Received: 14 December 2021 | Revised: 14 July 2022 | Accepted: 26 September 2022

DOI: 10.1002/ccr3.6434

CASE REPORT

Clinical Case Reports Open Access WILEY

Quadrivalvular nonbacterial thrombotic endocarditis in a patient with clear cell cervical cancer

Valentin Gabelmann[1] | **Felix Grabs**[1] | **Simon Diestelmeier**[1] | **Felix Heindl**[2] | **Markus Vosseler**[1] | **Thomas Münzel**[1,3] | **Ingo Sagoschen**[1] | **Johannes Wild**[1,3,4]

[1]Center for Cardiology, Cardiology I, Johannes Gutenberg-University Mainz, Mainz, Germany

[2]Department of Gynecology and Obstetrics, Comprehensive Cancer Center Erlangen-EMN (CCC ER-EMN), University Hospital Erlangen, Erlangen, Germany

[3]German Center for Cardiovascular Research (DZHK), Partner site RheinMain, Mainz, Germany

[4]Center for Thrombosis and Hemostasis (CTH), Johannes Gutenberg-University Mainz, Mainz, Germany

Correspondence
Johannes Wild, Center for Cardiology, Cardiology I, Johannes Gutenberg-University Mainz, Langenbeckstr. 1, 55131 Mainz, Germany.
Email: johannes.wild@unimedizin-mainz.de

Funding information
Boehringer Ingelheim Stiftung; German Interdisciplinary Association for Intensive Care and Emergency Medicine; German Federal Ministry for Education and Research, Grant/Award Number: BMBF EDU-V24; Stiftung Mainzer Herz

Abstract

Nonbacterial thrombotic endocarditis (NBTE) is a rare finding, which is mostly associated with malignant diseases leading to hypercoagulability. We report the case of a severe quadruple valve nonbacterial thrombotic endocarditis in a patient with clear cell cervical cancer.

KEYWORDS

cervical cancer, endocarditis, hypercoagulability, nonbacterial thrombotic endocarditis

1 | INTRODUCTION

Whereas venous thromboembolism (VTE) is a frequent clinical event in patients with cervical cancer,[1] nonbacterial thrombotic endocarditis (NBTE), formerly known as marantic endocarditis, has rarely been described associated with gynecological malignancy[2] and, in most of the cases, the diagnosis was confirmed postmortem.[3,4] NBTE is considered as a manifestation of an overall prothrombotic state[5] characterized by valve associated masses consisting of platelets and fibrin in absence of bacteria and without inflammatory destruction of the heart valves.

We report a case of NBTE of all heart valves and the atrial septum in a patient suffering from clear cell cervical cancer resulting in fatal venous and arterial thromboembolic events.

2 | CASE REPORT

A 52-year-old female patient was referred to our university medical center with suspected acute infectious endocarditis (IE). Nine days before, an ischemic stroke of the left middle cerebral artery had been diagnosed at the

referring hospital. ECG showed no evidence of atrial fibrillation supporting cardioembolic events. A transesophageal echocardiography was performed and vegetations adherent to the in-situ port catheter and the aortic valve were found. An acute infective endocarditis was suspected and empiric antibacterial treatment with ampicillin and gentamicin was initiated. Because of respiratory distress, a computed tomography scan of the pulmonary arteries was performed, which revealed bilateral pulmonary embolism. Thereupon, the patient was referred to our tertiary care hospital for further therapy.

Medical history revealed that the patient had clear cell carcinoma of the cervix at an advanced stage (FIGO IV4A). The carcinoma had been diagnosed 1 year ahead of the current admission and initially treated with lymphadenectomy, and concurrent platinum-containing radiochemotherapy. With recently identified lymphogenic progression, therapy with Navelbine had been initiated. In addition, the patient had a history of pulmonary embolism in November 2020 since then followed by oral treatment with the direct factor Xa inhibitor Edoxaban for therapeutic anticoagulation.

On admission to our unit, the patient presented with severe hemodynamic instability reflected by tachycardia and hypotension. Respiratory distress required high flow oxygen support (10 L/min) via facial mask. The patient had no fever. Laboratory findings showed moderately elevated C-reactive protein (137 mg/L), normal procalcitonin (0.5 ng/ml) and normal leukocyte counts (9.43/nl). Moreover, we detected mild thrombocytopenia (115/nl), anemia (serum hemoglobin 7.3 g/dl), and highly elevated d-dimers (15 mg/L). Notably, Troponin I (11,462 pg/ml) and BNP (2624 pg/ml) were as well elevated (Table 1 for relevant laboratory findings on admission).

Bedside transthoracic echocardiography on admission suggested large vegetations affecting the aortic valve, so we performed an urgent transesophageal echocardiography. Consistent with the earlier examination, we found large vegetations, not only on the aortic valve (Figure 1) but also affecting the mitral (Figure 2A,B) and the tricuspid valve (Figure 2C) with large floating masses within the right ventricle extending over the pulmonary valve into the pulmonary artery (Figure 2D). Notably, although the vegetations were very pronounced, there was no destruction of the valves and only moderate insufficiencies could be visualized (Figure 1B and 2B,C). We also detected vegetations adherent to the right side of the atrial septum (Figure 3) and impaired systolic function of the left ventricle.

We initiated microbiological diagnostics by taking three pairs of blood cultures as well as next generation sequencing (NGS)-based diagnostics for pathogen identification (Cell-free DNA was analyzed with Noscendo's CE-IVD marked DISQVER assay) and extended the antibiotic therapy by Flucloxacillin according to guidelines for IE. Given the malignant underlying disease and the low values of PCT, we additionally started therapeutic anticoagulation with unfractionated heparin and performed extended thrombophilia and coagulation diagnostics (Table 2).

After multidisciplinary discussion of the case, the experts jointly determined that surgical intervention was not recommended. Following circulatory deterioration, the patient died on our ICU due to shock-associated multiple organ failure only 2 days later.

TABLE 1 Laboratory findings on admission.

Test	Result	Reference Interval	Units
Creatinine	2.28	0.55–1.02	mg/dl
eGFR	24	50–98	ml/min/...
LDH	750	<245	U/L
CK	366	30–170	U/L
Troponin I	11,462	<24	pg/ml
BNP	2624	<100	pg/ml
CRP	137	<5	mg/l
Procalcitonin	0.5	<0.5	ng/ml
D-Dimer	15.04	<0.5	mg/l FEU
CA-125	4217	<35	U/ml
Leucocytes	9.43	3.5–10	per nl
Red blood cells	2.8	3.7–4.8	per pl
Hemoglobin	7.3	12–16	g/dl
Platelets	115	150–360	per nl

Abbreviations: BNP, brain natriuretic peptide; CK, creatine kinase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; LDH, lactate-dehydrogenase.

3 | DISCUSSION

Nonbacterial thrombotic endocarditis (NBTE) is a rare clinical finding and is likely underdiagnosed, although it is a serious manifestation of cancer-related hypercoagulability and a potentially life-threatening source of thromboembolism.[5] NBTE was first described by Ziegler in 1888 as fibrinous efflorescence on heart valves.[6] In 1936, the term was renamed "nonbacterial thrombotic endocarditis" by Gross and Friedberg[7] and defined as deposition of fibrin and platelets on heart valves without evidence of microorganisms. Most cases of NBTE are detected postmortem, and autopsy reports indicate an incidence of 1.2%.[8] Anatomically, the aortic valve is most commonly affected, followed by the mitral valve. Pulmonary and tricuspid valves are rarely affected.[8] Since NBTE is a rare finding, multivalvular NBTE is even rarer and quadrivalvular NBTE is a real rarity with very few published cases.[9–11]

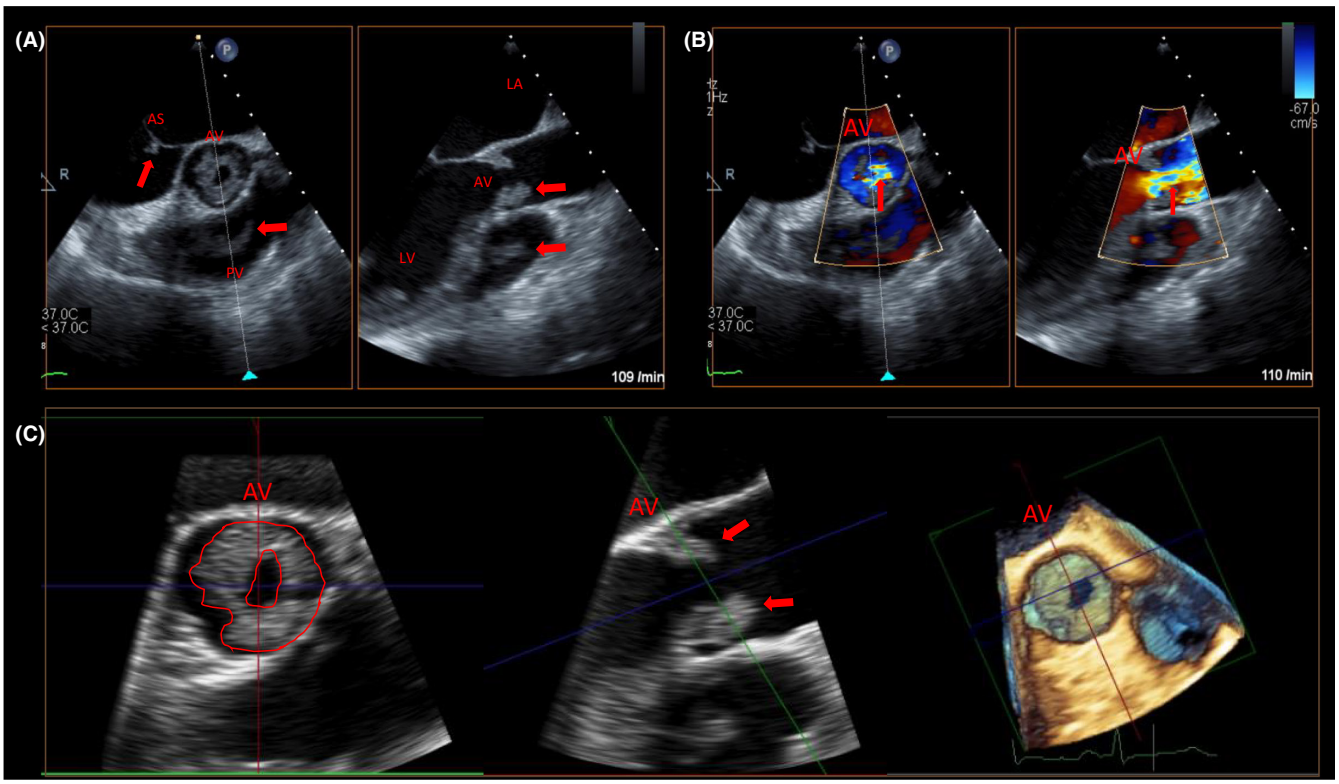

FIGURE 1 (A) Transesophageal echocardiography showing a large mass adhering to the aortic and pulmonary valves as well as the atrial septum. AV, aortic valve, AS, atrial septum; PV, Pulmonary valve. (B) Color doppler echocardiography demonstrating aortic valve insufficiency. (C) 3-D transesophageal echocardiography of the aortic valve. Arrows highlighting the vegetations.

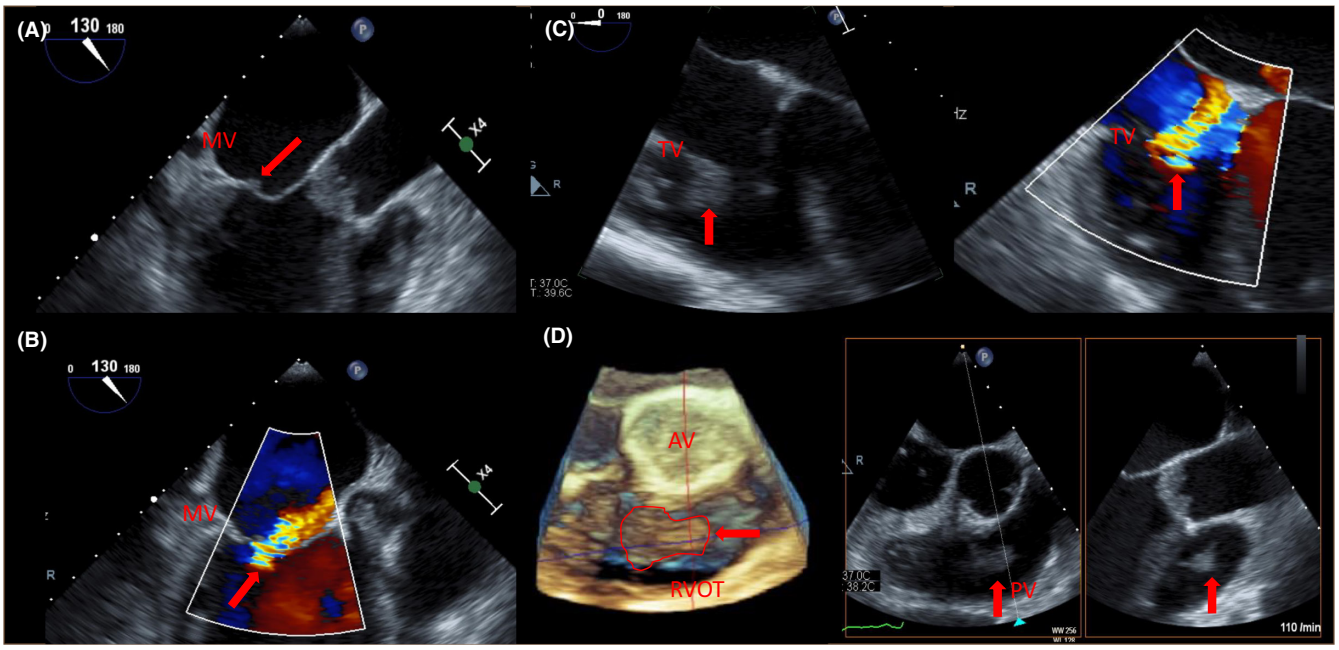

FIGURE 2 (A) 2-D Transesophageal echocardiography and (B) color doppler echocardiography with vegetations on the mitral valve (MV) and the resulting insufficiency. (C) Imaging of the tricuspid valve (TV) affected by NBTE and moderate to severe insufficiency. (D) 3-D and 2D-transesophageal echocardiography of the ventricular outflow tract (RVOT) and the pulmonary valve (PV). Arrows highlighting the vegetations.

The premortem diagnosis of NBTE is usually made on the basis of clinical and echocardiographic findings in conjunction with exclusion of an infectious cause of endocarditis. Because an autopsy (required by German law) was refused by the family, our diagnosis was also based on echocardiographic imaging after interdisciplinary

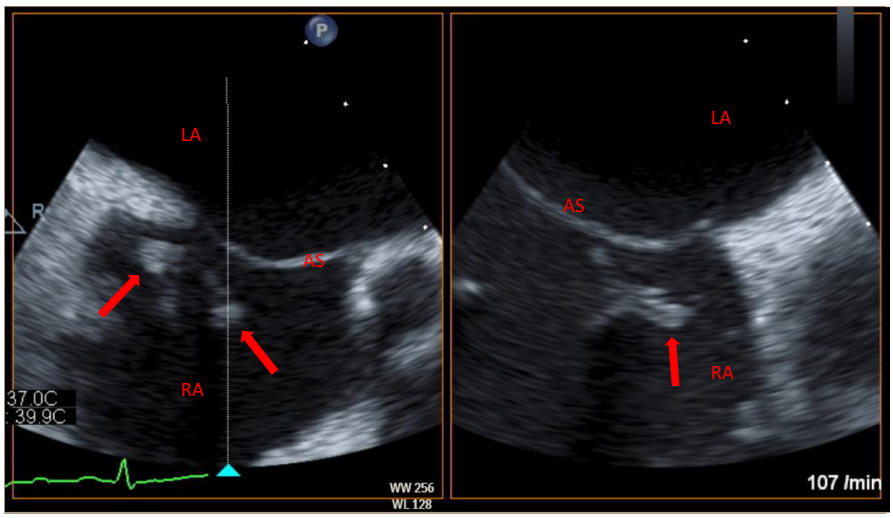

FIGURE 3 2-D Transesophageal echocardiography and X-plane images of the atrial septum (AS), the left atrium (LA) and the right atrium (RA) with arrows highlighting the vegetations.

TABLE 2 Extended thrombophilia and coagulation diagnostics.

Test	Result	Reference Interval	Units
INR	2.4		
APTT	35.5	25–37	sec
Fibrinogen	338	200–390	mg/dl
Anithrombin	114	80–130	%
Protein C	73	70–140	%
Protein S	138	65–150	%
Lupus anticoagulant	Negative		
Cardiolipin Ig-M Antibody	3.7	<16.6	CU
Cardiolipin Ig-G Antibody	3	<46	CU
Factor V-Leiden	wt/wt	wt/wt	wt/wt
Prothrombin-Mutation G20210A	wt/wt	wt/wt	wt/wt
Thrombin-Antithrombin-Complexes (TAT)	11.9	<4.1	µg/ml

Abbreviations: APTT, activated partial thromboplastin time; INR, international normalized ratio.

discussion and after negative results of microbiologic diagnostics. This is a major limitation of our report as we cannot provide a pathological evaluation of the vegetations. All of our conventional blood cultures and blood culture-negative endocarditis (BCNE)-diagnostics (detecting Bartonella henselaeae, Coxiella burnetii, Mycoplasma pneumoniae, Legionella pneumophila, and Tropheryma whipplei) as well as beta-D glucan remained negative. In addition, we used commercially available next generation sequencing (NGS)-based diagnostics for pathogen identification (Noscendo DISQVER®) that can detect bacteria, DNA viruses, fungi, and parasites in a single assay.[12] This highly sensitive assay also showed no evidence of a bacterial or fungal pathogen, so we are confident in diagnosing NBTE in our patient.

Regarding differential diagnoses, cardiac metastasis is also a very rare disease[13] and involvement of heart valves is an uncommon site for manifestation.[14] Evidence of cervical cancer metastasizing to the heart is available from several case reports in recent decades, but none involved the heart valves which makes the diagnosis very unlikely.

In a prospective study, NBTE was significantly more common in cancer patients.[15] Among gynecologic malignancies, ovarian cancer is the most common cancer associated with NBTE.[16] To our knowledge, neither a case of NBTE in a patient with clear cell cervical cancer nor a case of quadrivalvular NBTE in any gynecologic malignancy has been published so far.

Disseminated intravascular coagulation (DIC) can be detected in most NBTE patients,[5] indicating a poor prognosis overall. We would like to emphasize that in our case, NBTE developed in spite of pre-existing anticoagulation. Our patient did not meet the criteria for DIC based on the Overt DIC-score by the International Society for Thrombosis and Hemostasis[17] consisting of low platelet count, elevated levels of a fibrin-related marker, prolonged prothrombin time and decreased fibrinogen levels. Nevertheless, we found high levels of D-Dimers and thrombin-antithrombin complexes (TAT). The presence of TAT indicates ongoing, intravascular thrombin formation as well as the consumption of antithrombin and is associated with DIC.[18]

In addition, the patient showed severe venous and arterial thromboses. Thus, on the one hand, the stroke was likely caused by arterial thrombosis resulting from dislocated thrombotic material from the NBTE of the aortic valve. The occurrence of stroke is a disastrous prognostic sign in NBTE patients with a 6-month mortality of 80%.[19] On the other hand, the acute pulmonary embolisms can well be attributed to emboli from the marked thrombotic masses in the area of the tricuspid and pulmonary valves.

4 | CONCLUSION

To our best knowledge, we report the first case of a quadrivalvular nonbacterial endocarditis in a patient with a clear cell cervical cancer.

AUTHOR CONTRIBUTIONS

VG involved in imaging and drafting of the article; FG took the medical history of the patient; SD advised on imaging; FH, MV, TM, and IS critically revised the article; JW involved in imaging, concept, and drafting of the article.

ACKNOWLEDGEMENT

None.

FUNDING INFORMATION

JW received funding by the Boehringer Ingelheim Foundation "Novel and neglected cardiovascular risk factors: molecular mechanisms and therapeutic implications", by the German Federal Ministry for Education and Research (BMBF EDU-V24), by the University of Mainz ('Inneruniversitäre Forschungsförderung') and by the German Interdisciplinary Association for Intensive Care and Emergency Medicine ('DIVI Research Fellowship').

CONFLICT OF INTEREST

The authors report no conflict of interests.

DATA AVAILABILITY STATEMENT

All data are included in the manuscript.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

ORCID

Johannes Wild https://orcid.org/0000-0002-1446-8101

REFERENCES

1. Bleker SM, van Es N, van Gils L, et al. Clinical course of upper extremity deep vein thrombosis in patients with or without cancer: a systematic review. *Thromb Res*. 2016;140:S81-S88.
2. Orfanelli T, Sultanik E, Shell R, Gibbon D. Nonbacterial thrombotic endocarditis: a rare manifestation of gynecologic cancer. *Gynecol Oncol Rep*. 2016;17:72-74.
3. Erturk NK, Erturk A, Basaran D, Ozgul N. Synchronous ovarian and endometrial endometrioid adenocarcinoma presenting with nonbacterial thrombotic endocarditis and pulmonary thromboembolism: adenocarcinoma with thrombotic events. *Case Rep Obstet Gynecol*. 2015;2015:825404.
4. Aryana A, Esterbrooks DJ, Morris PC. Nonbacterial thrombotic endocarditis with recurrent embolic events as manifestation of ovarian neoplasm. *J Gen Intern Med*. 2006;21(12):C12-C15.
5. el-Shami K, Griffiths E, Streiff M. Nonbacterial thrombotic endocarditis in cancer patients: pathogenesis, diagnosis, and treatment. *Oncologist*. 2007;12(5):518-523.
6. Ziegler E. Ueber den Bau und die Entstehung der endocaridtis chen Efflorescenzen. *Ver Kong Inn Med*. 1888;7:339-343.
7. Gross L, Friedberg CK. Nonbacterial thrombotic endocarditis: classification and general description. *Arch Intern Med*. 1936;58(4):620-640.
8. Lopez JA, Ross RS, Fishbein MC, Siegel RJ. Nonbacterial thrombotic endocarditis: a review. *Am Heart J*. 1987;113(3):773-784.
9. Durie NM, Eisenstein LE, Cunha BA, Plummer MM. Quadrivalvular marantic endocarditis (ME) mimicking acute bacterial endocarditis (ABE). *Heart Lung*. 2007;36(2):154-158.
10. Vlismas PP, Heymann JJ, Marboe CC, Jorde UP, Sims DB. Quadravalvular noninfectious endocarditis. *JACC Case Rep*. 2019;1(3):350-354.
11. Laco J, Steiner I, Havel E. Nonbacterial thrombotic endocarditis involving all four cardiac valves. *Pathol Res Pract*. 2008;204(10):757-761.
12. Kattner S, Herbstreit F, Schmidt K, et al. Next-generation sequencing-based decision support for intensivists in difficult-to-diagnose disease states: a case report of invasive cerebral aspergillosis. *A A Pract*. 2021;15(5):e01447.
13. Hoppe UC, la Rosée K, Beuckelmann DJ, Erdmann E. Heart tumors–Their manifestation through uncharacteristic symptoms. *Dtsch Med Wochenschr*. 1997;122(17):551-557.
14. Butany J, Leong SW, Carmichael K, Komeda M. A 30-year analysis of cardiac neoplasms at autopsy. *Can J Cardiol*. 2005;21(8):675-680.
15. Edoute Y, Haim N, Rinkevich D, Brenner B, Reisner SA. Cardiac valvular vegetations in cancer patients: a prospective echocardiographic study of 200 patients. *Am J Med*. 1997;102(3):252-258.
16. Delgado G, Smith JP. Gynecological malignancy associated with nonbacterial thrombotic endocarditis (NBTE). *Gynecol Oncol*. 1975;3(3):205-209.
17. Gando S, Iba T, Eguchi Y, et al. A multicenter, prospective validation of disseminated intravascular coagulation diagnostic criteria for critically ill patients: comparing current criteria. *Crit Care Med*. 2006;34(3):625-631.
18. Mei H, Jiang Y, Luo L, et al. Evaluation the combined diagnostic value of TAT, PIC, tPAIC, and sTM in disseminated intravascular coagulation: a multi-center prospective observational study. *Thromb Res*. 2019;173:20-26.
19. Yoo J, Choi JK, Kim YD, et al. Outcome of stroke patients with cancer and nonbacterial thrombotic endocarditis. *J Stroke*. 2020;22(2):245-253.

How to cite this article: Gabelmann V, Grabs F, Diestelmeier S, et al. Quadrivalvular nonbacterial thrombotic endocarditis in a patient with clear cell cervical cancer. *Clin Case Rep*. 2022;10:e06434. doi: 10.1002/ccr3.6434