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CASE REPORT

Primary angiitis of the central nervous system associated with testicular tumor, a case report

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Abstract

A 32 year old man developed a 1-year history of episodic transient right sided neurological deficits, with bilateral predominantly white matter confluent lesions seen on MRI brain. Histological examination of the biopsy after an episode of intracerebral bleeding revealed features of granulomatous angiitis. There was no evidence of arteritis elsewhere in the body, nor a known secondary cause of vasculitis. During follow-up whilst on treatment, he developed a generalized lymphadenopathy. Systemic search for a primary malignancy revealed a burnt-out testicular cancer with extragonadal metastasis. The occurrence of primary angiitis of the nervous system with testicular cancer as paraneoplastic phenomenon has not been previously reported.

INTRODUCTION

Primary angiitis of the central nervous system (PACNS), also known as isolated angiitis of the central nervous system and Granulomatous angiitis of the nervous system, is a disorder in which vasculitis confined to the central nervous system occurs in the absence of any systemic disease as a cause of the vasculitis.[1] Originally thought to be extremely rare and highly fatal, it is now more increasingly recognized and successfully treated.[2] We report a patient with PACNS who presented with transient ischemic attacks who later developed a stroke-like syndrome with intracerebral hemorrhage. There was an associated testicular tumour with extragonadal metastasis. Such an association has not been reported previously.

CASE REPORT

A 32-year-old man with no known medical history presented with one-year history of episodic diplopia, followed by headaches, right upper limb numbness and paresis. The attacks were initially infrequent lasting 5-10 minutes, this progressed to 3-4 episodes daily lasting 10-20 minutes with full recovery. There was no history of altered awareness, fever or other systemic upset. He was a non-smoker with no history of illicit drug abuse. Various treatments prescribed earlier including aspirin and anticonvulsants did not provide any relief. A previous CT brain scan was normal. Examination was normal except bilateral mildly hyperemic optic discs with increased tortuosity of the veins. Visual field testing showed mild constriction bilaterally with normal blind spots.

Investigations done included blood sugar, full blood count, liver and renal function tests, ESR and LDH, ultrasound Doppler of the carotids, chest x-ray, cardiac echocardiogram, evoked potentials were all normal. Serology for HIV 1 and 2, hepatitis B and C, herpes, CMV, VDRL, mycoplasma and connective tissue including thrombophilic screening were all negative. EEG showed occasional slow waves posteriorly, more prominently over the left side. MRI brain showed two well-defined large hyperintense lesions on T2W images which were non-enhancing, involving the subcortical deep white matter over the left parieto-occipital and right semicentrum ovale, with possibly some involvement of the cortex . There were no surrounding edema or mass effect (fig.1).

Within a few days of presentation, he developed sudden onset of aphasia with right sided hemiplegia. Urgent CT brain revealed bleeding into the left parietal lesion. Cerebral

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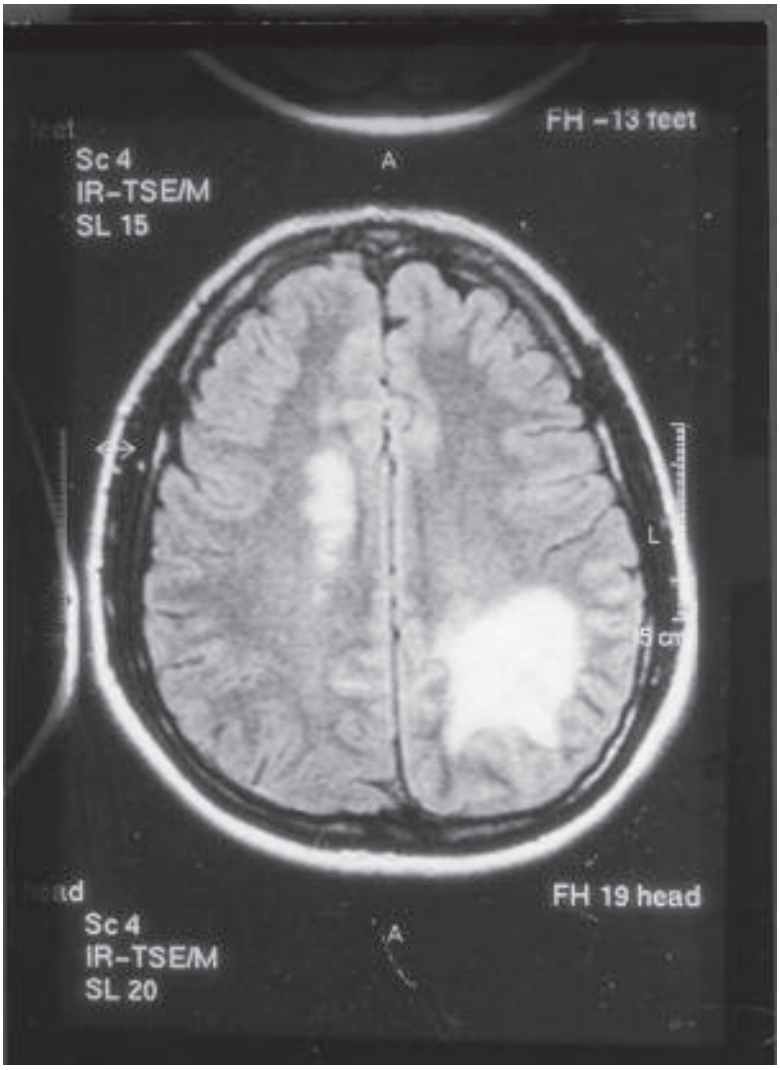

Figure 1: Axial T2 weighted FLAIR MRI of the brain showing hyperintense white matter lesions in the left parietal and right semi-centrum ovale.

angiogram showed a large area of hypovascularity in the left parietal area with mild surrounding hyperemia, but no evidence of aneurysms, arteriovenous malformations or vasospasm. He underwent craniotomy with evacuation of the clot. A stereotactic biopsy of the brain and white matter lesion at the bed of the hematoma was done. He was started on short course intravenous dexamethasone. He improved after the surgery, being able to ambulate with partial speech recovery. A lumbar puncture done 2 weeks after cessation of steroid showed 55 lymphocytes/mm^3 with normal biochemistry. There was no microscopic evidence of tuberculosis, fungus and malignant cells. As for the biopsy, a large blood vessel of arterial caliber in the meninges showed infiltration of its wall by a mixture of lymphocytes, histiocytes, epitheloid cells and occasional multinucleated giant cells. The lymphocytes were polyclonal in nature confirmed by mixed expression of CD 20 and CD 3. Smaller arteries in the cortex also showed similar infiltrates. Adjacent brain parenchyma showed sparse lymphocytic infiltrate and cellular debris. No obvious neuronal inclusion or organisms were noted (fig 2). The histopathological examination was consistent with a granulomatous vasculitis.

There was recurrent transient left upper limb numbness, which resolved with prednisolone 1mg/kg. A repeat MRI brain 3 months after initial presentation showed no change. Seven months after initial presentation, while on oral prednisolone 30mg/day, he developed bilateral multiple cervical lymphadenopathy. Chest x-ray

showed a right paratracheal lymph node enlargement, and CT scan of the mediastinum and abdomen revealed multiple discrete nodes in both supraclavicular regions, paraaortic, aortocaval, retrocaval and right paratracheal regions. The liver was mildly enlarged. Repeat MRI brain showed complete resolution of both white matter lesions with residual changes of a previous bleed in the left parietal region. Repeat lumbar puncture showed no malignant cells. A cervical lymph node excision biopsy (fig. 3) showed infiltration with sheets of malignant cells exhibiting pleomorphic vesicular nuclei, prominent nucleoli and abundant cytoplasm. These were immunoreactive for cytokeratin, placental alkaline phosphatase and beta HCG and alpha fetoprotein but not for leucocyte common antigen, S100 protein, epithelial membrane antigen and HMB 45. The features were consistent with metastatic germ cell tumour. The serum LDH, beta HCG and alpha fetoprotein were elevated at 1972 U/L, 5224 mIU/L and 429.5 ng/mL respectively. Testicular examination showed a very small discrete nodule on the upper pole of the right testis, confirmed on ultrasound to be hypoechoic. He underwent a right orchidectomy, microscopy showing extensive areas of fibrosis replacing the stroma. Remnants of seminiferous tubules were seen at the periphery with focal Leydig cell hyperplasia. In focal areas at the center of the lesion, 2 benign acini lined by mucous secreting columnar epithelium were seen accompanied by irregular smooth muscle fibres. Thickened vessels were seen in the fibrous stroma. No malignant cells were seen. The features were suggestive of a 'burnt-out' testicular malignancy most likely teratoma or germ cell tumour. A total body bone scan did not show evidence of bony metastasis. He was subsequently treated with cisplatinum, etoposide and bleomycin. Serial beta

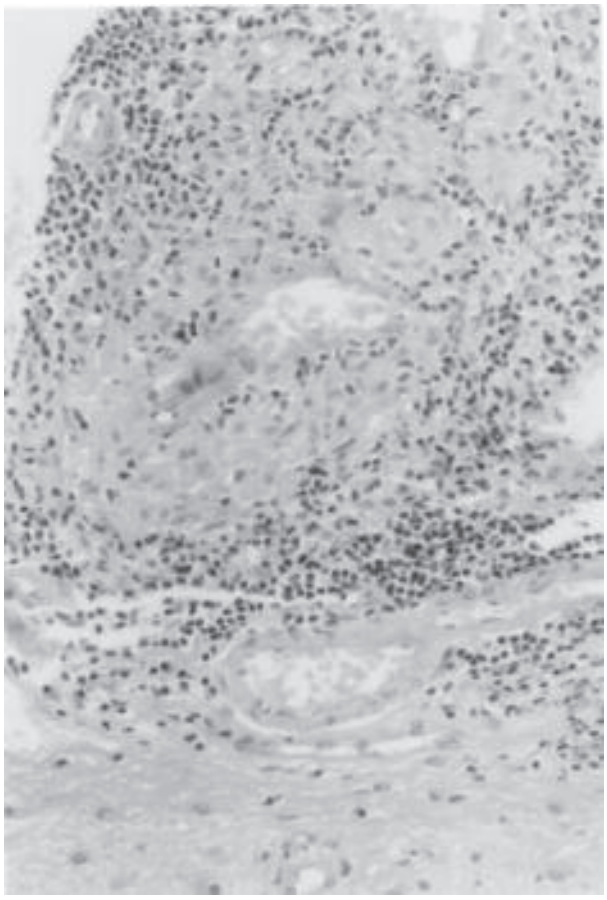

Figure 2: Photomicrograph of granulomatous inflammation of the meningeal blood vessel showing infiltration by epithelioid cells, giant cells and lymphocytes. H&E x 200.

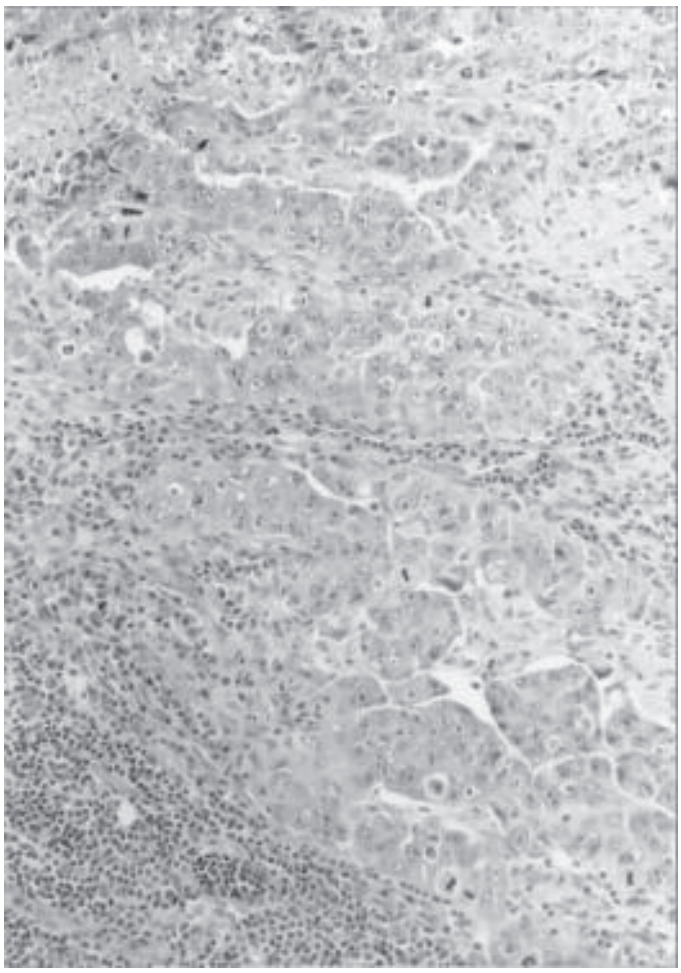

Figure 3: Photomicrograph of the metastatic germ cell tumour in the cervical lymph node. H&E x200.

HCG, LDH and alpha fetoprotein levels showed a downward trend to normal, with regression of the lymphadenopathy clinically and radiologically. There were no further episodes of neurological symptoms. The final diagnosis was extragonadal embryonal carcinoma presenting initially with granulomatous angiitis.

DISCUSSION

This patient was diagnosed to have PACNS based on the presence of central nervous system dysfunction, histopathology evidence of granulomatous angiitis, absence of vasculitis elsewhere in the body, and no known secondary cause of vasculitis.[1] PACNS was first defined by Cravioto and Feigin in 1959.[3] Until 1986, only 46 cases had been reported in the English literature, but by 1990, almost 100 new reports have been described.[2] There is striking clinical heterogeneity within the PACNS literature, partly due to variable diagnostic criteria, i.e. whether histopathological confirmation is required for the diagnosis.[2] As virtually any anatomic area of the central nervous system may be affected, a wide range of neurologic deficits may be seen. The main clinical features are headache, paresis, decreased cognition and consciousness, seizure, myelopathy, and fever.[1-6] Transient ischaemic attack[4] and intracerebral hemorrhage[1] as in this patient have both been previously described in patients with PACNS.

The diagnosis of PACNS is hampered by lack of reliable noninvasive tests. ESR may be elevated in only 10% of cases and there are no consistent abnormalities in serologies or autoimmune markers.[2] Analysis of the cerebrospinal fluid may be normal or show a small pleocytosis with elevation of protein.[2,3] MRI is usually abnormal and include multiple bilateral, supratentorial infarcts including lesions in the cortex, deep white matter and/or leptomeninges but the changes

are nonspecific and may also be normal.[2] A metanalysis by Calabrese et al in 1992 of 108 patients noted cerebral angiogram showing the classical beaded appearance of vasculitis was seen in only 25% of cases, with a normal angiogram in 39% of patients.[1] Biopsy is considered the gold standard but given the focal nature of the disease, it carries only a 75% sensitivity.[7,8]

PACNS has been known to be associated with Hodgekin's disease and HIV infection.[5] To our knowledge, this is the first report of testicular cancer associated with PACNS. However, testicular tumors have been shown to be associated with paraneoplastic limbic encephalitis.[9-12]

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