Pyrexia of unknown origin in a haemodialysis patient

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Introduction

The most common cause of pyrexial reactions in the haemodialysis patient remains bacterial infections. The incidence of infection is increased in the dialysis patient [1], particularly due to indwelling central venous catheters. Pyrexial reactions have been reported with microbacterial contamination of the dialysate [2], but these are now rare events, due to the regular testing of dialysate water. Occasionally, patients may react to a component in the extracorporeal circuit. These reactions vary from local eczematous skin eruptions, to a variety of systemic reactions, ranging from headache to anaphylaxis [3].

A case of recurrent intra- and post-dialysis fevers is presented as a teaching case.

Case

A 45-year-old man, who emigrated from the Caribbean to the UK when aged 8 years, developed end-stage kidney disease in July 2003. He had completed a 2-year course of anti-tuberculous chemotherapy for pulmonary TB in 1972.

He was started on peritoneal dialysis, but computerized tomographic scanning of his kidneys revealed suspicious areas bilaterally, and he underwent bilateral native nephrectomies. Renal histology simply showed interstitial fibrosis with a lymphocytic infiltration in keeping with chronic pyelonephritis. Histological stains and microbiological cultures for TB were negative. Following this surgery in September 2003, he started three times weekly haemodialysis using a polysulfone high flux dialyzer (FX80, Fresenius, Bad Homberg, Germany), a Fresenius 4008 dialysis machine fitted with ultrafilters (Fresenius, Bad Homberg, Germany) and enoxaparin anticoagulation. Access was initially through a right internal jugular catheter and then a radial fistula from January 2005.

A few months later he started to develop fevers, either during or more commonly following haemodialysis sessions, and his other dialysis sessions were associated with chest pains. These fevers increased in severity, such that he started to attend the hospital emergency department feeling unwell with documented pyrexias of around 38°C. Over the next 36 months, he was recorded as having attended the hospital emergency department on 22 occasions and was formally admitted to hospital 12 times, due to fevers and malaise. Typically, the fevers started during or shortly after the haemodialysis sessions. As this became a relatively common occurrence, he only attended the emergency department when he felt systemically unwell. In December 2006, he was admitted with a mycoplasma pneumonia.

During this period, more than 35 sets of blood cultures were taken, of which two grew coagulase negative staphylococci and one diphtheroids. The median C-reactive protein (CRP) was elevated (Figure 1), so an extensive search for parasitic infection was made, in view of his upbringing in the Caribbean. Serological testing for underlying parasitic, bacterial, viral and fungal infection was negative. Basic biochemical screening noted repeated normal thyroid function tests, immunoglobulins, lactate dehydrogenase and serum ACE. Extensive autoantibody screening noted a positive homogeneous staining for antinuclear antibody, but all other serological testing and specific ELISA tests were negative. Two transthoracic and one transoesophageal echocardiograms were normal, as were eight chest X-rays, two spiral CT scans of chest, abdomen and pelvis, and one isotope bone scan and one ventilation perfusion lung scan. A gallium scan had raised the suspicion of low-grade left hilar lymphadenopathy, but this disappeared on repeat scanning. A subsequent bronchoscopy and broncho-alveolar lavage were normal, with no evidence of TB, on microscopy or subsequent cultures [4,5].

In view of the history of rigors on dialysis and post-dialysis fevers, an allergic reaction was suspected [6] and the dialysis rinsing procedure changed to use 1.0 l isotonic saline followed by 0.5 l isotonic sodium bicarbonate.
in April 2006; this helped reduce his symptoms for several months or so. However, as his symptoms subsequently returned, additional investigations were undertaken, including the measurement of total serum IgE, which was raised at 463 kU/l (normal 0–120). Mast cell tryptase was increased both prior to dialysis, at 18.4 µg/l (normal 2–14), and post-dialysis, at 21.4 µg/l. Following his mycoplasma infection, ELISA antibodies to heparin-platelet factor 4 were positive, with an optical density of 1.375, but negative on subsequent screening. Although there was no fall in the peripheral platelet count, anticoagulation was switched from enoxaparin to danaparoid. RAST for ethylene oxide IgE was positive at 4.8 kUA/l (normal <0.35). It was noted that the peripheral eosinophil count had increased shortly after the start of haemodialysis (Figure 1). The dialysis blood lines were then changed to those sterilized by gamma irradiation, and his symptoms resolved. Ten months later, he remains well, serum IgE has fallen to 151 kUA/l, and the pre- and post-dialysis mast cell tryptase to 16.4 and 15.4 µg/l, respectively. IgE RAST to ethylene oxide remains positive at 2.26 kUA/l.

**Discussion**

When the fevers first started, the patient was dialyzing using a central venous access catheter. It was therefore initially assumed that he had bacterial colonization of his dialysis catheter [1], as manipulation of the catheter during dialysis may cause the release of bacterial products, resulting in pyrexia due to toll receptor activation of host monocytes. However, multiple blood cultures were negative. As there is a significant risk of possible bacterial seeding from a colonized venous catheter to heart valves, inter-vertebral discs and other soft tissues, he was investigated with standard trans-thoracic and trans-oesophageal echocardiograms and isotope bone and gallium scans.

As the fevers and hospital emergency department visits continued even when he dialyzed using an arterio-venous fistula, the search for infection widened, due to his previous history of pulmonary TB and childhood upbringing in the Caribbean. Stool samples, and serological testing for parasites and unusual bacteria and fungi were all negative.

Other possible causes of a pyrexia of unknown origin [4,5] were considered, and he underwent two spiral CT scans of his thorax, abdomen and pelvis, and two gallium scans to exclude underlying malignancy and occult infection. As one scan showed minor thoracic lymphadenopathy—due to a mycoplasma infection—he underwent bronchoscopy, which was normal, as was the broncho-alveolar lavage. Extensive and repeated immunological screening only noted a non-specific ANA staining.

Carefully evaluating the history, it was noted that he did not have fevers on Sundays, but typically developed fevers on Mondays, Wednesdays and Fridays, ... Fridays, in accordance with his dialysis schedule. Repeated dialysate water sampling showed that this complied with both microbiological and endotoxin standards for ultrapure dialysis water. To investigate whether he could have an allergic response to dialysis, mast cell tryptase was measured, both before and following dialysis. Typically, if there had been a major acute allergic reaction, the mast cell tryptase would rapidly increase and decline over the subsequent 24 h. In his case, both samples were equally increased. This would be in keeping with chronic exposure to an allergen, as with three times weekly haemodialysis.

It was thought most likely that he was having a reaction to dialysis, and the rinsing procedure was altered by the addition of isotonic bicarbonate to the standard 0.9% saline rinse. Bicarbonate rinsing has been reported to reduce dialyzer bradykinin generation [7]. Initially this increased rinsing procedure seemed to reduce both the severity and frequency of his symptoms; however, after several months his symptoms once again returned.

Following his mycoplasma infection he developed IgG antibodies to heparin-platelet factor 4. At that time he did not have thrombocytopenia, and his fevers and/or rigors typically started during or more commonly after dialysis had ended, rather than shortly after the administration of enoxaparin. Thus, it was felt that these reactions were not due to the heparin-platelet factor 4 antibodies [8]. Even so, enoxaparin was withdrawn, and replaced with danaparoid, with no significant resolution of his symptoms, or peripheral eosinophilia. Subsequent repeat testing showed that the antibodies had disappeared, and may have temporarily developed following the mycoplasma infection.

Patients can potentially develop allergies due to the numerous components of the extracorporeal circuit, ranging from local eczematous skin eruptions due to specific metal allergy associated with dialysis access needles, through to acute anaphylactoid reactions following administration of heparins for anticoagulation [3], direct dialyzer membrane reactions with bradykinin generation, and allergic reactions with ethylene oxide used to sterilize dialyzers and/or to the phthalates or methylmethacrylates located in the dialyzer header [2]. More rarely, these reactions can manifest as pyrexial reactions during or post-dialysis.

Occasionally γ-irradiated cellulosic dialyzers have been reported to release chemical components, including glycerol, acetylated carbohydrate, urethane derivatives and polypropylene glycol. These chemicals can lead to local
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irritation causing scleritis and iritis, and infrequently post-dialysis fevers [9].
When our patient initially started dialysis he used a steam sterilized dialyzer, and it had therefore been assumed that he was not exposed to any significant amount of ethylene oxide. A test for ethylene oxide sensitivity was performed and found to be positive. Following the replacement of ethylene oxide lines with gamma irradiated blood lines, his fevers resolved; as did the peripheral eosinophilia and the CRP fell to within the normal reference range and cause in addition his general health dramatically improved.
Ethylene oxide hypersensitivity was a well-recognized of acute allergic reactions on dialysis, when dialyzers were sterilized with ethylene oxide [10]. Ethylene oxide conjugates with albumin, and antibodies can form to these novel antigens. However, with changes in manufacturing processes, in particular the change to steam sterilization, ethylene oxide hypersensitivity reactions have declined over the last decade. Simple rinsing of ethylene oxide sterilized dialyzers reduced the incidence and severity of such reactions [2], and in this case, increasing the priming volume did initially reduce his symptoms. The importance of this case is to illustrate that lesser exposure to ethylene oxide, using ethylene oxide sterilized dialyzer blood lines, can cause pyrexial reactions, and peripheral eosinophilia.

Teaching points

1. Although rigors and fevers during and/or post-dialysis are most likely due to bacterial infection, other causes need to be considered.
2. Allergic reactions may be due to heparin allergy and/or heparin-platelet factor 4 antibodies, bradykinin generation due to the dialyzer or reactions to the glues used in the potting compounds in the dialyzer header and plasticizers.
3. Ethylene oxide allergy can cause a range of symptoms from acute allergic anaphylactic and asthmatic reactions to pyrexias, urticaria and pruritus.
4. Allergic reactions to the dialysis procedure should be considered in cases of peripheral eosinophilia and clinical history of reactions limited to the dialysis day, in particular when no symptoms occur during the second post-dialysis day.
5. Allergic reactions are supported by increased mast cell tryptase values, and specific serum ELISA and/or skin prick testing.

Conflict of interest statement. None declared.

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