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Case Report

Permanent Myocardial Fibrosis One-Year Following the mRNA COVID-19 Vaccine: An MRI Based Case Report

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Abstract

Introduction: Myocarditis is a disease that has varying severity. With over 250 million people receiving the m-RNA covid vaccine, there have been rare reports of myocarditis or other cardiovascular involvement. However, there is scant long term follow-up data.

Case: We report a 30-year-old otherwise healthy male who was hospitalized for chest pain 3 days after receiving the second dose of the covid-19 vaccination. He had high cardiac laboratory markers (cardiac troponin I peak of 22 ng/mL, normal <0.03 ng/mL) with dynamic ST segment elevations in the inferior and lateral leads. He had a subsequent coronary angiogram and echocardiogram that were normal with elevated inflammatory markers and hence, was diagnosed with myocarditis. He had a cardiac magnetic resonance (CMR) study approximately 8 weeks later (from the date of his second covid vaccine dose) that showed prominent mid to epicardial infero-lateral wall fibrosis (corresponding to the similar territory seen via electrocardiogram) with normal T1 and T2 mapping. A repeat CMR was performed 5 months later (from the second vaccine dose) that showed persistent, though partially resolving fibrosis, despite the full resolution of all symptoms and biomarkers. A third CMR study was performed 1 year from initial presentation that showed permanent though lessened fibrosis. The scar pattern on CMR is despite the normalization of all symptoms, cardiac and inflammatory biomarkers, and echocardiography in disease surveillance.

Conclusion: This case demonstrates acute myocarditis following the second dose of the mRNA covid-19 vaccination with evidence of myocardial fibrosis on initial CMR after 2 months and on follow-up CMR scans 5 months and 1 year, respectively, from vaccine administration. It provides insight into its natural course and an insidious recovery following mRNA vaccine related myocarditis as well as the utility of CMR in clinical management.

Keywords: Cardiac magnetic resonance imaging; CMR; Fibrosis; Covid vaccine; Myocarditis

Abbreviations: CMR: Cardiac Magnetic Resonance; COVID-19: Coronavirus Disease 2019; VAERS: Vaccine Adverse Event Reporting System; Tmax: Maximum Recorded Temperature; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; FEU: Fibrinogen Equivalent Unit; WBC: White Blood Cells; ESR: Erythrocyte Sedimentation Rate; CRP: C-reactive Protein; ECG: Electrocardiogram; LGE: Late Gadolinium Enhancement (fibrosis); PSIR- Phase Sensitive Inversion Recovery

Introduction

Myocarditis is a heterogeneous disease associated with acute or chronic inflammation of the myocardium with extremely varied clinical manifestations, ranging from mild to severe [1-5]. The association between myocarditis and other cardiovascular involvement from the covid-19 vaccines (Pfizer-BioNTech and Moderna) was notified by the US Centers for Disease Control and Prevention's safety committee on the June 23rd, 2021 [6]. As more than 250 million people have received at least one dose of COVID-19 vaccine in the United States, as of February 5th, 2022; rare reports of myocarditis have been made to the Vaccine Adverse Event Reporting System (VAERS) (I.e: Pfizer-BioNTech, Moderna) in the United States [7-10].

We report a case of an otherwise healthy young adult who presented to our hospital with acute myocarditis 3 days after receiving the second dose of the mRNA COVID-19 Vaccination. Cardiovascular Magnetic Resonance Imaging (CMR) was performed 2 months later that showed myocardial fibrosis of the lateral wall that persisted on scan 3 months following. A follow-up CMR (one year since symptoms) showed persistent fibrosis despite the full resolution of symptoms and normalization of inflammatory and cardiac biomarkers.

Case Report

A 30-year-old otherwise healthy male with no past medical history presented to our emergency department with substernal chest pain, 3 days after he had received the second dose of the mRNA COVID-19 Vaccine. He experienced flu-like symptoms including subjective fevers and general malaise within 1 day after vaccine administration. On day 3, he woke up at 5 AM with a sensation of pressure like chest pain that was substernal and associated with diaphoresis and mild nausea that prompted emergency room visit. His prior dose of the vaccine (1st dose) was several weeks earlier where he reported a mild flu-like illness that was self-limiting. He denied shortness of breath, cough, rhinorrhea, anosmia, or sick contacts, or prior exposure to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). There was no significant social history or a history of illicit drugs or alcohol use. Upon arrival to the hospital, the patient's blood pressure was 124/74 mm Hg; heart rate was 74 bpm, respiration was 20 bpm, temperature was 97.2 degrees F, SpO2 was 100% on room air. Physical examination was otherwise unremarkable.

Laboratory and imaging

Initial labs revealed a significant elevation in Troponin I of 15.4 ng/mL (normal range <0.03 ng/mL). D-dimer was <0.27 ug/ml Fibrinogen Equivalent Unit (FEU), (normal range <0.50 ug/mL FEU). A computed tomography angiography of his pulmonary arteries with intravenous contrast was performed emergently at the discretion of the emergency room physician (prior to d-dimer result and to rule out vaccine induced thrombo-embolism) that showed no evidence of pulmonary emboli, aortopathy or

acute pulmonary pathology. SARS-CoV-2 polymerase chain reaction (PCR) was negative. White blood cells (WBC) were 7 (thousand per cubic milliliter) K/uL (normal range: 4.5-10.3 K/uL). Neutrophil count was 60.8% (normal range 44.9-72.6%), Lymphocyte count was 23.7%, Eosinophil was 4.2% (normal range 0.0-7.2%), Basophil was 0.4% (normal range 0.2- 1.4%), Monocyte was 10.8% (normal range 4.6-13.9%). Erythrocyte sedimentation rate (ESR) was 11 (millimeters per hour) mm/hr (normal range 0-15 mm/hr). C-reactive protein (CRP) was 40.86 (milligrams per liter) mg/L (normal range: < 5.1 mg/L). A repeat Troponin trended upwards and peaked at 22.3 ng/ml.

Initial electrocardiogram (ECG) is listed in Figure 1, below. A repeat ECG revealed ST segment elevations in the inferior and lateral leads, Figure 2. Chest X-ray was without significant findings.

Hospital course

The patient was initially treated as an acute coronary syndrome due to the nature of his pain, elevated cardiac enzymes, and ECG abnormalities via guideline directed management for acute coronary syndrome. On the second day of hospitalization, he had undergone a coronary angiogram, which revealed no coronary artery disease. Transthoracic echocardiogram revealed no regional wall abnormalities and a left ventricular ejection fraction (EF) >55% with a normal right ventricular ejection fraction and no pericardial effusion. The patient was started on colchicine and ibuprofen with subsequent resolution of chest pain for the diagnosis of myo-pericarditis and subsequently discharged. The patient reported full resolution of all symptoms 3 weeks later with complete normalization of his ECG.

Two months later (since the second dose of COVID-19 Vaccine), the patient underwent elective CMR, using General Electric Signa Artist 1.5 Tesla with scan parameters of images in field of view 36 x 32 mm, slice thickness 8 mm, 0 mm spacing, matrix 200 x 200 pixels mm, number of excitations 1. Gadolinium-enhanced imaging was performed approximately 10 min after administration of 0.1 mmol/kg body weight of gadobutrol (Gadovist; Bayer). It revealed evidence of mid-epicardial fibrosis of the basal infero-lateral and lateral walls. There was homogenous signal intensity on T2 weighted images with normal native T1/T2 values on respective maps throughout the ventricle (Figure 3, a-e). The pericardium was normal in thickness without evidence of effusion or interventricular dependence.

The patient underwent follow-up CMR study 3 months after initial scan (5 months since the second vaccine dose) to document

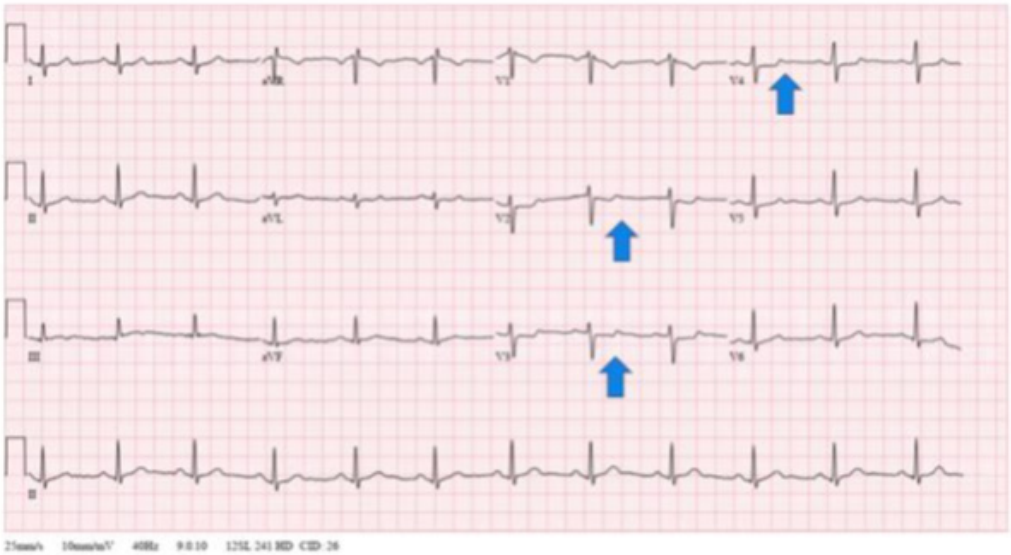


Figure 1: First ECG on the day of admission- showing sinus rhythm with T-wave inversions and ST segment depressions in precordial leads V2-V4 (arrows)

resolution of his fibrosis. It showed persistent, though diminished, fibrotic areas in the same corresponding territory as prior scan and normal T1 and T2 values on respective T1/T2 maps (Figure 4, a-e). He went an additional CMR (third scan) one year from initial presentation that showed persistent fibrotic scar pattern (Figure 5). The patient remained symptom free.

Discussion

Recently published reports suggest the rare occurrence of myocarditis in the young males, with less than *106* cases per million doses of the COVID-19 vaccine and in most instances within the first week after receiving the second dose of the COVID-19 vaccine.6 Almost one hundred percent of them had significantly elevated cardiac troponin levels (10-fold to 400-fold the upper limits of their respective reference ranges) [2,10-12]. Other recent reports suggest that prior exposure to either COVID-19 infection or the COVID-19 vaccine (1st dose) significantly increased the risk of myocarditis after the second exposure [5,13].

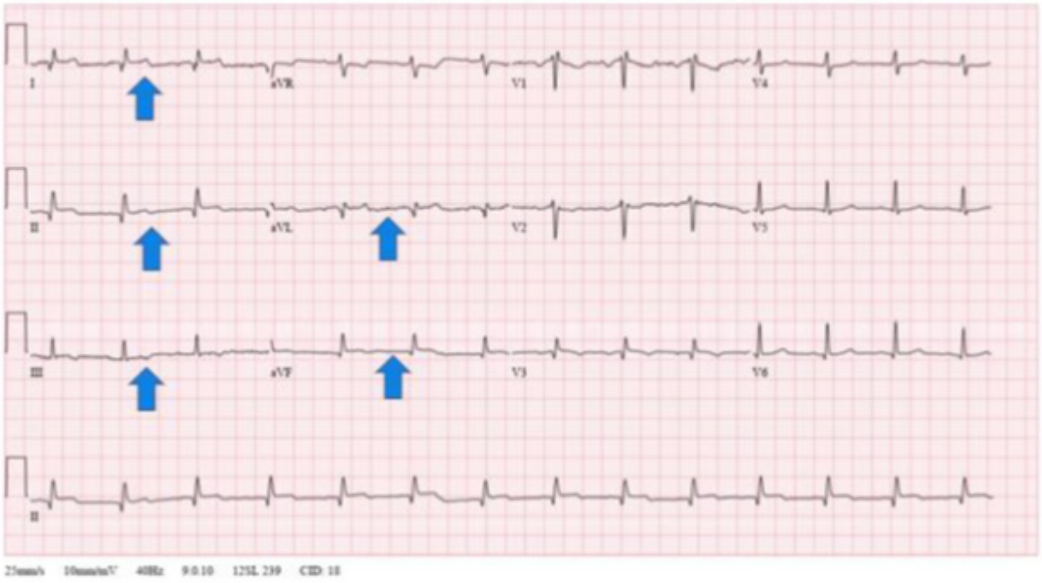
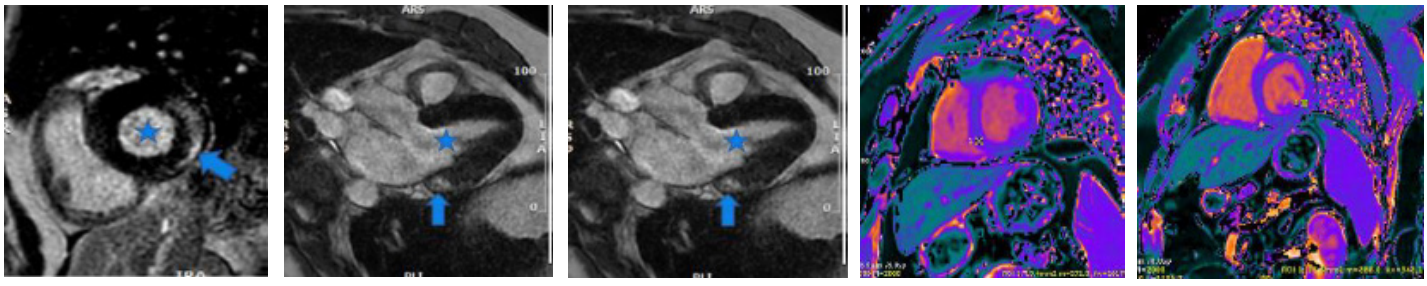


Figure 2: 2nd ECG on day 2- Sinus rhythm with nonspecific ST and T wave abnormality lead V3, and infero-lateral ST segment elevations (arrows) with low voltage.



a **b** **c** **d** **e**

Figure 3 (a-e): First CMR scan 2 months post presentation with basal segment, mid to epicardial LGE in the infero-lateral and lateral wall in white (blue arrows point to LGE, star denotes the left ventricular cavity); Phase-sensitive-inversion-recovery (PSIR) in short axis view (a); fast gradient echo in 3-chamber view (b) and gradient echo in short axis view (c); Unifrom T1 maps in short axis view (d-e, normal, T2 maps not shown).

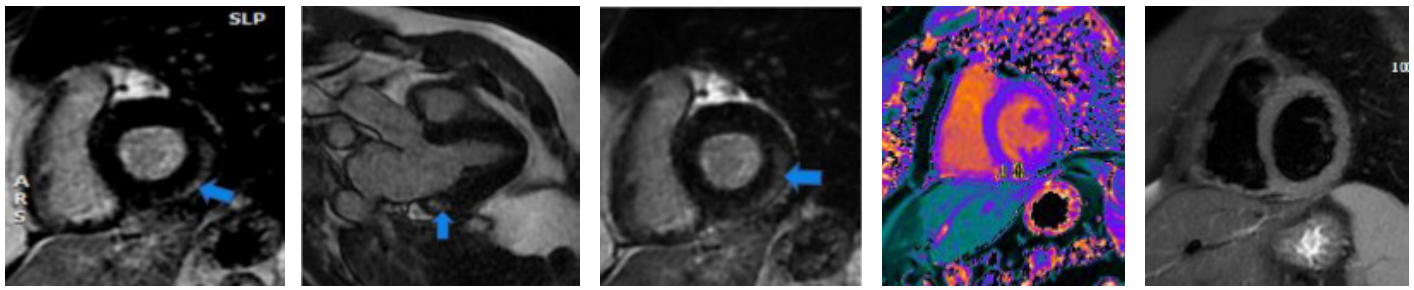


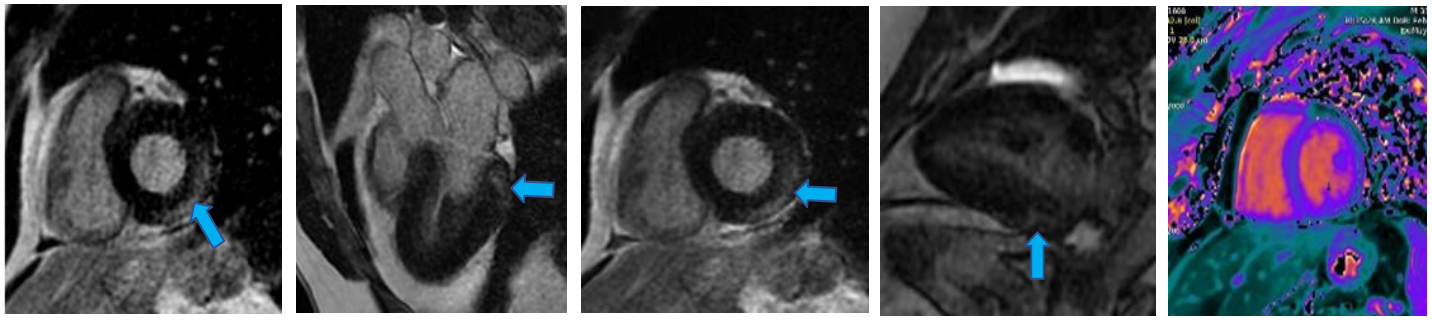
Figure 4 (a-e): Follow-up CMR 5 months from symptoms with partial resolution of infero-lateral and lateral wall fibrosis with LGE (blue arrows); PSIR short axis view (a); fast gradient echo in 3-chamber view (b); gradient echo short in axis view (c); T1 map with uniform signal at 1000 milliseconds in short axis view (d); T2 weighted image with fat saturation and homogenous signal intensity in short axis view (e).

The underlying mechanism of mRNA COVID-19 vaccine -induced myocarditis is yet to be discovered. However, possible theories suggest that excessive innate immune activation by both lipid non-particle and RNA components of COVID-19 vaccines can cause myocarditis. Once the endosomal toll-like receptors are activated they can trigger an inflammatory cascade that can lead to myocardial inflammation and injury [14].

Due to the wide variation in the severity of illness in myocarditis, ranging from self-limiting to fulminant heart failure with cardiogenic shock and / or death, the diagnosis and surveillance of myocarditis can be a challenge to clinicians [14,16,17]. Often, such a diagnosis is made clinically based on the history of various exposures to viral, infectious or immunization exposures [16]. Laboratory makers such as high sensitivity troponin assays as well as the evaluation of cardiac function via echocardiography are often the primary methods for its diagnosis, while myocardial biopsy is reserved for life threatening cases and is considered the gold standard. However, even with biopsy, there is not one widespread sole method for diagnosing myocarditis and often the laboratory, imaging and clinical history together is used [12-17]. Furthermore, despite the high prevalence of elevated laboratory inflammatory or biomarkers in acute phases, the utility in using such markers to aid in the assessment of chronic phases or resolution is not well established.

CMR is the gold standard in detecting cardiac anatomy and ventricular function and has been shown to have high accuracy for the diagnosis and surveillance of myocarditis [20,26]. Patients with acute myocarditis have been found to have significantly lower ejection fraction and wall motion abnormalities in comparison to echocardiography [27]. The tissue based CMR markers, such as T2-weighted ratio, early gadolinium enhancement, and late gadolinium enhancement (LGE) are used by The Lake Louise criteria, which is currently the recommended diagnostic criteria [18,19]. LGE effectively identifies the areas of damage of myocardium with high affinity [9]. The damage in the myocardium can be visualized after intravenous injection of gadolinium, which is retained for prolonged period in the damaged areas, such as scarred, fibrosed or edematous areas of the myocardium, due to different wash-in and wash-out kinetics [4,9]. This test has a reported sensitivity of 100% and specificity of 90%. [4,9].

Further advances in CMR have used T1 and T2 mapping with or without extracellular volume assessment and have shown to augment the diagnostic utility of CMR in myocarditis [18,20-22]. Myocardial ischemia, infarction or edema in focal areas of the myocardium can be detected by T1 or T2 weighted sequences with mapping [21]. T1 maps can detect edema in infarction with a high sensitivity and specificity [21]. On the other hand, T2-weighted sequences with mapping can assess myocardial edema in ischemic and other non-ischemic heart diseases, such as myocarditis, Takotsubo cardiomyopathy, and transplant rejection [21,24]. Some studies suggest that myocardial abnormalities can be detected to a greater extent along with the differentiation of the convalescent stages in myocarditis with native T1 mapping



a b c d e

Figure 5 (a-e): Follow-up CMR 12 months from initial presentation with persistent basal infero- lateral and lateral wall fibrosis with LGE (blue arrows); PSIR short axis view (a); fast gradient echo in 3-chamber view (b); gradient echo fiesta short in axis view (c); gradient echo fiesta in 2 chamber-view with fibrosis of the basal inferior wall taken at a lateral slice. (d); T1 map with uniform signal at 1000 milliseconds in short axis view (e).

when used in conjunction with T2-weighted imaging and LGE [22]. Other studies have suggested that acute myocarditis can be differentiated from recent heart failure by myocardial T2 values [22].

Our findings demonstrate multiple parameters that confirm myocarditis while demonstrating an insidious course. Our patient had significant ECG changes, elevated cardiac biomarkers (without evidence of coronary artery disease or vasospasm during angiography) in conjunction with recent vaccine exposure 3 days prior, and elevated inflammatory markers (CRP). He was hence diagnosed and treated for myocarditis. Due to his chest pain and nonspecific ECG changes, we treated him with a short course of non-steroidal anti-inflammatory medications overlapping with the clinical treatment of pericarditis. We were unaware at the time of treatment of the correspondence of his infero-lateral ECG changes with the same fibrotic territory later documented on CMR. Despite initial elevated cardiac markers, he had normal left ventricular function on echocardiography without wall motion abnormalities or effusion and resolved symptoms with clinical and hemodynamic stability and down trending biomarkers. We, hence, did not feel that myocardial biopsy or further pharmacotherapies were warranted and recommended to follow the patient closely on the outpatient basis. Our case had several limitations. After our patients first dose of covid-19 related vaccine, he had a self-limited illness. Due to this, he was not evaluated or screened for any cardiac involvement and we hence, had no objective data such as ECG, imaging, or cardiac or inflammatory biomarkers. In addition, his first CMR scan was scheduled electively due to resolved symptoms but was notably delayed due scheduling conflicts. Furthermore, he had no significant family history or other notable prior illness including covid-19 exposure, however, a prior insidious myocardial process such as subacute myocarditis cannot be excluded. However, we felt he had marked severity in symptoms shortly after the second dose of vaccine, which also correlated with laboratory biomarkers and dynamic ECG changes that suggested direct myocardial involvement related to the second vaccine dose. We may ultimately consider endomyocardial biopsy based on his clinical course and follow-up.

It is noteworthy that viral myocarditis and recent studies with covid-vaccine related myocarditis, compared with covid-19 myocarditis, has been shown to have a higher predominance of involving the lateral wall [25-27,28]. It remains unclear to us if such a similar location of fibrosis pattern in our patient following the vaccine administration is coincidental or ultimately related to mRNA vaccine technology. It is also of note that at the time of first CMR scan, the patient was symptom free and there was no concurrent myocardial edema on T2 weighted imaging or abnormalities on T1 or T2 mapping, respectively. Due to the normal T1 and T2 weighted images, as well as T1 and T2 mapping, we suspected that his myocarditis was subacute or resolving at the time of his first scan. We, hence, recommended close follow-up, holter monitoring for arrhythmias and limitation of intense aerobic

activities until further resolution of his fibrosis was demonstrated. We chose to repeat CMR scan in 3 months, however, this strategy was also not well defined in current guidelines and was at the provider discretion (along with the recommendations for aerobic exercise limitation). To our surprise, his repeat CMR 5 months and 1 year showed persistent fibrosis despite remaining symptom free with the normalization of all cardiac and inflammatory biomarkers. To the best of our knowledge, this is the only CMR based report that has documented the prolonged time course of 1 year of myocardial fibrosis in the setting of covid-19 vaccine related myocarditis. Overall, it correlates with a benign clinical course and sheds information on an insidious and slow resolution of myocardial fibrosis that may persist and lag in the time after improvement of symptoms and other biomarkers. Further and larger studies are suggested.

Conclusion

This case demonstrates persistent myocardial fibrosis on CMR 2 and 5 months, and 1 year from illness after the second dose of the mRNA vaccine. The fibrosis pattern has notably diminished in size but remains on most recent scan long after the normalization of all inflammatory and cardiac biomarkers and symptoms. The fibrosis location on CMR also correlates with initial ECG territorial involvement on presentation and provides insight into the natural course and insidious involvement of covid-19 vaccine related myocarditis as well as the utility of CMR in aiding its diagnosis and management.

Declarations

Ethical approval was not applicable for this paper.

Consent for publication was obtained. All images and data have been kept anonymous.

Availability of data and materials is available upon request.

All authors report no competing interests, funding or financial disclosures.

Author contributions

AFM Ashik Imran is the primary author.

Won Jun Park is an additional author and contributor.

Michael Sood is an additional primary author and mentor.

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