Septicaemia, thrombocytopaenia and thrombosis

Introduction

A case of Lemierre's syndrome with microangiopathy is presented. Lemierre's syndrome is a rare condition of severe anaerobic septicaemia, most commonly caused by *Fusobacterium* species, that induces thrombosis at usual sites. The upper respiratory tract is often the primary site of infection and it affects young healthy individuals. Microangiopathic thrombocytopaenia and anaemia occurred in this case requiring transfusion. This is the first description of microangiopathy in the literature in this condition. The case highlights decision making in severe sepsis with blood abnormalities and consideration of thrombotic thrombocytopaenia purpura as a potentially life-threatening differential.

Figure 1. Blood film on day 2. Platelet count $34x10^9$/litre.

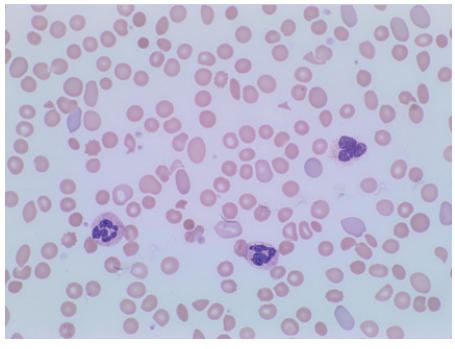
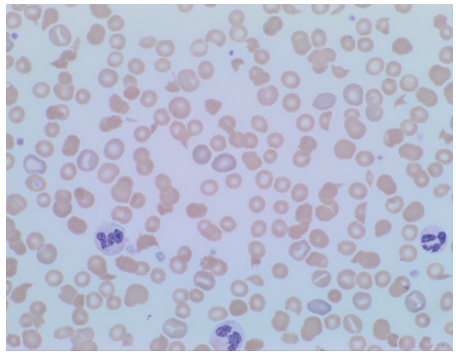


Figure 2. Blood film on day 5.



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CASE REPORT

A 45-year-old man presented to the emergency department with a 3-day history of sore throat, headache, neck pain and constitutional symptoms. He had no recent travel history and worked in an office. He was previously fit and well with no past medical history. On examination he had neck stiffness, Kerning's negative, some pharyngeal erythema, no rash or other localizing signs. He was afebrile, saturating on room air and normotensive.

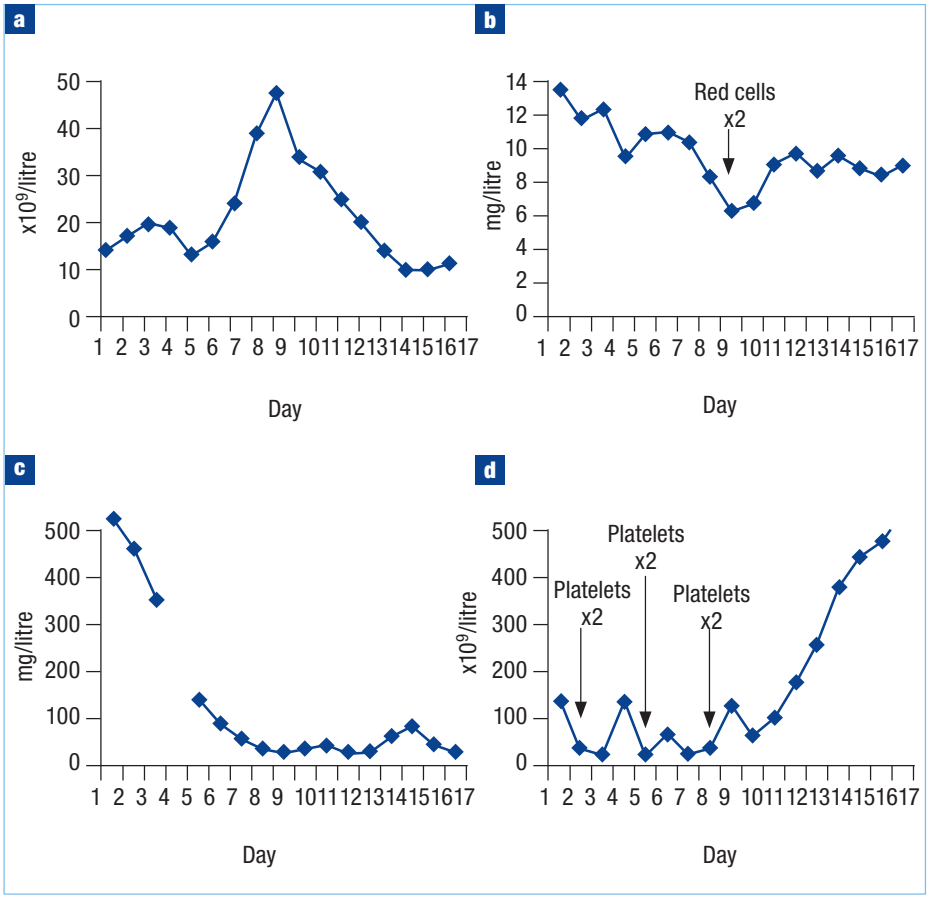
His initial blood tests were haemoglobin 13.5 g/litre, white cell count $14.4x10^9$/litre, platelets $137x10^9$/litre, C-reactive protein 532 mg/litre, creatinine 204 μmol/litre, activated partial thromboplastin time 32 seconds, prothrombin time 14.5 seconds, fibrinogen 7.5 g/litre, bilirubin 9 μmol/litre, alanine aminotransferase 22 U/litre, alkaline phosphatase 230 U/litre. Computed tomography of the head showed a tight appearance of basal cisterns without a focal cause. He was initially treated with antimicrobials, including ceftriaxone and aciclovir, for meningitis.

On day 2, it was noticed that he was developing some swelling of the right side of the neck. Computed tomography of the chest showed cervical chain mild lymphadenopathy and right internal jugular vein thrombosis. Otorrhoea, rhinorrhoea and headache became more prominent at this stage. Review by an ear nose and throat surgeon demonstrated bilateral middle ear effusion and nasoendoscopy oropharyngeal swelling. A diagnosis of Lemierre's syndrome was suggested at this stage.

With no external signs of bleeding, his repeat blood tests on day 2 were haemoglobin 11.8 g/litre, white cell count $17.8x10^9$/litre, C-reactive protein 461 mg/litre, platelets $34x10^9$/litre, activated partial thromboplastin time 33 seconds, prothrombin time 17.8 seconds, fibrinogen >7.0 g/litre, bilirubin 8 μmol/litre, alanine aminotransferase 35 U/litre, alkaline phosphatase 258 U/litre. Blood film (*Figure 1*) showed a reduced number of platelets with occasional giant platelets, occasional target cells and neutrophils with slight left shift. The patient had a case of severe sepsis, thrombosis and thrombocytopaenia. The decision taken initially was to attribute the thrombocytopaenia to microangiopathy from sepsis based on the blood film. He was treated with platelets, treatment dose low molecular heparin and antibiotics. Subsequent blood film (*Figure 2*) from day 5 showed plentiful red cell fragments with a normal clotting screen which led to reconsideration of the diagnosis. A sample was sent for ADAMTS13 and a specialist opinion was sought. The ADAMTS13 level was 42% which is normal. His haemoglobin level gradually declined during admission to 6.2 g/litre on day 9 requiring transfusion. Blood results and transfusions are shown in *Figure 3*.

The diagnosis of Lemierre's syndrome was supported by blood cultures yielding the anaerobe *Fusobacterium necrophorum* which was sensitive to metronidazole. This case was additionally complicated by cerebral venous sinus thrombosis causing raised intracranial pressure, sixth nerve palsies and fluctuating consciousness, and multiple asymptomatic lung septic emboli. He received ceftriaxone and metronidazole intravenously for a 2-week period followed by 4 weeks of oral metronidazole therapy and follow-up computed tomography imaging. The patient made a good clinical recovery and inflammatory markers confirmed a response to antibiotics. Anticoagulation with low molecular heparin was planned for 6 months.

Figure 3. Blood results and transfusions. **a.** Total white cell count. **b.** Haemoglobin level. **c.** C-reactive protein level. **d.** Platelet count.



LEARNING POINTS

- Multidisciplinary input is important in complex cases.
- Blood cultures can be valuable in the absence of fever.
- Assessment of a blood film in a patient with severe sepsis and low blood counts can be lifesaving.
- Consideration of thrombotic thrombocytopaenia purpura as a potential diagnosis is a medical emergency and sepsis may be a distractor.
- Early advice from specialists is paramount to save lives.

Discussion

Lemierre's syndrome is a rare condition of metastatic septicaemia resulting from *Fusobacterium* infection that affects young people (Riordan, 2007; Kuppalli et al, 2012). The oropharynx is thought to be the initial site in the majority of cases. Recognized sites of spread include the lungs, brain, liver and joints. Thrombosis at unusual sites is a feature of the condition and internal jugular vein thrombosis is common.

The thrombocytopaenia was initially diagnosed to be secondary to microangiopathy from sepsis based on the blood film and clinical picture. A repeat blood film on day 5 showed red cell fragments. The fatality of undiagnosed thrombotic thrombocytopaenia purpura is 90% (Scully et al, 2012).

The decision at this stage is challenging. The key question was whether sepsis was driving the depletion of platelets or whether sepsis could be a trigger for thrombotic thrombocytopaenic purpura. The pentad of thrombotic thrombocytopaenia purpura – thrombocytopaenia, microangiopathic haemolytic anaemia, neurological signs, renal dysfunction and fever – clearly overlaps with this case. Disseminated intravascular coagulation, haemolytic uraemic syndrome and antiphospholipid syndrome are other differentials. The level of thrombocytopaenia is not discriminatory. Haptoglobin levels are low, direct antiglobulin is negative and lactate dehydrogenase levels are raised in thrombotic thrombocytopaenia purpura whereas deranged clotting should not occur.

Deficiency of the von Willebrand factor cleavage protein ADAMTS13 results in platelet aggregation found in thrombotic thrombocytopaenia purpura. The sensitivity of the assay is high if ADAMTS13 is less than 5%. Inflammatory disorders alter ADAMTS13 levels but not to this degree. Paroxysmal nocturnal haemoglobinurea screen and anticardiolipin antibodies were negative.

There are no previous reports of severe microangiopathy in Lemierre's syndrome without overt disseminated intravascular coagulation. Plasma exchange in combination with steroids as an emergency is indicated if there is convincing evidence of thrombotic thrombocytopaenia purpura without an ADAMTS13 result as delay may significantly impair outcome. The patient was stable on day 5 and the decision was taken to wait 2 hours for the ADAMTS13 result rather than to transfer the patient to a tertiary centre.

This case demonstrates the importance of multidisciplinary input in complex cases, the value of blood cultures in the absence of fever and the assessment of a blood film in severe sepsis and low blood counts. Consideration of thrombotic thrombocytopaenia purpura as a potential diagnosis is a medical emergency and sepsis may be a distractor. If thrombotic thrombocytopaenia purpura had been diagnosed the management would have been different. The association of Lemierre's with thrombosis makes the diagnosis of thrombotic thrombocytopaenia purpura or microangiopathy in this case more difficult. **BJHM**

Kuppalli K, Livorsi D, Talati NJ, Osborn M (2012) Lemierre's syndrome due to *Fusobacterium necrophorum*. *Lancet Infects Dis* **12**(10): 808–815. https://doi.org/10.1016/S1473-3099(12)70089-0

Riordan T (2007) Human infection with *Fusobacterium necrophorum* (Necrobacillosis) with a focus on Lemierre's syndrome. *Clin Microbiol Rev* **20**(4): 622–659. https://doi.org/10.1128/CMR.00011-07

Scully M, Hunt BJ, Benjamin S et al (2012) Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. *Br J Haematol* **158**(3): 323–335. https://doi.org/10.1111/j.1365-2141.2012.09167.x