Original article

Cerebral venous thrombosis associated with extracranial tumours: a clinical series

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SUMMARY: Aim. *Cerebral Venous Thrombosis (CVT) may occur at the clinical onset of malignancies or complicate their course, even in a quiescent phase, and the literature contains several case reports linking the two diseases. However, thus far only one article has been written with the specific objective of reporting the characteristics of CVT in cancer patients. We therefore set out to analyse the clinical characteristics of CVT associated with extracranial tumours.*
Materials and Method. *We identified 9 cases of CVT in adults (> 15 years) affected by extracranial tumours seen in 6 hospitals from January 2004 to December 2009.*
Results. *The median age of patients was 40 years (range 24-75 years). Eight out of the 9 patients were female. Associated tumours were: lymphoma (4 patients); breast (2 patients), rhinopharyngeal (1 patient) and gastric (1 patient) carcinomas. One patient presented concurrent kidney tumour and melanoma. In the majority of patients (7/9), CVT onset was metachronous, while it was synchronous in the remainder. In all cases, diagnosis of CVT was based on cerebral angiography, CT venography or brain MRI/MR venography. Multiple sinuses were affected in 7 out of the 9 patients, and parenchymal lesions were also detected in 7 patients. In the acute phase, all patients were anticoagulated with unfractionated heparin (2 cases) or subcutaneous low-molecular-weight heparin (7 patients) at therapeutic doses. None went on to develop further haemorrhagic complications. At discharge, the patients presented a complete recovery in 4 of the 9 cases, mild sequelae in 4/9, and moderate sequelae in 1/9. At 6-month follow-up, 2 patients had died due to tumour progression, one patient presented arterial stroke, and one patient partial seizures.*
Conclusions. *In our cases, all female, the active phase of tumour and malignant haemolymphoproliferative diseases were associated with CVT. The anticoagulant therapy administered did not lead to an increased risk of haemorrhagic complications, and the patients' long-term prognoses were conditioned by the tumours themselves.*

KEY WORDS: *Cerebral venous thrombosis, Extracranial tumour, Outcome, Therapy.*

INTRODUCTION

Cerebral venous thrombosis may occur at the clinical onset of malignancies or complicate their course, even in a quiescent phase[11,19]. Raizer identified twenty cases of CVT (a prevalence of 0.3%) in a population

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LIST OF ACRONYMS AND ABBREVIATIONS: AE = Antiepileptic Therapy; AIRTUM = Associazione Italiana dei Registri TUMori; CT = Computed Tomography; CVT = Cerebral Venous Thrombosis; EFNS = European Federation of Neurological Societies; HM = Haematological Malignancies; ISCVT = International Study on Cerebral Vein and Dural Sinus Thrombosis; KPS = Karnofsky Performance Status; LMWH = Low-Molecular-Weight Heparin; MRI = Magnetic Resonance Imaging; mRS = Modified Rankin Scale; MSKCC = Memorial Sloan-Kettering Cancer Center; UFH = UnFractionated Heparin: SD = Standard Deviation: ST = Solid Tumours; SEER = Surveillance, Epidemiology and End Results.

of 7,029 cancer patients evaluated over about five years[17]. In a recent international multicenter study, which included 624 patients with symptomatic CVT, cancer represented a risk factor in 7.4% of these cases[8].

The literature contains several case reports linking cerebral venous thrombosis with malignancies[12]. However, thus far only one article has been written with the specific objective of reporting the characteristics of cerebral sinus thrombosis in cancer patients[17]. This collated data from the neurology database at the Memorial Sloan-Kettering Cancer Center on twenty cancer patients diagnosed with CVT between January 1994 and April 1998. Unlike our series, this sample also includes patients with intracranial neoplasms. Conversely, the other series documented in literature gathered data pertaining to cases of cerebral venous thrombosis in the general population[8], making it impossible to extrapolate the clinical and demographic features of CVT in the selected category of cancer patients.

Aim. Our objective was to analyse the clinical characteristics of CVT associated with extracranial tumours.

□ MATERIAL AND METHODS

We identified 9 cases of CVT in adults (> 15 years) affected by extracranial tumours seen in 6 local care provision institutions (6 from general hospitals, 2 from university hospitals and 1 from a research hospital) from January 2004 to December 2009 (Table 1). For inclusion, the diagnosis of CVT had to be confirmed by conventional angiography, CT venography, or brain MRI combined with MR venography.

The following information pertaining to these cases was reviewed in detail: demographic features; time span between symptom onset and hospital admission; evolution of symptoms and signs from onset to final diagnosis and follow-up; modified Rankin Scale score and Karnofsky performance status on admission and at discharge; imaging methods used; location of the thrombus; number, location, and size of any parenchymal lesion; associated tumour and disease staging; any other potential risk factors for cerebrovascular disease; type of CVT treatment; and follow-up at 6 months.

In the interests of clarity, the data collected is reported as percentages in both the text and the tables.

□ RESULTS

The median age was 40 years (range: 24-75 years), and 8 of the nine patients were female. In all cases, basal (pre-CVT) mRS was 0 and KPS 100%. The diagnosis of CVT was established by MRI/MR venography in 8 patients and intra-arterial angiography in one. The onset of CVT was acute in 4 patients, subacute in 4 patients, and in one case it was an accidental finding (imaging for the diagnosis of an arterial stroke). The clinical manifestations were: focal deficits (7/9), headache (6/9), seizures (4/9) and consciousness disorders (3/9). Isolated or associated headache was the most frequent clinical symptom at CVT onset (6 patients). The clinical features of all patients are shown in Table 2.

Associated tumours (all confirmed by histology) were: lymphoma (4 patients); and breast (2 patients), rhinopharyngeal (1 patient) and gastric (1 patient) carcinomas. One patient presented both a kidney tumour and a melanoma concurrently. In most of the patients (7/9), CVT onset was metachronous, while it was synchronous in the remainder. Malignancies were active in most cases (8/9). Associated risk factors detected were: chemotherapy in 4 patients, hyperhomocysteinaemia in 2; oral contraceptive in 2; factor V Leiden mutation in one and steroids in one[5,16]. In two patients malignancies represented the only risk factor for CVT.

Multiple sinuses were affected and MRI showed parenchymal lesions in 7 patients (only venous infarctions in 3 patients and satellite haemorrhages in 4). Parenchymal lesions were multiple in 3 patients. The sinuses involved are detailed in Table 3.

In the acute phase, all the patients were anticoagula-

Demographic and clinical data of our patients

Patients	*Sex*	*Age*	*Tumours*	*Other risk factors*	*Clinical onset of CVT*	*Clinical manifestations*	*Involved sinuses/veins*	*Parenchymal lesions*	*Therapy*	*Outcome at discharge*	*Outcome at 6 months*
ET	F	75	Breast carcinoma	Chemotherapy	Acute	Focal deficits, disorder of consciousness	Straight sinus, deep venous system	Yes	LMWH	mRS 2 KPS 60	Lost at follow up
LF	F	59	Gastric carcinoma	Steroids	Chance discovery	None	Lateral sinus, jugular vein	No	LMWH	mRS 0 KPS 100	Ischaemic stroke: mRS 3 KPS 50
BS	F	32	Lymphoma	None	Acute	Focal deficits, seizures	Superior sagittal sinus, lateral sinus	Yes	LMWH	mRS 0 KPS 90	mRS 6
SC	F	29	Lymphoma	Chemotherapy	Acute	Headache, focal deficits, seizures	Superior sagittal sinus	Yes	LMWH	mRS 0 KPS 100	mRS 0 KPS 100
RV	F	40	Breast carcinoma	Oral contraceptive, hyperhomo-cysteinaemia	Subacute	Headache, focal deficits	Straight sinus, deep venous system, lateral sinus	Yes	Unfractionated heparin	mRS 2 KPS 70	mRS 0 KPS 100
FP	F	24	Lymphoma	Chemotherapy, factor V Leiden mutation	Acute	Headache, focal deficits, seizures	Superior sagittal sinus	Yes	LMWH	mRS 1 KPS 100	mRS 1 KPS 100
BE	F	31	Lymphoma	Chemotherapy, oral contraceptive, MTHFR A1298C mutation	Subacute	Headache, focal deficits, seizures, disorder of consciousness	Superior sagittal sinus, lateral sinus	Yes	Unfractionated heparin	mRS 0 KPS 100	Seizures mRS 0 KPS 100
PAM	F	59	Kidney tumor and melanoma	Hyperhomo-cysteinaemia	Subacute	Headache, focal deficits	Superior sagittal sinus, straight sinus, lateral sinus	Yes	LMWH	mRS 1 KPS 100	mRS1 KPS 100
GC	M	61	Rhinopharyngeal carcinoma	None	Subacute	Headache, disorder of consciousness, ocular movement deficits	Cavernous sinus	No	LMWH	mRS 3 KPS 50	mRS 6

Table 1. Demographic and clinical data of our patients.

Clinical manifestations

Clinical manifestations	*Our patients (%)*	*Raizer's study*	*Masuhr's Review*
Headache	6 (*67%*)	40%	75-95%
Focal deficits	7 (*78%*)	20%	40-60%
Early seizures	4 (*44%*)	30%	35-50%
Consciousness disorders	3 (*33%*)	15%	15-19%

Table 2. Clinical manifestations.

Occluded cerebral sinuses and/or veins

Occluded sinuses/veins	*No. of Cases*	*%*
Superior sagittal sinus	5	56
Lateral sinus	5	56
Straight sinus	3	33
Deep venous system	2	22
Jugular veins	1	11
Cavernous sinus	1	11

Table 3. Occluded cerebral sinuses and/or veins.

Outcome at discharge			
	Our patients		***ISCVT****
	No. of Cases	***%***	***%***
Death	0	0	4.3
Modified Rankin Scale			
mRS 0	4	44	27.2
mRS 1	2	22	38.5
mRS 2	2	22	15.4
mRS 3	1	11	6.9
mRS 4	0	0	5.3
mRS 5	0	0	2.4
Karnofsky performance status			
100	5	56	--
90	1	11	--
70	1	11	--
60	1	11	--
50	1	11	--

Table 4. Outcome. *Legend*: * = International Study on Cerebral Vein and Dural Sinus Thrombosis. Data pertaining to all the cases[8].

Analysis of the two subgroups		
	HM (*4 Patients*)	***ST*** (*5 Patients*)
Median age	30 years	59 years
Female	4 (100%)	4 (80%)
Clinical manifestation		
- Headache	*3 (75%)*	*3 (60%)*
- Focal deficits	*4 (100%)*	*3 (60%)*
- Seizures	*4 (100%)*	*0 (0%)*
- Consciousness disorders	*1 (25%)*	*4 (40%)*
Thrombosis of cerebral deep venous system	0 (0%)	3 (60%)
Outcome at discharge		
- Median mRS	*0*	*2*
- Median KPS	*100*	*70*

Table 5. Analysis of the two subgroups: Haematological Malignancies (HM) and Solid Tumours (ST).

ted with unfractionated heparin (2 cases) or subcutaneous low-molecular-weight heparin (7 patients) at therapeutic doses. No patient went on to develop further haemorrhagic complications.

Additional treatments included analgesic drugs (3 patients) and antibiotic therapy (2 patients). Only half (2/4) of our patients with early seizures were prescribed prophylactic antiepileptic therapy.

Detailed information on outcome at discharge was available for all patients (Table 4). This showed a complete recovery (mRS 0) in 4 patients, mild sequelae (mRS 1-2) in 4 and moderate sequelae (mRS 3) in one. Median KPS was 100% and average KPS 86% (SD 20.1, range: 50-100%).

At 6-month follow-up, 2 patients had died due to tumour progression, one patient had suffered an arterial stroke, and one patient had developed partial seizures.

We divided the patients into two subgroups: those with haematological malignancies (HM, 4 patients) and those with solid tumours (ST, 5 patients), as shown in Table 5. Although the sample was small, some differences between the two sub-groups did emerge. In particular, the patients with HM were younger and developed focal deficits and seizures more frequently than the ST subgroup. The patients with ST had a more frequent involvement of the deep cerebral venous system and a worse prognosis in the short term.

□ DISCUSSION

Ferro's multicenter study reports data on CVT in the general population, and the data regarding their subgroup of cancer patients cannot therefore be extrapolated[8]. In the ISCVT, the median age was 37 years (range: 16-89), and 74.5% of the patients were female. These demographic features, pertaining to the general population, are similar to those describing our series of cancer patients and are those recently reported in the literature[2,8,14].

In Raizer's retrospective study at the MSKCC, New York[17], the median age of patients was 44.5 years (range: 10-71) with a prevalence of male gender (80% of the patients). It is nevertheless important to note that Raizer's study also included paediatric patients, who present a different gender prevalence for CVT.

In our series, 4 patients exhibited haematological malignancies and 5 solid tumours. This is similar to Raizer's sample: he found 9 patients (44.5%) with

HM and 11 patients (55.5%) with ST[17]. According to the AIRTUM (Italian Tumour Registry) Work Group[1], haematologic malignancies make up 9.5% of all the extracranial tumours registered in Italy. Similar data are reported for the US on the SEER website (http://seer.cancer.gov/). Judging by the higher prevalence of haematological tumours in both our series and that documented by Raizer with respect to the general cancer population, it may be possible to postulate an increased risk of CVT and haemolymphoproliferative disease[15].

Recent reviews of the literature report a frequency of focal signs of 40-60%, mainly related to the presence of parenchymal lesions[14]. In Ferro's multicenter prospective study, the greatest cumulative reported focal deficit was 65%[8], whereas in our patients the incidence of neurological focal signs was 78%. This difference may be due to a greater presence of parenchymal lesions in our series (78%) than in similar data reported in the general population (63% in the ISCVT). In contrast, Raizer reported a frequency of focal deficits of 20%[17], significantly lower than both our series and literature data.

Although in our patients headache was not the most frequent clinical manifestation in the course of the disease, as it is in the literature[5,14], it was the principal symptom of CVT onset (6/9 cases). As there is a strong correlation between early CVT diagnosis and favourable outcome (*quoad vitam and quoad valetudinem*)[8,9], headache should not be underestimated in cancer patients, even when brain CT scan is normal (as is the case in 30% of confirmed CVTs in the general population)[2]. Where there is cause for clinical doubt, brain MRI/MR venography should be performed.

In the literature, the incidence of early seizures is 35-50% of the cases[14]. Indeed, four patients (44%) in our series presented seizures, as did 30% of Raizer's patients[17]. In our cases, the seizures were associated with focal deficits and parenchymal lesions, seen by neuroimaging (cerebral CT or MRI), and thrombosis of superior sagittal sinus, as reported in the literature[7]. In the Portuguese series[9], late seizures occurred within the first year, and a visible haemorrhagic lesion in the acute imaging was the strongest predictor of post-acute seizures. In all series together, however, late seizures were more common in patients with early symptomatic seizures than in those patients with none[6,9]. In our series, one patient developed late partial seizures at 6-month follow-up. She had also presented early seizures over the course of her CVT, and the brain CT scan in the Emergency Room showed venous infarction with haemorrhagic lesions. Although we agree with the EFNS guideline suggestion that AE represents a "reasonable" therapeutic option - for up to one year - in patients with early seizures and haemorrhagic lesions on admission brain scan[6], the patient in question was not given any prophylactic antiepileptic therapy. Epilepsy in cancer patients is a major concern, mainly as regards indications to treatment, as well as the toxicity and pharmacokinetic and pharmacodynamic interactions of coadministered drugs[18,20].

The management of cerebral venous thrombosis associated with cancer is extrapolated from the treatment of CVT from all causes[11,19]. Anticoagulants with body-weight-adjusted subcutaneous low-molecular-weight heparin or unfractionated heparin are widely used as first-line therapy[2,6,8]. Anticoagulant therapy should also be used in patients with intraparenchymal haemorrhage[6].

In our series, the anticoagulant therapy did not affect the cytotoxic/cytostatic treatment, and was not associated with any further haemorrhagic complications. Hence, although ours is a small series of patients, and in spite of all the problems of potential haematological toxicity and interference with other drugs, our experience confirms the usefulness of anticoagulant therapy in the subgroup of patients with CVT associated with extracranial tumours[13].

A subgroup analysis of the ISCVT sample shows how malignancies did not represent a risk factor for mortality 30 days after CVT[4]. Our data yield similar results, as in our patients cancer did not influence the short-term outcome of CVT if diagnosed and treated early. It is impossible to draw a correlation between anticoagulant therapy and outcome at discharge in Raizer's study[17]. In fact, there were multiple types of treatment (no therapy, anticoagulant therapy, fresh-frozen plasma, cranial radiotherapy in metastatic infiltration) and the outcome of each therapy was not reported.

In ISCVT, malignancies represented a relevant risk factor for disability and death at long-term follow-up (hazard ratio for mortality and dependency 2.90, 95% CI 1.60-5.08)[4]. This result may be explained by the tumour progression, as confirmed in our series (two patients died within the first year as a consequence of their cancer). In Raizer's study too, in most cases the long-term negative outcome was due to malignancies and it was not a direct consequence of CVT[17].

Analysis of our data showed a significantly lower

median age in patients with HM (30 years) than in those with ST (59 years). This is also in line with Raizer's findings[17]. However, we also observed a poor outcome at discharge (evaluated by mRS and KPS) in patients with solid tumours, and a highly significant difference in seizure frequency between the two subgroups (100% in HM; 0% in ST).
The difference in short-term outcome may be explained by the fact that consciousness disorders and thrombosis of the deep venous system were more frequent in the ST group, whose median age was > 37 years. These are known as risk factors for poor prognosis of CVT in the general population[3,10].

□ CONCLUSION

In our cases, all female, the active tumour phase and malignant haemolymphoproliferative diseases were associated with CVT. Anticoagulant therapy did not increase the risk of haemorrhagic complications, and the patients' general long-term prognosis was only influenced by the cancer.

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