CLINICAL NEUROSCIENCES

A Case of Rapid Deterioration in a Patient with Progressive Multifocal Leukoencephalopathy

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ABSTRACT

This is a case of unexpected rapid deterioration from a seemingly mundane presentation in a 63-year-old man with no significant past medical history. This case also exhibited a combination of rarer complications in relation to treatment, which are seldom considered upon initiation.

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PRESENTATION

A 63-year-old retired gentleman presented to our institution via the accident and emergency department by referral from his primary care physician. He presented with new onset symptoms resembling postural hypotension. He reported feeling generally unwell for a period of 2 days and decided to seek medical opinion after developing light-headedness for a period of 24 hours prior to presentation. He did not lose consciousness during these episodes but had to immediately sit down and took a total of 5-10 minutes to fully recover.

He had no significant past medical history, reporting to enjoy good health to date. His only prior admission was for an uncomplicated appendectomy at 13 years old. He informed us that he did not regularly attend his local physician, stating that his most recent encounter before this episode was 5 years prior, for a minor illness that resolved without treatment within a week.

Regarding his drug history, he was taking no medications at the time of presentation apart from supplementation of a multivitamin and Echinacea extract. He had no known drug allergies.

Regarding his social history, he lived at home with his partner of 20 years. Prior to admission, he was fully independent with his activities of daily living, still drove, and was enjoying his new-found retirement from a management position for the past year.

There was an unremarkable family history, with both parents passing away in their late 80s.

He believed that his presentation could be attributed to a minor viral infection that was just affecting him in an odd way. He subsequently alluded to concerns that it could be due to something more serious, however, he would not elaborate further.

On initial examination, at A&E he appeared generally well – apyrexial with stable observations and a national early warning score (NEWS) of zero. Full blood count (FBC), urea and electrolytes (U&E), C-reactive protein (CRP), liver function tests (LFTs) and clotting profiles were taken for further investigation. Over the next hour, the patient deteriorated rapidly. 1 hour after the initial assessment his blood pressure had fallen from 138/90 mmHg to 78/72 mmHg, his heart rate dropped from 88 bpm to 43 bpm, temperature remained at 37.1oC, but his respiratory rate had increased from 18 to 42 and GCS dropped to 14. He was unable to maintain a patent airway and was subsequently intubated and transferred to the intensive care department. Immediate management included a noradrenaline infusion to maintain blood pressure and an ECG which showed sinus bradycardia of 44 bpm.

INVESTIGATIONS

Having satisfied the criteria for quick sepsis-related organ failure assessment (qSOFA), a decision was made to initiate the sepsis-6 pathway, despite not satisfying the systemic inflammatory response syndrome (SIRS) criteria. He was placed on hourly neurological observations whilst awaiting blood

results and cultures. A CT head results showed no gross abnormality.

Blood results showed a low-normal white cell count of 4.1 x 10-9 per litre and were otherwise unremarkable. Chest X-ray showed moderate perihilar reticular blebbing with a small left-sided pleural effusion.

A viral screen proved negative for Hepatitis A, B & C, as well as Cytomegalovirus & Epstein Barr Virus. Following the chest X-ray findings, a bronchial lavage was performed and proved positive for Pneumocystis jirovecii (PCP).

Following this, a viral screen for HIV was requested which came back positive and showed a CD4 count of 49cells/mm3, confirming a diagnosis of acquired immunodeficiency syndrome (AIDS). The patient had not been on HAART treatment previously and was not known to be HIV positive prior to admission.

An MRI scan was undertaken which had findings indicative of progressive multifocal leukoencephalopathy (PML). Definitive diagnosis of PML is only possible by brain biopsy, however, this is rarely undertaken, and not attempted in this case.

DIFFERENTIAL DIAGNOSIS

- PML (Progressive multifocal leukoencephalopathy)
- AIDS (Acquired Immunodeficiency Syndrome)
- PCP (Pneumocystis jirovecii pneumonia)
- IRIS (Immune Reconstitution Inflammation Syndrome)

TREATMENT

Empirical antibiotics were started (flucloxacillin & gentamycin) prior to the bronchial lavage as part of local sepsis-6 guidelines. Following the diagnosis of PCP, antibiotic therapy was de-escalated according to local antibiotic guidelines.

Following the MRI finding of PML, it is best practice to treat the underlying cause, in this case, the HIV load. As he was found to have such a profoundly low CD4 count, highly active antiretroviral treatment (HAART) treatment was initiated. This was met with a severe allergic reaction consisting of a widespread rash and dramatic increase in LFTs. Given the lack of alternative, consultant opinion was that HAART therapy should continue, despite the reaction.

Following improvement in his condition over the 48 hours, he dramatically deteriorated, spiking a temperature of 41oC, consistent with immune reconstitution inflammation syndrome (IRIS).

IRIS is a condition in which the immune system shows a delayed recovery secondary to HAART therapy, resulting in a delayed response to a previously acquired infection – in this case, PCP. The cytokine storm that followed was controlled through steroid therapy, whilst the underlying infection was being treated.

DISCUSSION

This case was interesting for a number of reasons. Firstly, the rapidity of the patient's decline is remarkable. Our patient reported a 2-day history of a mundane, generalised illness and postural hypotension. His history and initial clinical examination were thoroughly unremarkable. The profound and sudden deterioration in the patient, to the point of being unable to maintain a stable airway, is enough to make the stomach of any responsible physician sink.

Secondly, the initial investigations conducted in the A&E department returned many key findings required to piece together this clinical picture. With each result came an avenue of treatment that would usually be considered to be of benefit. However, in this case, rare side effects such as allergies to HAART, and the development of IRIS, both complicate the picture.

The diagnosis of PCP is rarely found in the healthy population, and so it was upon this discovery that a further barrage of viral screens was requested. The most common reason for infection by PCP is due to immunosuppression. It was not thought that this patient was positive for HIV upon initial deterioration. A key learning point from this case would be to suspect HIV in the case of rapid deterioration.

HIV/AIDS is a spectrum of disorders caused via infection with HIV. HIV is a retrovirus that infects CD4+ T-cells in the immune system, causing their destruction. Initial infection can be symptomless or present with an influenza-type illness. It is worth considering if our patient was describing this initial reaction when describing his last presentation to his GP 5-years previous to this admission.

Treatment for HIV/AIDS is by HAART. This involves the simultaneous treatment of multiple stages of the HIV replication-cycle and has been effective in reducing the progression of HIV to AIDS, with estimations of saving 700,000 lives per year (Fauci & Folkers, 2012). Although allergic reactions to HAART are documented, they are not common, reported to be around 2% (Chaponda *et al*., 2011). In this patient, the treatment with HAART was immediately necessary in order to stop the JC virus progressing the PML. The downside of initialising treatment of HAART in a patient with known PCP is that it opens the possibility of IRIS.

IRIS is another rare, but well-documented disorder in which treatment with HAART allows the immune system to recover, only to then have a sensitivity reaction to a previously acquired infection, in this case, PCP. In this case, the risk of allowing the JC virus to continue damaging the central nervous system was deemed higher than the risks posed by continuing HAART, even in the presence of PCP.

PML is likewise a rare diagnosis, especially in the western world, seen in less than 1 in 200,000 people (NORD, 2017). It is caused by the John Cunningham Virus (JCV) which is common, but rarely provides symptoms. It is only in the vulnerable and immunosuppressed where the JCV can migrate across the blood brain barrier and cause profound and widespread demyelination of the white matter in the central nervous system. This is due to JCV-induced lysis of oligodendrocytes (Pavlovic *et al.,* 2015). Once this has happened, the mortality rate is 30% within the first 3 months and up to 50-60% within 2 years, with survivors showing varying degrees of neurological impairment (Ensig *et al.,* 2009; Tan *et al.,* 2010).

As there is no effective anti-JCV treatment, patients with PML rely on HAART to boost the immune response to infection (Clifford *et al.,* 2014). The only definitive diagnosis for PML is by brain biopsy, however, this is seldom undertaken clinically due to the combination of it being a high-risk procedure, and the target patient group being too unwell to tolerate the procedure.

In short, the interest of this presentation was in its mundanity. Yet, through rapid deterioration and a series of uncommon reactions, it kept all physicians and intensivists on their toes throughout his care.

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