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REVIEW

Multiple cerebral infarction linked to underlying cancer: a review of Trousseau syndrome-related cerebral infarction

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Abstract

Trousseau syndrome is a cancer-associated hypercoagulative state leading to venous or arterial thromboembolic events. Cerebral infarction is the most common result of arterial embolism and the pathogenesis is complicated, mainly associated with hypercoagulation and non-bacterial thrombotic endocarditis. On magnetic resonance imaging, multiple lesions are dispersed in more than two territories of the brain, often simultaneously involving the bilateral anterior and posterior circulation. Elevated plasma levels of D-dimer and fibrinogen degradation products may be seen in these patients. There are high rates of short-term recurrence of stroke and sudden death, highlighting the need for early recognition and appropriate treatment of Trousseau syndrome-associated cerebral infarction.

Key words: Cancer; Cerebral infarction; Hypercoagulative state; Thromboembolic events; Trousseau syndrome

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Introduction

Trousseau syndrome was first defined as thrombophlebitis in the context of underlying cancer in 1865 (Trousseau, 1865). This definition was extended to various venous and arterial thromboembolic events associated with malignant tumours by Sack et al (1977), including venous thromboembolism, arterial thrombosis, non-bacterial thrombotic endocarditis and acute or chronic disseminated intravascular coagulation. Trousseau syndrome has become the second most common cause of death in patients with tumour (Khorana, 2010), secondary to death from the malignant tumour itself, so early recognition and appropriate treatment of Trousseau syndrome is essential.

Clinical characteristics

Trousseau syndrome is considered a response of the coagulation and fibrinolytic systems to a tumour. The appropriate degree of reaction may reduce or even prevent tumour metastasis, while overreaction may promote the proliferation of tumour cells, metastasis, angiogenesis in tumour tissue, and various thromboembolic events (Rickles and Edwards, 1983). The clinical manifestations of Trousseau syndrome include:

1. Venous thromboembolism, such as deep venous thrombosis or pulmonary embolism
2. Arterial thrombosis, such as acute cerebrovascular disease, myocardial infarction or extremity arterial occlusion
3. Non-bacterial thrombotic endocarditis
4. Acute or chronic disseminated intravascular coagulation.

The frequency of different types of cancer in patients with Trousseau syndrome presenting with ischaemic stroke is not well established. One study found that 21.2% of cases were gastric cancer, 16% were lung cancer, 14.1% were colorectal cancer, and 12.8% were hepatobiliary cancer, while the remaining 35.9% were other cancers, such as breast, pancreatic, cervical, renal or bladder cancer (Kim and Lee, 2014). Another study found that the most common cancers found in patients with Trousseau syndrome were lung, prostate, breast, colorectal, pancreatic, gastric and other cancers (Schwarzbach et al, 2012). In 2020, a study in China, that included 416 consecutive patients with cerebral infarction

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and malignant tumour, reported that the top 10 most common tumours in patients with Trousseau syndrome were lung cancer, oesophageal cancer, gastric cancer, breast cancer, liver cancer, colon cancer, rectal cancer, cervical cancer, intracranial cancer and pancreatic cancer (Ren et al, 2020). These inconsistent results may be a result of the different sample sizes, different incidence rates of various types of tumours in various regions, and different follow-up periods.

Cerebral infarction was the most common type of arterial embolism. An autopsy study on 3426 patients with tumours (excluding CNS tumours) found that approximately 7.5% patients had cerebral infarction, and almost half of the latter (45.7%) were symptomatic (Graus et al, 1985). The incidence of cerebral infarction in patients with a malignant tumour was 1.5 times higher than that in the general population (Chen et al, 2011). A study of 5106 patients with ischaemic stroke found that 24 patients (0.4%) had underlying malignancies (Taccone et al, 2008). Although only 0.4% of this population had malignant tumours, the proportion of cancer-related cerebral infarction was as high as 22% when the imaging features of cerebral infarction were seen in three or more cerebral vascular distribution areas. This study also concluded that, in the absence of an identifiable embolic source for ischaemic infarction, cancer-associated hypercoagulation accounts for 75% of cases (Finelli and Nouh, 2016). Similarly, a cohort study enrolling 348 patients with cryptogenic stroke showed that 20.4% patients had active cancer, and 10 additional patients (0.3%) were identified to have underlying malignancy after performing a comprehensive workup, in which all 10 patients showed elevated D-dimer levels and multiple infarcts involving multiple vascular territories (Kim et al, 2012). Bao et al's (2020) study, which included 31 patients identified as having cerebral infarction resulting from Trousseau syndrome, reported that 71% were admitted to the hospital for acute cerebral infarction and subsequently identified as having underlying malignancy during hospitalisation and 87.1% showed multiple lesions in multiple vascular territories. These studies suggested that cerebral infarction may precede cancer. Occult malignancies should be considered in patients with multiple cerebral infarctions, especially in those with elevated D-dimer levels, multiple lesions in multiple vascular territories, and absence of a clear embolus source.

Pathogenesis

The pathogenesis of Trousseau syndrome is unclear. It is thought to be related to non-bacterial thrombotic endocarditis and hypercoagulability.

Non-bacterial thrombotic endocarditis

Non-bacterial thrombotic endocarditis is considered the most common cause of cerebral infarction in patients with malignancy (Ojeda et al, 1985; Matsumoto et al, 2016). The vegetations in non-bacterial thrombotic endocarditis comprise fibrin thrombi, which could block intracranial arteries after shedding and lead to cerebral infarction. However, in these studies the thrombi were small and fragmented, while the detection rate was extremely low. The diagnosis rate on autopsy was approximately 32%, mostly seen in patients with mucinous adenocarcinoma. Transoesophageal echocardiography is effective in detecting heart vegetations and screening for non-bacterial thrombotic endocarditis, so clinicians should pay more attention to non-bacterial thrombotic endocarditis in patients with malignant tumours, especially those in a hypercoagulable state. Clinicians should perform transoesophageal echocardiography to increase the detection rate of non-bacterial thrombotic endocarditis and allow treatment to reduce the incidence of acute cerebral infarction in patients with tumour.

Hypercoagulability

The hypercoagulable state leads to the formation of microthrombi in the blood vessels. Approximately 90% of patients with malignant tumours have a hypercoagulable state (Spyropoulos et al, 2009).

The main mechanisms of hypercoagulability are activation of the coagulation system, reduction of anticoagulant activity and inhibition of the fibrinolytic system.

Activation of the coagulation system

Activation of the coagulation system involves increased expression and release of tissue factor, endothelial cell injury and increased secretion of cancer procoagulant. The endothelium does not express tissue factor under normal circumstances, but cancer cells produce inflammatory cytokines and angiogenic factors which induce the expression of tissue factor in vascular cells. Cancer cells can also induce monocytes or macrophages to release tissue factor. Tissue factor can directly induce conversion of coagulation factor VII to VIIa, activate the exogenous coagulation pathway, and initiate the coagulation cascade. The tissue factor level has been positively correlated with tumour stage, and patients with tumours with higher tissue factor levels are at greater risk of developing venous thromboembolism (Sthuri et al, 2009). Malignancies interact with vascular walls through the expression of GPIIB IIIA integrin (Adess et al, 2006), damaging the continuity of the vascular endothelium and activating coagulation factor XII to initiate the endogenous coagulation pathway.

Up to 85% of patients with cancer have elevated serum levels of cancer procoagulant. If vitamin K is present, cancer procoagulant directly promotes the conversion of factor X to factor Xa and can promote platelet aggregation and thrombi stabilisation (Shou and Cui, 2012).

Reduction of anticoagulant activity

The damaged vascular endothelium cannot produce antithrombin III, so antithrombin III levels in patients with malignant tumours are decreased. Tumour cells induce macrophages to produce cytokines, such as tumour necrosis factor-α and interleukin-1, which can influence the anticoagulant effect of the protein C system.

Inhibition of the fibrinolytic system

Plasminogen activator inhibitor-1 secreted by tumour cells can weaken the fibrinolytic system, resulting in a hypercoagulable state.

Risk factors

The risk factors for cancer-associated thrombosis (including cerebral infarction) are grouped into three categories (Ikushima et al, 2016):

1. Patient-related features, including older age, long-term immobility, elevated leukocyte and platelet counts, history of thrombosis, obesity, acute infections and heart disease
2. Treatment-related features, including anticancer agents, hormonal drugs, tamoxifen, growth factors and antiangiogenic agents that are known to increase the risk of thrombosis. Surgery and use of central venous catheters are treatment-associated mechanical causes
3. Cancer-related features, including primary site, cancer stage, compression or direct invasion of large vessels, mucin from adenocarcinoma and tissue factor expression.

Laboratory tests

Elevated plasma levels of D-dimer and fibrinogen degradation products may be observed in these patients. Kono et al (2012) showed that cancer-associated ischaemic stroke is associated with elevated D-dimer and fibrinogen degradation product levels even after controlling for several common risk factors of stroke and advanced cancer, which suggested that elevated D-dimer and fibrinogen degradation product levels may be independent risk factors for Trousseau syndrome-associated ischaemic stroke. Moreover, D-dimer levels were also significantly higher in the Trousseau syndrome-related ischaemic stroke group than the atrial fibrillation-related group, not only in the acute phase but also the subacute phase. Patients with Trousseau syndrome-related ischaemic stroke with D-dimer levels of >9.0 μg/ml had a higher probability of death within 90 days (Ito et al, 2018). A highly significant correlation between D-dimer levels and number of embolic signals detected by transcranial Doppler has been reported in patients with cancer-related stroke (Seok et al, 2010). Therefore, the D-dimer level may be a useful predictor of the prognosis of patients with Trousseau syndrome, and patients with higher D-dimer levels should receive total management for the prevention of recurrent stroke.

Magnetic resonance imaging of the brain

The magnetic resonance imaging pattern of Trousseau syndrome-related infarction is of multiple lesions in more than two vascular territories of the brain. Some cases often present with watershed infarction simultaneously involving the bilateral anterior and posterior circulation without stenosis of corresponding large vessels, with a few having a single lesion. As malignant tumour-related cerebral infarction is characterised by a high recurrence rate in the short term (Kwon et al, 2007), brain magnetic resonance imaging can simultaneously show cerebral infarction lesions in the acute, subacute and chronic stages. The most frequently involved areas are the cortex and subcortex, followed by the cerebellar hemisphere and corpus callosum; the deep brain structures and brainstem are rarely involved (Sun et al, 2016). Typical magnetic resonance imaging presentations are shown in Figure 1. In terms of imaging, these lesions need to be differentiated from cerebral metastases. In contrast-enhanced computed tomography and magnetic resonance imaging, most Trousseau syndrome-related cerebral infarction lesions are non-enhanced and non-circular, but some can show circular enhancement. These can be difficult to differentiate from cerebral metastases solely based on images. It is necessary to combine medical history, laboratory examination and response to treatment effect in this instance. Re-examining enhanced magnetic resonance imaging 1 month after treatment is recommended to make a correct diagnosis.

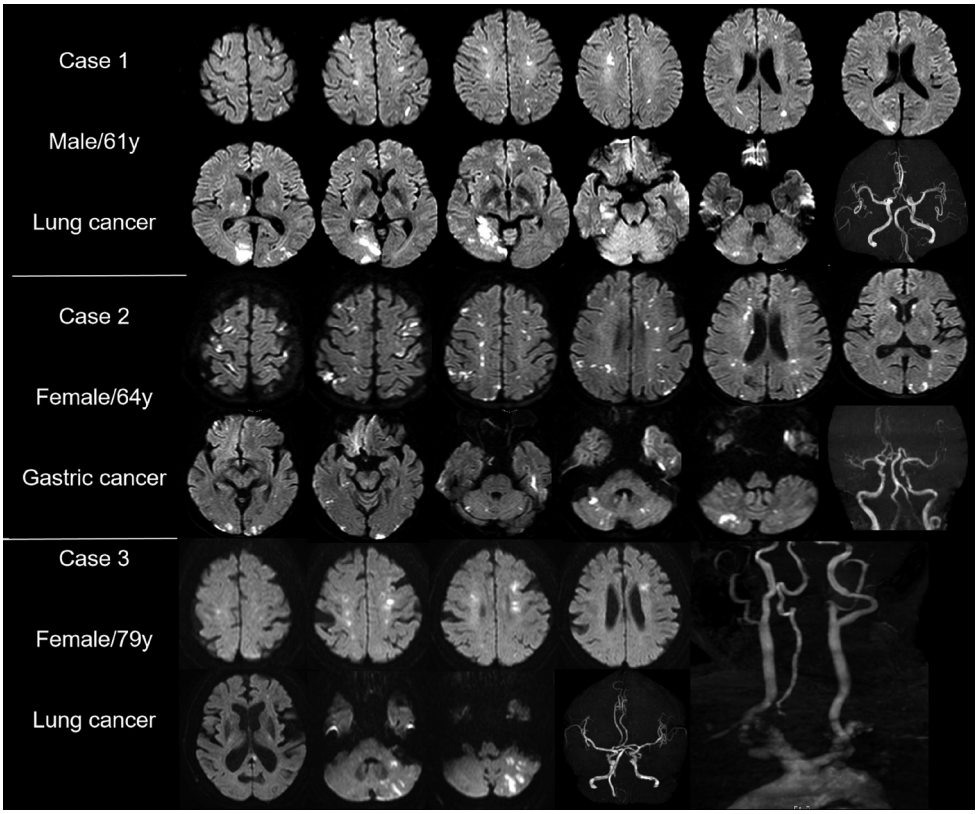

Figure 1. Magnetic resonance imaging pattern of cerebral infarction resulting from Trousseau syndrome. Case 1 was a 61-year-old man diagnosed with lung cancer. Multiple lesions were dispersed in the bilateral frontal lobes, parietal lobes, occipital lobes and cerebellum, as well as the right temporal lobe and right thalamus. Case 2 was a 64-year-old woman diagnosed with gastric cancer. Multiple lesions were dispersed in the bilateral frontal lobes, parietal lobes, occipital lobes and cerebellum, and the bilateral caudate nucleus was even involved. The lesions mostly presented with watershed infarctions. Case 3 was a 79-year-old woman diagnosed with lung cancer. Multiple lesions were dispersed in the bilateral frontal lobes, parietal lobes and the left cerebellum, and the corpus callosum was also involved.

Therapy

Ultra-early treatment

Intravenous thrombolysis is an effective treatment for ultra-early acute cerebral infarction, which can significantly improve the degree of disability of patients with stroke. Some studies support that intravenous thrombolytic therapy does not increase the risk of intracranial haemorrhage in patients with Trousseau syndrome-related cerebral infarction compared with those with general cerebral infarction. In patients who otherwise meet the criteria for thrombolytic therapy, intravenous alteplase can be considered. However, there are still conflicting studies. These patients may have a worsened outcome after intravenous alteplase (Nam et al, 2017). Studies showed that thrombolysis for acute Trousseau syndrome-related ischaemic stroke may be associated with a higher risk of intracranial haemorrhage, and the location of haemorrhage transformation in patients with Trousseau syndrome-related cerebral infarction is different from that of non-cancer-related cerebral infarction. The latter mostly occurs in infarction lesions or adjacent areas, while the former may also be located in brain areas away from the infarcted tissue, and there are often multiple haemorrhagic lesions (Ikeda et al, 2015). These issues require further investigation.

Secondary prevention

Given the high recurrence of stroke in the short term in patients with Trousseau syndrome-related cerebral infarction, appropriate secondary prevention must be started as soon as possible. Anticancer therapy for the causative tumour is important for preventing thromboembolic events, as it can improve the hypercoagulable state. D-dimer and fibrinogen degradation product levels correlate with the effect of anticancer therapy. Early initiation of an anticoagulant is the gold standard approach to prevent Trousseau syndrome-related thromboembolism events, with antiplatelet therapy believed to be ineffective. A meta-analysis showed that giving low molecular weight heparin led to a decrease in total mortality and lower incidence of haemorrhage compared to unfractionated heparin (Rocha et al, 2000). Moreover, low molecular weight heparin is recommended as the first-choice drug for both initial and long-term treatment of cancer-associated venous thromboembolism by two consensus guidelines (Lyman et al, 2015; Streiff et al, 2015). However, the treatment of Trousseau syndrome-associated stroke is complicated because of its various pathogeneses. Heparin has been used to treat non-bacterial thrombotic endocarditis, but there is no definite evidence of benefit, and Takasugi et al (2017) showed that tumour embolism is resistant to heparin administration. New oral anticoagulants, such as rivaroxaban, apixaban and dabigatran, are superior to warfarin in terms of easier administration and lower risk of bleeding, and there is no need to monitor international normalised ratios. New oral anticoagulants might be beneficial for the management of Trousseau syndrome-related thromboembolic events (Beyer-Westendorf et al, 2011), but there are insufficient data.

Prognosis

Trousseau syndrome has a poor prognosis. The mortality rate of Trousseau syndrome-related stroke is 25–30% compared with 14% of patients with stroke without cancer. Trousseau syndrome-related stroke has a short survival period – more than half of deaths occurred within 6 months of stroke (Zhang et al, 2007).

Conclusions

Clinicians need to pay more attention to Trousseau syndrome considering the high morbidity, recurrence rate, and mortality of Trousseau syndrome-related cerebral infarction. Occult malignancies should be considered in patients with multiple cerebral infarctions, especially those that lack a clear embolus source.

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Key points

- Cerebral infarction is the most common arterial embolism event resulting from Trousseau syndrome. It may be the first clinical manifestation of a potential malignancy and may occur before cancer.
- The pathogenesis of Trousseau syndrome-associated cerebral infarction is complicated, and is mainly associated with hypercoagulation and non-bacterial thrombotic endocarditis.
- The magnetic resonance imaging pattern show multiple lesions in more than two territories of the brain, which often simultaneously involve the bilateral anterior and posterior circulation.
- The efficacy and safety of intravenous thrombolysis for Trousseau syndrome-associated cerebral infarction needs further investigation.
- Anticancer and anticoagulant therapies are the main approaches to prevent Trousseau syndrome-related thromboembolism events, while antiplatelet therapy is thought to be ineffective.
- Trousseau syndrome-associated cerebral infarction has high rates of short-term recurrence of stroke and sudden death.
- Occult malignancies should be considered in patients with multiple cerebral infarction lesions without a clear embolus source.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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