

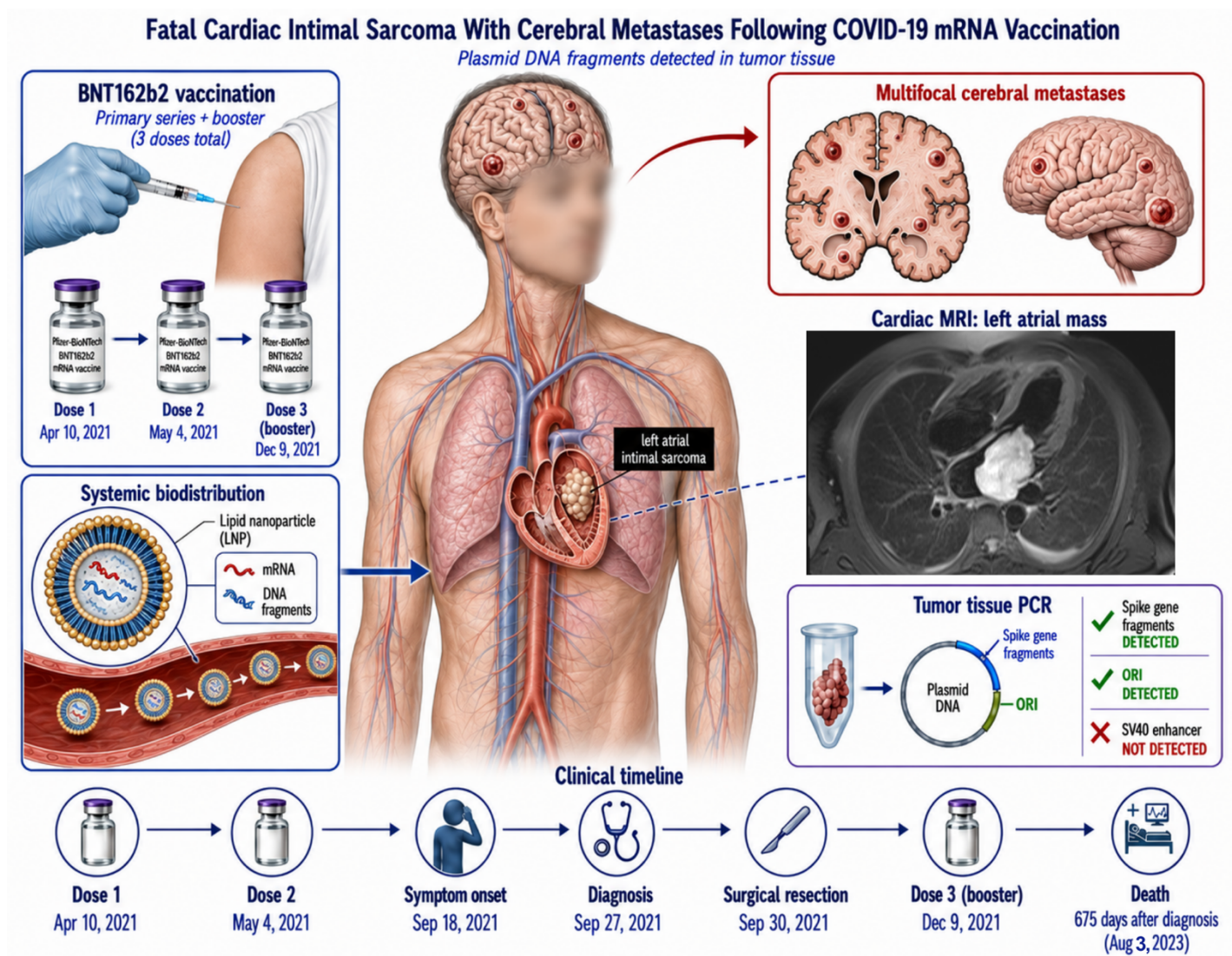
Fatal Cardiac Intimal Sarcoma in a 35-Year-Old Male Following COVID-19 mRNA Vaccination: Plasmid DNA Fragments Encoding the S-Protein Detected in Tumor Tissue

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Abstract

Background: Primary cardiac intimal sarcoma is an exceedingly rare and aggressive malignancy of the heart, characterized by poorly differentiated spindle-shaped cells, frequent MDM2 gene amplification, and a propensity for early metastasis. Residual plasmid DNA from the manufacturing process, carrying a theoretical risk for insertional mutagenesis, has been quantified in mRNA COVID-19 vaccine products at levels far exceeding regulatory thresholds, with direct delivery into human cells by a lipid nanoparticle carrier.

Case Presentation: We present the case of a 35-year-old male with no personal or family history of malignancy and no identified hereditary cancer predisposition who was diagnosed with primary cardiac intimal sarcoma of the left atrium with multifocal cerebral metastases 170 days after his first dose, and 146 days after his second dose, of the Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine. The diagnosis was established only at surgical resection. Comprehensive molecular profiling at a CLIA-certified reference laboratory demonstrated MDM2 and KDR (VEGFR2) amplification, consistent with intimal sarcoma. Whole-body FDG PET/CT showed no extracardiac disease besides cerebral metastases, supporting a cardiac primary. In 2025, archived tissue from the resected left atrial tumor underwent two qualitative research-use analyses. Polymerase chain reaction of total tissue DNA detected three codon-optimized vaccine spike (S) protein coding fragments — distinguishable from wild-type SARS-CoV-2 — and the plasmid backbone origin of replication (ORI) sequence; the SV40 enhancer was not detected. A separate analysis of the same material found no viral S protein nor SARS-CoV-2 nucleocapsid protein, ruling out infection as a source of genetic material. Despite multimodal treatment including surgical resection, doxorubicin-based chemotherapy, radiotherapy, gamma knife radiosurgery, and a total of four craniotomies, the patient developed progressive multifocal cerebral metastases, sustained an intratumoral brainstem hemorrhage, and died 675 days after diagnosis. Serial neuroimaging documented a tumor volume doubling time of approximately 10 days. At that rate, growing the 175 cm³ primary from a single transformed cell would have taken 350 to 385 days — and over 900 days at published sarcoma doubling times — yet only 170 days elapsed between vaccination and diagnosis, indicating acceleration of pre-existing occult disease.

Conclusions: This case documents the recovery of vaccine-derived plasmid DNA sequences from tumor tissue in a patient who developed an exceptionally rare and aggressive cardiac malignancy within 170 days of mRNA COVID-19 vaccination, in the absence of any identified oncologic risk factor. mRNA COVID-19 vaccination is a potential determinant of this malignancy. These findings add to converging in vitro, case-level and population-level evidence concerning the oncogenic potential of residual plasmid DNA in mRNA vaccine products and warrant urgent systematic investigation.

Keywords: cardiac intimal sarcoma; mRNA vaccine; residual plasmid DNA; COVID-19; BNT162b2; MDM2 amplification; case report

1. Introduction

Primary cardiac tumors are exceptionally rare. In a review of 12,485 consecutive autopsies, only seven primary cardiac tumors were identified, an incidence of 0.056% [1]. Malignant primary cardiac tumors are rarer still: analysis of the Surveillance, Epidemiology and End Results registry identified 551 primary malignant cardiac tumors among more than 7.3 million registered cancers, or 0.008%, with sarcomas accounting for the majority [2]. Cardiac intimal sarcoma represents a distinct and particularly aggressive subtype characterized by poorly differentiated mesenchymal spindle cells, a predilection for the left atrium, and a strong association with MDM2 gene amplification [3,4]. In the largest reported series of 100 primary cardiac sarcomas, Neuville et al. identified intimal sarcoma as the most common subtype, accounting for 42% of cases, with 83% of these tumors arising from the left heart [3]. The prognosis for primary cardiac sarcoma remains dismal: median overall survival was 17.2 months among 124 patients in the French Sarcoma Group series and 20 months in a single-institution series of 95 resected patients, reflecting the tumor's aggressive biology and tendency for early metastatic dissemination [4,5].

mRNA-based COVID-19 vaccines were deployed globally on an unprecedented scale following abbreviated preclinical evaluation, and neither genotoxicity nor carcinogenicity studies were conducted before authorization [6]. The Pfizer-BioNTech BNT162b2 product administered in this case uses nucleoside-modified mRNA encoding the SARS-CoV-2 spike (S) protein, encapsulated in lipid nanoparticles (LNPs) [7]; the Moderna mRNA-1273 product employs the same platform. During large-scale manufacturing the mRNA is transcribed in vitro from Escherichia coli–derived plasmid DNA templates, and purification is incomplete: independent quantification by fluorometry found total DNA in every vial tested to exceed the residual DNA limit set by the U.S. Food and Drug Administration and the World Health Organization by 36- to 627-fold across Pfizer-BioNTech and Moderna products; for the Pfizer-BioNTech product administered in this case, the excess ranged from 36- to 153-fold [8]. Because the lipid nanoparticle platform is capable of encapsulating and delivering both RNA and DNA fragments [9] Residual plasmid DNA present during product manufacturing can be co-encapsulated with the mRNA and subsequently delivered into human cells [8].

Evidence bearing on a relationship between mRNA vaccination and malignancy has accumulated from several sources. In vitro, BNT162b2 has been shown to enter human hepatocytes and to

undergo intracellular reverse transcription into DNA within six hours, with concurrent changes in expression and nuclear distribution of the endogenous reverse transcriptase LINE-1 [10]; a subsequent case report described a vaccine plasmid-derived S-protein sequence integrated at chromosome 19q13.42 in a patient with aggressive stage IV bladder cancer arising after mRNA vaccination [11]. At the population level, a cohort of 8.4 million individuals in South Korea found significantly increased one-year risks of multiple cancers following COVID-19 vaccination [12], and a systematic review of 69 publications identified 333 patients across 27 countries, sarcomas among them, in whom malignancy followed COVID-19 vaccination or infection, concluding that the collective worldwide evidence underscores a biologically plausible connection between COVID-19 vaccination and cancer [13]. A convergent analysis of the primary literature has since identified 35 distinct mechanisms by which the mRNA–lipid nanoparticle platform may induce or accelerate malignancy, converging on proto-oncogene activation, mutation pressure, protein–protein interaction network interference, and cancer stem-cell clonal acceleration, and proposing a concurrent-hit model in which simultaneous delivery of several oncogenic inputs compresses a multi-hit sequence that ordinarily unfolds over years [14]. Vaccine-derived material has further been shown to persist in humans far longer than originally assumed: in a longitudinally characterized case, vaccine mRNA was amplified from circulating exosomes 1,284 days after the final dose, and vaccine plasmid DNA elements — three S-protein gene fragments, both plasmid backbone origins of replication, and the SV40 enhancer — were recovered from somatic tissue at 1,364 days [15].

Herein we report a previously healthy 35-year-old male who was diagnosed with primary cardiac intimal sarcoma of the left atrium with multifocal cerebral metastases 170 days after his first dose of the Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine, and in whom molecular analysis of tumor tissue subsequently identified vaccine-derived plasmid DNA sequences. We present the clinical timeline, pathological findings, molecular profiling results, and the tissue analyses, and set out the basis for our assessment that mRNA vaccination is the most proximal oncogenic exposure to this malignancy.

2. Case Presentation

2.1 Patient History and Pre-Vaccination Health Status

The patient was a 35-year-old male. His medical history included remote traumatic brain injury: the diagnostic computed tomography of the head performed at presentation described postoperative changes of a left temporal craniotomy that were already present on a comparison study from 2004, and the medical record documents a history of a ballistic (BB) wound and of seizures. Subsequent magnetic resonance imaging noted mildly asymmetric volume loss in the left anterior temporal lobe consistent with this remote injury. There is no established relationship between remote head trauma or intracranial surgery and the development of primary cardiac sarcoma, and no radiation therapy had been administered at any time; the history is reported here for completeness.

In late May 2019 the patient sustained a concussion resulting in vestibular dysfunction and episodic dizziness, for which he was followed by a neurologist. Post-traumatic stress disorder was also documented and reported by the family to have been well controlled. According to the family and to records held outside the treating institution, a brain magnetic resonance imaging study performed in July 2020 in the course of that neurological follow-up was unremarkable and showed no intracranial mass lesion; this study was not available for direct comparison at the time of presentation and the original images could not subsequently be located.

The patient had no personal or family history of malignancy. Genetic testing performed after the cancer diagnosis identified no hereditary cancer predisposition. He had no history of therapeutic radiation exposure to the chest and no known occupational carcinogen exposure. The family reports that no member of the household, including the patient, was infected with SARS-CoV-2 at any point before or after vaccination; testing consisted of one pharmacy-administered test and multiple home antigen tests, all negative. No confirmatory anti-nucleocapsid serology was performed. He was, apart from the residual post-concussive symptoms described above, in his usual state of health.

2.2 COVID-19 Vaccination

The patient received his first dose of the Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine on April 10, 2021 (Lot EW0158, expiry 7/31/21), and the second dose on May 4, 2021 (Lot EW0172, expiry 8/31/21). Both doses were administered before the onset of any symptoms attributable to the malignancy. A third dose was administered on December 9, 2021 (Pfizer, Lot 331308A), approximately ten weeks after the cancer diagnosis and during active chemotherapy; it

therefore postdates all events relevant to tumor initiation, and postdates the September 30, 2021 cardiac resection from which the tissue subsequently analyzed was taken. All three administrations were documented on a CDC COVID-19 Vaccination Record Card.

2.3 Symptom Onset and Initial Presentation

On September 18, 2021 — 161 days after the first vaccine dose and 137 days after completion of the primary series — the patient developed new-onset headache and malaise. That evening, while driving, he struck a parked vehicle. This collision was subsequently attributed to loss of right peripheral vision secondary to the left occipital mass. Progressive dizziness, headache, and vomiting prompted an emergency department presentation on September 27, 2021, 170 days after the first dose and 146 days after the second.

The sequence of vaccination, symptom onset, diagnosis, treatment, and disease progression is summarized in **Table 1**.

Date	Event
Late May 2019	Concussion with vestibular dysfunction and episodic dizziness; neurology follow-up
July 2020	Brain MRI (outside institution) reported unremarkable, no intracranial mass lesion
10 April 2021	First dose Pfizer-BioNTech BNT162b2 (Lot EW0158)
4 May 2021	Second dose Pfizer-BioNTech BNT162b2 (Lot EW0172)
18 September 2021	New-onset headache and malaise; motor vehicle collision from right visual field loss (161 days after dose 1)
27 September 2021	Emergency presentation. MRI: 7.2 cm left occipital mass with multifocal cerebral metastases. CT: left atrial mass, 44 × 59 mm (170 days after dose 1; 146 days after dose 2)
28 September 2021	Echocardiography: severe functional mitral stenosis. Cardiac MRI impression favored left atrial appendage myxoma with thrombus
30 September 2021	Sternotomy with resection of left atrial mass (9.0 × 7.0 × 5.3 cm); frozen section: high-grade intimal sarcoma
8 October 2021	Left occipital craniotomy; pathology confirmed metastatic high-grade sarcoma
27 October 2021	Molecular profiling: MDM2 and KDR amplification, MSI-stable, TMB low, PD-L1 negative
5 November 2021	Gamma knife radiosurgery to residual cerebral metastases
9 November 2021	Whole-body FDG PET/CT: no FDG-avid extracardiac disease
Mid-November 2021	Doxorubicin-based chemotherapy commenced; cardiac radiotherapy completed January 2022

9 December 2021	Third dose Pfizer-BioNTech BNT162b2 (Lot 331308A), during chemotherapy
26 May 2022	Chemotherapy completed. Surveillance MRI: new 3.5 mm left pontine lesion; enlargement of treated lesions
28 August 2022	Multiple new cerebral metastases, including a 35 × 37 × 41 mm left cerebellar mass (94 days after prior MRI)
29–30 August 2022	Right temporal and suboccipital craniotomies
8 March 2023	Brainstem metastasis 2.0 cm (0.7 cm on 12 January 2023); resection, radiosurgery and re-irradiation all deemed infeasible
25 May 2023	Intratumoral brainstem hemorrhage, 2.7 × 2.4 × 3.8 cm
2 August 2023	Emergency presentation with dyspnea; pulmonary emboli identified
3 August 2023	Death, 675 days after diagnosis and 845 days after the first vaccine dose
August–November 2025	Qualitative molecular analyses of archived cardiac tumor tissue

Table 1. Clinical timeline of vaccination, diagnosis, treatment, and disease course. Intervals from vaccination are given from the first and second doses of the primary series. The third dose postdates the cancer diagnosis and the cardiac resection from which the tissue subsequently analyzed was taken.

2.4 Diagnostic Workup

Non-contrast computed tomography of the head on September 27, 2021 demonstrated a predominantly cystic mass with probable solid components in the medial posterior left cerebral hemisphere, centered at the temporo-parieto-occipital confluence and measuring approximately 6.2 × 3.3 × 4.9 cm, with extensive vasogenic edema and 8 mm of rightward midline shift. A separate 7 × 6 mm hyperdense lesion was identified in the superior right parietal lobe. No prior intracranial imaging was available for comparison.

Contrast-enhanced magnetic resonance imaging of the brain the same day confirmed a peripherally enhancing, partially cystic left occipital lesion measuring 7.2 × 3.8 × 3.7 cm with 0.7 cm of rightward midline shift. Critically, the study also demonstrated additional smaller peripherally enhancing lesions in the right superior parietal lobule (0.7 cm), the right temporal lobe (0.5 cm), and the left frontal lobe (0.6 cm), establishing multifocal metastatic disease at presentation. A focal 2.1 cm region of T2 hyperintensity in the left parietal calvarium was considered indeterminate, possibly a hemangioma, with osseous metastasis not excluded.

Contrast-enhanced computed tomography of the chest, abdomen, and pelvis identified a large hypoenhancing mass filling the left atrium and extending into the left atrial appendage, with portions prolapsing through the mitral valve into the left ventricle, measuring approximately 44 ×

59 mm. A 5 mm solid right upper lobe pulmonary nodule and a 10 mm right hilar lymph node were also noted. No subdiaphragmatic disease was identified. The radiologic differential at that point favored massive thrombus versus a primary cardiac tumor such as myxoma.

Complete transthoracic echocardiography on September 28, 2021 demonstrated a large, partially cystic left atrial mass measuring approximately 7×4 cm that protruded in and out of the mitral valve. The point of attachment was not fully visualized but the mass appeared to originate from the left upper pulmonary vein. It caused severe functional mitral stenosis with a mean diastolic gradient of 15 mmHg at a heart rate of 63 beats per minute. The reporting cardiologist considered the appearance more suggestive of cardiac neoplasm than of thrombus. A limited contrast-enhanced study performed later the same day described the mass as arising from the left atrial appendage, exceeding 50 mm in maximal dimension, and remaining unenhanced after administration of an ultrasound contrast agent, raising the alternative possibilities of left atrial thrombus or a poorly perfused tumor.

Cardiac magnetic resonance imaging with and without contrast, also performed on September 28, 2021 (1.5T scanner; SSFP cine, black-blood HASTE axial stack, phase-contrast flow analysis, rest first-pass perfusion, and late gadolinium enhancement), demonstrated a heterogeneous left atrial mass extending from the left atrial appendage. Biventricular volumes and systolic function were normal (LVEF 69%, RVEF 60%) and the left atrial volume index was elevated at 61 mL/m². Notably, the reported impression did not favor malignancy: the proximal portion of the mass arising in the left atrial appendage perfused slowly but showed late gadolinium enhancement with high T1/T2 signal and was interpreted as most consistent with a left atrial appendage myxoma, while the bulk of the mass, which neither perfused nor enhanced, was interpreted as thrombus of varying stages. The mitral valve was reported as normal appearing without significant stenosis on this study, in contrast to the echocardiographic findings. This discordance is characteristic of left atrial intimal sarcoma, which is well recognized to mimic myxoma and thrombus on non-invasive imaging and to be diagnosed definitively only at surgery [4,5].

The left atrial mass is shown on T2-weighted dark blood imaging from this study in **Figure 1**.

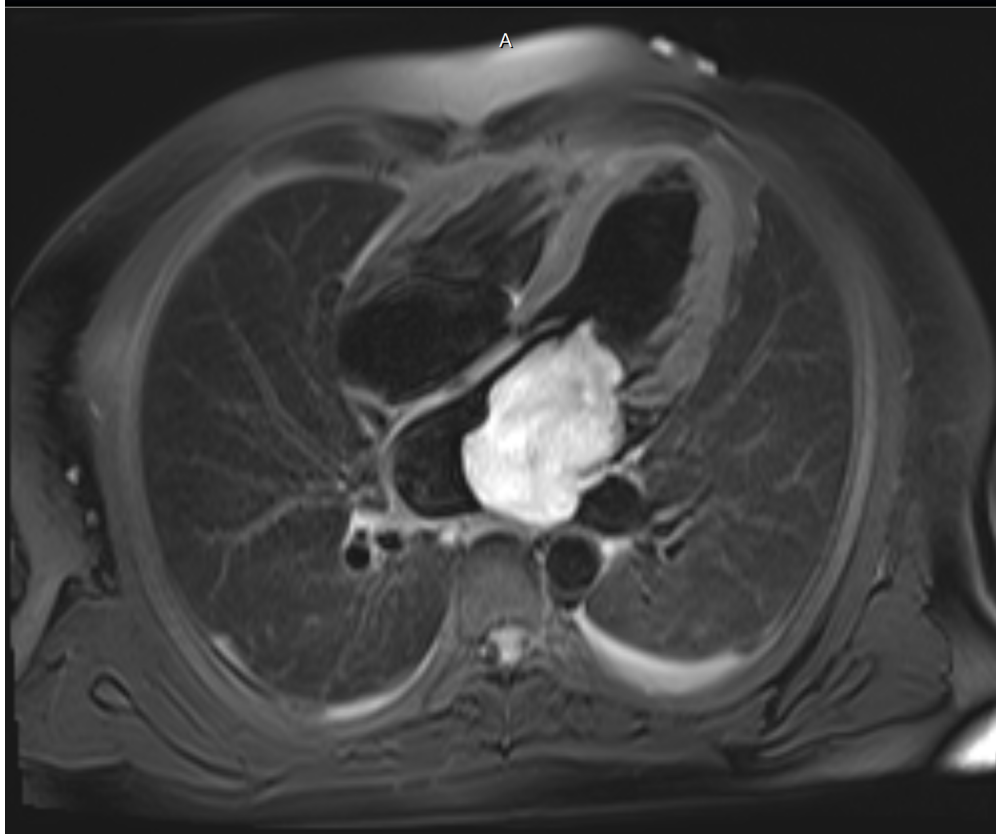


Figure 1. Cardiac magnetic resonance imaging, 28 September 2021: T2-weighted dark blood image of the left atrial mass. Oblique axial image at the four-chamber level. A large, lobulated, markedly hyperintense and internally heterogeneous mass occupies the left atrium and extends from the left atrial appendage, sharply demarcated against the suppressed intracavitary blood pool, myocardium, and mediastinal fat. The marked T2 hyperintensity reflects high tissue water content and is consistent with the mixed cellular, hemorrhagic, and necrotic composition subsequently confirmed at pathological examination, in which hemorrhage and necrosis affected approximately 80% of the resected specimen. Sequence: fat-saturated T2-weighted turbo spin-echo dark blood with parallel imaging; TE 61 ms; TR 1825 ms; slice thickness 5 mm; acquisition matrix 256×125 ; field strength 1.5 T. A, anterior.

2.5 Surgical Management and Pathological Findings

On September 30, 2021, the patient underwent median sternotomy with resection of the left atrial mass. Intraoperative transesophageal echocardiography prior to bypass demonstrated a 6.8×4.8 cm mass in the left atrium originating from the left atrial appendage and prolapsing through the mitral valve into the left ventricle, with moderate-to-severe mitral stenosis attributable to the mass. Following excision, no residual mitral stenosis or regurgitation was present and biventricular function was preserved.

Gross pathological examination of the left atrial mass revealed a largely intact, soft, boggy, red-tan, smooth-surfaced soft tissue mass measuring $9.0 \times 7.0 \times 5.3$ cm, ragged at one end over a 4 cm segment. Sectioning showed a soft, solid, fleshy, heterogeneous, dusky gray and focally gelatinous cut surface with variable red, yellow, and tan-white regions. Hemorrhage and necrosis affected approximately 80% of the specimen, with more viable tissue peripherally. A separate left atrial mass margin ($4 \times 1 \times 1$ cm) and the left atrial appendage ($5 \times 3 \times 1.2$ cm) were submitted separately. Frozen section and subsequent histopathological analysis identified a pleomorphic high-grade mesenchymal malignancy consistent with primary intimal sarcoma.

On October 7, 2021, a stereotactic localization MRI demonstrated that the left occipital mass had decreased modestly in size to 58×38 mm from 70×38 mm, with reduced edema and midline shift, consistent with the effect of corticosteroid therapy. On October 8, 2021, the patient underwent left occipital craniotomy with resection of the mass; pathology confirmed metastatic high-grade sarcoma. Post-operative imaging on October 8, 2021 demonstrated interval resection with a small amount of curvilinear enhancement along the anterior margin of the resection cavity and several persistent small enhancing metastases.

Gamma knife radiosurgery was performed on November 5, 2021 to address the remaining small, non-resectable cerebral lesions. Whole-body FDG PET/CT from skull base to mid-thigh on November 9, 2021 demonstrated no evidence of FDG-avid metastatic disease, with the caveat that evaluation for residual disease in the brain and heart was suboptimal. This finding argues against an occult extracardiac sarcoma primary and supports classification of the atrial lesion as the primary tumor. An implantable venous access port was placed on November 10, 2021 in preparation for systemic therapy.

2.6 Comprehensive Molecular Profiling

Comprehensive molecular profiling was performed at a CLIA-certified commercial reference laboratory on the cardiac specimen (Specimen ID: S21-22404-A10, collected September 30, 2021; specimen received October 20, 2021; report dated October 27, 2021). The pathologic diagnosis on the submitted material was native heart, left atrial appendage tumor, frozen section: pleomorphic high-grade mesenchymal malignancy consistent with primary intimal sarcoma.

Microsatellite instability status was stable by next-generation sequencing. Tumor mutational burden was low at 7 mutations per megabase. Genomic loss of heterozygosity was high, with 17% of tested genomic segments exhibiting LOH against an assay threshold of $\geq 16\%$. No NTRK1/2/3 gene fusions were detected. PD-L1 expression by immunohistochemistry (SP142 clone) was negative at 0%. Mismatch repair proteins MLH1, MSH2, MSH6, and PMS2 were intact by immunohistochemistry, consistent with proficient mismatch repair. Copy number alteration analysis by next-generation sequencing detected amplification of KDR (VEGFR2) and MDM2. Genes with intermediate copy number results included CCND3, FGF10, MYC, and RICTOR; FLT4 and HOOK3 were indeterminate. AXIN2, BTK, HDAC1, MED12, PIK3CB, PRKACA, and PTPN11 were indeterminate by tumor DNA sequencing owing to low coverage. HLA genotyping from RNA sequencing revealed HLA-A*03:01/A*02:01, HLA-B*35:01/B*41:01, and HLA-C*04:01/C*17:01. Seventy-five targeted therapy clinical trials were identified by the laboratory's trial-matching service on the basis of the KDR and MDM2 findings.

The report carried an explicit caveat that the immunohistochemistry and chromogenic in situ hybridization assays were performed on tissue preserved with an unknown fixative, that the stains employed are validated only for formalin-fixed paraffin-embedded tissue, and that results should be interpreted with caution given the potential for false negative results. This qualification applies to the PD-L1 and mismatch repair findings reported above.

2.7 Treatment Course and Disease Progression

Beginning in mid-November 2021, the patient received inpatient doxorubicin-based chemotherapy on a monthly cycle. Cardiac radiotherapy was administered concurrently and was completed in January 2022. Chemotherapy continued until late May 2022, by which point the cumulative doxorubicin dose exceeded 300 mg/m², prompting initiation of low-dose ACE inhibitor and beta-blocker therapy. Surveillance consisted of brain magnetic resonance imaging and cardiac magnetic resonance at approximately three-month intervals.

Cardiac disease control was durable. Follow-up cardiac MRI on November 2, 2021 demonstrated normal chamber sizes with LVEF 57% and no residual mass, and computed tomography of the chest, abdomen, and pelvis on February 25, 2022 showed interval resection of the left atrial sarcoma with no evidence of local recurrence or thoracic metastatic disease. No cardiac recurrence was documented at any point in the subsequent disease course.

Intracranial disease followed a markedly different trajectory. Brain MRI on February 24, 2022 showed interval decrease in the size of the surgical cavity and of the treated right temporal and right parietal lesions. However, surveillance MRI on May 26, 2022 documented early progression rather than remission: mildly thicker nodular enhancement measuring approximately 6×5 mm along the posterior aspect of the operative bed, enlargement of previously treated lesions in the right occipital lobe (4 mm, previously 2 mm) and right posterior temporal lobe (4×4 mm, previously 3×1.5 mm), and a new 3.5 mm enhancing lesion in the left pons that the reporting radiologist considered concerning for an enlarging metastasis. No additional new lesions were identified at that time.

On August 28, 2022 — three months and two days after that surveillance study — the patient presented to the emergency department with ten days of headache, vomiting, dizziness, and new difficulty ambulating. Magnetic resonance imaging demonstrated multiple new supratentorial and infratentorial enhancing lesions. These included a new solid-cystic left cerebellar mass measuring $35 \times 37 \times 41$ mm with mass effect on the medulla and left middle cerebellar peduncle, extending inferiorly to the level of the foramen magnum; a $35 \times 24 \times 24$ mm right temporal lobe mass at the site of what had been a 4×4 mm nodule three months earlier; enlargement of the left pontine lesion from 3.5 mm to 10 mm; a 16 mm right occipital lesion; a new 17 mm left precentral gyrus lesion; and multiple additional smaller new lesions in both frontal lobes and the right parietal region. Ventricular prominence raised concern for obstructive hydrocephalus. Contemporaneous computed tomography of the chest, abdomen, and pelvis showed no acute or suspicious findings and no subdiaphragmatic metastatic disease. These serial studies document growth of at least two intracranial metastases from 4 mm or less to over 35 mm within a 94-day interval.

On August 29–30, 2022 the patient underwent right temporal craniotomy and suboccipital craniotomy for resection of the right temporal and left cerebellar masses respectively, with no definite residual enhancement in either surgical cavity on post-operative imaging. Following these procedures his functional status and quality of life deteriorated substantially. A further left frontoparietal craniotomy was performed in the autumn of 2022; it is documented on all subsequent neuroimaging from November 4, 2022 onward, though the operative record was not among the materials reviewed. Brain MRI on November 4, 2022 showed a mixed treatment

response, including a new small metastasis in the superior left cerebellum, and imaging on January 12, 2023 was entirely stable.

In early March 2023, progressive right-sided weakness involving both the upper and lower extremities developed. Magnetic resonance imaging on March 8, 2023 demonstrated interval enlargement of several metastatic foci, most notably the brainstem lesion, which measured 2.0 cm having been 0.7 cm on January 12, 2023, extending through the left midbrain and pons with diffuse circumferential enhancement and new central susceptibility artifact indicating microhemorrhage. The left occipital lesion had enlarged from 2.4 cm to 3.6 cm. Neurosurgical resection, gamma knife radiosurgery, and repeat radiotherapy were all deemed infeasible given the location of the brainstem lesion. By May 11, 2023 the brainstem metastasis measured 2.8×2.7 cm with increased mass effect on the midbrain, pons, and fourth ventricle.

On May 25, 2023 the patient presented with acute neurological deterioration. Computed tomography demonstrated hemorrhage within the left paramedian pons extending into the midbrain and left middle cerebellar peduncle, measuring approximately $2.7 \times 2.4 \times 3.8$ cm with an internal fluid-fluid level, associated with the known brainstem metastasis. He sustained a further substantial loss of motor and bulbar function following this event, progressing to inability to ambulate, severely impaired speech, and dependence for all activities of daily living, while remaining cognitively intact. Surveillance MRI on June 29, 2023 showed increasing size with decreasing peripheral enhancement of the multifocal hemorrhagic metastases, and imaging on July 24, 2023 showed the multifocal hemorrhagic and necrotic metastases to be stable or decreased in size relative to the prior study, with the dominant left upper pontine mass measuring $15 \times 20 \times 24$ mm.

On August 2, 2023 the patient was transported by ambulance to the emergency department with acute dyspnea. Computed tomographic pulmonary angiography demonstrated pulmonary emboli in the secondary branches of the right upper, middle, and lower lobe pulmonary arteries, with questionable filling defects in the left lower lobe branches and no right heart strain. Computed tomography of the head the same day showed grossly stable multifocal edema and a maturing, smaller hemorrhage in the left dorsal pons, without new complications. The patient died on August 3, 2023, 675 days after diagnosis and 845 days after his first vaccine dose.

2.8 Post-Mortem Molecular Analyses of Archived Tumor Tissue

In 2025, archived tissue from the left atrial tumor resected on September 30, 2021 underwent two separate qualitative analyses, performed between August 20 and November 5, 2025. Both assays are designated for research purposes and are not approved for clinical diagnostic use. Results of both analyses are summarized in **Table 2**.

2.8.1 Detection of plasmid DNA fragments

Total DNA, comprising genomic DNA together with all DNA fragments, was isolated from the cardiac tumor tissue and tested by polymerase chain reaction for five target sequences: three regions of the S-protein gene, corresponding to the front, middle, and end of the gene; the origin of replication (ORI); and the SV40 enhancer. All three S-protein gene fragments and the ORI sequence were detected. The SV40 enhancer was not detected. The same six-amplicon panel — three spike gene targets, two plasmid backbone origin-of-replication targets, and an SV40 enhancer target — together with its primer sequences, its vaccine-vial positive control, and its non-template negative control, has been described in full elsewhere [15].

The assay is reported to detect sequences derived from the Pfizer-BioNTech and Moderna mRNA COVID-19 vaccine products, and the reported interpretation stated that the detected sequences are present in the Pfizer/BioNTech and Moderna plasmid DNA are synthetic and are not present in the SARS-CoV-2 virus. The report explicitly stated that whether the detected sequences are integrated into the human genome was not assessed and cannot be determined by this method, since isolation of total DNA does not permit differentiation between extrachromosomal and integrated forms.

2.8.2 Detection of spike and nucleocapsid protein

A separate analysis of the same cardiac tumor material tested for the presence of S protein and SARS-CoV-2 nucleocapsid protein in the tissue. Both were negative. The reported interpretation was that there was no evidence of viral or vaccine spike and the intact protein is therefore most likely not causative for the development of the tumor, while noting that transformation of normal cells by other vaccine-derived factors, such as plasmid DNA fragments absorbed via lipid nanoparticles, was not investigated by that assay and could not be excluded on its basis.

The report further noted that no antibodies or probes certified under In Vitro Diagnostic Regulation (EU) 2017/746 are currently available for the antigens and nucleic acid sequences in question, that

the reagents used are by definition experimental and restricted to research use, and that confirmation by an independent method should be considered depending on the clinical findings.

Target sequence	Result
S-protein gene fragment 1 (5' region)	Positive
S-protein gene fragment 2 (central region)	Positive
S-protein gene fragment 3 (3' region)	Positive
Origin of replication (ORI)	Positive
SV40 enhancer	Negative
S protein	Negative
SARS-CoV-2 nucleocapsid protein	Negative

Table 2. Results of qualitative molecular analyses performed on archived tissue from the resected left atrial tumor. Analyses performed between 20 August and 5 November 2025. Rows one to five were obtained by polymerase chain reaction of total tissue DNA; rows six and seven by protein-level detection in the same material. All assays are designated for research use and are not approved for diagnostic procedures.

3. Discussion

This case report presents several observations that merit careful scientific consideration. First, we document the occurrence of an exceptionally rare and aggressive primary cardiac intimal sarcoma in a young adult male with no identifiable oncologic risk factors, diagnosed within a narrow temporal window following mRNA COVID-19 vaccination. He had no clinical or serological evidence of prior SARS-CoV-2 infection. Notably, relevant prior neuroimaging for a post-concussion workup includes an unremarkable brain MRI 14 months prior to the diagnosis of cerebral metastases. Second, comprehensive molecular profiling confirmed hallmark features of intimal sarcoma, including MDM2 amplification, and whole-body PET/CT argued against an occult extracardiac primary. Third, analysis of archived tumor tissue four years after resection detected vaccine-derived plasmid DNA sequences, while a parallel analysis of the same material found no detectable S protein.

3.1 Diagnostic Considerations in Primary Cardiac Intimal Sarcoma

Primary cardiac intimal sarcoma is among the rarest of human malignancies [2,3]. In the landmark study by Neuville et al. analyzing 100 primary cardiac sarcomas, intimal sarcomas were identified by the defining molecular hallmark of MDM2 amplification, which was detected exclusively in

this subtype and not in angiosarcomas or other cardiac sarcoma variants [3]. The molecular profile of the present case is consistent with these established features: MDM2 amplification was detected alongside KDR (VEGFR2) amplification in this tumor. Anti-angiogenic therapy has been evaluated in MDM2-positive intimal sarcoma, where pazopanib has been used within multi-agent regimens [16]. The high genomic loss of heterozygosity, low tumor mutational burden, microsatellite stability, and PD-L1 negativity are likewise consistent with the reported profile of this entity and account for the absence of an immunotherapeutic option in this patient.

The imaging course in this case illustrates a well-documented diagnostic pitfall. Despite a large mass causing severe functional mitral stenosis on echocardiography, the cardiac magnetic resonance impression favored a left atrial appendage myxoma with associated thrombus of varying stages, and the initial computed tomographic differential favored massive thrombus versus myxoma. The correct diagnosis was established only on frozen section at resection. Prolapse of a left atrial mass through the mitral valve with functional stenosis is a well-recognized feature of left atrial tumors that mimics myxoma and frequently leads to initial misdiagnosis [4,5]. Clinicians should be aware that a left atrial mass in a young adult, even when imaging characteristics suggest a benign etiology, warrants tissue diagnosis, particularly where the mass is large, heterogeneous, and associated with systemic findings.

3.2 Growth Kinetics and Acceleration of Occult Disease

The growth kinetics documented in this case are notable. The resected primary measured $9.0 \times 7.0 \times 5.3$ cm with hemorrhage and necrosis affecting 80% of the specimen, and multifocal cerebral metastases were already present, 170 days after the first vaccine dose. More directly, serial neuroimaging provides an internally controlled measure of this tumor's growth rate: on May 26, 2022 the right posterior temporal metastasis measured 4×4 mm and no left cerebellar lesion was identified, whereas on August 28, 2022, 94 days later, the right temporal lesion measured $35 \times 24 \times 24$ mm and a new left cerebellar mass measured $35 \times 37 \times 41$ mm. Growth of this magnitude over a three-month interval, in a patient who had completed doxorubicin-based chemotherapy and cranial radiotherapy, provides an internally controlled ascertainment of this tumor's growth rate. Published volume doubling times for sarcoma metastases supply a benchmark against which that rate can be judged. In a series of 40 patients with bone and soft-tissue sarcoma assessed on sequential computed tomography, the median volume doubling time was 21.5 days overall and 26

days for soft-tissue sarcoma specifically [17]; an independent series of 52 metastases in 21 patients reported a median of 34.9 days with a 95% range of 3.9 to 352 days [18]. The rate measured in the present case is therefore approximately two- to three-fold faster than the reported median while remaining within the published range. That second series also found the growth of sarcoma metastases to be well described by a simple exponential function, without evidence of Gompertzian deceleration [18] — the assumption on which the extrapolation below depends.

Applied in that way, the arithmetic is informative. A volume ratio of approximately 670-fold over 94 days corresponds to a volume doubling time of approximately 10 days. The resected primary measured $9.0 \times 7.0 \times 5.3$ cm, a volume of roughly 175 cm^3 , which is on the order of 35 to 38 volume doublings from a single transformed cell. At the doubling time measured in this patient's own tumor, that corresponds to approximately 350 to 385 days of growth, and takes no account of the additional time required for metastatic dissemination. Only 170 days elapsed between the first vaccine dose and diagnosis. Substituting the published soft-tissue sarcoma median of 26 days for the rate measured in this patient would extend that estimate to roughly 910 to 990 days, so the discrepancy does not depend on the unusually rapid growth observed here.

The more parsimonious interpretation of this discrepancy is therefore not that mRNA vaccination initiated this malignancy *de novo*, but that a small, occult and clinically silent sarcoma was already present at the time of vaccination and that its growth and metastatic behavior were then drastically accelerated. A lesion of that size may have been undetectable by any available means, and might have remained indolent, been contained by immune surveillance, or never become clinically manifest. This is the phenotype the concurrent-hit model predicts: not a uniform excess of new cancers, but accelerated progression and metastatic outgrowth in susceptible hosts, including those carrying dormant micrometastases or occult residual disease [14]. On this account the relevant mechanisms are those of tumor promotion rather than initiation: sustained inflammation, impaired immune surveillance, immune tolerance associated with IgG4 class switching, and the structural genomic instability documented in tissue following mRNA vaccination [15]. This framework accords with the population-level data, in which excess cancer risk was detectable within a single year of vaccination [12] — an interval far too short for the initiation of most solid tumors, but fully compatible with the acceleration of pre-existing subclinical disease — and it is the mechanism proposed for the rapid post-vaccination malignancies catalogued elsewhere [13].

Under either account the conclusion is the same. Whether mRNA vaccination initiated this sarcoma or accelerated an occult one, it is the exposure that converted a clinically silent lesion into a 9 cm, widely metastatic and ultimately fatal malignancy within 170 days.

3.3 Detection of Vaccine-Derived Plasmid DNA in Tumor Tissue

The recovery of vaccine-derived plasmid DNA sequences from the primary cardiac tumor requires careful qualification. The manufacturing route by which such sequences reach human tissue is described above: residual plasmid DNA persisting after in vitro transcription is co-encapsulated within the lipid nanoparticle and delivered intracellularly with each dose [8,9]. What this case adds is the recovery of those sequences from malignant tissue itself.

Two technical points warrant statement. The assays were qualitative research-use tests, and Sanger sequencing of the amplification products from this specimen would further strengthen the finding, as has been performed for the origin-of-replication amplicon of this panel in other tissue [15]. In addition, while codon-optimized spike gene sequences are distinguishable from wild-type SARS-CoV-2 and are therefore specific to the vaccine construct, the origin of replication is a generic plasmid backbone element; the specificity of this result rests on the three independent spike gene fragments rather than on ORI positivity. A third consideration bears on the negative protein result specifically. The analyzed material had been archived for approximately four years at the time of testing. Antigen decay in archival paraffin-embedded tissue is a recognized phenomenon that worsens with storage time and can generate false-negative immunohistochemical results, whereas DNA in the same material remains cross-linked, stable and amplifiable, particularly for short amplicons of the size targeted here [19,20]. The molecular profiling laboratory had independently recorded in 2021 that this specimen was preserved with an unknown fixative, that its stains were validated only for formalin-fixed material, and that results should be interpreted with caution given the potential for false-negative results. A negative S protein result on four-year-old archival tissue therefore does not establish that S protein was absent at the time of resection, whereas the DNA findings are not subject to the same constraint.

The negative S-protein and nucleocapsid protein results warrant equal emphasis. The reported interpretation of that assay was that full-length, intact S protein produced by the mRNA vaccine in vivo was not playing a role at the tissue level. The concurrent absence of nucleocapsid protein is consistent with the family's report of no prior SARS-CoV-2 infection and establishes that any

vaccine-derived material in this tissue did not originate from infection or by the production of S protein from the mRNA given as the immunization procedure. The sensitivity of the spike assay has not been established and no certified reagents exist for these targets, so this result does not rule out the presence of S-protein fragments. If residual plasmid DNA is to be implicated, the relevant hypotheses concern the inserted synthetic plasmid DNA itself played an oncogenic role, perhaps by impairing DNA repair or promoting tumor cell proliferation in some other manner.

3.4 Persistence of Vaccine-Derived Material and Epidemiological Context

Three lines of evidence bear directly on this finding. Aldén et al. showed that BNT162b2 enters human liver cells and is reverse transcribed intracellularly into DNA within six hours, accompanied by increased nuclear distribution of LINE-1 ORF1p [10]. Catanzaro et al. reported a vaccine plasmid–derived spike sequence integrated at chromosome 19q13.42 in circulating tumor DNA from a patient with aggressive stage IV bladder cancer following mRNA vaccination [11]. Most directly, Hulscher et al. recovered vaccine plasmid DNA elements — three spike gene fragments, both origins of replication, and the SV40 enhancer — from somatic tissue 1,364 days after vaccination, together with vaccine mRNA in circulating exosomes at 1,284 days and S-protein deposition in endothelial cells, perivascular macrophages and nerve fibers, with nucleocapsid absent throughout [15]. Vaccine-derived genetic material therefore persists in human tissue for years, and the extended intracellular presence of multiple vaccine components raises the possibility of extrachromosomal persistence or insertional events [15].

Detection of vaccine-derived DNA and of S protein are dissociable. In that same series, vaccine plasmid DNA was recovered from tissue in which no spike-encoded mRNA was detectable, while S protein persisted in other compartments [15]. Plasmid DNA fragments are chemically stable and require neither transcription nor translation in order to persist. The absence of S protein in the present tumor therefore does not weigh against the DNA finding, particularly as no certified antibodies exist for these fragments and the performing laboratory recommends confirmation by an independent method.

These molecular observations are paralleled by epidemiological signals. In a population-based cohort of 8,407,849 individuals in South Korea, COVID-19 vaccination was associated with significantly increased one-year risks of thyroid (HR 1.35, 95% CI 1.21–1.51), gastric (HR 1.34, 1.13–1.58), colorectal (HR 1.28, 1.12–1.47), lung (HR 1.53, 1.25–1.87), breast (HR 1.20, 1.07–

1.34), and prostate (HR 1.69, 1.35–2.11) cancer; mRNA vaccines specifically were associated with increased risks of thyroid, colorectal, lung, and breast cancer [12]. A systematic review of 69 publications spanning January 2020 to October 2025 identified 66 article-level reports describing 333 patients across 27 countries in whom malignancy followed COVID-19 vaccination or infection, together with two population-level cohorts and a longitudinal analysis of 1.3 million United States military personnel. Sarcomas were among the malignancies reported, and the authors concluded that the collective worldwide evidence from 2020 to 2025 underscores a biologically plausible connection between COVID-19 vaccination and cancer [13].

Several mechanisms link residual plasmid DNA in mRNA vaccines to oncogenesis. Kyriakopoulos, Seneff, and colleagues have proposed mechanisms by which nucleoside-modified mRNA may deregulate endogenous transposable elements, leading to reverse transcription of vaccine sequences, insertional mutagenesis, and sustained DNA damage [14,21]. The theoretical risk of integration is amplified when DNA is delivered via lipid nanoparticles, which bypass extracellular barriers and deposit their cargo directly into the cytoplasm [8,21]. The FDA's guidance for plasmid DNA vaccines acknowledged the theoretical possibility that DNA integration could activate oncogenes or disrupt tumor suppressor function [22]. The FDA has stated that no safety concerns related to residual DNA have been identified in pharmacovigilance data from the more than one billion doses administered to date [23]. Passive pharmacovigilance systems, however, are not designed to detect malignancies with multi-year latency, and no active surveillance program for oncologic outcomes was established at rollout [13].

3.5 HLA Class I Susceptibility, Limited Cardiac Immunosurveillance, and Proto-Oncogenic Risk

The defining genomic lesion in this tumor is amplification of MDM2, a proto-oncogene whose gene product collapses tumor-suppressor control at the p53–MDM2 protein–protein interaction (PPI). MDM2 binds the N-terminal transactivation domain of p53, blocks p53-dependent transcription, and, as an E3 ubiquitin ligase, targets p53 for proteasomal degradation; amplification of MDM2 therefore phenocopies TP53 loss while leaving a wild-type p53 allele functionally silent [3,24,25,26]. That PPI is the central hub of the p53 tumor-suppressor cluster and the molecular hallmark that distinguishes cardiac intimal sarcoma from other primary cardiac sarcomas [3,27]. Oliner, Vogelstein and colleagues established that MDM2 amplification in human sarcomas is itself an oncogenic event that allows escape from p53-regulated growth control [26]. Independent

experimental work has shown that the SARS-CoV-2 spike disrupts the p53–MDM2 interaction and suppresses p53 transcriptional activation of p21(WAF1), DR5, and MDM2, thereby increasing cancer-cell viability after genotoxic stress [28]. In the present case, spike was not recovered from a four-year-old archival tumor, so a sustained spike–p53 PPI cannot be inferred in the resected mass; the finding remains mechanistically decisive because residual vaccine plasmid DNA encoding codon-optimized spike, together with the plasmid origin of replication, was recovered from the same specimen [11,15]. The copy-number landscape places this tumor in the copy-number-high intimal-sarcoma subtype, which is associated with an immune-cold (non-inflamed) immunophenotype rather than the MSI-H-like inflamed subtype [27]. High genomic loss of heterozygosity (17%), low tumor mutational burden (7 mutations/megabase), microsatellite stability, and PD-L1 negativity (0%) constitute the immune-cold molecular phenotype and account for the tumor's failed adaptive surveillance.

Oncogenic genomes act through rewired PPI networks rather than through isolated genes [29]. Four interaction clusters can be resolved from the molecular profile of this case, and they communicate with one another rather than operating as linear pathways. Cluster 1 is the p53–MDM2 tumor-suppressor module, already converted into a proto-oncogenic driver by MDM2 amplification [24,25,26]. Cluster 2 is the KDR/VEGFR2 angiogenic module: amplified VEGFR2 engages VEGFA, SRC, SHC1, NCK1, PLCG1, and PI3K at the endothelial and tumor-cell membrane and drives migration, permeability, and survival [30]. Cluster 3 is the cell-cycle and translational-growth module defined by intermediate copy-number gains in MYC and CCND3 (G1/S progression) together with RICTOR, the defining subunit of mTORC2. MYC is a canonical proto-oncogene whose activation orchestrates biomass accumulation, proliferation, and immune evasion [31]. The mTOR PPI network is modular: coordinated groups of binary interactions, including the mTOR–RICTOR edge, remodel independently of simple upstream-to-downstream phosphorylation cascades and cross-talk extensively with PI3K, AKT, MYC, and translation-initiation complexes [32,33]. Cluster 4 is the antigen-presentation module and the host HLA susceptibility locus. The patient's class I genotype — HLA-A*03:01/A*02:01, HLA-B*35:01/B*41:01, and HLA-C*04:01/C*17:01 — specifies which peptides can be displayed; HLA-A*02:01 and HLA-B*35:01 are established presenters of spike-derived epitopes. In a low-TMB, PD-L1-negative, immune-cold sarcoma, this same restricted immunopeptidome, compounded by antigen-processing defects common across sarcoma histotypes, yields few

neoantigens for CD8⁺ T-cell surveillance [34,35]. Cross-cluster communication links these modules: VEGFR2–PI3K input activates the RICTOR–mTORC2 cluster; mTORC1/2 activity stabilizes MYC and drives cyclin-D-dependent proliferation; MYC and mTOR jointly reprogram translation and blunt immune visibility [31]; and failure of the p53–MDM2 cluster removes the checkpoint that would otherwise arrest this circuit after DNA damage or insertional stress [26,29,32,33].

Those four clusters do not operate in a lymphoid organ. They operate in the heart, an organ whose immune system is specialized for restraint rather than for tumor clearance [36,37]. Under homeostasis, the myocardium is populated chiefly by self-renewing, CCR2-negative resident macrophages that perform debris clearance, electrical support, and repair, not by dense professional antigen-presenting networks [36]. Resident cardiac T cells exist, including tissue-resident memory populations, but they are sparse, checkpoint-constrained, and tuned to contain infection and autoimmunity against cardiac myosin rather than to survey a copy-number-high sarcoma [37]. Cardiomyocytes and endothelium express immune-checkpoint ligands as a physiologic brake; the same brake that protects the heart from ICI-myocarditis limits effector CD8 activity against a nascent intimal clone [36,37]. Lymphatic drainage of the left atrial endocardium is limited compared with skin or gut. The cardiac immunology cited here characterizes the heart's immune architecture in homeostasis, infection and autoimmunity; neither source addresses malignancy in the heart, and the extension of these constraints to tumor immunosurveillance is our inference rather than a published finding. The result is a three-layer surveillance failure: (i) an organ that does not readily recruit and sustain cytotoxic T-cell effectors; (ii) a tumor that is genomically immune-cold and neoantigen-poor; (iii) a host HLA class I genotype that can present defined spike peptides but cannot offset a low-TMB sarcoma arising in that niche. Genomic collapse defines the tumor. An immune-cold molecular phenotype defines its invisibility. HLA class I restriction defines the host's limited peptide display. Limited cardiac immunosurveillance defines the anatomic theater in which those failures coincided. Proto-oncogene amplification (MDM2, MYC) defines the forward drive.

These host–tumor–organ features become clinically decisive only against the serial BNT162b2 exposure this patient received. Nucleoside-modified spike mRNA is co-packaged with residual *Escherichia coli*–derived plasmid DNA fragments inside lipid nanoparticles that encapsulate and

deliver both RNA and DNA [9]; both nucleic acids are delivered directly into the cytoplasm of transfected cells with every dose [8,9,21]. Independent vial surveys have quantified residual plasmid DNA, including spike-gene fragments and origin-of-replication sequences, at levels that, across multiple lots, exceeded the FDA and WHO residual-DNA limit by 36- to 627-fold across both products, and by 36- to 153-fold in the Pfizer-BioNTech product relevant to this case [8]. Because the LNP is engineered for efficient cellular uptake and endosomal escape [9], contaminating DNA is not an extracellular impurity: it is an intracellular payload, repeated with each injection. Whole-body single-cell imaging has subsequently shown that intramuscular LNP–spike mRNA reaches cardiac endothelium as an off-target compartment and remodels the cardiac proteome [38]. That cardiac tropism deposits serial platform cargo into the precise niche whose immune system is least configured for adaptive clearance of a transformed endothelial/intimal clone [36,37,38].

Once inside the cell, several overlapping mechanisms of action convert that repeated payload into a proto-oncogenic, tumor-promoting insult. First, BNT162b2 enters human cells and is reverse-transcribed into DNA within six hours, with concurrent nuclear redistribution of the endogenous reverse transcriptase LINE-1 ORF1p [10]; nucleoside-modified mRNA has been proposed to more broadly deregulate transposable elements, amplifying insertional risk and sustained DNA damage [14,21]. Second, vaccine plasmid–derived spike sequence has been recovered as an integrated event at chromosome 19q13.42 in circulating tumor DNA from a patient with aggressive post-vaccination bladder cancer [11], and the same six-amplicon plasmid panel used here recovered three spike-gene fragments plus origin-of-replication sequence from somatic tissue 1,364 days after vaccination [15]. Integration was not assayed in the present cardiac specimen, but the DNA finding is not thereby weakened: plasmid fragments are chemically stable, do not require transcription or translation to persist, and were recovered from the primary tumor itself. The FDA has long acknowledged that residual DNA can, in principle, activate oncogenes or disrupt tumor-suppressor function, and impair DNA repair mechanisms [22]. Third, S protein interrupts the p53–MDM2 PPI and suppresses p53 target-gene activation [28]. In a tumor that already carries MDM2 proto-oncogene amplification, any spike-mediated further disablement of residual p53 function is a second hit on the same suppressor hub — an increment re-delivered with each serial dose. Fourth, the LNP carrier itself is highly inflammatory, driving neutrophil infiltration and cytokine release independent of the mRNA cargo [39]. In most tissues, that inflammation might recruit effectors;

in the heart, it more readily recruits CCR2-positive monocyte-derived macrophages that remodel rather than reject, while the resident CCR2-negative pool remains repair-biased [36]. Fifth, repeated mRNA vaccination induces a class switch toward noninflammatory, spike-specific IgG4 [40], a humoral state associated with reduced Fc-effector function and impaired clearance of transfected or transformed cells — the immune-tolerance mechanism already invoked for rapid post-vaccination malignancies [13]. Serial dosing therefore stacks LNP inflammation and IgG4 tolerance onto an organ that already constrains T-cell killing.

Serial BNT162b2 dosing is the relevant exposure, not any single injection. Doses one and two fall inside the 170-day interval in which a 9 cm, already metastatic cardiac primary declared itself and are therefore the initiating or early-accelerating doses. The third dose was given during chemotherapy, after histologic diagnosis; it did not start the tumor. It extended the same LNP–mRNA–plasmid platform to an established immune-cold sarcoma, located in a poorly surveilled cardiac niche, at the exact dose associated with spike-specific IgG4 class switching [40]. Rapid post-exposure progression of solid tumors after repeated mRNA vaccination is the pattern compiled across 333 malignancies [13]. In this case, serial vaccination is the promotional continuum: initiation or early acceleration with the first two doses, and continued platform-driven progression after the third, inside an organ whose immune system is structurally limited in its capacity to stop that progression [36,37].

Taken together, the putative mechanisms of action form a coherent causal chain rather than a list of isolated associations. Residual plasmid DNA and spike mRNA were delivered three times by LNPs into a cardiac endothelial/intimal niche whose baseline immunosurveillance is checkpoint-constrained and macrophage-repair-biased [8,36,37,38]; intracellular reverse transcription and years-long persistence of vaccine nucleic acids are documented in human cells and tissue [10,11,15]; proto-oncogene amplification of MDM2 and intermediate gain of MYC wired a suppressor-failed, growth-addicted circuit that is further vulnerable to spike-mediated interruption of the residual p53–MDM2 PPI [24,25,26,28,31]; VEGFR2, CCND3, and RICTOR gains completed angiogenic and mTORC2 clusters [27,29,30,32,33]; and a low-TMB, PD-L1-negative, HLA-restricted, immune-cold immunophenotype plus IgG4-skewed humoral memory after serial dosing left little adaptive containment [34,35,40]. Population-level one-year excesses of multiple solid tumors after COVID-19 vaccination [12] and 333 compiled post-exposure malignancies

across 27 countries, including sarcomas [13], are the epidemiologic expression of this same serial promotional and proto-oncogenic biology. No alternative exposure — hereditary predisposition, prior radiation, occupational carcinogen, or documented SARS-CoV-2 infection — accounts for an occult or newly initiated lesion becoming a 9 cm, widely metastatic, fatal cardiac intimal sarcoma within 170 days of the first BNT162b2 dose, then progressing through a third platform dose to death 675 days after diagnosis. The weight of this case is the convergence of the vaccine construct recovered from the primary tumor, limited cardiac immunosurveillance, HLA class I restriction of a genomically collapsed and immune-cold sarcoma, proto-oncogene-driven failure of tumor suppression at a defined PPI, the rewired cross-cluster network, and serial delivery of the platform that produced that construct [8,10,11,12,13,15,21,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40].

The interacting elements of this model — MDM2-driven collapse of p53 control, the rewired protein–protein interaction clusters, the constraints on cardiac immunosurveillance, the host HLA class I genotype, and serial platform exposure — are shown together in **Figure 2**.

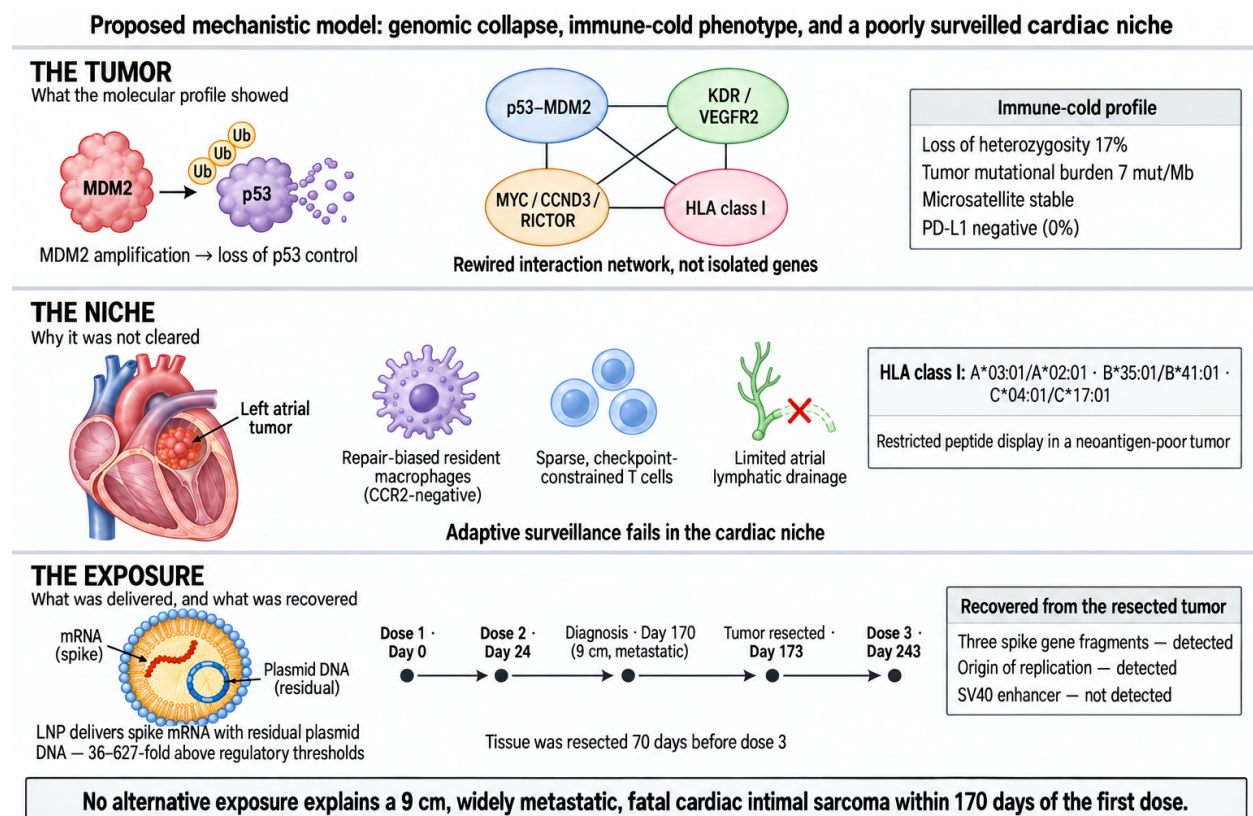


Figure 2. Proposed mechanistic model. MDM2 amplification collapses p53 tumor-suppressor control at the p53–MDM2 protein–protein interaction, converting a suppressor hub into a proto-oncogenic driver. Four interacting clusters — p53–MDM2, KDR/VEGFR2 angiogenic signaling, the MYC/CCND3/RICTOR cell-cycle and translational-growth module, and antigen presentation restricted by the host HLA class I genotype — communicate across the network rather than acting as linear pathways. The copy-number-high, microsatellite-stable, PD-L1-negative, low-tumor-mutational-burden profile defines an immune-cold phenotype. These features operate within the heart, an organ whose resident immune populations are configured for repair and restraint rather than tumor clearance. Serial BNT162b2 exposure delivers spike mRNA together with residual plasmid DNA into this niche. The model is proposed rather than demonstrated; the elements shown were not individually tested in this patient.

3.6 Assessment

mRNA COVID-19 vaccination is a possible determinant of this malignancy. An exceptionally rare cardiac sarcoma arose in a previously healthy young adult with no oncologic risk factor, no hereditary predisposition, no therapeutic radiation exposure and no documented SARS-CoV-2 infection; it was already 9 cm and widely metastatic within 170 days of vaccination; its own measured doubling time places de novo growth from a single cell at 350 to 385 days, so the tumor was accelerated rather than initiated within that window; and vaccine-derived plasmid DNA sequences were recovered from the primary cardiac tumor itself, from tissue resected 70 days before the third dose and therefore attributable only to the primary series. No alternative exposure accounts for these findings, and no competing explanation has been identified. Formal proof of causation is not attainable from a single patient; the weight of this case lies in the convergence of independent lines of evidence, including the recovery of the vaccine construct itself from the primary tumor.

This case adds to a rapidly growing body of evidence that demands urgent investigation rather than continued dismissal. An extremely rare malignancy in a young adult, a proximate temporal relationship with a novel vaccine platform, and the recovery of vaccine-derived DNA sequences from the affected tissue together constitute a signal that cannot responsibly be set aside. Genome-wide integration analyses in vaccinated individuals, systematic tissue surveys, active oncologic surveillance, and mechanistic studies are needed without further delay.

The vaccination history, systemic biodistribution of the lipid nanoparticle carrier, tumor and metastatic burden, molecular findings in tumor tissue, and clinical course are summarized together in **Figure 3**.

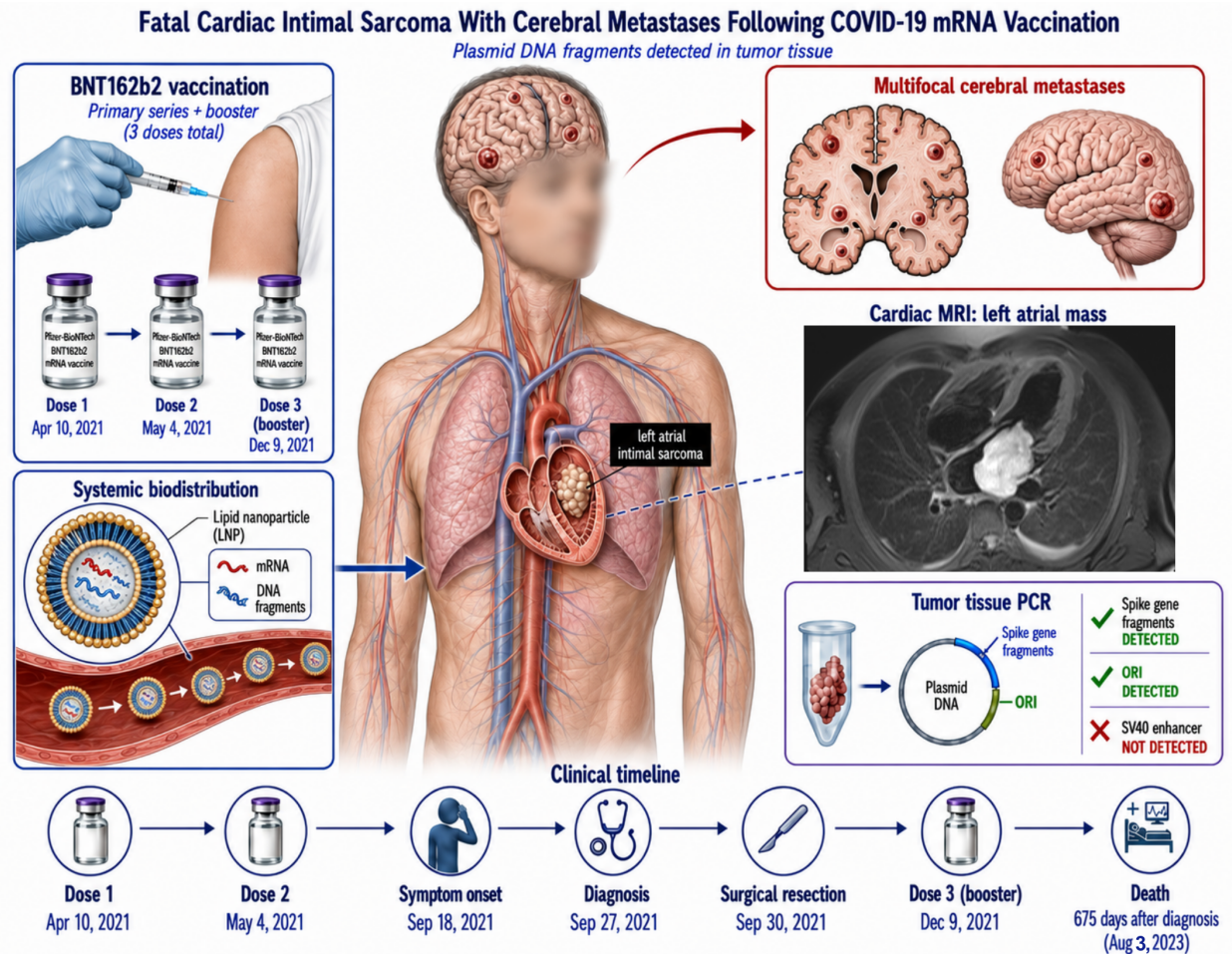


Figure 3. Integrated summary of the clinical course, tumor burden, and molecular findings. Three doses of the Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine were administered on April 10, 2021, May 4, 2021, and December 9, 2021; the third dose postdates both the diagnosis and the cardiac resection from which the analyzed tissue was taken. Residual plasmid DNA fragments co-encapsulated within the lipid nanoparticle carrier are delivered intracellularly upon administration; the biodistribution pathway shown is the proposed route and was not directly measured in this case. Symptom onset occurred 161 days after the first dose and diagnosis 170 days after the first dose, with a left atrial intimal sarcoma and multifocal cerebral metastases identified at presentation. Cardiac magnetic resonance imaging shows the left atrial mass on T2-weighted dark blood imaging. Polymerase chain reaction of DNA extracted from the resected left atrial tumor detected three S-protein gene fragments and the origin of replication; the SV40 enhancer was not detected. The patient died on August 3, 2023, 675 days after diagnosis. Anatomical illustrations are schematic and not patient-specific.

4. Conclusions

We present a previously healthy 35-year-old man in whom primary cardiac intimal sarcoma of the left atrium, with multifocal cerebral metastases already established, was diagnosed 170 days after

his first dose of the Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine, and who died 675 days later. Vaccine-derived plasmid DNA sequences — three independent S-protein encoding gene fragments and the plasmid origin of replication — were recovered from the resected primary tumor.

Several features of this case constrain its interpretation more tightly than a temporal association alone. The analyzed tissue was resected 70 days before the third dose, so the sequences recovered can derive only from the primary series. The S-protein gene fragments are codon-optimized and therefore distinguishable from wild-type SARS-CoV-2, which excludes prior infection as their origin. Consistent with this, nucleocapsid protein was not detected in the tumor and the patient had no documented SARS-CoV-2 infection. Whole-body FDG PET/CT showed no extracardiac FDG-avid disease, supporting a cardiac primary rather than metastasis from an occult source. Comprehensive profiling identified no hereditary predisposition, and the history contained no therapeutic radiation and no occupational carcinogen exposure.

The tumor's growth kinetics model infers tumor growth acceleration after vaccination. Serial imaging across a 94-day interval gives a volume doubling time of approximately ten days; applied to a 175 cm³ primary, growth from a single transformed cell would require 350 to 385 days, against the 170 days available. On conventional growth kinetics the tumor was more likely accelerated than initiated within the post-vaccination window — the phenotype predicted by a concurrent-hit model in which simultaneous oncogenic inputs compress a multi-hit sequence that ordinarily runs over years [14]. Initiation cannot be excluded, since the extrapolation assumes growth from a single transformed cell and the transforming potential of nucleic-acid vaccine platforms in somatic tissue remains uncharacterized. The molecular profile supplies a permissive substrate for that acceleration: MDM2 amplification collapsing p53 control, intermediate gain of MYC, and a copy-number-high, microsatellite-stable, PD-L1-negative, low-mutational-burden immunophenotype arising in an organ whose resident immune populations are configured for repair rather than tumor clearance.

mRNA COVID-19 vaccination is a possible determinant of this malignancy. No alternative exposure accounts for these findings, and the case aligns with population-level data in which excess cancer risk is detectable within a single year of vaccination [12] and with 333 post-vaccination malignancies compiled across 27 countries, sarcomas among them [13]. What

distinguishes this report is that the vaccine construct was recovered from the malignant tissue itself. That finding warrants systematic investigation into the persistence, tissue distribution, and genomic fate of residual plasmid DNA delivered by lipid nanoparticle-based mRNA platforms — through genome-wide integration analyses in vaccinated individuals, tissue surveys with appropriate controls, and active oncologic surveillance.

Declarations

Ethics Approval and Consent to Participate

This report describes a single-patient case based on retrospective review of medical records, imaging, molecular analyses, and other clinical documentation. Written informed consent was obtained from the patient's next of kin for the use of the deceased patient's medical records and other relevant health information for research and documentation purposes. The signed consent specifically authorized access to medical records, imaging, diagnostic testing, specialist reports, and other relevant health information.

Consent for Publication

Written informed consent for publication of the case report was obtained from the patient's next of kin. The consent provided for the use of the deceased patient's medical information for research purposes, with confidentiality protections for both the patient and next of kin.

Conflicts of Interest

The authors declare no conflicts of interest.

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This research received no external funding.

Data Availability

All data supporting the findings of this case are contained within the article.

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