An uncomplementary situation

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INTRODUCTION

A 23 year old man was admitted to hospital having collapsed on a flight back to the UK from Spain.

He had begun to feel unwell the evening before with fever, diarrhoea, vomiting and severe myalgia. In the morning he struggled to get to the airport due to worsening leg pain and eventually collapsed in the airplane toilet during the flight. His past medical history was notable for paroxysmal nocturnal haemoglobinuria (PNH), for which he had been receiving infusions of eculizumab, a monoclonal antibody which binds complement C5 and prevents formation of the membrane attack complex (Figure 1), for the preceding two months.

He was attended by a fellow passenger, an off-duty paramedic, who noted a non-blanching rash on his limbs and made a diagnosis of meningococcal sepsis. On arrival, the plane was met by an ambulance crew who administered intramuscular benzylpenicillin and rushed the patient to hospital.

In the emergency department he was hypotensive, tachycardic and tachypnoeic with a fever, had a rapidly progressing purpuric rash mainly affecting his lower limbs (Figures 2, 3 and 4) and a mild headache but no meningism. Venous lactate was 8.3mmol/l, CRP 91mg/L, Neutrophils 7.35x10^9/L, Platelets 75x10^9/L, Haemoglobin 94g/L, INR 1.6, with normal renal function and liver enzymes. He received intravenous ceftriaxone and fluids and was transferred to the Intensive Care Unit for inotropic support. Household contacts were given ciprofloxacin prophylaxis.

PROGRESS

Eculizumab, given two-weekly, was due the day after admission. After advice from the national PNH service in Leeds, this was administered to prevent massive haemolysis and thrombosis.

He stabilised in intensive care but developed marked derangement of his liver function tests (Figure 5). A CT scan was performed to rule out hepatic vein thrombosis (thrombosis is the leading cause of deaths in patients with PNH).[1] There was no evidence of hepatic vein thrombosis, but significant hepatomegaly was noted (Figure 6). In addition, there was considerable peribronchial thickening in both lungs, most pronounced in the lower lobes and some additional peripheral nodularity in the mid and lower zones, most likely representing an intense lymphatic response to acute infection (Figure 7).

Neisseria meningitidis (W135 strain) was identified by PCR from an EDTA blood sample taken on admission; blood cultures and throat swab were negative.

He received 7 days of ceftriaxone and his condition slowly improved. He was discharged from ICU after 4 days and discharged home after 10 days in hospital. On review of his medical record he had received meningococcal (*Menveo* – A, C, W135 and Y conjugate vaccine) and pneumococcal vaccines two weeks prior to this admission, and was taking prophylactic phenoxymethylpenicillin.

CLINICAL IMAGES AND RESULTS

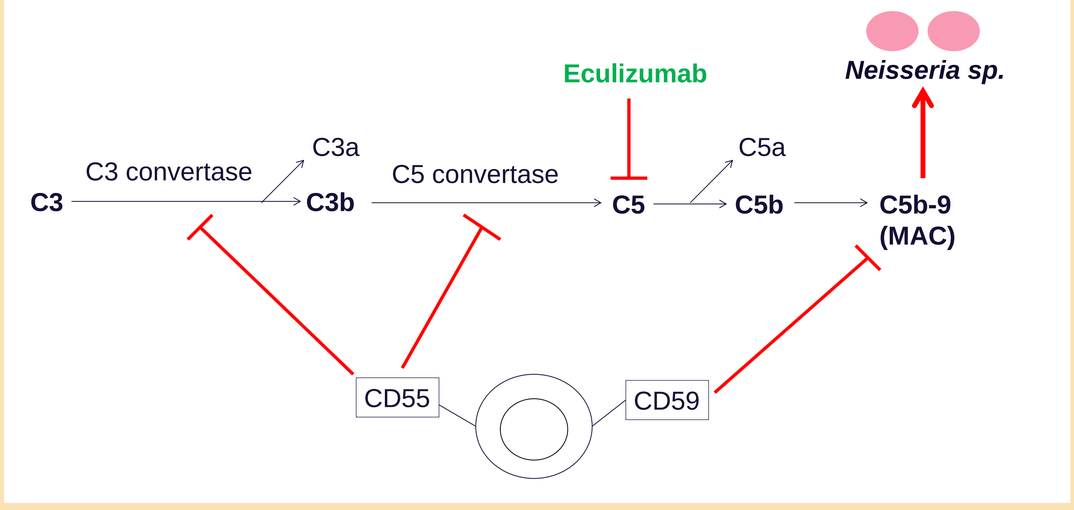
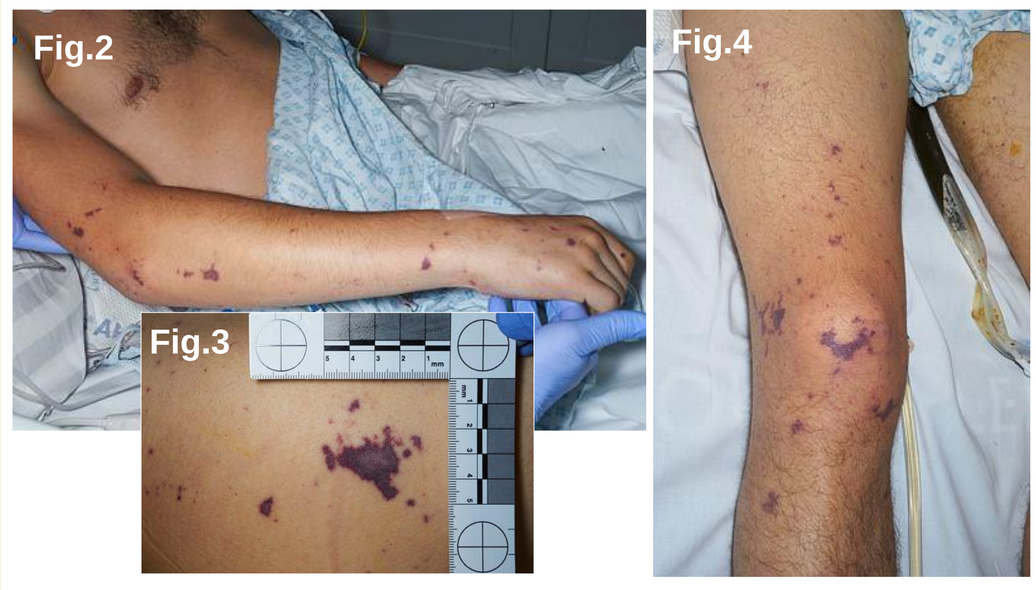


Figure 1. PNH erythrocytes lack complement inhibitors CD55 and CD59, resulting in complement-mediated intravascular (CD59) and extravascular (CD55) haemolysis. Eculizumab blocks C5, preventing formation of the membrane attack complex (MAC), which kills both CD59- intravascular erythrocytes and *Neisseria sp.* through the insertion of a pore into the cell membrane.



Figures 2, 3 and 4. Purpura

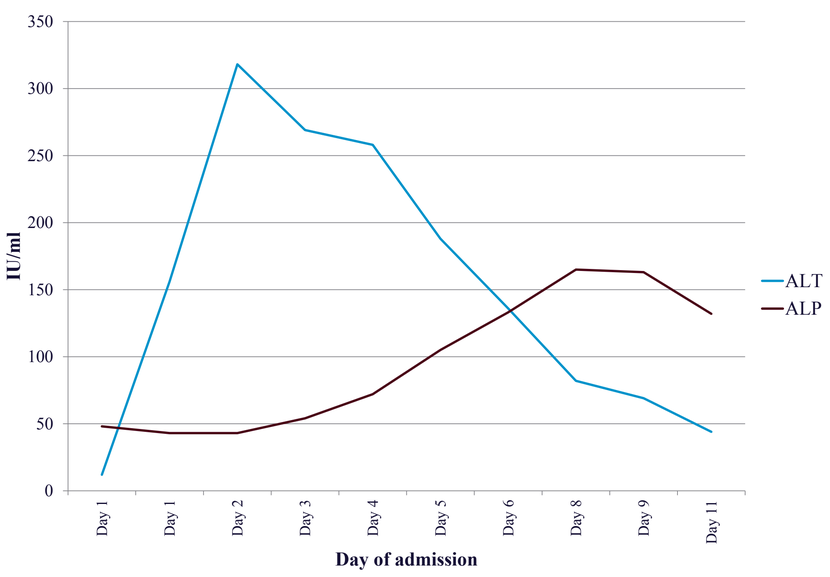


Figure 5. Trend of ALT and ALP from admission to discharge.

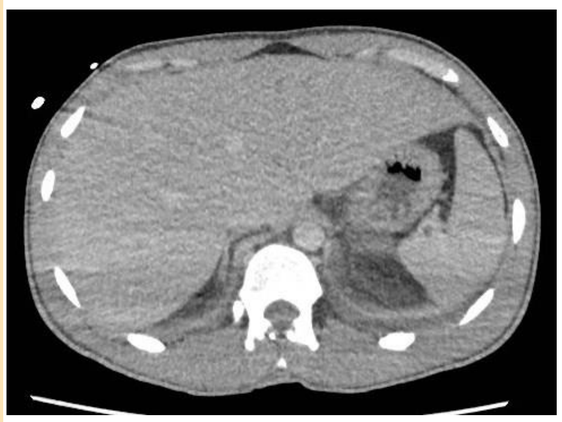


Figure 6. CT abdomen: Hepatomegaly (20cm craniocaudally), an interval increase compared with imaging 3 months previously.

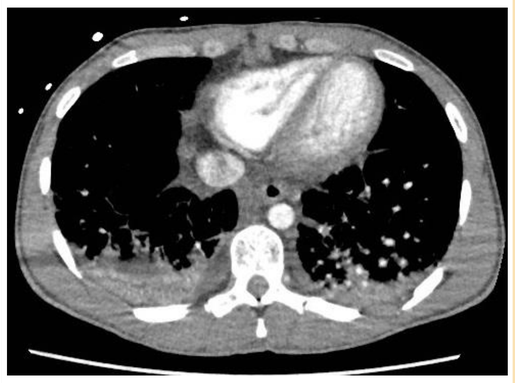


Figure 7. CT thorax with contrast: interstitial septal thickening, bilateral pleural effusions

DISCUSSION

Anti-complement therapy is the most effective way to reduce haemolysis and thrombosis in PNH, which are a result of complement-mediated haemolysis due to the absence of cell surface complement regulatory proteins (CD55 and CD59).

Invasive meningococcal disease is significantly more common in patients receiving eculizumab, and it is standard practice to give meningococcal vaccines in addition to penicillin prophylaxis. Despite this cases still occur and a recent CDC report details 16 cases of eculizumab-associated meningococcal disease despite such precautions.[2]

6 cases of meningococcal sepsis have been seen in patients receiving eculizumab from the Leeds PNH Service, but purpuric rash is rare (seen only in this case). The rate of meningococcal infection on eculizumab is 0.25 infections/100 patient years on therapy.[3]

CONCLUSIONS

This case highlights:

- the importance of heightened awareness of this disease in this small subset of patients, particularly as it may present atypically
- the importance of rapid identification of and prompt antimicrobial and supportive treatment for sepsis
- the important role of molecular diagnostics (PCR in this case) in determining the cause of infection

ACKNOWLEDGEMENTS

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REFERENCES

1. Hillmen P, Muus P, Roth A et al. Long-term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal noctural haemoglobinuria. Brit J Haem, 2013; **162**: 62-73

2. McNamara et al. High Risk for Invasive Meningococcal Disease Among Patients Receiving Eculizumab (Soliris) Despite Receipt of Meningococcal Vaccine. MMWR July 14, 2017; **66**, 27

3. Personal communication, Professor Peter Hillmen, Consultant Haematologist, St James's University Hospital, Leeds