

**Supplementary Table 1: Summary of investigations – Case 1.**

| Test                    | Results  | Comments  |
|-------------------------|--|---|
| Microbiology            |  |   |
| Standard blood cultures | Serial cultures - no growth after 5 days   |   |
| Urine MCS               | Serial cultures - no white cells on microscopy; no growth  |   |
| Sputum MCS              | Respiratory flora  |   |
| Syphilis serology       | Syphilis antibody: positive<br>TPHA: positive<br>RPR: negative<br>Treponema pallidum IgM: negative | In keeping with past syphilis - known to have had treatment for late latent syphilis in 2018  |
| CSF bacterial PCR       | <i>N. meningitidis</i> and <i>S. pneumoniae</i> not detected                                       |   |
| CSF bacterial cultures  | No growth  |   |
| CSF TPHA/RPR            | Not detected   |   |
| CT/GC NAAT              | Urine/throat/rectal negative   |   |
| Mycobacterial cultures  | 7x AFB blood culture no growth after 6 weeks<br>1x AFB sputum no growth after 8 weeks              | <i>Mycobacterium genavense</i> was identified by in-house PCR posthumously from blood culture |

|                       |   |   |
|-----------------------|---|---|
|                       | 1x AFB CSF no growth after 8 weeks  |   |
| Stool studies         | MCS no growth and <i>C. difficile</i> screen negative   | Loose stools  |
| Virology              |   |   |
| HIV serology and PCR  | <p>On initial presentation D0:<br/> HIV PCR 8,500,000 copies/mL<br/> HIV antigen/antibody (4<sup>th</sup> generation assay) – positive<br/> HIV avidity – high<br/> CD4 82 cells/mm<sup>3</sup>; 7% absolute count</p> <p>On readmission D28<br/> HIV viral load of 2,800 copies/mL and absolute CD4 102 cells/mm<sup>3</sup>; 16% absolute count</p> | <p>HIV unlikely to have been acquired in the last 4 months</p> <p>Anti-retrovirals commenced on D12</p> |
| CSF viral PCRs        | CMV, EBV, adenovirus, HSV, VZV, enterovirus, parechovirus negative  |   |
| Respiratory viral PCR | Nil detected  |   |

|                                     |   |   |
|-------------------------------------|---|---|
| Stool studies                       | Rotavirus, norovirus, astrovirus, sapovirus not detected          | Loose stool                                     |
| Mycology                            |   |   |
| CSF CrAG                            | Negative  |   |
| Serum BDG                           | 244 pg/mL (D6),<br>>500 pg/mL (D9)<br><br>>500 pg/mL (D39)        | Positive (cut-off >80 pg/mL)                    |
| Sputum PCP PCR                      | Positive for <i>Pneumocystis jirovecii</i>                        | Sputum PCP PCR                                  |
| Serum CrAG                          | Negative  |   |
| Histoplasma serology                | Positive for <i>Histoplasma capsulatum</i> antibodies (titre 1:2) | Panfungal PCR negative; antigens negative       |
| Sputum culture                      | <i>Aspergillus fumigatus</i>                                      | Uncertain clinical significance                 |
| Parasitology                        |   |   |
| EDTA PCR/bone marrow for leishmania | Negative  | PCR negative; no amastigotes seen on microscopy |
| Toxoplasma IgG (serum)              | X2 - not detected   |   |
| Toxoplasma PCR CSF                  | Not detected  |   |
| Strongyloides serology              | Positive (Elisa O.D: 1.276; cut-off: 0.745)                       | Managed with two doses of ivermectin            |

|                              |   |   |
|------------------------------|---|---|
| Stool studies                | Ova, cysts, and parasites negative  | Loose stool   |
| Immunology                   |   |   |
| HLA-B57                      | Negative  |   |
| Biochemistry                 |   |   |
| CSF biochemistry             | Unremarkable  |   |
| Plasma ammonia               | Normal  |   |
| Imaging                      |   |   |
| EEG                          | Irregular slow-dominated background ( $\theta/\delta$ range)  | Consistent with mild-moderately severe encephalopathy<br>No seizures or epileptiform activity |
| CT Head                      | No acute intracranial changes   | Extensive white matter abnormalities noted<br>CT head with contrast                           |
| CT TAP with CT angiogram     | No source of GI bleed<br>Rectal faecaloma with presumed reactive proctitis  | Triple-phase CT abdomen/pelvis done due to per rectum bleeding                                |
| Transthoracic echocardiogram | Unremarkable  | No evidence of infective endocarditis or vegetations on scan                                  |
| MRI head                     | Imaging appearances are most in keeping with PML, and would be atypical for ADEM, toxoplasmosis, or encephalitis. | MRI head with contrast  |

Day 0: Day of initial admission.

ADEM: acute disseminated encephalomyelitis; BDG:  $\beta$ -D-glucan; CMV: cytomegalovirus; CrAG: cryptococcal antigen; CSF: cerebrospinal fluid; CT: *chlamydia trachomatis*; CT TAP: computed tomography thorax, abdomen, and pelvis; EBV: Epstein-Barr virus; EDTA: ethylenediaminetetraacetic acid; ELISA O.D: enzyme-linked immunosorbent assay optical density; GC: gonococcus (*Neisseria gonorrhoeae*); IgG: immunoglobulin G; IgM: immunoglobulin M; HLA-B57: human leukocyte antigen B57; HSV: herpes simplex virus; MCS: Microscopy, culture, and sensitivity; NAAT: nucleic acid amplification test; PCP: pneumocystis pneumonia; PML: progressive multifocal leukoencephalopathy; RPR: rapid plasma reagin; TPHA: treponema pallidum hemagglutination assay; VZV: varicella zoster virus.