Drug induced thrombotic microangiopathy caused by levofloxacin

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Abstract

Thrombotic microangiopathy is a rare but serious manifestation of a variety of diseases. The key features are microangiopathic haemolysis, thrombocytopaenia, renal dysfunction and neurological symptoms. Here we discuss the case of a previously well male presenting with community-acquired pneumonia who developed thrombotic microangiopathy during admission. This case illustrates the difficulties in the differential diagnosis and reminds us of the importance of the peripheral blood film in identifying the cause of thrombocytopaenia. One life-threatening cause of thrombotic microangiopathy is thrombotic thrombocytopaenia purpura and when that diagnosis is suspected emergency plasma exchange is essential. Many drugs can cause thrombotic microangiopathy and here we highlight the commonly-prescribed antibiotic levofloxacin as the culprit.

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Introduction

Thrombotic microangiopathy (TMA) is characterised by microvascular and macrovascular occlusion with associated microangiopathic haemolysis and thrombocytopaenia. Peripheral blood film features are red cell fragmentation (schistocytes), polychromasia, and anaemia. Other laboratory features include elevated lactate dehydrogenase, reticulocytosis, low/absent haptoglobin, and a negative direct antiglobulin test result. Causes of TMA include thrombotic thrombocytopenia purpura (TTP), haemolytic uraemic syndrome (HUS), drug-induced (e.g. ciclosporin), malignancy and viral infections such as HIV and hepatitis C. When assessing a new case, the possibility of TTP has to be considered as this condition is a medical emergency requiring urgent initiation of plasma exchange. Confirmation of TTP requires measurement of serum enzymatic activity of A Disintegrin and Metalloproteinase, with a Thrombospondin type 1 motif, member 13 (ADAMTS13).

Case presentation

A 56-year-old male oil industry worker was admitted to the medical assessment unit with a 5 day history of cough, rigors and shortness of breath. He had returned to the UK seven days prior after five weeks working in various regions of Kuwait. His past medical history included non ST-elevation myocardial infarction treated with percutaneous coronary intervention for which he was on aspirin, bisoprolol, ramipril and atorvastatin. He was a chronic smoker of 20 pack-years.

On examination he had bibasal crepitations and was treated for severe community-acquired pneumonia. Transfer to the intensive care unit was required due to type 1 respiratory failure and septic shock requiring a period of ventilation and inotropic support.

A full blood count on admission showed haemoglobin of 122 g/l, white cell count of 11.8×10^9/l with a neutrophilia, and a normal platelet count. Liver function tests were normal but urea and creatinine were elevated at 22 mmol/l and 210 umol/L, respectively. C-reactive protein was elevated at 338 mg/l. Chest X-ray showed evidence of bilateral basal consolidation.

On day 3 of admission, *Legionella pneumophilia* infection was confirmed with legionella DNA detected in sputum and bronco alveolar lavage and he was commenced on levofloxacin. It was thought that the infection was acquired in Kuwait and he was at risk being a male middle-aged smoker. Sputum cultures also isolated *Escherichia coli* with sensitivity to levofloxacin, clarithromycin and ceftazidime. He was making a good recovery with improvement in his oxygen requirements and renal function and was stepped down from intensive care to the respiratory ward. His chest X-ray showed significant improvement.

After 3 days of levofloxacin treatment he started to develop anaemia, thrombocytopaenia and deterioration of renal function. By day 9 of levofloxacin, haemoglobin was 72 g/L and platelet count was 52 x 10^9/L. Coagulation profile was normal

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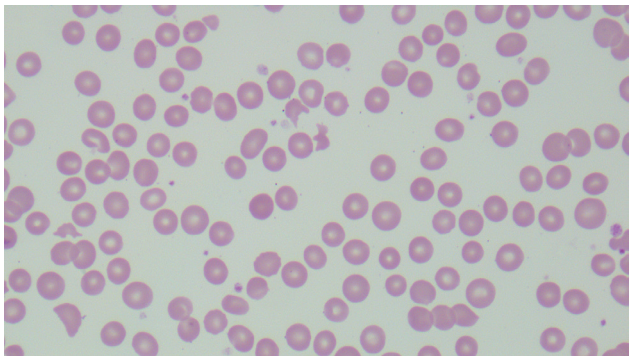
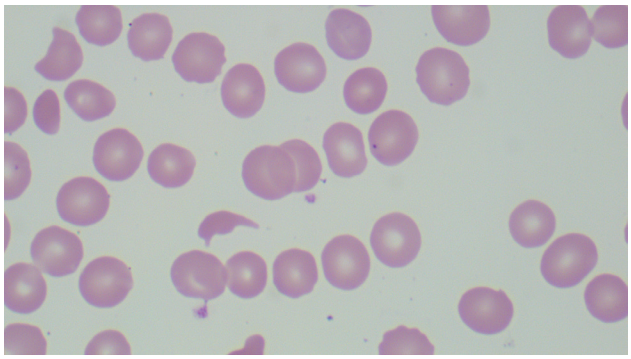
Figures 1 and 2 Peripheral blood films on day 9 of levofloxacin confirming red cell fragmentation and thrombocytopenia





excluding disseminated intravascular coagulation. Heparin-induced thrombocytopenia was considered but 4T score was low and the PF4 ELISA screening test was negative. A peripheral blood film showed marked red cell fragmentation (Figures 1 and 2) consistent with TMA. Lactate dehydrogenase was 1330 U/L, creatinine 246 umol/L, bilirubin 39 umol/L. He had no neurological symptoms. Troponin I was negative. Autoantibody screening was negative and complement components were within normal range. He had extensive investigations for infections including those which are associated with TTP such as HIV and cytomegalovirus (Table 1).

Urgent haematology opinion was sought with TTP or drug induced TMA (DiTMA) as the main differential diagnoses. Differentiating the two was not possible during the acute presentation. Therapeutic plasma exchange (TPE) was commenced immediately due to the high mortality rate in TTP without urgent treatment, pending the ADAMTS13 result. Review of blood results showed a clear deterioration in haemoglobin, platelet count, creatinine and bilirubin on commencement of levofloxacin, which subsequently resolved on drug withdrawal and TPE. Levofloxacin was changed to ceftazidime as per sensitivities of *E. coli* under guidance of a consultant microbiologist who felt *L. pneumophilia* had been adequately treated. He made a rapid recovery with normalisation of platelet count, lactate dehydrogenase and renal function. The ADAMTS13 level was 28%, consistent with a diagnosis of DiTMA allowing cessation of TPE.

We have recently seen another similar case in a 66-year-old male. He had a background of alcoholic liver disease and was treated with levofloxacin for a lower respiratory tract infection. Microangiopathic haemolysis and thrombocytopaenia (platelets 24 x10^9/l) were confirmed on peripheral blood film 5 days after commencing levofloxacin. His baseline performance status was very poor precluding TPE but his haemoglobin improved and platelet count returned to normal after stopping levofloxacin with resolution of TMA on the blood film.

Discussion

There are many aetiologies of TMA such as HUS, infections, autoimmune disorders, malignancy and drugs,[1] but DiTMA, TTP and atypical haemolytic uraemic syndrome (aHUS) are the most likely differential diagnoses in this case. Cases of TTP due to infection with *L. pneumophilia* have been reported. In view of the high mortality of untreated TTP, the patient received TPE until an ADAMTS13 level was available. The exclusion of aHUS is more difficult as specific tests are not routinely available but the response to drug cessation and TPE made this unlikely. In this case, the clear association between starting levofloxacin and the development of laboratory parameters associated with TMA strongly favour a drug-induced aetiology.

TTP is a rare haematological emergency resulting from a deficiency of ADAMTS13, a serine metalloprotease required for the cleavage of high molecular weight von Willebrand factor multimers. In the majority of cases, low ADAMTS13 levels are due to anti-ADAMTS13 autoantibodies.[2] Other features of TTP include varying degrees of end organ damage involving the kidneys, central nervous system and heart. Immediate TPE is the standard treatment, as it removes the anti-ADAMTS13 IgG antibody and replaces a large volume of plasma containing the missing enzyme. Immunosuppression with high dose corticosteroids is commenced in conjunction with TPE.[2]

HUS is a multisystem disorder associated with complement dysregulation. Bacterial toxins such as Verocytotoxin produced by *E. coli* 0157 or Shiga toxin produced by *Shigella* species trigger diarrhoea-associated HUS. It can also occur sporadically due to inherited mutations in complement regulatory proteins, such as complement factor H, complement factor I and CD46 (membrane cofactor protein), when it is termed aHUS. Poor response to TPE and normal ADAMTS13 activity should raise the suspicion of aHUS. Rapid identification of aHUS and prompt treatment with an anti-C5 monoclonal antibody, eculizumab, is essential.[3]

The distinction between TTP and aHUS can be very difficult but some clinical and laboratory features are helpful. Neurological features are more common in TTP and renal dysfunction tends to be mild, whereas dialysis is often required in aHUS. Hypertension and proteinuria are more common in aHUS and DiTMA. The ADAMTS13 level is very useful but results usually take 10–14 days so TPE is usually indicated while awaiting results. In TTP the ADAMTS13 is typically < 10% of normal activity, whereas in aHUS it is usually much higher, often above 50%. Before the widespread availability of the ADAMTS13 assay and better understanding of aHUS, many cases were classified as TTP which now would be considered TMA from

Table 1 Summary of infection screen

Test	Result
Adenovirus DNA	Not detected
Corona virus RNA	Not detected
MERS Corona virus UpE	Not detected
Influenza B RNA	Not detected
Metapneumovirus PCR	Not detected
Mycoplasma pneumoniae PCR	Not detected
Parainfluenza (inc types 1, 2, and 4) RNA	Not detected
Rhinovirus RNA	Not detected
Hepatitis B surface antigen	Negative
Hepatitis C antibody	Negative
HIV types 1 and 2 antigen and antibody	Negative
AFB stain, sputum and BAL	Negative
Fungal smear, sputum and BAL	Negative
M. tuberculosis, sputum and BAL	Negative
Adenovirus PCR, sputum and BAL	Negative
Legionella antigen urine	Negative
Legionella PCR, sputum and BAL	Positive
Pneumocystis PCR, sputum and BAL	Negative
Aspergillus antigen, sputum and BAL	Negative
Bacterial culture sputum	*E. coli*

AFB, acid-fast bacillus; BAL, broncho alveolar lavage; PCR, polymerase chain reaction

another cause. Careful review of drug history and timing of onset of illness and laboratory abnormalities such as anaemia, thrombocytopaenia, raised creatinine and bilirubin are key to diagnosing DiTMA.

Several drugs have been recognised in DiTMA. It is characterised by new onset hypertension, proteinuria and kidney injury in association with the drug history.[4,5] Two different mechanisms have been proposed: immune-mediated reactions and direct, toxic effects of the drug. Immune mediated DiTMA was first recognised in a patient with repeated episodes of acute kidney injury, haemolysis and thrombocytopaenia with use of quinine. Drug exposure results in antibody production to various cell types causing microvascular injury and consumption of platelets. The mechanism for a direct toxic effect of a drug is not well understood but it may involve decreased expression of vascular endothelial growth factor and direct endothelial injury.

Fluoroquinolones are frequently prescribed anti-bacterials particularly for community-acquired pneumonia and are generally well-tolerated. Levofloxacin is a synthetic antibacterial agent which acts on the DNA-DNA-gyrase complex and topoisomerase IV. Common side effects include gastrointestinal intolerance, increased risk of tendonitis and tendon rupture, QT prolongation and hypersensitivity reactions. Fluoroquinolones including levofloxacin have been reported to cause severe haemolysis and immune mediated thrombocytopenia.[6] There are reports of TTP and HUS associated with fluoroquinolones with a published series resulting in withdrawal of temafloxacin from the market.[7] Rare fatal cases of TTP associated with ciprofloxacin have also been reported.[8] To the authors' knowledge, levofloxacin-associated TMA has not been previously described. The underlying mechanism of fluoroquinolone-mediated TMA is not fully understood but immune mediated antibody production has been proposed.[7,8]

The first step in the management is stopping the potentially offending drug. Haematological improvement takes several days while improvement in renal function is slower and in some cases a complete recovery may not be seen. TPE is often initiated as, until ADAMTS13 levels are available, it is difficult to exclude TTP but there is no clear benefit in the management of DiTMA. There is evidence that re-exposure to the drug will precipitate a further episode of TMA and should be avoided.

This case highlights the diagnostic difficulties faced by physicians at acute presentation of TMA. Urgent initiation of TPE remains the mainstay of treatment with further decisions guided by clinical response and specialised tests such as ADAMT13. It is important for physicians to be aware of drugs that may cause this condition; this report highlights the commonly used antibiotic levofloxacin as a potential cause of DiTMA.

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