Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Thrombotic thrombocytopenic purpura secondary to *Streptococcus*

M.J. Morrin a,*, F.G.C. Jones a, J. McConville b, C. Arnold a, B. Mullan c, G.G. Lavery c, M.F. McMullin a

a Department of Haematology, Belfast City Hospital, Lisburn Road, Belfast BT9 7AB, United Kingdom
b Department of Neurology, Royal Victoria Hospital, Grosvenor Road, Belfast BT12 6BA, United Kingdom
c Regional Intensive Care Unit, Royal Victoria Hospital, Grosvenor Road, Belfast BT12 6BA, United Kingdom

Received 23 May 2005; accepted 6 June 2005

Abstract

We describe a 16 year old female who developed thrombotic thrombocytopenic purpura (TTP) following infection due to *Streptococcus*. Initially presenting a fever and systemic upset she progressed to develop dialysis dependent acute renal failure, seizures, thrombocytopenia and a haemolytic anaemia—the pentad of features seen in TTP. Prior to the diagnosis she was found to have unexplained and previously undescribed MRI findings of diffuse increased signal intensity in the white matter of the left cerebellar hemisphere posteriorly and also increased signal intensity in the overlying cortex. She was commenced on plasmapheresis, and her anaemia, thrombocytopenia, creatinine and LDH all fully responded. In addition, she had no further seizures following plasmapheresis and has not relapsed to date.

We review both the rare association of TTP and streptococcal infection, and the neuroradiological findings described in the literature. This is only the third case report describing TTP following streptococcal infection, and only the second in the era of plasmapheresis.

© 2006 Elsevier Ltd. All rights reserved.

1. Introduction

A 16 year old female initially presented to general physicians with a three week history of a sore throat, generalised arthralgia, nausea, intermittent headaches, and general lethargy. She was well clinically, with a mild fever 37.5° and an erythematous maculopapular rash around the neck, thorax and upper abdomen and the right ankle. Fully alert and orientated, clinically she had no neurological signs. Initial full blood count revealed leucocytosis of 11.11 × 10⁹/l, with a Hb of 13.9 (11.5–16.5) g/dl, neutrophils 8.78 (2–7.5) × 10⁹/l, lymphocytes 0.64 (1.5–3.5) × 10⁹/l, and platelets 198 × 10⁹/l. Her inflammatory markers were raised...
and a provisional diagnosis of a bacterial/viral illness was made.

Within 24 h she deteriorated rapidly, initially becoming acutely confused, and then developing several episodes of tonic/clonic seizure activity. This responded to diazepam and then intravenous phenytoin. A computerised tomography (CT) brain scan at this stage was performed and was unremarkable. Cerebrospinal fluid (CSF) protein was raised at 1.08 (0.15–0.4) but CSF analysis, including microscopy and culture was otherwise normal. An electroencephalogram (EEG) was normal.

She recovered from this episode and there was a slow but gradual improvement in her initial symptoms, but a notable persistent episodic fever despite multiple broad spectrum intravenous antibiotics. Blood, sputum and urine cultures all failed to grow any organism. Atypical pneumonia serology was normal. Autoimmune screen, vasculitic screen, and complement were all normal. EBV IgM, CMV IgM, measles IgM and mumps IgM were all negative. PCR for parainfluenza, influenza A and B, coronavirus and metapneumovirus were all negative. RSV and adenovirus PCR were also negative.

Some 16 days after initially presenting she had several further tonic/clonic seizures which was refractory to initial treatment with diazepam and phenytoin and she required sedation and was transferred to Intensive Care. Over the subsequent days she required sedation and intravenous phenytoin in addition to general supportive care and inotropic support. Neurological assessment on reduced sedation did not reveal any localised neurological findings with the only finding that of bilateral upgoing plantar reflexes. She developed acute oliguric renal failure—the aetiology of which was unclear, but felt to be either secondary to sepsis or drug induced.

An antistreptolysin O titre from prior to this deterioration was significantly raised at 800 IU/ml. CT brain scanning was repeated and was again normal. However, a gadolinium enhanced MRI was undertaken and this showed diffuse increased signal intensity in the white matter of the left cerebellar hemisphere posteriorly and also increased signal intensity in the overlying cortex with effacement of the cortical sulci. The appearances were felt to be suggestive of a diffuse inflammatory process affecting principally the left cerebellar hemisphere but also involving the cerebellar vermis and the thalami. The appearances were initially felt to be suggestive of a direct viral infection causing acute viral cerebellitis or an acute disseminated encephalomyelitis.

Several days after the onset of these further seizures she developed increasing thrombocytopenia, her platelet count initially falling to $96 \times 10^9/l$ then falling to $31 \times 10^9/l$ 48 h later. Examination of her peripheral blood at this stage revealed features of haemolysis with red cell fragments. Her reticulocyte was markedly raised at 176 and her LDH raised at 5108 U/l. This thrombocytopenia, renal failure, neurological and pyrexia were all consistent with a diagnosis of thrombotic thrombocytopenic purpura, and plasma exchange with cryodeplete fresh frozen plasma was commenced.

At this stage she was still sedated, ventilated, requiring both isotropic support and her renal failure had become haemodialysis dependant. She had no further seizures.

Within 48 h of treatment with plasma exchange her platelets improved to $61 \times 10^9/l$, the LDH fell, and reticulocyte count fell. Plasma exchange was continued daily for 10 days at which stage the platelet count had improved to $150 \times 10^9/l$ and the LDH response plateaued at between 618 and 666 U/l.

Over this period of time she required both ongoing haemodialysis and ICU support, but was successfully weaned off ventilation, inotropic support and sedation becoming fully alert, responsive and with no residual neurological deficit. She did not relapse on withdrawal of plasmapheresis and her platelet count continued to improve. Her renal function improved and dialysis was successfully withdrawn. She made a gradual uneventful recovery. She had no further seizures. Her platelet count was $209 \times 10^9/l$ on discharge. Seven months on, she had no further episodes of TTP.

2. Discussion

Thrombotic thrombocytopenic purpura (TTP), as seen here, is characterized by the clinical pentad
of fever, neurological abnormalities, thrombocytopenia, microangiopathic haemolytic anaemia and renal impairment [1]. As TTP has a high mortality if untreated [2] prompt diagnosis and prompt treatment is essential, and is therefore a haematological emergency. This case highlights how the neurological symptoms and renal dysfunction may predate the onset of thrombocytopenia or haemolysis and therefore lead subsequent diagnostic difficulty.

It is well established that TTP may arise in association with infection where it follows the development of an inhibitory antibody to metalloprotease which breaks down high molecular weight multimers of von Willebrand factor (VWF). This is only the third reported case of TTP following streptococcal infection, and only the second in either immunocompetent patient and the second case since the advent of plasmapheresis [3].

The last reported case was that of an immunocompetent 50 year old lady who presented with pneumococcal bacteraemia and in addition thrombocytopenia, microangiopathic haemolytic anaemia, renal failure, and neurologically she became disorientated. She responded to plasma exchange but relapsed on discontinuation and required re-initiation of plasma exchange [3]. The authors discuss how the production of the enzyme neuramidase by *Streptococcus pneumoniae* has been suggested as a possible agent in the pathogenesis of the thrombotic process of TTP.

TTP may occur secondary to autoimmune conditions, in particular with lupus [1]. Given the development of anti streptolysin antibody in this case, this must raise the possibility of an autoimmune role in the pathogenesis in this rare association.

This case highlights the markedly abnormal neuroradiological findings that may be found in patients with TTP. Furthermore, in this case CT scanning was found to be normal whilst subsequent MRI scanning with enhancement was markedly abnormal. This suggests that MRI scanning may be the initial imaging of choice in patients.

The neuroradiological findings in TTP, either by CT or MRI, have only been briefly described. They are of importance in any undiagnosed case of TTP in that they may suggest the diagnosis.

TTP has an incidence of 1 in 500,000. In the largest series reported it was found 50% of patients with TTP had brain lesions on CT scanning [4].

A series of 12 patients assessed by CT, MRI or both revealed acute brain lesions in 75% of patients [5]. They also found MRI to be more sensitive, with abnormal findings in 88% of patients whilst CT was found to be abnormal in 45%. Three types of radiological lesions were seen: bilateral cerebral oedema, ischaemic strokes and one case of haematomas [5]. This would suggest—as was the case with our patient—MRI is more sensitive than CT scanning.

In contrast, Fiorani et al. [6] undertook MRI scanning in five patients with TTP with neurological manifestations, and the result of MRI scanning in all five patients was entirely normal. In addition they also performed single photon emission tomography (SPET) in two patients in the acute phase of the disease which showed reduced cerebral blood flow in both.

It appears therefore the neuroradiological findings are diverse. The MRI findings in this case—of increased signal in the cerebellar hemisphere—has only been described infrequently and therefore was it understandable TTP was not initially considered. TTP remains a diagnostic challenge and a condition where high level of suspicion is essential in patients with unexplained neurological disease.

References

[1] Moake JL. Thrombotic microangiopathies. NEJM 2002;347: 589–600.
[2] Firkin F et al., editors. De Gruchy’s clinical haematology in medical practice. 5th ed. Blackwell Scientific Publications; 1989. p. 391.
[3] Myers KA, Marrie TJ. Thrombotic microangiopathy associated with *Streptococcus pneumoniae* bacteraemia: case report and review. Clin Infect Dis 1993;17(6):1037–40.
[4] Kay AC et al. Prognostic significance of computed tomography of the brain in thrombotic thrombocytopenic purpura. Mayo Clin Proc 1991;66:602–7.
[5] Bakshi R et al. Thrombotic thrombocytopenic purpura: brain CT and MRI findings in 12 patients. Neurology 1999;52:1285.
[6] Fiorani et al. Brain MRI and SPET in thrombotic thrombocytopenic purpura. Ital J Neurol Sci 1995;16(3):149–51.