Listeria meningitis and resultant symptomatic hydrocephalus complicating infliximab treatment for ulcerative colitis

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Case report

A 75-year-old Caucasian male with a history of UC since 1970 remained in clinical remission until 2004 when he started to develop recurrent flares despite being on a maintenance therapy with 5-aminosalicylates and as a result required repeated courses of steroids. In 2011, he was commenced on a further reducing course of prednisolone along with 6-mercaptopurine but could not tolerate the latter due to incessant nausea and abdominal pain, and, therefore, continued to take prednisolone (15 mg/day) till June 2012 when he developed a severe life-threatening flare which did not respond to intravenous steroids (100 mg four times a day of hydrocortisone) necessitating rescue therapy with infliximab (5 mg/kg) with a good response. He was discharged home, and two weeks later received his second dose of infliximab.

Two weeks following the second dose of infliximab, the patient presented with an episode of abdominal pain and collapse. On examination, he was hypotensive, tachycardic, febrile (38.9°C) and hypoxic (oxygen saturations of 91% on room air). There was no history of recent travel and no dietary risk factors for listeriosis were identified. Abdominal examination revealed tenderness in the right iliac fossa. His initial blood tests showed haemoglobin of 8.6 g/dL, normal white cell count and a raised CRP of 193 mg/L. Chest X-ray showed bilateral lower zone consolidation. He was diagnosed with severe chest sepsis and on-going colitis, and was transferred to intensive care unit and commenced on co-amoxiclavulanic acid and gentamicin. On day 1 of admission he developed signs of meningism; cerebrospinal fluid (CSF) Gram stain showed Gram-positive rods. Co-amoxiclavulanic acid was switched to meropenem and rifampicin whilst gentamicin was continued. On day 2, blood and CSF cultures grew Listeria species, later identified as Listeria monocytogenes. On day 5, there was a reduction in his Glasgow coma scale (GCS) from 15/15 to 8/15 and he underwent a computed tomography (CT) scan of his brain which showed dilatation of the ventricles suggesting raised intracranial pressure (ICP) and hydrocephalus. He was intubated and ventilated and subsequently transferred to a specialist neurosurgical unit where he had external ventricular drain insertion and ICP monitoring. He made a gradual recovery and after four months of hospital stay was subsequently discharged home.

Discussion

Listeria monocytogenes is a Gram-positive rod with a median incubation period of 35 days (range 1 to 91 days). It is known to cause sepsis and meningitis mainly in elderly patients, pregnant women, neonates and immunocompromised hosts. It can be acquired through food, notably soft or unpasteurized cheese, unwashed vegetables and uncooked meat. The British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) have published concise guidelines on safety of anti-TNF therapies. It is therefore of high importance that patients on treatment with anti-TNF agents be informed of dietary risk factors for listeriosis; patient information leaflets are available in this regard.

The spectrum of clinical syndromes caused by Listeria infection is wide and includes febrile...
gastroenteritis, bacteraemia, meningitis and meningoencephalitis. Focal infections such as septic arthritis, endocarditis and cholecystitis have also been described.4

Anti-tumour necrosis factor agents such as infliximab and adalimumab have dramatically changed the management of inflammatory bowel disease over the past few years. In the UK, infliximab and adalimumab are licensed for use in Crohn’s disease to achieve and maintain remission whereas in ulcerative colitis, infliximab is the only licensed anti-TNF agent and its use is limited for rescue therapy for severe acute flare up of UC not responding to intravenous corticosteroids.

Infliximab is a human/murine chimeric monoclonal antibody which acts against TNF-α. TNF-α is an important part of host immune response and immunosuppression with anti-TNF α agents is associated with an increased incidence of developing listeriosis.5 The mechanism of how anti-TNF α agents predispose to Listeria infections is not clear; however, it is known that immunity to Listeria is mainly mediated through T-cell lymphokine activation of macrophages and these macrophages are then responsible to clear Listeria from the blood6 by secreting TNF and nitric oxide. It is therefore proposed that anti-TNF agents predispose to Listeria infections by inhibiting secretion of TNF by macrophages.

The exact prevalence of Listeriosis is not known but in 2006 Dixon et al. reported three cases of listeriosis in 7664 patients treated with anti-TNF alpha agents8 which is significantly higher in comparison to incidence of listeriosis in general population estimated to be 0.7 in 100,000.7 In 2010, a literature review of the association of infliximab with Listeria identified 92 cases in the Food and Drug Administration Adverse Event Reporting System. Out of these 92 cases, 69 patients (75%) were reported to have listeria meningitis and 14 out of these 69 patients (20.3%) also had encephalitis. An overall mortality of 17.4% (16/92 cases) was reported and out of these 93.8% (15/16 fatalities) had meningitis.6 This highlights the importance of early recognition of listeria infections especially listeria meningitis due to its high mortality.

It is also important to note that third generation cephalosporins (usual empirical treatment for suspected meningitis) are not active against Listeria.8,9 There are second-line agents for patients allergic to penicillins and these include trimethoprim/sulphamethoxazole, erythromycin, vancomycin10 and meropenem.11 Even though our patient was not allergic to penicillin, meropenem was the preferred antibiotic of choice to provide broad-spectrum cover for chest and abdominal sepsis in addition to cover for Listeria infection.

Conclusion

Even though L. monocytogenes is an uncommon pathogen, clinicians should consider this organism as a source of sepsis and meningitis in immunocompromised individuals, including those on anti-TNF alpha agents. In our patient, it is worth mentioning that he had been on multiple courses of steroids prior to initiating anti-TNF treatment and this may have contributed to the underlying immunosuppression. The meningitis UK guidelines suggest prescribing ampicillin for all patients with suspected meningitis above the age of 55 years to cover for Listeria.9 Our case also raises the discussion as to whether all immunocompromised patients (regardless of their age) suspected of meningitis should be treated empirically with ampicillin to cover for Listeria. Finally, hydrocephalus should be suspected in patients with meningitis (listeria meningitis in this case) who develop reduced conscious level to help guide any subsequent interventions.

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