2017 年 7 月 4 日　レビュー

Trousseau　syndrome

→　潜在性の悪性腫瘍の遠隔効果により神経症状を生じる傍腫瘍性
　　神経神経症候群（paraneoplastic neurologic syndrome）の一つ
　悪性腫瘍に伴う血液凝固亢進により脳梗塞を生じる病態
がん患者の剖検例では約 14.6%に脳血管障害の合併がある

（病態）

１）腫瘍自身による圧迫や閉塞
２）血小板や凝固機能異常を介した血管閉塞
３）化学療法や放射線療法など治療に合併する脳梗塞

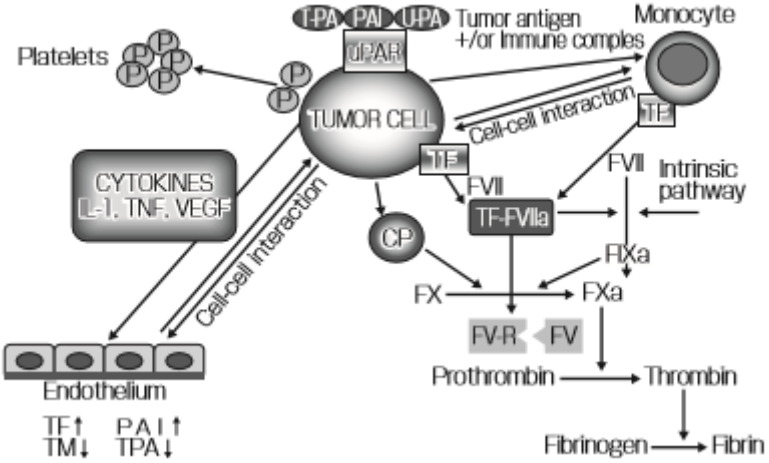
（特徴）

固形がんに多く、その中でも乳がんや子宮がんなどの
　婦人科的腫瘍が最も多い
次に多いのが、肺がん、消化器がん、腎臓がん、前立腺がん　など
皮質梗塞が多くみられる
血液凝固マーカーの亢進を認める

（原因）

・脳は、トロンボプラスチンが豊富で、トロンボモジュリンが乏しく、
　DIC の標的臓器になりやすい。
・DIC に併発した非細菌性心内膜炎による心原性脳梗塞
・深部静脈血栓症を併発した卵円孔開存による奇異性脳塞栓
・血管炎の合併
　（腫瘍関連性抗原抗体反応や血管内皮細胞と悪性腫瘍の共通抗原
　による交差反応）
・治療に伴う脳梗塞
　Cisplatin, Methotrexate, L^asparaginase, estramustine, Tamoxifen
　などが報告があるが、リスクは比較的低く、十分なエビデンスもない
・もちろん　PS　の低下
・その他（血管内凝固による微小血栓・塞栓、細菌性塞栓、腫瘍塞栓、
　脳静脈・静脈洞血栓症　など）

★　原因が多彩で混在していることが多い。



・腫瘍細胞は凝固カスケードを活性化する組織因子、腫瘍プロコアグラント、第 V 因子受容体受容体などの細胞性プロコアグラントや線溶タンパク、線溶インヒビターおよびそれらの受容体を発現するとともに、各種サイトカインや腫瘍抗原とその免疫複合体を介して血小板、単球、内皮細胞とその細胞間相互作用を引き起こしてさらに凝固活性化を促進し、血栓形成をもたらす。

★固形がんで過剰発現している組織因子は凝固カスケードを活性化するのみならず、がんの成長、血管新生、転移を促進する。

(labo data)

・フィブリノーゲンの低下や上昇（代償されている慢性の DIC)

・FDP, TAT, D ダイマー の上昇 （8 症例の検討、全例でみられる）

・β トロンボグロブリンと血小板第 IV 因子の上昇傾向

★血液凝固マーカーの上昇は、原因か結果かわからない。

(治療)

原疾患の治療 と 抗凝固療法

→ヘパリンが第一選択薬

長期化する場合には低分子ヘパリンやヘパリノイドの皮下注射

★低分子ヘパリンは抗血管新生作用があり、担がん動物モデルでアポトーシスを誘導することや、ヘパリンがインテグリン依存性の細胞接着を抑制して細胞間相互作用を抑制することによりがん転移を抑制するとの報告もある。

Best Practice & Research Clinical Haematology 22 (2009) 93–101

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

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

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Treatment of venous thromboembolism in cancer patients

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Keywords:
venous thromboembolism
deep vein thrombosis
pulmonary embolism
cancer
neoplasm
low-molecular-weight heparin
warfarin
antiocoagulants
vena cava filter
treatment

Venous thromboembolism (VTE) is a major cause of morbidity and mortality in patients with cancer. Monotherapy with low-molecular-weight heparin is the recommended first-line approach in cancer patients with newly diagnosed VTE, and is usually continued for a minimum of 3–6 months. Other management issues that require further research include optimal duration of anticoagulant therapy, treatment of recurrent VTE, the role of vena cava filters, the effects of VTE and its treatment on quality of life, and the impact of anticoagulants on survival. Newer anticoagulants hold promise in providing more effective and convenient treatment of VTE for this high-risk population, but further studies are awaited.

Table 1
Clinical trials of long-term anticoagulation for the prevention of recurrent venous thromboembolism (VTE) in cancer patients.

Study	No. of patients, *N*	Study treatments	Primary outcome, *n/N* (%)
			Recurrent VTE or major bleeding
Meyer et al (2002) [27]	146	Enoxaparin 1.5 mg/kg × 3 months	7/71 (9.9)
		Enoxaparin 1.5 mg/kg × 4 days + warfarin × 3 months	15/75 (20.0)
			Symptomatic, recurrent VTE
Lee et al (2003) [26]	676	Dalteparin 200 U/kg × 1 month then ~150 U/kg for 5 months	27/338 (8.0)
		Dalteparin 200 U/kg × 5 days + warfarin × 6 months	53/338 (15.7)
Deitcher et al (2006) [28]	91	Enoxaparin 1.0 mg/kg q12 h × 5 days then:	Recurrent VTE or symptomatic extension
		Enoxaparin 1.0 mg/kg × 3 months	1/29 (3.4)
		Enoxaparin 1.5 mg/kg × 3 months	1/32 (3.1)
		Warfarin × 3 months	2/30 (6.7)
			Recurrent VTE
Hull et al (2006) [29]	200	Tinzaparin 175 U/kg × 3 months	6/100 (6.0)
		UFH × 7 days + warfarin × 3 months	10/100 (10.0)

U, units; UFH, unfractionated heparin.

Practice points

- traditional therapy with warfarin or other VKAs are associated with a high risk of recurrent thrombosis and bleeding in cancer patients with VTE
- treatment with LMWH is the recommended first-line approach in cancer patients with newly diagnosed VTE
- treatment duration should be individualized based on the stage or extent of the cancer, risk of recurrent VTE, risk of serious bleeding, clinical status and personal preference of the patient
- evidence for the efficacy and safety of IVC filters is very limited, and they should not be used in patients who can receive anticoagulants
- frequent evaluation of patients is necessary to tailor therapy to indiviudal risks, needs and preference

High grade glioma と DVT

Thrombosis Research 137 (2016) 184–188

Contents lists available at ScienceDirect

Thrombosis Research

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

Full Length Article

Recurrent venous thromboembolism in glioblastoma

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ARTICLE INFO

Article history:
Received 14 July 2015
Received in revised form 17 November 2015
Accepted 19 November 2015
Available online 22 November 2015

Keywords:
Deep vein thrombosis
Cancer associated thrombosis
Glioblastoma multiforme
Pulmonary embolism
Venous thromboembolism

ABSTRACT

Background: Patients with glioblastoma (GBM) are at increased risk of initial and recurrent venous thromboembolism (VTE) but rates of recurrence and real-world treatment choices are incompletely understood.
Objectives: We aim to describe the treatment of incident VTE, report incidence and risk factors for recurrence.
Patients/methods: We conducted a retrospective cohort study of consecutive Cleveland Clinic patients with GBM presenting with objectively diagnosed deep vein thrombosis (DVT) or pulmonary embolism (PE) from 2007 to 2013 with at least 6-month follow-up. We collected information on patient demographics, VTE incidence, treatment and recurrence. Data were analyzed using multivariate logistic regression analysis.
Results: Of 450 patients with GBM, 145 (32.2%) developed VTE and comprised the study population. Of these, 11 (7.6%) experienced PE, 117 (80.7%) had DVT and 16 (11%) had DVT as well as PE. Fifty five (37.9%) VTE events occurred in the first 30 post-operative days and 56 (38.6%) during chemotherapy. Thirty one (21.4%) patients were untreated. Treatments included enoxaparin (N = 36, 24.8%), warfarin (15, 10.3%) or vena cava filters either alone (N = 39, 26.9%) or in combination with anticoagulation (N = 21, 14.5%). Recurrent VTE occurred in 39 patients (26.9%).In multivariate analysis, lack of long term anticoagulation (HR 11.2, CI 1.5–86.3, $p < 0.05$) and the presence of second primary malignancy (HR 3.69, CI 1.2–11.1, $p < 0.05$) were significantly associated with recurrent VTE.
Conclusion: VTE and recurrent VTE are highly prevalent throughout the disease course among patients with GBM. Long term anticoagulation is associated with reduced risk of recurrent VTE but is often not utilized.

Comparison between patients with and without recurrent VTE in the setting of GBM. VTE — venous thromboembolism, GBM — glioblastoma, VEGF — vascular endothelial growth factor, IVC — inferior vena cava.

	Recurrent VTE	No recurrent VTE	p-Value
N	39	106	–
Body mass index (mean)	28.6	29.7	0.226
Age (mean)	63.2	64.1	0.783
Gender			
Female	12 (30.8)	48 (45.3)	0.166
Blood group (N = 140)			0.06
A and AB	20	61	
B and O	19	40	
VTE prior to diagnosis of GBM	5 (12.8)	8 (7.5)	0.52
Use of VEGF inhibitors	9 (23.1)	26 (24.5)	0.77
Antecedent cancer	9 (23.1)	7 (6.6)	0.0012
IVC filter placement	20 (51.3)	40 (37.7)	0.20
Use of anticoagulation for index VTE	16 (41)	59 (55.7)	0.17
Lifelong anticoagulation	1 (2.6)	26 (24.5)	0.005

2007 年から 6 年間　クリーブランド病院で GBM 患者の検討

450 症例中 145 症例（32.2%）で VTE、11 症例(7.6%)が PE

39 症例(29.6%)が repeat VTE/PE

37.9%が術後 1 か月以内　38.6%が chemo 中

Venous Thromboembolism in Patients with High-Grade Glioma

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Semin Thromb Hemost 2016;42:877–883.

Abstract

Venous thromboembolism (VTE), incorporating both deep vein thrombosis and pulmonary embolism, is a common, morbid, and potentially fatal condition. Patients undergoing surgery are at increased risk of VTE due to many perioperative factors, and patients undergoing surgery for high-grade glioma (HGG) have been found to be at an even higher risk than general surgical patients. Chemical prophylaxis of VTE during the postneurosurgical period remains one of the major dilemmas in modern neurosurgical practice due to a potential increased risk of devastating intracranial hemorrhage in the setting of anticoagulation. In this review, we aim to summarize the prevalence of VTE in patients with HGG and discuss relevant risk factors for the development of VTE after surgery for this malignancy. We also review options for VTE prophylaxis in the postoperative period and discuss appropriate management of these complex patients.

Keywords

- neurosurgery
- VTE
- craniotomy
- high-grade glioma

なぜとりわけ high grade glioma に thromboembolism が多いのか？

Neuro-Oncology 14:iv73–iv80, 2012.
doi:10.1093/neuonc/nos197

Thromboembolic disease in patients with high-grade glioma

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Most patients with GBM tend to have reduced mobility or limb paresis.

Table 1. Risk factors for thromboembolic events in malignant glioma patients

Patient Factors
Age (especially >75)[4]
ABO bloodtype (A, AB)[13]
Prior deep vein thrombosis or pulmonary embolism
Leg paresis, prolonged immobility[2,6]
Multiple medical comorbidities
Obesity
Glioma-associated Factors
Tumor grade (high > low-grade glioma)[3,4]
Intraluminal thrombosis in surgical specimen[15]
Recurrent disease
Tumour size (>5 cm)[3,4]
Post-operative residual disease (biopsy>partial>gross total resection)[14]
Treatment-associated factors
Post-operative period
Chemotherapy[61]
VEGF targeted treatment[38]
Hormonal therapy
Venous access devices
Possible biomarkers
Thrombocytosis, anemia, leukocytosis[62–64]
Activated coagulation factors (D-dimers, thrombin-antithrombin complexes)[62]
Biomarkers to be evaluated further
Tissue Factor (antigen, activity levels, circulated microparticles)[31,32]
Molecular phenotype (EGFRviii overexpression, PTEN loss or mutation)

TF(thromboplastin)

principal initiator of coagulation

47kD transmembrane glycoprotein

long extracellular domain が Factor VIIa と interact

内皮障害時に TF-Factor VIIa binding が proteolytic cascade を activate する。これに引き続いて、Factor X と Thrombin generation が fibrin 沈着や血小板の activation を引き起こす。

VEGF の regulation も行っている

glioma で発現が確認され、high grade ほど発現が高い。

バイオマーカーとしての利用？？

バイオマーカー

診断、悪性度診断、再発の予測、治療効果の判定　などなど

参考文献

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その他引用したものは、本文中に記入しています