Case report

Cardiac sarcoidosis in a patient with testicular seminoma

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SUMMARY

Sarcoidosis is a multisystem disorder characterised by non-caseating granulomas that typically affect the lungs, skin and lymph nodes. Sarcoidosis has been associated with various cancers, and we describe the case of a patient with systemic sarcoidosis associated with testicular seminoma. This was originally diagnosed as stable sarcoid-like reaction. He subsequently presented with ventricular tachycardia. Cardiovascular MRI suggested cardiac sarcoidosis, which was confirmed by myocardial biopsy. This case highlights the association between some types of cancer and sarcoidosis. In addition, it highlights the importance of close follow-up for patients with a history of malignancy to monitor for sarcoid-like reactions and sarcoidosis, which are often difficult to differentiate clinically.

BACKGROUND

The description of sarcoidosis in patients with a history of solid tumours is limited to case reports and series.¹ Within this cohort, it is not known what proportion have cardiac involvement, which can be associated with systolic dysfunction and cardiac arrhythmia. This case report highlights both the relationship between cancer and systemic sarcoidosis, as well as the caution necessary when diagnosing sarcoid-like reactions.

CASE PRESENTATION

A 43-year-old man presented to the emergency department with a 1-week history of lethargy, reduced appetite, vomiting, loose stools and then a 1-day history of palpitations. On arrival, he was found to be in monomorphic ventricular tachycardia (VT) requiring direct current (DC) cardioversion. He had a medical history of testicular cancer treated with right orchidectomy 1 year previously. The histological analysis revealed this to be a classical seminoma, which was treated with surgical excision. A postoperative CT scan of the thorax demonstrated mediastinal lymph nodes that showed uptake of tracer on fludeoxyglucose positron emission tomography/CT (FDG-PET/CT). Biopsy demonstrated these to be non-necrotising granulomas. His WHO performance status was 0 and his pulmonary function tests were normal (forced expiratory volume in 1 s 127%, forced vital capacity 124%). A diagnosis of stable sarcoid-like reaction was made at that time.

INVESTIGATIONS

On the current admission, blood tests revealed acute kidney injury (creatinine 139 µmol/L, sodium

of 121 mmol/L, potassium 6.4 mmol/L) and were otherwise unremarkable. Following cardioversion, his clinical and biochemical parameters promptly recovered. An echocardiogram demonstrated a dilated left ventricular cavity with moderately impaired left ventricular systolic function (ejection fraction 40%–45%). Cardiovascular MR (CMR) was performed to investigate the cause of the left ventricular impairment and arrhythmia. This showed moderate–severe left ventricular systolic impairment with an ejection fraction of 36%. The basal anterior wall and some of the basal anteroseptum were thinned and akinetic (figure 1A). Non-ischaemic late gadolinium enhancement was present in these segments and some of the basal anterolateral wall (figure 1B). This is a marker of increased extracellular volume in those areas, which in this case probably reflects fibrosis and possibly inflammation, although specific imaging for inflammation with T2-weighted sequences was normal. The CMR also showed diffuse lung parenchymal abnormalities. The clinical presentation, together with the pattern of late enhancement and lung abnormalities were highly suggestive of cardiac sarcoidosis, although CMR does not offer a definitive diagnosis, which was then confirmed on a right ventricular septal myocardial biopsy, which is the gold standard investigation. Serum ACE was normal and a subsequent FDG-PET/CT demonstrated uptake in the basal anteroseptum and some of the anterior segments (figure 1C), as well as multiple upper zone pulmonary nodules (figure 2A,B), suggesting active inflammation.

DIFFERENTIAL DIAGNOSIS

The most important differential in a patient presenting with VT in the context of severe systolic impairment is of ischaemic heart disease. Following cardioversion, further history and examination was not suggestive of this, there were no dynamic ECG changes, and serial high-sensitivity troponin I samples were not significantly elevated. His potassium was elevated at 6.4 mmol/L, but there were no other ECG features of hyperkalaemia and no other contributory electrolyte abnormalities. His baseline ECG did not indicate a channelopathy nor was he on predisposing medication. The history of lethargy, vomiting, loose stools and reduced appetite raised viral myocarditis as a differential diagnosis. However, viral screens, including coxsackie and other enteroviruses, were negative. Significant pulmonary nodule uptake on subsequent FDG-PET/CT raised the suspicion of primary seminoma

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Figure 1 (A) A still taken at end systole showing the left and right ventricles. The anterior and some of the anteroseptal walls (arrowed) are shown to be thin and akinetic. A small pericardial effusion is also seen. (B) Corresponding late gadolinium enhancement image. Areas of enhancement in the myocardium are shown as white (arrowed). (C) fludeoxyglucose positron emission tomography CT image showing uptake in the anteroseptum and into some of the anterior wall (arrowed). LV, left ventricle; RV, right ventricle.

recurrence with pulmonary metastases. However, the CMR pattern of late enhancement was suggestive of sarcoidosis, which was subsequently confirmed by the gold standard test of right ventricular septal biopsy, and pulmonary lymph node biopsy was devoid of malignant cells.

TREATMENT

An implantable cardioverter-defibrillator (ICD) was inserted as secondary prevention, and the sarcoidosis was treated with a reducing regimen of prednisolone. He has been maintained on methotrexate.

OUTCOME AND FOLLOW-UP

He is currently asymptomatic and had no ICD (Implantable Cardioverter-Defibrillator) shocks over the last 2 years.

DISCUSSION

Sarcoidosis is a multisystem disease characterised by non-caseating granulomas. Activated CD4+ T lymphocytes are thought to recognise the cytoskeleton component vimentin on human leucocyte antigen-DR3 expressing cells. Associated cytokine mediators, including interleukin-17 (IL-17), IL-22 and interferon- γ , then drive an inflammatory response that results in granuloma formation. Paradoxically, this local inflammation is associated with anergy, which may contribute to an observed relationship between sarcoidosis and cancer, particularly skin,

haematopoietic, upper gastrointestinal tract, kidney, liver and colorectal sites.^{2,3}

An association between testicular cancer, particularly seminoma and sarcoidosis has also been described.⁴ Testicular cancer may precede or follow a diagnosis of sarcoidosis or they may develop concomitantly. In a review of 64 reports in the literature, a diagnosis of testicular cancer was made before sarcoidosis in 55% of cases and in tandem in a further 31%.⁴ In this case report, it is unknown if the patient had undiagnosed sarcoidosis prior to the presentation of testicular seminoma. If this had been the case, it is plausible that the initial misdiagnosis of sarcoid-like reaction would not have been made.

Sarcoid-like granulomatous reactions have also been described. Such reactions are a well documented, but poorly defined, phenomenon in patients with cancer. They are typically described in the incident tumour, local lymph nodes or remote from the cancer, although the pathophysiology is poorly understood.⁵ They have been attributed to tumour-derived antigens provoking CD4+ T lymphocyte activation and granuloma formation and have identical histological appearances and cellular composition to granulomas in sarcoidosis.^{5,6} Pragmatically, sarcoid-like reactions are diagnosed when there is an identifiable precipitant, histological evidence of non-caseating granuloma and a lack of other features of sarcoidosis, although such features are not well defined.⁷ Furthermore, patients with sarcoid-like reactions typically have normal vitamin D, calcium and ACE concentrations, without cardiac or central nervous system involvement.⁸ Nevertheless, close follow-up of patients

Patient's perspective

Three years on from my initial admission, I am well and I enjoy a normal quality of life. On arrival to hospital, the cause of my arrhythmias was unclear and I was apprehensive about this uncertainty. At the same time however, I was grateful for the honesty and openness of the doctors in declaring they too were unsure but would endeavour to find out. While I was aware of the initial diagnosis of the changes in my lungs and what it meant, I was not made aware there was a possibility of this being systemic sarcoidosis. Although I knew it was rare, I would have preferred that this was communicated to me on my initial diagnosis as it may have changed my decision to not take prophylactic steroids in the first instance.

Learning points

- ▶ We present a case of sarcoidosis associated with testicular seminoma that presented with cardiac involvement.
- ▶ Sarcoidosis can be associated with various cancers and can be a life-threatening problem, particularly when the heart is affected.
- ▶ Physicians managing patients with cancer should be aware of this unusual relationship and the investigations available to make the diagnosis.
- ▶ Sarcoidosis and sarcoid-like reactions can be difficult to differentiate; no guidelines currently exist in clinical practice to help guide investigation and management.
- ▶ Close follow-up for patients diagnosed with sarcoid-like reactions with a history of cancer is important to monitor progression and provides surveillance for development of genuine sarcoidosis.

Figure 2 Coronal (A) and transverse (B) fludeoxyglucose positron emission tomography/CT images demonstrating low-level uptake in multiple pulmonary nodules (arrowed) predominantly in the right upper zone.

diagnosed with sarcoid-like reactions with a history of cancer would mitigate the risk of missing genuine sarcoidosis and development in to severe complicating systemic disease.

It can be difficult to distinguish cancer-related sarcoid-like reactions from genuine sarcoidosis. No guidelines currently exist for clinicians to differentiate between the two, possibly owing to a paucity of evidence in this field. In our patient, the diagnosis of sarcoid-like reaction in the mediastinum, without other organ involvement, was thought to confer a favourable prognosis. However, such granulomatous disease may be part of a sarcoidosis spectrum and a high index of suspicion for systemic sarcoidosis is appropriate.⁹

Contributors All authors included agree that they have made: substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data; have been involved in drafting the work or revising it critically for important intellectual content; have given final approval of the version published; have an agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Specifically, the authors have contributed the following: DB has been involved in writing the manuscript, in particular researching and writing the pathophysiology of sarcoidosis and sarcoid-like reactions of the discussion section. He has also been involved in critical revision of final draft, preparation of figures, contacting patient in the initial drafts and managing the project overall. DS has been responsible for the conception of manuscript, preparation of figures and interpretation of cardiac MRI and its clinical significance. He has also provided critical review of final draft and provided his clinical and research experience in editing the final case report. PB has been involved with demonstrating the patients perspective, differential diagnosis and gaining consent

from the patient. He has also been involved in editing the general manuscript. In addition his role has included finalising the document format and making it relative to the BMJ requirements for case reports. MW has been responsible for writing manuscript and has contributed to the preparation of figures and overall format.

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