Journal of Neurology (2019) 266:1389–1393
https://doi.org/10.1007/s00415-019-09270-8

ORIGINAL COMMUNICATION

Granulomatous CNS inflammation associated with seminoma

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Received: 12 January 2019 / Revised: 27 February 2019 / Accepted: 5 March 2019 / Published online: 11 March 2019

Abstract
Two cases in which a neurological disorder was identified pathologically to be due to a granulomatous infiltration were found after diagnosis to have an associated testicular seminoma with pathologically proven lymphatic metastasis. We present the clinical and imaging features, and pathological appearances of the lymphatic tissue and the brain. We summarise the literature to date and discuss the pathogenesis of the disorder and its treatment.

Keywords Sarcoidosis · Neurosarcoidosis · Seminoma

Introduction

Sarcoidosis is an uncommon multisystem disorder, characterised histologically by the presence of epithelioid granulomas and an absence of identifiable organisms or foreign particles [1]. It most commonly involves the intrathoracic lymph nodes, lung, skin, and eyes. Involvement of the nervous system does occur [2], largely in the context of other organ involvement. In 10% it is the only manifestation [3].

The association of testicular cancer with sarcoidosis or what has been termed a 'sarcoid-like reaction' has been well established. Most of these patients have seminoma [4, 5]. This may occur at sites of known tumour as well as distant sites with no microscopic evidence of malignancy; however, as far as we are aware, involvement of the central nervous system has not been described. We report two patients presenting with symptoms due to biopsy-proven granulomatous brain lesions, who were subsequently discovered to have metastatic seminoma. Neither patient had evidence of tumour on brain biopsy. These cases represent the first reports of a potentially under-recognized central nervous system inflammatory syndrome associated with seminoma.

Case 1

A 29-year-old previously well man presented with a 2-week history of malaise, hearing loss and horizontal diplopia followed by a generalized tonic clonic seizure. Examination revealed gaze-evoked horizontal nystagmus, left-sided sensorineural hearing loss and mild dysmetria of the upper limbs. Brain MRI demonstrated T2 hyperintense lesions in the left mesial temporal lobe and bilateral cerebellar peduncles (Fig. 1). CSF revealed 36×10^6/L mononuclear cells. Autoimmune and vasculitic screens of serum and CSF were unremarkable, including antibody screen for limbic and autoimmune encephalitis. Serum and CSF angiotensin-converting enzyme (ACE) levels were normal. The patient subsequently developed a severe amnestic syndrome. Interval MRI scan showed progression of the brain lesions with patchy contrast enhancement and meningeal enhancement in the left temporal region (Fig. 1).

An empirical trial of intravenous steroids was given without a clinical response. Testicular ultrasound, performed as part of a malignancy screen demonstrated a $33 \times 13 \times 24$ mm

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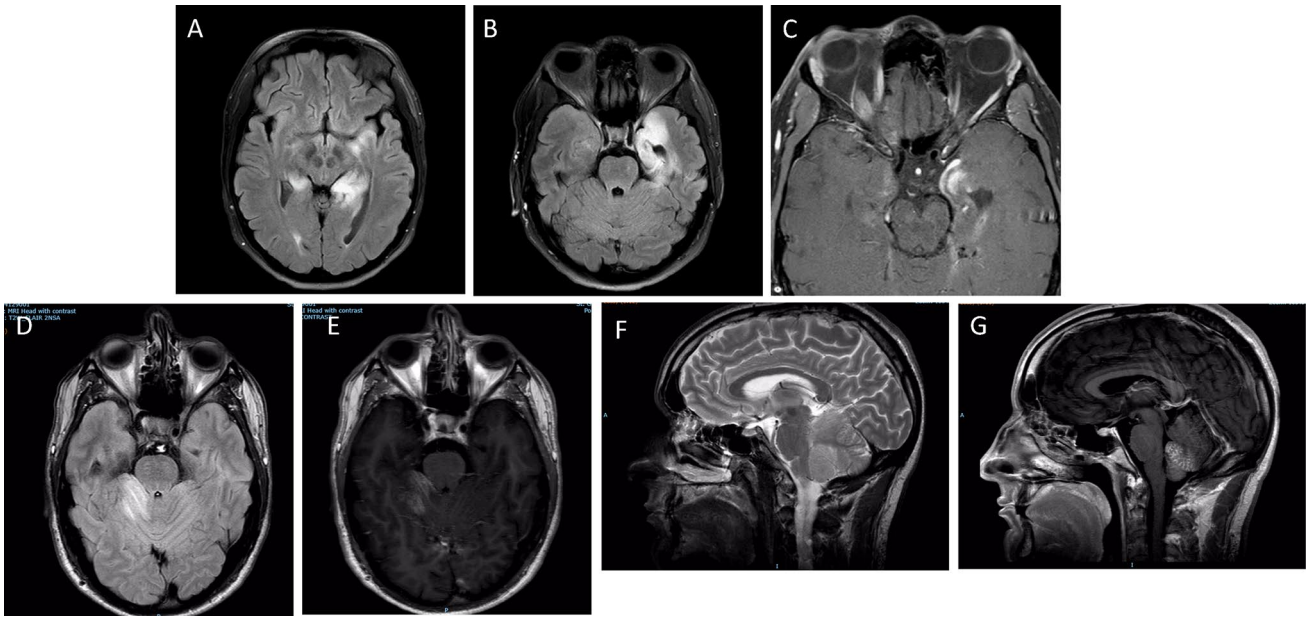

Fig. 1 Case 1: **a, b** axial FLAIR sequence MRI demonstrating hyperintensity of the left mesial temporal lobe, with **c** leptomeningeal and adjacent parenchymal enhancement on post-contrast T1-weighted imaging. Case 2: MRI scan of brain showing the imaging features at diagnosis; **d, f** T2-weighted axial and sagittal MRI showing high signal and swelling within the right cerebellar vermis and hemisphere, **e, g** T1-weighted MRI following administration of contrast showing enhancement of the same region

mass in the left testis. Abdominal CT scan revealed a 10 × 8 mm para-aortic lymph node. The patient underwent left orchidectomy, with an initial pathology report describing a fibrotic, atrophic testis with surrounding histiocytic response and a granulomatous appearance but no specific features of malignancy.

Biopsy was performed of the left temporal lesion and associated meninges showed granulomatous inflammation without evidence for tumour (Fig. 2). Re-analysis of the testicular biopsy with placental alkaline phosphatase (PLAP) staining showed the presence of a regressed seminoma within the fibrotic granulomatous change. Biopsy of the left para-aortic lymph node revealed metastatic seminoma. In addition to scattered malignant cells, non-necrotising granulomas were seen. The brain biopsy was re-analysed for any evidence of tumour dissemination, including placental alkaline phosphatase (PLAP) immunohistochemistry, which was absent.

The patient was diagnosed with metastatic seminoma and associated 'sarcoid—like granulomatous encephalitis'. He underwent treatment for seminoma with bleomycin, etoposide and cisplatin (BEP) chemotherapy. Given the degree of disability associated with the CNS inflammation the patient was also treated with six cycles of IV cyclophosphamide and a weaning course of oral corticosteroids. The patient returned home despite with residual cognitive deficits; however, was readmitted to a hospital 9 months later following a series of generalized seizures. Despite attempts to optimise anti-epileptics, the patient died of presumed SUDEP shortly after, with post-mortem results outstanding.

Case 2

A 39 year-old previously well man developed an increasingly severe progressive cerebellar syndrome. The patient's symptoms had started insidiously 16 months previously. MRI brain had revealed a contrast-enhancing lesion affecting the cerebellar vermis and right cerebellum (Fig. 1). A systemic evaluation revealed no associated pathology and the investigating clinicians proceeded to a biopsy of the lesion. This showed a granulomatous inflammation without evidence for infection or tumour (Fig. 2). The patient had no evidence of other organ involvement and a diagnosis of isolated neurosarcoidosis was made. He was referred to the centre for Neurosarcoidosis where the biopsy was revaluated and a granulomatous infiltration compatible with sarcoidosis was agreed. He received treatment with steroids, methotrexate and infliximab but did not improve.

A reassessment was made. Whole-body CT PET demonstrated an intensely PET-avid 23 × 27 × 26 mm left para-aortic lymph node, which was biopsied percutaneously and demonstrated metastatic seminoma, with associated granulomatous reaction (Fig. 3). Testicular ultrasound revealed no discrete lesion, but extensive testicular microlithiasis, making parenchymal assessment difficult. The patient's

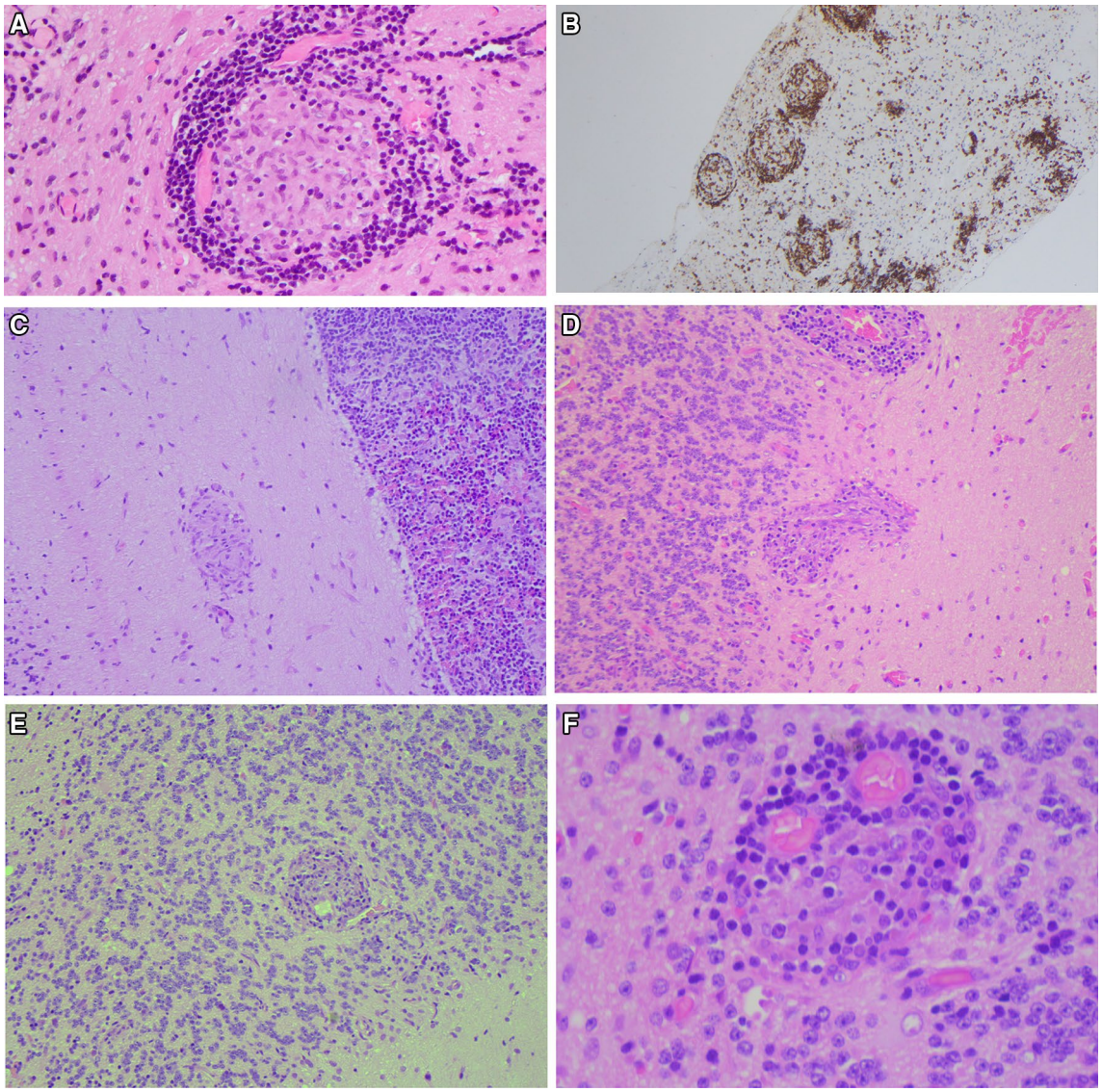

Fig. 2 Case 1: histological examination of brain showing discrete non-necrotizing epithelioid granulomas containing rare giant cells, often adjacent associated with small blood vessels, without any pathological features of vasculitis (**a**). The granulomas were surrounded by small lymphocytes. The lymphocytes were a mixture of CD3-positive T lymphocytes (**b**) and CD20-positive B lymphocytes (not shown). The T cells were concentrated in and around the granulomas; however, they also were present as scattered cells within the cortex. The B lymphocytes were present around the granulomas, but less frequent within the granulomas themselves and very scarce within the cortex away from the granulomas. Lymphocytes were also present in the leptomeninges. A marked reactive astrogliosis was present in the brain parenchyma. Case 2: histological examination of brain showed a severe infiltration of small, well-formed epithelioid granulomas in the cerebellar leptomeninges (not illustrated), and within the cerebellar cortex (including both molecular and granular cell layers) (**c**–**f**). Giant cells were present. The granulomas were non-necrotic and were associated with an infiltrate of small lymphocytes. CD3-positive T-lymphocytes were present in the leptomeninges, within the granulomas, and also diffusely infiltrated the cerebellar cortex as scattered cells. The CD20-positive B lymphocytes were very frequent in the leptomeninges and frequent in and around the granulomas, but were scarce within the cortex away from the granulomas. Plasma cells were frequent as scattered diffusely infiltrating cells within the cerebellar cortex, particularly in the granular cell layer, but were scanty in the leptomeninges and within the granulomas. Stains for bacteria, mycobacteria and fungi were negative. No evidence of neoplasia was identified. PLAP staining was negative. Although the granulomas were often intimately associated with small vessels (capillaries, venules, and arterioles), and appeared in places to follow vessels from the leptomeninges to the cortex, no definite vasculitis was seen, and fibrinoid necrosis was not a feature

brain biopsy was re-examined for the presence of seminoma, including staining for PLAP, which was absent. The patient underwent treatment with chemotherapy and methotrexate and infliximab were discontinued, then reinstated when it became clear that he was relapsing within the nervous system. With infliximab he again stabilized but did not improve.

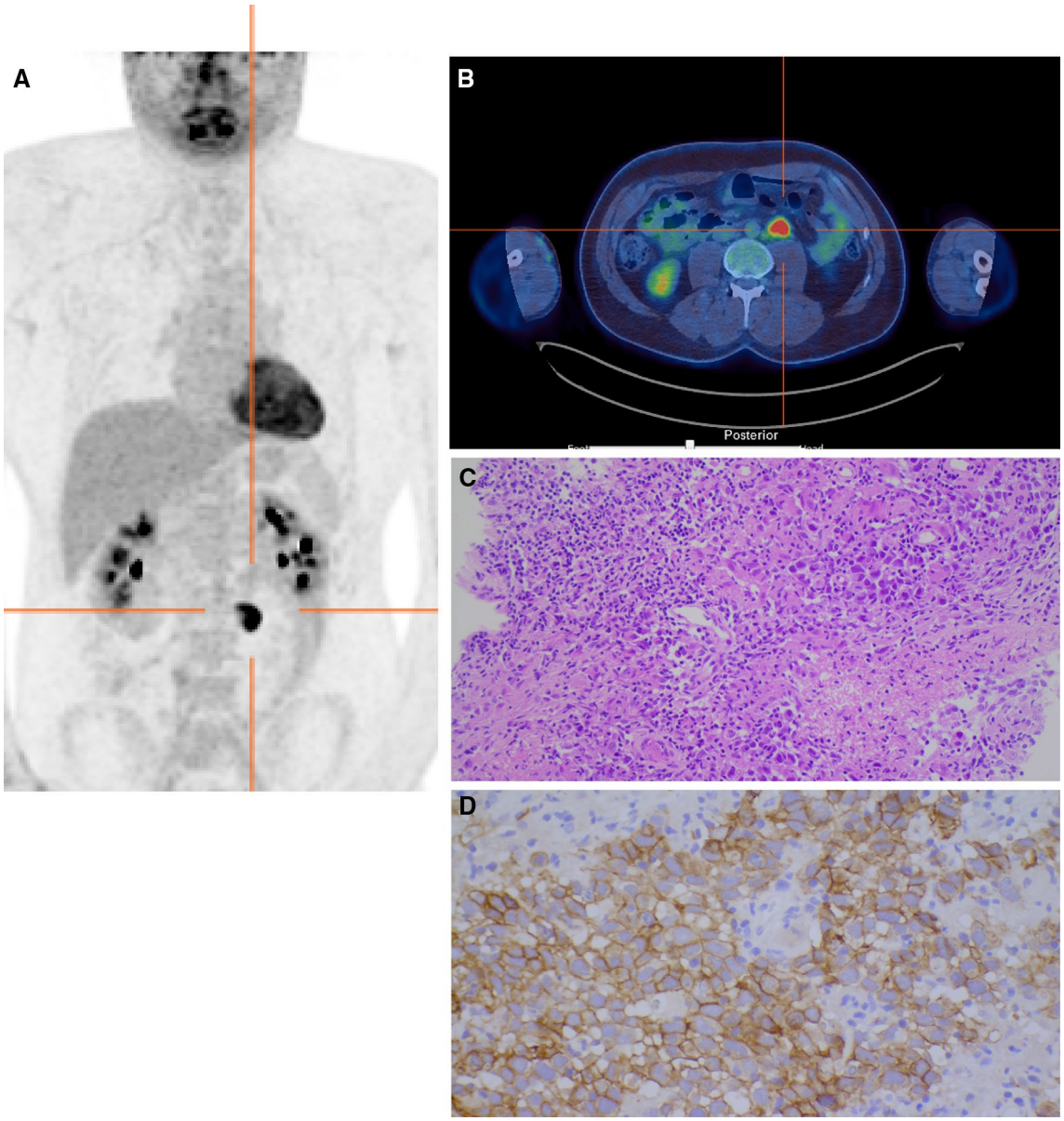

Fig. 3 Case 2: **a, b** 18-F FDG PET scan of the abdomen showing uptake of tracer within an enlarged para-aortic lymph node. Note the absence of uptake in mediastinal and other nodes. Histology of the para-aortic lymph node biopsy showed a partially necrotic granulomatous infiltrate composed of epithelioid macrophages and associated lymphocytes, and widespread infiltration by neoplastic cells (**c**); the neoplastic infiltrate was extensively necrotic. The neoplastic cells were strongly positive for Oct 3–4 (a marker of seminoma) on immunohistochemical staining (**d**)

Discussion

An association between testicular cancer and sarcoidosis has been recognized since the early 1980s [5] and case reports and case series have emerged since that time. Although granulomatous inflammation can be found in association with other malignancies, it appears to be most often associated with testicular cancer, lung cancer and lymphoproliferative disease [6].

A review of the literature in 2007 found 64 cases of concomitant sarcoidosis and testicular cancer, 62% of whom had seminoma [4]. Sites of sarcoid-like reaction included the testis and draining inguinal or retroperitoneal lymph nodes, however it was also found in the lung and hilar/mediastinal lymph nodes, even in the absence of regional spread of the neoplastic cells [4]. Concomitant granulomatous involvement of the peritoneum has also been described in a patient with seminoma otherwise localized to the testis [7]. Peritoneal and intrathoracic metastasis from seminoma

is extremely rare in the absence of regional spread of disease [4, 7]. Metastasis to the CNS is also uncommon [8].

The discovery of granulomatous inflammation in these sites, particularly our patients with CNS involvement, suggests that this might in fact be a systemic reaction to tumour antigen, rather than a local response to metastatic disease. In the review by Paparel and colleagues [4], testicular cancer was diagnosed either prior or concomitantly with sarcoidosis in 86% of cases. In both of our patients, granulomatous CNS inflammation was diagnosed prior to the discovery of their malignancy, symptoms of which had not been described by either patient. This emphasizes the need for a more widespread understanding of this syndrome amongst clinicians, so that timely cancer screening can occur.

It appears that in certain cases a sarcoid-like reaction may develop within the neoplastic tissue and subsequently within its metastatic spread, whilst in others the disease becomes autonomous and behaves more like the systemic disease, in which granulomatous inflammation develops distant from the site of neoplasia. This implies that sarcoid-like reactions, which are type IV-mediated responses against persistent antigenic stimulation, may develop in response to antigenic stimulation by the neoplastic cells both locally and systemically, leading to a more widespread systemic disease including involvement of the nervous system. Although we cannot entirely exclude the possibility that deposits of tumour cells within the central nervous system may have induced a granulomatous reaction and subsequently regressed, in neither case was there morphological or immunohistochemical evidence of seminoma or other malignancy in the brain specimens.

It is notable too that in each case no evidence for seminoma was found within the testis, and in case 1 there was evidence for a granulomatous reaction with fibrosis, which implies that a sarcoid-like reaction may begin as a protective and destructive anti-tumour mechanism. Care should thereby be taken in treating the granulomatous disease and not the tumour lest this may lead to an unmasking of the neoplastic disease.

Whilst previous cases of a systemic sarcoid-like reaction in conjunction with seminoma have largely regressed spontaneously [4], in the central nervous system, small foci of injury have the potential to cause devastating disability, and it is clear that these patients may require high-dose immunosuppression. Our experience of treating case 2 suggests that the TNFα blocking biological agent infliximab proffers additional benefits.

Conclusion

Testicular cancer and particularly seminoma may produce granulomatous inflammation at sites of origin of the tumour and its metastases, or distant to that site, including the central nervous system. Isolated non-infective granulomatous brain lesions, including suspected Neurosarcoidosis, should prompt a search for underlying malignancy including dedicated imaging of the testis.

Author contributions SW and JM were joint first authors. JM SW, MG and DPK were responsible for the study concept and design, acquisition of data and analysis and interpretation. All authors were responsible for a critical revision of the manuscript for important intellectual content. DPK was the study supervisor.

Funding Dr. Kidd receives royalties from Elsevier and Springer-Verlag. He reports no other disclosures. Dr. Massey has received honoraria from Biogen Idec, Merck, Sanofi Genzyme and Teva, outside the submitted work.

Compliance with ethical standards

Conflicts of interest There are no conflicts of interest.

Ethical standards Both patients consented to their clinical details being reported and the work has been conducted in compliance with the Declaration of Helsinki.

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