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Case Report

Ixekizumab-Induced Cardiac Sarcoidosis: A Case Report

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ABSTRACT

A 58-year-old man with a history of hypertension and psoriasis presented with acute-onset heart failure with an ejection fraction of 25%-30%. During the work-up, cardiac magnetic resonance imaging showed a pattern of inflammation consistent with sarcoidosis, which was confirmed with (18)F-fluorodeoxyglucose positron emission tomography . The patient was recently initiated on ixekizumab for psoriasis, which was then discontinued. This discontinuation resulted in complete resolution of cardiac sarcoidosis, with establishment of normal ejection fraction. This result suggests a potential causal association of ixekizumab-induced cardiac sarcoidosis, which is a rare phenomenon. Elucidation of the mechanism behind the effect of ixekizumab may provide insights into the possible mechanism(s) behind cardiac sarcoidosis.

RÉSUMÉ

Nous exposons le cas d'un homme de 58 ans ayant des antécédents d'hypertension et de psoriasis qui a présenté une insuffisance cardiaque d'apparition soudaine avec fraction d'éjection de 25 à 30 %. À l'investigation, l'imagerie par résonance magnétique cardiaque a révélé une inflammation évocatrice d'une sarcoïdose, un diagnostic qui a été confirmé par tomographie par émission de positons au ^{18}F-fluorodésoxyglucose. Le patient avait récemment commencé un traitement par l'ixékizumab contre le psoriasis, qui a par la suite été abandonné. La sarcoïdose cardiaque est complètement disparue à l'arrêt de ce médicament, et la fraction d'éjection est redevenue normale. Ce résultat indique qu'il pourrait y avoir un lien de causalité entre l'ixékizumab et l'apparition d'une sarcoïdose cardiaque, un phénomène somme toute rare. L'élucidation du mode d'action de l'ixékizumab pourrait fournir des pistes pour expliquer les mécanismes à l'origine de la sarcoïdose cardiaque.

Ixekizumab is a high-affinity immunoglobulin G4 monoclonal antibody against interleukin (IL)-17a. It is currently approved for the treatment for plaque psoriasis. Its safety profile has been explored predominantly through the UNCOVER trials (Trials of Ixekizumab in Moderate-to-Severe Plaque Psoriasis), which only identified hypertension as a cardiovascular adverse event and was noted in ~7.5% of the patients.[1,2] We present a potential case of ixekizumab-induced cardiac sarcoidosis.

Case Presentation

A 58-year-old man with a history of hypertension and psoriasis presented to an outside hospital with a 1-week history of dyspnea. His only medications were losartan 50 mg (hypertension) and ixekizumab (started on 80 mg subcutaneously once every 4 weeks at 6 weeks prior to the presentation). Atrial fibrillation was noted, with an ejection fraction (EF) of 20%-25% with global wall motion abnormality (Video 1, view video online). A single-photon emission computed tomography scan was done, which was normal. He was discharged after an electrical cardioversion.

He presented to our hospital 1 day after cardioversion, with worsening dyspnea. At the time of presentation, the patient was on metoprolol and rivaroxaban. Physical exam was benign other than sinus tachycardia and bilateral pitting edema. Laboratory work-up demonstrated significantly elevated brain natriuretic peptide at 3066 pg/mL (< 125 pg/mL) but normal complete blood count, electrolytes, and troponin level. An electrocardiogram showed normal sinus rhythm with no conduction abnormalities (Supplemental Fig. S1A). A computed tomography chest scan

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See page 120 for disclosure information.

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Novel Teaching Points

- IL-17 antagonist may precipitate cardiac sarcoidosis.
- Future research should look at an IL-17—mediated mechanism as a possible cause/effect of cardiac sarcoidosis.
- Emergence of new biologics warrant thorough analysis, as they may have detrimental effects on cardiac health.

demonstrated mediastinal/hilar lymphadenopathy with scattered pulmonary nodules. During the follow-up, echocardiogram 2 months after initial assessment showed reduced EF of 43%, left atrial volume of 58 ml/m^2 with grade-III diastolic dysfunction, and mild mitral and tricuspid regurgitation. Given that there was an interval improvement in left ventricular EF, it was felt that the decreased left ventricular EF might have been due to tachycardia-induced cardiomyopathy. The patient underwent extensive work-up, as indicated in Figure 1A. Investigations were remarkable for only a positive Coxsackie B titer; however, given the high-level titer, this was deemed to be a chronic infection.

The patient also underwent cardiac magnetic resonance imaging (Fig. 1, B and C), which was significant for mid-wall fibrosis predominantly in the basal septum. The pattern of the cardiac magnetic resonance imaging scan, along with hilar lymphadenopathy, raised suspicion for potential sarcoidosis; thus, fluorodeoxyglucose positron emission tomography (PET) imaging was performed. The patient fasted for at least 15 hours prior to PET imaging. The PET scan showed illumination of the basal segment as well as the right atrial region (Fig. 2A), as well as hilar nodes (Supplemental Fig. S1B).

On day 9 of hospitalization, the patient underwent endobronchial ultrasound-guided fine-needle aspiration of lymph node station 7, with pathology demonstrating non-necrotizing granulomas, with negative culture and no malignant cells seen, concerning for sarcoidosis. Due to a previous report of ixekizumab-induced pulmonary sarcoidosis,[3] this medication was discontinued. High-intensity steroids were deferred, as the patient was stable. A cardiac biopsy was not performed.

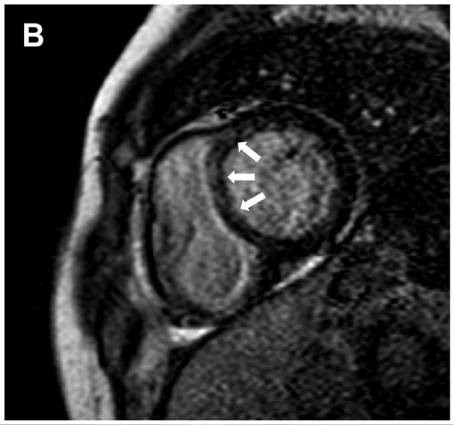
At outpatient follow-up at 6 weeks post-discharge, there were no new symptoms. Despite this, a repeat echocardiogram demonstrated an EF of 20%, and atrial fibrillation. Thus, the decision was made to readmit the patient for a 3-day course of intravenous steroids with maintenance oral prednisone. He also underwent cardioversion and was started on amiodarone. He was discharged in stable condition. He presented to our cardiology clinic 1 month after his last discharge from the hospital. A repeat cardiac PET scan was negative for any active inflammation, (18)F-fluorodeoxyglucose uptake, or scar (Fig. 2B). An echocardiogram demonstrated an EF of 56% at this 6-month follow-up visit.

Discussion

Drug-induced sarcoidosis-like reactions (DISR) are a rare phenomenon, which have been most commonly associated

A

	Tests	Results
Infectious	Viral panel (coxsackie, EBV, enterovirus, adeno) Fungitell assay, Tb, histoplasma, AFB culture, HIV	Coxsackie B Type 5 (1:80)
Inflammatory	ANA	Negative
Endocrine	Metanephrines, TSH, HgA1c, Aldo/renin, Ace/angiotensin,	Negative
Metabolic	Selenium, carnitine, Ferritin, iron/TIBC, Vitamin B1	Negative



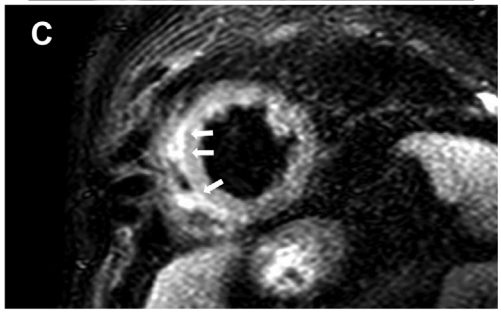


Figure 1. (**A**) Studies performed to rule out non-ischemic cardiomyopathy. (**B**) Gadolinium contrast magnetic resonance imaging. Cross-sectional imaging of the myocardium shows mid-wall fibrosis (**B, C**) with predominance of enhancement in basal septal region (as indicated by white arrows). AFB, acid-fast bacillus; ANA, antinuclear antibody; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; Tb, tuberculosis; TIBC, total iron binding capacity; TSH, thyroid-stimulating hormone.

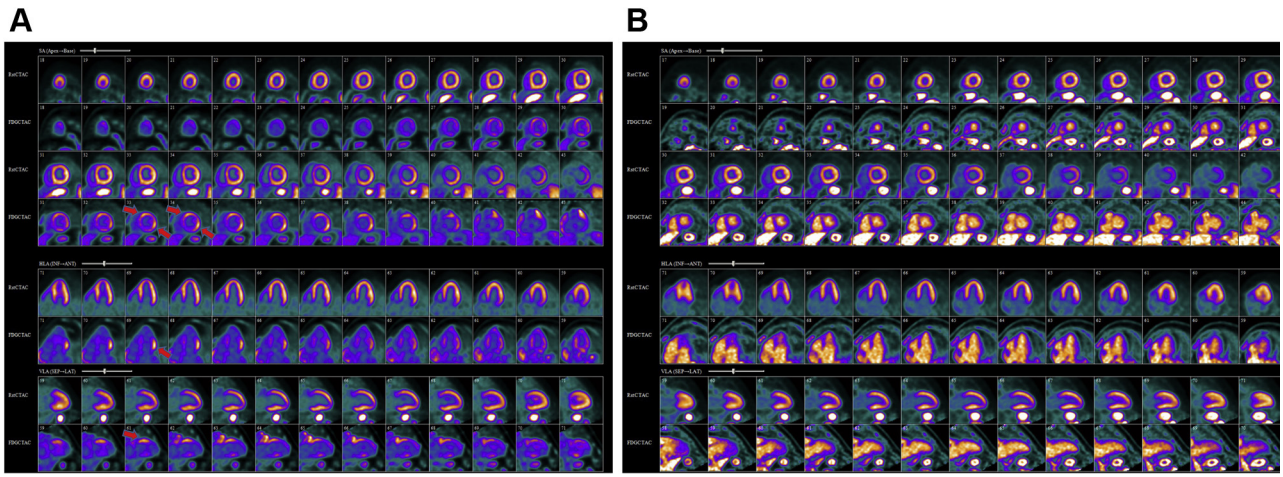


Figure 2. (**A**) Positron emission tomography (PET) scan with rest and (18)F-fluorodeoxyglucose positron emission tomography (FDG) uptake. PET scan showed illumination of FDG in the basal anteroseptal segment, basal inferolateral segment, basal anterolateral segment, and basal anterior segment indicating inflammation. The area of interest is marked with **red arrows**. (**B**) PET scan with FDG uptake: No discernable FDG uptake can be seen in these images.

with immune checkpoint inhibitors.[4] This adverse effect can be difficult to differentiate from true sarcoidosis, as it can induce granulomatous reaction; however, DISR tends to disappear upon discontinuation of the offending agent. The median time between discontinuation of the offending agent and remission was 6 months.[4] In cases in which disease is persistent or recurrent, steroids may be used. Ixekizumab is a monoclonal antibody targeting IL-17A used for the treatment of psoriasis. A prior case report has identified drug-induced sarcoidosis with primarily pulmonary involvement.[3,5] Our case reports highlight identification of possible ixekizumab-induced cardiac sarcoidosis. The clinical timeline of our patient, including improvement upon removal of the offending agent within 10 weeks, provides strong evidence supporting a case of possible drug-induced cardiac sarcoidosis. Furthermore, complete disappearance of cardiac inflammation after discontinuation of ixekizumab is consistent with DISR. Additionally, per the Naranjo algorithm, it was a probable adverse drug reaction[6] (6 points—2 points on the adverse event post drug administration; 1 point for improvement with the removal of medication; 2 points for no alternative cause can be identified; 1 point for the adverse event was confirmed by objective evidence).

Other possibilities to entertain include that tachycardia induced cardiomyopathy, which was the initial clinical impression. Of note, our patient had prior CT scans before the initiation of ixekizumab, and there was no evidence of any lymphadenopathy. However, this does not completely preclude the presence of subclinical sarcoidosis or the potential of ixekizumab to uncover it.

Conclusion

We present an interesting case of suspected cardiac sarcoidosis induced by ixekizumab. Therefore, attention should be paid to the new generation of biologic agents that can cause unwarranted effects on cardiac health.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2020.08.012.