

**The Clot Thickens - a sinister combination of TIA and DVT**

Journal:	<i>Clinical Medicine</i>
Manuscript ID	CM-2016-0426
Manuscript Type:	Acute medical care
Keywords:	Cancer related stroke, TIA, Hypercoaguable state, Pancreatic cancer, DVT

SCHOLARONE™  
Manuscripts

View Only

## Abstract

We present the case of a 65-year-old man who presented with two transient ischaemic attacks (TIAs), a deep vein thrombosis (DVT), followed by recurrent ischaemic strokes. After a thorough investigation, the only cause identified was a previously undiagnosed metastatic pancreatic cancer. We describe the work-up and management of this presentation, and discuss the aetiology of cancer-related stroke and its management.

## Keywords

TIA, ischaemic stroke, pancreatic cancer, DVT, hypercoagulable state, cancer related stroke, anticoagulation

## Case Presentation

A 65 year old man presented to the accident and emergency department after the sudden onset of a “clumsy” right hand, during which he could not use a computer mouse for 45 minutes, followed by complete resolution. The day before, he noticed that he could not see the person sitting on his left during a meeting; this lasted for around 30 minutes and also fully resolved. Two weeks prior he had a swollen left calf which he had thought was “gout”. He had no cardiovascular risk factors, no past medical history and took no medications. He had not taken any long haul flights. Neurological and general examination was normal and he was consistently afebrile. ECG showed sinus rhythm. Full blood

1  
2  
3 count, electrolytes and clotting screen were normal but he had an ALT of 60 IU/L  
4  
5 and CRP 9 mg/L. Acute CT imaging of the brain and CT angiography of the  
6  
7 common carotid, vertebral and intracranial arteries were normal. A doppler  
8  
9 study of the left leg showed a deep vein thrombosis (DVT) in the popliteal vein.  
10  
11

## 12 13 14 15 **Diagnosis**

16  
17  
18  
19  
20 The initial clinical diagnosis was recurrent transient ischemic attack (TIA)  
21  
22 affecting two different cerebral vascular territories: the left homonymous  
23  
24 hemianopia localised to the right visual cortex (right posterior cerebral artery  
25  
26 territory); while the clumsy right hand localised to the left motor cortex (left  
27  
28 middle cerebral artery territory). He also had an unprovoked DVT. We  
29  
30 considered a cardioembolic aetiology for his TIAs, with the DVT as a potential  
31  
32 source (possibly causing paradoxical embolism) through a patent foramen ovale;  
33  
34 or a hypercoagulable state.  
35  
36  
37  
38  
39  
40  
41

## 42 **Initial management and prognosis**

43  
44  
45  
46 We thought that he was at very high risk for recurrent ischaemic stroke, so he  
47  
48 was admitted to the Hyper Acute Stroke Unit (HASU). He was given Aspirin  
49  
50 300mg OD and Atorvastatin 80mg ON, and placed on a cardiac monitor to detect  
51  
52 any paroxysmal atrial fibrillation. MRI imaging the next day revealed multiple  
53  
54 territory small infarcts on diffusion-weighted images (DWI), which did not  
55  
56 enhance with gadolinium (Figure 1). A transthoracic echo (TTE) did not find any  
57  
58 valve vegetations, patent foramen ovale or ventricular thrombus, with a normal  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

ejection fraction. Ward cardiac monitoring for 2 days showed no atrial fibrillation. There was no evidence of fluctuating pyrexia and inflammatory markers were unremarkable apart from the slight rise in CRP. Therefore, endocarditis was considered to be very unlikely. His unprovoked DVT was investigated with a CT chest, abdomen and pelvis, which showed a pancreatic tail mass and liver metastases (Figure 2). A subsequent 72-hour cardiac monitor showed sinus rhythm throughout.

He was anticoagulated with treatment dose low molecular weight heparin (LMWH). He was discharged 2 days after admission, still asymptomatic. Liver biopsy later confirmed metastatic pancreatic adenocarcinoma. Because his prognosis was poor, he was offered palliative chemotherapy.

### **Case progression and outcome**

One month after discharge he represented with new aphasia, which only partially improved, leaving some word finding difficulty. He had stopped his LMWH the day before in order to have a tunnelled central line inserted for his chemotherapy. Repeat MRI showed new DWI lesions in multiple territories. He was recommenced on LMWH and discharged. He was readmitted 10 days later with right sided weakness and a left middle cerebral artery proximal thrombus; despite thrombectomy he had residual dense right hemiparesis and severe aphasia. Given his poor prognosis he was given palliative care. He died 11 weeks after his initial presentation.

## Discussion

Thrombosis is the second most common cause of death in patients with cancer. However, arterial thrombosis, such as stroke or TIA in association with cancer, is important but often under-recognized.<sup>1</sup> As in this case, stroke or TIA may be the presentation of an occult cancer. A prospective study showed a higher risk of stroke shortly after diagnosis with lung, colorectal and pancreatic cancer; the cumulative incidence for stroke with pancreatic cancer was 3.4% at 3 months after diagnosis.<sup>2</sup>

In our reported case, we considered several sources of cerebral emboli. Paradoxical embolism is possible from the DVT through a left to right shunt, but this was not found on TTE; similarly, non bacterial thrombotic endocarditis (NBTE) was also possible, but unlikely in the absence of high fever or vegetations on TTE. Unfortunately the patient became unwell before a bubble-contrast echocardiogram could be performed to fully exclude a patent foramen ovale. Given the recurrent nature of his strokes, and his DVT, it is more likely that the patient had a hypercoagulable state due to pancreatic cancer, increasing the risk of spontaneous arterial and venous thrombo-emboli. However, the pathophysiology of thrombosis in cancer is multifactorial. Various mechanisms have been proposed such as procoagulants secreted from tumours, endothelial dysfunction from inflammatory cytokines, hepatic involvement, and the venous stasis caused by solid tumours.<sup>3</sup> Pancreatic cancer is associated with a very high risk of venous thromboembolism (VTE), with an incidence of around 35%.<sup>2</sup>

1  
2  
3 We suggest that the diagnosis of cancer related stroke should be considered in  
4  
5 the following circumstances: a lack of any competing stroke aetiology after  
6  
7 adequate investigation; active malignancy (and potential hypercoagulable state);  
8  
9 multiple vascular territory cerebral infarcts on DWI; venous thrombosis as well  
10  
11 as arterial emboli; and elevated D-Dimer levels. A retrospective study of 33  
12  
13 patients with cancer-related stroke and elevated D-Dimer levels showed that  
14  
15 84% had infarcts in >2 vascular territories, and 78% had microembolic  
16  
17 scattering similar to our case. There was also evidence of previous cerebral  
18  
19 infarction in 50%. This suggests that patients with cancer-related stroke are at  
20  
21 high risk of multiple territory embolism and recurrent stroke.<sup>4</sup>  
22  
23  
24  
25  
26  
27  
28  
29

30 Several randomized controlled trials have shown that LMWH is superior to  
31  
32 warfarin as secondary prevention for cancer-related venous thromboembolism.  
33  
34 Current guidance recommends using LMWH over warfarin, and there is no  
35  
36 evidence for direct acting oral anticoagulants (DOACs).<sup>5</sup> There are no guidelines  
37  
38 for secondary prevention of cancer-related stroke, though one study showed  
39  
40 reduced cerebral embolic signals and D-dimer levels with anticoagulant use.<sup>6</sup>  
41  
42 Thus, we suggest that it is reasonable to use LMWH following cancer-related  
43  
44 ischaemic stroke.  
45  
46  
47  
48  
49  
50

51 The timing of anticoagulation after ischaemic stroke from any cause requires  
52  
53 careful consideration of the risk of recurrent ischaemic stroke versus the risk of  
54  
55 haemorrhagic transformation of infarcts. In our patient, the size of the initial  
56  
57 infarcts was small, and the risk of bleeding was likely to be low. The risk of  
58  
59  
60

1  
2  
3 ischaemic stroke recurrence was considered very high, so immediate treatment  
4  
5 was initiated.  
6  
7  
8  
9

### 10 **Learning points**

- 11  
12  
13  
14  
15 1. Cancer increases the risk of stroke, TIA, and VTE, partly through  
16 hypercoagulability.  
17
- 18  
19  
20 2. Stroke and TIA, especially with VTE, can be the initial presentation of an  
21 occult cancer.  
22  
23
- 24  
25 3. MRI with multiple territory DWI infarcts with no other explanation  
26 should raise the suspicion of cancer-related stroke.  
27  
28
- 29  
30 4. Studies suggest the risk of recurrent stroke in patients with cancer is  
31 higher than in other stroke aetiologies.  
32  
33
- 34  
35 5. Based on the limited evidence available we recommend treatment with  
36 LMWH rather than oral anticoagulants for cancer-related stroke.  
37  
38  
39  
40

41  
42 *Written informed consent was obtained from the patient to publish the clinical*  
43  
44 *details and images in this article.*  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## References

- 1 Khorana, A. A., *et al.* Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost* 2007;5:632-634.
- 2 Bonnerot, Mathieu, *et al.* Cerebral ischemic events in patients with pancreatic cancer: A retrospective cohort study of 17 patients and a literature review. *Medicine* 2016;95:e4009.
- 3 Bick, Rodger L. Cancer-associated thrombosis. *N Engl J Med* 2003;349:109-110.
- 4 Schwarzbach, Christopher Jan, *et al.* DWI Lesion Patterns in Cancer-Related Stroke-Specifying the Phenotype. *Cerebrovasc Dis Extra* 2015;5:139-145.
- 5 Lyman, Gary H., *et al.* Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update 2014. *J Clin Oncol* 2015;33:654-656.
6. Seok JM, Kim SG, Kim JW *et al.* Coagulopathy and embolic signal in cancer patients with ischemic stroke. *Ann Neurol* 2010;68:213-219.



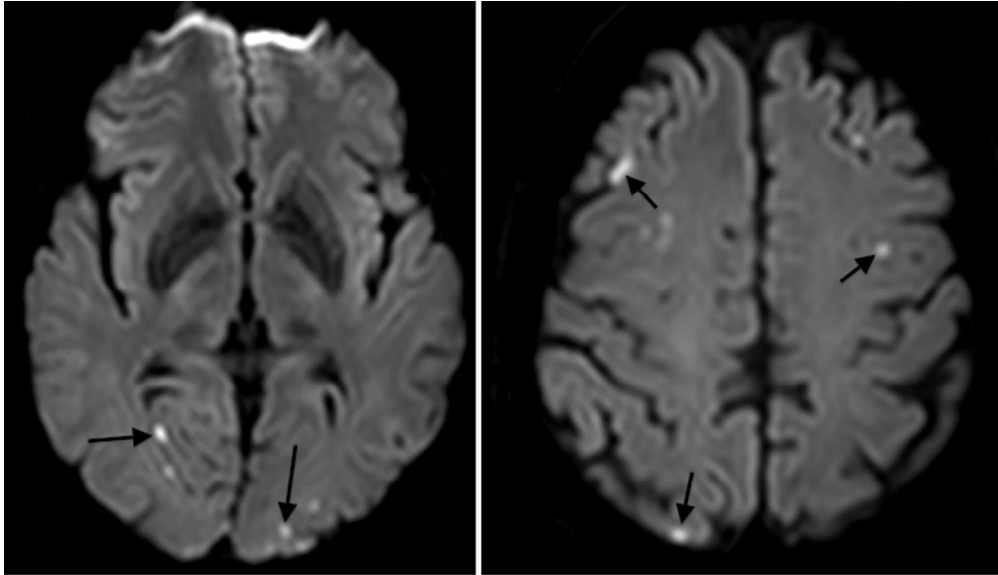


Figure 1: Axial diffusion-weighted magnetic resonance images acquired during the initial hospital admission, showing multiple infarcts bilaterally in the middle cerebral artery and posterior cerebral artery territories (black arrows).

261x149mm (72 x 72 DPI)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

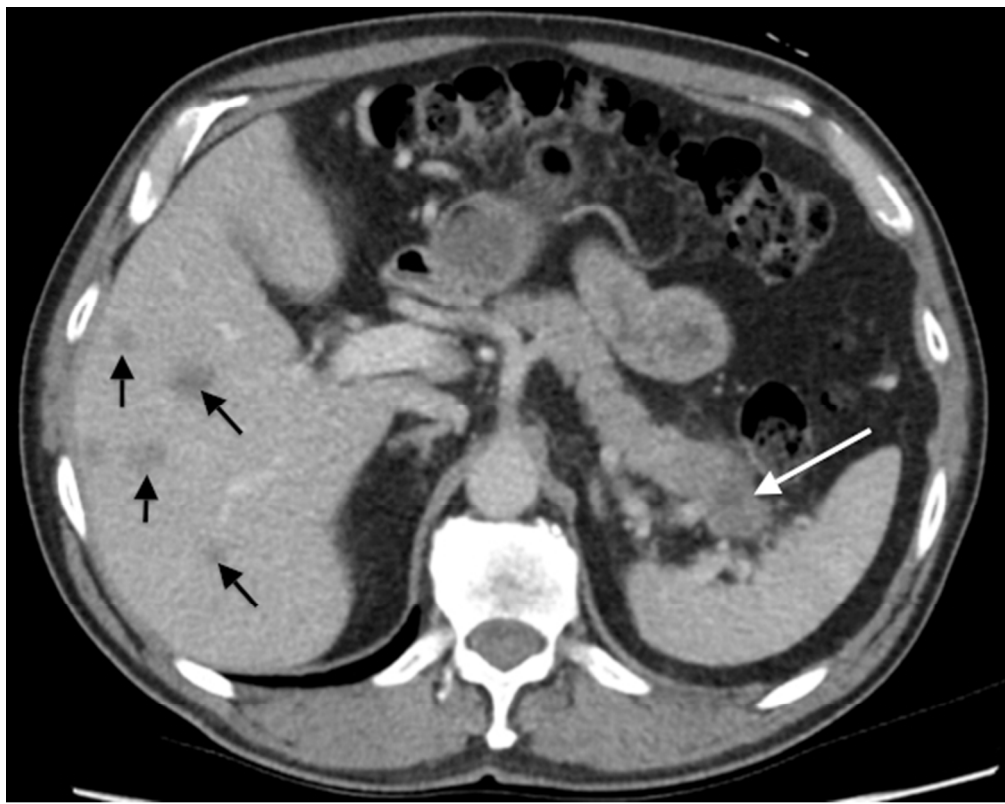


Figure 2: A mass in the tail of the pancreas (white arrow), with multiple liver metastases (black arrows).

205x163mm (72 x 72 DPI)

Only