CASE REPORT

Haemophilus influenzae infection of a prosthetic knee joint in a patient with CLL: a vaccine preventable disease

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SUMMARY

A 71-year-old man was admitted with a 2-day history of the hot and swollen right knee in December 2012. He had undergone a primary cemented right total knee replacement (TKR) in 2002. He also had a history of chronic lymphatic leukaemia (CLL), haemolytic anaemia and splenomegaly, and was in partial remission following chemotherapy in 2008. He underwent arthroscopic washout of right TKR on admission. Blood cultures on admission and joint fluid specimen grew *Haemophilus influenzae* (Hi). The isolate was identified as a non-encapsulated Hi strain by the reference laboratory. Non-encapsulated Hi strains rarely cause invasive disease. CLL with splenomegaly may have predisposed our patient to severe invasive disease. A recently licensed 10-valent pneumococcal vaccine conjugated to the immunogenic outer membrane protein D of Hi could potentially prevent invasive Hi disease. Routine vaccination should be considered in all patients with prosthetic joints and predisposing comorbidities.

BACKGROUND

Prosthetic joint infections (PJIs) are a serious complication of joint arthroplasty which may lead to further revision or excision arthroplasty procedures, prolonged hospital stay, long courses of intravenous antibiotics and poor functional outcomes. The incidence of infection following hip replacement is around 1% and knee replacement is around 0.7%.¹ Modification of preoperative risk factors is important to prevent PJI. Gram negative (GN) organisms account for a minority of cases of PJI but are more difficult to treat and are associated with limited success.² *Haemophilus influenzae* serotype B (Hib) is a well-known GN cause of osteomyelitis and septic arthritis. The incidence of invasive infection due to this organism has decreased due to the introduction of routine childhood immunisation against Hib. This vaccination does not however protect against other Hi serotypes or non-typable strains.

To our knowledge, there are only two documented cases in the literature of a PJI due to *Haemophilus influenzae* (Hi).^{3,4} The case presented is that of a man with chronic lymphatic leukaemia (CLL) who developed a PJI due to a non-typable Hi (NT-Hi). Haematological conditions which cause immunosuppression may increase the risk of invasive infection due to these rarer Hi serotypes. A recently licensed 10-valent pneumococcal vaccine conjugated to the immunogenic outer

membrane protein D of Hi, could potentially prevent invasive Hi disease.

This case highlights the importance of vaccination against Hi in patients with haematological malignancies particularly in the context of a prosthetic joint.

CASE PRESENTATION

A 71-year-old man presented with a sudden onset of painful and swollen right knee with no history of preceding trauma and was unable to bear weight. He had a history of CLL, haemolytic anaemia, splenomegaly and hypertension. He had received chemotherapy and was in partial remission since 1998. He had undergone primary cemented right knee arthroplasty in 2002 and left total knee replacement in 1999. There was no history of joint infection in both the joints and he did not undergo any revision joint surgery. Prior to this acute admission, he was treated for infective exacerbation of chronic obstructive pulmonary disease with several courses of antibiotics by the general practitioner. He did not report any fevers or rigors.

On examination, his right knee was swollen and generally tender with a decreased range of active and passive movement secondary to pain. Sensation and pulses were intact in all limbs.

INVESTIGATIONS

Knee X-ray did not show any clear fracture (figure 1). Biochemical analysis of his blood showed C reactive protein (CRP) 82 mg/L (0–10 mg/L), haemoglobin (Hb) 93 g/L (130–180 g/L), white cell count $250 \times 10^9/L$ ($4\text{--}11 \times 10^9/L$), platelet count $77 \times 10^9/L$ ($150\text{--}400 \times 10^9/L$) and erythrocyte sedimentation rate (ESR) 60 mm/h (1–20 mm/h). Blood cultures collected on admission grew Hi.

DIFFERENTIAL DIAGNOSIS

Infected haemarthrosis of prosthetic knee joint.

TREATMENT

Patient presented with acute haematogeneous peri-prosthetic knee infection, and a well fixed stable implant, and therefore he underwent an arthroscopic washout of his right knee the following day which revealed frank pus. He was started on empirical intravenous piperacillin–tazobactam 4.5 g eight hourly. Microscopy showed numerous leucocytes and cultures grew Hi which was susceptible to amoxicillin, coamoxiclav, ciprofloxacin, cefotaxime and ceftriaxone. The isolate was sent to the

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Figure 1 X-ray images of the right knee on admission.

reference laboratory for confirmation of identification and serotyping. Hi was identified as a non-typable strain. His antibiotic therapy was switched to intravenous amoxicillin 2 g six hourly for a duration of 6 weeks. After contacting the patient's general practitioner it was discovered that he had not been vaccinated against Hib after his diagnosis of CLL. He also required two units of blood transfusion during his postoperative period.

A week after the first washout, his knee continued to remain swollen and painful despite appropriate antibiotics and his CRP continued to rise to 236 mg/L. He underwent a second arthroscopic washout 9 days after the first washout which drained yellow turbid fluid. Microscopy showed numerous leucocytes, crystals and Gram stain did not show any GN bacilli and also the cultures were negative. The antibiotic therapy was changed from high dose amoxicillin to ceftriaxone 2 g once a day. His range of movement increased following second washout, swelling decreased and CRP levels also decreased down to 21 mg/L. However, he developed a drop in Hb and required another two units of blood transfusion.

OUTCOME AND FOLLOW-UP

He completed a total of 6-week course of ceftriaxone 2 g once a day (4 weeks as an inpatient and 2 weeks as an outpatient). He was reviewed in the outpatient clinic at 8th week. The clinical examination of his knee was normal and he could flex his knee from around 20° to 90°. A repeat CRP 2 weeks after stopping antibiotics was 8 mg/L. There was no evidence of clinical, radiological or microbiological treatment failure at 6-month follow-up appointment. Clinical examination of knee was normal, ESR 12 mm/h, CRP 12 mg/L and X-ray of knee did not show any evidence of prosthesis loosening. We achieved the clinical cure at 6-month follow-up. He will be followed up at 12 months to ensure there is no relapse.

DISCUSSION

The number of primary hip and knee replacements has been increasing over the past decade, with nearly 160 000 such procedures being performed in England in 2011.⁵ Periprosthetic

infection is a devastating complication and the cost of treating PJI ranges from £20 000 to £40 000 per patient. If recognised and treated early, acute haematogenous infection of prosthetic joint can be managed with debridement and retention of implant alone. This treatment strategy may fail especially in GN PJIs and patients may need revision or resection arthroplasty. It is likely that routine vaccination prior to joint replacement surgery may have prevented this infection.

Hi is a GN bacterial pathogen and a well-known cause of acute otitis media, osteomyelitis and septic arthritis. Polysaccharide capsule is a key virulence factor and anticapsular antibodies are protective against invasive disease. It is differentiated into six serotypes (a–f) based on the composition of capsular polysaccharides and non-typable strains (NT-Hi).⁶ Before the introduction of the Hib conjugate vaccine in the 1990s, infection by serotype b accounted for >80% of invasive Hi infections. These were most common among immunocompetent children <5 years old.⁷ Non-type b Hi infections were present usually as opportunistic infections in the elderly immunocompromised or those with other predisposing conditions such as chronic respiratory problems. Since the routine vaccination programme for children incorporated the Hib conjugate vaccine, the incidence of invasive Hib infection has significantly been reduced and maintained such.

The Hib conjugate vaccine does not however protect against other Hi serotypes or against NT-Hi. In countries with established Hib immunisation programmes the incidence of NT-Hi invasive infections is now higher than the incidence of invasive Hib infections. Studies have shown that NT-Hi is now the most commonly isolated strain of Hi causing invasive infection being isolated in up to 73% of cases.⁸ There was a concern that the decline in the incidence of invasive Hib infections would cause the emergence of disease caused by other serotypes of Hi or NT-Hi and fill the ecological niche, however, this has not been shown to be the case.⁹ The population affected by invasive NT-Hi is different to that affected by Hib in which it affects older persons and is also associated with high mortality.¹⁰ In the former group, studies have shown that more than half of these

patients had predisposing medical problems which included impaired immunity and chronic respiratory disease.^{8 11–13}

With this link between immunocompromised individuals and invasive NT-Hi already suggested previously, it is a likely explanation that the patient in the present case study developed this infection in his prosthetic joint secondary to his immunocompromised status due to his CLL. It is likely that our patient probably had Hi chest infection which was complicated by Hi bacteraemia and haematogenous dissemination to the prosthetic knee joint. Not only is CLL the most common haematological malignancy in the UK¹⁴ but also the main cause of morbidity and mortality in these patients are due to infection.¹⁵ Immunosuppression in these patients is caused by several factors which include disease-related immunosuppression (due to humoral and cellular immune dysfunction) and immunosuppression caused by agents used to treat the condition.¹⁵ These patients are at higher risk of opportunistic infections. British Committee for Standards in Haematology guidelines, for the prevention and treatment of infection in patients with absent or dysfunctional spleen, recommend that all patients at risk should receive pneumococcal, Hib conjugate and meningococcal conjugate vaccines.¹⁶ The current polysaccharide-based Hib vaccine does not protect against other strains of Hi or NT-Hi. A recently licensed 10-valent pneumococcal vaccine conjugated to the immunogenic outer membrane protein D of Hi has been developed. A large efficacy trial testing a prototype of this vaccine has shown that the use of Hi protein D as a carrier has provided protection against acute otitis media caused by the NT-Hi.^{17,18} There is a potential for this new vaccine to prevent invasive NT-Hi disease including PJIs in high-risk patients and this should be explored with further clinical studies.

Learning points

- ▶ All patients newly diagnosed with chronic lymphatic leukaemia and other haematological malignancies need to be vaccinated against *Haemophilus influenzae* serotype b, non-capsulated *Haemophilus influenzae* strains and pneumococci.
- ▶ Routine vaccination may be helpful in patients with prosthetic joints and haematological malignancies that predispose to bacterial infections.
- ▶ Prosthetic joint infection is a serious complication of joint arthroplasty and may lead to poor patient outcomes.

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Competing interests None.

Patient consent Obtained.

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