CASE

Alemtuzumab and Fatal Myocarditis

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PRACTICAL IMPLICATIONS

The serious, often fatal disorder giant cell myocarditis may represent a new autoimmune complication of alemtuzumab used in multiple sclerosis.

Alemtuzumab is a lymphocyte-depleting monoclonal antibody targeting CD52 and is a highly effective treatment for relapsing-remitting multiple sclerosis (RRMS). However, it has a serious safety profile, including autoimmunity, often delayed, in some 40% of patients.[1] We describe an individual in whom fatal inflammatory myocarditis occurred over 2 years after alemtuzumab.

A 32-year-old previously well man presented with a 4-week episode of subacute-onset left hemisensory loss, followed by 2 days of painful tonic spasms of the right hand. MRI scanning showed a right high cervical lesion, together with several white matter lesions in the brain with characteristics highly suggestive of inflammatory demyelination. He was treated with a 3-day course of high-dose intravenous methylprednisolone but had a further episode 2 weeks later, with repeat MRI scanning showing multiple new lesions. He was then treated with alemtuzumab, 12 mg daily for 5 days. He had no further clinical episodes, and repeat MRI brain scanning showed no new lesion formation; he received a second course of alemtuzumab (12 mg daily for 3 days) 12 months later.

Two years later, he remained relapse free, and repeat MRI brain imaging again showed no new lesions. However, he developed symptomatic hyperthyroidism with positive antithyroid antibodies; he was treated with carbimazole but rapidly became hypothyroid and required thyroxine treatment.

Eight months later, 27 months after his second course of alemtuzumab, he was urgently admitted with acute severe chest pain, rapidly progressing to cardiogenic shock. Echocardiography confirmed severe biventricular failure with normal vessels on coronary angiography. He was transferred to a specialist heart hospital where intensive support, including peripheral venoarterial extracorporal membrane oxygenation, an intra-aortic balloon pump, and the insertion of a left ventricular impella, was instituted, but he developed multiorgan failure and died 3 weeks after admission.

An autopsy study of the heart (figure) revealed complete transmural necrosis with infiltration by lymphocytes and giant cells throughout the myocardium and widespread necrosis of myocytes, involving both atria and ventricles. There were no granulomata and no signs of vasculitis; eosinophils were largely absent. The conclusion was that of fatal giant cell myocarditis.

Giant cell myocarditis is a rare disorder. We have been unable to identify other cases that have followed immunosuppressive therapies, and it remains impossible to be certain of a link in the current case to alemtuzumab treatment last received 27 months earlier. However, the wide range of autoimmune complications occurring in well over a third of patients receiving alemtuzumab,[1] some emerging years after treatment, (arguably coupled with the occurrence of myocarditis only a few months after the development of autoimmune thyroid disease), clearly if circumstantially implicate alemtuzumab.

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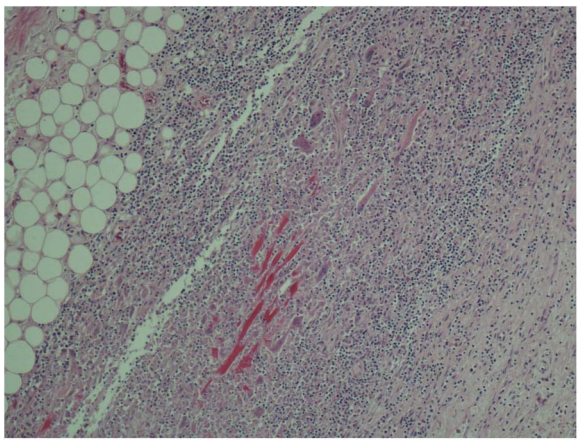
Figure Autopsy Study of the Heart



Hematoxylin and eosin stained section of the right ventricle showing dead hypereosinophilic myocytes surrounded by giant cells and lymphocytes with extensive necrosis. ×500.

Inflammatory myocarditis carries a mortality of some 50%. Many cases are idiopathic; alternatively, while not reported after other drugs used for autoimmune disease, inflammatory myocarditis, including giant cell myocarditis,[2] is well recognized if uncommon consequence of immune checkpoint inhibitors[3] used in various malignancies. Perhaps surprisingly, given our current case description, case reports have appeared in recent years, indicating that refractory giant cell myocarditis may be successfully *treated* with alemtuzumab and calling for further study of this therapeutic possibility.[4,5]

We report a case of fatal giant cell myocarditis after alemtuzumab administration in a patient with RRMS. Secondary autoimmunity is a well-known risk of alemtuzumab, and this case adds an important new potential side effect to its profile. Clinicians should be aware of this risk. Alemtuzumab may paradoxically be a useful treatment for giant cell myocarditis arising in other circumstances: that it may trigger this complex heart disorder should, however, introduce some caution into exploring its therapeutic potential in autoimmune cardiac disease.

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Name	Location	Contribution
Neil Scolding, PhD, FRCP	University of Bristol, UK	Conceived the study and wrote first draft
Hiam Ali, FRCPath	United Kingdom	Major role in histopathologic results and content of the manuscript
Mary Sheppard, PhD, FRCPath	St George's Medical School, London, UK	Major role in histopathologic results and content of the manuscript
Andre Simon, PhD, FRCS	Harefield Hospital, UK	Confirmed clinical cardiological details and edited the manuscript content

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