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Case Report

Non-bacterial thrombotic endocarditis in pancreatic cancer and other high-risk malignancies: the case for prophylactic treatment

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Abstract

Non-bacterial thrombotic endocarditis (NBTE) typically affects patients with underlying adenocarcinoma, often of pancreatic origin. If untreated, it can lead to serious morbidity and mortality, including recurrent ischaemic stroke. NBTE is frequently missed or confused with infective endocarditis, leading to inappropriate management. We present the case of a 54-year-old male with newly diagnosed pancreatic malignancy (CA19–9 >120 000) who suffered recurrent deep-vein-thromboses and multiple ischaemic strokes despite full anticoagulation therapy. Transoesophageal echocardiography was correctly performed, but only after a second stroke was NBTE considered. We recommend early clinical suspicion and investigation for NBTE in patients with known or suspected malignancy presenting with neurological symptoms consistent with stroke. Initial calculations indicate this could also be cost-effective. Further, the patient's significantly elevated tumour-markers and NBTE-severity raise the possibility of a link; if further research established a reliable relationship, routine surveillance of high-risk malignancies could identify patients who might benefit from earlier echocardiography and anticoagulation management.

INTRODUCTION

Non-bacterial thrombotic endocarditis (NBTE) involves sterile vegetations consisting of fibrin and platelets aggregating on healthy heart valves; if dislodged, they can result in systemic emboli [1]. NBTE is notoriously difficult to diagnose because it has no pathognomonic signs and is often missed or confused with infective endocarditis (IE). Diagnosis relies on clinical suspicion and echocardiography; as NBTE classically results in bilateral valve vegetations (unlike IE which is mostly unilateral) and causes less significant valvular destruction [1], echocardiography is valuable in distinguishing NBTE from its infective counterpart. If undetected, NBTE can cause significant mortality and morbidity, including valvular dysfunction, cardiac failure and systemic emboli—*often arterial*—in the form of multiple/recurrent ischaemic strokes [1].

NBTE results from a prothrombotic state, often seen in malignancies (especially adenocarcinoma), disseminated intravascular coagulation and certain autoimmune diseases [2]. These conditions have well-established associations with venous thromboembolism (VTE)—the commonest manifestation of malignant hypercoagulability [3]. However, NBTE can also lead to *arterial* embolic events, typically in the form of acute ischaemic stroke. When IE leads to stroke, these are typically focal or single-territory, whereas NBTE causes widely distributed strokes in multiple cerebral territories [1]. The first presentation of NBTE may be focal-neurology, consistent with stroke; in patients with known or suspected malignancy, echocardiography should be undertaken to exclude valvular vegetations as a cause of the cerebral infarct. Adopting a low threshold for suspecting NBTE means any patient with known/likely malignancy and new neurological symptoms consistent with stroke should receive urgent echocardiography [4] and anticoagulation.

CASE REPORT

A 54-year-old male presented with a seemingly unprovoked right below-knee deep vein thrombosis (DVT). Computed tomography imaging revealed liver metastases and a primary adenocarcinoma favouring upper gastrointestinal/hepatobiliary origin, likely pancreatic, given CA19–9 was > 120 000. Ten weeks after the DVT,

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Table 1. Blood test results

Test	Results	Clinical Implications
WCC	7.4	Normal
Hb	106	Low
MCV	81	Normal
Platelets	468	Slightly elevated
INR	1.2	Normal
Prothrombin time	13.2	Normal
Activated partial prothrombin time	32	Normal
Fibrinogen	3.9	Normal
CRP	52	Slightly elevated
ESR	7	Normal
D-dimer	9372	Significantly elevated
HbA1c	38	Normal
ANA, ANCA	Negative	Normal
Immunoglobulins	Normal	Normal
Complement C3/C4	Normal	Normal
Rheumatoid factor	Negative	Normal
Factor V Leiden Mutation	Negative	Normal
Protein C/S activity and concentration	Normal	Normal
Antiphospholipid antibodies	Negative	Normal
3x Peripheral blood cultures	No growth	Normal
CA19–9	>120 000	Significantly elevated
Anti-factor Xa level (for BD dosing)	0.8	

the patient suffered a major cerebral ischaemic stroke involving numerous anterior and posterior territories; several demonstrated significant haemorrhagic transformation. Electrocardiography showed normal sinus rhythm, with no evidence of atrial fibrillation, whereas urgent echocardiography excluded an obvious cardioembolic source. He showed remarkable improvement, but while on aspirin (stroke-treatment guidelines) and 120 000 IU/ml of enoxaparin (low molecular weight heparin [LMWH], consistent with VTE-treatment guidelines) he developed a left above-knee DVT and further cerebral ischaemic stroke 6 days post-admission, again involving several territories with shower-emboli patterning on repeat magnetic resonance imaging. The patient remained apyrexic throughout and haemocultures from different sites yielded no growths, essentially excluding bacterial endocarditis (although around 70% of all endocarditis cases return negative blood cultures [5]); a full thrombophilia screen produced negative results, eliminating Antiphospholipid Syndrome (Table 1). Because of the rarity of NBTE and the challenge of diagnosis, it was only considered after IE, thrombophilia and cardiac arrhythmias had all been excluded. Repeat echocardiography showed small echogenic-mass lesions on the tips of the mitral-valve leaflets, highly suspicious for NBTE (Table 2). Enoxaparin was increased to maximum 120 000 UI/ml twice daily (alongside aspirin) and factor-Xa levels taken. The patient remained free from further thromboembolic phenomena and was discharged with enoxaparin and aspirin but deemed unsuitable for chemotherapy, given the extent of disease and risk of further embolic events. He died of metastatic carcinomatosis, 5 months post-diagnosis of the initial right-calf DVT.

DISCUSSION

While this case is by no means novel, it nevertheless raises some interesting clinical features meriting further research, and also illustrates the need to reconsider current management of NBTE in high-risk malignancies. Investigation of the patient's right-calf DVT confirmed an underlying malignancy; however, despite the initial stroke involving multiple embolic infarcts in different cerebral territories, it was not until he had a further ischaemic stroke that NBTE was considered and the initial echocardiogram re-reviewed by a specialist. As his initial stroke was highly suggestive of cardioembolism *and* he had a known malignancy, NBTE should have been considered more promptly. Furthermore, the NBTE did not respond to maximum anticoagulation, potentially due to the extent of the cancer, suggesting disease-burden and clinical manifestation of NBTE may be linked. These points are discussed below.

Tumour-marker levels may be elevated in pancreatic cancer due to cholestasis, but this was not the case here. It is therefore conceivable that there is a *speculative* link between tumour-marker levels and poor response to standard anticoagulation [6]. Although there is a corpus of evidence linking tumour-markers with NBTE, there is a paucity of literature reporting a reliable correlation that could be used predictively to determine which patients might benefit from early intervention. As the patient's cancer had already metastasised at

Table 2. Imaging results

Modality	Result
CT TAP	Hypodense mass in the body of the pancreas, extensive liver metastases, probable peritoneal deposits
MRI Head (1)	Ischaemic infarcts in left cerebral anterior and posterior territories, with significant haemorrhagic transformation
Echocardiogram	Small echogenic mass lesions on tips of mitral valve leaflets
MRI Head (2)	Shower emboli throughout both cerebral hemispheres

presentation, with significantly elevated CA19–9, it is conceivable disease-activity (as indicated by tumour-markers) and the severity of NBTE/thromboembolic potential are connected, and may explain his reduced response to conventional treatment. Further analysis of the relationship between tumour-markers and degree of pro-thrombotic state is therefore needed. Because of its enhanced ability to reduce the risk of further clot-formation, LMWH has traditionally been the treatment for VTE in cancer patients [7]. However, this case suggests there may be a subset of patients for whom this is ineffective; if a relationship between the severity of NBTE clinical manifestation and tumour-markers was established, at-risk patients could be identified via biomarker surveillance, and alternative treatments considered (such as direct oral-anticoagulants), for those patients where standard LMWH-treatment may be ineffective.

This suggestion gains cogency from the fact that pancreatic, colorectal and prostate cancer already have established associations with NBTE *and* have widely used (albeit sometimes controversial) tumour-markers. If a *reliable* correlation between these biomarkers and NBTE-severity was found, cut-off points for surveillance echocardiography or prophylactic LMWH could be identified. Clearly, further research is needed, but as monitoring of tumour-markers is already part of UK cancer-management, this information could be extended to predict and stratify risk of thromboembolic events.

Additional screening clearly has resource implications, though superficial costings suggest potential savings to the NHS. The estimated cost of an echocardiogram is £65–£222 [8], whereas prophylactic anticoagulation with LMWH is around £15.00pw [9]. Although the total cost of anticoagulation depends on duration of use, a rough per-patient annual total would be around £1000. In contrast, the mean per-patient annual health and social-care cost of acute stroke has been estimated at £46 000 (range £19 000–£107 000—[10]). The benefits of screening (particularly in colorectal and prostate cancer which typically confer good prognoses and have a proven link to NBTE), could have financial and patient benefit. However, the real risk of serious/fatal haemorrhagic and non-haemorrhagic consequences of long-term anticoagulation would have to be considered. Although proper cost–benefit analyses are needed, these cursory figures nevertheless suggest that screening-costs should not automatically be viewed as an obstacle to prophylactic management. In short, *not* screening for NBTE may be more costly than a comprehensive screening-programme. Moreover, if a reliable link was established between tumour-markers and NBTE severity, outcome predictors could be developed that would refine the protocol and reduce costs further.

In conclusion, while this is not a unique case, it nonetheless highlights two points: first, the imperative for adopting a lower threshold for suspecting NBTE, as a specific consequence of pro-thrombotic state, in any patient with confirmed or suspected malignancy presenting with neurological symptoms; and secondly, the need to establish whether there is a reliable relationship between severity of NBTE clinical manifestation and cancer-burden that could be used predictively to inform treatment and reduce overall care-costs.

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CONFLICTS OF INTEREST/COMPETING INTERESTS

The authors have no conflicts of interest to declare.

FUNDING

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ETHICS

Ethical approval was not required.

CONSENT

Although UK data protection legislation does not apply to a deceased patient, in order to comply with the principles of medical ethics and professional courtesy, written, informed consent was obtained from the patient's legally declared next of kin, using the BioMedCentral consent form.

GUARANTOR

Dr Laura Spurgeon.

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