Fig. 1. Typical brain MRI of cancer-associated acute ischemic stroke.
A 60-year-old man who initially presented with left hemiparesis. Subsequently acute ischemic stroke was diagnosed. The brain DWI-MRI showed multiple infarct lesions in multiple vascular territories on bilateral hemispheres (A, B, C) and small-scattered lesions in the right and predominant in left hemisphere (D). At the same time, a chest-CT showed a pulmonary nodule and pulmonary embolism (E), after work-up a pulmonary adenocarcinoma was diagnosed 1 month later. The PET-CT (F) documented the right apical active nodule and mediastinum multiple ganglia.

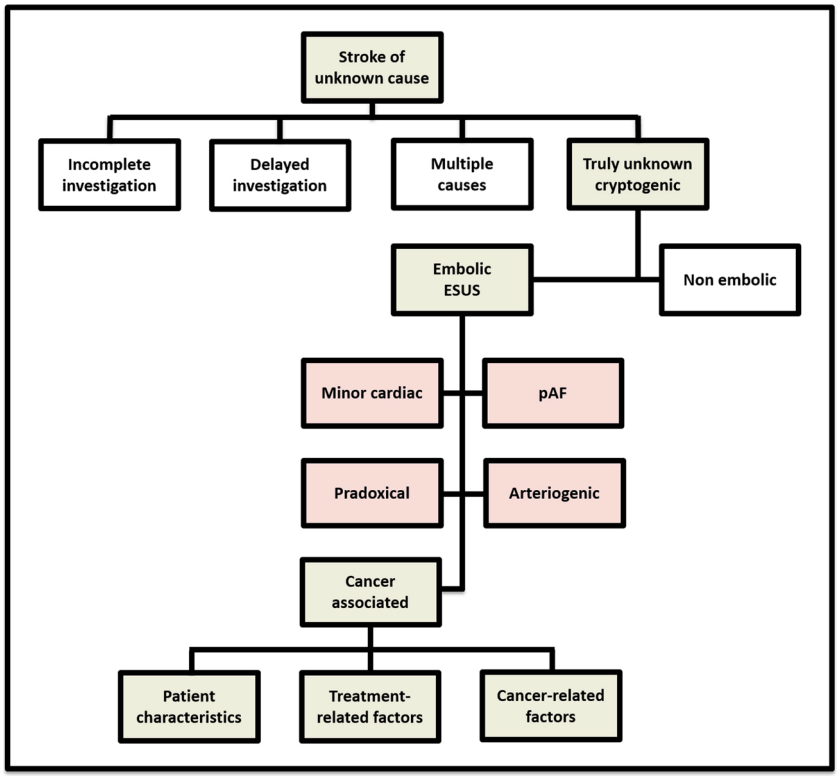

Fig. 2. Pathophysiology of cancer-associated thrombosis remains partially unknown. This figure illustrates the diagnostic sequence of a patient with stroke considering cancer as a possible etiology after ruling out other nosological entities. Finally, the pathogenesis and risk factors of cancer-associated thrombosis are presented into three categories: patient characteristics, treatment-related issues, and cancer-specific factors.

patients with malignancy, cryptogenic stroke is more frequent and has a stronger association with cancer (Dearborn et al., 2014; Cocho et al., 2015).

4. What kind of cancer associated risk factors play a role in stroke development?

Both cancer and cerebrovascular disease share a significant amount of risk factors. These are more common in the aging population and are burdened with vascular risk factors. Indeed, reports have showed that the prevalence of such vascular risk factors (hypertension & smoking, hyperlipidemia, diabetes mellitus, alcoholism, obesity, atrial fibrillation) is similar between cancer stroke patients and non-cancer stroke patients (Dearborn et al., 2014; Quintas et al., 2018; Selvik et al., 2014). Given the high prevalence and pathogenic effect of vascular risk factors, it is not surprising that these are still the most frequent cause of stroke, even among cancer population (Dearborn et al., 2014). On the same note, reports have demonstrated that the proportion of conventional stroke mechanisms (atherosclerotic, cardioembolic, lacunar) are approximately equal between patients with and without cancer (Dearborn et al., 2014). Additionally, some studies have demonstrated that atherosclerosis is the most common cause of ischemic stroke in patients with neoplasia (Kim and Lee, 2014). However, data is conflicting as other studies have established that on the contrary, conventional vascular risk factors were less relevant in ischemic stroke cancer patients (Shin et al., 2016).

The mechanisms of stroke in the context of cancer is not entirely elucidated. Since vascular risk factors are highly prevalent on stroke patients regardless of their cancer status, whether both diseases processes arise independently and simultaneously or if cancer has a direct influence on the pathophysiology of stroke is still unclear. (Fig. 3).

4.1. Coagulopathy

Hypercoagulability is regarded as the most significant mechanism of cryptogenic stroke in patients with cancer (Grazioli et al., 2018). It was first described by Trousseau in 1865 in the setting of gastric carcinoma and migratory thrombophlebitis. Tumor cells release pro-coagulant molecules, tissue factor and cancer procoagulant (a cysteine protease), that heightens the coagulation cascade. In addition, other cytokines are released such as TNF-alpha, IL-1 and IL-6 (Grisold et al., 2009). These molecules act as pro coagulants by: i). Inducing cells to express tissue factor, ii). Inhibiting Protein C activation and iii). Shedding vascular endothelial cells and therefore further thickening blood (Dearborn et al., 2014). It constitutes a paraneoplastic and yet poorly understood phenomenon that decreases survival in affected individuals (Schwarzbach et al., 2012; Lee et al., 2017).

Other coagulopathies, including disseminated intravascular coagulation (DIC) present more frequently in stroke patients with cancer (Dearborn et al., 2014). Several studies have tried to use laboratory markers to quantify coagulopathy. D-dimer is a marker of an activated coagulation system. Cancer stroke patients have higher D-dimer levels compared to patients with stroke and no cancer (Kim et al., 2010; Dearborn et al., 2014; Quintas et al., 2018; Schwarzbach et al., 2012; Lee et al., 2017). It is also an independent predictor for stroke of non-conventional mechanisms and is significantly associated to cancer in multiple studies (Kim et al., 2010; Álvarez-Pérez et al., 2012). Seok et al. found a higher prevalence of micro embolisms in transcranial doppler recordings of cancer stroke patients, predominantly in those with unconventional stroke mechanisms which correlated significantly with D-dimer levels (Seok et al., 2010). However, D-dimer is a non-specific marker, it can become elevated in numerous circumstances including cancer patients without stroke (Schwarzbach et al., 2012).

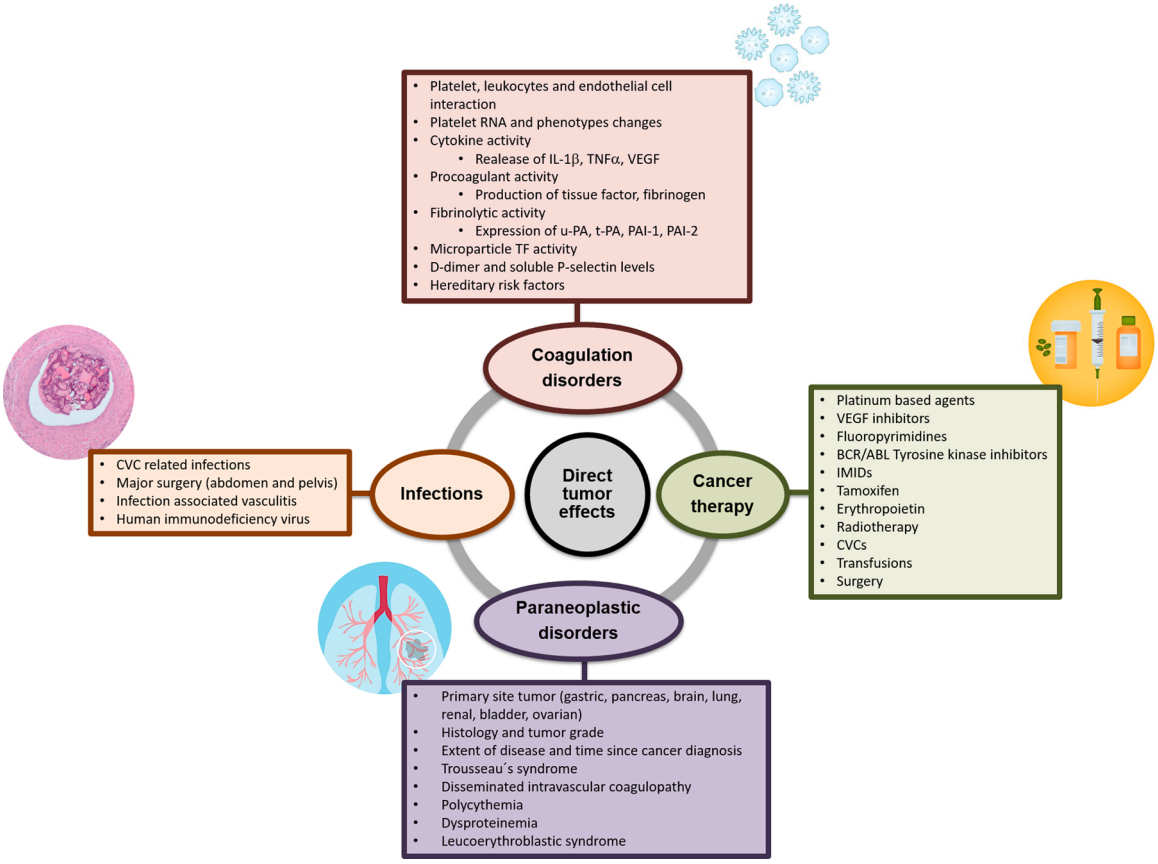

Fig. 3. Interaction of multiple factors involved in the pathogenesis of arterial thrombosis in cancer patients. IMIDs: immunomodulatory drugs; TKI: tyrosine kinase inhibitors; VEGF: vascular endothelial growth factor; TNF: tumor necrosis factor; u-PA: urokinase-type plasminogen activator; t-PA: tissue plasminogen activator; PAI-1 and 2: plasminogen activator inhibitor-1 and 2; TF: tissue factor; CVCs: central venous catheter; BCR/ABL: Philadelphia chromosome.

4.2. Cancer site and histologic subtype

Adenocarcinoma of the lung and adenocarcinomas of the gastrointestinal tract are the most common type of malignancies among cancer stroke patients across multiple cohorts (Kim et al., 2010; Dearborn et al., 2014; Navi et al., 2014). Adenocarcinomas are the most common histologic subtypes in stroke and cancer series (Dearborn et al., 2014; Quintas et al., 2018; Lee et al., 2017; Álvarez-Pérez et al., 2012). This is probably because they are frequently associated with clotting disorders via its production and secretion of mucin, a high molecular weight particle that interacts with cell adhesion molecules (P and L-selectins) and induces micro thrombi formation (Schwarzbach et al., 2012). Other common cancers in stroke cohorts are prostate, breast, bladder, gynecological cancer, pancreatic and melanoma (Dearborn et al., 2014; Quintas et al., 2018; Zhang et al., 2007; Navi et al., 2015). Hematological malignancies like non-Hodgkin lymphoma have also been reported (Quintas et al., 2018). Outstandingly, patients with smoking-related cancers have higher risk of stroke (lung, colon, bladder, rectum, pancreas, kidney, stomach, and head and neck) (Andersen and Olsen, 2018).

Additional but infrequent direct cancer mechanisms for stroke also include the occurrence of an embolism to the brain from heart tumors, hematologic malignancies like polycythemia vera's hyperviscosity syndrome and direct infiltration of vascular structures such as the case of intravascular lymphoma (Dearborn et al., 2014; Grisold et al., 2009).

4.3. Non-bacterial thrombotic endocarditis (NBTE)

In NBTE, sterile vegetations in the cardiac valves that are thought to develop due to valve attachment of disrupted fibrin that forms a matrix for platelets to bind. One of the most common targets for emboli due to NBTE is the cerebral circulation. NBTE is found as one of the most prevalent risk factors in cancer and stroke in studies (Navi et al., 2014; Sun et al., 2016). It is related with mucinous carcinomas mainly of pancreatic origin (Grisold et al., 2009).

4.4. Tumor mass effect

The tumor mass itself or its surrounding edema can cause direct compression of blood vessels in the brain, causing ischemia of the affected territory. This must be differenced from a hemorrhagic conversion of a brain metastasis leading instead to a hemorrhagic stroke. This phenomenon has also been described in primary brain neoplasia such as high-grade glioma and benign tumors like meningioma. Surgery of this type of tumors is related with perioperative stroke but the mechanism is not defined yet (Grisold et al., 2009).

4.5. Cancer treatment

Although not well characterized, long term, head and neck radiation therapy causes a medium-large vessel vasculopathy with similar findings to Moyamoya syndrome, were carotid arteries become stenosed and are associated with an abnormal meshwork of vessels and transdural anastomosis distally from the affected sections (Kuroda and Houkin, 2008; Cross and Glantz, 2003). Studies have found that head and neck radiation therapy significantly increase the risk of stroke; one analysis in particular described the rate of stroke as being 1.44 times higher in the radiation therapy group than in the reference cohort (Dearborn et al. (2014)). Numerous chemotherapy agents like methotrexate, cisplatin, L-asparaginase, estramustine, bevacizumab and hormone therapies have

been associated with increased risk of stroke in the context of thromboembolic events (Dearborn et al. (2014); Grisold et al., 2009). Bevacizumab (BVZ) and other antiangiogenetic therapies are associated with a higher risk of bleeding and risk of stroke. Treatment of recurrent glioblastoma multiform is based on the antagonism of Vascular Endothelial Growth Factor (VEGF) that is overexpressed in this kind of tumors. There are reports of ischemic stroke between 3.8%–7.5% and brain hemorrhage in 3.6 % up to 5% in patients treated with BVZ (Auer et al., 2017). Most of the ischemic strokes appeared in patients with longer treatments of antiangiogenic therapy (16.2 months vs 2.6 months in controls) and hemorrhagic stroke occurrences were mostly related with the disease progression and appeared earlier during the treatment (median, 2.6 months) (Fraum et al., 2011). In a recent meta-analysis of solid tumors with brain metastases and use of BVZ, there was no statistical evidence of increased risk for intracerebral hemorrhages (Yang et al., 2018) with an OR of 1.2 (CI 95 % 0.69–2.09) and $p = 0.53$ between BVZ arm vs the control group. Interestingly, BVZ can be used again as one of last resources in treatment of high grade gliomas, even in patients that had bled in the past, however, the rebleeding risk remains low in retrospective series (6%) (Lin et al., 2017).

5. Are there any biomarkers for occult malignancy in stroke patients?

Studies have demonstrated that older age, smoking history, prior cancer diagnosis, occurrence of venous thromboembolism, elevated CRP, ESR, D-dimer and fibrinogen values, decreased hemoglobin, and LDL values, can be predictors for an occult neoplasm in stroke patients (Uemura et al., 2010; Lee et al., 2014; Selvik et al., 2015; Quintas et al., 2018; Selvik et al., 2018, 2014; Grazioli et al., 2018; Álvarez-Pérez et al., 2012). The Norwegian Stroke Research Registry identified that active cancer was found in 5% of 1646 ischemic stroke patients. Increased D-dimer (OR = 1.1, 95 % CI: 1.1–1.2,), lower hemoglobin (OR = 0.6, 95 % CI: 0.5−0.7), smoking (OR = 2.2, 95 % CI: 1.2–4.3) and history of previous stroke of undetermined etiology (OR = 1.9, 95 % CI: 1.1–3.3) were independently associated with active cancer. With this information they calculated a predictive score that included elevated D-dimer (>3 mg/L), lower hemoglobin (<12.0 g/dL) and previous or current smoking. The area under the curve (AUC) of the predictive score was 0.73 in patients younger than 75 years. With a cancer prevalence of 5% among ischemic stroke patients, if a patient had a score of 3, their probability of active cancer would be of 53 % (Selvik et al., 2018). Another observational study identified that patients with both D-dimer ≥1.3 ng/dl and hemoglobin <12.8 g/dL more frequently had occult malignancy than patients without these clinical parameters ($p = 0.009$) (Fonseca and Ferro, 2015). Finally, a retrospective study performed in the Stroke Unite of the Hospital of Perugia Italy, identified that 4.4 % of the 2.209 patients with acute ischemic stroke had active cancer. Age >65 years (OR = 2.84, 95 % CI:1.12−7.19), LDL Cholesterol level >70 mg/dL (OR = 1.92, 95 % CI:1.06−3.47) and cryptogenic stroke subtype (OR = 1.93, 95 % CI:1.22−3.04) were independently associated with cancer. Furthermore, overall mortality rate during the hospital stay was greater in patients with active cancer (21.5 % vs. 10 % $p < 0.05$) (Grazioli et al., 2018).

Patients with ischemic stroke and active cancer have elevated inflammatory markers and hypercoagulability markers. A retrospective study that included 631 patients with ischemic stroke detected significantly higher levels of fibrinogen and CRP in patients with stroke of undetermined cause and occult malignancy. CRP > 20 mg/L had a sensitivity of 75 % and specificity of 96 % and fibrinogen levels > 600 mg/dL had a sensitivity of 67 % and specificity of 91 % for diagnosis of occult malignancy among ischemic stroke patients (Cocho et al., 2015). Another study identified an association between cancer-associated ischemic stroke and elevated D-dimer and fibrin degradation products event after controlling for hypertension, hyperlipidemia and advanced cancer (stage IV) (Kono et al., 2012).

Multiple studies have confirmed higher values of D-dimer in patients with cancer and stroke, regardless of etiology, comparing to those without cancer (Dearborn et al., 2014; Quintas et al., 2018). Additionally, D-dimer has been shown to be a marker of cancer induced hypercoagulability (Guo et al., 2014; Kono et al., 2012; Nezu et al., 2018). D-dimer also increases the risk of early recurrent events after an initial acute stroke (Nam et al., 2017a, b). Studies have shown correlation between micro embolic signal and D-dimer; this may suggest that anticoagulation has the potential to decrease cancer-induced hypercoagulability (Dearborn et al., 2014). Furthermore, this data suggests that D-dimer levels can be a marker to monitor the effect of anticoagulation therapy in these patients (Guo et al., 2014; Nezu et al., 2018; Nam et al., 2017a). However, controversy also exists on the value of these biomarkers for secondary stroke prevention since its levels are influenced by other confounding factors (i.e. age, cancer itself).

6. Can we suspect cancer in stroke patients based on the imaging findings?

The stroke pattern (multiple vs. single lesion), risk factors (NBTE (Gon et al., 2016), hypercoagulation, intravascular coagulation) and prognosis (higher mortality (Kneihsl et al., 2016), and longer stay) are different in the patients with cryptogenic stroke and active cancer (Schwarzbach et al., 2012). Radiological findings such as multiple acute cerebral infarcts and specific cancer-related stroke patterns on diffusion-weighted imaging (DWI) have also been suggested (Schwarzbach et al., 2015; Hong et al., 2009). The cancer-active group was associated with various DWI lesions in multiple vascular territories than the other groups, suggesting an embolic stroke mechanism. Notably, a multiple scattered lesion pattern which in some studies appears to be specific for patients with active cancer, was associated to higher D-dimer and CRP concentrations (Fig. 4) (Kim et al., 2012; Kim and Lee, 2014). Hence, active cancer patients who present with infarction in multiple vascular territories or focal lesions on MRI, indicating proximal embolism could have cancer-associated hypercoagulation as the underlying stroke mechanism.

7. Is there any temporal relationship between stroke and cancer?

A prospective cohort that followed 1282 patients with stroke during a mean of almost 27 months, 4.3 % of the patients were diagnosed with cancer with a time to diagnosis of 14 months (Selvik et al., 2015). In another longitudinal retrospective study, cancer diagnosis was made in 7.61 % of patients in an average of 6 months, with 44.8 % of diagnoses made within the first 6 months (Quintas et al., 2018). Nevertheless, in patients with occult malignancy, the risk of stroke was increased even one year prior to cancer diagnosis, (RR 1.75, 95 % CI: 1.14–1.75). For occult cancer, the risk of stroke increased as the time of cancer diagnosis approached. For non-occult cancer, it declined over time after diagnosis. This might reflect the effect of tumor load on the risk of stroke. The Surveillance, Epidemiology, and End Results (SEER) registry, a matched case-control study with almost 374,331 pairs of patients, showed that in the Medicare database - the arterial thromboembolic events progressively increased as the cancer diagnosis date approached, peaking during the 30 days immediately before cancer diagnosis, with 0,62 % events in the cancer group and 0,11 % in controls ($p < 0.001$) (Nezu et al., 2018). During the 360 day period, there were 0.78 % ischemic strokes diagnosed in cancer patients versus 0.49 % in cancer-free controls ($p < 0.001$).Remarkably, patients with cancer associated stroke and other thromboembolic events have usually reached metastatic disease by the time of their stroke presentation (Navi et al., 2014).

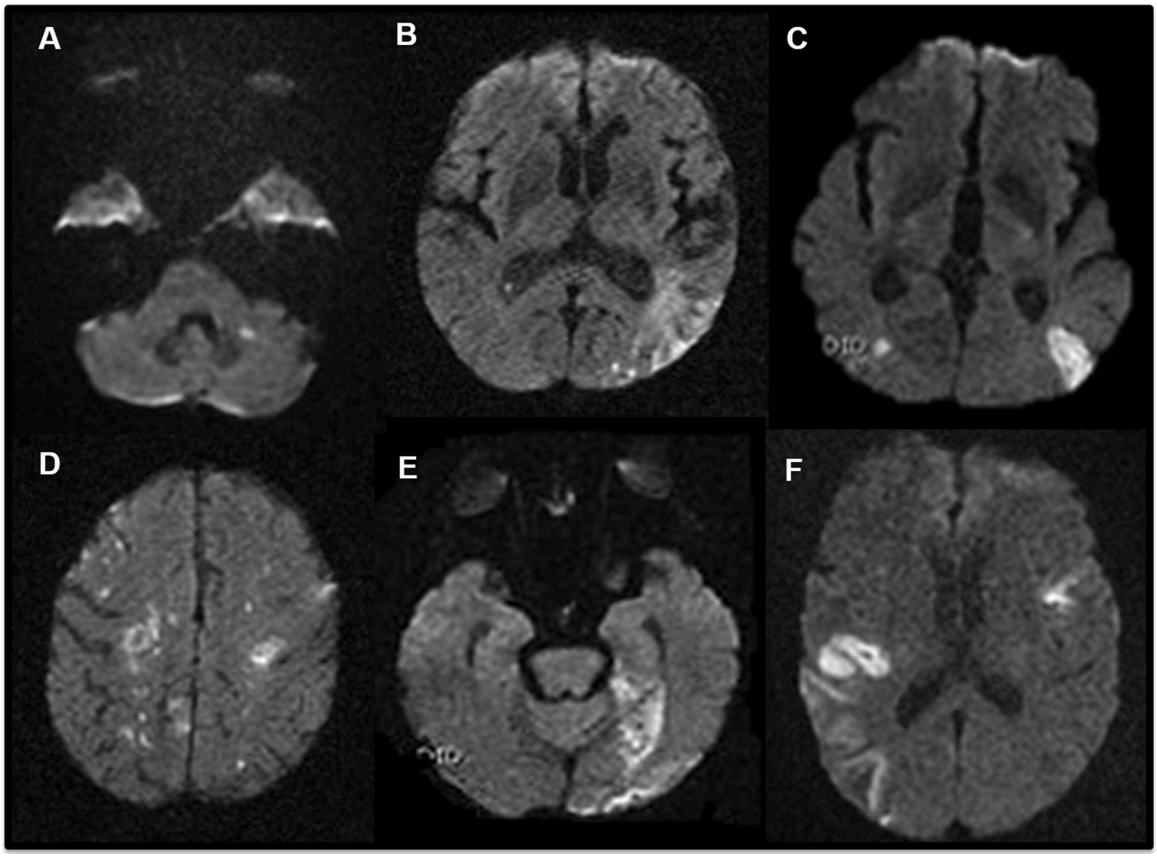

Fig. 4. Characterization of DWI lesion patterns according to number and localization.
A. Single acute lesion. B. Multiple acute lesions in one vascular territory with (micro-) embolic scattering of infarction. C. Multiple acute lesions in >1 vascular territory (bihemispheric anterior circulation lesions) without (micro-) embolic scattering of infarction. D. Multiple acute lesions in >1 vascular territory (bihemispheric anterior circulation lesions) with micro- embolic scattering of infarction. E–F. Multiple acute lesions in >1 vascular territory (anterior and posterior circulation lesions) with microembolic scattering of infarction

8. Is there any therapy to prevent a new stroke in active cancer patients?

Identification and management of stroke risk factors independent of cancer is still the priority (Dearborn et al., 2014). Controlling hypertension, hyperlipidemia, and diabetes, as well as encouraging life-style modifications including smoking cessation should be the mainstay of treatment, especially considering how cancer itself largely shares these conventional cardiovascular risk factors. Similarly, initiation of anticoagulation therapy remains standard upon the discovery of atrial fibrillation or proven hypercoagulable states, as these pathologies should still be considered as main thromboembolic mechanisms in patients with or without cancer. On the same note, patients without proven need for anticoagulation should be therefore initiated on antiplatelet therapy. However, there is not enough evidence to support the role of antiplatelet and or anticoagulation therapy in the secondary prevention of cancer related stroke (Dearborn et al., 2014).

Unfortunately, there are no clear guidelines regarding secondary stroke prevention and treatment in active cancer patients, nor it is addressed in existing stroke or cancer guidelines. Currently, most clinicians rely on extrapolated data of non-stroke studies i.e. prophylaxis for cancer associated venous thrombosis (Lee et al., 2003) and their clinical experience (Lyman et al., 2015). Despite the widespread descriptions of the hypercoagulable state of patients with cancer and the significant short-term risk of recurrence of ischemic stroke and other thromboembolic events, anticoagulation therapy recommendations for cancer associated strokes are controversial, as the risk of ischemic stroke recurrence is heavily weighted against the risk of hemorrhage (Navi et al., 2014).

Currently, there is no conclusive evidence regarding the benefits of anticoagulant therapy in cancer- associated stroke patients. A few studies directly assessed anticoagulation treatment in the context of stroke recurrence. A recent retrospective study by Jang et al. aimed to compare treatment with enoxaparin, a low molecular weight heparin, (n = 29) and warfarin (n = 50) for secondary prevention of cancer associated stroke. D-dimer levels were used as a biomarker for recurrent thromboembolic events. They suggested that treatment with LMWH may be more effective than warfarin for lowering the D-Dimer levels, and in theory, the risk of stroke recurrence in patients with cancer-associated stroke. However, the data is limited due to retrospective nature of the study, small sample size and the specificity of D-Dimer as a biomarker (Jang et al., 2015). Another study aimed to measure the effect of anticoagulation (LMWH, UH or warfarin) on micro-embolic signals of the middle cerebral artery -measured with transcranial doppler- in stroke patients with cancer; their findings suggested that embolic signals were more common in patients with high D-Dimer levels, and that anticoagulation therapy decreased D-Dimer (Seok et al., 2010). Additional larger studies are on their way; an ongoing randomized phase I/II clinical trial that will compare the effects of enoxaparin versus aspirin in patients with active cancer and recent first-ever acute ischemic stroke. It will assess primary safety (i.e. intracranial hemorrhage, major bleeding, death) and feasibility outcomes, and secondary efficacy outcomes (i.e. recurrent ischemic stroke, other thrombotic events, and functional outcomes) It is estimated to be completed by December 2019 (Navi et al., 2018).

Additionally, there is also no clear data on which should be the

anticoagulant therapy of choice, in consequence most clinical conducts rely on extrapolated data (Dearborn et al., 2014). The CLOT study established the use of dalteparin (a LMWH) in patients with cancer and acute venous thromboembolism. Patients treated with LMWH had lower recurrence events compared to those taking oral anticoagulants (Lee et al., 2003). Interestingly, large clinical trials have demonstrated that systemic anticoagulation increases the rate of hemorrhage in ischemic stroke patients (Wang et al., 2012; Berge et al., 2000; Investigators for the Trial of Org 10172 in Acute Stroke Treatment (TOAST), 1998). Yet, the efficacy or safety profile of anticoagulation therapies has not been studied specifically in the subgroup of cancer patients.

Although anticoagulation has also been proposed in NBTE in order to control the embolic phenomenon and prevent chronic disseminated intravascular coagulation, there are no studies that directly evaluate treatment approaches for other specific cancer induced stroke mechanisms.

In conclusion, developing a method for the selection of high-risk patients who may benefit from specific treatment seems to be the best approach. Large scale prospective studies are needed to build algorithms of risk-stratified prophylaxis in patients with active malignancy for the prevention of acute and recurrent strokes.

Finally, before considering any therapy, it is recommended to screen for cancer status, patient performance of the subject and establishing cancer prognosis, as these factors must be weighted accordingly when therapeutic approaches are discussed.

9. Are there predictors for outcomes in stroke and cancer subjects?

The clinical predictors of survival are poorly understood in stroke cancer patients. One study found no difference in prognosis between patients with and without unknown cancer. Although the same treatment was performed in both groups, there were no differences in functional outcome at 3 months (Quintas et al., 2018). In retrospective studies, the high D-dimer levels, systemic metastases and diabetes mellitus were identified as predictors of poor overall survival (Shin et al., 2016). D-dimer levels and initial NIHSS are good indicators for recurrence and early neurological deterioration (Nam et al., 2017b). In other publications, active cancer, stroke involvement of multiple vascular territories, high NIHSS at admission, and high PCR levels are independent predictors of early death (Kneihsl et al., 2016). Additionally, hemorrhagic transformation was found to be a predictor of poor outcome (Nam et al., 2017a). In patients with hypercoagulability, a decrease in D-dimer levels independently predicts odds for survival. This means that correction of hypercoagulation followed by decreasing levels of D-dimer could have a protective role and increase survival (Lee et al., 2017).

10. Is there a difference between the acute stroke treatment in cancer patients and patients without malignancies?

According to previous literature using data from the Nationwide Inpatient Sample (2009–2010), acute stroke treatment with thrombolytics or thrombectomy did not show an increase in mortality or ICH in patients with cancer. In this study (Murthy et al., 2013), around 800 patients were treated with thrombolysis (76 %) and thrombectomy (24 %). Specifically in cancer patients, the results in mortality for thrombolysis was 10.9 %, and 16.1 % for thrombectomy, when compared with non-cancer population, with a mortality of 8.5 % and 16.6 % respectively (Murthy et al., 2013). In a posterior study using data from National Inpatient Sample from years 2013−14, cancer patients treated with thrombolysis showed an increase in ICH OR = 1.6 (CI 95 % 1.17–2.17), but not in mortality OR = 1.24 (CI 95 % 0.88–1.76) (Weeda and Bohm, 2018). Although recent guidelines do not contraindicate the use of thrombolysis in patients with comorbid cancer, it is important to investigate and consider factors that might increase the odds for brain hemorrhage before treating this patients, including thrombocytopenia, coagulation factor deficiencies related with the type of cancer (i.e. leukemia) or with the therapy (i.e. chemotherapy), and coexistent brain metastases or recent surgery (Demaerschalk et al., 2016). In the last update of AHA/ASA stroke guidelines it was considered the use of rt-PA in comorbid cancer subjects with a life expectancy of at least 6 months, establishing a recommendation IIb, level C (Powers et al., 2019). Finally, stroke is a complication for high grade gliomas ≈ 0.1 % mostly during the post-operative period (Kamiya-Matsuoka et al., 2015), and for these intra-axial tumors lytic therapies are absolutely contraindicated (Powers et al., 2019) contrary to extra-axial lesions like meningiomas were the risk of ICH is really low.

11. Conclusion

Stroke and cancer are significant public health problems that share various epidemiological risk factors. These conditions represent a huge cost for healthcare systems and increased population disability rate. Early cancer identification in stroke survivors and extensive cardiovascular risk factor control is advocated as primary points in order to mitigate the burden generated from both diseases. Recognizing a “truly” cryptogenic stroke group facilitates the correct selection of stroke patients to screen for occult malignancy. There is a need for establishing clinical guidelines that include proper biomarkers and follow up algorithms to screen for cancer in stoke patients as well as for primary and secondary prevention of both diseases.

Funding

The present investigation has not received specific grants from agencies of the public sector, commercial sector or non-profit entities.

CRediT authorship contribution statement

Ruth A. Salazar-Camelo: Methodology, Writing - original draft. **Eder A. Moreno-Vargas:** Project administration, Writing - review & editing. **Andrés F. Cardona:** . **Hernán F. Bayona-Ortiz:** Conceptualization, Methodology, Writing - review & editing.

Declaration of Competing Interest

None to declare.

Acknowledgment

To Natalia Ramírez and Elisa Margarita Sánchez for the figure and graphic material preparation.

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