LESSON OF THE MONTH

Systemic vasculitis or not? That is the question

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Case story

A 49 year old white man was admitted after an episode of uncontrolled "twitching" of his left arm and hand that lasted 5-10 minutes. He reported difficulty in finding his words for a few days. Past medical history included three unexplained deep vein thromboses, therefore he was receiving long term warfarin. Clinical examination and limited laboratory tests were unremarkable and he was discharged the same day with no follow up.

In the following days he gradually developed weakness of the right side of his body, headaches, nausea and increasing speech difficulties. He was readmitted four weeks later, after a sustained episode of "twitching" of the right arm, which on this occasion was correctly recognised to be a focal seizure. Systemic features such as malaise, fever or weight loss were absent and recent foreign travel was denied; 4/5 weakness of the right limbs, an expressive dysphasia and apathy were noted but no other psychiatric symptoms were present. Chest radiography was normal. Brain computed tomography showed an area of mixed attenuation in the left posterior frontal region extending into both the temporal and parietal region. There was mass effect with compression of the left anterior horn and slight bowing of the anterior midline structures to the right. These appearances suggested a left frontoparietal malignant tumour, probably a diffuse glioma. He was given carbamazepine 200 mg twice daily and dexamethasone 4 mg four times a day.

Smear examination of a stereotactic brain biopsy from the left frontal lobe, rather than confirming a glioma, revealed a granulomatous inflammatory process and as tuberculosis could not be excluded, triple therapy was started (isoniazid, rifampicin, pyrazinamide) and samples sent for microbiology. Postoperative brain magnetic resonance imaging showed a diffuse swelling with ill defined enhancing abnormality in the left frontoparietal region. The appearances were unusual suggesting a granulomatous (tuberculosis, neurosarcoid) or a malignant process (fig 1). Definitive histological examination of the brain biopsy revealed a granulomatous angiitis affecting small vessels (fig 2). No caseation or organisms were identified on special stains and molecular amplification studies (PCR) for tuberculosis were negative. Subsequent cultures also proved negative. ANCA (MPO and PR3), ANA, anti-

dsDNA antibodies, anticardiolipin antibodies and lupus anticoagulant were all negative and complement and immunoglobulin levels were normal. The diagnosis of primary angiitis of the central nervous system (PACNS) was made and prednisolone 60 mg daily started. Anti-tuberculous treatment was discontinued on the third week.

Twelve days after the brain biopsy, an intermittent fever developed (up to 39°C), accompanied by eosinophilia (1.07×10^9) and a gradual, slow rise of the liver enzymes (γ -glutamyltransferase and alanine transaminase), which despite further investigations including abdominal ultrasound remained unexplained. The bone marrow trephine revealed the presence of numerous small ill defined granulomas without vasculitis or evidence of a lymphoma.

Three weeks after the brain biopsy and while the previous investigations were in progress, a purpuric rash appeared on both his lower legs (fig 3) and C reactive protein rose to 136 mg/l. Skin biopsy showed a lymphocytic vasculitis devoid of granulomas.

One week after the onset of the rash a regimen of weekly intravenous pulses of 1 g cyclophosphamide and 1 g methylprednisolone was started (patient's weight 85 kg) despite concerns about his unexplained continuing

Figure 1 Brain magnetic resonance imaging before treatment. Diffuse swelling with ill defined enhancing abnormality in the left frontoparietal region.

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Accepted for publication
21 May 1999

Figure 2 Brain biopsy from the left frontal lobe showing granulomatous vasculitis in superficial cerebral cortex (haematoxylin and eosin $\times 100$).

fever and abnormal liver enzymes. At this juncture his treatment was prednisolone 30 mg daily, mesna and ondansetron with each infusion, ranitidine and alternate daily cotrimoxazole for *Pneumocystis carinii* pneumonia prophylaxis. Three days after the second pulse he developed a new rash that covered the whole body (fig 3), which was attributed to cotrimoxazole and indeed this rash subsided within a few days after discontinuing the drug. His γ -glutamyltransferase had by this time increased to 536 U/l and alanine transaminase 797 U/l. After further detailed review of the patient, carbamazepine was considered to be the probable cause of the vasculitic rash, fever and the abnormal liver function tests and hence gabapentine was substituted as hepatotoxicity related to this agent is unusual. The eosinophil count returned to normal after a few days and the vasculitic rash settled over the next three weeks.

One week after the withdrawal of carbamazepine he developed mild jaundice, which became pronounced 10 days later. His γ -glutamyltransferase had reached 990 U/l, alanine transaminase 3006 U/l, bilirubin 135 μ mol/l and INR >10. Screen for viral hepatitis was negative and the abdominal ultrasound only showed a mild splenomegaly. The cytotoxic treatment was temporarily withdrawn. Liver biopsy showed normal architecture. The portal tracts were expanded by a mixed inflammatory infiltrate and proliferating bile ducts that were infiltrated by acute inflammatory cells. There was marked centrilobular cholestasis with hydropic degeneration of liver cells. Discrete epithelioid granulomas were present in the liver parenchyma and the portal tracts (fig 4). These appearances suggested large bile duct obstruction with granulomatous hepatitis and a drug induced hepatitis could explain this variety of changes. Five weeks later the liver function tests had returned to normal.

Repeat magnetic resonance imaging that was performed after the patient had received 4 g of intravenous cyclophosphamide and methylprednisolone, showed that the granulomatous process had regressed dramatically (fig 5).

Figure 3 Carbamazepine induced vasculitic rash on the lower legs. The rash on the upper legs is a reaction to cotrimoxazole.

Frontal lobe function had returned to normal and there was no neurological deficit or further fits. Cyclophosphamide was gradually reduced to 1 g every three weeks, oral prednisolone to 5 mg daily and gabapentine was discontinued.

Unfortunately at this stage he relapsed developing four grand mal seizures. Frequency of cyclophosphamide pulses and dose of corticosteroids were increased and anticonvulsant therapy was reintroduced resulting in stabilisation of his condition. Currently, one year after the diagnosis he remains well taking oral cyclophosphamide 150 mg daily, gabapentine 600 mg daily and warfarin.

Discussion

PACNS is a rare condition. Histologically it involves medium sized and small arteries of the meninges and cortex. Granulomatous vasculitis occurs in less than 50% of biopsies.¹

It represents a diagnostic problem and should be considered in patients with unexplained headaches, focal or diffuse neurological deficits, behavioural changes, or myelopathy. CNS tumours, lymphoma, systemic vasculitis, sarcoidosis, infections (tuberculosis, syphilis, fungal, viral, parasitic) and migraine are only some of the conditions that should be included in the differential diagnosis.¹ There are no specific tests for PACNS. CSF studies can reveal the findings of an aseptic meningitis. Diagnosis should be based on the combination of biopsy and imaging studies. Magnetic resonance imaging is more sensitive than computed tomography but findings may be difficult to differentiate from other conditions.² Angiography findings are not diagnostic but findings of beading, narrowing, occlusions or microaneurysms of the vessels may be suggestive.²⁻⁴

Figure 4 Liver biopsy. Well circumscribed granuloma within hepatic lobule (haematoxylin and eosin $\times 200$).

Figure 5 Follow up magnetic resonance imaging of the brain. Marked improvement in comparison with previous scan with relatively small residual areas of the frontal lobe granulomatous process.

Therefore a combination approach including magnetic resonance imaging, angiography, brain biopsy and clinical appraisal is recommended. Angiography was not performed in this case as the brain biopsy was diagnostic, however it can have a role but negative angiography does not exclude PACNS as elegantly demonstrated in a recent case report.⁵

In our case the initial suspicion of tuberculosis was excluded following the culture, special stains and negative tissue PCR.

The vasculitic rash on the lower legs led to the consideration of a systemic vasculitis rather than PACNS. However, the latter is notable for its lack of extracranial features,^{3 6-8} and the differing type of vasculitis in the brain and skin was puzzling.

A reaction to carbamazepine was considered a possible explanation for the complex clinical picture and indeed withdrawal of the drug led to rapid improvement of the rash and fever. Drug interactions cannot be ignored as plasma carbamazepine concentration can be increased

by the concurrent administration of isoniazid, and interestingly isoniazid hepatotoxicity is increased in the presence of carbamazepine as the metabolism of isoniazid is changes leading to an increase in its hepatotoxic metabolite. The delay in withdrawing carbamazepine may have also attributed to the development of icteric hepatitis and corticosteroid treatment probably reduced the severity of the reaction.

Carbamazepine can induce a multisystem reaction presenting with fever, eosinophilia, rash, lymphadenopathy and hepatitis.⁹ Cutaneous vasculitis¹⁰ and bone marrow granulomas¹¹ have also been reported. Hepatitis is both hepatocellular and cholestatic and hepatic granulomas are usually present.^{12 13} The reaction is not dose related suggesting an immunological mechanism.¹³ Although manifestations usually settle after cessation of the drug, corticosteroid treatment can be beneficial.^{9 10}

The widespread rash caused by co-trimoxazole confused things further especially in the presence of the carbamazepine rash confined to the lower legs. It was unlikely that both rashes had one single cause and cessation of co-trimoxazole was a simple and reasonable measure, as similar reactions to this drug are not uncommon. The rationale for the use of co-trimoxazole is based on our own published experience in connective tissue diseases¹⁴ and the subject has recently been reviewed.¹⁵

Sarcoidosis is another disease that can affect the CNS and involve other organs but in CNS sarcoidosis vascular involvement is virtually unknown,⁷ necrosis is generally absent and there is a tendency to involve the base of the brain.³ Liver dysfunction in sarcoidosis is unusual and the subsequent response to discontinuing carbamazepine was revealing.

The patient's response to cytotoxic and corticosteroid treatment was dramatic. His further fits after reducing cyclophosphamide dose and stopping gabapentine, may represent reactivation of the vasculitic process or residual scarring requiring long term cytotoxic and anti-convulsant treatment.

The lessons

- The protean manifestations of PACNS make diagnosis a problem. Careful history and clinical examination as well as high index of suspicion are essential. The initial focal fit and dysphasia should have been followed up with further investigations.
- There is a great diversity of the PACNS computed tomography and magnetic resonance imaging findings. Diagnosis should be based on a combination of magnetic resonance imaging, biopsy and angiography.
- PACNS is an isolated disorder with no extracranial features.
- The disease may respond dramatically to cytotoxics and corticosteroids.
- Drug side effects and interactions should always be considered. Carbamazepine can induce a multisystemic reaction and concurrent administration with isoniazid should be done with caution.

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Unusual and memorable

Series editor: Gary D Wright

A 44 year old woman presented with a 12 month history of increasing left hip pain, particularly severe on weightbearing. On examination she had fine, sparse hair, a flattened nasal bridge, and short digits (fig 1 and fig 2). Her left hip was globally restricted and painful. Fifteen years previously her daughter attended a paediatric hospital with Perthes' disease. An observant paediatrician diagnosed Trichorhinophalangeal syndrome (TRPS) type I in our patient, her father, paternal grandmother, a younger brother and her daughter. Radiographs of our patient's hands showed typical changes with cone shaped modelling of the phalangeal epiphyses (fig 3). Radiographs of her pelvis showed features of avascular necrosis and advanced degenerative change of the left hip (fig 4).

Figure 1

Figure 2

Figure 3

Figure 4

TRPS is a rare autosomal dominant condition first described by Giedion in 1966¹ and thought to be caused by a deletion on chromosome 8q24.² TRPS type I is characterised by the features illustrated and differs from TRPS type II, which also presents with multiple exostoses, short stature, and mental handicap. Hip abnormalities are common in children with TRPS as a result of epiphyseal dysplasia or avascular necrosis.³ Hip abnormalities presenting in adulthood are rare.

Our patient has undergone a left total hip replacement and is recovering well.

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