TITLE OF CASE

Early intravenous immunoglobulin therapy for group A β-haemolytic streptococcal meningitis with toxic shock syndrome.

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SUMMARY

A female in her forties was transferred to a Sydney (Australia) based tertiary hospital, following presentation to a regional hospital with Group A streptococcal (GAS) oto-mastoiditis; complicated by meningitis, venous sinus thrombosis, hemorrhagic cerebral infarction and subdural empyema.

She rapidly deteriorated with profound cardiovascular collapse. Despite initiation of high dose vasoactive therapy, she remained shocked and developed multi-organ dysfunction syndrome. Early intravenous immunoglobulin therapy (140g in 2 doses) was initiated as an adjunct to antimicrobial, surgical and supportive care for refractory streptococcal toxic shock syndrome.

Over the course of a 12-day ICU stay she made good progress with de-escalation of her vasoactive supportive care and reversal of her organ injuries. She was subsequently discharged to ward based care. At her 3-month follow-up appointment she had significantly reduced neurological deficit. Five months following her presentation to hospital she had returned to full-time work.

BACKGROUND

Streptococcus pyogenes is a beta-haemolytic Lancefield serogroup A bacterium also known as Group A *Streptococcus* (GAS). GAS infections typically demonstrate a bimodal distribution, namely paediatric and elderly populations.[1-3] GAS is a known commensal of the upper respiratory tract and is estimated to be the cause of pharyngitis / tonsillitis for 1 in 8 adult cases.[1] Infections due to GAS range in severity from mild skin and soft tissue involvement[4] to severe invasive infections to sites, including the central nervous system (CNS). GAS is a highly toxigenic organism, and invasive infections may be complicated by streptococcal toxic shock syndrome (STSS)[5], and/or extensive tissue damage and necrosis (e.g. necrotizing fasciitis). In comparison, staphylococcal toxic shock syndrome often occurs with localized infection.[6] In the United States there are 9,000-11,500 cases of invasive disease per annum (3.2-3.9/100,000 population). STSS represents 6-7% of cases[7] and is associated with increased disease severity and mortality.[8] Meningitis has been reported as a complication of 1-2% of GAS invasive infections, with a mortality of 23-27%.[3, 9, 10]

We present a case of otogenic GAS meningo-encephalitis complicated by subdural empyema, venous sinus thromboses, and STSS.

CASE PRESENTATION

A previously well woman in her forties presented from home to a regional Emergency Department, with acute signs of meningism and a subacute history of an upper respiratory tract infection. She had recently been diagnosed with otitis media, and commenced eardrops three days earlier. She experienced worsening of her symptoms with the development of progressive left side headache radiating into the neck, prompting her presentation to the hospital.

At presentation, she was febrile to 41.3˚C, tachycardic and rapidly became hypotensive, requiring fluid resuscitation and vasopressor support with noradrenaline. There was evidence of multi-organ dysfunction with an acute kidney injury, acute hepatitis and disseminated intravascular coagulopathy.

INVESTIGATIONS AND TREATMENT

Imaging demonstrated oto-mastoiditis (with invasion through the petrous temporal bone), pneumocephalus, subdural empyema, and a perforated tympanic membrane. A brain MRI confirmed left-sided otomastoiditis, with associated cortical venous, sigmoid/transverse and superior sagittal sinus thromboses (septic thrombophlebitis), secondary venous haemorrhagic infarcts involving the left parietal lobe and right superior frontal lobe with associated subarachnoid haemorrhage.

Empirical antibiotics (piperacillin/tazobactam 4.0g/0.5g q6h) were commenced immediately on presentation. The patient was intubated in the context of a deteriorating level of consciousness and urgently transferred to a tertiary hospital for specialist neurological, neurosurgical and ENT care. By the time she arrived at the tertiary hospital she was shocked with a lactic acidosis. An echocardiogram revealed global systolic dysfunction with a left ventricular ejection fraction of 35%, likely a reflection of sepsis-induced acute cardiomyopathy and multi-organ failure. Cardiovascular support was escalated with the addition of vasopressin (0.04units/min) and milrinone (0.24mcg/kg/min). At this stage her noradrenaline requirements were above 0.57mcg/kg/min.

Blood cultures taken on presentation grew *Streptococcus*, and antibiotics were rationalized to benzylpenicillin. Linezolid was added owing to preferable CNS penetration. Intravenous immunoglobulin (IVIg) was administered in the face of refractory vasoplegia and cardiogenic shock, secondary to STSS. She received a total of 140g in 2 doses (day 1 and day 2).

Emergency left cortical mastoidectomy and abscess drainage was performed for source control, but mechanical thrombectomy via angiography was not performed due to low clot burden, uncertain benefit in this complex setting, multi-factorial brain injury and estimated high risk of the procedure in the context of likely friable vasculature and coagulopathy.

The vasopressor requirements started to abate from day 2, and the patient gradually improved. Her renal function stabilized without need for continuous renal replacement therapy (CRRT).

Successful extubation was achieved by day 10 after sufficient neurological recovery. A progression scan, on day seven, demonstrated evolution of a non-occlusive thrombus in the left transverse/sigmoid sinus triggered the commencement of unfractionated heparin infusion. Clinical concern regarding her multicomparment intracranial haemorrhages and drainage of her cranial empyema had delayed the commencement of full anticoagulative therapy. She was subsequently transferred to the ward on day 12, with 2/5 power to her right leg.

Her management included a 6-week course of IV antibiotic therapy, and ongoing therapeutic dose low molecular weight heparin (LMWH) injections for superior sagittal and sigmoid/transverse sinuses thromboses. After further recovery at a peripheral hospital closer to home, she was discharged to a full-time rehabilitation program at which point she still required assistance for transfer to and from the bathroom, with ongoing residual right lower limb weakness. A 6-month follow-up brain MRI showed resolving venous sinus thromboses.

OUTCOME AND FOLLOW-UP

Three months following her initial presentation she had made a near-complete recovery with minimal right leg weakness and a normal gait. There was a mild left-sided hearing deficit and paraesthesia around the left buttock. At this point she had returned to part time work. Five months after presentation she made a return to full time employment. Progress imaging studies confirmed resolution of meningitis and subdural empyema with stable appearances of the superior sagittal sinus thrombosis. Anticoagulation was continued long-term following an initial six months of therapy.

DISCUSSION

We have presented a case of GAS oto-mastoiditis complicated by meningitis, venous sinus thrombosis and hemorrhagic cerebral infarction, subdural empyema, and toxic shock syndrome. Meningitis is seldom encountered together with STSS. In this context it would be expected to be associated with increased disease severity and mortality.[8] A Dutch group (Lucas MJ et al, 2015) found that otitis and sinusitis preceded GAS meningitis in 92% of patients. Of these, half went on to develop ongoing neurological sequelae.[8] This association with otitis is well described in the literature.[11-15] The air-filled sinuses provide a physical route of entry for invasive infection. This process can be facilitated by concurrent/preceding viral infections[16], in particular influenza.[17] The latter might be of relevance in this case given the sharp increase in cases of opportunistic bacterial infections during the flu-season in NSW.

Our patient had an excellent clinical outcome, despite extensive CNS involvement with multi-organ failure and STSS, which in combination have a reported mortality of up to 70%[18-22] even with aggressive supportive and antibiotic therapy. Interestingly, as illustrated in this case, the more severe cases of GAS do not show the aforementioned bimodal pattern of disease for GAS bacteraemia, nor a predisposition for those patients with underlying diseases.[23-26]

Streptococcal toxic shock syndrome is a systemic illness centered on capillary leak and characterised by hypotension, hypoalbuminaemia and generalised nonpitting oedema.[6] Additionally, there is varying severity of vasoplegia and increased risk of disseminated intravascular coagulation, myocardial suppression, renal failure, ARDS and multiorgan failure. During the first 24h of her ICU admission, our patient developed most of these complications. Although there is considerable overlap between severe sepsis and STSS, this case was treated as STSS based on the microbiology results (blood culture), severity of the clinical picture and rapid progression despite antibiotics and supportive care.

STSS is a toxin driven phenomenon. Specifically, a group of powerful immunostimulatory exotoxins, which collectively are referred to as pyrogenic toxins[27, 28] that induce T-cell expansion.[29-31] Streptococcal superantigens (SSAg) are a group of extracellular peptide molecules, which are important virulence factors in invasive GAS infections. They share the following properties: pyrogenicity and increased susceptibility to endotoxic shock, [32] mitogenicity for T-cell subsets defined by the variable region of the T cell receptor beta chain (Tc*RVβ*)[33] and suppressed immunoglobulin production.[34] Thus, SSAg can modulate both the humoral and cellular components of the immune response to GAS. Pro-inflammatory cytokines including, TNFα, IL-2 and IFNγ, play an important role in the resultant endothelial leak, cardiovascular collapse and multiorgan dysfunction seen in STSS.

Strains of GAS are differentiated by antigenic variation of the M protein, which is encoded by the *emm* gene.[8] The M protein plays an important role in determining the virulence of GAS, [35, 36] by attenuating the phagocytic response to streptococci by polymorphonuclear leukocytes.[37] The M protein is also immunogenic and elicits protective antibodies. Over 220 *emm* types have been identified with widely variant global distribution and a likely association between various *emm* types and certain clinical manifestations.[38] For example, e*mm* types 1, 3 and 49 are associated with invasive disease with e*mm* types 1 and 3 accounting for the majority of strains isolated from patients with STSS.[16]

Blood culture isolates from our patient typed as *emm* type 6.103 (*emm* cluster Clade Y), which is an unusual type in our geographical location. Our patient had not undertaken recent travel but in her public service role had engaged with some East African and South Asian refugees a week prior to onset of symptoms, raising the possibility that colonization of the oropharynx may have occurred at that time. Additionally, in the days leading up to her presentation she was in brief but close contact with a 10-month old baby. A potential role for *emm* type 6 in stimulating T-cell responses via TNFα and TNFß has been postulated by Kotb et al.,[39] providing a link between M-protein and immunological signalling pathways mediating virulence.

IVIg was added to the treatment in view of the rapid progression and severity of the clinical picture despite adequate surgical source control, timely commencement of IV antibiotics and haemodynamic support. IVIg is a gamma globulin obtained from purified pooled plasma from thousands of donor samples.[40] It is speculated that IVIg acts as an immunomodulator, in

particular the humoral pathways including, inhibition of the complement membrane attack complex, enhanced opsonisation of bacteria and neutralisation of superantigens.[7] Regarding the latter, experimental models have demonstrated that pooled IVIg can inhibit in vitro stimulation of peripheral blood T-cells by the superantigen, staph-toxin.[41] This would be consistent with a potential immunoregulatory role for IVIg in vivo.

The evidence supporting the use of IVIg in STSS remains limited, and there is no consensus recommendation. A 2003 European study randomised patients to IV clindamycin with IV benzylpenicillin (OR IV cefuroxime) and either high dose IVIg (1g/kg day 1, 0.5g/kg days 2 and 3) or 1% albumin (placebo).[42] The study suffered from lack of recruitment. Of the 120 patients (to be randomised 1:1) the study was powered for, only 21 were randomised. A reduction in mortality at 28 days (10% vs 36%, primary endpoint) was observed but this was not statistically significant. Similarly, a Canadian observational study (Kaul et al. 1999)[43] reported improved survival at 30 days (67% vs 34%, p=0.02) however there was no difference in duration of ventilation or length of hospital stay. Despite the lack of compelling evidence, IVIg may have a role in a particular subset of patients. The National Blood Authority (Australia) sets out criteria for the clinical use of IVIg in Streptococcal TSS. The criteria highlights that a patient qualifies for the early use of IVIg when there is probable or confirmed diagnosis of STSS and “failure to achieve rapid improvement with fluid resuscitation, inotropes, surgery, antibiotic therapy and other supportive measures”.[44] The early use of IVIg in this case may have contributed to the rapid improvement in the clinical picture.

Linezolid is a oxazolidinone, the first of its class approved for clinical use.[45] It has excellent bacteriostatic activity against almost all gram positive bacteria and is a therapeutic option for the treatment of methicillin-resistant species of staphylococci.[46-48] Linezolid inhibits bacterial protein synthesis by blocking the fusion of 30s and 50s ribosomal subunits.[49] It specifically acts at a different time point of the bacterial translation process resulting in limited if any cross-resistance to other classes of antibiotics[45]. It is known to have excellent penetration of the blood brain barrier with reported in vivo CSF:plasma ratio of 0.7-1.6.[50, 51] Linezolid was chosen in addition to benzylpenicillin based on local expert guidance. In the context of a rapidly deteriorating patient with known gram positive (GAS) sepsis involving the CNS it had a theoretical benefit. It has also been postulated to disrupt the BBB in part due to its inhibition of mitochondrial protein synthesis,[45] this may have facilitated the CNS penetrance of benzylpenicillin.

LEARNING POINTS/TAKE HOME MESSAGES *3-5 bullet points*

1. Invasive GAS infection of the CNS can lead to complications associated with a high level of morbidity and mortality including, multi-organ dysfunction syndrome, CNS venous-thrombosis and stroke.
2. Streptococcal toxic shock syndrome can rapidly result in overwhelming cardiovascular embarrassment requiring ICU level monitoring and haemodynamic support.

3. Early implementation of intravenous immunoglobulin, albeit lacking in high-level evidence, may be a useful adjunctive therapy in those patients with refractory STSS.

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