Clinical Oncology: Case Reports

Case Report

A SCITECHNOL JOURNAL

Paraneoplastic Non-Bacterial Thrombotic Endocarditis in a Kras Mutant Pulmonary Adenocarcinoma

James Mark Debono[1*], Sara Micallef[2], Christa Marie Vella[2], Nicola Dingli[3], Janabel Said[1], Kevin John Schembri[4], David Pisani[5]

Abstract

Marantic endocarditis, also known as Nonbacterial Thrombotic Endocarditis (NBTE), is a rare and complex disease which challenges clinicians and researchers alike due to its multifactorial aetiology, diverse clinical presentations, and limited available treatment options. Here we report a case of marantic endocarditis with cerebral, renal and peripheral vascular infarctions in a 43-years-old lady with a KRAS G12C mutant adenocarcinoma of the lung who presented with a left sided 7th CN palsy, left upper and lower limb hemiplegia, complete aphasia and fixed right gaze palsy. Initial imaging showed findings suggestive of a thrombotic CVA and a thrombectomy was carried out. She subsequently suffered a series of thromboembolic phenomena including several Janeway lesions and splinter haemorrhages, right lower lobe lung infarction, right renal infarction and multiple bilateral cerebral infarctions. Infective endocarditis was suspected and TTE (transthorac-ic echocardiogram) showed aortic valve vegetations. However, serial blood cultures were negative. An aortic valve replacement was carried out which confirmed NBTE. She was later started on Sotorasib in an attempt to offer palliative control of her pulmonary adenocarcinoma.

Keywords: Coronary Artery Bypass Grafting (CABG); Cardiac imaging; Left Ventricular (LV); Echocardiography; Computed Tomography (CT); Cardiotoxicity

Introduction

NBTE has been historically associated with advanced-stage malignancies, although it can also be observed in other conditions, such as autoimmune diseases, connective tissue disorders, and chronic debilitating illnesses. Unlike infectious endocarditis, which results from bacterial or fungal infections, marantic endocarditis is characterized by the formation of sterile fibrin and platelet-rich thrombi on the cardiac valves which predispose affected individuals to life-threatening embolic events, such as cerebrovascular accidents, myocardial infarctions and peripheral arterial embolisms. The exact mechanisms underlying the formation of these thrombi in the absence of infection remain an area of active research, with theories suggesting that underlying inflammatory processes leading to endothelial cell injury and aberrant coagulation cascades may play pivotal roles [1,2].

The vegetations in NBTE lack the typical inflammatory reactions found in infective endocarditis. This fact, coupled with minimal cellular organisation in NBTE vegetations, cause the vegetations to be more susceptible to fragmentation. This explains why marantic endocarditis typically causes less cardiac valvular dysfunction whilst having a significantly higher risk of embolic events when compared to IE patients [3].

***Corresponding author:** Dr. James Mark Debono
Department of Oncology, Sir Anthony Mamo Oncology Centre, Imsida, Malta E-mail: james.m.debono@gov.mt

Received: Nov 01, 2024; Manuscript No: COCR-24-153845 **Editor Assigned:** Nov 09, 2024; PreQC Id: COCR-24-153845 (PQ) **Reviewed:** Nov 20, 2024; QC No: COCR-24-153845 (Q) **Revised:** Nov 24, 2024; Manuscript No: COCR-24-153845 (R) **Published:** Nov 30, 2024; DOI: 10.4173/cocr.7(11).363

Case Presentation

A 43-years-old female, with a newly diagnosed stage IVb, 20% PD-L1 positive, KRAS G12C mutant adenocarcinoma of the lung with me-tastases to left axillary lymph nodes, left adrenal gland and right fron-tal lobe with a performance status of 0, presented to the Emergency Department in view of sudden onset left-sided facial nerve palsy, left upper and lower limb weakness, complete aphasia and fixed right gaze palsy. The patient reported a history of frontal headaches but denied other features suggestive of Raised Intracranial Pressure (RICP).

The patient had a history of subsegmental pulmonary embolism a month prior to presentation to ED and was therefore on treatment dose Rivaroxaban. She also had a history of thalassaemia, partial thyroidectomy and right breast DCIS with comedo necrosis (intermediate to high grade) which was diagnosed while under investigation for lung cancer.

On review at the emergency department the patient was noted to have a Glasgow Coma Scale score of 15, however was drowsy and off her baseline. She was able to follow commands and reply to questions appropriately with prompting, however she was noted to have slurred speech. On examination she was found to have dense left-sided hemiplegia (Medical Research Council score of 0/5 in all muscle groups) including the upper limbs, lower limbs and face. She was also noted to have left-sided visual neglect and gaze deviation towards the right. The national institutes of health stroke scale was calculated to be 17 (Table 1).

A non-contrast CT scan of the brain and cranial cavity was done, which revealed no significant acute intracranial abnormality. The patient went on to have a CT stroke done, which showed the presence of an intra-arterial occlusive lesion within the right M1 segment which was amenable for mechanical thrombectomy and poor collateral supply in the right hemisphere. CT perfusion demonstrated a large area at risk of ischaemia within the right Middle Cerebral Artery (MCA) territory (Figures 1 and 2).

Mechanical thrombectomy was carried out without immediate complications. A repeat CT brain 24 hours post procedure showed ischaemic changes and a small subarachnoid haemorrhage in the right Middle Cerebral Artery (MCA) territory.

MR imaging of the brain was also carried out on the day of admission (Figure 3). This showed large confluent areas of cortical swelling and restricted diffusion across the right MCA territory and in the splenium of corpus callosum in keeping with subacute infarction. There were also innumerable foci of T2 hyperintensity and restricted diffusion scattered throughout the brain bilaterally in keeping with embolic phenomena.

Table 1: National institutes of health stroke scale.

S. No.	Assessment Component	Criteria
1	Level of consciousness	0 = Alert, keenly responsive
		1 = Not alert, but arousable by minor stimulation
		2 = Not alert, requries repeated stimulation
		3 = Unresponsive or responds only with reflex
2	A. Level of consciousness questions:	0 = Answers two questions correctly
	B. What is your age?	1 = Answers of question correctly
	C. What is the month?	2 = Answers neither questions correctly
3	Level of consciousness commands: Open and close your eyes gripand release your hand	0 = Performs both tasks correctly
		1 = Performs one task correctly
		2 = Performs neither task correctly
4	Best gaze	0 = Normal
		1 = Partial gaze palsy
		2 = forced deviation
5	Visual	0 = No visual lost
		1 = Partial hemianopia
		2 = Complete hemianopia
		3 = Bilateral hemianopia
6	Fasial palsy	0 = Normal symmteric movements
		1 = Minor paralysis
		2 = Partial paralysis
		3 = Complete paralysis of one or both sides
7	Motor arm, left arm and right arm	0 = No drift
		1 = Drift
		2 = Some effort against gravity
		3 = No effort against gravity
		4 = No movement
8	Motor leg, left leg and right leg	0 = No drift
		1 = Drift
		2 = Some effort against gravity
		3 = No effort against gravity
		4 = No movement
9	Limb ataxia	0 = Absent
		1 = Present in one limb
		2 = Present in two limbs
10	Sensory	0 = Normal, no sensory loss
		1 = Mild-to-moderate sensory loss
		2 = Severe- to-total sensory loss
11	Best language	0 = No aphasia, normal
		1 = Mild-to-moderate aphasia
		2 = Severe aphasia
		3 = Mute, global aphasia
12	Dysarthria	0 = Normal
		1 = Mild-to-moderate dysarthria
		2 = Severe dysarthria

13	Extinction and inattention	0 = No abnormality
		1 = Visual, tactile, auditory, spatial or personal inattention
Score = 0-42		

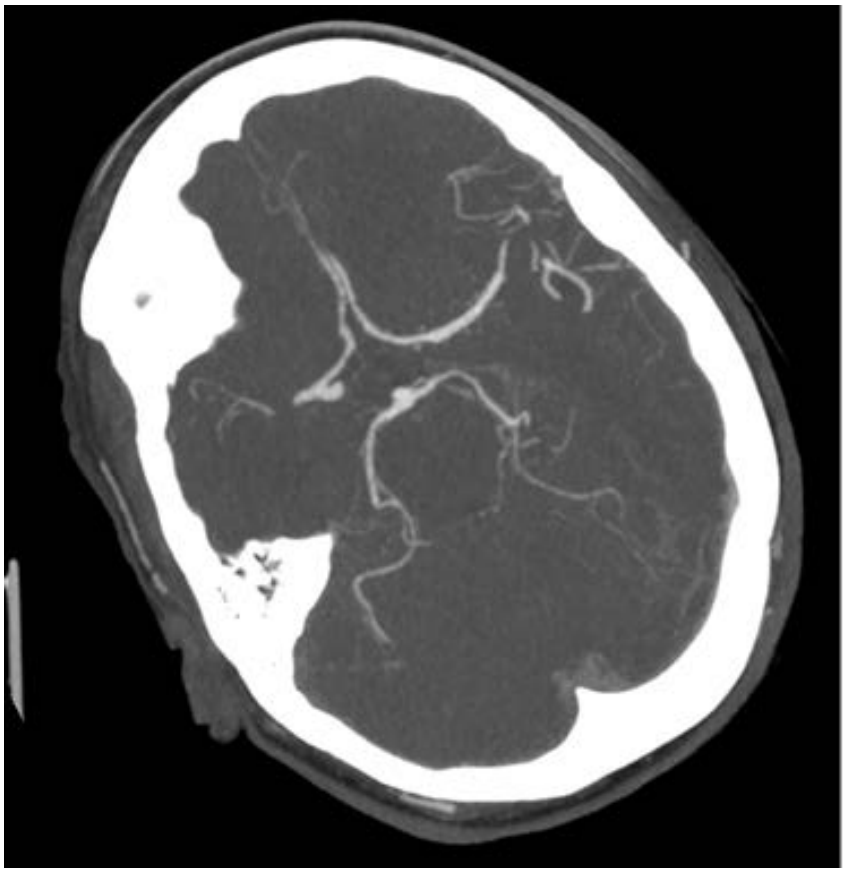

Figure 1: CT Angiography showing intra-arterial occlusive lesion within the right M1 segment.

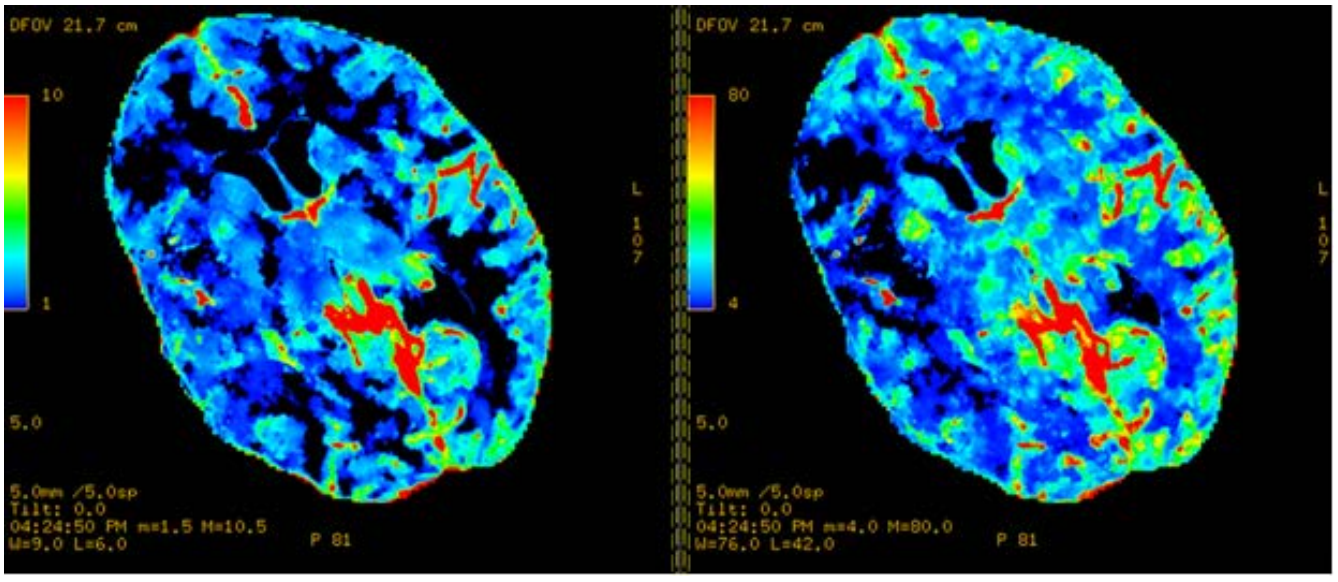

Figure 2: CT Perfusion showing area at risk within right MCA territory.

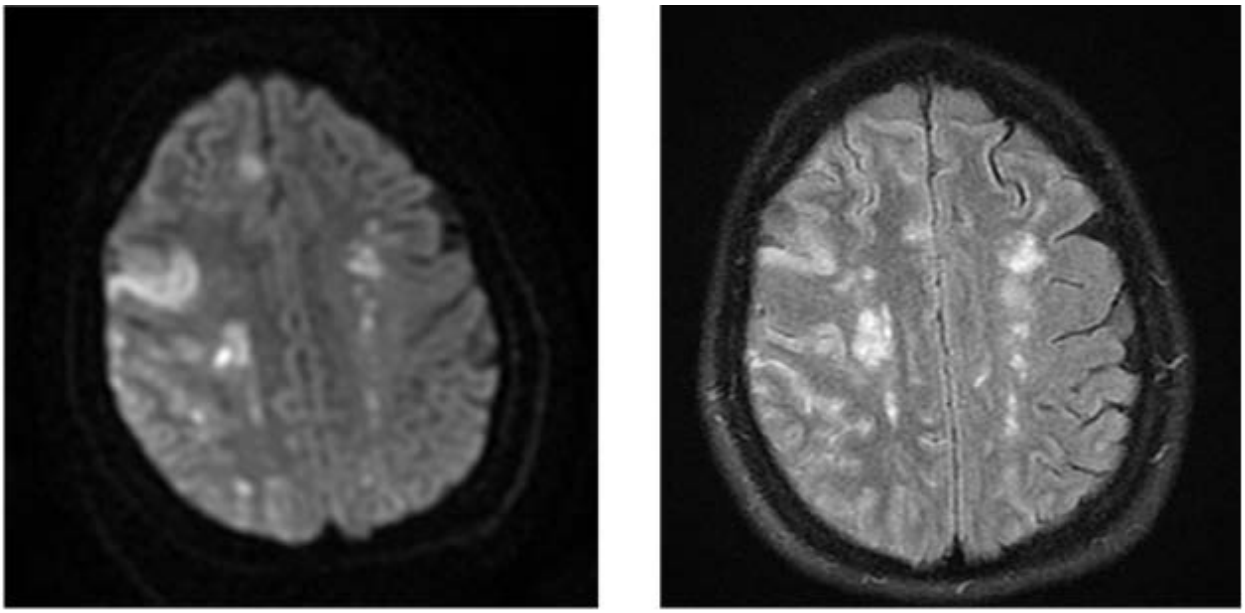

Figure 3: Diffusion weighted image and FLAIR images showing infarcts in both right and left hemispheres.

After the thrombectomy, the patient was admitted to the Stroke Unit for further observation. Bloods were taken which showed a high white blood cell count of 21.62 × 10^9/L (Reference range: 4.3 - 11.4 × 10^9/L). The rest of the blood tests requested, including renal profile, liver function test, coagulation and inflammatory screen were within normal limits.

On re-assessment, the patient was noted to have splinter haemorrhages, Janeway lesions and dusky discolouration on her fingers and toes bilaterally (Figures 4-8). Cardiac auscultation revealed no murmurs and parameters, including temperature, were normal. These signs, coupled with the MR findings of multiple cerebral infarctions and CT findings of right lower lung and right renal infarctions, raised the suspicion of potential infective endocarditis with secondary embolic phenomena.

Figure 4: Dusky discolouration of fingertips and Janeway lesions.

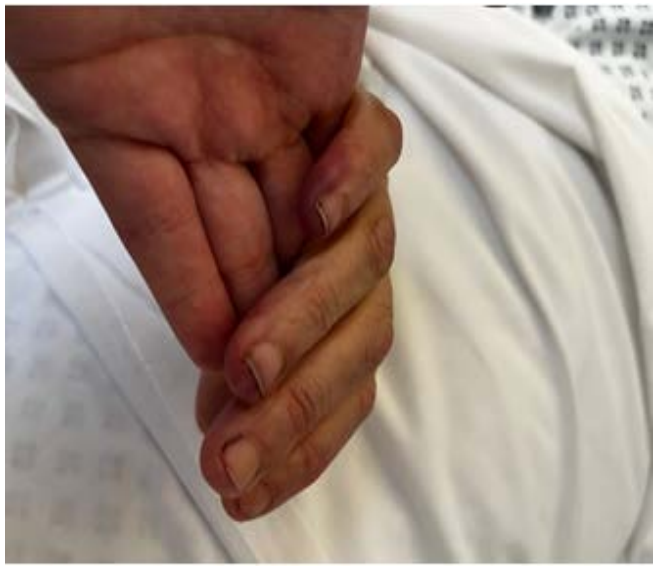

Figure 5: Splinter haemorrhages on nails.

Figure 6: Dusky discolouration of index and middle fingers.

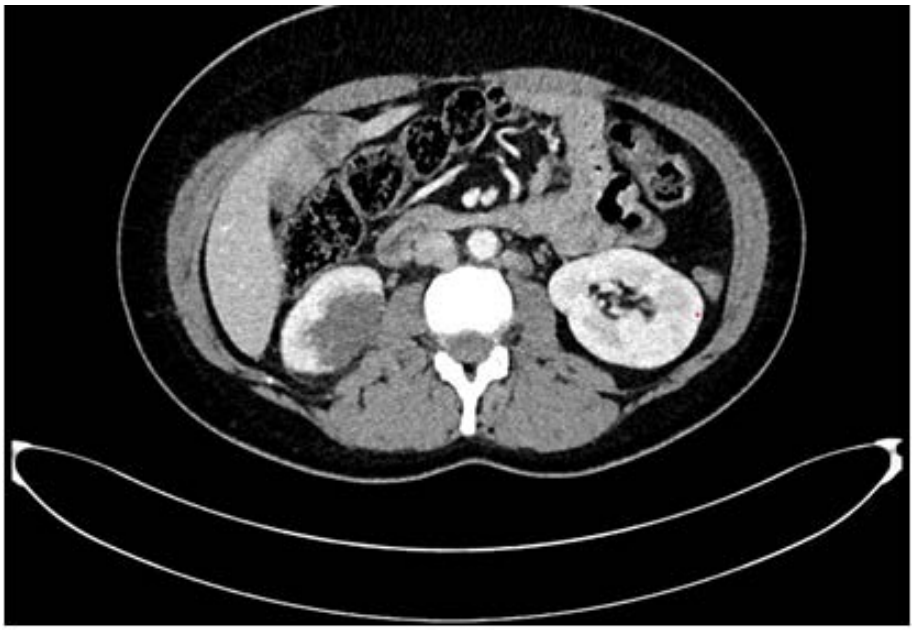

Figure 7: Right renal infarction on CT.

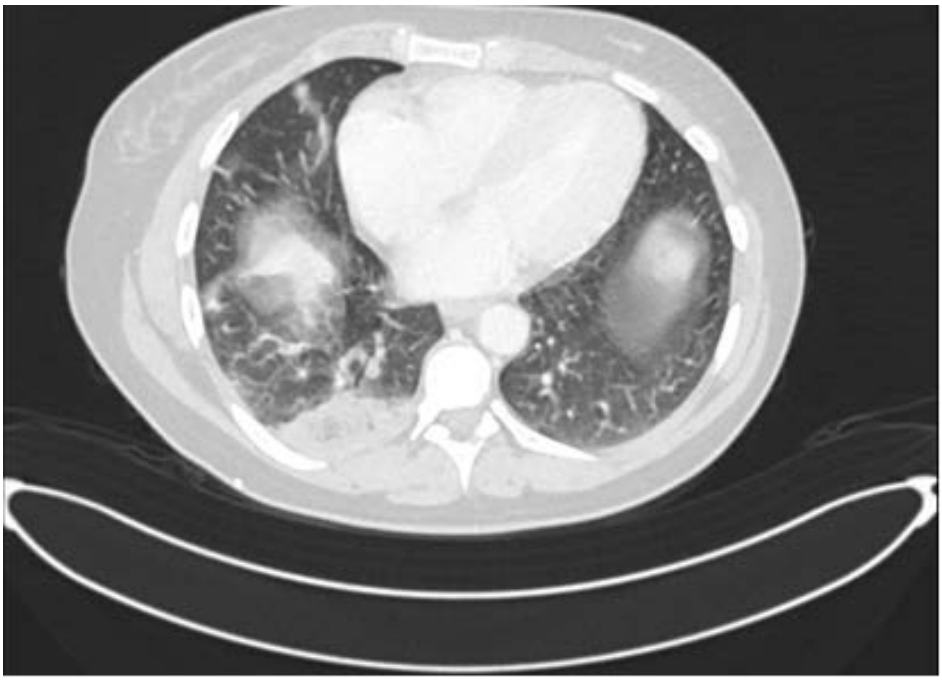

Figure 8: Right lower lobe infarction.

A transthoracic echocardiogram was therefore performed to confirm the suspicion of Infective Endocarditis (IE). This showed normal left and right ventricular function with an Ejection Fraction (EF) of 65 %, severe (AR) Aortic Regurgitation and the presence of a fluttering structure on the AoV. Trans-oesophageal echocardiography was done for a more detailed assessement of the Aortic velocity (AoV). This confirmed again the presence of thickened Non-Coronary Cusp (NCC) and Left Coronary Cusp (LCC) aortic valve leaflets with vegetations causing severe AR, mild AS (mean gradient 14mmHg) and mild MR. There was no evidence of aortic root abscesses (Figures 9 and 10).

After discussion with the infectious disease specialists, the patient was started on intravenous ceftriaxone and teicoplanin as treatment of infective endocarditis. Prior to starting antibiotics, 3 separate sets of blood cultures were taken. With the absence of microbial growth from multiple sets of blood cultures, no episodes of fever and persistently normal inflammatory markers, it was decided to stop intravenous antibiotics after 7 days, switch Rivaroxaban to low molecular weight heparin and consider the patient for surgery as the suspicion of NBTE was now higher than that of IE. The patient proceeded to have aortic valve replacement surgery. During the procedure, vegetations on both the non-coronary cusp and left coronary cusp of the aortic valve were noted. The aortic valve was removed and replaced with a biosynthetic prosthesis with no peri-operative or post-operative complications.

The aortic valve leaflets were sent for histological evaluation and culture. Microscopic examination showed polypoid deposits of fibrin on the valvular spongiosa within which were scattered foamy histiocytes, rare lymphocytes and occasional neutrophil polymorphs. Mild myxomatous degeneration of the valvular fibrosa was also appreciated. No

bacterial, fungal or mycobacterial organisms were identified on Gram stain, Grocott / PAS-D and Ziehl-Neelsen stains respectively. No valvular involvement by malignant cells was evident. The excised valve was also sent for tissue culture, all of which yielded no positive results. In view of the above histological findings and persistently negative blood cultures suggestive of non-infective endocarditis, intravenous antibiotics were stopped after a total of 12 days (Figure 11).

The patient underwent an intensive physiotherapy, occupational, speech language and psychology therapy programme with some improvement in her speech, facial paresis and limb mobility, albeit there was still a significant residual deficit with a decline in her performance status from 1 (pre-embolic event) to 3. It was decided to forego any plan of starting systemic anti-cancer therapy in the form of chemo-immunotherapy due to her poor PS. With a TPS of 20%, single agent immune checkpoint inhibition was also not considered as an ideal option. The finding of a KRAS G12C mutation on an NGS panel, led us to start TKI treatment in the form of sotorasib with the hope of achieving a relatively rapid response. Unfortunately, 3 weeks after the commencement of KRAS inhibition therapy, the patient was brought to casualty with an acute confusional state followed by cardiac arrest within a few minutes of presentation to the emergency service. Resuscitation was attempted for 30 minutes with persistent PEA throughout all cycles before declaring the patient deceased.

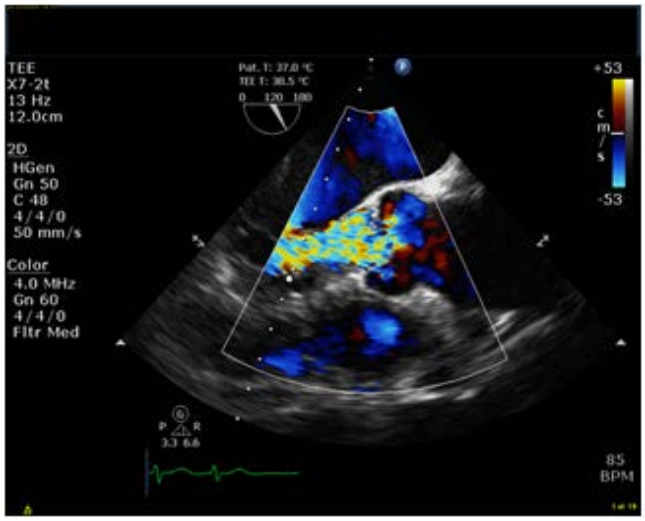

Figure 9: TOE Short axis AoV showing severe AR.

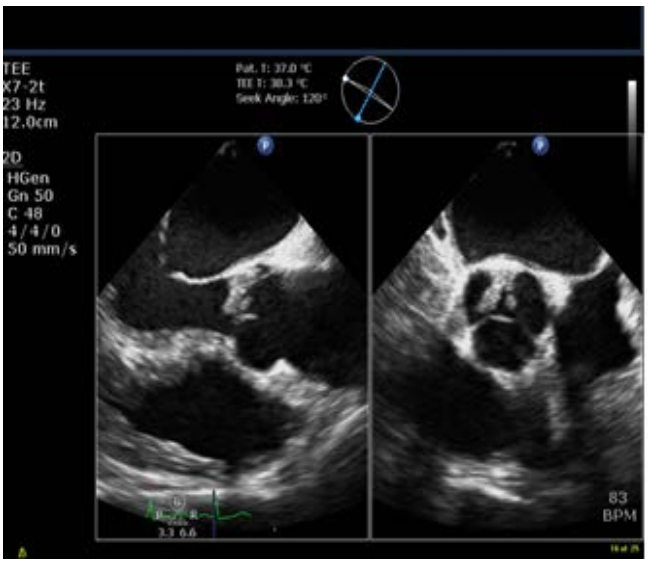

Figure 10: TOE Short axis AoV showing thickened NCC and LCC aortic valve leaflets with vegetations.

Figure 11: Vegetation on Aortic Valve (AR).

Discussion

Despite a well-known connection between advanced malignancy, hypercoagulable states and NBTE, cancer-associated marantic endocarditis is considered a rare entity. It is most commonly associated with lung and pancreatic malignancies, although NBTE in other malignancies such as melanoma and breast carcinomas have also been reported [4,5].

The importance of being vigilant for this phenomenon lies mainly in its association with a dismal prognosis and high morbidity rates, the latter mainly being secondary to high rates of systemic embolic events, quoted at 42%-50%. The incidence of embolic CVAs in NBTE is in fact higher in marantic endocarditis (33%) than in infective endocarditis (19%) [6]. This is further compounded by the relative lack of cardiac murmurs, occurring in less than 50% of cases and fever being an uncommon finding as in the case reported here[7,8]. Echocardiographic findings are thus vital in such scenarios to detect the presence of valvular vegetations, albeit the distinction between sterile and infective vegetations is still difficult. Historically, sterile vegetations are described as having no independent motion on the cardiac valves as was observed in this case. However, other features such as having a small, sessile nature with irregular borders, broad-based attachment to the valves and a heterogenous echo density were not evident [7].

The Modified Duke's Criteria, with 1 Major criterion (evidence of endocardial involvement on TTE/TOE) and 1 Minor criterion (presence of vascular phenomena) rendered a possible diagnosis of infective endocarditis and so antibiotics were commenced. However, the absence of fever, absence of raised inflammatory markers and persistently negative blood cultures, in the context of a stage 4 malignancy raised the suspicion of NBTE.

In contrast to IE, which in itself is not an indication for anti-coagulation [9]. The treatment of NBTE typically involves systemic anti-coag-

ulation, with low molecular weight heparin or unfractionated heparin being the treatment of choice [2,7,10]. Life-long anti-coagulation has demonstrated to reduce the risk of further embolic events, which is understandable when considering the hypercoagulable aetiology of Non-Bacterial Thrombotic Endocarditis (NBTE).

On the other hand, the absence of guidelines makes the role of surgical intervention in NBTE less clear. Careful consideration of several factors, including the degree of valvular dysfunction, presence or absence of heart failure, risk of further embolic events, performance status and overall prognosis should be taken into account. Overall, it seems that surgical intervention in properly selected cases drives overall survival upwards [2].

Finally, the treatment of the underlying malignancy which is creating the hypercoagulable state and driving valvular endothelial injury, is a paramount attempt at improving the prognosis. In this case, we felt that the patient was not fit enough for the standard platinum-based triplet chemo-immunotherapy treatment for lung adenocarcinoma. Single agent immunotherapy was also not considered to be ideal considering that the TPS score was less than 50%. Knowing that the patient had a KRAS G12C mutation, we decided to proceed with Sotorasib as typically TKI treatment is associated with relatively fast response rates. Ultimately prognosis in NBTE is very poor, especially in stage 4 disease and lung carcinomas [2,11].

Conclusion

Non-bacterial endocarditis remains a challenging condition despite the significant advances in cancer treatments over the past years. Its early recognition and treatment are essential to prevent the devastating morbidity patients can be left with secondary to embolic phenomena and cardiac dysfunction. More awareness on this life-threatening condition is essential and so is further research in the aetiological mechanism underlying NBTE and the proposition of clear guidelines to help clinicians navigate through this complex phenomenon.

References

1. Waller BF, Knapp WS, & Edwards JE. (1973). Marantic valvular vegetations. Circulation. 48:644-650.
2. Rahouma M, Khairallah S, Dabsha A, Elkharbotly IA, Baudo M, et al.(2023). Lung cancer as a leading cause among paraneoplastic non-bacterial thrombotic endocarditis: a meta-analysis of individual patients' data. Cancers. 15: 1848.
3. Zadok OIB, Spectre G, & Leader A. (2022). Cancer-associated non-bacterial thrombotic endocarditis. Thromb Res. 213: S127-S132.
4. Glancy DL, & Roberts WC. (1968). The heart in malignant melanoma: a study of 70 autopsy cases. Am. J. Cardiol. 21: 555-571.
5. Arvold ND, Hsu L, Chen WY, Benzaquen LR, Weiss SE. (2011). Marantic endocarditis with cardioembolic strokes mimicking leptomeningeal metastases in breast cancer. J Clin Oncol. 29: e743-e746.
6. Tai MLS, Tan ECL, Ang CC, Liam CK. (2016). Recurrent cerebral infarcts secondary to marantic endocarditis in a patient with adenocarcinoma of the lung. Singap Med J. 57: 524.
7. Umeojiako WI, Kasouridis I, Sargent R, Ghani S. (2019). Atypical marantic endocarditis. BMJ Case Rep CP. 12: e232057.
8. Parker N, Atallah R, Ojile N, Chamoun K, Nehme, F. et al. (2020). Nonbacterial thrombotic endocarditis. Kans J Med. 13: 61.
9. Zhu X, Wang Z, Ferrari MW, Ferrari-Kuehne K, Hsi DH, et al. (2023). Management of anticoagulation in patients with infective endocarditis. Thromb Res. 229: 15-25.
10. Wang J, Monga N, Mopala P, Husnain M. (2020). Development of nonbacterial thrombotic endocarditis while on systemic anticoagulation in pancreatic cancer: a case report. Cureus. 12.
11. Quintero-Martinez JA, Hindy JR, El Zein S, Michelena HI, Nkomo VT. et al. (2022). Contemporary demographics, diagnostics and outcomes in non-bacterial thrombotic endocarditis. Heart. 108:1637-1643.

Author A iliations Top

[1]*Department of Oncology, Sir Anthony Mamo Oncology Centre, Imsida, Malta*
[2]*Department of Medicine, Mater Dei Hospital, Imsida, Malta*
[3]*Department of Neurosciences, Mater Dei Hospital, Imsida, Malta*
[4]*Department of Cardiothoracic Surgery, Imsida, Malta*
[5]*Department of Histopathology, Imsida, Malta*